

Harveian Oration 2012: Halving premature death

Taken from the transcript of a lecture given by Richard Peto at the Royal College of Physicians

Introduction

This Oration is dedicated to two twentieth-century physicians. One is Richard Doll, who was born 100 years ago this month and, with Bradford Hill, was the first person in Britain to do really good work on the link between smoking and lung cancer, and subsequently between smoking and many other diseases.^{1–4} The other is Charles Fletcher who, 50 years ago, wrote the original report of the Royal College of Physicians on smoking and health.⁵ This was the first such report that any public body in the world had produced, and it directly inspired the first report on smoking and health by the US Surgeon General, which was published two years later.⁶ Because of Richard Doll and Charles Fletcher, the UK has experienced the fastest decrease in tobacco-attributed mortality in the world over the past half-century. The other main reason we had the fastest decrease in the world is that half a century ago the UK had the world's worst tobacco-attributed mortality rates.^{7,8}

A historical overview: trends from the nineteenth century to today in developed countries

I don't, however, want to talk just about reducing mortality from tobacco, but about halving premature death in general. The aim of the epidemiological study of mortality is not to achieve eternal life, but to help people avoid premature death and reach old age. For this we need to avoid childhood mortality and premature mortality in adult life from external causes and from disease.

Fig 1 shows the percent survival to age 70 of French males who were unlucky enough to be born in 1896. As in many European countries at the time, about a quarter died in early childhood (and for children in some big, unhygienic cities, the proportion dying in childhood would have been well over a quarter). Then, as French males born in 1896 were of military age at the start of the 1914–18 War, a third of those who were still alive in 1914 were dead five years later, and many survivors were horribly wounded. Then, of the 50% of the 1896 cohort who made it to middle age (here defined as 35–69), half died in middle age. Such high child and adult death rates are no longer seen anywhere.

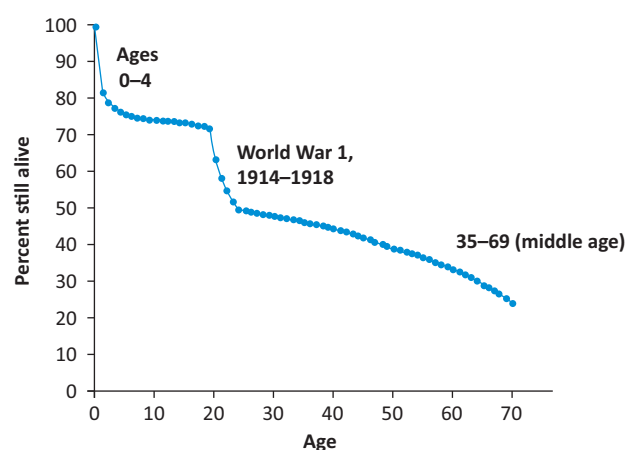


Fig 1. Percentage survival to age 70 in French males born in 1896.

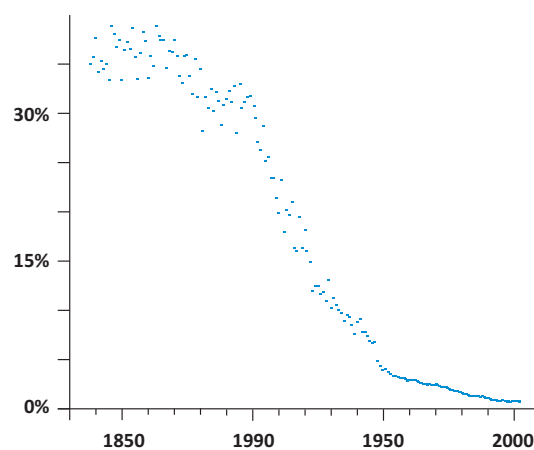


Fig 2. Male under-5 mortality in England and Wales, 1838–2002.

Reproduced courtesy of Gary Whitlock, Clinical Trial Service Unit, University of Oxford. Data taken from the reports of the registrar general for England and Wales.

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Fig 2 shows the under-5 mortality rates for males (figures for females were very similar) in England and Wales from 1838, when death rates began to be recorded, to 2002. Back in the mid-nineteenth century, about a third of all children died before they were five years old; indeed, many died while being born, or in the first year of life. In most areas there were no

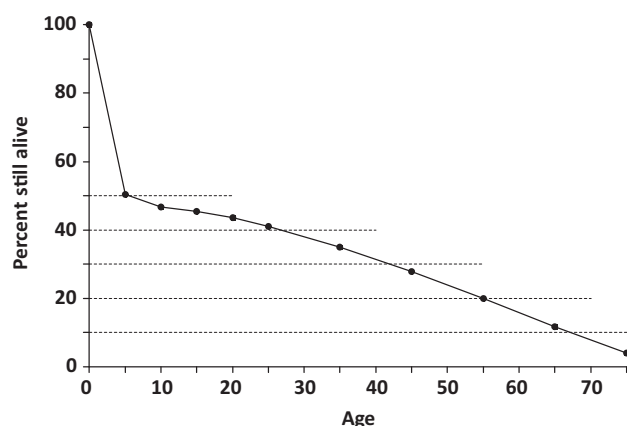


Fig 3. Mortality rates in Liverpool in 1860 rates. These were among the highest mortality rates in all of England and Wales. Reproduced from Sargant (1866).⁹

sewers that worked properly, water was contaminated, disease was everywhere and obstetric care was poor. Mortality rates were far worse than the national average in large cities during the nineteenth century, with half of all children in Liverpool dying before the age of five (Fig 3);⁹ the risks would have been similarly bad in the East End of London, or in central Manchester or Glasgow. As Fig 2 shows, little had changed by 1900; still in the first decade of the twentieth century, when my mother was born, nearly a quarter of the children born in Britain were dying before the age of five.

Then during the first half of the twentieth century – not in response to any great improvements in medical treatment, because nearly all the drugs didn't work – the UK had an enormous decrease in under-5 mortality. From 25% around the beginning of the century, UK under-5 mortality was down to about 5% when I was born in the 1940s and it is now about 0.5%, an overall decrease since 1860 by a factor of about 70, and child mortality is still decreasing. The improvements in child mortality during the first few decades of the century were due mainly to public health measures – such as vaccination programmes, clean milk and water and better nutrition – rather than medical treatment. There is now no country in the world – even Afghanistan or Sierra Leone during wartime – where the under-five mortality rates are as bad as they were in the richest countries in the world in 1860.

Fig 4 shows, in steps of 50 years, how the pattern of survival changed from 1860 to the present. The figure describes the period death rates for males, but females faced similar hazards. From 1860 to 1910 survival improved, but the overall pattern remained similar. Going from 1910 to 1960, however, the pattern is qualitatively different. Under-5 mortality decreased tenfold, and adult mortality rates halved. And now, at 2010 death rates, serious numbers survive into their 90s. Only fifty years ago, very few people lived that long, and almost nobody lived beyond 100.

This large decrease in mortality throughout Western Europe a century ago led some, such as McKeown,^{10,11} to the disputed^{12,13} conclusion that what is needed to achieve similar decreases in mortality in developing countries today is not medicine but social change. This is of course a non-sequitur – the fact that it wasn't medicine that drove death rates down 100 years ago, when most medicines were ineffective, is irrelevant to the substantial further

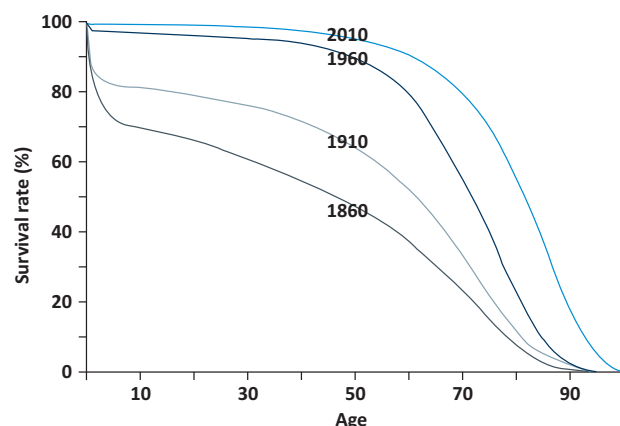


Fig 4. Percentage survival at period rates for males in England & Wales. Figure reproduced courtesy of Gary Whitlock, Clinical Trial Service Unit, University of Oxford. Data taken from the reports of the registrar-general for England and Wales and the Human Mortality Database.

benefits we could get by much wider delivery of the effective medicines of today. Of course it would be wonderful if substantial social improvements could be achieved as well, but while we encourage such social changes the effective delivery of basic modern vaccines and medicines could and should play a vital role.

The decreases in mortality that happened in rich countries in 1850–1950 are now, with a few horrible exceptions, happening throughout the world. If they continue, and nothing catastrophic goes wrong, then the two-century period between about 1850 and 2050 (a few decades hence) will be seen as the time when, world-wide, we virtually eliminated premature death, getting humanity to the point where, if you're born without any serious congenital problems, you have a really good chance of surviving throughout childhood, throughout early adult life, and throughout middle age, to reach old age. We are quite a long way down that track already, and although we still have some way to go, we are on the whole making rapid progress. To maintain that progress, however, we need to take today's few big causes seriously, and avoid new catastrophes.

Are today's big causes modifiable?

Every major cause of death – particular types of cancer; stroke; suicide; TB; HIV – that is a big problem in one population is much less common in some other population. This shows that wherever they are common, they don't have to be.¹⁴ Except for skin diseases that depend on pigmentation, the big differences in disease rates between one population and another are not chiefly genetic: if a Japanese population moves to Hawaii, or California, and they live like Hawaiians or Californians, then they will die like Hawaiians and Californians. These differences in disease rates are caused by humanly avoidable differences in the ways different populations live. Moreover, within particular populations there are also big variations over time in mortality rates among people of a given age from particular diseases, which again cannot be caused by genetic factors.

