Trends in cigarette consumption cannot fully explain trends in British lung cancer rates

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Abstract

Study objectives—To determine whether British lung cancer (LC) trends are adequately explained by cigarette smoking trends, and whether modelling using aggregated smoking prevalence estimates can validly replace modelling using individual smoking histories.

Methods—Observed LC trends for 1955–1985 for both sexes and three age groups were compared with multistage model predictions using smoking history data from two surveys (HALS, AHIP). The modelling used the individual smoking data directly or aggregated prevalence estimates. It allowed for variation in age of starting and stopping smoking, amount smoked, tar levels, and environmental tobacco smoke (ETS) exposure.

Results—Observed male LC rates fell faster than predicted by a model (with the first and penultimate stages assumed affected by smoking) that allowed for variation in amount smoked and in tar level (with some provision for “compensation”), and was based on aggregated smoking data from HALS. The discrepancy equated to an annual change unexplained by smoking of –2.4%, –2.8%, and –1.9% for ages 35–44, 45–54, and 55–64. The annual unexplained changes were less in women, and reversed at age 55–64; –1.7%, –0.8%, and +0.8% for the three ages. They were similar using individual smoking histories (–2.6%, –1.8%, and –1.6% for men; –0.9%, –0.5%, and +0.2% for women). The discrepancies were unexplained by plausible alternative multistage parameters, full allowance for tar reduction, alternative estimates of amount smoked, or ETS.

Conclusions—British LC trends cannot be fully explained by cigarette consumption trends, implying factors other than cigarette smoking contribute importantly to overall risk. Predictions using aggregated prevalence estimates provide useful information.

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We compare observed British LC trends for 1955–85 with trends predicted based only on smoking, using smoking history data for people from the 1984–85 Health and Lifestyle Study (HALS)⁴ and patients with diseases “probably or definitely not associated with smoking” from the Alderson Hospital In-Patients Study (AHIP).⁵ Elsewhere we show recalled data from these studies permit estimation of sex and cohort specific trends in smoking prevalence accurately mirroring trends evident in surveys conducted since 1948 for the Tobacco Manufacturers Association (TMA) (submitted for publication). We predict risk using a multistage carcinogenesis model⁶ allowing for people to start and stop smoking at different times and to vary their “dose” from cigarettes (from changes in amount smoked or tar level).

Other studies predicting LC trends^{7–9} have not used individual smoking history data, but aggregated data in the form of age and sex specific smoking prevalence estimates at different times. We also apply the model to aggregated data derived from HALS and AHIP, to assess the usefulness of this method.

Methods

DEATH RATES AND POPULATIONS

Population and mortality data for England and Wales (EW), and Scotland, by sex and age (35–39, 40–44 ..., 60–64) were obtained from WHO¹⁰ for 1955, 1956 ... 1985. Populations for single years of age were estimated by dividing five year age group data by five. Observed rates are presented by 10 year ages (35–44 ... 55–64) adjusted to the single year age distribution of the sex specific EW population in 1970. Observed rates for age 35–44 are smoothed using five year averages. Although diagnosis of LC is inaccurate,¹¹ no misdiagnosis adjustment has been made as no meaningful improvements in detection of LC have occurred since 1955.¹²

MULTISTAGE CARCINOGENESIS MODELS

The multistage model was introduced⁶ to explain cancer death rates often rising as an approximate power of age.^{13 14} It assumes a cell only generates a cancer after undergoing a number of heritable changes. For each person, the relevant tissue initially contains N normal cells, each equally likely to progress to cancer. The progression occurs in a specific order, the background rate for each change being constant. Carcinogens increase transition rate(s) above background.

We used the multistage model based on a detailed review,¹⁵ concluding predictions based on it should be reliable. The model is flexible and tractable. Its predictions fit in reasonably

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Peto *et al*¹ estimated over 90% of male lung cancer (LC) deaths in developed countries were attributable to smoking. There are, however, many other LC risk factors, including occupational, dietary, psychological and familial factors, previous lung disease, exposures to chemicals, and air pollution.^{2 3} How much mortality arises from these factors is uncertain.

Table 1 Values of d_1 and d_2 used to define multistage models with chosen values of ratio of first to penultimate stage effects ($d_1:d_2$) and smoking risk (R)*

$d_1:d_2$	$R = 10$		$R = 20$		$R = 40$	
	d_1	d_2	d_1	d_2	d_1	d_2
1:0	32.85	0.00	69.34	0.00	142.33	0.00
5:1	9.20	1.84	14.79	2.96	22.70	4.54
2:1	5.76	2.88	9.29	4.64	14.29	7.14
1:1	3.86	3.86	6.32	6.32	9.83	9.83
1:2	2.48	4.96	4.17	8.34	6.62	13.23
1:5	1.28	6.41	2.27	11.35	3.75	18.75
0:1	0.00	9.02	0.00	19.04	0.00	39.08

* R is the risk for a smoker smoking a standard "dose" from cigarettes for three quarters of his life relative to that of a never smoker; $K-1 = 4.5$ has been assumed.

well with the approximate power law relation of incidence with duration of exposure to a strong carcinogen,^{14 16 17} the lack of relation of incidence with age, given duration, for some carcinogens,¹⁷⁻¹⁹ initiation/promotion studies showing cancer requires multiple exposures in a specific order,^{20 21} increases in incidence from an exposure long ceased,^{16 22 23} evidence of a quadratic dose response for some carcinogens,^{24 25} and the joint effect of two carcinogens often being multiplicative or super additive.²⁶ Some suggest^{27 28} the model inadequately describes risk after quitting smoking but this was based on limited data,¹⁵ larger data sets^{23 29} showing patterns consistent with multistage predictions^{15 30} and conflicting with another model proposed.²⁸

Our review,¹⁵ based partly on other work,³⁰⁻³³ fully describes how incidence depends on age, dose, duration and cessation of exposure, and the number of stages affected.

