APPENDIX 7/2

Flue cured and blended cigarettes

Attempting to derive estimates for COPD

Author : P N Lee
Date : 16th March 2006

1. Background

In a note dated 11.10.2005 (t:\Barbara\FlueBlended_COPD.doc), Barbara Forey described her attempts to extract relevant information from the database Alison Thornton had prepared for PM. This was limited by the fact that it considered only current, and not former, smokers.

Later, in a note dated 16.12.05 (t:\Pauline\Reports\fluecured2.doc), I described an attempt to obtain more studies.

This study describes the results of an exercise aimed at deriving estimates of the current smoker and exsmoker relative risks for the eight countries in the flue cured/blended project.

2. Methods

Attention was limited to age-adjusted estimates for COPD mortality based on prospective studies, as previous work had shown that less restrictive conditions (e.g. including estimates for all respiratory disease or those based on cross-sectional or case-control studies had led to extremely variable estimates). All the relative risk estimates and 95% confidence intervals were derived from the source papers, in some cases leading to somewhat different estimates from those given by Alison earlier.

3. The studies

Table 1 lists the studies providing relevant data and relevant features of them. It can be seen that of the 12 studies, 3 are from the UK, 8 from the USA and 1 from Denmark with no data from Australia, Canada, Austria, Germany or the Netherlands. This limits the ability usefully to compare flue cured and blended cigarettes.

None of the studies involved any deaths in the last 15 years. Based on an approximate mid period of the follow-up period, one could classify the studies into two groups – more recent (midpoints 1981-1986; WALD, FRIEDMAN, SPEIZER, STERLING, CPS II, LANGE) and less recent (midpoints 1966-1975; DOLL, PETO, MARCUS, VETERANS, CPS I, TOCKMAN).

The disease was always referred to by the authors as chronic obstructive pulmonary disease (COPD) or chronic obstructive lung disease (COLD) which are equivalent. However, the actual ICD codes used in the definition were not always the same, and in two studies (MARCUS, LANGE), deaths with COPD as the contributory cause of death were also included as well as those where was classified as the underlying cause of death.

The definition of smoking varied somewhat. In most studies, it relates to cigarette smoking regardless of other product, whereas in some studies it relates to cigarettes only. One study did not provide a definition of smoking.

Five of the studies provided results only for men whilst the other seven provided results for both sexes.

4. The relative risks

In many of the studies the relative risks and confidence limits had to be estimated from data provided in the source papers. All of the relative risks presented in Table 2 are age-adjusted apart from that for PETO, which is also adjusted for region, and the current smoking estimate for VETERANS which is unadjusted. In that study, crude and age-adjusted estimates were quite similar for ex smokers (crude 4.65, 3.96-5.45; age-adjusted 4.10, 3.60-4.80).

The relative risks shown in Table 2 are given separately by smoking (current, ex) sex and country. Within country, they are sorted on approximate midpoint of the period of follow-up, with the earliest study shown first.

A number of immediate observations can be made from inspection of the data:

1) The association of COPD with both current and ex smoking is very clear. Of the 37 estimates, 13 are 10.0 or higher and all but 6 are statistically significant at $p<0.05$. All of those that are not significant have wide confidence limits.
2) The estimates are higher for current than for ex smokers. For males, 10 of the 11 studies with estimates for both show higher relative risks in current smokers, while for females all 7 do.
3) The estimates show some tendency for the relative risk to be higher in men than in women. This is consistently seen in the earlier US studies, but is not evident in CPS II or STERLING, while in the single Danish study relative risks are higher for women (albeit with wide confidence intervals).
4) The two studies that did not restrict attention to COPD as the underlying cause of death (LANGE, MARCUS) appeared to have lower than expected relative risks.

5. Meta-analyses

5.1 Current smoking

Table 3 shows the results of meta-analyses for current smoking based on all the relevant estimates in Table 2. The table shows the fixed and random effects estimates for the total data and for various subsets. The first heterogeneity chisquared shown relates to within study variation, with its degrees of freedom one less than N, the number of relative risks on which the estimate is based. The second heterogeneity chisquared relates to variation between subsets. Here the corresponding degrees of freedom are 1 for variation by sex or by recency of study and 2 for variation by country.

There is highly significant variation between the estimates. This is predominantly due to the low relative risks for females in the less recent studies. For the more recent studies, there is no significant heterogeneity with the overall estimate 11.59 (10.05-13.37). However, virtually all the weight for the more recent studies comes from the US studies, the estimates from the WALD and LANGE studies having wide confidence intervals. Within the more recent US studies, there is no significant variation by sex.

