Factors that determine the risk reduction for lung cancer following smoking cessation and their quantitative effect on the observed risk reduction

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Date : 28th December 2007

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EXECUTIVE SUMMARY

It is well known that, relative to the risk in continuing smokers, the risk of lung cancer declines on quitting (ignoring the apparent increase in risk associated with very short-term quitting, likely due to some smokers quitting because of disease). The decline is continuous, with risk in long-term quitters often observed to be less than 10% of that of continuing smokers of the same age. Though the decline is evident in numerous populations, little attention has been given in the literature as to whether the magnitude of the decline varies by other factors.

This document presents evidence from three sources.

Multistage model predictions Based on a multistage model, the effect on the magnitude of the decline in quitting is investigated in relation to variation in dose, age of starting to smoke, age, duration and aspects of the model.

A review of the published epidemiological evidence 32 papers were identified that reported data from 25 studies. Factors most commonly considered were sex (16 studies) and amount smoked (11 studies) with other factors considered, in at most 3 studies, being age, race, age of starting to smoke, duration of smoking, pack-years, cigarette type and inhalation. Many of the studies were too small to provide precise estimates and the statistical analyses reported were not always appropriate.

Analyses of data from CPS I and II Based on the data sets we retain from these studies, the effects of variation in age, sex, number of cigarettes smoked and age of starting to smoke on the decline in risk following quitting were investigated.

Of the nine factors considered in these investigations, there was either no indication of any effect, or the data were too limited to come to a conclusion, for four (race, pack-years, type of cigarette smoked and inhalation). For the other five factors we note the following:

Age The data are consistent in suggesting that, for a given time of quit, the decline in risk following quitting is more rapid in younger age groups. Although the number

of published studies providing data is quite limited, our analysis based on CPS I and II shows this effect quite clearly.

Sex Sex is the factor with most available data and the published evidence suggests a somewhat faster decline in risk in females than in males. However our analyses of CPS I and II did not find this difference, after adjusting for age and other factors.

Number smoked The multistage predictions clearly show that the decline in risk is more rapid for heavier smokers. Although epidemiological data are available from a number of studies, their findings are rather unclear (see section 3.7), and we could detect no significant difference in the rate of decline by amount smoked in our analyses of CPS I and II.

Duration of smoking The limited epidemiological evidence is consistent with the predictions of the multistage model that the decline is more rapid in those who have a shorter duration of smoking. This result is clearly not independent of the results for age, given above.

Age of starting to smoke Since, for a given age and time of quit, later starting is implied by a shorter duration of smoking, it is not surprising that the multistage model also predicts a more rapid decline in those who have a later age of starting to smoke. This observation is supported by limited published evidence, but not by our analyses of CPS I and II where the decline was somewhat greater in early starters. It is unclear why this should be so.

The main overall impression from the work carried out is that estimates of the extent of the declines in lung cancer risk following quitting derived from the whole population(s) studied are likely to apply with a reasonable degree of accuracy to subsets of the population. The exception to this is subsets defined by age, where the evidence seems quite clear that the decline is more rapid in younger people.

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1. Introduction

The fact that the risk of lung cancer declines on quitting smoking relative to continuing smoking has been known for many years (US Surgeon General, 1990). In 2000 I conducted a review of evidence from larger studies (minimum 500 lung cancer cases) (Lee, 2000) which included the following paragraph in its executive summary:

"Years stopped smoking Among ex-smokers, risk of lung cancer (and all the major histological types) clearly declines with increasing time given up. For those giving up smoking for 25 years or longer, an increased risk of lung cancer (compared to never smokers) is still evident, by about 2-fold. Compared to current smokers, risk declines with increasing time given up (an apparent increase in risk seen in some studies associated with very short-term giving up being likely to be an artefact caused by quitting because of disease). The decline can be seen within categories of amount smoked."

Such evidence is valuable *inter alia* for considering the likely benefit from switching to reduced risk products (RRPs) – thus if 10 years quitting halves risk of lung cancer relative to continuing to smoke, switching to an RRP that reduces exposure to relevant smoke constituents by a half would probably only be expected to reduce risk by about a quarter.

Accurate predictions of the benefits of quitting (or switching to an RRP) will depend on accurate knowledge of the magnitude of the risk reduction, and how this depends on other relevant factors, including age, sex, age of starting to smoke, duration of smoking and daily amount smoked. While many studies have reported risk estimates by time of quit (relative to continuing smokers or never smokers), there is less published evidence on whether the risk pattern in quitters varies by other factors. Partly this is because of the large number of lung cancers necessary to quantify these effects precisely.

The objective of the work described here is therefore to investigate in detail how the pattern of decline in the lung cancer relative risk following

quitting varies by other major risk factors. Note that in this work we restrict attention to the overall risk of lung cancer regardless of histological type. Some evidence on how the risk varies by histological type is given in Tables 9.2 and 9.4 of my earlier review (Lee, 2000).

The work is divided into three parts. In section 2 we investigate how we would expect the decline in quitting to vary by dose, age of starting to smoke and age, assuming a multistage model. In section 3 we update and extend the earlier literature review (Lee, 2000) and summarize the available epidemiological evidence relating the decline following quitting to other factors. In section 4 we present the results of some additional analyses based on the versions of CPS I and CPS II databases we have inhouse. The overall findings are discussed in section 5, with conclusions drawn in section 6.

2. Predictions of the effect of quitting based on a multistage model

2.1 Introduction

As noted above, the risk of lung cancer in quitters decreases, the extent of the decline increasing with increasing time of quitting. Before considering epidemiological evidence of variations in the extent of this decline with other factors, it is worth considering on a theoretical basis what variation one might expect in relation to the key factors age, age of starting to smoke, and dose of smoking.

To look at this we consider a multistage model with k stages, the first and penultimate stage being affected by smoking. A review by one of us (PNL) (Lee, 1995) describes the properties, strengths and weaknesses of this model in considerable detail, and also presents various relevant formulae. We keep to the notation of that review and define:

S	age of starting to smoke
D	duration of smoking
F	period of quit
T	age (= S+D+F)
d_1	"effective excess dose" from smoking for stage 1
d_2	"effective excess dose" from smoking for penultimate stage

Note that if, for the ith stage of the multistage process, the transition probability is 1 unit in the absence of smoking and 1+d units in the presence of smoking, the "effective excess dose" is defined as d.

The excess risk at time T, I_t, is proportional to:

$$d_1 [(D+F)^{k-1} - F^{k-1}] + d_2 [(D+S)^{k-1} - S^{k-1}] + d_1 d_2 D^{k-1}$$

The risk in never smokers of age T is proportional to T^{k-1} with the same constant of proportionality (the actual constant being irrelevant as we are concerned only with relative risks).

To illustrate the predictions of the model, consider the case of $d_1 = d_2 = 8$, S = 20 and T = 60, with D varying from 40 to 0 and F concomitantly varying from 0 (current smokers) to 40 (never smoked). The following relative risks can be calculated:

Years quit (F)	Relative risk vs never smokers	Relative risk vs current smokers	Relative excess risk vs current smokers
0 (current smokers)	30.04	1.00 (base)	1.00 (base)
5	21.94	0.73	0.72
10	15.67	0.52	0.51
15	10.95	0.36	0.34
20	7.52	0.25	0.22
25	5.08	0.17	0.14
30	3.37	0.11	0.08
35	2.10	0.07	0.04
40 (never smokers)	1.00 (base)	0.03	0.00

S = 20; T = 60; $d_1=d_2=8$; D = T-S-F varies with F

The relative risks show a pattern apparently not dissimilar from that seen in numerous epidemiological studies. Although results are usually presented as relative risks vs either never or current smokers, also shown in the last column is the relative excess risk, which may perhaps be more generalizable to other scenarios.

The results above can be used as a basis for seeing how the pattern of decline varies by the other factors in the model.

2.2 Varying the dose

Keeping all other factors constant, we can investigate how the relative risk varies by the effective excess dose. We continue to assume that $d_1 = d_2$. Clearly the relative risks vs never smokers will vary markedly, so we look at relative and excess risk vs current smokers. Here we have:

Years quit (F)	d =	Relative risk vs current smokers 8	6	4	2	Relative excess risk 8	6	4	2
0 (current smokers)		1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
5		0.73	0.74	0.77	0.82	0.72	0.73	0.75	0.77
10		0.52	0.55	0.59	0.67	0.51	0.52	0.55	0.59
15		0.36	0.40	0.45	0.56	0.34	0.36	0.39	0.44
20		0.25	0.28	0.34	0.46	0.22	0.24	0.27	0.32
25		0.17	0.20	0.26	0.39	0.14	0.16	0.18	0.23
30		0.11	0.14	0.20	0.33	0.08	0.09	0.11	0.15
35		0.07	0.09	0.14	0.27	0.04	0.04	0.06	0.07
40 (never smokers)		0.03	0.05	0.09	0.21	0.00	0.00	0.00	0.00

S = 20; T = 60; $d_1 = d_2$; D = T-S-F varies with F

For the four values of d chosen, the current smoking/never smoking relative risks are 30.04 (d = 8), 19.22 (d = 6), 10.78 (d = 4) and 4.70 (d = 2), which reasonably indicates the spread between heavy and light smoking.

It can be seen that as d decreases, the relative risk, and to a lesser extent the relative excess risk, increases for a given number of years quit. The advantage of quitting, measured in either way, is greater for those for whom smoking contributes most to their risk (heavy smokers).

2.3 Varying the age of starting to smoke

Again, keeping all other factors constant one can investigate how the relative risk varies by age of starting to smoke. Here we have:

Years quit (F)	S =	Relative risk vs current smokers 10	15	20	30	Relative excess risk 10	15	20	30
0 (current smokers)		1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
5		0.77	0.75	0.73	0.69	0.76	0.74	0.72	0.67
10		0.58	0.55	0.52	0.47	0.57	0.54	0.51	0.44
15		0.43	0.39	0.36	0.31	0.41	0.38	0.34	0.27
20		0.31	0.28	0.25	0.20	0.30	0.26	0.22	0.15
25		0.22	0.19	0.17	0.12	0.21	0.17	0.14	0.07
30		0.16	0.13	0.11	0.06	0.14	0.11	0.08	0.00

T = 60; $d_1=d_2=8$; D = T-S-F varies with F and S

Note that for smokers starting at age 30, F = 30 represents never smokers, but for earlier starting smokers F = 30 represents subjects who started to smoke then quit.

Here, for a given time quit, both the relative risk and the relative excess risk decline continuously with increasing age of starting to smoke. This seems to be because in later starting smokers a given time of quit represents a greater proportion of the subject's smoking duration.

2.4 Varying the age

Again, keeping all factors constant one can investigate how the relative risk varies by age. Here we have:

		Relative risk vs current smokers				Relative excess risk			
Years quit (F)	T =	50	60	70	80	50	60	70	80
0 (current smokers)		1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
5		0.67	0.73	0.77	0.81	0.65	0.72	0.77	0.80
10		0.43	0.52	0.59	0.64	0.41	0.51	0.58	0.63
15		0.27	0.36	0.44	0.51	0.24	0.34	0.43	0.49
20		0.16	0.25	0.33	0.39	0.13	0.22	0.31	0.38
25		0.09	0.17	0.24	0.30	0.06	0.14	0.22	0.29
30		0.04	0.11	0.17	0.23	0.00	0.08	0.15	0.21

S = 20; $d_1=d_2=8$; D = T-S-F varies with S and T

Here, for a given time quit, both the relative risk and the relative excess risk increase with increasing age. This seems to be because in younger smokers a given time of quit represents a greater proportion of the subject's smoking duration.