For a non-smoker risk at age T is approximated by:

$$R_n(T) = aT^{K-1}$$

a is a constant and K the number of stages.

For a smoker starting at age S and smoking for duration D ($= T-S$) risk increases, depending on the stages affected by smoking. Following previous work^{15 32-34} attention was restricted to models with only the first and penultimate stages affected. Risk at age T is approximated by:

$$R_c(T) = a(T^{K-1} + d_1 D^{K-1} + d_2 (T^{K-1} - S^{K-1}) + d_1 d_2 D^{K-1})$$

d_1 and d_2 are excess effects relative to background for the first and penultimate stages—that is, $d=4$ implies smoking multiplies the background probability by 5.

Table 2 Estimates of cigarettes smoked per smoker*, based on TMA surveys since 1950, and on alternative guesses/estimates at earlier years

Year†	Men		Women	
	GB(1)	GB(2)	GB(1)	GB(2)
1890	10	1	5	1
1905	10	4	5	1
1935	10	10	5	5
1950		15		8
1955		18		10
1960		19		11
1965		19		12
1970		20		14
1975		22		16
1980		21		17
1985		20		16

* From 1950, the alternatives, GB(1) and GB(2), are the same.
† Data for intermediate years estimated by linear interpolation.

Table 3 Sales weighted average tar yield (SWAT) of UK cigarettes (mg/cig), according to two different sources

Year	TMA SWAT	Wald SWAT
1937		32.9
1944		32.2
1951		29.5
1958		30.4
1965	31.5	26.0
1966	30.3	
1967	26.0	
1968	23.9	
1969	23.9	25.7
1970	22.5	23.6
1971	21.3	22.3
1972	20.5	21.0
1973	18.7	19.9
1974	18.1	19.3
1975	17.9	18.8
1976	17.8	17.9
1977	17.4	17.6
1978	17.4	17.5
1979	16.8	16.8
1980	16.3	16.4
1981	15.8	15.9
1982	15.4	15.4
1983	15.0	15.1
1984	14.6	14.8
1985	14.4	14.4

We allowed for various values of $d_1:d_2$ and of the strength (R) of the association of smoking with LC. R is defined as the risk, relative to a non-smoker, of a smoker who, for three quarters of his life, smokes a standard "dose" (vide infra). Table 1 shows the $d_1:d_2$ and R values we used and the corresponding d_1 and d_2 values for $K-1=4.5$. The seven $d_1:d_2$ values are not equally plausible. $d_1:d_2=1:0$ cannot explain the declining risk on smoking cessation, while $d_1:d_2=0:1$ cannot explain the strong relation of risk to age of starting given age. Model fitting work we reviewed¹⁵ suggests $d_1=d_2$, Brown and Chu³⁰ presenting analyses suggesting best fit for $d_1:d_2=1:2$.

Elsewhere, we¹⁵ extended the above formula to allow for quitting smoking, and more generally for intermediate periods of cessation. Here, we further allow for changing number smoked or tar level. For someone living in T equal annual periods ($i = 1, \dots, T$) during which the "dose" from cigarettes is Z_i , risk at time T is approximated by:

$$R_v(T) = a(T^{K-1} + d_1 \sum_{i=1}^T F_i Z_i + d_2 \sum_{i=1}^T G_i Z_i + d_1 d_2 \sum_{i=1}^T \sum_{j=1}^T H_{ij} Z_i Z_j)$$

where $F_i = (T-i+1)^{K-1} - (T-i)^{K-1}$
 $G_i = F_{T-i+1}$ and
 $H_{ij} = 1$ if $i=j$, or
 $H_{ij} = (j-i+1)^{K-1} - 2(j-i)^{K-1} + (j-i-1)^{K-1}$ if $i < j$

The formula predicts risk using smoking data every year up to age T . We also allowed a "lag time" between LC onset and mortality, so smoking to age T would predict mortality at age $T+L$. In many analyses "standard multistage parameter values" of $d_1:d_2 = 1:2$, $R = 20$, $L = 5$ and $K-1 = 4.5$ are used. Alternative values (see tables 1 and 6) are sometimes used in analyses.

SMOKING DATA

HALS and AHIP are described fully elsewhere (submitted data).^{4 5} Here only the regular cigarette smoking data are used. HALS, but not

Table 4 Average tar level at two time points by sex and birth cohort (AHIP study)

Sex	Birth cohort	Current*		10 years ago*	
		N†	Tar level (mg/cig)	N†	Tar level (mg/cig)
Men	1900–09	46	16.6	103	28.6
	1910–19	197	17.4	364	27.6
	1920–29	276	17.0	445	28.6
	1930–39	212	17.7	313	29.1
	1940–49	69	17.4	102	28.6
Women	1900–09	32	15.3	60	28.1
	1910–19	151	16.0	283	27.9
	1920–29	261	15.6	359	26.3
	1930–39	125	15.5	157	25.0
	1940–49	26	15.1	32	22.3

* Relative to year of hospital admission. † Number of smokers of manufactured cigarettes for whom tar delivery of usual brand was available.