Table 4 repeats the analysis restricting attention to the studies with results for COPD as the underlying cause of death. This markedly reduced the variability of the estimates for males based on less recent studies in the USA, but did not affect the conclusion that estimates were relatively low in females in less recent studies.

5.2 Ex smoking

Table 5 shows the results of meta-analyses for ex smoking based on all the relevant estimates in Table 2. Again, there is highly significant variation, with a major contributor being the difference between the male estimates for the two large US less recent studies (CPS I 7.16, 5.79-8.87; VETERANS 4.10, 3.60-4.80). As with current smoking, the more recent studies show little evidence of variation, with a combined estimate of 7.05 (5.97-8.32) and little variation by sex. With the WALD study providing no

useful results for ex smokers, virtually the whole of the more recent data for ex smoking comes from the US.

Omitting the MARCUS and LANGE studies (results not shown in detail) only reduced the total heterogeneity slightly, from 52.00 on 17 d.f. to 44.18 on 14 d.f. It had little effect on the combined estimate for the more recent studies, changing it from 7.05 (5.97-8.32) to 7.38 (6.74-8.09).

6. Conclusion

For the purposes of the flue cured/blended analyses, which will mainly consider more recent data, it seems reasonable to use the relative risk estimates of 11.59 for current smoking and 7.05 for ex smoking, applying them to both males and females. Data from CPS II [1] do not suggest any marked variation in relative risk by age and these estimates can be taken to apply generally. The data come mainly from the US; with none at all for five of the countries, and do not provide very useful light on the flue cured/blended difference. However, they do not suggest any marked difference between the UK (flue cured) and the US or Denmark (blended).

Calculations relevant to deriving the relative risks are available in:

T:\PNLEE\COPDCALCS.XLS

while the meta-analyses themselves are run from:

T:\PNLEE\METACOPD.XLS

TABLE 1 – Details of studies with relevant estimates

Short name	Title	Country	Follow-up period	Definition of COPD	Definition of smoking	Sexes with results	References
DOLL	British Doctors	UK	1951 to 1991	COLD undefined	Cigarettes	M	[2]
PETO	Five male samples	UK	1954-61 to 1982	ICD 8; 490-492, 519	Cigarettes	M	[3]
WALD	BUPA	UK	1975-82 to 1993	ICD 9; 416, 491, 492, 496, 519	Cigarettes only[a]	M	[4]
FRIEDMAN	Kaiser Permanente	USA	1979-86 to 1987	ICD 9; COPD	Cigarettes only	M, F	[5]
MARCUS	Honolulu Heart	USA	1965 to 1984	COPD[b]	Cigarettes	M	[6]
VETERANS	US Veterans	USA	1954 to 1979	ICD 7; COPD	Cigarettes	M	[7,8]
SPEIZER	Six cities	USA	1974-77 to 1986	ICD 8; 490-496	Cigarettes	M, F	[9]
STERLING	NMFS/NHIS	USA	1986[d]	ICD9; 490-492, 496	Undefined	M, F	[10]
CPS I	CPS I	USA	1959 to 1972	ICD 7; 500-502, 527.1	Cigarettes	M, F	[11]
CPS II	CPS II	USA	1982 to 1988[e]	ICD 9; 490-492, 496	Cigarettes	M, F	[12,13][f]
TOCKMAN	Washington County	USA	1963 to 1975	ICD 7; 502, 527.1[g]	Cigarettes	M, F	[14]
LANGE	Copenhagen City Heart	Denmark	1976 to 1989	ICD 8; 490-492[h]	Cigarettes only	M, F	[15]

[a] Data for ex smokers are only for those who stopped smoking over 20 years before entry and involve only one death in ex smokers, so have been omitted.
[b] Includes deaths from unspecified bronchitis, chronic bronchitis, emphysema, asthma, bronchiectasis and chronic obstructive lung/airway disease classified as underlying or contributory.
[c] Data for current smokers come from reference [8]. Data for exsmokers come from reference [7].
[d] Deaths occurring in a representative sample of US adults in 1986 were linked to corresponding populations in a different representative sample of US adults in 1987.
[e] Data for ex smokers are only for four year follow-up.
[f] Data for current smokers come from reference [12] and data for ex smokers from reference [13].
[g] Plus deaths with underlying cause specified as COPD.
[h] Includes deaths classified as underlying or contributory.