A striking example is provided by the male mortality rates in different Chinese counties during the 1970s, when the great

Chinese Cancer Atlas was compiled.^{15,16} About 200 miles south of Beijing, 20% would die before age 70 from oesophageal cancer; 200 miles west of Beijing, fewer than 1% would do so. (For comparison, at 2010 UK death rates only 20% of men would die from any cause before age 70: see Fig 4.) Similarly, if you go down to the Yangtze and stop at the last county on the left, 10% of the men would die from liver cancer or liver cirrhosis; stop a couple of hundred miles upriver and fewer than 1% would do so. Up in the north of China, stroke is the commonest cause of death and there are counties where 20% die from stroke before 70 and many more are disabled; further south, it's ten times less common.

An even more striking example of a major avoidable cause of death is alcohol in Russia – or, more precisely, massive vodka consumption, mainly by men. In most countries I have worked in, tobacco causes far more deaths than alcohol. In Russia, however, alcohol causes even more deaths than tobacco, at least in early adult life. At current UK death rates a man has only a 7% risk of dying before 55. In contrast, at 2005 Russian death rates this risk was 37%, and alcohol was the chief reason.^{17–19}

When Gorbachev came to power in 1985 he immediately introduced anti-alcohol laws that led to total vodka use going down by about a quarter. Next year, the overall male death rate at ages 15–54 had dropped by about a quarter just because of that one measure. (The female death rate also went down, partly because they too were drinking less, and partly they were no longer quite as likely to be murdered.)

Within a few years, however, Gorbachev's alcohol controls started to fail, so after 1988 the Russian mortality rates started to rise, and when the Soviet Union collapsed at the end of 1991 all alcohol controls vanished and mortality skyrocketed. From 1991 to 1994 half of all industry ceased functioning, half of all jobs went, if people had any money they lost 96% of it because there was 2500% inflation, food became more expensive and village-produced vodka was cheap and available.

After 1994 the economic situation stabilised for a few years, during which the death rate fell until the 1998 collapse of the rouble, following which mortality rates shot up and stayed high until 2005. After 2005 the mortality rates have again been falling, but even at 2010 death rates a quarter of all Russian men would die before age 55.

David Zaridze interviewed the families of 50,000 adults who had died during 1990–2001 to find what the dead person used to drink, and found that those who drank about a bottle of vodka a day had (in comparison with those who drank less than a bottle a week) about twice the risk of dying of disease and about 8 times the risk of dying from accident or violence, and that the alcohol-associated causes of death accounted fully for the wild fluctuations in national mortality rates.^{17,18} There are also indirect effects of alcohol: a woman who drinks a bottle of vodka a day was 15 times more likely to commit suicide and 20 times more likely to be murdered than a non-drinker.¹⁷

Because of this and other studies, anti-alcohol laws were introduced by the Russian government in 2010. The price of vodka has been tripled, street sales are limited after 10pm, and campaigns warning of the dangers are being run. So far these controls seem popular, and President Putin is now introducing tobacco controls as well. If both alcohol and tobacco-attributed mortality can be greatly reduced, Russia could soon have normal Western European death rates.

Reducing premature death in different age groups

The avoidable causes of death in infancy, childhood, early adult life and middle age are very different. I shall therefore consider separately ages 0–4, 5–34 and middle age, which I am going to define as running from 35–69. I am 69 this year, and a lot of my friends have asked me if I'm going to change the goalposts next year: I'm not. If you look up the definition of middle age in the dictionary, it's 'That period between youth and old age, variously reckoned to suit the reckoner'. So, to suit my reckoning, I want it to be old enough for chronic disease to be important, but not so old that people think you're better dead anyway. Although death in your early 70s could well be considered premature, I'm going to stick with 35–69 as my definition of premature – and, if you die in your 60s, you could well be losing 20 good years.

Early childhood (ages 0–4)

Worldwide, childhood mortality is falling rapidly. What happened in Britain in the first half of the century has been happening in low-income countries in the past half-century. At 1950 death rates, about a quarter of all the children in the world would have died before the age of five – like Britain around 1900. Worldwide under-5 mortality had dropped to 14% by the 1970s, 9% by the 1990s, 7% by the early 2000s, and about 5% (7 million out of 135 million live-births) now – like Britain around 1950 (Fig 2).^{20–22} 7 million is still a lot of child deaths, but if under-5 mortality rates had not shown the improvement they did in the past 50 years, the figure would have been 30 million. On the other hand, if childhood death rates were the same worldwide as they are now in the UK, the figure would be under 1 million. Under-5 mortality has been halved twice since 1950, and it can be halved again if the world continues to take the reduction in under-5 mortality as seriously over the next 20 years as it has done over the past decade.

If we look back to the 9 or 10 million childhood deaths in the year 2000, what caused them? HIV was not a major cause of death in this young age range. The Global Burden of Disease estimates put out by the World Bank in 2006²³ show that 2 or 3 million were dying during the process of being born (not including the 2 or 3 million late stillbirths of viable fetuses): being born is dangerous. Giving birth is also dangerous: about 0.3 million mothers a year die in childbirth, which is about 1000 a day, and if a mother dies in the developing world the survival chances of her older children are reduced.

Next came acute respiratory infections (about 2 million), diarrhoea (also about 2 million), and malaria (over 1 million – far more than all other parasitic diseases combined). Then, because we are talking about the period 10 years ago, about 1 million died from vaccine-preventable diseases, with the biggest number being from measles (0.6 million). Since 2000, however, energetic vaccination programmes have reduced measles deaths by about two-thirds down to about 0.2 million, showing that real change is possible. Likewise, childhood deaths from malaria have decreased by about a third over the past decade, as a result of people taking measures such as bed nets, effective medication and mosquito control more seriously.

The Millennium Development Goal of a two-thirds reduction in 1990 under-5 mortality rates will probably not be achieved by the target date of 2015, but if progress in the next decade

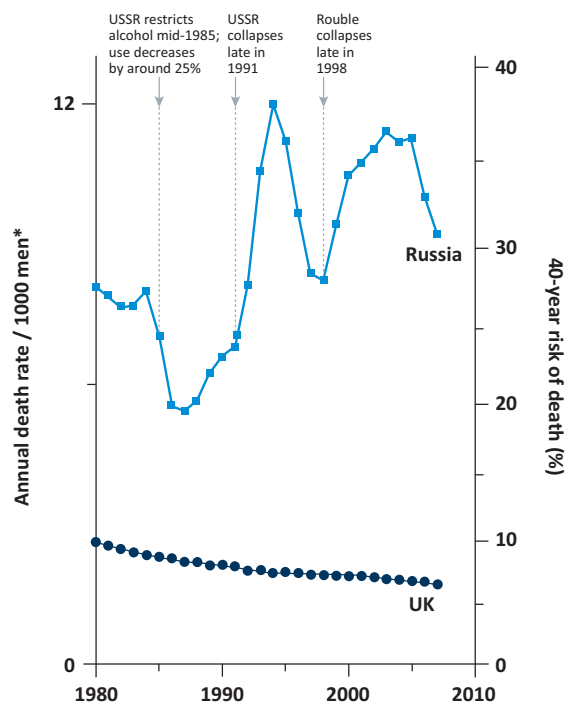


Fig 5. All cause mortality in males aged 15–54 in Russia and England, 1980–2007. *Mean of rates in component 5-year age groups (15–19 to 50–54). Reproduced with permission from Zaridze *et al.* 2009.¹⁷

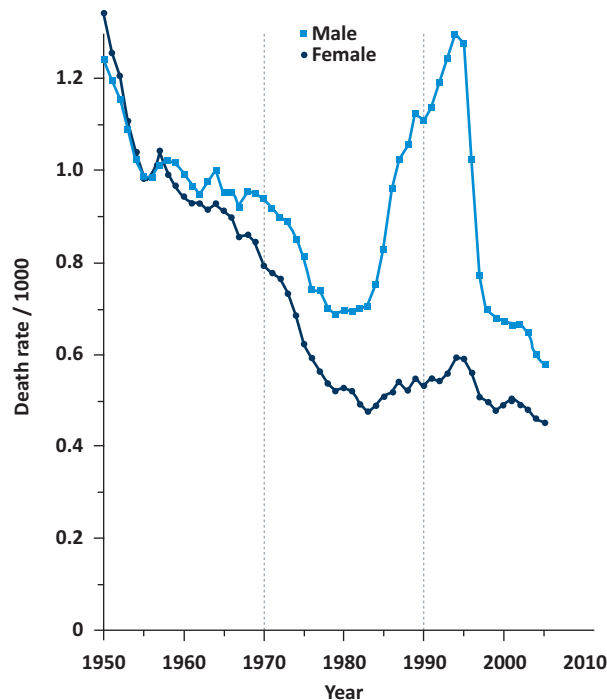


Fig 6. All medical mortality in males and females in the US at ages 30–34, 1950–2005. Data from WHO mortality and UN population estimates.

continues to be as rapid as in the last decade then it should be achieved by the early 2020s. There is still much that can be done to reduce malaria deaths, acute respiratory infections are usually curable by cheap antibiotics, diarrhoea deaths can be greatly reduced by oral rehydration therapy and birth attendants – not necessarily fully trained doctors in expensive clinics, but people with enough training to know how to avoid mothers dying of haemorrhage or infection – can reduce maternal and perinatal mortality. The costs are small compared to the costs of medical care in the West.

Later childhood and early adult life (ages 5–34)

In the next age group, 5–34, the Global Burden of Disease project estimates there were about 7 million deaths in 2000²³ and 5 million in 2010.^{20–22} Much of the mortality in young adults is due to external causes such as suicide, violence and accidents. Taking all age groups together, there are almost a million deaths a year from suicide and more than a million a year from traffic accidents. Social factors affect these risks, and again this can be shown by comparing different countries, or different populations within the same country. Within China, for example, we can find different rural counties where the suicide rates differ ten-fold. In Russia, half of all deaths at ages 5–34 are from non-medical causes, mostly directly or indirectly because of vodka. In many developing countries, traffic accidents are a major cause of death that could be reduced substantially.