AHIP, included handrolled cigarettes. In both studies ages of starting and stopping were available. HALS recorded current or usual amount smoked, while AHIP recorded amount smoked at intervals from age 16 and brand smoked in the 10 years before admission.

Aggregated estimates, by sex, cohort, and year, of cigarette smoking prevalence in HALS and AHIP and of consumption per smoker in AHIP were calculated as previously (submitted data).

Simpler consumption estimates, by sex and year, were also used (table 2). From 1950 data came from TMA. Earlier data were “guesstimates”. Between the 1930s and 1950s we assumed consumption/smoker approximately doubled, using limited evidence from USA³⁵ and Norway³⁶ (consistent with the rise in UK sales³⁷) and from AHIP. Before 1935, we assumed consumption was either constant before 1935 (GB(1) estimate) or rising from 1/day in 1890 for men and 1905 for women (GB(2) estimate).

Data³⁷ from TMA and Wald on sales weighted average tar (SWAT) delivery of UK cigarettes are shown in table 3. Both sources

give SWAT falling from about 32 to 13 mg/cigarette. TMA saw no reason to believe levels fell much before 1965,³⁸ but Wald claims earlier falls. Data for early years are assumed equal to the first value given, intermediate values being estimated by interpolation.

Individual smoking histories

Smoking histories were estimated for HALS and AHIP. For HALS, subjects were assumed to have smoked continuously from age of starting to interview or age of stopping. For AHIP, for each year between age of starting and hospital admission or stopping, cigarette consumption was estimated from the nearest available data on number smoked.

Table 4 shows tar level from AHIP for two time points. Current level was available for 93% of current smokers, being slightly lower for women than men, not varying with age, and similar to SWAT for the same period. For smokers 10 years ago, tar was available for 90% of men and 85% of women. For women, it increased with age. Levels were somewhat higher than SWAT.

When tar was unavailable from AHIP, it was estimated by multiplying SWAT by the ratio of AHIP tar to SWAT for the nearest available time point.

“Dose” to a smoker

“Dose” to a smoker in year i , Z_i , was defined relative to a standard smoker of 20 cig/day of 31.5 mg/cig tar. In analyses considering cigarette consumption, “dose” was estimated by dividing consumption by 20. In analyses considering tar, “dose” was multiplied by either $\text{tar}/31.5$ or $\sqrt{\text{tar}/31.5}$, the latter attempting allowance for “compensation” for reduced yield by increased inhalation or puff number.^{39 40}

Table 5 Fifteen year percentage changes (by sex, age, and period) in the lung cancer rate observed and in that predicted from the HALS study using the aggregate method, and different methods of estimating “dose” from cigarettes

Country	Men						Women						
	35–44		45–54		55–64		35–44		45–54		55–64		
	1955–1970	1970–1985	1958–1970*	1970–1985	1955–1970	1970–1985	1955–1970	1970–1985	1955–1970	1970–1985	1958–1970*	1970–1985	
Britain	–21.3	–44.3	–12.4	–37.6	13.9	–21.9	36.5	–23.7	91.6	–12.9	77.0	66.6	
England and Wales	–22.4	–45.0	–13.8	–39.1	13.4	–23.0	35.1	–24.1	89.0	–12.7	75.4	64.2	
Dose assumptions													
Cig per smoker	Tar per cigarette	ETS (F)	Predicted changes (%)†										
Constant‡	Constant	0.00	–6.3	–13.7	0.5	–19.1	–7.7	32.0	–5.7	64.3	0.6	36.2	49.7
GB(1)	Constant	0.00	29.3	1.4	28.8	1.5	16.4	60.1	26.4	76.7	36.4	45.4	79.0
GB(1)	TMA-sqrt	0.00	29.3	–16.7	28.8	–14.2	0.7	60.1	5.9	76.7	16.6	45.4	55.4
GB(1)	TMA-full	0.00	29.3	–30.5	28.8	–26.3	–11.3	60.1	–9.6	76.7	1.5	45.4	37.2
GB(2)	Constant	0.00	30.3	1.4	32.4	1.6	18.8	60.4	26.4	78.8	36.5	48.2	80.2
GB(2)	TMA-sqrt	0.00§	30.3	–16.7	32.4	–14.2	2.9	60.4	5.9	78.8	16.7	48.2	56.4
GB(2)	TMA-full	0.00	30.3	–30.5	32.4	–26.2	–9.5	60.4	–9.6	78.8	1.5	48.2	38.2
GB(2)	Wald-sqrt	0.00	24.8	–13.5	28.6	–12.1	4.6	55.2	9.5	73.6	19.5	45.4	59.1
GB(2)	Wald-full	0.00	19.6	–25.2	25.0	–23.0	–6.7	50.2	–3.5	68.8	6.2	42.7	42.4
AHIP	Constant	0.00	8.2	–4.1	15.5	–8.3	9.6	38.0	16.5	69.6	22.0	44.0	60.9
AHIP	TMA-sqrt	0.00	8.2	–21.8	15.5	–23.0	–5.5	38.0	–3.0	69.6	4.1	44.0	40.0
AHIP	TMA-full	0.00	8.2	–35.2	15.5	–34.3	–17.1	38.0	–17.7	69.6	–9.6	44.0	23.9
GB(2)	TMA-sqrt	0.05	32.2	–14.7	33.6	–12.2	4.5	61.1	8.0	78.3	18.7	48.3	56.7
GB(2)	TMA-sqrt	0.20	37.4	–9.3	36.9	–6.7	9.2	63.3	13.5	78.0	24.2	49.5	57.7