2.5 Varying the duration

For a given age, varying the age of starting to smoke is equivalent to varying the duration of smoking. Similarly, for a given age of starting to smoke, varying the age is equivalent to varying the duration of smoking. Additional calculations are not necessary. The message remains that for a given number of years of quitting, the extent of the reduction (compared to current smokers) following quitting increases with decreasing duration of smoking.

2.6 Relative contribution of the first and penultimate stage

With S and T held constant, the table below shows the effect of varying the relative contributions of the first stage effect (d_1) and the

penultimate stage effect (d_2). For a given value of d_1 the value of d_2 is selected so that the current/never smoker relative risk remains constant (at 19.22).

		Relative risk vs current smokers					Relative excess risk				
	d_1 =	18	12	6	3	2	18	12	6	3	2
Years quit (F)	d_2 =	2.047	3.246	6	9.360	11.333	2.047	3.246	6	9.360	11.333
0 (current smokers)		1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
5		0.79	0.76	0.74	0.75	0.75	0.78	0.75	0.73	0.73	0.74
10		0.62	0.58	0.55	0.54	0.55	0.60	0.56	0.52	0.52	0.52
15		0.49	0.44	0.40	0.39	0.39	0.47	0.41	0.36	0.36	0.36
20		0.39	0.33	0.28	0.27	0.28	0.36	0.30	0.24	0.23	0.24
25		0.31	0.25	0.20	0.19	0.19	0.27	0.21	0.16	0.14	0.14
30		0.23	0.18	0.14	0.13	0.13	0.19	0.14	0.09	0.08	0.08

S = 20; T = 60; d = T-S-F varies with F

Where the effect of smoking comes largely from a first stage effect (high d_1), the relative risks on quitting decline somewhat more slowly. However, there is very little variation in the extent of decline as d_2 increases from a value equal to d_1. It has been claimed that data are fitted better by a model in which d_2 is about twice d_1 (see Lee, 1995) but the assumption is clearly not crucial to the predicted decline following quitting.

2.7 Effect of changing the number of stages

With all other variables held constant, we now vary the number of stages:

		Relative risk vs current smokers				Relative excess risk			
Years quit (F)	k =	3	4	5	6	3	4	5	6
0 (current smokers)		1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
5		0.81	0.74	0.69	0.65	0.80	0.73	0.67	0.62
10		0.64	0.55	0.48	0.42	0.63	0.52	0.44	0.37
15		0.49	0.40	0.33	0.29	0.47	0.36	0.29	0.23
20		0.36	0.28	0.24	0.21	0.33	0.24	0.19	0.15
25		0.25	0.20	0.18	0.17	0.22	0.16	0.12	0.10
30		0.16	0.14	0.14	0.14	0.13	0.09	0.08	0.07

S = 20; T = 60; d_1=d_2=6; D = T-S-F varies with F

Here the decline on quitting increases with the number of stages. Note that the predicted current smoker/never smoker relative risk declines with the number of stages, being 25, 19.22, 15.22 and 12.51 for, respectively, k = 3, 4, 5 and 6. However, this cannot be the full explanation of the increased decline on quitting with the number of stages, as the variation with d for a given k is much less than this (see the table in the section "varying the dose").

2.8 Conclusion

It has been shown that the decline on quitting (relative to current smoking) varies with the nature of the multistage model, more so with the number of stages than with the relative contribution of the effects on the two stages. No doubt other models, not investigated here, would predict different declines. However, the two main conclusions from our analyses seem likely to us to be robust to the choice of model. The first is that, for a given quit period, the decline in heavy smokers is steeper than the decline in light smokers. While this is clearly seen when the decline is expressed in terms of relative risk (and to be expected as heavy smokers have more scope for decline), it is also evident to a lesser extent when the decline is expressed in terms of relative excess risk. The second conclusion is that, for a given quit period, the decline is greater the shorter the duration of smoking. This is again to be expected as one would expect 10 years quitting to reverse the effect of 10 years smoking faster than it would reverse the effect of 50 years smoking. This pattern can be seen by fixing age and varying age of starting to smoke, or *vice versa*.

3. A review of the published epidemiological evidence

3.1 Sources

In the IESLC project (Lee et al., 2003a; Lee et al., 2003b), we identified all studies of smoking and lung cancer published in the last century involving at least 100 lung cancer cases. On the database for each study we identified those studies which provided data on risk by time of quit, and then looked at the relevant publications from those studies to see if information was presented on risk by time of quit separately for any other factors. We also carried out a MEDLINE search of studies in humans in the last 10 years on "lung cancer and smoking cessation". By inspection of the abstracts and, where relevant, the papers themselves, we identified some additional relevant studies.

Overall, we identified 32 papers from 25 studies. Table 3.1 summarizes the data available and the data sources. 16 of these studies present estimates by sex and 11 by amount smoked. Other factors were much less often considered; age (3 studies), age of starting to smoke (1), duration of smoking (3), race (1), pack-years (2), cigarette type (3) and inhalation (1).

The relevant data are considered in the sections that follow.

TABLE 3.1 Available data on lung cancer risk in ex-smokers jointly by time of quit and by other factors

Study (type)	Factor	Source Reference	Source Table
USA			
9 state (P)	Cigs/day	Hammond & Horn, 1958	Figure 5
US Veterans (9)	Cigs/day	Hrubec & McLaughlin, 1997	Table 4
	Cigs/day x age began x age	Kahn, 1966	Appendix Table D
Roswell Park (C-C)	Cigs/day	Graham & Levin, 1971	Table 3
	Duration		Tables 5 and 6
CPS I (P)	Cigs/day	Hammond, 1972	Table 3
	Sex x cigs/day	Burns et al., 1997	Tables 3 and 4
8 city (C-C)	Sex	Wynder & Stellman, 1977	Tables 9 and 10
New Mexico (C-C)	Race	Humble et al., 1985	Text p 147
6 city (C-C)	Sex x cigs/day	Higgins & Wynder, 1988	Tables 2 and 3
CPS II (P)	Sex	US Surgeon General, 1990	Table 3
	Cigs/day	Garfinkel & Stellman, 1988	Table 6
	Age	Halpern et al., 1993	Table 3
	Sex x cigs/day	Samet, 1991	Table 1
Iowa (P)	Pack-years	Ebbert et al., 2003	Table 2
CANADA			
3 city (C-C)	Sex	Risch et al., 1993	Table 6
ARGENTINA			
Buenos Aires (C-C)	Black/blond cigs	Matos et al., 1998	Table 4
CUBA			
Havana (C-C)	Sex	Joly et al., 1983	Table 6
UK			
Multicentre (C-C)	Sex	Doll & Hill, 1952	Table VI
NE England (C-C)	Sex	Dean et al., 1977	Supplement Tbl 9
10 regions (C-C)	Sex	Alderson et al., 1985	Table 3
W Scotland (P)	Cigs/day	Gillis et al., 1988	Figure 3
SW England (C-C)	Sex	Darby et al., 1998	Table 3
	Sex	Peto et al., 2000	Table 1

TABLE 3.1 (cont'd.) Available data on lung cancer risk in ex-smokers jointly by time of quit and by other factors

Study (type)	Factor	Source Reference	Source Table
FRANCE			
16 hospitals (C-C)	Cigs/day	Benhamou et al., 1989	Table III
	Duration	Benhamou et al., 1989	Table III
	Light/mixed/dark cigs	Benhamou et al., 1989	Table III
	Filter/mixed/non-filter	Benhamou et al., 1989	Table III
	Manufactured/mixed/hand-Rolled	Benhamou et al., 1989	Table III
EUROPEAN MULTICENTRE			
5 countries (C-C)	Sex	Lubin & Blot, 1984	Table 5
	Sex	Lubin et al., 1984	Table I
	Sex x cigs/day	Lubin et al., 1984	Table III
	Sex x filter/mixed/nonfilter	Lubin et al., 1984	Table III
	Sex x inhalation frequency	Lubin et al., 1984	Table III
	Sex x inhalation depth	Lubin et al., 1984	Table III
6 countries (C-C)	Sex x cigs/day	Simonato et al., 2001	Table VIII
	Duration	Agudo et al., 2000	Table III
CHINA			
Shanghai (C-C)	Sex	Gao et al., 1988	Table 3
JAPAN			
6 prefectures (P)	Sex	Hirayama, 1990	Table 19
Osaka (C-C)	Sex	Sobue et al., 1994	Table II
Nationwide (P)	Age x pack-years	Ando et al., 2003	Table III

3.2 Sex

Table 3.2 summarizes data from 14 studies on how the decline in lung cancer risk following quitting varies by sex. The relative risks vs current smokers are shown on the left of the relative risks vs never smokers, the former with confidence intervals, the latter without. Relative risks above 10 are shown to 1 decimal place and below 10 to 2 decimal places (if available). The relative risks vs never smokers are generally higher in males, due to the higher relative risks for current smoking in males in many of the studies, and the extent of decline vs current smokers over the first 10 years or so following quitting is perhaps of more interest. Below we comment on the results from the individual studies based on the data in the table. Where appropriate, comparisons are made of the male and female risks following quitting for a given period, but no formal attempt has generally been made to carry out a statistical test of interaction based on the difference in the fitted slopes in the two sexes.

The data for CPS I (Burns et al., 1997) are only available vs never smokers. CI cannot be calculated from the information presented in the paper. The authors comment for males that rate ratios for males decline, but seem to plateau once 20 years of cessation has been reached. They also note that the number of former smokers are much smaller in females than in males and do not allow a clear conclusion to be drawn for females. It should be noted that these analyses are difficult to interpret, as they are adjusted for duration of smoking, which is intrinsically linked to time quit. (The CPS I data will be analyzed further in section 4.)

The data from the 8 city case-control study (Wynder & Stellman, 1977) do not show any clear difference between the sexes. The authors note that the "same trends" occur for females as males but "smaller numbers of historical long-term quitters impose longer error bounds on the tabulated risks for women than for men."

The data from the later 6 city case-control study (Higgins & Wynder, 1988) again show no very clear difference between the sexes. The authors

note that "In men, the decline was consistent, but in women the risk was higher in those who had quit for 30 years and over than in either the 10 to 19 or the 20 to 29 years group. The confidence intervals indicate that this could well be due to small numbers." For both this and the previous study, the estimates are unadjusted for age. However, the cases and controls were age-matched.

The data shown from CPS II came from the 1990 US Surgeon General Report (US Surgeon General, 1990). After three years the relative risks vs current smokers are consistently somewhat lower in women than men for a given period of quit, but never significantly so. More limited data, cited in a review paper (Samet, 1991), are not presented in Table 3.2. (The CPS II data will be analyzed further in section 4.)

Based on the Canadian 3 city case-control study (Risch et al., 1993) the authors presented estimates for each sex of the decline in risk per 10 years of quitting. The estimated decline was somewhat greater for females, but the difference was not statistically significant. It should be noted that these analyses are difficult to interpret, as they are adjusted for pack-years which is intrinsically linked to time quit.

A case-control study in Havana (Joly et al., 1983) only reports results by two times of quit (1-4, 5+ years). The results show no significant difference between the sexes.

