Mortality reduction from quitting smoking in Hong Kong: population-wide proportional mortality study

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(2986 words)

Abstract

Background The effects of smoking cessation might be different in different populations. Proportional mortality studies of all deaths, relating the certified cause to retrospectively determined smoking habits, have helped assess the hazards of smoking in Hong Kong, and further analyses can help assess the effects of prolonged cessation (although not of recent cessation, as life-threatening disease can itself cause cessation, particularly in old age).

Methods The LIMOR study sought the certified causes of all deaths in 1998, and interviewed 81% of families at death registries to determine the decedent's smoking history. Cases were deaths from pre-defined diseases of interest (N=15 356); controls were deaths from pre-defined non-smoking-related diseases (N=5 023). Case vs control odds ratios for ex-smokers vs smokers were calculated by age-, sex- and education-standardised logistic regression. These are described as mortality rate ratios (RRs), with a group-specific confidence interval (CI).

Results For the aggregate of all deaths from any of the diseases of interest at ages 35-69 years, the RRs for current smoking, quitting 0-4, 5-9 or 10+ years ago, and never-smoking were, respectively, RR=1 (95%CI 0.86-1.17), 0.91 (0.73-1.14), 0.71 (0.49-1.02), 0.66 (0.50-0.87) and 0.43 (0.37-0.48). Younger age of quitting (25-44 or 45-64) appeared to be associated with greater protection: RR=0.58 (0.38-0.88) and 0.71 (0.54-0.93), respectively. These patterns were less clear at older ages, particularly for death from emphysema.

Conclusions Longer durations of smoking cessation are associated with progressively lower mortality rates from the diseases of interest. For sustainable monitoring of tobacco-attributed mortality, approximate years since last smoked should be recorded during death registration.

(250/250 words)

Keywords: smoking cessation, proportional mortality study, epidemiology, death certificate, Hong Kong China, health benefit

Topic: harm reduction, Hong Kong, death record, epidemiology, case-control study, smoking cessation

Key Messages

- There is limited evidence from low- and middle-income countries (LMICs) about the effects of cessation, and in populations comparison of current mortality rates in smokers and ex-smokers would under-estimate the benefits of quitting. Proportional mortality studies could provide a timely low-cost alternative than prospective cohort studies, at least for assessing the effects of long-term cessation, in addition to the harms of smoking.
- Taking the advantage of a proportional mortality study in Hong Kong, where is the most urbanized and Westernized Chinese city, and the tobacco epidemic reached its peak about 20 years earlier than in China mainland, we examined the effects of cessation by comparing the proportions of ex-smokers and current-smokers among those dying from particular diseases.
- The benefits of quitting that longer durations of smoking cessation are associated with progressively lower mortality rates from the diseases of interest can be observed by using the proportional mortality study design.

Introduction

Although smoking-attributed mortality is decreasing steadily among men in most developed countries, it is still increasing in many developing countries.[1,2] In China, with 20% of the world's population consuming 40% of the world's cigarettes, smoking-attributed deaths will continue to increase over the next few decades, unless there is widespread cessation.[3] Prospective studies from developed countries provide strong quantitative evidence that stopping smoking works.[4-7] For example, UK smokers who stop before age 40 (preferably well before 40) avoid over 90% of the excess mortality rates among continuing smokers.[8] As yet, there is limited evidence from low- and middle-income countries (LMICs) about the effects of cessation,[9] and in populations where the risks among smokers are still rising, comparison of current mortality rates in smokers and ex-smokers would under-estimate the benefits of quitting.

As the epidemic of death from tobacco is at a more advanced stage in Hong Kong than in mainland China, studies in Hong Kong could be particularly informative. The ideal would be a large prospective study that carefully limits the effects of reverse causality, whereby life-threatening disease may make smokers stop (for chronic obstructive pulmonary disease [COPD], this can happen many years before death, artificially reducing the death rate among the smokers and increasing it substantially among the ex-smokers). However, cohort studies are difficult to conduct, expensive, and take many years to deliver results,[10-13] so retrospective studies are also needed, although these tools have to consider carefully how reverse causality might distort their findings, particularly for COPD.

Proportional mortality studies that involve only dead subjects (comparing the proportions of ever-smokers and never-smokers among those dying from particular diseases) could provide a timely low-cost alternative, at least for assessing the effects of long-term cessation. Proportional mortality studies have been used to investigate the harms of smoking, mostly in developing countries, but the benefits of quitting were not reported,[14-19] partly for fear of producing results that are substantially biased by reverse causality, and some reports did not mention whether quitting was asked. The Hong Kong Lifestyle and Mortality (HK LIMOR) study sought from family members information about the previous smoking habits of all who died in Hong Kong in 1998, including information on how long ago the dead person had stopped smoking, but the main report combined the ex-smokers with those who had continued smoking until the last year of their life (so it compared those who had ever smoked versus those who had never smoked).[20] We now report its findings according to the duration of quitting.

Methods

The study methods and results on smoking and various other factors associated have been reported previously (Supplementary materials, p7).[20-27] We have found the definition of dead cases and controls in the most recent proportional mortality case-control study most appropriate for the HK LIMOR study,[9] with cases being deaths from diseases that could be caused by smoking, and controls being deaths from all non-smoking related causes (Supplementary Table s1, p2).[19] Details of the assessment of quitting are in Supplementary Part I (Supplementary materials, p8). Present analysis only used deaths with additional quitting data collected in the second half of all deaths in 1998. To compare our previous results for all deaths on the harms of smoking (dead cases versus living controls),[20] we also included the results comparing dead cases with dead controls (Supplementary Table s2, p3).