* Twelve year change. † Predicted changes for men age 55–64 before 1970 not presented as only two year period available. ‡ Constant at 20 cigarettes per smoker.

§ “Standard” model. All predictions use a multistage model with $d_1:d_2=1:2$, $R=20$, $K-1=4.5$, $L=5$, and the Swartz smoking submodel with $S'=15$.

Figure 1 Comparison of observed lung cancer trends in EW for men aged 45–54 and those predicted from the HALS study using the aggregate method and different methods of estimating “dose”. * Constant=20 cigarettes per smoker per day, no tar correction, no dose from ETS; variable = GB(2) estimate of cigarettes per smoker, no tar correction, no dose from ETS; † Except where shown otherwise, predictions use GB(2) estimate of cigarettes per smoker, TMA estimates of tar per cigarette with square root correction and no dose from ETS. All predictions use a multistage model with $d_1:d_2=1:2$, $R=20$, $K-1=4.5$, $L=5$, and the Swartz smoking submodel with $S=15$.

Environmental tobacco smoke (ETS) exposure

To allow for ETS exposure, π_i , the dose from ETS, was added to Z_i , the dose from smoking. π_i was estimated by $C_i F_i$, with C_i the average number smoked per adult in the population estimated from sales data³⁷ and F a factor representing α , the average number of adults a subject is exposed to, multiplied by β , the strength of a cigarette smoked passively relative to one smoked actively. α and β cannot be estimated, but F can be. Based on cotinine, ETS exposed non-smokers have a nicotine intake no more than 0.2 cigarettes per day.³ For $C_i=10$ (about the maximum UK level), this implies F is no more than 0.02. We used higher F values, 0.05 and 0.2, because values below 0.05 hardly affected predictions and because relative exposure from passive and active smoking is higher for some vapour phase constituents.⁴¹ Even so,

$F = 0.2$ is implausibly high, estimates using it being included only to show effects of ETS on predictions were minimal.

RISK PREDICTION

Individual method

For each subject risk was estimated for each age from 35 to 64, using smoking history up to L years before, taking account of age of starting and stopping and, according to the model, the variable “dose” from cigarettes. For $L=0$, estimates were calculated to 1985 (HALS) or year of admission (AHIP).

For both sexes, each year from 1955 to 1985 and each age from 35 to 64, predictions were averaged from all relevant subjects, if ≥ 10 . Rates for ages 35–44, 45–54, and 55–64 were then calculated for years where the full 10 year age range was present, age adjusted to the 1970 EW population. Thus subjects born in 1900 contributed to the 55–64 rate as 55 year olds in 1955, 56 year olds in 1956, etc, until they exceeded the age limit in 1965. As, for both sexes in AHIP, the earliest cohort with 10+ subjects was born in 1904, predictions are only available from 1958 and 1968 for ages 45–54 and 55–64 respectively. In HALS, the earliest cohorts with 10+ subjects were born in 1901 (men) and 1898 (women), so predictions started earlier. For AHIP, reducing numbers of subjects in each cohort after hospital admissions started made predictions less reliable for the final few years.

Aggregate method

As described by Swartz,⁷ cohort based smoking prevalence estimates and a smoking “sub-model” were used to generate estimates of proportions starting and stopping smoking at each combination of ages. For each subgroup LC risks were then calculated as in the individual method. The predicted age adjusted rate for the whole population was also calculated equivalently, but weighting each subgroup according to size. Following Swartz, we assumed 10 year birth cohort prevalence data applied to the mid-year, interpolating prevalences for cohorts born in intermediate years.

Three smoking submodels were used: (1) “Swartz”⁷ assumes that, whenever prevalence in a cohort increases, the appropriate number of never smokers become smokers, and whenever it decreases, an equal proportion of each age of starting subgroup of current smokers become ex-smokers (subjects cannot stop then restart. The probability of quitting is independent of age of starting); (2) “Swartz with drift”⁷ assumes additional never smoking subjects, equal to 0.5% of current smokers, start smoking each year, an identical number of current smokers becoming ex-smokers; (3) “Townsend”⁸ assumes subjects are ranked by “desire to smoke”. When prevalence increases, ex-smokers smoking previously for the longest time are assumed to restart, never smokers becoming smokers only if no ex-smokers are available. When prevalence decreases, most recent starters are assumed to become ex-smokers.