A very early case-control study in the UK (Doll & Hill, 1952) again shows no evident difference between the sexes. However, the numbers of quitters of 10+ years among the cases was extremely low (14 in men, 1 in women).

The case-control study in NE England (Dean et al., 1977) reported lower RRs for quitters in females than males for a given time of quit. However, numbers of cases in quitters were low (27 in males, 7 in females) and the differences are not statistically significant.

The 10 region UK case-control study (Alderson et al., 1985) shows no clear differences in the decline between the sexes.

Results from the more recent case-control study in South West England have been reported in two papers (Darby et al., 1998; Peto et al., 2000), data from the later reference being shown in Table 3.2. For 10 years and for 20+ years quitting the relative risks for females are significantly ($p<0.05$) less than those for males.

While the European 5 country study (Lubin & Blot, 1984) presents detailed data for males, the results for females are based on far fewer cases and estimates are only given for 1-4 and 5+ yeas quit. No clear difference between the sexes is evident. The data presented are unadjusted for age, but the cases and controls were matched on age. Additional results are reported elsewhere (Lubin et al., 1984) but these are adjusted for duration of smoking, which seems completely inappropriate.

The results from the recent European 6 country study (Simonato et al., 2001) are based on quite large numbers of quitters, 1838 in males and 216 in females. The decline is clearly steeper in females, the relative risks being significantly ($p<0.05$) lower for 2-9, 10-19 and 20-29 years quit, though not for 30+ years quit.

Results are also available for two Asian studies. In the case-control study in Shanghai (Gao et al., 1988) the pattern was, unusually, of a slower decline in females than males. However, the difference was not significant for any time of quit, the analyses being based on 142 cases in male quitters and 67 cases in female quitters.

The results from the Japanese 6 prefecture prospective study (Hirayama, 1990) have extremely wide confidence intervals for females, so are based on too few deaths in quitters for any useful conclusion to be drawn.

The overall results generally show a clear decline following quitting (apart from the first year or two) but many of the studies, and particularly the earlier ones, are based on too few lung cancer cases in female quitters for any reliable comparison of male and female declines. The pattern, where one is seen, is for the decline to be more rapid in females than males, most clearly evident in two recent large case-control studies (Peto et al., 2000; Simonato et al., 2001).

As an approximate overall test of the difference, I used the data for the category containing 8 years quitting to estimate the female/male ratio of relative risks and its confidence interval. 8 years was chosen as (a) one wished to avoid very short quitting periods with the artefactual increase in risk, (b) a number of studies did not provide data for long-term quitting, and (c) 10 years is not so appropriate as it falls at the beginning of periods in some studies and at the end in others. Meta-analyzing the individual female/male ratios from 13 studies with data available an overall estimate of 0.83 (95% CI 0.72-0.96) was obtained. Thus the overall data suggest a somewhat faster decline in risk in females than in males.

TABLE 3.2 Relative risk of lung cancer by time quit and sex

Study, reference, adjustment factors and source	No. of cases[a]	Time quit (years)	RR by sex[b] Male	Female	Male	Female
					vs never smokers	
USA, CPS I	Not	2-4			13.1	2.85
(Burns et al., 1997)	given	5-9			8.44	1.51
Adjusted for age & duration		10-14			4.61	0.58
Data for whites		15-19			2.89	3.19
RRs as given		20-24			2.04	2.52
CI not available		25-29			1.19	2.61
		30-34			1.84	
		35-39			3.18	
		Never			1.00	1.00
			vs current smokers		**vs never smokers**	
USA, 8 city	988M,	Current	1.00	1.00		
(Wynder & Stellman, 1977)	306F	1-3	1.60 (1.27-2.02)	1.49 (0.99-2.24)	31.2	8.00
Unadjusted		4-6	0.81 (0.61-1.09)	0.78 (0.40-1.50)	15.9	4.19
RR (CI) calculated		7-10	0.72 (0.53-0.97)	0.87 (0.45-1.68)	13.9	4.66
		11-15	0.57 (0.40-0.83)	1.30 (0.64-2.64)	11.2	7.02
		16+	0.21 (0.14-0.32)	0.13 (0.03-0.54)	4.14	0.72
		Never	-	-	1.00	1.00
			vs current smokers		**vs never smokers**	
USA, 6 city	2085M,	Current	1.00	1.00	-	-
(Higgins & Wynder, 1988)	1012F	1-4	1.09 (0.87-1.36)	0.85 (0.61-1.19)	17.4	9.3
Unadjusted		5-9	0.45 (0.35-0.59)	0.44 (0.31-1.64)	7.2	4.8
RR (CI) calculated		10-19	0.38 (0.31-0.47)	0.20 (0.14-0.29)	6.1	2.2
		20-29	0.23 (0.17-0.32)	0.15 (0.09-0.26)	3.7	1.6
		30+	0.12 (0.07-0.19)	0.23 (0.11-0.48)	1.9	2.6
		Never	-	-	1.0	1.0
			vs current smokers		**vs never smokers**	
USA, CPSII	2309M,	Current	1.00	1.00		
(US Surgeon General, 1990)	1003F	<1	1.77 (1.44-2.18)	1.88 (1.34-2.63)	38.8	23.4
Adjusted for age		1-2	1.28 (1.10-1.49)	1.23 (0.93-1.63)	28.1	15.4
RR (CI) calculated		3-5	0.85 (0.72-0.99)	0.74 (0.56-1.00)	18.6	9.26
		6-10	0.52 (0.45-0.61)	0.38 (0.27-0.54)	11.4	4.79
		11-15	0.39 (0.33-0.46)	0.28 (0.19-0.42)	8.61	3.52
		16+	0.17 (0.15-0.20)	0.14 (0.10-0.19)	3.83	1.76
		Never	-	-	1.00	1.00
Canada, 3 city	403M,	Per 10 yr	0.65 (0.50-0.85)	0.52 (0.35-0.78)		
(Risch et al., 1993)	442F	stopped				
Adjusted for age, borough, pack-years						
Data as given						
			vs current smokers		**vs never smokers**	
Cuba, Havana	564M,	Current	1.00	1.00	-	-
(Joly et al., 1983)	218F	1-4	1.23 (0.76-1.97)	1.73 (0.76-4.11)	19.2	12.9
Unadjusted		5+	0.49 (0.36-0.68)	0.57 (0.28-1.19)	7.68	4.30
RR (CI) calculated		Never	-	-	1.00	1.00
			vs current smokers		**vs never smokers**	
UK, Multicentre	1357M,	Current	1.00	1.00	-	-
(Doll & Hill, 1952)	108F	1-9	0.68 (0.48-0.98)	1.06 (0.35-3.21)	6.51	2.21
Unadjusted		10+	0.26 (0.14-0.48)	0.35 (0.03-4.03)	2.49	0.74
RR (CI) calculated		Never	-	-	1.00	1.00

TABLE 3.2 Relative risk of lung cancer by time quit and sex **(cont'd.)**

Study, reference, adjustment factors And source	No. of cases[a]	Time quit (years)	RR by sex[b] Male	Female	Male	Female
			vs current smokers		**vs never smokers**	
NE England	427M,	Current	1.00	1.00	-	-
(Dean et al., 1977)	150F	1-4	0.62 (0.40-0.96)	0.27 (0.10-0.75)	4.67	1.63
Adjusted for age		5-8	0.56 (0.29-1.10)	0.18 (0.03-1.32)	4.16	1.09
RR (CI) calculated		9-19	0.40 (0.23-0.70)		2.99	
		9+		0.12 (0.03-0.49)		0.72
		19+	0.18 (0.09-0.38)		1.31	-
		Never	-	-	1.00	1.00
			vs current smokers		**vs never smokers**	
UK, 10 regions	400M,	Current	1.00	1.00	-	-
(Alderson et al., 1985)	605F	1-4	1.81 (1.24-1.65)	2.08 (1.49-2.91)	18.7	9.67
Adjusted for age		5-10	0.43 (0.26-0.71)	0.65 (0.43-0.99)	4.45	3.02
CI calculated		11+	0.32 (0.20-0.52)	0.28 (0.17-0.46)	3.31	1.30
		Never	-	-	1.00	1.00
			vs current smokers		**vs never smokers**	
SW England	667M,	Current	1.00	1.00	-	-
(Peto et al., 2000)	315F	1-9	0.66 (0.52-0.83)	0.69 (0.48-1.00)	22.0	13.8
Adjusted for age		10-19	0.44 (0.34-0.57)	0.21 (0.12-0.36)	14.7	4.20
CI calculated		20-29	0.20 (0.13-0.30)		6.67	
		20+		0.05 (0.02-0.10)		1.00
		30+	0.10 (0.06-0.17)		3.33	
		Never	-	-	1.00	1.00
			vs current smokers		**vs never smokers**	
European 5 countries	6920M,	Current	1.00	1.00	-	-
(Lubin & Blot, 1984)	884F	1-4	1.10 (1.00-1.22)	1.11 (0.75-1.64)	11.7	4.25
Unadjusted		5-9	0.71 (0.62-0.80)		7.49	
RR (CI) calculated		10-14	0.55 (0.47-0.63)		5.78	
		5+		0.45 (0.31-0.66)		1.73
		15-19	0.36 (0.29-0.44)		3.80	
		20+	0.26 (0.23-0.31)		2.79	
		Never	-	-	1.00	1.00
			vs current smokers		**vs never smokers**	
European 6 countries	6035M,	Current	1.00	1.00	-	-
(Simonato et al., 2001)	1574F	2-9	0.66 (0.59-0.73)	0.41 (0.31-0.55)	16.5	3.73
Adjusted for age,		10-19	0.27 (0.24-0.31)	0.19 (0.14-0.27)	6.75	1.73
education, centre		20-29	0.17 (0.14-0.20)	0.08 (0.05-0.14)	4.25	0.73
RRs vs never		30+	0.08 (0.06-0.10)	0.13 (0.08-0.21)	2.00	1.18
smokers calculated		Never	0.04 (0.03-0.05)	0.11 (0.10-0.14)	1.00	1.00
			vs current smokers		**vs never smokers**	
China, Shanghai	733M,	Current	1.00	1.00	-	-
(Gao et al., 1988)	672F	1-4	1.77 (1.22-2.56)	2.48 (1.15-5.38)	6.9	7.2
Age, education		5-9	0.79 (0.45-1.40)	1.34 (0.51-3.53)	3.1	3.9
RR (CI) calculated		10+	0.28 (0.14-0.57)	0.76 (0.34-1.67)	1.1	2.2
for vs current smokers		Never	-	-	1.0	1.0
			vs current smokers		**vs never smokers**	
Japan, 6 prefectures	1323M,	Current	1.00	1.00	-	-
(Hirayama, 1990)	426F	1-4	0.46 (0.26-0.81)	1.59 (0.47-5.35)	2.03	3.72
Age		5-9	0.36 (0.15-0.84)	1.41 (0.24-8.37)	1.59	3.29
RR (CI) calculated		10+	0.31 (0.14-0.71)	0.41 (0.01-13.37)	1.38	0.97
for v current smokers		Never	-	-	1.00	1.00

[a] Number of cases are for current, former and never smokers combined unless stated

[b] RRs vs current smokers are generally shown on the left with CI; RRs v never smokers are generally shown on the right without CI

3.3 Race

Information on whether the decline in lung cancer risk following quitting varies by race is extremely limited. The only relevant reference is from the New Mexico study (Humble et al., 1985) where the authors describe an analysis of data for ex-smokers based on a logistic model including amount and duration of smoking cessation. The effects of smoking cessation were found to be similar for non-Hispanics ($ß = -0.070$, $p<0.001$) and Hispanics ($ß= 0.057$, $p<0.001$). The interaction term for ethnicity and years since stopping was not significant. The study involved 521 lung cancer cases, though the number in ex-smokers was not given.