TABLE 2 - Age adjusted relative risks (95% confidence intervals) by smoking status, sex and country

		Current vs never smokers		Ex vs never smokers	
Country	Study	Male	Female	Male	Female
UK	PETO	22.62 (1.41-363.2)	-	12.58 (0.75-211.6)	-
	DOLL	12.70 (7.13-22.62)	-	5.70 (3.18-10.23)	-
	WALD	29.50 (3.96-220.0)	-	-	-
USA	CPS I	11.87 (9.82-14.36)	5.48 (4.36-6.89)	7.16 (5.79-8.87)	3.41 (2.15-5.40)
	VETERANS	9.00 (7.78-10.41)	-	4.10 (3.60-4.80)	-
	TOCKMAN	7.18 (3.13-14.65)	3.45 (1.66-7.17)	4.99 (2.08-11.96)	0.83 (0.11-6.34)
	MARCUS	2.31 (1.28-4.16)	-	2.34 (1.21-4.53)	-
	SPEIZER	12.18 (0.73-204.62)	4.28 (1.50-12.20)	11.09 (0.66-186.37)	3.80 (1.17-12.35)
	FRIEDMAN	10.00 (3.30-30.90)	9.00 (3.00-26.60)	4.66 (1.50-14.45)	3.29 (0.92-11.83)
	CPS II	11.70 (9.10-15.00)	12.80 (10.40-15.90)	8.75 (6.48-11.80)	7.04 (5.33-9.30)
	STERLING	7.32 (4.13-12.97)	12.63 (7.64-20.88)	6.77 (4.24-10.82)	6.14 (3.82-9.85)
DENMARK	LANGE	6.70 (2.14-21.00)	15.61 (3.62-67.34)	3.00 (0.90-10.00)	11.00 (2.50-53.0)

TABLE 3 - Meta-analyses of current smoker/never smoker relative risk

Estimates	N	Fixed effects Relative risk (95% CI)	Random effects Relative risk (95% CI)	Heterogeneity chisquared, p Within	Between
All	19	9.35 (8.62-10.14)	8.41 (6.74-10.51)	75.71***	
Males	12	9.76 (8.84-10.76)	8.83 (6.84-11.40)	34.51***	
Females	7	8.55 (7.42-9.86)	7.78 (4.85-12.50)	38.97***	2.23^{NS}
UK	3	13.81 (8.02-23.80)	13.81 (8.02-23.80)	0.75^{NS}	
USA	14	9.27 (8.54-10.06)	7.91 (6.20-10.09)	72.14***	
Denmark	2	9.23 (3.75-22.70)	9.23 (3.75-22.70)	0.80^{NS}	2.02^{NS}
Less recent	8	8.44 (7.64-9.31)	6.87 (4.82-9.78)	53.68***	
More recent	11	11.59 (10.05-13.37)	11.59 (10.05-13.37)	9.06^{NS}	12.97***
USA - males	8	9.67 (8.75-10.69)	8.26 (6.17-11.05)	31.75***	
- females	6	8.50 (7.37-9.81)	7.37 (4.49-12.12)	38.31***	2.08^{NS}
USA - less recent	6	8.32 (7.53-9.20)	6.13 (4.15-9.05)	51.20***	
- more recent	8	11.60 (10.04-13.41)	11.60 (10.04-13.41)	7.18^{NS}	13.76***
USA - less recent - males	4	9.40 (8.40-10.52)	7.11 (4.53-11.15)	28.33***	
- females	2	5.26 (4.23-6.54)	5.26 (4.23-6.54)	1.40^{NS}	21.47***
USA - more recent - males	4	10.83 (8.66-13.54)	10.83 (8.66-13.54)	2.19^{NS}	
- females	4	12.20 (10.09-14.74)	11.30 (8.17-15.63)	4.35^{NS}	0.64^{NS}

*** $p<0.001$ ** $p<0.01$ * $p<0.05$ (*) $p<0.1$ NS $p\geq 0.1$

TABLE 4 - Meta-analyses of current smoker/never smoker relative risk omitting studies which included deaths with COPD as contributory cause