Statistical analysis

Case versus control odds ratios for the quitting status were calculated by unconditional logistic regression, adjusted for 5-year age group, sex and education, and are described as mortality rate ratios (RRs, calculated as odds ratios). To assess the association of stopping smoking with smoking-attributed mortality by the age of quitting, the RR was calculated for never smokers, and quitters who stopped smoking at the age of 25-44 and 45-64 years, compared with current smokers. Group specific confidence interval (CI) for the current smokers RR of 1.00 was calculated to reflect the variance of the log risk in the current smokers using Plummer's method.[28] To select the appropriate age range, mortality RRs were calculated for main cause-specific deaths by smoking history (ever vs never smokers) in all deaths (Supplementary Tables s3 and s4, p4-5). Smoking was expected to cause few deaths before age 35 years, and cause of death information can be unreliable in old age, so subjects aged 35-84 years at death were included. As most of those killed by smoking would otherwise have survived beyond age 70, but a minority would have died by 70, we stratified the age into two groups (middle age: 35-69 or old age: 70-84 years) for all the analyses. All analyses were conducted using R 3.3.1.

Results

Mortality by duration of quitting

There were 9772 male and 5584 female cases, and 2503 male and 2520 female controls. The cases and controls had similar demographic characteristics, with a mean (SD) age 70.2 (10.7) and 68.2 (12.0) years, respectively (Supplementary Table s5, p6).

Table 1 shows that in middle age (35-69 years), all the RRs among long-term quitters (versus current smokers) were lower: RR 0.50 (95% CI 0.33-0.74) for lung cancer, 0.92 (0.66-1.28) for smoking-related cancer, 0.40 (0.27-0.61) for CVD and 0.81 (0.49-1.33) for COPD. But in old age (70-84 years), the RR for COPD was higher (1.40, 1.11-1.76). Quitters who had stopped for 5-9 years also had lower lung cancer, smoking-related cancer and CVD mortality risks, but higher COPD mortality risks compared with current smokers. New quitters who had stopped for less than 5 years had lower CVD mortality risks: RR 0.56 (95% CI 0.41-0.78) in middle age and 0.90 (0.68-1.18) in old age. However, the remainder RRs among new quitters (versus current smokers) in old age were higher, probably because of ill-quitter effect.

Figure 1 shows declining trends of RRs for all deaths of interest from current smoking to quitting for less than 5, 5-9 and 10+ years, and never smoking: RR 1.00 (95% CI 0.86-1.17), 0.91 (0.73-1.14), 0.71 (0.49-1.02), 0.66 (0.50-0.87) and 0.43 (0.37-0.48) in middle age (p for linear trend: 0.006), and 1.00 (0.86-1.16), 1.06 (0.85-1.32), 0.86 (0.64-1.16), 0.87 (0.74-1.03) and 0.55 (0.50-0.61) in old age (p for linear trend: 0.19).

Mortality by age of quitting

Figure 2 also shows a clear declining trend of mortality risk from current smoking to quitting at the age of 45-64 and 25-44 years, and never smoking for all deaths of interest in middle age: 1.00 (0.86-1.17), 0.71 (0.54-0.93), 0.58 (0.38-0.88) and 0.43 (0.37-0.49), p for linear trend 0.003. However, subjects in old age (70-84 years) who stopped at younger age (25-44 years) had higher mortality risks: 1.47 (0.51-4.22), but this was based on only 31 subjects (27 cases and 4 controls), so it is not statistically reliable.

Table 2 shows mortality RRs for the other 4 disease groupings (causable by smoking) by age of quitting versus current smoking. Subjects in middle age (35-69 years) who stopped smoking at younger age (25-44 years) had non-significantly (with overlapping 95% CIs) lower mortality risks than those who stopped smoking at older age (45-64 years) for lung cancer (RR 0.41, 95% CI 0.22-0.78 versus 0.61, 0.42-0.88), CVD (0.36, 0.18-0.70 versus 0.51, 0.35-0.73), and all deaths of interest (0.58, 0.38-0.88 versus 0.71, 0.54-0.93, Figure 2), respectively. Few quitters stopped before age 45 years, so the estimates of quitting at the age of 25-44 years in old age are not statistically reliable. Among subjects who had stopped at ages 45-64 years, the RRs for lung cancer, smoking-related cancer and CVD were lower, but those for COPD were still substantially higher than current smokers: RR 1.12 (95% CI 0.73-1.72) in middle age and 1.59 (1.20-2.11) in old age.

Discussion

The purpose of the HK LIMOR study was to estimate the smoking-attributed mortality in Hong Kong, where the tobacco epidemic has reached a fairly advanced stage,[20] while the present analysis is first to investigate the health benefits of quitting using proportional mortality study design. We found lower RRs of cause-specific mortality associated with longer duration of quitting and quitting at younger age. These benefits have not been reported in previous proportional mortality studies, probably because the information on quitting (or ex-smokers) is unavailable.

Reverse causality, as in many cohort studies, was observed in the present analysis for COPD, which is most subject to ill-quitter effect.[29] COPD typically develops among smokers with slowly worsening respiratory symptoms over many years, during which some may quit smoking when necessitated by their worsening condition. Thus, ill-quitter effect would be more common for COPD than cardiovascular disease, especially among older people with longer duration of smoking and symptoms, and lower ability to recover.[30] Indeed, in the present analysis, reverse causality was observed for COPD in middle aged subjects who had quit for 5-9 years and in old age regardless of duration of quitting. To clarify this issue, collecting information on the reason of quitting is essential and recommended.