Clearly no conclusions can be drawn.

3.4 Age

Only two studies have provided relevant data. This is perhaps because of the confounding between age and period of quit with younger subjects being unable to have quit for a long time.

One of the studies was CPSII where an analysis was presented (Halpern et al., 1993) giving relative risks, compared to current smokers, for never smokers and quitters by age (55, 65 and 75) and by age of quit (30-39..... 60-64). In Table 3.3 the data are re-cast so that they are by age and by years quit. It should be noted that the relative risks presented come from a complex fitted model. The data are given without CI and no formal tests are presented as to whether the decline varies by age, but inspection of the table suggests that (as predicted in section 2.4) the decline is less steep in older people. (These data will be analyzed in more detail in section 4.)

The other study was the US Veterans study. An early publication (Kahn, 1966) gave very detailed data on lung cancer deaths and person years of observation for 160 combinations of age (55-64, 65-74), number smoked (1-9, 10-20, 21-39, 40+ per day), age of starting to smoke (<15, 15-19, 20-24, 25+ years) and years quit (current, 1-4, 5-9, 10-14, 15+ years).

These data were analyzed using GLIM, assuming a Poisson distribution, a log link, and an offset of log (person years). The deviance (chisquared) to be explained, on 159 degrees of freedom (d.f.), was 475.80. Models adding one variable at a time as factors showed a highly significant reduction in deviance due to each of cigs/day (147.3 on 3 d.f., $p<0.001$), age (24.59 on 1 d.f., $p<0.001$), age of starting to smoke (89.1 on 3 d.f., $p<0.001$) and years quit (118.57 on 4 d.f., $p<0.001$). A model including all four factors but no interactions explained the data quite well (residual deviance 120.61 on 148 d.f.). Including interactions of years quit with cigs/day, age and age of starting to smoke decreased the deviance by, respectively, 17.08 on 12 d.f., 6.06 on 4 d.f. and 9.53 on 12 d.f., with the corresponding F statistics (based on the ratio of the explained deviance per d.f. to the residual deviance per d.f.) 1.86 (on 12, 136 d.f.), 1.90 (on 4, 144 d.f.) and 0.97 (on 12, 36 d.f.). The

interaction for number smoked is statistically significant (at $p<0.05$) but the other two are not.

An alternative and probably superior analysis was carried out including linear terms for the four factors, coding the cigs/day groups of 1-9, 10-20, 21-39 and 40+ as 5, 15, 30 and 50 and the years quit groups of 0, 1-4, 5-9, 10-14, 15+ as 0, 2.5, 7.5, 12.5 and 25, with the age of starting to smoke groups treated as equal increments. The model without interactions had a residual deviance of 147.51 on 155 d.f. Adding interactions of cigs/day or of age of starting to smoke had virtually no effect on the deviance (each drops of 0.02 on 1 d.f.) but there was a somewhat larger drop with age (3.04 on 1 d.f., $0.05<p<0.1$). The interaction term was positive suggesting a larger drop for a given year of quit in the younger age group. It should be noted that the data are only available for a limited age range (55-64, 65-74).

It should be noted that while the first analysis (using four levels for number smoked and five for years quit) showed a significant interaction between number smoked and years quit, the second analysis (using a single linear term for each) did not. This implies that there was no difference by number smoked in the overall tendency for risk to decline with years quit, but some unexplained variation in the shape of the declining curve by number smoked. The second analysis seems more appropriate to our objectives.

Table 3.4 summarizes relevant data from this study.

The data from CPS II and the US Veterans Study both suggest that the decline in risk is somewhat more rapid in younger than older quitters.

TABLE 3.3 CPS II fitted relative risks vs current smokers by age, time quit and sex (Halpern et al., 1993)*

Smoking group	Male Age 55	Age 65	Age 75	Female Age 55	Age 65	Age 75
Current smokers	1.00	1.00	1.00	1.00	1.00	1.00
Years quit						
6-10		0.56			0.60	
6-15	0.36			0.40		
11-15		0.29	0.45		0.33	0.49
16-20			0.27			0.31
16-25	0.14	0.18		0.17	0.22	
21-25			0.19			0.23
26-30						
26-35		0.09	0.12		0.11	0.15
31-35						
36-40						
36-45			0.07			0.10
41-45						
Never smoked	0.05	0.03	0.03	0.07	0.05	0.04

*The original data were given by age of quit and have been converted to be by time of quit

TABLE 3.4 Data from the US Veterans' study (Kahn, 1966) by years of quit and by age, age of starting to smoke or cigs/day smoked†

		Years of quit				
Variable/Level	Statistic*	0	1-4	5-9	10-14	15+
Age						
55-64	PY	183955	12266	19038	12715	26911
	D	342	21	20	6	6
	RR	1.00	0.92	0.57	0.25	0.12
65-74	PY	108703	3340	12725	10387	23390
	D	295	7	19	20	13
	RR	1.00	0.77	0.55	0.71	0.20
Age start						
<15	PY	21376	1129	2467	1655	4824
	D	80	6	5	1	4
	RR	1.00	1.42	0.54	0.16	0.22
15-19	PY	128363	6051	12461	9222	22154
	D	332	14	16	12	11
	RR	1.00	0.89	0.50	0.50	0.19
20-24	PY	92238	4738	9808	7312	15966
	D	176	5	15	10	3
	RR	1.00	0.55	0.80	0.72	0.10
25+	PY	50681	3688	7027	4913	7357
	D	49	3	3	3	1
	RR	1.00	0.84	0.44	0.63	0.14
Cigs/day						
1-9	PY	29720	1353	3398	2937	12059
	D	20	0	3	1	0
	RR	1.00	1.00	1.31	0.51	0.00
10-20	PY	135408	7260	14869	10899	23501
	D	233	8	10	7	12
	RR	1.00	0.64	0.39	0.37	0.30
21-39	PY	101533	5077	9743	6697	10813
	D	285	17	18	13	6
	RR	1.00	1.19	0.66	0.69	0.20
40+	PY	25997	1916	3753	2569	3928
	D	99	3	8	5	1
	RR	1.00	0.41	0.56	0.51	0.07

† Over 99.5% of the US Veterans were men, and the data were not presented by sex

* PY = person-years, D = deaths from lung cancer, RR = relative risk vs current smokers

3.5 Duration of smoking

Analysis by duration is complicated by the fact that long term quitters must of necessity have had a short duration of smoking. The results from two studies that provide relevant data are summarised in Table 3.5.

The data from the Roswell Park study (Graham & Levin, 1971) show no clear differences by duration in the RR vs current smokers. These are based on only 63 lung cancer cases in quitters, 26 who had smoked for <41 years and 37 for longer. The authors also present results comparing durations of <31 and 31+ years, but the results for the <31 years group were only based on 7 cases in quitters and are not summarised here.

The data from the French part of the five country multicentre study (Benhamou et al., 1989) are based on rather more lung cancer cases in quitters (281). The authors did not formally test whether the decline in risk following quitting varies by number smoked. Inspection of the results in Table 3.5 suggests (consistently with the data in section 2.4) that longer term quitting results in more of a decline in risk for the shorter duration group (1-25 years).

The results are clearly too limited for reliable conclusions to be drawn, but such as they are seem consistent with the results in section 3.4 suggesting that effects of shorter term smoking are more rapidly reversed than are effects of longer term smoking.

TABLE 3.5 Decline in risk following quitting by duration of smoking

Study reference and adjustment factors	Sex (cases)	Period Quit	RR for duration (yrs) <41	41+	<41	41+
			vs current (0-6 mo)		**vs never**	
Roswell Park, USA	Male	0-6 mo	1.00	1.00	-	-
(Graham & Levin, 1971)	(157)	7-12 mo	0.65 (0.27.1.53)	0.62 (0.13-2.97)	19.2	83.3
No adjustment		13-36 mo	0.23 (0.09-0.59)	0.29 (0.08-1.05)	6.7	38.4
		37-120 mo	0.06 (0.02-0.22)	0.29 (0.06-1.31)	1.9	38.4
		124 mo	0.03 (0.01-0.14)	0.04 (0.01-0.22)	0.9	4.8
		Never	0.03 (0.02-0.06)	0.01 (0.00-0.02)	1.0	1.0
			1-25	26-35	36+	
			vs current			
France 16 hospital	Male	Current	1.00	1.00	1.00	
(Benhamou et al., 1989)	(1057)	1-4 yr	1.00 (0.43-2.35)	1.13 (0.63-2.01)	1.48 (0.88-2.49)	
Adjusted for age		5-9 yr	1.00 (0.44-2.29)	0.50 (0.24-1.03)	0.67 (0.36-1.25)	
and no. smoked		10-19 yr	0.10 (0.05-0.20)	0.63 (0.31-1.26)	0.57 (0.27-1.19)	
		20+ yr	0.20 (0.10-0.40)	0.56 (0.23-1.39)	0.33 (0.09-1.20)	

3.6 Age of starting to smoke

The only relevant data available on age of starting to smoke are from the US Veteran's study (Kahn, 1966). The results, already summarised in section 3.4 and Table 3.4, show no evidence that the decline in risk after quitting varies by age of starting to smoke.

3.7 Number of cigarettes per day

Results from 10 studies are summarized in Table 3.6. The style of the table is similar to Table 3.2 except that there is variation between study in the grouping used for number of cigarettes smoked, shown by the headings above the relative risks changing.

The USA 9 state study (Hammond & Horn, 1958) provided limited data without confidence intervals in a figure. There is a suggestion that the decline is more rapid in smokers of <20 cigs/day than in smokers of 20+ cigs/day but this cannot be assessed reliably.

A report based on 26 year follow-up of the US Veterans Study (Hrubec & McLaughlin, 1997) only presented relative risks compared to never smokers. After long-term cessation it was clear that the lighter smokers had more nearly approached never smokers rates than had the heavier smokers. As discussed already in section 3.4 (and Table 3.4), an analysis based on shorter follow-up (Kahn, 1966) showed no interaction between amount smoked and years quit.

In the US Roswell Park case-control study (Graham & Levin, 1971), no clear difference in the rate of decline following quitting was seen between smokers of <20 and 20+ cigs/day. However, there were only 10 cases in quitters smoking <10 cigs/day.

A report based on the CPS I study (Hammond, 1972) showed a tendency for the decline following quitting to be more rapid in lighter smokers, though the difference was never significant for any given time of quit. A later paper (Burns et al., 1997) presents results by more groupings of cigs/day (and years of quit). However, these are not presented as they are extensive, have no confidence intervals, and are only relative to never smokers. (A more detailed analysis of the CPS I data is in any case given in section 4).

Data from the USA 6 city case-control study (Higgins & Wynder, 1988) are only available vs never smokers. There is a pattern, more evident in males than in females, for relative risks to approach never smokers levels more quickly in lighter smokers. It should be noted that numbers of cases in some cells are quite small, particularly heavy smoking long-term quitters in females.