Estimates	N	Fixed effects Relative risk (95% CI)	Random effects Relative risk (95% CI)	Heterogeneity chisquared, p Within	Between
All	16	9.61 (8.85-10.43)	9.21 (7.49-11.31)	52.87***	
Males	10	10.20 (9.23-11.27)	10.35 (9.11-11.75)	10.38^{NS}	
Females	6	8.50 (7.37-9.81)	7.37 (4.49-12.12)	38.31***	4.18^{NS}
UK	3	13.81 (8.02-23.80)	13.81 (8.02-23.80)	0.75^{NS}	
USA	13	9.53 (8.77-10.35)	8.82 (7.09-10.98)	50.37***	1.75^{N}
Denmark	0				
Less recent	7	8.75 (7.92-9.67)	8.07 (5.87-11.10)	34.59***	
More recent	9	11.66 (10.10-13.47)	11.66 (10.09-13.47)	8.01^{NS}	10.27**
USA - males	7	10.09 (9.11-11.17)	10.18 (8.77-11.81)	8.40	
- females	6	8.50 (7.37-9.81)	7.37 (4.49-12.12)	38.31***	$3.66^{(*)}$
USA - less recent	5	8.64 (7.81-9.57)	7.39 (5.19-10.52)	32.49***	
- more recent	8	11.60 (10.04-13.41)	11.60 (10.04-13.41)	7.18^{NS}	10.70***
USA - less recent - males	3	9.91 (8.84-11.11)	9.98 (7.82-12.74)	$5.73^{(*)}$	
- females	2	5.26 (4.23-6.54)	4.98 (3.45-7.19)	1.40	25.36***
USA - more recent - males	4	10.83 (8.66-13.54)	10.83 (8.66-13.54)	2.19^{NS}	
- females	4	12.20 (10.09-14.74)	11.30 (8.17-15.63)	4.35^{NS}	0.64^{NS}

*** $p<0.001$ ** $p<0.01$ * $p<0.05$ (*) $p<0.1$ NS $p\geq0.1$

TABLE 5 - Meta-analyses of ex smoker/never smoker relative risk

Estimates	N	Fixed effects Relative risk (95% CI)	Random effects Relative risk (95% CI)	Heterogeneity chisquared, p Within	Between
All	18	5.32 (4.85-5.83)	5.28 (4.24-6.59)	52.00***	
Males	11	5.24 (4.72-5.80)	5.43 (4.05-7.26)	39.13***	
Females	7	5.66 (4.61-6.94)	4.95 (3.37-7.27)	$12.43^{(*)}$	0.44^{N}
UK	2	5.89 (3.32-10.43)	5.89 (3.32-10.43)	0.29^{NS}	
USA	14	5.31 (4.83-5.83)	5.21 (4.08-6.64)	49.85***	
Denmark	2	4.94 (1.92-12.71)	5.26 (1.49-18.57)	1.72^{NS}	0.14^{NS}
Less recent	8	4.69 (4.20-5.24)	4.36 (3.14-6.07)	28.30***	
More recent	10	7.05 (5.97-8.32)	7.05 (5.97-8.32)	7.65^{NS}	16.05**
USA – males	8	5.24 (4.72-5.82)	5.49 (3.93-7.67)	37.86***	
- females	6	5.59 (4.55-6.87)	4.71 (3.14-7.05)	11.69*	0.30^{NS}
USA - less recent	6	4.65 (4.16-5.21)	4.07 (2.79-5.94)	27.38***	
- more recent	8	7.13 (6.03-8.44)	7.38 (6.74-8.09)	5.37^{NS}	17.10***
USA - less recent – males	4	4.77 (4.25-5.36)	4.53 (2.92-7.02)	22.67***	
- females	2	3.18 (2.03-4.98)	2.41 (6.73-7.94)	1.78	$2.93^{(*)}$
USA - more recent – males	4	7.93 (6.20-10.14)	7.93 (6.20-10.14)	1.75^{N}	
- females	4	6.49 (5.15-8.18)	6.49 (5.15-8.18)	2.26^{NS}	1.36^{NS}

*** p<0.001 ** p<0.01 * p<0.05 (*) p<0.1

References

1. Thun MJ, Day-Lally C, Myers DG, Calle EE, Dana F, Zhu B-P, *et al*. Age and the exposure-response relationships between cigarette smoking and premature death in Cancer Prevention Study II. In: Burns D, Garfinkel L, Samet JM, editors. *Changes in cigarette-related disease risks and their implications for prevention and control*. Rockville, Maryland: US Department of Health and Human Services, National Institutes of Health, National Cancer Institute, 1997;383-475. (Smoking and Tobacco Control. Monograph 8.) NIH Publication No. 97-4213.