Table 6 Fifteen year percentage changes (by sex, age, and period) in the lung cancer rate observed and in that predicted from the HALS study using the aggregate method, and differing multistage model parameters and smoking submodels

Country	Men						Women					
	35-44		45-54		55-64		35-44		45-54		55-64	
	1955-1970	1970-1985	1958-1970*	1970-1985	1955-1970	1970-1985	1955-1970	1970-1985	1955-1970	1970-1985	1958-1970*	1970-1985
England and Wales	-22.4	-45.0	-13.8	-39.1	13.4	-23.0	35.1	-24.1	89.0	-12.7	75.4	64.2
Model assumptions	Predicted changes (%)†											
Standard	30.3	-16.7	32.4	-14.2		2.9	60.4	5.9	78.8	16.7	48.2	56.4
Varying $d_1:d_2$												
1:0	26.5	15.1	33.7	19.2		43.3	34.1	20.9	61.4	36.3	35.9	92.3
5:1	34.4	-8.8	38.9	-3.5		17.2	44.2	10.4	61.8	23.4	36.8	65.6
2:1	33.0	-12.5	36.6	-8.1		11.2	50.4	8.3	67.7	20.5	40.6	61.3
1:1	31.6	-14.9	34.6	-11.3		6.8	55.5	7.0	73.1	18.4	44.3	58.6
1:5	28.7	-18.6	29.9	-17.2		-1.6	66.1	4.8	85.7	14.8	52.9	54.2
0:1	26.4	-21.1	25.9	-21.7		-8.6	75.3	3.2	97.7	12.1	61.3	51.1
Varying R												
10	24.5	-15.7	26.1	-14.2		0.2	43.4	4.0	53.9	11.9	32.6	40.0
40	36.0	-16.9	38.7	-13.1		6.2	77.7	8.2	106.4	22.0	65.3	74.2
Varying K-1												
3	37.0	-11.9	38.7	-7.5		12.7	60.0	11.8	80.5	22.6	47.7	64.6
6	26.6	-21.1	27.9	-19.6		-5.0	62.7	1.5	79.0	12.4	49.3	50.4
Varying L												
0	18.2	-23.9	20.2	-19.7		-5.0	54.6	-3.5	76.0	8.8	44.3	48.8
10	35.3	-6.8	36.4	-5.9		13.3	59.7	14.9	76.1	24.1	46.8	63.4
Varying smoking submodel												
Swartz with drift	29.9	-16.8	31.7	-14.4		2.3	60.1	5.7	77.9	16.2	47.5	54.9
Townsend	30.5	-15.6	33.2	-13.3		3.3	60.5	6.5	79.3	17.3	48.7	57.5
Varying S'												
12	31.4	-15.2	33.9	-13.5		3.7	61.7	6.5	79.7	17.3	48.4	57.5
21	25.4	-20.7	27.6	-17.5		-1.5	55.2	2.0	72.8	13.5	46.2	50.3

* Twelve year change. † Predicted changes for men age 55-64 before 1970 not presented as only two year period available. All predictions use GB(2) estimates of cigarettes per smoker, TMA estimates of tar per cigarette with square root correction and no dose from ETS. The standard multistage model uses $d_1:d_2=1:2$, $R=20$, $K-1=4.5$, $L=5$, and the Swartz smoking submodel with $S'=15$. Other models shown vary one parameter at a time.

The different ways the submodels treat prevalence increases made little difference, as most increases occurred together at the younger ages, relatively few smokers restarting under "Townsend". The treatment of prevalence decreases had more effect, with the Swartz submodels, especially with drift, minimising, and "Townsend" maximising, long term smoking.

For each submodel, a minimum age when smoking can start, S' , was set. Although $S'=0$ could be used, so fully accounting for the age of starting pattern in each cohort, prevalence estimates among children were based on small numbers, the method of handling 10 year cohorts lending additional uncertainty. Thus, for 10 year olds born in 1904, prevalence is estimated from the 1900-1909 cohort in 1914, who being aged 5-14 will not have had homogeneous smoking habits. Swartz⁷ used $S' = 21$ or 18, but we usually used $S' = 15$, higher values masking the different patterns of starting smoking by cohort, and reducing the occurrence of long term smoking.

Ten year cohorts based on at least 20 subjects were included, the earliest being 1900-1909 for both sexes in AHIP and men in HALS, and 1890-1899 for women in HALS.

Changes in rates

In tables 5-8, percentage changes in rates are presented for 1955-1970 and 1970-1985, or the nearest periods with predictions available. In figures 1-4, rates are shown annually over the 30 year period, relative to 1970 = 100%. In the text a percentage change (P_1) is said to be

greater than another (P_2), if $P_1 > P_2$. Thus, a 20% increase is said to be greater than any increase <20% or any decrease, while a 20% decrease is greater than any decrease >20%.

Results

COMPARISON OF OBSERVED AND PREDICTED TRENDS USING THE AGGREGATE METHOD

Table 5 compares percentage changes in LC rates observed in Britain and EW with predictions using the aggregate method, HALS prevalence estimates, standard multistage parameter values, and the "Swartz" submodel with $S'=15$. Predicted changes are shown for different estimated "dose" from cigarettes, with varying allowances for cigarettes/smoker, tar/cigarette and ETS. Figure 1 shows fuller details for men aged 45-54 of observed EW rates and some predicted rates. Patterns in observed rates are similar whether or not Scotland is included, so only EW rates are used subsequently.