The data presented from CPS II are from the 1990 US Surgeon General Report (US Surgeon General, 1990). There is a tendency, more evident in females than males, for risk to decline more quickly in lighter smokers. Two other publications also present results (not shown in Table 3.6) by cigs/day and years of quit. An analysis of the data for females (Garfinkel & Stellman, 1988) also suggests a more rapid decline in lighter smokers, while a review paper (Samet, 1991) merely cites the US Surgeon General results.

The West Scotland case-control study (Gillis et al., 1988) presents some relative risks in a figure, the values of which have been estimated as accurately as feasible. No clear difference between the three smoking groups (1-14, 15-24, 25+) in the decline following quitting is evident.

The data from the French 16 hospital study (Benhamou et al., 1989) are adjusted for duration of smoking, which makes the findings difficult to interpret. Here the pattern is for the decline to be greater in heavier smokers.

The data from the European 5 country study (Lubin et al., 1984), of which the French 16 hospital study (Benhamou et al., 1989) forms a part, are also inappropriately adjusted for duration and furthermore are only available without confidence intervals. Again, the pattern is for the decline to be greater in heavier smokers.

The final data set available is from the European 6 country study (Simonato et al., 2001). The data for males are based on a total of 1838 cases in quitters, with only one of the cells (35+ /day quit for 30+ yrs) based on less than 5 cases. As a result, the pattern is reasonably clear and indicates a more rapid decline in heavier smokers. For women, the pattern is much less clear.

Here the data are based on far fewer cases, only 216 in total, the numbers of cases are very small in some cells, particularly where longer quit times (20+ years) are combined with heavier consumption (15+ cigs/day) and the number of cases is only 6 in total for those six cells combined.

Overall, the evidence as to whether the decline in risk of lung cancer varies by amount smoked is rather unclear. The last three studies considered (Benhamou et al., 1989; Lubin et al., 1984; Simonato et al., 2001), all in Europe, all suggest (consistent with the predictions of section 2) that the decline is more rapid in heavier smokers. However two of these studies (Benhamou et al., 1989; Lubin et al., 1984) confused the analysis by adjusting for duration of smoking. Of the other studies, four (Gillis et al., 1988; Graham & Levin, 1971; Higgins & Wynder, 1988; Kahn, 1966) did not report relevant results, reported very limited data indeed, or found no difference in the decline by amount smoked. Of the remaining three, one (US Surgeon General, 1990) reported results consistent with the decline being more rapid in lighter smokers, with the other two (Hammond, 1972; Hammond & Horn, 1958) reporting unclear results suggestive of the same conclusion.

From these data it is unclear whether the decline in risk is more or less rapid in heavier smokers.

TABLE 3.6 Relative risks of lung cancer by time quit and number smoked

Study, reference adjustment factors and source	No. of cases	Sex	Time quit (years)	RR by number smoked per day			
				<20	20+		
				vs current smokers			
USA, 9 state	448M	Male	Current	1.00	1.00		
(Hammond & Horn, 1958)			<1	0.97	1.26		
Adjusted for age			1-10	0.62	0.49		
RR calculated from rates			>10	0.14	0.39		
CI not available							
				1-9	10-20	21-29	40+
				vs never smokers			
US Veterans	1106M	Male	<5	7.6 (2.3-24.9)	12.5 (7.1-21.7)	20.6 (11.9-35.6)	26.9 (13.6-53.4)
(Hrubec & McLaughlin, 1997)	(Never		5-9	3.6 (1.5-9.0)	5.1 (3.3-8.0)	11.5 (7.8-17.0)	13.6 (8.0-22.9)
Adjusted for age	+ quit)		10-19	2.2 (1.3-3.6)	4.3 (3.4-5.4)	6.8 (5.4-8.7)	7.8 (5.6-10.9)
Data as given			20-29	1.7 (1.0-2.8)	3.3 (2.6-4.1)	3.4 (2.6-4.5)	5.9 (4.2-8.3)
			30-39	0.5 (0.2-1.3)	2.1 (1.5-2.9)	2.8 (1.9-4.3)	4.5 (2.6-7.9)
See also Table 3.4			40+	1.1 (0.6-1.9)	1.6 (1.0-2.4)	1.8 (0.9-3.3)	2.3 (0.9-6.2)
			Never	1.0	1.0	1.0	1.0
				1-19	20+	1-19	20+
				vs current smokers		**vs never smokers**	
USA, Roswell Park	483M	Male	Current	1.00	1.00	-	-
(Graham & Levin, 1971)			<1	1.47 (0.46-4.67)	2.41 (1.66-3.50)	8.82	30.00
Adjusted for age			1-4	0.94 (0.38-2.23)	0.86 (0.57-1.31)	5.64	10.73
RR (CI) calculated			5-9	0.20 (0.03-1.42)	0.53 (0.32-0.87)	1.18	6.55
			10+	0.09 (0.01-0.66)	0.09 (0.03-0.23)	0.55	1.09
			Never	-	-	1.00	1.00
				1-19	20+	1-19	20+
				vs current smokers		**vs never smokers**	
USA, CPSI	1095M	Male	Current	1.00	1.00	-	-
(Hammond, 1972)			<1	0.95 (0.39-2.31)	1.04 (0.73-1.48)	7.13	17.7
Adjusted for age			1-4	0.44 (0.20-1.00)	0.60 (0.44-0.81)	3.31	10.1
RR (CI) calculated			5-9	0.17 (0.04-0.67)	0.38 (0.27-0.55)	1.25	6.50
			10+	0.06 (0.01-0.24)	0.11 (0.06-0.19)	0.44	1.81
			Never	-	-	1.00	1.00
				1-10	11-20	26-30	31-40	41+
				vs never smokers				
USA, 6 city	598M,	Male	1-4	5.5	13.3	17.0	18.3	35.6
(Higgins & Wynder, 1988)	320F		5-9	3.8	4.8	12.5	11.4	6.5
Unadjusted	(never		10-19	2.4	4.9	5.9	9.6	8.6
RR as given	+ quit)		20-29	2.3	3.6	3.8	5.1	4.8
			30+	0.8	1.8	3.8	3.1	1.8
			Never	1.0	1.0	1.0	1.0	1.0
				vs never smokers				
		Female	1-4	3.2	9.4	18.1	20.3	7.9
			5-9	1.8	8.3	2.6	5.5	6.2
			10-19	1.6	2.2	1.5	2.2	6.2
			20-29	0.8	2.2	7.9	1.8	7.3
			30+	2.8	3.4	-	-	-
			Never	1.0	1.0	1.0	1.0	1.0

TABLE 3.6 Relative risks of lung cancer by time quit and number smoked **(cont'd.)**

Study, reference adjustment factors and source	No. of cases	Sex	Time quit (years)	RR by number smoked per day			
				1-20	21+	1-20	21+
				vs current smokers		**vs never smokers**	
USA, CPS II	2309M,	Male	Current	1.00	1.00	-	-
(US Surgeon General, 1990)	1003F		<1	1.42 (1.00-2.02)	1.88 (1.45-2.44)	26.7	50.7
Adjusted for age			1-2	1.19 (0.93-1.52)	1.23 (1.01-1.51)	22.4	20.9
RR(CI) vs current			3-5	0.88 (0.70-1.11)	0.78 (0.63-0.97)	16.5	20.9
smokers calculated			6-10	0.46 (0.37-0.58)	0.56 (0.45-0.69)	8.7	15.0
			11-15	0.32 (0.25-0.41)	0.47 (0.38-0.58)	6.0	12.6
			16+	0.16 (0.14-0.20)	0.20 (0.17-0.25)	3.1	5.5
			Never	-	-	1.0	1.0
				1-19	20+	1-19	20+
				vs current smokers			
		Female	Current	1.00	1.00	-	-
			<1	1.08 (0.44-2.64)	2.10 (1.46-3.03)	7.9	34.3
			1-2	1.25 (0.71-2.20)	1.20 (0.87-1.64)	9.1	19.5
			3-5	0.40 (0.19-0.85)	0.90 (0.65-1.23)	2.9	14.6
			6-10	0.14 (0.05-0.37)	0.56 (0.39-1.80)	1.0	9.1
			11-15	0.21 (0.09-0.46)	0.36 (0.23-0.57)	1.5	5.9
			16+	0.19 (0.12-0.30)	0.16 (0.10-0.26)	1.4	2.6
			Never	-	-	1.0	1.0
				1-14	15-24	25+	1-14	15-24	25+
				vs current smokers			**vs never smokers**		
West Scotland	656M	Male	Current	1.0	1.0	1.0	-	-	-
(Gillis et al., 1988)			1-5	1.1	0.9	0.8	4.9	6.6	5.9
Adjusted for age			6-10	0.8	0.6	0.6	3.6	4.1	4.8
and matching			11-15	0.5	0.5	0.6	2.3	3.7	4.4
factors			16-20	0.4	0.3	0.3	1.8	2.3	2.6
Estimated from			21+	0.1	0.2	0.3	0.3	1.3	1.9
Graph			Never	-	-	-	1.0	1.0	1.0
				1-9	10-19	20+			
				vs current smokers					
France, 16 hospitals	1057M	Male	Current	1.00	1.00	1.00			
(Benhamou et al., 1989)	(Current		1-4	3.30 (1.27-8.59)	1.58 (0.82-3.06)	1.12 (0.63-1.97)			
Adjusted for age	+ quit)		5-9	0.50 (0.10-2.45)	0.63 (0.27-1.44)	0.65 (0.35-1.21)			
and duration of			10-19	0.90 (0.29-2.75)	0.42 (0.16-1.06)	0.37 (0.19-0.71)			
smoking			20+	0.50 (0.08-3.20)	0.83 (0.27-2.61)	0.25 (0.06-1.07)			
RR (CI) calculated									
				1-9	10-19	20-29	30+		
				vs current smokers					
European, 5	6631M,	Male	Current	1.00	1.00	1.00	1.00		
countries	551F		1-4	1.47	1.31	1.08	0.86		
(Lubin et al., 1984)			5-9	0.90	0.88	0.75	0.80		
Adjusted for			10+	0.67	0.61	0.51	0.40		
duration of smoking									
As given		Female	Current	1.00	1.00	1.00	1.00		
CI not available			1-4	1.55	1.04	0.95	-		
			5-9	1.16	0.62	0.64	0.24		
			10+	0.66	0.20	0.33	0.42		

TABLE 3.6 Relative risks of lung cancer by time quit and number smoked **(cont'd./2)**