To study the benefits of quitting in proportional mortality studies, differential misclassification of quitting between deaths and healthy subjects may occur using living controls. Indeed, in HK LIMOR study, we found that the proportion of ex-smokers (or quitters) in all the deaths was higher than that in healthy subjects, particularly the proportion in dead cases (deaths from diseases causable by smoking) was much higher than that in living controls.[9] It is plausible that dead subjects were more likely to have quit due to ill health than healthy living subjects. We took advantage of the strength of the definition of dead cases and dead controls in the most recent mortality case-control study, which is that any ill-quitter effect in dead cases should be similar to those in dead controls, to examine the benefits of quitting. As, however, quitting must have reduced some risks from certain deaths in the dead control group (for example, some of those from diabetes and colorectal cancer),[31] the present analyses may have slightly underestimated the benefits of quitting. Indeed, in old age (70-84 years), the RRs among ex-smokers are slightly smaller than those in our previous prospective cohort study of older Chinese in Hong Kong.[12] However, in middle age (35-69 years), the lower RRs (versus current smokers) among all the quitters in Table 1 were consistently observed for all deaths of interest and CVD, particularly among new quitters who had stopped smoking for less than 5 years (for CVD: 44%, 95% CI 22-59%), which are consistent with the U.S. Surgeon General's Reports on Smoking and Tobacco Use (USSG) Report 2010 that rapid risk reduction of vascular mortality by about 50% can be observed after quitting for 1 year.

To help monitor the tobacco epidemic, the methods of proportional mortality study should be used in any other populations where death registration is organized centrally. As interviewing was done in death registries, the HK LIMOR study had a high coverage of all deaths (81%), and a short time interval between death and interview, reducing recall error. Moreover, the analytical strategies in the present study using deaths from smoking-related causes as cases and those from non-smoking related causes as controls, could be used to assess the benefits of quitting, in addition to the harms of smoking.

Several limitations should be considered. First, the definitions of cases and controls in previous proportional mortality studies varied. For example, some diseases such as breast cancer and colorectal cancer are considered to be causally related to smoking by the 2014 USSG Report, but were defined as controls in our study. Smoking was associated with reduced risk of Parkinson's disease, ulcerative colitis and endometrial cancer, but we analyzed them as cases.[31] Nonetheless, there is no consensus of the definitions of cases and controls in mortality case-control studies.[9] Further research is warranted by collaborating all proportional mortality studies in the world to determine the most appropriate definition for studying smoking or other factors.[32] The HK LIMOR study was conducted in 1998 to investigate the relation between smoking and mortality. The results might not be generalised to the present situation in Hong Kong but should be relevant to show the great benefits of stopping smoking in China mainland. A new mortality case-control study in Hong Kong and in China mainland (or any other LMICs) is warranted. To monitor the tobacco epidemic routinely, a new method of the proportional mortality study for collecting data is recommended as in the South Africa's and the Tianjin's proportional mortality studies that the smoking status of the deceased is routinely recorded on the new death certificate for long-term sustainable monitoring.[16, 33]

The tobacco epidemic in Hong Kong (the most urbanized and Westernized Chinese city) reached its peak about 20 years earlier than in China mainland, but about 20 years later than in developed Western countries.[12] Hong Kong has been a forewarning model for China mainland.[20]

The mortality relative risk has already reached 3 in the United Kingdom, United States and Australia, which could be followed by China mainland and other LMICs undergoing rapid economic development in the next few decades. Stopping smoking is one of the most practicable ways to avoid a large proportion of smoking-attributable deaths, particularly premature deaths (age 35-69).[34]

Quitting, however, is uncommon in China mainland and other LMICs. Ex-smokers are far fewer than current smokers in most LMICs, particularly those who stopped smoking at young age (before 45 years). However, with increasing smoking cessation from more effective tobacco-control measures in developing regions,[2] the applicability of proportional mortality studies should expand. Moreover, many higher income countries also have no or limited prospective data showing the harms of smoking the benefits of quitting. Proportional mortality studies can provide evidence that smoking skills, and our present study has shown this study design could also provide evidence that stopping smoking works in populations with reasonably reliable underlying causes of deaths by adding simple questions of smoking and the duration of quitting at death. Evidence of the health benefits of quitting is needed to support strong tobacco control policies and provide smoking cessation services, and to motivate people to quit before illnesses occur.

In conclusion, the health benefits of quitting can be observed by using the proportional mortality study design. In populations with reliable underlying causes of deaths in middle age, this study design is recommended to estimate the benefits of quitting and the harms of smoking with timeliness and low costs. One simple question about smoking (never, ex- and current smoking 10 years ago, or even better including the duration of quitting at death) should be added to death notification forms (at least be recorded during death registration) to monitor the tobacco epidemic.

Acknowledgments

The chief acknowledgment is to the relatives who provided information for this study, the research staff and the Immigration Department and Department of Health (Dr KH Mak) of the Government of the Hong Kong Special Administrative Region. We thank Paul McGale for advice on data analysis, and Lin Xu for revising the manuscript.

Contributors: THL and SYH designed and conducted the study in consultation with RP, and SYH is the guarantor for the paper; ZMM analysed the data, wrote the first draft and has checked the accuracy and completeness of the references; all authors revised it critically for important intellectual content, and contributed to final approval of the paper.