For men, observed rates fell throughout virtually the whole period for ages 35-44 and 45-54. For age 55-64, a slight rise to 1960 preceded a plateau, then a fall. With no allowance for variation in cigarettes/smoker or tar/cigarette, predicted changes considerably exceeded observed changes in both time periods and all age groups (that is, predicted rates fell less than observed rates). When the rise in cigarettes/smoker was allowed for, the discrepancy between observed and predicted trends increased, more using the simpler GB estimates of cigarettes/smoker than using the

Figure 2 Comparison of observed lung cancer trends in EW for men aged 45–54 and those predicted from the HALS study using the aggregate method and differing multistage model parameters. All predictions use the Swartz smoking submodel with $S'=15$, GB(2) estimates of cigarettes per smoker, TMA estimates of tar per cigarette with square root correction and no dose from ETS. The standard multistage model uses $d_1:d_2=1:2$, $R=20$, $K-1=4.5$, $L=5$. Other models shown vary one parameter at a time.

Figure 3 Comparison of observed lung cancer trends in EW for men aged 45–54 and those predicted using the aggregate method from the HALS or AHIP studies. All predictions use GB(2) estimates of cigarettes per smoker, TMA estimates of tar per cigarette with square root correction and no dose from ETS, the standard multistage model ($d_1:d_2=1:2$, $R=20$, $K-1=4.5$, $L=5$), and the Swartz smoking submodel with $S'=15$.

cohort specific AHIP estimates. Differences between predictions based on GB(1) and GB(2) were small, particularly at younger ages. Predicted risk increased less in the later period when declining tar/cigarette was allowed for, reducing the discrepancy. The discrepancy was little affected by using Wald rather than TMA tar data. When ETS was allowed for, predicted risk increased with increasing F , but only minimally for the lower, more plausible, value. Using a “standard” reasonable set of assumptions, data and multistage parameters:

- (i) GB(2) cigarettes/smoker data,
- (ii) square root tar correction, using TMA data,
- (iii) no ETS correction,
- (iv) $d_1:d_2=1:2$, $R=20$, $L=5$ and $K-1=4.5$, and
- (v) the “Swartz” submodel, with $S'=15$

the discrepancy between observed and predicted rates in men equates to an annual change in risk unexplained by smoking of -2.4% for age 35–44 (1955–85), -2.8% for age 45–54 (1958–85), and -1.9% for age 55–64 (1968–85). Even using full tar correction and AHIP cohort specific cigarettes/smoker estimates, the “dose” assumptions bringing predicted and observed changes closest, the discrepancies equated to annual changes of -1.6% , -1.4% , and -0.5% for the three ages.

For women, rates in the two younger age groups peaked, at around 1970 and 1980 respectively, then declined. In the oldest age group rates rose steadily. For the two younger age groups, predicted and observed changes over the earlier period were similar, but in the later period predicted changes were greater. In the oldest age group observed changes were generally lower than predicted changes. Effects of differing dose assumptions on predictions were similar to those for men, except varying cigarettes/smoker or ETS little affected predictions in the earlier period. The discrepancy between observed and predicted rates was smaller for women than men, equivalent annually, with the “standard” assumptions, to -1.7% for age 35–44 (1955–85), -0.8% for age 45–54 (1955–85) and $+0.8\%$ for age 55–64 (1958–85), or with full tar correction and AHIP cohort specific cigarette/smoker estimates to -0.3% , $+0.2\%$, and $+1.8\%$ respectively.

Table 6 shows the effects of varying the multistage parameters $d_1:d_2$, R , L and $K-1$ and the smoking submodel, using the aggregate method, HALS smoking prevalence estimates, GB(2) estimates of cigarettes/smoker and TMA tar estimates with square root correction. Figure 2 shows some predicted rates for men aged 45–54. Increasing $d_1:d_2$, decreasing K or increasing L predicted higher changes for men and for the later period for women, but similar or lower changes for women in the earlier period. Increasing R nearly always predicted higher changes. Varying the smoking submodel had little effect. Increasing S' predicted lower changes. However, effects of differing assumptions were generally small compared with the difference between observed rates and those predicted by the standard model, and, except

Table 7 Fifteen year percentage changes (by sex, age, and period) in the lung cancer rate observed and in that predicted from the AHIP study using the aggregate method, and differing assumptions