Study, reference adjustment factors and source	No. of cases	Sex	Time quit (years)	RR by number smoked per day				
				<5	5-14	15-24	25-34	35+
				vs current smokers				
European, 6 countries (Simonato et al., 2001) Adjusted for age, education, centre RRs vs never smokers calculated	6035M, 1574F	Male	Current	1.00	1.00	1.00	1.00	1.00
			2-9	0.80(0.46-1.39)	0.65(0.54-0.79)	0.68(0.58-0.80)	0.66(0.49-0.91)	0.45(0.29-0.69)
			10-19	0.27(0.14-0.53)	0.34(0.28-0.41)	0.26(0.21-0.31)	0.19(0.14-0.27)	0.34(0.21-0.53)
			20-29	0.25(0.12-0.56)	0.23(0.18-0.29)	0.16(0.12-0.21)	0.17(0.11-0.28)	0.09(0.05-0.18)
			30+	0.13(0.06-0.27)	0.12(0.09-0.17)	0.08(0.05-0.12)	0.06(0.02-0.15)	0.07(0.02-0.20)
				vs never smokers				
			2-9	6.67	10.8	22.7	33.0	22.5
			10-19	2.25	5.67	8.67	9.50	17.0
			20-29	2.08	3.83	5.33	8.50	4.50
			30+	1.08	2.00	2.67	3.00	3.50
			Never	1.00	1.00	1.00	1.00	1.00
				vs current smokers				
		Female	Current	1.00	1.00	1.00	1.00	1.00
			2-9	0.68(0.30-1.56)	0.56(0.36-0.87)	0.29(0.18-0.48)	0.27(0.09-0.86)	0.70(0.12-3.94)
			10-19	0.21(0.08-0.54)	0.22(0.13-0.37)	0.26(0.14-0.48)	0.44(0.12-1.60)	0.03(0.01-0.19)
			20-29	0.14(0.04-0.51)	0.11(0.05-0.25)	0.10(0.03-0.39)	0.16(0.02-1.08)	0
			30+	0.37(0.16-0.86)	0.29(0.14-0.61)	0.04(0.00-0.29)	0.00	0
				vs never smokers				
			2-9	1.70	3.73	4.14	6.75	35.0
			10-19	0.53	1.47	3.71	11.0	1.5
			20-29	0.35	0.73	1.43	4.00	0.00
			30+	0.93	1.93	0.57	0.00	0.00
			Never	1.00	1.00	1.00	1.00	1.00

[a] Number of cases are for current, former and never smokers combined unless stated
[b] RRs vs current smokers are generally shown with CI; RRs vs never smokers are generally shown without CI

3.8 Pack-years

Table 3.7 summarizes the data by pack-years from the two studies providing data. A limitation is the small number of cases in longer-term quitters in the heavy pack-years group.

In the Iowa study (Ebbert et al., 2003) the authors note that "Lung cancer risk generally decreased with increasing time since smoking cessation (test for trend within each pack-year strata and for both strata combined $p<0.001$)." While this may be true, the trend in the 1-19 pack-years group is hardly smooth with the RR dropping rapidly on quitting and not apparently dropping further with time. The estimated 25-fold (RR = 0.04) reduction in risk following quitting within 5 years seems remarkable, bearing in mind the rest of the literature.

The tendency for the decline to be steeper in the lower pack-year group in the Iowa study is not clearly evident in the Japanese nationwide study (Ando et al., 2003).

The overall evidence must be too limited to make any conclusion, although given the general difficulties of interpreting pack-year data, which make an unjustified implicit assumption that duration and amount smoked contribute equally to lung cancer risk, it is not clear that further data would add much.

TABLE 3.7 Decline in risk following quitting by pack-years†

Study/ Reference	Sex (cases)	Period quit (years)	RR by pack-years			
			1-19	20+	1-19	20+
			vs current smokers		**vs never smokers**	
Iowa	Female	Current	1.00	1.00	-	-
(Ebbert et al., 2003)	(144)	1-5	0.04(0.01-0.28)	0.9(0.7-1.1	0.7	15.3
Adjusted for age,		6-10	0.24(0.10-0.58)	0.5(0.3-0.8)	4.2	9.4
physical activity,		11-20	0.13(0.06-0.27)	0.2(0.1-0.4)	2.1	4.3
education, BMI,		21-30	0.16(0.09-0.31)	0.4(0.2-0.9)	2.8	7.3
waist circum-		31+	0.06(0.02-0.17)	No cases	1.1	No cases
ference,		Never	-	-	1.0	1.0
alcohol and fruit						
			1-39	40+	1-39	40+
			vs current smokers		**vs never smokers**	
Japan nationwide	Male	Current	1.00	1.00	-	-
(Ando et al., 2003)	(340)	1-9	0.61(0.14-1.08)	0.81(0.53-1.10)	2.06	5.16
Adjusted for age*		10+	0.37(0.16-0.57)	0.24(0.09-0.40)	1.23	1.54
(estimated)		Never	-	-	1.00	1.00

† RRs are as given in the Iowa study but are calculated from data given for the Japan national study

* Data for age 60-79

3.9 Type of cigarette smoked

Relevant results are available from three studies and are summarized in Table 3.8.

The data from the Buenos Aires study (Matos et al., 1998) are based on rather few cases, only 38 in quitters, and the declines following quitting are clearly not significantly different for smokers of only black and only blond cigarettes.

Although the data from the French part of the 5 country European study (Benhamou et al., 1989) are based on 281 lung cancer cases in quitters, the numbers in some individual cells are still not large and the relative risk estimates still have wide CI. Even though there appear to be substantial differences (e.g. light vs mixed vs dark for 20+ yrs quitting and manufactured vs mixed vs handrolled for 10-19 yrs quitting) these are never statistically significant.

The overall results from the 5 country European study (Lubin et al., 1984) are presented without CI, but do not suggest any particular difference in either sex between filter, mixed and non-filter cigarette smokers in the decline following quitting.

It should be noted that in the last two studies cited (Benhamou et al., 1989; Lubin et al., 1984) the relative risks are inappropriately adjusted for duration of smoking.

Overall the evidence is not very useful, but such as it is does not suggest that the decline in risk following quitting varies materially by cigarette type.

TABLE 3.8 Decline in risk following quitting by type of cigarette smoked*

Study, reference and adjustment factors	Sex (cases)	Period quit (years)	RR by cigarette type			
			Only black	Only blond	Only black	Only blond
			vs current		**vs never**	
Buenos Aires	Male	Current	1.0	1.0	-	-
(Matos et al., 1998)	(122)	1-5	3.5(0.2-22.7)	0.9(0.3-2.7)	35.0	9.0
Adjusted for age and		6-10	1.1(0.2-5.0)	0.4(0.1-1.4)	11.0	4.0
hospital		11+	0.2(0.04-0.8)	0.2(0.1-0.5)	2.0	2.0
		Never	0.1(0.04-0.2)	0.1(0.05-0.2)	1.0	1.0
			Light	Mixed	Dark	
			vs current			
France 16 hospitals	Male	Current	1.00	1.00	1.00	
(Benhamou et al., 1989)	(1057)	1-4	0.70(0.11-4.37)	2.50(0.68-9.14)	1.32(0.51-3.41)	
Adjusted for age and		5-9	0.70(0.12-4.20)	1.05(0.22-4.94)	0.72(0.27-1.93)	
duration of smoking		10-19	0.50(0.07-3.54)	0.80(0.17-3.76)	0.40(0.14-1.14)	
		20+	0.40(0.08-2.12)	1.25(0.17-9.18)	0.32(0.10-1.01)	
			Filter	Mixed	Non-filter	
			vs current			
		Current	1.00	1.00	1.00	
		1-4	1.40(0.67-2.95)	1.17(0.62-2.04)	1.42(0.97-2.08)	
		5-9	1.30(0.38-4.50)	0.78(0.44-1.39)	0.58(0.37-0.91)	
		10-19	0.60(0.40-0.90)	0.33(0.13-0.89)	0.32(0.20-0.49)	
		20+	0.30(0.12-0.75)	0.44(0.10-2.02)	0.26(0.15-0.47)	
			Manufactured	Mixed	Handrolled	
			vs current			
		Current	1.00	1.00	1.00	
		1-4	1.30(1.00-1.69)	1.50(0.74-3.02)	3.83(1.39-10.56)	
		5-9	0.60(0.40-0.90)	1.42(0.56-3.56)	0.83(0.32-2.14)	
		10-19	0.40(0.28-0.57)	1.17(0.33-4.11)	0.17(0.06-0.47)	
		20+	0.30(0.17-0.52)	0.33(0.08-1.41)	0.08(0.01-0.60)	
			Filter	Mixed	Non-filter	
			vs current			
European 5 country	Male	Current	1.00	1.00	1.00	
multicentre	(6631)	1-4	1.11	0.98	1.12	
(Lubin et al., 1984)		5-9	0.91	0.69	0.64	
Adjusted for duration		10+	0.34	0.53	0.33	
of smoking						
	Female	Current	1.00	1.00	1.00	
	(551)	1-4	0.88	0.73	2.16	
		5-9	0.83	0.61	0.65	
		10-19	0.25	0.27	0.30	

* Data as given except for France 16 hospital study where RRs and CIs were estimated

3.10 Inhalation

The 5 country European multicentre study (Lubin et al., 1984) presented risk by time of quit and two aspects of inhalation. The available data are summarized in Table 3.9. The authors do not present confidence intervals or information from which these can be calculated. They note that "there was some indication of a greater reduction in risk for those who inhaled less often or deeply", but judging from the context this difference was not significant. As noted earlier, the analyses for this study are inappropriately adjusted for duration.

TABLE 3.9 Decline in risk following quitting by frequency and depth of inhalation

Study, reference and adjustment factors	Sex (cases)	Period quit (years)	RR by inhalation frequency: All the time	Most of the time	Part of the time	Rarely or never
			vs current smokers			
European 5 country multicentre	Male	Current	1.00	1.00	1.00	1.00
(Lubin et al., 1984)	(6631)	1-4	1.01	1.81	0.97	1.13
Adjusted for duration of smoking		5-9	0.71	0.66	0.81	0.69
		10+	0.50	0.43	0.60	0.39
	Female	Current	1.00	1.00	1.00	1.00
	(551)	1-4	0.95	1.53	0.94	1.49
		5-9	0.93	0.52	0.19	1.02
		10+	0.35	0.57	0.35	0.29
			RR by inhalation depth: Deeply	Moderately	Slightly or never	
			vs current smokers			
	Male	Current	1.00	1.00	1.00	
	(6631)	1-4	0.94	1.22	1.19	
		5-9	0.67	0.73	0.67	
		10+	0.47	0.43	0.37	
	Female	Current	1.00	1,00	1.00	
	(551)	1-4	0.90	1.01	1.31	
		5-9	1.09	1.68	0.16	
		10+	0.58	0.47	0.32	

Data as given

3.11 Overview of published evidence

The published epidemiological evidence relevant to the question of interest is rather limited. While a number of authors do present data on the decline following quitting subdivided by other factors, they do this more to demonstrate that the decline in risk is evident in a variety of subsets of the population (which is clearly true) than to test whether the slope of the decline varies over subset (which is rarely if ever tested).

For some factors (race, age of starting to smoke, pack years, type of cigarette and inhalation) there is no real indication of any such variation, but the available data are extremely limited (or inappropriately analysed). For age and duration of smoking the evidence is also limited, but tends to suggest that reversibility of effect is more rapid for short-term than for long-term smokers. For sex there is considerably more evidence, and the overall data suggest that the decline in risk following quitting is somewhat faster in females than in males. For number of cigarettes smoked there is also a reasonable amount of evidence, but the data are inconclusive, with some studies suggesting the decline is more rapid in heavier smokers and some that it is more rapid in lighter smokers.