Funding

This work was supported by the Hong Kong Health Services Research Committee (631012) and the Hong Kong Council on Smoking and Health, plus direct support to CTSU by the Imperial Cancer Research Fund and the Medical Research Council. The sponsors of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

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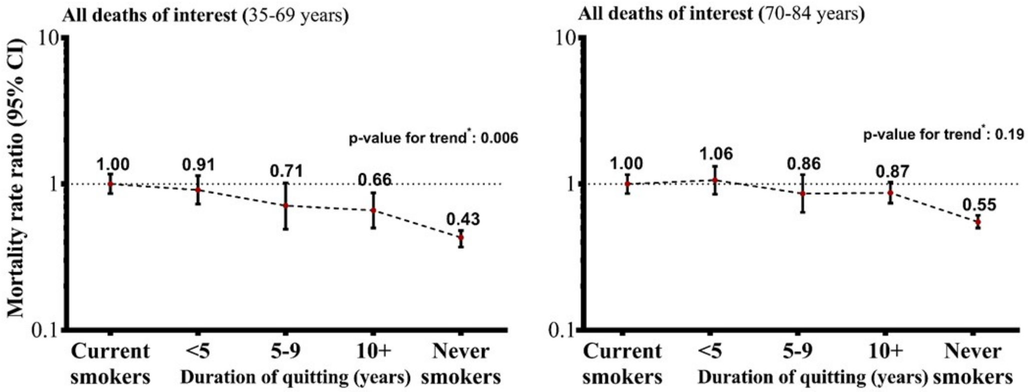
Figure 1 Duration of smoking cessation and mortality from all deaths of interest—mortality rate ratios (RR, 95% CI) comparing ex- or never-smokers vs current smokers

Deaths from selected diseases vs deaths from control diseases, at ages 35-69 or 70-84 years (both sexes)



	Current smokers	<5	5-9	10+	Never smokers
RR (35-69 years)	**1.00** (953)	**0.91** (421)	**0.71** (131)	**0.66** (221)	**0.43** (1242)
95% CI (35-69 years)	0.86-1.17	0.73-1.14	0.49-1.02	0.50-0.87	0.37-0.48
RR (70-84 years)	**1.00** (982)	**1.06** (491)	**0.86** (222)	**0.87** (770)	**0.55** (2021)
95% CI (70-84 years)	0.86-1.16	0.85-1.32	0.64-1.16	0.74-1.03	0.50-0.61

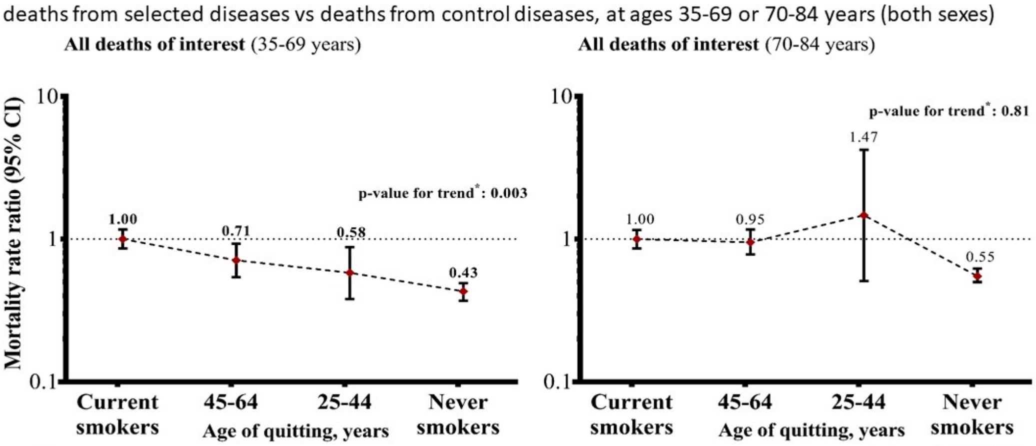
Numbers of cases (ie, deaths from the disease of interest) are given in brackets after each RR. Numbers of controls in current/ ex <5/ ex 5-9/ ex ≥10 years/ never smokers are 194/96/36/65/744 at ages 35-69 years, and 200/95/54/175/826 at ages 70-84 years.

CI: group-specific confidence interval for the age-, sex- and education-adjusted RR, reflecting the variance of the log risk in only that one group.

* Trend test in smokers, excluding never smokers; if trend tests in this table included never smokers, both would have yielded p<0.001.

Figure 2 Age at smoking cessation and mortality from all deaths of interest—mortality rate ratios (RR, 95% CI) comparing ex- or never-smokers vs current smokers

To limit reverse causality, analyses exclude those who stopped <5 years ago, or at age>65. They compare deaths from selected diseases vs deaths from control diseases, at ages 35-69 or 70-84 years (both sexes)



	Current smokers	45-64	25-44	Never smokers
RR (35-69 years)	**1.00** (953)	**0.71** (267)	**0.58** (83)	**0.43** (1242)
95% CI (35-69 years)	0.86-1.17	0.54-0.93	0.38-0.88	0.37-0.49
RR (70-84 years)	**1.00** (982)	**0.95** (521)	**1.47** (27)	**0.55** (2021)
95% CI (70-84 years)	0.86-1.16	0.78-1.17	0.51-4.22	0.50-0.62

Numbers of cases (ie, deaths from the disease of interest) are given in brackets after each RR. Numbers of controls in current/ ex 45-64/ ex 25-44 years/ never smokers are 194/137/41/744 at ages 35-69 years, and 200/113/4/826 at ages 70-84 years.