In many countries HIV remains a major cause of death among young adults although drug treatment can play a major role in reducing transmission and mortality. We don't have good statistics in the key area, which is Africa, but mortality

statistics for America illustrate the extraordinary relevance of this one cause of death. Fig 6 shows the death rates from disease of young Americans aged 30–34 from 1950–2010. Death rates continued to decrease until the 1980s, when they suddenly turned round because of HIV and went up and up, until protease-based combination therapy began to be used widely. People are now staying alive with their infections²⁴ and if they're treated properly, they're not so infectious. Of course, the main HIV epidemic is in sub-Saharan Africa, but the picture there is less well documented. Whether or not current HIV mortality rates can be halved, effective action to reduce transmission and treat infection can halve what HIV mortality will otherwise be in the 2020s.

Middle age (ages 35–69)

The most recent Global Burden of Disease estimates that in 2010 there were 12 million deaths before middle age, 18 million in middle age (35–69) and 23 million in old age.^{20–22} The deaths in early childhood are of those born recently, but the deaths in middle age are of people born around the middle of the century, when the world's population was much lower, so the denominator is much smaller. Instead of thinking of the 53 million who died in 2010, consider instead what would happen at 2010 death rates to the 135 million born in 2010. About 15 million will die before age 35, then of the 120 million who reach age 35 about 40 million will die in middle age, mostly from vascular disease (15 million) or cancer (10 million), and 80 million will die in old age. Can we halve the number who will die in middle age, reducing it from 40 million down to 20 million?

If we halve the death rates in each age group this will approximately halve the risk of death before age 70, but still nearly all of us will die before 100. For, at current UK death rates, by the time you get to 90, a quarter die each year, so only 1 in 10 reach 100, and if you do get to 100 then half die every year, so only 1 in 1000 of those who reach 100 will reach 110. So, whether or not it would be a good thing to live beyond 100, halving the age-specific death rates in each year of age would have little absolute effect on the proportion dying before 100, and even less absolute effect on the proportion dying before 110.

It would, however, almost halve the number of premature deaths, ie, deaths before old age. So, how can mortality rates in middle age be halved? The two most causes of death in middle age are vascular mortality and cancer, which we will now look at separately.

Vascular mortality

Fig 7 shows the extraordinary decrease over the last 60 years in UK stroke mortality rates. At 1950s rates, more than 5% would die from stroke before age 70; now, fewer than 1% do so, and the rates are still falling. Before 1980, doctors didn't know how to prevent stroke with effective treatments such as aspirin, statins, diuretics and other blood-pressure-lowering drugs, yet stroke death rates were falling, perhaps reflecting some aspect of social progress (as stroke rates are much higher in the poor than in the rich, and society is getting more prosperous). Most vascular deaths are from heart disease rather than stroke.

Fig 8 shows overall vascular mortality in the UK, which in terms of absolute decreases is even more striking. At the 1970 death rates, almost a quarter of UK men would die from vascular disease before age 70. (All such calculations are of what the risk of death would be in the hypothetical absence of any other causes.) Now this risk is down to only 6%, a four-fold reduction, and it is still falling, due partly to the big decrease in smoking, partly to favourable changes in diet (despite the increasing prevalence of obesity and diabetes in the UK), and partly to successive improvements in treatment.

Although UK vascular mortality rates have decreased steeply, worldwide, ischaemic heart disease still accounts for more deaths, and more years of life lost, than any other disease, with stroke close behind. What can be done to reduce vascular mortality? Prevention is better than cure (especially since a first heart attack or stroke can be fatal or permanently disabling), but secondary prevention now contributes substantially to lowering vascular mortality in high income countries and could do so affordably in low and middle income countries.

Once people have been diagnosed as having occlusive vascular disease, long-term treatment with effective generic drugs can reduce by more than half the chances of having a major heart attack or stroke over the next few years. Drugs such as statins, aspirin, diuretics and other blood-pressure lowering medication would work, but are insufficiently used. Surveys in India and China of people who have had a heart attack or stroke show that few are on any of the simple medications that would, in combination, halve their recurrence rate, although such medication should be affordable by anybody who could afford the diagnosis of vascular disease.

Worldwide, vascular mortality could be reduced substantially by effective action against four main causes: tobacco, blood pressure, blood lipids and obesity.

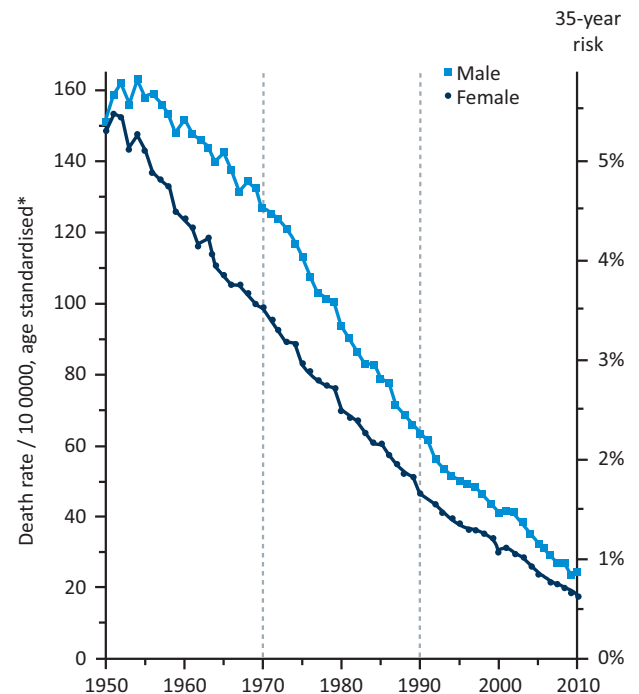


Fig 7. Cerebrovascular disease mortality at ages 35–69 in males and females in the UK 1950–2005. Data from WHO mortality and UN population estimates. *Mean of annual rates in the seven component five-year age groups.

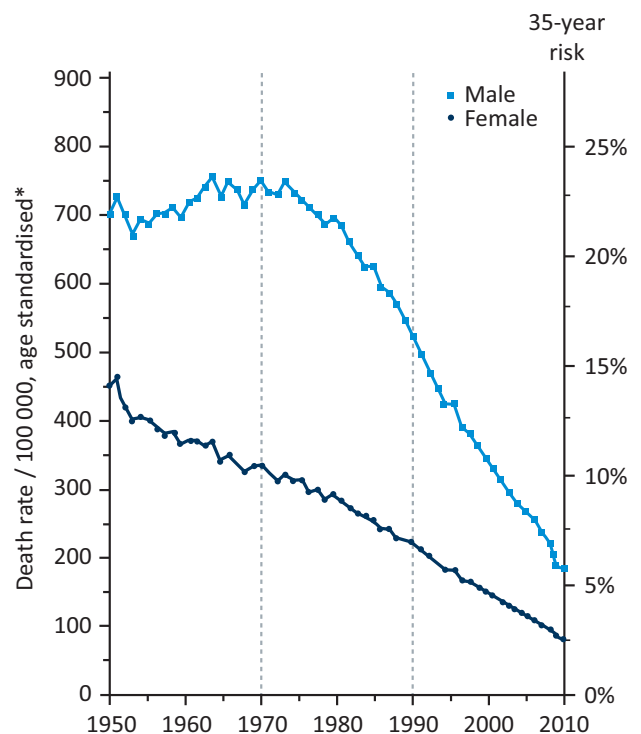


Fig 8. All vascular mortality at ages 35–69 in males and females in the UK 1950–2005. Data from WHO mortality and UN population estimates. *Mean of annual rates in the seven component five-year age groups.

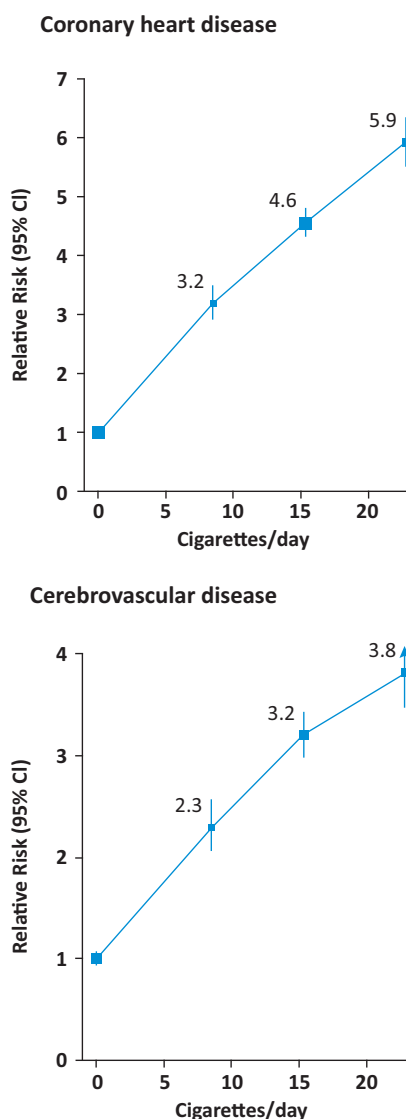


Fig 9. Vascular mortality by amount smoked. Data from the Million Women Study.²⁵

Vascular mortality and tobacco

Valerie Beral's Million Women Study is the first large prospective study in which many women had smoked substantial numbers of cigarettes throughout their adult life, and therefore experienced the full hazards of smoking.²⁵ This is women of my own generation, born around the early 1940s; even if women born earlier did smoke, they generally did not smoke as heavily in early adult life, so did not experience the full hazards in middle age. Fig 9 shows the effects on vascular mortality. Comparing the risks of death in middle age among women who smoked only 10 cigarettes a day versus women who never smoked, the smokers had more than three times the coronary heart disease mortality and more than double the stroke mortality.