4. Further analyses based on the CPS studies

4.1 Introduction

To study further the relationship between the risk reduction for lung cancer and sex, number of cigarettes smoked per day and age of starting to smoke, we used the data we had from CPS I and CPS II. Table 4.1 shows the numbers of subjects who were current or exsmokers (by years of quit) by study and sex, as well as the corresponding numbers of lung cancer deaths. Overall the analyses involve 627415 current smokers and 424099 ex-smokers, with 4878 lung cancer deaths in current smokers and 2353 deaths in ex-smokers. 1582 of these deaths are in CPS II males, 445 in CPS II females, 310 in CPS I males and only 16 in CPS females. The small numbers of deaths in CPS I females limits severely the accuracy of estimates for this group. Table 4.1 also reveals a deficiency in lung cancer deaths in long-term quitters in CPS I. Here there are only 36 deaths in quitters for more than 10 years, as compared to 861 in CPS II.

Table 4.2 similarly shows the numbers of subjects who were current or exsmokers (by years of quit) by study and age, as well as the corresponding numbers of lung cancer deaths. The total number of subjects for CPS I is very slightly less than that in Table 4.1 due to missing values for age. As would be expected, average time of quit increases with age among exsmokers.

4.2 Stage I analyses

At the first stage of analysis we estimated the relative risks (relative to current smokers) for ex-smokers by years of quit, separately within each level of the four factors of interest (age, sex, number of cigarettes, age started to smoke) and for CPS I, CPS II and the combined studies.

Table 4.3 presents selected results comparing the unadjusted declines by broad age groups. In both studies the decline is faster at age 40-59 than at age 60-79, very clearly so for CPS II, where the decline is slowest at age 80-99. Results for age 20-29 in either study, or for age 80-99 for CPS I are not shown due to small numbers of deaths. Further analyses in this section adjust for age and, where appropriate, other factors.

Table 4.4 presents selected results comparing the declines for males and females. For CPS II the patterns of decline (after the first year) in the two sexes are quite similar when adjustment is made only for age, and are even more similar when adjustment is made also for amount smoked per day and age of starting to smoke. For CPS I the numbers of lung cancers in ex-smoking females makes the confidence intervals wide, but the declines seem grossly similar. The combined data show, in both sexes, that the decline in risk following quitting is about 15% after 1-4 years, 55% after 5-9 years, about 70% after 10-19 years and about 85-90% after 20+ years.

Table 4.5 presents the results of analyses comparing declines by daily amount smoked, after adjustment for age (and, where appropriate, study). Sex was not adjusted for given the similarity of the trends in the two sexes in Table 4.4. While the patterns of decline seem broadly similar for smokers of 1-9, 10-19, 20, 21-39, 40 and 41+ cigs/day, there seems to be some indication that the decline within 10 years of quitting is greater in lighter smokers.

Table 4.6 presents the results of analyses comparing declines by age of starting to smoke, after adjustment for age, number smoked per day (and, where appropriate, study). Numbers starting to smoke at ages 35+ are very low and it is only really possible to compare the declines for those starting to smoke at ages <15, 15-24 and 25-34. It should also be noted that, in CPS I, information on age of starting to smoke is only available for about 20% of ex-smokers, further limiting numbers. For CPS II (and also for the combined data) the declines in risk following quitting for those starting at ages <15, 15-24 and 25-34 seem quite similar, although there is a suggestion that the reduction in risk following quitting for 10+ years is not as rapid in later starting groups.

4.3 Stage II analyses

The stage I analyses provide estimates of the relative risk by years of quit by level of the factor of interest (age: Table 4.3, sex: Table 4.4, number smoked: Table 4.5, and age of starting to smoke: Table 4.6) but do not allow

ready statistical comparison of the declines by level. One could use the estimates of the relative risks and CI for a specific time of quit to compare, for example, the decline in males and females. However interest is more in statistical comparison of the overall pattern of decline.

To investigate this further we used procedures we developed for estimating the increase in lung cancer risk among nonsmokers per cigarette smoked per day by the husband (Fry & Lee, 2000) to estimate the slope of the decline. The estimation assumed midpoints of 0.5, 3.0, 7.5, 15 and 30 for the five categories of years to quit, and the estimates (adjusted for age, study and, where appropriate, amount smoked) derived are shown in Table 4.7. Here β is the estimate decline in log risk per year smoked. Thus, for example, for men who have quit for 10-19 years, the estimated relative risk is given by $\exp(-0.0773*15) = 0.31$. This compares with the observed value of 0.28 (see Table 4.7).

Given these independent estimates by level, we then tested for differences over strata.

Although the data for age 20-39 are too limited for useful inference, it is very clear that there is a tendency for the decline to be more rapid at younger ages. Thus the difference between the estimates of β of -0.0802 for age 40-59 and -0.0537 for age 60-79 is highly significant ($p<0.001$), and the trend continues with an even shallower decline, $\beta = -0.0304$, at age 80-99.

The difference in β between the sexes is 0.0054 (SE 0.0044), so that the slightly less steep decline in females is not significant.

There was no significant overall difference between the six estimates of β by amount smoked. Although the estimated decline was greatest for the 41+/day group, the estimated additional decline per category of amount smoked (coded as 1, 2, 3, 4, 5, 6) was only -0.0013 (SE 0.0013) and not significant. Thus there is no significant tendency for the magnitude of the decline to increase with amount smoked.

For age of starting to smoke, estimates were made for <15, 15-24, 25-34 and 35+ years. Thus the sparse data for 35-44 and 45+ years were combined, though even then the β estimate had a relatively high standard error. Here there was some tendency for the decline to be less steep in later starters, with an estimated additional 0.0097 (SE 0.0037, $p<0.01$) per category of age of start.

TABLE 4.1 Numbers of subjects (N) and deaths (d) from lung cancer by study, sex and length of cessation of smoking (CPS I and II)

				Ex-smoker by years of quit					
Study	Sex	Statistic	Current smokers	<1	1-4	5-9	10-19	20+	Total
CPS I	Male	N	211478	7665	17796	18596	17798	12054	73909
		d	1555	83	114	79	29	5	310
	Female	N	161910	3892	8037	6640	7858	3791	30218
		d	176	7	4	3	1	1	16
	Total	N	373388	11557	25833	25236	25656	15845	104127
		d	1731	90	118	82	30	6	326
CPS II	Male	N	119429	4950	24251	26480	64968	64226	184875
		d	2056	127	457	293	464	241	1582
	Female	N	134598	4384	19825	20815	46064	44009	135097
		d	1091	55	152	82	104	52	445
	Total	N	254027	9334	44076	47295	111032	108235	319972
		d	3147	182	609	375	568	293	2027
CPS I+ II	Male	N	330907	12615	42047	45076	82766	76280	258784
		d	3611	210	571	372	493	246	1892
	Female	N	296508	8276	27862	27455	53922	47800	165315
		d	1267	62	156	85	105	53	461
	Total	N	627415	20891	69909	72531	136688	124080	424099
		D	4878	272	727	457	598	299	2353

TABLE 4.2 Numbers of subjects (N) and deaths (d) from lung cancer by study, age and length of cessation of smoking (CPS I and II)

				Ex-smoker by years of quit					
Study	Age	Statistic	Current smokers	<1	1-4	5-9	10-19	20+	Total
CPS I	20-39	N	40149	1198	2106	1872	1683	98	6957
		d	23	1	0	0	0	0	1
	40-59	N	275592	8115	17396	17179	17360	9766	69816
		d	981	49	50	27	7	1	134
	60-79	N	56689	2210	6204	6068	6450	5747	26679
		d	722	40	66	52	22	4	184
	80+	N	951	34	126	117	162	234	673
		d	5	0	2	3	1	1	7
	Total	N	373381	11557	25832	25236	25655	15845	104125
		d	1731	90	118	82	30	6	326
CPS II	20-39	N	15570	687	2701	2997	4035	183	10603
		d	6	1	1	0	0	0	2
	40-59	N	163188	5849	26089	27138	66707	52695	178478
		d	1230	77	186	81	112	34	490
	60-79	N	73863	2762	15036	16831	39318	52682	126629
		d	1860	103	411	288	422	234	1458
	80+	N	1406	36	250	329	972	2675	4262
		d	51	1	11	6	34	25	77
	Total	N	254027	9334	44076	47295	111032	108235	319972
		d	3147	182	609	375	568	293	2027
CPS I+ II	20-39	N	55719	1885	4807	48690	5718	281	17560
		d	29	2	1	0	0	0	3
	40-59	N	438780	13964	43485	44317	84067	62461	248294
		d	2211	126	236	108	119	35	624
	60-79	N	130552	4972	21240	22899	45768	58429	153308
		d	2582	143	477	340	444	238	1642
	80+	N	2357	70	376	446	1134	2909	4935
		d	56	1	13	9	35	26	84
	Total	N	627408	20891	69908	72531	136687	124080	424097
		d	4878	272	727	457	598	299	2353

TABLE 4.3 RRs and CIs by time of quit, stratified by age (CPS I and II)

Study	Age	Current smokers	Ex-smoker by years of quit				
			<1	1-4	5-9	10-15	20+
CPS I	40-59	1.00	1.71 (1.28-2.27)	0.81 (0.61-1.07)	0.44 (0.30-0.64)	0.11 (0.05-0.24)	0.03 (0.004-0.20)
	60-79	1.00	1.45 (1.06-2.00)	0.85 (0.66-1.10)	0.67 (0.51-0.89)	0.27 (0.18-0.41)	0.05 (0.02-0.14)
CPS II	40-59	1.00	1.76 (1.40-2.22)	0.95 (0.81-1.11)	0.39 (0.31-0.49)	0.22 (0.18-0.27)	0.08 (0.06-0.12)
	60-79	1.00	1.52 (1.24-1.85)	1.11 (0.99-1.23)	0.68 (0.60-0.77)	0.42 (0.38-0.47)	0.17 (0.15-0.20)
	80-99	1.00	0.82 (0.11-5.93)	1.29 (0.67-2.47)	0.52 (0.22-1.21)	0.96 (0.63-1.49)	0.25 (0.15-0.40)
CPS I+II	40-59	1.00	1.80 (1.51-2.16)	1.08 (0.94-1.23)	0.48 (0.40-0.58)	0.28 (0.23-0.33)	0.11 (0.08-0.15)
	60-79	1.00	1.49 (1.26-1.76)	1.15 (1.04-1.27)	0.75 (0.67-0.84)	0.48 (0.43-0.53)	0.20 (0.17-0.23)
	80-99	1.00	0.63 (0.09-4.58)	1.50 (0.82-2.75)	0.86 (0.42-1.74)	1.27 (0.83-1.93)	0.35 (0.22-0.55)

TABLE 4.4 RRs and CIs by time of quit, stratified by sex with various adjustment factors (CPS I and II)