Country	Men						Women					
	35-44		45-54		55-64		35-44		45-54		55-64	
	1955-1970	1970-1979*	1958-1970*	1970-1985	1955-1970	1970-1985	1955-1970	1970-1979*	1955-1970	1970-1985	1955-1970	1970-1985
England and Wales	-22.4	-33.5	-13.8	-39.1	13.4	-23.0	35.1	-20.9	68.9	-12.7	87.3	64.2
<i>Dose assumptions</i>												
Cig per smoker	Tar per cigarette	Model assumptions	Predicted changes (%)†									
Constant‡	Constant	Standard	4.5	-7.7	8.1	-12.6	-0.2	28.4	-3.2	59.2	-2.9	45.5
GB(2)	Constant	Standard	43.2	2.3	38.1	9.1	25.8	57.2	15.6	70.0	30.9	74.7
GB(2)	TMA-sqrt	Standard	43.2	-7.7	38.1	-7.7	8.9	57.2	5.2	70.0	11.9	51.8
GB(2)	TMA-full	Standard	43.2	-16.0	38.1	-20.6	-4.1	57.2	-3.4	70.0	-2.7	34.2
AHIP	Constant	Standard	19.6	-0.9	21.8	-1.4	16.9	33.8	10.4	61.0	16.6	55.7
AHIP	TMA-sqrt	Standard	19.6	-11.1	21.8	-17.1	0.9	33.8	0.2	61.0	-0.6	35.6
AHIP	TMA-full	Standard	19.6	-19.4	21.8	-29.2	-11.4	33.8	-8.3	61.0	-13.7	20.2
GB(2)	TMA-sqrt	d ₁ :d ₂ =2:1	45.8	-3.5	44.5	-0.5	19.1	49.9	7.5	62.3	18.4	59.0
GB(2)	TMA-sqrt	R=40	51.1	-6.8	46.4	-5.8	13.4	73.3	7.3	91.9	17.1	68.0
GB(2)	TMA-sqrt	K=1=6	38.9	-12.4	32.5	-14.1	0.2	57.6	1.2	69.8	6.5	44.3
GB(2)	TMA-sqrt	L=0§	29.1	-11.6	25.5		50.3	0.2	63.4			

* Change less than 15 years. † Predicted changes for age 55-64 before 1970 not presented as only two year period available. ‡ Constant at 20 cigarettes per smoker. § Predictions not available after 1980. All predictions use the Swartz smoking submodel with S²=15, no dose ETS, and, except as shown, a multistage model with d₁:d₂=1:2, R=20, K=1=4.5, L=5.

for some models for the oldest women, the discrepancies remained.

In table 6, only one parameter was varied at once. Further analyses (not shown) used different combinations of parameter values and dose estimates. Effects of varying parameters were generally similar to those described above, and discrepancies between observed and predicted trends remained.

Our main predictions based on aggregated data, presented in table 5, used prevalence estimates from HALS because of its greater age range and representativeness. Some equivalent analyses, based on AHIP are shown in table 7 while figure 3 compares results with those previously discussed. Results based on AHIP and HALS were generally similar, unsurprisingly because their prevalence estimates agree well (submitted data). For men, predictions rose slightly more and peaked slightly later using AHIP, increasing the discrepancy. For women, the difference was generally the opposite and much smaller.

COMPARING PREDICTIONS USING THE AGGREGATE AND INDIVIDUAL METHODS

Table 8 compares predictions from the two methods using standard multistage parameter values. For the aggregate method, the "Swartz" submodel with S²=15 was used, either with constant cigarettes/smoker and constant tar/cigarette, or GB(2) cigarettes/smoker, TMA tar/cigarette and square root correction. Individual method estimates were based on (a) constant cigarettes/smoker (using only the ages of starting and stopping) and constant tar/cigarette, (b) the person's varying cigarettes/smoker history but TMA SWAT values for all cigarettes (with square root correction), or (c) the person's history of both cigarettes/smoker and tar/cigarette (again with square root correction). Estimates for (b) and (c) were

available only from AHIP. Figure 4 shows selected results for variable cigarettes/smoker.

Except for women aged 55-64, the individual method generally predicted lower changes than the aggregate method. Allowing tar/cigarette to vary individually also predicted lower changes than if the same value was assumed for all smokers, but only slightly. In the earlier period (not studied for age 55-64), using the individual method little affected the discrepancy between observed and predicted trends. However, for the later period, predictions using the individual method were closer to observed trends. If the last few years of predictions (known to be less reliable) are ignored, this is also true for women age 55-64, where the discrepancy predicted by the aggregate method had been in the opposite direction.

However, the discrepancy remained for men, and women aged 35-44. For instance, using individual cigarettes/smoker and tar/cigarette with square root correction, the discrepancy over the whole period was equivalent to an annual change in risk unexplained by smoking for men of -2.6% for age 35-44 (1955-1979), -1.8% for age 45-54 (1958-85), and -1.6% for age 55-64 (1968-85) and for women of -0.9% for age 35-44 (1955-79), -0.5% for age 45-54 (1958-84), and +0.2% for age 55-64 (1968-85).

Further analyses (not shown) were run using the individual method, comparable to those for the aggregate method in table 6 and figure 2. The direction of the effect on predicted changes of varying d₁:d₂, R, K-1 or L was similar using both methods in both sexes. The additional analyses confirmed the patterns of discrepancy reported above using the aggregate data and using the individual data with standard multistage parameters.