Vascular mortality and blood pressure

The Prospective Studies Collaboration, which brought together 60 different prospective studies with a total of a million adults

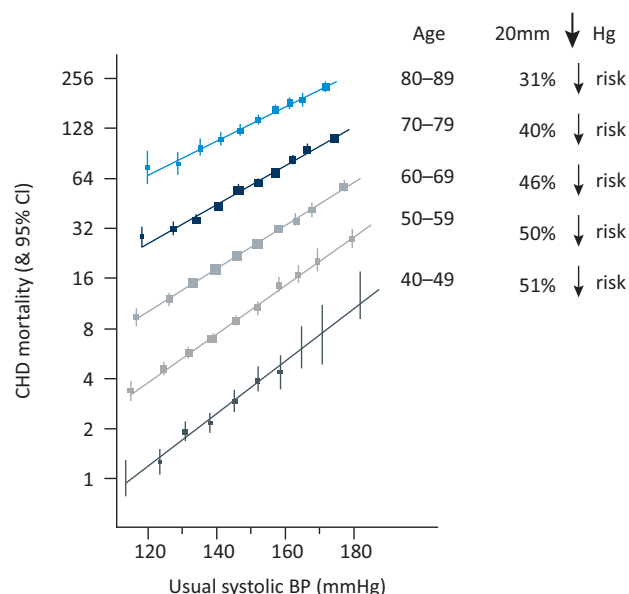


Fig 10. Ischaemic heart disease deaths at ages 40–89: age-specific risk versus usual systolic blood pressure. Data taken from the 34,000 deaths included in the Prospective Studies Collaboration. Reproduced with permission from Lewington *et al.* 2002.²⁶

and corrected carefully for the diluting effects of measurement error, yielded a simple conclusion: a difference of only 20mmHg in systolic blood pressure (SBP) halves vascular mortality in middle age, with no threshold within the range we currently consider normal.²⁶ Fig 10 shows these results for heart disease. (Results for stroke are slightly steeper.) Between the ages of 40–60, each step of 20mmHg in systolic blood pressure halves the risk of death, and the lines are almost as steep even in the older age groups.

Vascular mortality and blood lipids

Randomised trials of statin versus no statin or of a higher versus a lower dose of statin involve a total of 170,000 patients in 26 trials,²⁷ and show that a reduction in LDL cholesterol of 2 mmol/l reduces vascular risk by 40% in the 5-year timescales studied; the effects of a lifelong cholesterol difference of this magnitude might be somewhat greater. Non-vascular mortality was unaffected: fears that cholesterol reduction might significantly increase mortality from causes such as suicide or cancer are untrue – demonstrating the potential harm of flippant comments about drugs causing nameless hazards.

Vascular mortality and obesity

Fig 11 – courtesy of Gary Whitlock, who led the Prospective Studies Collaboration report on the body-mass index (BMI) – shows that above a BMI of 25 kg/m², each additional 10 units of BMI approximately doubles the vascular mortality rate.²⁸ This means that an individual with a BMI of 35 has double the vascular mortality of a person with a BMI of 25. But, although obesity is getting more prevalent and therefore accounts for a progressively bigger fraction of all vascular mortality, this is a

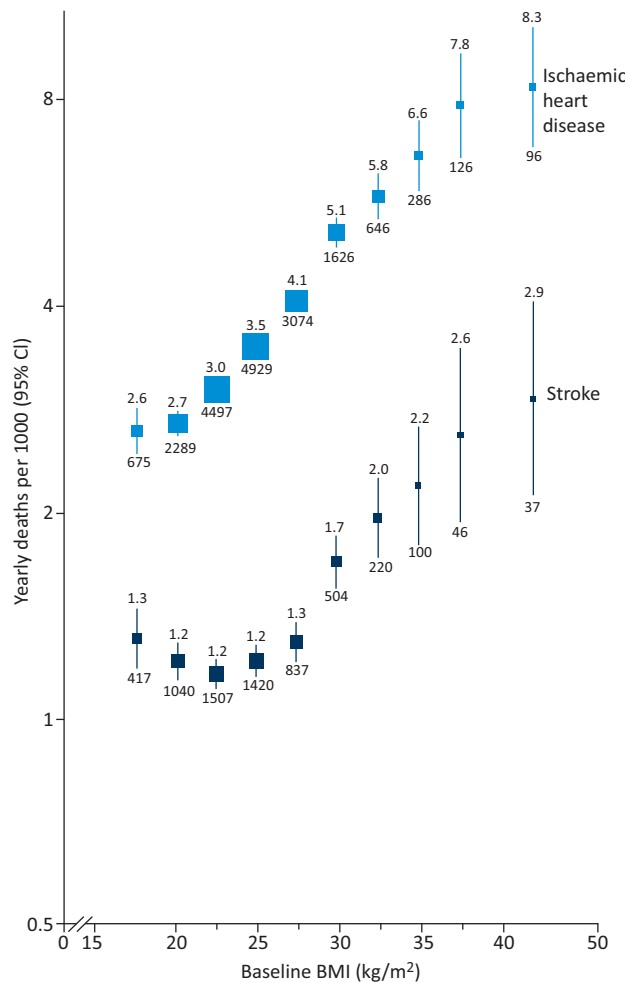


Fig 11. The relationship between obesity and mortality from stroke and coronary heart disease. Reproduced with permission from Whitlock *et al.* 2009.²⁸

bigger fraction of a rapidly decreasing total (Figs 7 and 8). So, the total number of vascular deaths from obesity is probably going down, not up, in the UK.

Cancer mortality

The trends in UK cancer mortality since 1950 are of international relevance. Fig 12 shows UK and US breast cancer mortality. Before the 1980s the rates were rising slowly because of social changes (eg, better nutrition in childhood, fewer early pregnancies and less breastfeeding). In the 1980s, however, this slow increase was halted and then sharply reversed by a succession of treatment improvements – earlier diagnosis, better local control, chemotherapy (then better chemotherapy), endocrine therapy (then better endocrine therapy), etc. Each improvement had only a moderate effect on long-term survival, assessed reliably by putting together all the randomised trials in the world,^{29–31} but in aggregate they have halved breast cancer mortality in middle age. The UK has had the best decrease in breast cancer mortality in the world, so the NHS is doing something right!

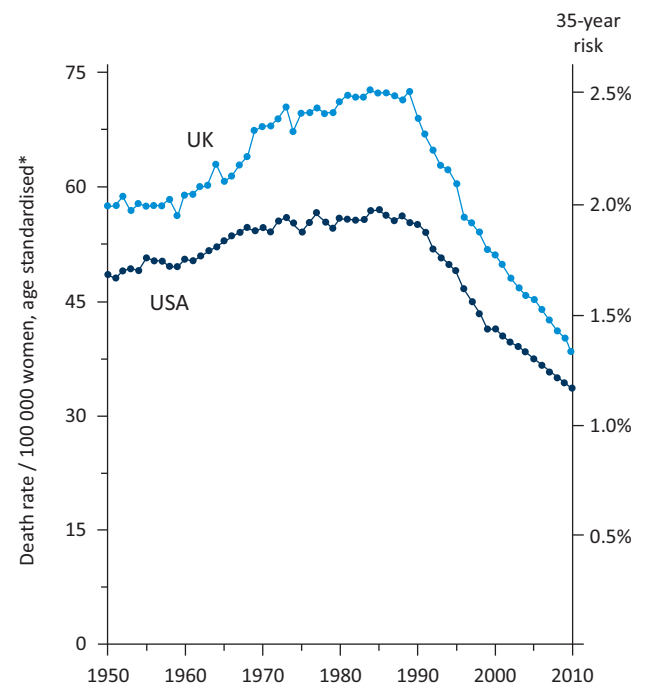


Fig 12. Breast cancer mortality at ages 35–69 in the UK and US since 1950. *Mean of annual rates in the seven component 5-year age groups. Data from the Early Breast Cancer Trialists' Collaborative Group (EBCTCG).

The UK has also had the best 40-year decrease in lung cancer mortality in the world,^{7,8} although this is not mainly due to improved treatment, as the disease is still generally incurable. Fig 13 shows the UK mortality trends for the four most important types of cancer in men, with notes on the main reasons for the recent trends. Stomach cancer mortality has decreased to only a tenth of what it was (decreasing from 70/100,000 in 1950 down to 7/100,000 in 2010). The main reasons for this are not understood, and stomach cancer, like lung cancer, is still generally incurable. Prostate cancer mortality has remained roughly constant. Colorectal cancer mortality rates have decreased by about a quarter since 1990, probably due to better local control and chemotherapy. All these changes are, however, dwarfed by the huge rise and then fall in male lung cancer mortality, predominantly due to increases and, since 1970, decreases in the eventual effects of smoking. The non-smoker mortality rate from lung cancer is low (only 7/100,000 – less than half that from prostate cancer) and has probably been approximately constant.⁷ The lung cancer rates in Fig 13 are, of course, for the whole male population: if they were just for smokers, they would be far higher.

Fig 14 shows the corresponding trends for the four main types of cancer in women (plotted on a different scale, as the female hazards have not been as extreme). Breast and lung cancer dominate, and in recent years breast cancer mortality has fallen below lung cancer mortality in this age group (and is well below lung cancer mortality in older women). UK lung cancer mortality rates are lower among women than among men, but much higher than among non-smoking women, whose lung cancer mortality rates have been approximately constant at about 7/100,000,⁷ as in non-smoking men. The

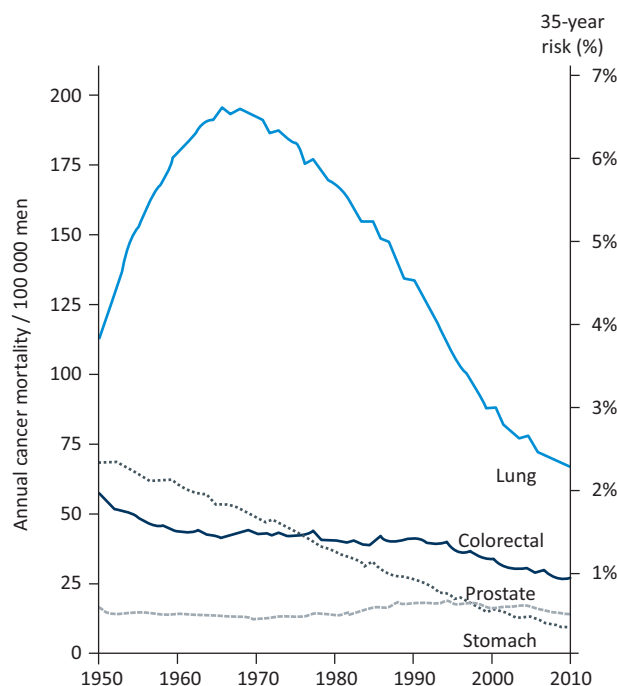


Fig 13. UK cancer mortality trends in men at ages 35–69, 1950–2007. Data from selected sites.