Study	Adjustment factors	Sex	Current smokers	Ex-smoker by years of quit				
				<1	1-4	5-9	10-19	20+
CPS II	Age	Male	1.00	1.51 (1.26-1.80)	0.99 (0.90-1.10)	0.54 (0.48-0.62)	0.33 (0.30-0.36)	0.13 (0.11-0.15)
		Female	1.00	1.64 (1.25-2.15)	0.92 (0.77-1.09)	0.46 (0.37-0.57)	0.27 (0.22-0.33)	0.11 (0.08-0.14)
	Age,NCigs	Male	1.00	1.34 (1.12-1.61)	0.89 (0.80-0.99)	0.49 (0.43-0.55)	0.29 (0.26-0.33)	0.13 (0.11-0.15)
		Female	1.00	1.55 (1.18-2.04)	0.89 (0.75-1.05)	0.46 (0.37-0.58)	0.29 (0.24-0.36)	0.15 (0.11-0.20)
	Age,NCigs, age start	Male	1.00	1.36 (1.13-1.63)	0.91 (0.82-1.01)	0.50 (0.44-0.57)	0.29 (0.26-0.32)	0.13 (0.11-0.15)
		Female	1.00	1.59 (1.21-2.09)	0.88 (0.74-1.04)	0.44 (0.35-0.55)	0.28 (0.23-0.34)	0.13 (0.09-0.17)
CPS I	Age,NCigs	Male	1.00	1.30 (1.04-1.62)	0.67 (0.56-0.82)	0.42 (0.34-0.53)	0.16 (0.11-0.23)	0.03 (0.01-0.08)
		Female	1.00	1.68 (0.79-3.58)	0.47 (0.17-1.27)	0.43 (0.14-1.34)	0.13 (0.02-0.95)	0.25 (0.04-1.84)
Combined	Age,NCigs, study	Male	1.00	1.32 (1.15-1.52)	0.83 (0.76-0.91)	0.47 (0.42-0.52)	0.28 (0.25-0.31)	0.12 (0.10-0.14)
		Female	1.00	1.56 (1.21-2.02)	0.87 (0.73-1.02)	0.46 (0.37-0.57)	0.29 (0.23-0.35)	0.15 (0.11-0.20)

TABLE 4.5 RRs and CIs by time of quit, stratified by number of cigarettes smoked, adjusted for age(CPS I and II)

Study	No. of cigs/day	Current smokers	Ex-smoker by years of quit <1	1-4	5-9	10-19	20+
CPS II	1-9	1.00	1.95 (1.00-3.81)	0.47 (0.27-0.82)	0.34 (0.19-0.61)	0.32 (0.22-0.46)	0.16 (0.11-0.22)
	10-19	1.00	0.93 (0.51-1.69)	0.97 (0.73-1.28)	0.35 (0.24-0.53)	0.29 (0.22-0.38)	0.14 (0.10-0.19)
	20	1.00	1.26 (0.94-1.69)	0.97 (0.83-1.13)	0.49 (0.40-0.60)	0.33 (0.28-0.39)	0.14 (0.11-0.18)
	21-39	1.00	1.58 (1.14-2.18)	0.93 (0.76-1.14)	0.59 (0.46-0.75)	0.31 (0.25-0.39)	0.18 (0.13-0.25)
	40	1.00	1.71 (1.25-2.36)	1.04 (0.86-1.26)	0.62 (0.49-0.77)	0.34 (0.27-0.42)	0.15 (0.10-0.21)
	41+	1.00	1.46 (0.96-2.22)	0.72 (0.54-0.96)	0.44 (0.31-0.61)	0.27 (0.20-0.36)	0.11 (0.06-0.18)
CPS I	1-9	1.00	0.91 (0.29-2.86)	0.59 (0.24-1.44)	0.31 (0.08-1.25)	0.11 (0.02-0.82)	0.12 (0.02-0.85)
	10-19	1.00	0.80 (0.38-1.69)	0.62 (0.36-1.08)	0.53 (0.29-0.97)	0.22 (0.09-0.52)	0.11 (0.03-0.43)
	20	1.00	1.86 (1.36-2.55)	0.82 (0.61-1.10)	0.37 (0.24-0.57)	0.17 (0.09-0.32)	0.02 (0.00-0.17)
	21-39	1.00	0.95 (0.55-1.65)	0.63 (0.41-0.99)	0.53 (0.34-0.84)	0.22 (0.11-0.48)	0.00
	40	1.00	1.30 (0.74-2.28)	0.63 (0.38-1.06)	0.52 (0.30-0.88)	0.16 (0.06-0.42)	0.07 (0.01-0.48)
	41+	1.00	2.43 (1.20-4.91)	1.05 (0.53-2.08)	0.87 (0.43-1.73)	0.18 (0.04-0.81)	0.00
Combined (stratified for study)	1-9	1.00	1.52 (0.85-2.70)	0.49 (0.31-0.80)	0.34 (0.20-0.58)	0.30 (0.21-0.43)	0.16 (0.11-0.22)
	10-19	1.00	0.87 (0.55-1.39)	0.87 (0.68-1.12)	0.40 (0.28-0.55)	0.28 (0.21-0.37)	0.14 (0.10-0.19)
	20	1.00	1.49 (1.20-1.84)	0.93 (0.81-1.07)	0.47 (0.39-0.56)	0.32 (0.27-0.37)	0.13 (0.11-0.17)
	21-39	1.00	1.36 (1.03-1.70)	0.86 (0.72-1.04)	0.57 (0.46-0.71)	0.30 (0.24-0.38)	0.17 (0.12-0.23)
	40	1.00	1.59 (1.21-2.10)	0.97 0.81-1.16)	0.60 (0.49-0.74)	0.32 (0.26-0.40)	0.14 (0.10-0.20)
	41+	1.00	1.64 (1.15-2.35)	0.76 (0.58-0.99)	0.49 (0.36-0.65)	0.26 (0.20-0.35)	0.10 (0.06-0.18)

TABLE 4.6 RRs and CIs by time of quit, stratified by age of starting to smoke, adjusted for age and number smoked (CPS I and II)

Study	Age of start	Current smokers	Ex-smoker by years of quit				
			<1	1-4	5-9	10-19	20+
CPS II	<15	1.00	2.26 (1.67-3.05)	0.97 (0.78-1.21)	0.59 (0.46-0.77)	0.26 (0.20-0.34)	0.14 (0.09-0.20)
	15-24	1.00	1.30 (1.08-1.56)	0.91 (0.82-1.01)	0.48 (0.43-0.55)	0.32 (0.28-0.35)	0.13 (0.12-0.16)
	25-34	1.00	1.22 (0.57-2.59)	1.04 (0.72-1.52)	0.56 (0.35-0.89)	0.35 (0.23-0.51)	0.20 (0.13-0.33)
	35-44	1.00	1.52 (0.20-11.69)	1.16 (0.38-3.53)	0.48 (0.11-2.08)	0.21 (0.05-0.90)	0.50 (0.19-1.34)
	45+	1.00	2.80 (0.31-25.71)	1.03 (0.13-8.48)	0.00	1.34 (0.25-7.31)	0.45 (0.04-5.02)
CPS I	<15	1.00	0.78 (0.19-3.16)	0.54 (0.17-1.69)	0.85 (0.31-2.35)	0.00	0.00
	15-24	1.00	2.13 (1.23-3.68)	0.63 (0.31-1.26)	1.03 (0.59-1.80)	0.56 (0.25-1.25)	0.00
	25-34	1.00	0.00	2.25 (0.31-16.36)	0.00	0.00	0.00
	35-44	1.00	0.00	0.00	0.00	0.00	0.00
	45+	1.00	0.00	0.00	0.00	0.00	0.00
Combined (stratified for study)	<15	1.00	2.09 (1.56-2.80)	0.95 (0.77-1.17)	0.60 (0.47-0.78)	0.26 (0.20-0.34)	0.14 (0.09-0.20)
	15-24	1.00	1.36 (1.14-1.61)	0.90 (0.81-1.00)	0.50 (0.44-0.56)	0.32 (0.29-0.35)	0.13 (0.12-0.15)
	25-34	1.00	1.15 (0.54-2.44)	1.06 (0.73-1.54)	0.55 (0.35-0.87)	0.34 (0.23-0.51)	0.20 (0.13-0.33)
	35-44	1.00	1.37 (0.18-10.36)	1.14 (0.38-3.44)	0.47 (0.11-2.03)	0.21 (0.05-0.89)	0.49 (0.18-1.31)
	45+	1.00	2.79 (0.30-25.53)	0.97 (0.12-7.83)	0.00	1.32 (0.24-7.13)	0.45 (0.04-4.99)

TABLE 4.7 Log decline in risk per year stopped (SE) by strata (CPS I and II)

Stratum	Adjustment factors	β	SE β
Age 20-39	None	-0.2396	0.3339
40-59		-0.0802	0.0041
60-79		-0.0537	0.0020
80-99		-0.0304	0.0075
Males	Age, Ncigs, study	-0.0773	0.0020
Females		-0.0719	0.0039
1-9/day	Age, study	-0.0670	0.0055
10-19/day		-0.0727	0.0047
20/day		-0.0717	0.0031
21-39/day		-0.0672	0.0044
40/day		-0.0698	0.0045
41+/day		-0.0854	0.0068
Start <15	Age, Ncigs, study	-0.0707	0.0057
15-24		-0.0712	0.0020
25-34		-0.0582	0.0069
35+		-0.0276	0.0141

5. Discussion and conclusions

In the previous three sections data have been summarized relating the extent of the decline in lung cancer risk following quitting to various factors, some not smoking related (age, sex, race) and some smoking related (number smoked, duration, age of starting, pack-years, type of cigarette smoked and inhalation). The data come from three sources – theoretical predictions based on the multistage model (section 2), a review of available epidemiological evidence (section 3) and our own calculations based on CPS I and II (section 4).

Table 5.1 briefly summarizes the results of these investigations. Of the nine factors considered, there was either no indication of any effect, or the data were too limited to come to a conclusion, for four (race, pack-years, type of cigarette smoked and inhalation). For the other five factors we note the following:

Age The data are consistent in suggesting that, for a given time of quit, the decline in risk following quitting is more rapid in younger age groups. Although the number of published studies providing data is quite limited, our analysis based on CPS I and II shows this effect quite clearly.

Sex Sex is the factor with most available data and the published evidence suggests a somewhat faster decline in risk in females than in males. However our analyses of CPS I and II did not find this difference, after adjusting for age and other factors.

Number smoked The multistage predictions clearly show that the decline in risk is more rapid for heavier smokers. Although epidemiological data are available from a number of studies, their findings are rather unclear (see section 3.7), and we could detect no significant difference in the rate of decline by amount smoked in our analyses of CPS I and II.

Duration of smoking The limited epidemiological evidence is consistent with the predictions of the multistage model that the decline is more rapid in

those who have a shorter duration of smoking. This result is clearly not independent of the results for age, given above.

Age of starting to smoke Since, for a given age and time of quit, later starting is implied by a shorter duration of smoking, it is not surprising that the multistage model also predicts a more rapid decline in those who have a later age of starting to smoke. This observation is supported by limited published evidence, but not by our analyses of CPS I and II where the decline was somewhat greater in early starters. It is unclear why this should be so.

The main overall impression from the work carried out is that estimates of the extent of the declines in lung cancer risk following quitting derived from the whole population(s) studied are likely to apply with a reasonable degree of accuracy to subsets of the population. The exception to this is subsets defined by age, where the evidence seems quite clear that the decline is more rapid in younger people.

TABLE 5.1 Summary of evidence comparing the decline in risk following quitting by levels of various factors

	Level associated with a steeper decline in risk		
Factor of interest	Multistage model	Epidemiological evidence	CPS I/II
Age	Younger ages	Younger ages	Younger ages
Sex	-	Females	No difference
Race	-	Data too limited	-
Duration of smoking	Short duration	Short duration (but data limited)	-
Age of starting to smoke	Late starting	No difference (data limited)	Early starting
Cigarettes per day	Heavy smokers	Data conflicting	Heavy smokers (not significant)
Pack-years	-	Data too limited	-
Type of cigarette smoked	-	No difference (data limited)	-
Inhalation	-	No obvious difference (data poor)	-

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