CI: group-specific confidence interval for the age-, sex- and education-adjusted RR, reflecting the variance of the log risk in only that one group.

* Trend test in smokers, excluding never smokers; if trend tests in this table included never smokers, both would have yielded p<0.001.

Table 1: Duration of smoking cessation and mortality from 4 smoking-related diseases—mortality rate ratios (RR, 95% CI) comparing ex- or never-smokers vs current smokers

Deaths from selected diseases vs deaths from control diseases, at ages 35-69 or 70-84 years (both sexes)

	Current smokers	Duration of quitting			Trend p-value†	Never smokers
		<5 years	5-9 years	≥10 years		
Lung cancer						
Age 35-69	**1.00** (231)	**1.23** (141)	**0.66** (28)	**0.50** (40)	<0.001	**0.22** (187)
	0.82-1.21	0.95-1.60	0.40-1.08	0.33-0.74		0.18-0.28
Age 70-84	**1.00** (228)	**1.21** (132)	**0.79** (47)	**0.62** (121)	0.001	**0.19** (174)
	0.83-1.21	0.93-1.59	0.53-1.17	0.49-0.78		0.16-0.23
Other smoking-related cancer						
Age 35-69	**1.00** (284)	**1.11** (151)	**0.72** (36)	**0.92** (84)	0.55	**0.58** (471)
	0.83-1.20	0.88-1.47	0.45-1.15	0.66-1.28		0.50-0.68
Age 70-84	**1.00** (166)	**0.93** (73)	**0.66** (29)	**0.67** (95)	0.011	**0.60** (318)
	0.81-1.23	0.69-1.27	0.42-1.05	0.52-0.86		0.51-0.71
Cardiovascular disease						
Age 35-69	**1.00** (231)	**0.56** (66)	**0.59** (28)	**0.40** (37)	<0.001	**0.46** (338)
	0.82-1.22	0.41-0.78	0.36-0.98	0.27-0.61		0.38-0.54
Age 70-84	**1.00** (266)	**0.90** (111)	**0.72** (49)	**0.83** (197)	0.15	**0.76** (785)
	0.83-1.20	0.68-1.18	0.48-1.06	0.67-1.02		0.67-0.86
COPD						
Age 35-69	**1.00** (66)	**0.72** (24)	**1.35** (19)	**0.81** (22)	0.79	**0.26** (46)
	0.75-1.34	0.46-1.14	0.76-2.42	0.49-1.33		0.18-0.38
Age 70-84	**1.00** (104)	**1.34** (67)	**1.59** (42)	**1.40** (134)	0.050	**0.26** (106)
	0.79-1.27	0.97-1.85	1.05-2.41	1.11-1.76		0.21-0.33

Numbers of cases (ie, deaths from the disease of interest) are given in brackets after each RR. Numbers of controls in current/ ex <5/ ex 5-9/ ex ≥10 years/ never smokers are 194/96/36/65/744 at ages 35-69 years, and 200/95/54/175/826 at ages 70-84 years.

CI: group-specific confidence interval for the age-, sex- and education-adjusted RR, reflecting the variance of the log risk in only that one group.

† Trend test in smokers, excluding never smokers; if trend tests in this table included never smokers, each would have yielded p<0.05.

Other smoking-related cancers: upper aerodigestive, stomach, liver, pancreas, cervix, urinary, and myeloid leukaemia (ICD-9 140-51, 155-7, 160-1, 179-80, 184, 188-9, 205). Cardiovascular disease: stroke and ischaemic heart disease (ICD-9 430-8, 410-4, 440-8). COPD: chronic obstructive pulmonary disease (ICD-9 415-7, 490-6); heterogeneity by sex was p<0.05 only for COPD.

Table 2: Age at smoking cessation and mortality from 4 smoking-related diseases—mortality rate ratios (RR, 95% CI) comparing ex- or never-smokers vs current smokers

To limit reverse causality, analyses exclude those who stopped <5 years ago, or at age>65. They compare deaths from selected diseases vs deaths from control diseases, at ages 35-69 or 70-84 years (both sexes)

	Current smokers	Age at quitting		Trend p-value†	Never smokers
		45-64 years	25-44 years		
Lung cancer					
Age 35-69	**1.00** (231) 0.83-1.21	**0.61** (53) 0.42-0.88	**0.41** (14) 0.22-0.78	<0.001	**0.22** (187) 0.17-0.27
Age 70-84	**1.00** (228) 0.83-1.21	**0.66** (86) 0.50-0.88	**0.78** (4) 0.19-3.16	0.015	**0.19** (174) 0.15-0.23
Other smoking-related cancer					
Age 35-69	**1.00** (284) 0.83-1.20	**0.84** (81) 0.60-1.17	**0.84** (38) 0.52-1.36	0.35	**0.58** (471) 0.50-0.69
Age 70-84	**1.00** (166) 0.81-1.23	**0.71** (69) 0.53-0.97	**1.00** (4) 0.25-4.07	0.08	**0.60** (318) 0.51-0.71
Cardiovascular disease					
Age 35-69	**1.00** (231) 0.82-1.21	**0.51** (53) 0.35-0.73	**0.36** (12) 0.18-0.70	<0.001	**0.46** (338) 0.39-0.55
Age 70-84	**1.00** (266) 0.83-1.20	**0.90** (133) 0.69-1.15	**2.08** (10) 0.65-6.66	0.82	**0.76** (785) 0.66-0.87
COPD					
Age 35-69	**1.00** (66) 0.75-1.32	**1.12** (36) 0.73-1.72	**0.60** (5) 0.23-1.60	0.78	**0.26** (46) 0.18-0.38
Age 70-84	**1.00** (104) 0.79-1.27	**1.59** (92) 1.20-2.11	**2.83** (6) 0.74-10.8	0.008	**0.26** (106) 0.20-0.33

Numbers of cases (ie, deaths from the disease of interest) are given in brackets after each RR. Numbers of controls in current/ ex 45-64/ ex 25-44 years/ never smokers are 194/137/41/744 at ages 35-69 years, and 200/113/4/826 at ages 70-84 years.