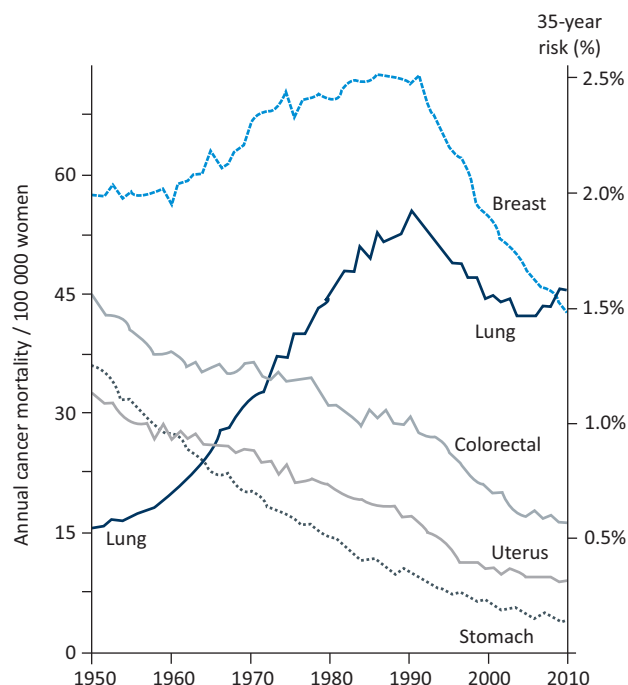


Fig 14. UK cancer mortality trends in women at ages 35–69, 1950–2007. Data from selected sites.

decrease in colorectal cancer mortality is, as in men, the result of improved treatment and, again as in men, we don't know what mainly caused the tenfold decrease in stomach cancer mortality (from 35/100,000 down to 3.3/100,000).

The apparently steady decrease in uterus (mainly cervical) cancer mortality is interesting. My brother Julian Peto has shown nicely that although the mortality rates had been falling until the 1980s there would have been a major increase since then due to changes in sexual behaviour and carcinogenic human papilloma virus (HPV) infection, except that the NHS cervical screening programme came just in time to avoid this; so, the UK now has only about 1000 instead of several thousand deaths a year from cervical cancer.³²

Non-tobacco causes of cancer

Worldwide, chronic infection is a major avoidable cause of cancer.³³ Carcinogenic types of HPV cause a few hundred thousand cancer deaths a year, mainly from cervical cancer. *H pylori* causes several hundred thousand deaths a year from stomach cancer. Hepatitis B virus (and, to a lesser extent, hepatitis C virus) causes about a million deaths a year from liver cancer or liver cirrhosis (and the hazards of are made far greater in China, Africa and elsewhere by fungal contamination of stored carbohydrates which can be reduced by better food storage). Other infective agents, including HIV, impact on cancer rates, as do alcohol, obesity, some less well characterised dietary factors and some occupational and environmental pollutants (particularly asbestos dust and coal smoke), but still much the biggest cause of cancer is tobacco, particularly in countries such as the UK or US where smoking began long ago.³⁴

Cancer and tobacco

Fig 15 shows the trends in UK mortality from any type of cancer. The lower line shows mortality at ages 0–34, which halved from 0.4% in 1970 to 0.2% in 2010, due mainly to better treatment. (Tobacco causes few deaths at these young ages.) On the same scale, the upper lines show the much higher mortality rates at ages 35–69. At 1970 death rates, about 14% of men and 9% of women would die from cancer before age 70; at 2010 death rates, only 8% of men and 6% of women would do so.

These trends can be subdivided^{7,8} into the part caused by smoking and the part not (Fig 16), showing what cancer death rates would have looked like if nobody smoked and what was added by smoking. Lung cancer accounts for about 80% of tobacco-attributed mortality, but smoking can also cause cancer of the throat, oesophagus, pharynx, larynx, pancreas, liver, bladder, renal pelvis and other sites; the tobacco-attributed mortality therefore includes most but not all of the lung cancer mortality plus appropriate proportions of the mortality from various other types of cancer. The effects on cancer mortality rates since 1990 of various treatment improvements can be seen in the male and, particularly, the female cancer mortality that is not attributed to smoking.

The extraordinary effects of smoking, particularly among men, can also be seen in Fig 16. In 1970, smoking was causing much more than half of all male cancer mortality, and a growing proportion of all female cancer mortality. Tobacco-attributed cancer mortality is now well under half of what it was in 1970 among men, and well under half of what it would have become among women if their 1970 smoking patterns had remained unchanged. Still, however, smoking is causing about a quarter

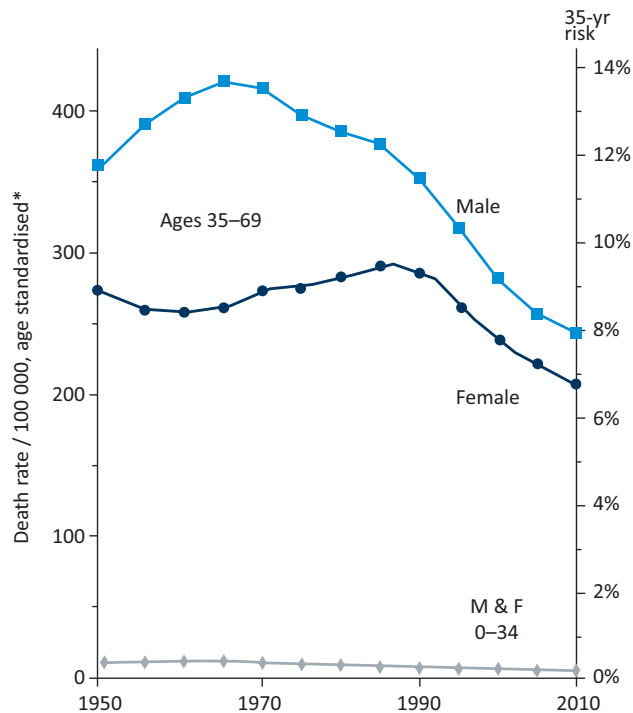


Figure 15. Total cancer mortality at ages 0–34 and 35–69 in the UK, 1950–2007. *Mean of annual rates per 100,000 in component 5-year age groups. Data from WHO mortality and UN population estimates.

of all UK cancer deaths.⁸ These are the effects of smoking in the entire population; if smokers are compared directly with non-smokers or with ex-smokers, the contrast is even more extreme.

Figs 17 and 18 show the results of the UK Million Women Study for lung cancer mortality.²⁵ Because the study is large and the smokers (and ex-smokers) had on average started when they were only 19 years old, the full hazards of smoking and benefits of stopping among women can be seen reliably for the first time. Among the half-million lifelong non-smokers, followed for 12 years in late middle age, ‘only’ 700 died from lung cancer; they have, by definition, a relative risk of 1. The y-axes show not absolute death rates, but risks relative to otherwise similar never-smokers.

Women who smoke only a few cigarettes a day throughout adult life and have 10 times the lung cancer risk of non-smokers; the average smoker has 24 times the non-smoker’s risk (a 2300% excess).

But, what happens if smokers stop? Both the continuing smokers and the ex-smokers had started at about the same age and had smoked about the same number of cigarettes a day. Fig 18 relates the age at which women stopped smoking to their lung cancer mortality rates decades later. As the study is so large, even small residual risks can be assessed reliably. Among women who stopped at about age 30, there was still a small but significant excess of lung cancer deaths several decades later – 86 deaths, instead of the 46 that would have been expected at non-smoker lung cancer rates. This excess is, however, only about 3% of the excess lung cancer mortality in those who continue smoking, so 97% of the excess risk has been avoided by stopping. Those who smoked until about age 40 before stopping had 3 or 4 times the

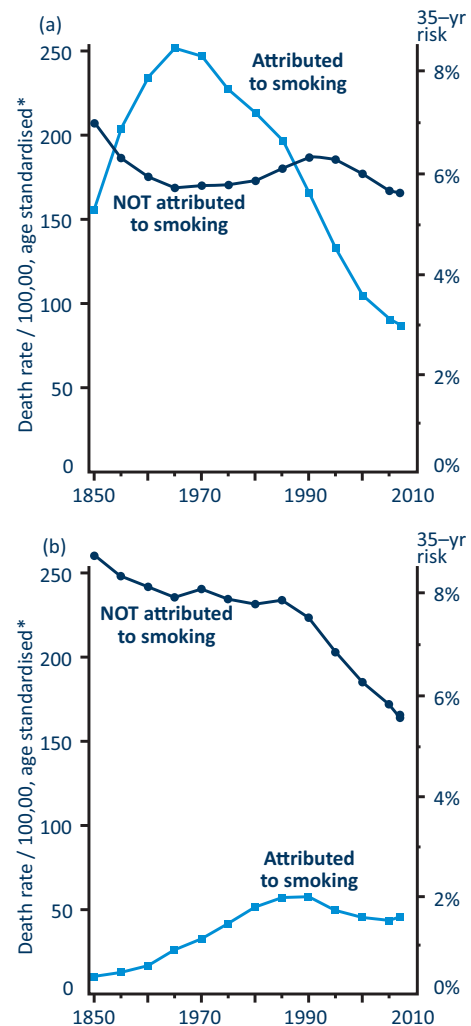


Fig 16. UK cancer mortality 1950–2007 attributed to smoking, or not attributed to smoking, in (a) men and (b) women. Rates and 35-year percentage risks at ages 35–69. *Mean of annual rates per 100,000 in component 5-year age groups. Data from WHO mortality and UN population estimates.

lung cancer rate of non-smokers, so their 20 years of smoking caused substantial permanent damage. But, by stopping at 40, they avoided 90% of the excess risk among continuing smokers.