2. Doll R, Peto R, Wheatley K, Gray R, Sutherland I. Mortality in relation to smoking: 40 years' observations on male British doctors. *BMJ* 1994;**309**:901-11.

3. Peto R, Speizer FE, Cochrane AL, Moore F, Fletcher CM, Tinker CM, *et al*. The relevance in adults of air-flow obstruction, but not of mucus hypersecretion, to mortality from chronic lung disease. Results from 20 years of prospective observation. *Am Rev Respir Dis* 1983;**128**:491-500.

4. Wald NJ, Watt HC. Prospective study of effect of switching from cigarettes to pipes or cigars on mortality from three smoking related diseases. *BMJ* 1997;**314**:1860-3.

5. Friedman GD, Tekawa I, Sadler M, Sidney S. Smoking and mortality: the Kaiser Permanente experience. In: Burns D, Garfinkel L, Samet JM, editors. *Changes in cigarette-related disease risks and their implications for prevention and control*. Rockville, Maryland: US Department of Health and Human Services, National Institutes of Health, National Cancer Institute, 1997;477-99. (Smoking and Tobacco Control. Monograph 8.) NIH Publication No. 97-4213.

6. Marcus EB, Buist AS, MacLean CJ, Yano K. Twenty-year trends in mortality from chronic obstructive pulmonary disease: the Honolulu heart program. *Am J Respir Crit Care Med* 1989;**140**:S64-S68.

7. Hrubec Z, McLaughlin JK. Former cigarette smoking and mortality among U.S. veterans: a 26-year followup, 1954 to 1980. In: Burns D, Garfinkel L, Samet JM, editors. *Changes in cigarette-related disease risks and their implications for prevention and control*. Rockville, Maryland: US Department of Health and Human Services, National Institutes of Health, National Cancer Institute, 1997;501-30. (Smoking and Tobacco Control. Monograph 8.) NIH Publication No. 97-4213.

8. Rogot E, Hrubec Z. Trends in mortality from chronic obstructive pulmonary disease among U.S. veterans: 1954 to 1979. *Am Rev Respir Dis* 1989;**140**:S69-S75.

9. Speizer FE, Fay ME, Dockery DW, Ferris BG, Jr. Chronic obstructive pulmonary disease mortality in six US cities. *Am J Respir Crit Care Med* 1989;**140**:S49-S55.

10. Sterling TD, Rosenbaum WL, Weinkam JJ. Risk attribution and tobacco-related deaths. *Am J Epidemiol* 1993;**138**:128-39.

11. Burns DM, Shanks TG, Choi W, Thun MJ, Heath CW, Jr., Garfinkel L. The American Cancer Society cancer prevention study I: 12-year follow-up of 1 million men and women. In: Burns D, Garfinkel L, Samet JM, editors. *Changes in cigarette-related disease risks and their implications for prevention and control*. Rockville, Maryland: US Department of Health and Human Services, National Institutes of Health, National Cancer Institute, 1997;113-304. (Smoking and Tobacco Control. Monograph 8.) NIH Publication No. 97-4213.

12. Thun MJ, Day-Lally C, Myers DG, Calle EE, Dana Flanders W, Zhu B-P, *et al*. Trends in tobacco smoking and mortality from cigarette use in cancer prevention studies I (1959 through 1965) and II 1982 through 1988. In: Burns D, Garfinkel L, Samet JM, editors. *Changes in cigarette-related disease risks and their implications for prevention and control*. Rockville, Maryland: US Department of Health and Human Services, National Institutes of Health, National Cancer Institute, 1997;305-82. (Smoking and Tobacco Control. Monograph 8.) NIH Publication No. 97-4213.

13. US Surgeon General. *Reducing the health consequences of smoking. 25 years of progress. A report of the Surgeon General*. Rockville, Maryland: US Department of Health and Human Services; Public Health Services; 1989. DHHS Publication No. (CDC) 89-8411.

14. Tockman MS, Comstock GW. Respiratory risk factors and mortality: longitudinal studies in Washington County, Maryland. *Am Rev Respir Dis* 1989;**140**:S56-S63.

15. Lange P, Nyboe J, Appleyard M, Jensen G, Schnohr P. Relationship of the type of tobacco and inhalation pattern to pulmonary and total mortality. *Eur Respir J* 1992;**5**:1111-7.