CI: group-specific confidence interval for the age-, sex- and education-adjusted RR, reflecting the variance of the log risk in only that one group.

† Trend test in smokers, excluding never smokers; if trend tests in this table included never smokers, each would have yielded $p<0.01$.

Other smoking-related cancers: upper aerodigestive, stomach, liver, pancreas, cervix, urinary, and myeloid leukaemia (ICD-9 140-51, 155-7, 160-1, 179-80, 184, 188-9, 205). Cardiovascular disease: stroke and ischaemic heart disease (ICD-9 430-8, 410-4, 440-8). COPD: chronic obstructive pulmonary disease (ICD-9 415-7, 490-6); heterogeneity was $p<0.05$ by sex only for COPD.

Supplementary materials

Content list

Supplementary Table s1. Underlying causes of death and ICD-9 codes for the cases and controls as defined according to Sitas et al 2013 in all deaths, Hong Kong 1998

Underlying cause(s) of death, and corresponding ICD-9 code(s)	No. of deaths (% of all cases or all controls)
Cases	
Tuberculosis: 10-18, 137	213 (1.1)
Chronic obstructive pulmonary disease: 415-417, 490-496	1830 (9.4)
Other respiratory diseases: 41, 79, 381-382, 460-466, 470-478, 481-488, 500-508, 510-519	3523 (18.0)
Stroke: 430-438	2940 (15.1)
Ischaemic heart disease: 410-414, 440-448	3052 (15.6)
Other cardiovascular diseases: 401-405, 420-429, 451-459	1222 (6.3)
Lung cancer: 162	2909 (14.9)
Upper aerodigestive cancer: 140-150, 160-161	946 (4.8)
Stomach, liver, pancreas cancer: 151, 155-156, 157	2220 (11.4)
Cervix or urinary cancer, myeloid leukaemia: 179-180, 184, 188-189, 205	564 (2.9)
†Parkinson's disease, ulcerative colitis, endometrial cancer: 332, 556 and 569, 182	107 (0.5)
Total cases	**19 526 (100%)**
Controls	
Diabetes and endocrine: 240-246, 249-259, 270-279, 282-285, 289, 266, 780, 998 and Nutritional deficiencies: 240-246, 260-269, 280-281, 286-288	557 (9.2)
Infectious and parasitic diseases: 1-9, 20-27, 30-41, 45-66, 70-79, 80-88, 90-104, 110-118, 120-136, 138, 139	471 (7.8)
Cancers (excluding those included in the cases): 152-154, 158-159, 163-165, 170-175, 181, 183, 185-187, 190-194, 200-204, 206-208	2537 (41.8)
Diseases of the nervous system: 320-331, 333-359	106 (1.7)
Digestive diseases: 530, 540-543, 550-553, 555, 558, 570-579	855 (14.1)
Genitourinary diseases: 580-629	1278 (21.1)
Musculoskeletal diseases: 710-739	52 (0.9)
Skin infections and disorders: 680-709	47 (0.8)
Benign neoplasms: 210-229	9 (0.1)
Miscellaneous and minor conditions, and Congenital anomalies: 740-759, and 740-779	10 (0.2)
Acute rheumatic fever and chronic rheumatic heart diseases: 390-398	154 (2.5)
Oral conditions: 520-529	0
Diseases of the sense organs: 360-380	0
Total controls	**6 076 (100%)**

Deaths from ill-defined and unknown causes were excluded (as we did not know whether they should be cases or controls). Deaths from Kaposi's sarcoma, other HIV-related disease, external causes, cirrhosis, or mental and behavioural disorders were also excluded, as any association with smoking could be non-causal, probably due to confounding by alcohol use).

† Smoking was associated with reduced risk.

Table s2. Smoking history and mortality from all deaths of interest and 4 smoking-related diseases—mortality rate ratio (RR, 95% CI) comparing current or ex-smokers vs never smokers

Deaths from selected diseases vs deaths from control diseases, at ages 35-69 or 70-84 (both sexes)

	Never smokers	Ex-smokers	Current smokers
All deaths of interest			
Age 35-69	**1.00** (2503) 0.91-1.10	**1.33** (476) 1.11-1.61	**2.04** (2996) 1.87-2.22
Age 70-84	**1.00** (4217) 0.93-1.07	**1.49** (1526) 1.33-1.67	**1.76** (3594) 1.62-1.91
Lung cancer			
Age 35-69	**1.00** (370) 0.85-1.17	**1.99** (90) 1.53-2.59	**4.19** (771) 3.77-4.65
Age 70-84	**1.00** (360) 0.87-1.15	**3.01** (235) 2.56-3.54	**4.98** (793) 4.48-5.54
Other smoking-related cancer			
Age 35-69	**1.00** (928) 0.89-1.12	**1.30** (165) 1.04-1.63	**1.63** (933) 1.47-1.80
Age 70-84	**1.00** (639) 0.89-1.12	**1.10** (192) 0.92-1.31	**1.47** (543) 1.31-1.65
Cardiovascular disease			
Age 35-69	**1.00** (721) 0.88-1.13	**0.88** (98) 0.68-1.15	**1.64** (674) 1.47-1.83
Age 70-84	**1.00** (1763) 0.92-1.09	**1.02** (413) 0.88-1.17	**1.18** (955) 1.07-1.31
COPD			
Age 35-69	**1.00** (101) 0.78-1.28	**2.78** (54) 2.01-3.84	**3.12** (217) 2.67-3.64
Age 70-84	**1.00** (242) 0.86-1.17	**4.94** (299) 4.23-5.75	**4.61** (552) 4.11-5.17