Fig 19 shows UK lung cancer death rates among males and females in early middle age (35–44). In males, there has been a six-fold decrease, from 18/100,000 in the 1950s to 3/100,000 in the 2000s. In this age range lung cancer is rare, so the impact on overall mortality is small, but this six-fold decrease is important because it is a harbinger of the decreases to be expected 20 years later at ages 55–64 and 40 years later at ages 75–84. This sixfold decrease among men was caused chiefly by changes in the effects of smoking on UK lung cancer mortality rates rather than changes in treatment (which still usually fails) or changes in air pollution or other co-factors. As evidence for this, we have a control group only 20 miles away who experienced the same changes in air pollution but had a different history of smoking patterns – the French.

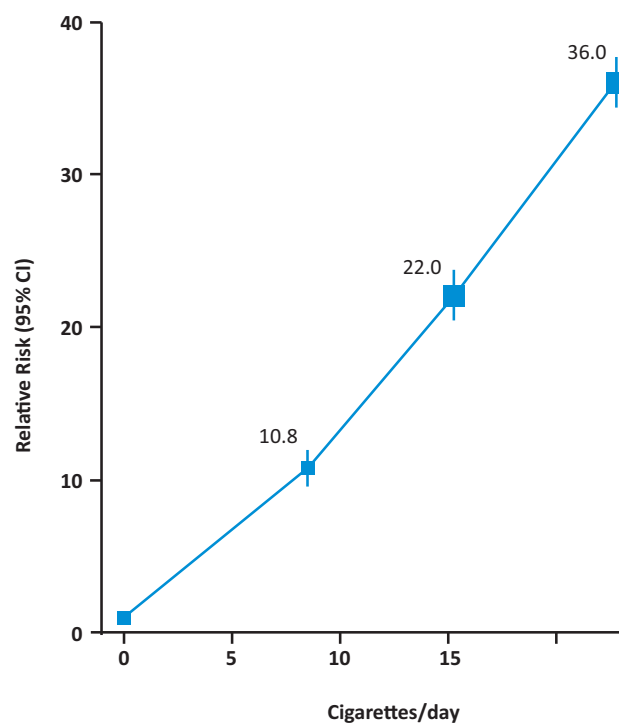


Fig 17. Lung cancer mortality in women by amount smoked. Data from the Million Women Study.²⁵

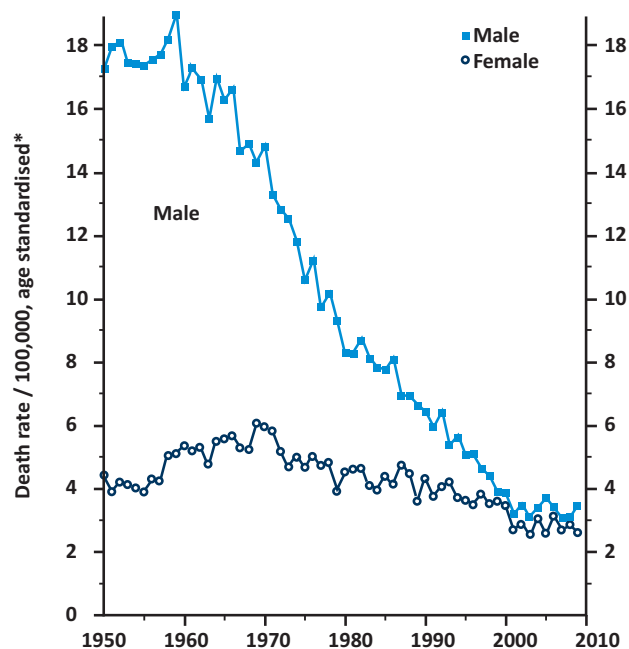


Fig 19. Lung cancer mortality at ages 35–44 in males and females in the UK 1950–2009. *Mean of annual rates per 100,000 in component 5-year age groups. Data from WHO mortality and UN population estimates.

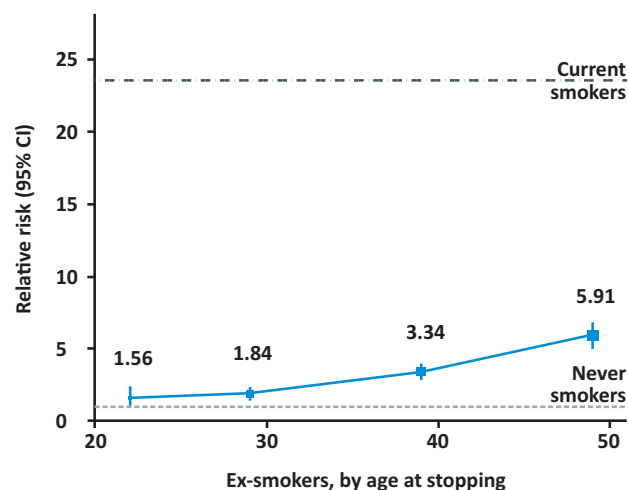


Fig 18. Ex-smoker lung cancer mortality by age at stopping. Data from the Million Women Study.²⁵

Fig 20 shows lung cancer death rates at ages 35–44 in the UK and France up to 1997. Before and during the Second World War, UK men smoked substantial numbers of cigarettes from age 18, whereas French men did not; in the 1940s the British smoked about ten times as many cigarettes as the French, but over the next few decades consumption decreased substantially among British men but increased substantially among French men (and, after the 1960s, French women).

Tobacco and all-cause mortality

Today, men in the UK have around 10 years more life expectancy than at 1960 death rates (Fig 4), and most but not all of this is because of the large decrease in tobacco-attributed mortality. The Royal College of Physicians, with its 1962 report⁵ and its help in the foundation of Action on Smoking and Health (ASH), can take much credit for that, as can ASH itself, although serious political change took decades.

Fig 21 shows the changes since 1960 in the probability that, at the death rates of the time, a 35-year-old man would die before 70.^{7,8} At 1960 death rates, 42% of 35-year-old men would die before 70, and 19 of those 42 deaths would have been from smoking: nearly half of all UK male mortality in middle age. In 1970 the risks were still the same, but from 1970–2010 the risk decreased by more than half, from 41% dead down to 19% dead, an absolute gain of 22%, and the main reason for this is that the risk of being killed in middle age by smoking decreased from 19% to only 4%, an absolute gain of 15%. In 1970 British men had the worst tobacco-attributed mortality in the world, and since then we have had the best decrease in the world in tobacco-attributed mortality. Fig 22 shows the corresponding pattern among women.^{7,8} UK women never had the same hazards that men did, and before a complete generation of women had smoked all their lives, many women gave up smoking, so the large increase in smoking-attributed deaths that would have happened stalled. At 1980 or 1990 death rates, 5% of all women would have been killed by tobacco before age 70; now the risk is 3% and falling. Women live on average four years longer than men, but this difference was previously eight years, chiefly because of smoking.

Figs 23 and 24 show all-cause mortality by amount smoked in continuing smokers and by age at stopping in ex-smokers

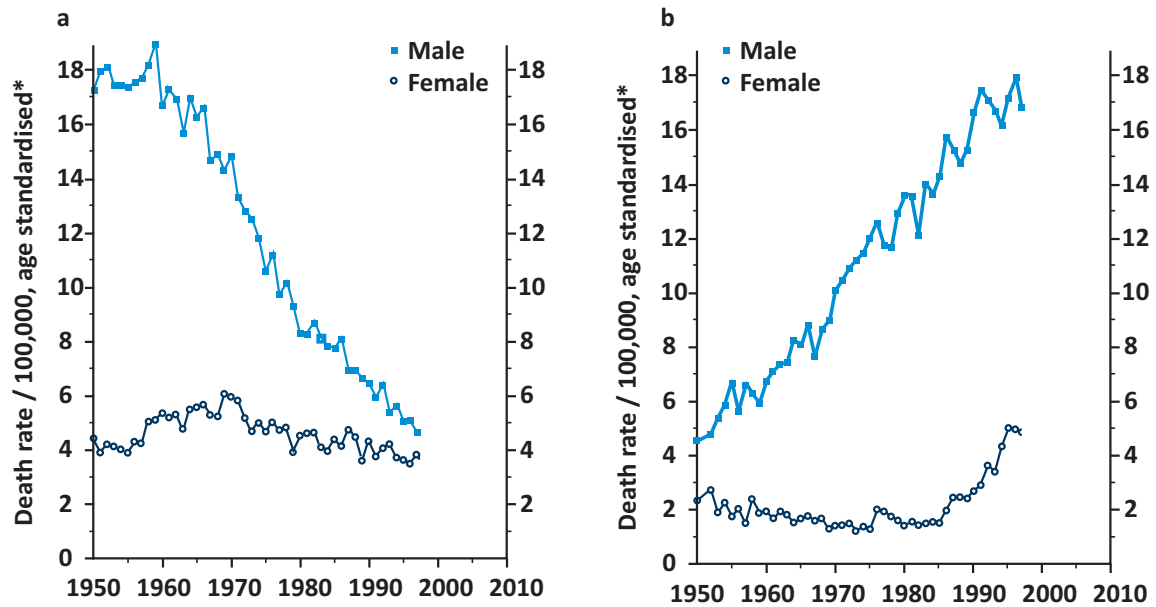


Fig 20. Lung cancer mortality at ages 35–44 in males and females in the UK and France 1950–1997. (a) Lung cancer mortality at ages 35–44 years in the United Kingdom. (b) Lung cancer mortality at ages 35–44 years in France.*Mean of annual rates per 100,000 in component 5-year age groups. Data from WHO mortality and UN population estimates.

in the Million Women Study, for UK women born around 1940.²⁵ Even just a few cigarettes a day doubles the risk of dying in middle age, but, as with lung cancer mortality, stopping at ages 30 or 40 avoids, respectively, 97% or 90% of the excess mortality decades later. Smoking kills, stopping works.

Similar findings, but based on smaller numbers, emerged from the 50-year follow-up³⁵ of Richard Doll's 1951 prospective study of smoking and death among male British doctors born in the first few decades of the century. Fig 25 compares doctors who never smoked with doctors who carried on smoking cigarettes, finding a ten-year shift in survival pattern. The difference in mortality mostly came from diseases like lung cancer, bronchitis and heart attacks that can be caused by smoking. Doctors who stopped smoking at about age 40 lost only about one year, indicating (as in the Million Women Study) that stopping at 40 avoids 90% of the excess risk in those who continue.