Numbers of cases (ie, deaths from the disease of interest) are given in brackets after each RR. Numbers of controls in never/ex-/current smokers are 1461/149/640 at ages 35-69 years, and 1655/367/734 at ages 70-84 years.

CI: group-specific confidence interval for the age-, sex- and education-adjusted RR, reflecting the variance of the log risk in only that one group.

Other smoking-related cancers: upper aerodigestive, stomach, liver, pancreas, cervix, urinary, and myeloid leukaemia (ICD-9 140-51, 155-7, 160-1, 179-80, 184, 188-9, 205).

Cardiovascular disease: stroke and ischaemic heart disease (ICD-9 430-8, 410-4, 440-8).

COPD: chronic obstructive pulmonary disease (ICD-9 415-7, 490-6); heterogeneity by sex was $p<0.05$ only for COPD.

Supplementary Table s3. Smoking history and mortality from all deaths of interest—mortality rate ratios (RR 95% CI) comparing ever smokers vs never smokers by age

Deaths from selected diseases vs deaths from control diseases, at ages 35-59, 60-69, 70-79, 80-84 or 85+ years and sex

Age at death (years)	Sex	Case	Control	RR (95% CI)
		No of subjects ever smoked/ never smoked	No of subjects ever smoked/ never smoked	
35-59	Men	1148/527	263/247	**2.00** (1.63-2.46)
	Women	55 /580	20 /498	**2.01** (1.20-3.51)
	Both	1203/1107	283/745	**1.97** (1.63-2.39)
60-69	Men	2006/629	417/246	**1.86** (1.55-2.24)
	Women	189 /767	57 /470	**2.12** (1.54-2.95)
	Both	2195/1396	474/716	**1.93** (1.64-2.26)
70-79	Men	2792/935	579/328	**1.68** (1.44-1.96)
	Women	666 /1696	181/799	**1.73** (1.44-2.09)
	Both	3458/2631	760/1127	**1.70** (1.51, 1.92)
80-84	Men	1115/467	229/148	**1.55** (1.22-1.97)
	Women	431 /1119	88 /380	**1.63** (1.27-2.12)
	Both	1546/1586	317/528	**1.57** (1.32-1.87)
85+	Men	853 /605	167/155	**1.28** (1.00-1.64)
	Women	515 /2049	116/553	**1.19** (0.95-1.50)
	Both	1368/2654	283/708	**1.24** (1.05-1.46)
Selected age range*				
Age 35-69	Men	3154/1156	680/493	**1.93** (1.68-2.22)
	Women	244 /1347	77 /968	**2.10** (1.60-2.78)
	Both	3398/2503	757/1461	**1.95** (1.72-2.20)
Age 70-84	Men	3907/1402	808 /476	**1.64** (1.44-1.87)
	Women	1097/2815	269 /1179	**1.70** (1.46-1.98)
	Both	5004/4217	1077/1655	**1.66** (1.51-1.84)

CI: confidence interval for the age-, sex- and education-adjusted RR.

* Heterogeneity by age group (35-69 or 70-84 years) was p<0.05.

Supplementary Table s4. Smoking history and mortality from 4 smoking-related diseases—mortality rate ratios (RR) comparing ever smokers vs never smokers

Deaths from selected diseases vs deaths from control diseases, at ages 35-69 or 70-84 years and sex

Cause of death	Sex	Case No of subjects ever/ never smoked	Control No of subjects ever/ never smoked	RR (95% CI)
Lung cancer				
Age 35-69	Men	779/128	680/493	**4.20** (3.36-5.27)
	Women	68 /242	77 /968	**3.35** (2.32-4.84)
	Both	847/370	757/1461	**3.92** (3.25-4.75)
Age 70-84	Men	789 /86	808 /476	**5.30** (4.13-6.86)
	Women	228 /274	269 /1179	**3.65** (2.93-4.56)
	Both	1017/360	1077/1655	**4.33** (3.69-5.10)
Other smoking-related cancer				
Age 35-69	Men	1021/478	680/493	**1.63** (1.38-1.92)
	Women	58 /450	77 /968	**1.64** (1.14-2.37)
	Both	1079/928	757/1461	**1.61** (1.39-1.87)
Age 70-84	Men	610/246	808 /476	**1.42** (1.18-1.72)
	Women	112/393	269 /1179	**1.22** (0.95-1.57)
	Both	722/639	1077/1655	**1.35** (1.16-1.56)
Cardiovascular disease				
Age 35-69	Men	680/324	680/493	**1.47** (1.23-1.76)
	Women	62 /397	77 /968	**1.58** (1.09-2.28)
	Both	742/721	757/1461	**1.48** (1.26-1.74)
Age 70-84	Men	1005/550	808 /476	**1.09** (0.93-1.27)
	Women	322 /1213	269 /1179	**1.17** (0.97-1.40)
	Both	1327/1763	1077/1655	**1.13** (0.99-1.26)
COPD				
Age 35-69	Men	239/61	680/493	**2.39** (1.76-3.30)
	Women	27 /40	77 /968	**8.15** (4.57-14.5)
	Both	266/101	757/1461	**3.08** (2.31-4.12)
Age 70-84	Men	627/98	808 /476	**3.66** (2.88-4.69)
	Women	202/144	269 /1179	**6.05** (4.70-7.82)
	Both	829/242	1077/1655	**4.70** (3.93-5.63)

CI: confidence interval for the age-, sex- and education-adjusted RR.