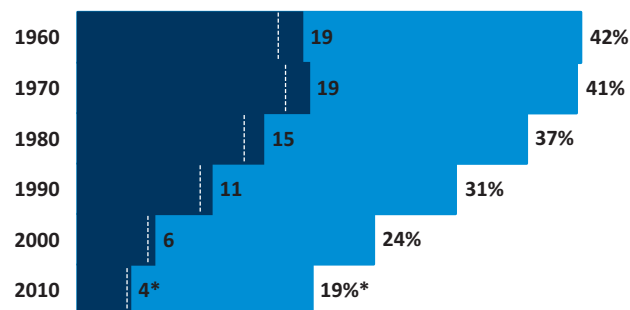


Fig 21. Population risk of a 35-year-old male dying at ages 35–69 from smoking (shaded) or from any cause (shaded and white), 1960–2010, UK. Note, most of those killed by smoking would otherwise have survived beyond age 70, but a minority (shaded area to right of dotted line) would have died by 70 without smoking.

Fig 26 contrasts the ten-year survival difference between male smokers and non-smokers³⁵ with the 3-year and 10-year survival differences produced by moderate obesity (body mass index [BMI] 30–35 kg/m²) and by morbid obesity (BMI >40) in comparison with a BMI of about 24, where mortality is minimal.^{28,36} In countries such as the UK, where substantial minorities smoke or are moderately obese but few are morbidly obese, smoking still matters more than adiposity, although this could change. Smoking currently causes about 20% of all UK deaths before 70, whereas adiposity (as indicated by the BMI)

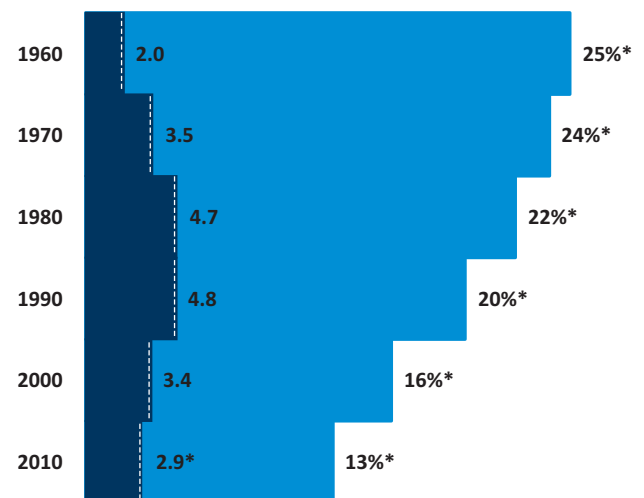


Fig 22. Population risk of a 35-year-old female dying at ages 35–69 from smoking (shaded) or from any cause (shaded and white), 1960–2010, UK. Note, most of those killed by smoking would otherwise have survived beyond age 70, but a minority (shaded area to right of dotted line) would have died by 70 without smoking.

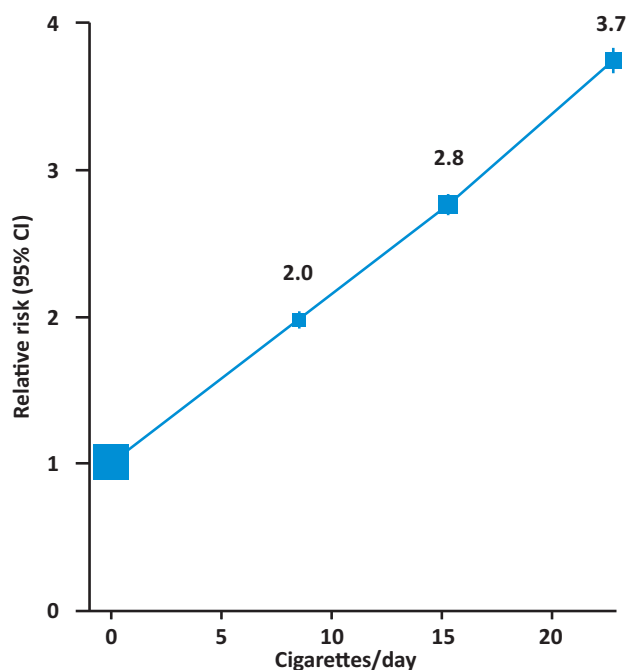


Fig 23. All-cause mortality in women by amount smoked. Data from the Million Women Study.²⁵

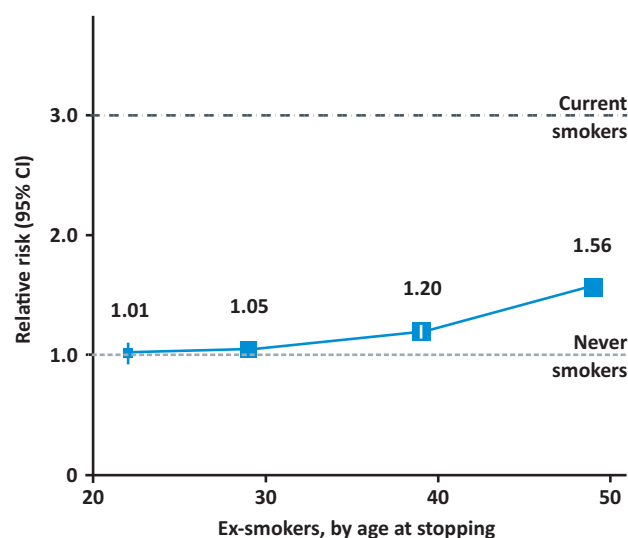


Fig 24. Ex-smoker all-cause mortality by age at stopping. Data from the Million Women Study.²⁵

causes about 10%, but these proportions will change. The relative importance of smoking, alcohol and overweight as determinants of premature adult mortality differs greatly between different populations. For example, in female Arab populations the effects of obesity predominate. But for the UK, tobacco is still twice as important as obesity as a cause of premature death today.

Is the picture improving?

In 1950 when the evidence for the link between smoking and mortality first came out, 80% of men and 40% of women in the

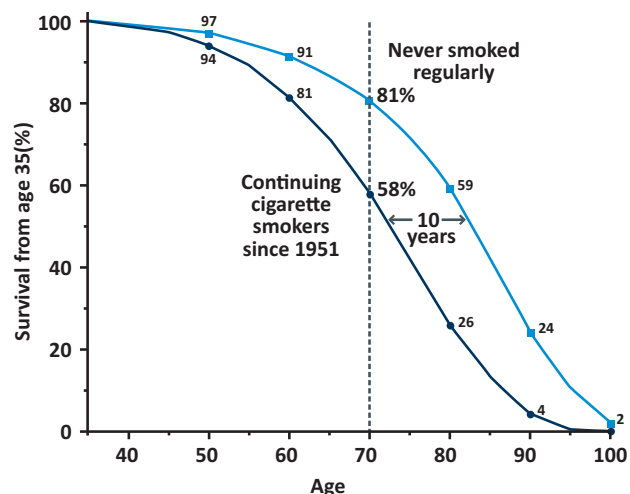


Fig 25. UK male doctors born 1900–1930: continuing cigarettes versus never smokers, 50-year follow-up of mortality, 1951–2001.

UK smoked. By 1970 70% of men and 50% of women (still 60% of all UK adults) smoked, and cigarette sales per adult were substantially higher than in 1950. Now, the UK adult prevalence is about 20% in both sexes – a threefold decrease in prevalence since 1970, matched by a threefold decrease in cigarette sales per adult, a big change over four decades.

The news is not so good elsewhere, however. Fig 27 shows cigarette production in China since 1950. The dip at the end of the 1950s is the time of the Great Chinese Famine where approximately 40 million died. There was a huge increase the 1970s and 1980s, which slowed in the 1990s but then resumed, much faster than population growth – this is an increase in cigarette consumption per man. In China, the prevalence of smoking in women born since 1950 is less than 1% and the prevalence in men is about 60%. The main increase in cigarette consumption occurred 40 years in China than in the US. By 1950 smoking caused 12% of all US deaths in middle age; by 1990, this reached 33%. By 1990, smoking caused 12% of all Chinese male deaths in middle age, and by 2030 (which is not far from now) it will cause about 33%. Approximately two thirds of the young men smoke, and about half of those who do will eventually be killed by tobacco.

In India, a study based on interviews with the families of a random sample of 120,000 of all adult deaths concluded that there will be a million tobacco-attributed deaths per year in India during the 2010s – about 0.7 million in middle age and 0.3 million in old age.³⁷

Worldwide, in the first quarter of this century there will be about 150 million deaths from smoking if current smoking patterns continue; many of these have already happened. In the second quarter, there will be about 300 million – so, about 450 million in total in the first half of the century.³⁸ We have already running at about 5 million tobacco-attributed deaths a year, and in the second half of the century, we're going to be running at more than 10 million a year – more than 100 million tobacco-attributed deaths per decade – if we keep on with 30 million new smokers a year, most of whom will not quit. This means that there will be something like 1,000 million tobacco

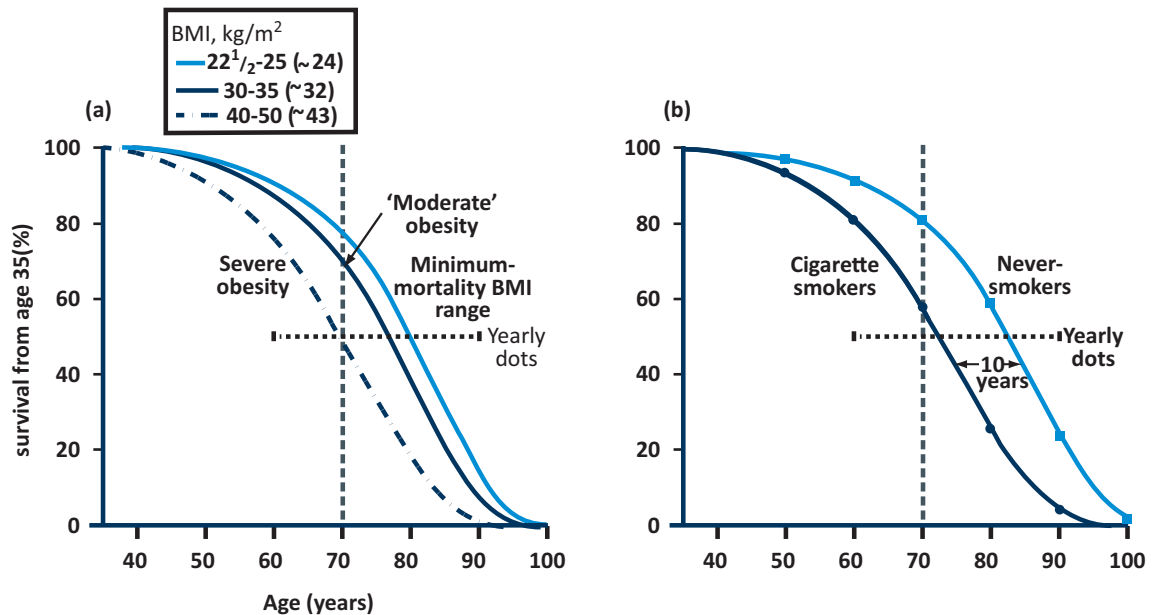


Fig 26. Relative effects of obesity and smoking in males. Data from the Prospective Studies Collaboration in males (a)²⁸ and the Male British Doctors' Study (b).³⁵

deaths in this century if we just carry on the way we are. That compares to about 100 million tobacco-attributed deaths in the twentieth century. And if we want to do something about the deaths in the first half of this century, we have to help adults who smoke to stop. If we can persuade children not to start, that would have a great impact in the second half of the century, but in the first half, adult cessation is essential. Adult cessation is going to be a big determinant of what happens in the second half too.

How can we achieve widespread cessation? Again, let's look at the French. At the beginning of the 1990s, the French did what I wish other governments would do: tripled the price of cigarettes (Fig 28). From 1950 to 1990 cigarettes had become cheaper in real terms, and then suddenly, the price tripled in 15 years, and cigarette consumption halved.

What about French government income from tobacco? Fig 29 shows that it doubled, from €6 billion to €12 billion euros (adjusted for inflation). The Chinese government takes about

10% of its income from cigarettes. Why not make it more, and save many lives?

In Britain over the last 120 years (1890–2010), the two biggest falls in cigarette consumption coincided with the two biggest increases in price (Fig 30). In 1947 and again in 1981, the government increased cigarette prices substantially: they took more money, but consumption dropped. Since the 1990s, all the effort put into reducing smoking – advertising bans, restrictions on smoking in public places, propaganda – have led to annual decreases of 5% in recent years. That is a 5% per year reduction in the biggest cause of death we have, but it's hard work compared with putting prices up. If the European Union had imposed EU-wide price increases at the beginning of the economic crisis, they would have more money to address Europe's financial problems and we would have fewer tobacco deaths.

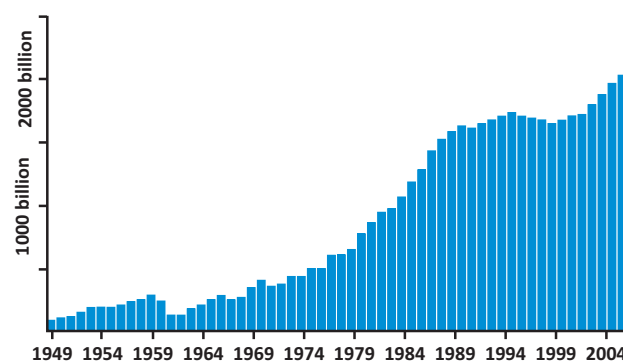


Fig 27. Cigarette production in China from 1950–2010.

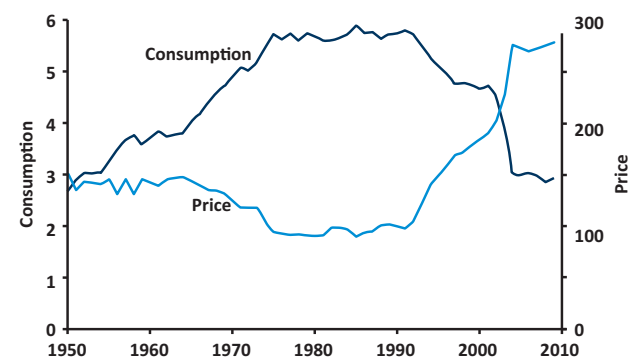


Fig 28. Cigarette price versus daily consumption by adults aged 15 and above in France, 1950–2010. Price is inflation-adjusted.

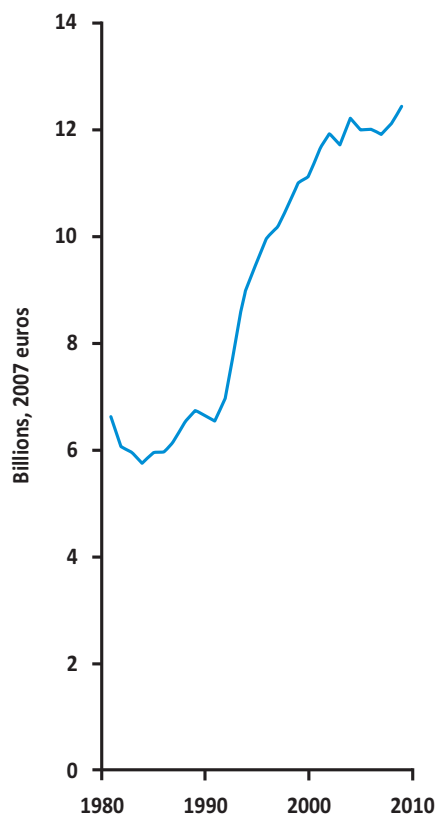


Fig 29. Government income from tobacco in France, 1990–2005.
Reproduced courtesy of Catherine Hill, INSERM.

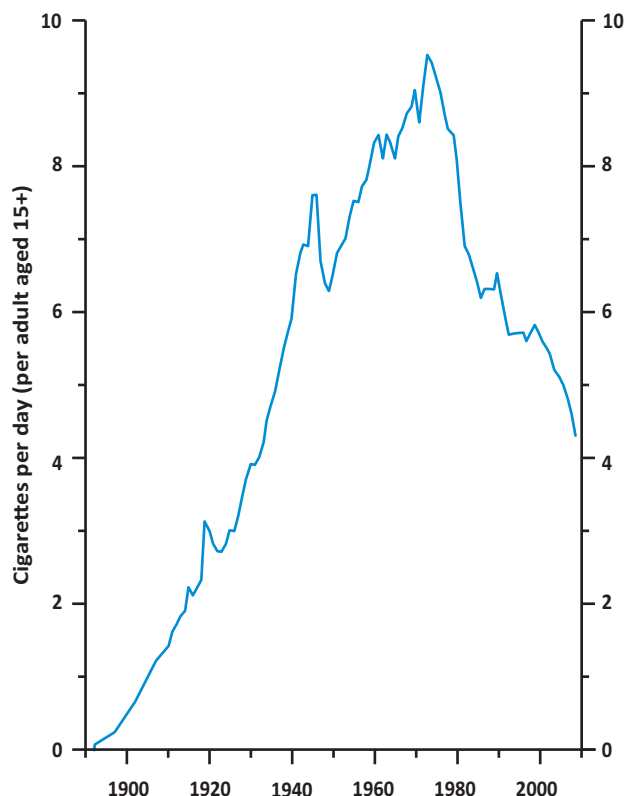


Fig 30. UK cigarette consumption, 1890–2009.

Conclusion

Overall, mortality rates are falling worldwide, with a few major exceptions. Death rates in childhood, early adulthood and middle age are going down, and since 1970 life expectancy has been increasing by an average of 3–4 years per decade,^{20–22} despite various catastrophes. Worldwide, there have been only five major causes of death that have increased substantially in some major countries over the last 20 years: HIV (eg South Africa), tobacco (eg in China), alcohol (eg in Russia), obesity (eg in the US) and war (eg in the Congo). To continue the reductions of the past few decades in premature death, we need to avoid catastrophes and to take the big things seriously:

- Avoid catastrophic wars – 10 million died in the First World War, 50 million died in the Second World War, and we don't want 200 million dead in the Third World War.
- Avoid famines – 40 million died in the Chinese famine of 1959–62 because of collectivisation of agriculture.
- Avoid epidemic infection – current estimates suggest that about 60 million died in the 1918–1919 influenza epidemic.
- Avoid social collapse – the world could get so much worse that in half a century's time they will be thinking 'Why worry about minor details like smoking, when you remember the catastrophes of the 2040s?'.
- Don't confuse the few big causes with the many smaller ones, and do take the big causes seriously, even if only a moderate reduction in those big causes can be achieved – better a moderate reduction in a big cause than a big reduction in a small cause.

Don't wait for ideal health systems throughout Africa and Asia before trying to increase the uptake of a few critical health interventions – health systems matter enormously, but some interventions could be made a lot more available now that will save millions of lives; people need some simple, cost-effective treatments to be more widely available. I shall conclude, as I opened, with Richard Doll,³⁹ whose centenary falls this month. The year before he died we published together the 50-year results from his study of smoking and death in British Doctors.³⁵ He had stopped smoking himself in 1949 as his first results were emerging, which probably saved his own life. The results that he and his generation of epidemiologists and medical statisticians produced, augmented in recent decades by large-scale randomised evidence of the efficacy of many treatments, have already saved tens of millions of lives, and if the world takes the findings from the old and new statistical studies of large populations appropriately seriously, we can avoid hundreds of millions of premature deaths this century. As Richard Doll wrote 20 years ago, death in old age is inevitable, but death before old age is not.⁴⁰ ■

Note

This paper was prepared from a transcript taken from the Harveian Oration delivered on 18 October 2012 at the Royal College of Physicians.

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