Other smoking-related cancers: upper aerodigestive, stomach, liver, pancreas, cervix, urinary, and myeloid leukaemia (ICD-9 140-51, 155-7, 160-1, 179-80, 184, 188-9, 205).

Cardiovascular disease: stroke and ischaemic heart disease (ICD-9 430-8, 410-4, 440-8).

COPD: chronic obstructive pulmonary disease (ICD-9 415-7, 490-6); heterogeneity by sex was $p<0.05$ only for COPD.

Supplementary Table s5. Demographic characteristics (%) of cases and controls[†] in all deaths (aged 35-84 years), Hong Kong 1998

	Cases (15 356)	**Controls** (2 503)
Age at death, years		
35-69	39.0	45.0
70-84	61.0	55.0
Men	49.8	63.6
Education		
None	36.9	35.3
Primary	41.2	41.2
Secondary and higher	21.9	23.5
Type of housing		
Public/hut/shared	57.4	56.5
Self-owned	36.8	38.3
Quarter/others	5.8	5.3
Quitting status, 2nd half of all the 1998 deaths		
Current smokers	26.0	15.9
Quitters	30.3	21.0
Never smokers	43.8	63.2
Duration of quitting, 2nd half of all the 1998 deaths		
Current smokers	26.0	15.9
Quitters, years: <5	12.2	7.7
5-9	4.7	3.6
≥10	13.3	9.7
Never smokers	43.8	63.2
Age at quitting, 2nd half of all the 1998 deaths		
Current smokers	26.0	15.9
Age at quitting, years: 25-44	1.9	1.8
45-64	15.5	10.1
65+	12.8	9.0
Never smokers	43.8	63.2

[†] Deaths from diseases as in Sitas et al 2013.

Supplementary Part I. Methods of the HK LIMOR study

The HK LIMOR study was a proportional mortality case-control study of adult (aged 30 years or above) deaths in ethnic Chinese in 1998, including 81% of all registered deaths. Inspired by the first mortality case-control study by Liu et al in China, the HK LIMOR study was designed primarily to estimate smoking-attributed mortality, but also collected information on other behaviours and demographic characteristics 10 years ago in all deaths (January-December, 1998), and duration of quitting before death in the second half of all deaths (June-December, 1998). A standardized questionnaire was completed by the person registering the death (proxy informant), who was usually an educated family member familiar with the decedent. Such proxy information has been shown to be reliable. The World Health Organization's International Classification of Diseases-9th revision (ICD-9) was used to classify the causes of death by the Hong Kong Department of Health.

Supplementary Part II. Additional details of definitions of smoking and quitting

Quitting status was measured by “How long had the decedent been quitting smoking consecutively before death?”. The twelve options were provided as “never smoked”, “didn’t quit”, “less than 1 year”, “1-2 years”, “3-4 years”, “5-6 years”, “7-9 years”, “10-14 years”, “15-19 years”, “20-29 years”, “30 years or more”, and “don’t know”. The question was asked in Chinese as “由過身前計起，死者連續戒煙了多少年？可選 1）從不吸，2）沒有戒，3）少於 1 年，4）1-2 年，5）3-4 年，6）5-6 年，7）7-9 年，8）10-14 年，9）15-19 年，10）20-29 年，11）30 年或以上，和 12）不知道”.

Subjects who chose “didn’t quit” were classified as current smokers, and those who chose “never smoked” were classified as never smokers. Quitters were those who chose other options of “less than 1 year”, “1-2 years”, “3-4 years”, “5-6 years”, “7-9 years”, “10-14 years”, “15-19 years”, “20-29 years” and “30 years or more”. Subjects who chose “don’t know” were excluded (N=101). Quitting status at death was classified into 5 groups in the second half of deaths: current smokers (reference group), quitters who had stopped smoking for less than 5, 5-9 and 10+ years, and never smokers. Subjects who had stopped smoking for less than 5 years or after the age of 65 years were excluded in order to limit reverse causality, where quitting was due to ill health, often at older ages.

Smoking status was measured by “Ten years ago, in about 1988, had the decedent ever smoked? (including hand-rolled cigarettes)” with responses of “yes, smoked daily”, “yes, smoked occasionally (less than 7 cigarettes weekly), “already quit”, “never smoked”, and “don’t know”. The question was asked in Chinese as “十年前， 即約在 1988 年時，死者曾否試過吸煙仔？（包括手卷煙）。可選 1）有，每天都吸，2）有，間中吸（每星期少於 7 枝），3）曾吸，但當時已戒，4）從不吸，和 5）不知道”.

Subjects who chose “yes, smoked daily” and “yes, smoked occasionally (less than 7 cigarettes weekly)” were classified as current smokers. Subjects who chose “already quit” were classified as ex-smokers. Subjects who chose “never smoked” were classified as never smokers. Subjects who chose “don’t know” were excluded (N=90). In all deaths, smoking status 10 years ago was classified into 3 groups: current smokers (reference group), ex-smokers, and never smokers.