Further analyses (not shown) demonstrated that limited data on current/latest cigarettes/

Table 8 Fifteen year percentage changes in observed lung cancer rate and in predicted risk estimates using the aggregate or individual method

<i>A HALS study</i>												
	<i>Men</i>						<i>Women</i>					
	<i>35–44</i>		<i>45–54</i>		<i>55–64</i>		<i>35–44</i>		<i>45–54</i>		<i>55–64</i>	
	<i>1955–1970</i>	<i>1970–1985</i>	<i>1958–1970*</i>	<i>1970–1985</i>	<i>1955–1970</i>	<i>1970–1985</i>	<i>1955–1970</i>	<i>1970–1985</i>	<i>1955–1970</i>	<i>1970–1985</i>	<i>1955–1970</i>	<i>1970–1985</i>
<i>Country</i>	<i>Observed changes (%)</i>											
England and Wales	–22.4	–45.0	–13.8	–39.1	13.4	–23.0	35.1	–24.1	89.0	–12.7	87.3	64.2
<i>Does assumption</i>												
<i>Method</i>	<i>Cigs per smoker</i>	<i>Tar per cigarette</i>	<i>Predicted changes (%)†</i>									
Aggregate	Constant‡	Constant	–6.3	–13.7	0.5	–19.1	–7.7	32.0	–5.7	64.3	0.6	49.7
Individual	Constant‡	Constant	–6.8	–14.0	–10.0	–20.8	–9.1	38.6	–10.0	66.2	5.4	60.2
<i>B AHIP study</i>												
	<i>Men</i>						<i>Women</i>					
	<i>35–44</i>		<i>45–54</i>		<i>55–64</i>		<i>35–44</i>		<i>45–54</i>		<i>55–64</i>	
	<i>1955–1970</i>	<i>1970–1979*</i>	<i>1958–1970*</i>	<i>1970–1985</i>	<i>1955–1970</i>	<i>1970–1985</i>	<i>1955–1970</i>	<i>1970–1979*</i>	<i>1958–1970*</i>	<i>1970–1984*</i>	<i>1955–1970</i>	<i>1970–1985</i>
<i>Country</i>	<i>Observed changes (%)</i>											
England and Wales	–22.4	–33.5	–13.8	–39.1	13.4	–23.0	35.1	–20.9	68.9	–7.1	87.3	64.2
<i>Dose assumptions</i>												
<i>Method</i>	<i>Cigs per smoker</i>	<i>Tar per cigarette</i>	<i>Predicted changes (%)†</i>									
Aggregate	Constant‡	Constant	4.5	–7.7	8.1	–12.6	–0.2	28.4	–3.2	59.2	–1.6	45.5
Individual	Constant‡	Constant	5.2	–11.3	–0.5	–18.8	–3.9	37.1	–7.4	73.0	–4.5	54.5
Aggregate	GB(2)	TMA-sqrt	43.2	–7.7	38.1	–7.7	8.9	57.2	5.2	70.0	12.4	51.8
Individual	Individual	TMA-sqrt	25.2	–18.9	13.5	–24.5	–1.0	41.9	–2.8	85.5	–7.5	34.9
Individual	Individual	Individual-sqrt	22.8	–20.5	17.9	–27.2	–5.5	42.7	–7.9	99.2	–11.3	36.4

* Change less than 15 years—where predictions are available for different periods for the different methods, the maximum period available for both is shown. † Predicted changes for age 55–64 before 1970 not presented as only six year period or less available. ‡ Constant at 20 cigarettes per smoker. All predictions use multistage model with $d_1, d_2=1:2$, $R=20$, $K-1=4.5$, $L=5$. Aggregate method uses Swartz smoking submodel with $S'=15$.

smoker, as available in HALS, could not usefully contribute to the individual method.

OTHER TOBACCO PRODUCTS

The analyses so far only consider cigarette smoking. Based on limited data from HALS and AHIP on prevalence of pipe and cigar smoking and from TMA⁴² on trends in consumption/smoker, we attempted (results not shown) to assess the effect of allowing for pipe and cigar smoking on risk predictions in men. Not surprisingly, because, for many years, cigarettes formed the substantial proportion by weight of total tobacco sales,³⁷ such allowance negligibly affected predicted trends.

Discussion

Using a multistage model and cigarette smoking data we predicted LC trends by sex and age for 1955–1985 and ages 35–64. Smoking histories were obtained from questionnaires. All models reflected changes in smoking prevalence, using either aggregated estimates by 10 year birth cohort, or a person's data on age of starting and stopping. Variation in “dose” from cigarettes was allowed for in various ways, variation in cigarettes/smoker substantially affecting predictions over the whole period, with variation in tar/cigarette affecting predicted trends in later years. However, data sources

(whether of prevalence, cigarettes/smoker or tar/cigarette) and allowance for ETS had relatively little effect, as did varying the multi-stage parameters, provided reasonably plausible values were considered. Using individual smoking histories instead of aggregated data had a reasonably small impact.

For men, models allowing for variation in cigarettes/smoker and tar/cigarette (corrected to allow for “compensation”) predicted changes exceeding observed changes throughout the period studied. Basing predictions on individual smoking histories rather than aggregated data reduced this discrepancy in later years, but still represented an annual unexplained change of –1 to –2%. Even with, implausibly, no allowance for “compensation”, the discrepancy remained clearly evident.

For women, nearly all model variants predicted trends similar to those observed for 1955–1970. For ages 35–44 and 45–54, models allowing for variation in cigarettes/smoker and tar/cigarette (with a square root correction), predicted changes exceeding observed changes for 1970–1985. As for men, this discrepancy was reduced using individual smoking histories. Although remaining clear for age 35–44, it was virtually eliminated for age 45–54. For age 55–64, however, predicted changes in 1970–1985 were generally lower than observed

Figure 4 Comparison of observed lung cancer trends in EW, by sex and age, and those predicted from the AHIP study using the aggregate or individual methods. All predictions use multistage model with $d_1, d_2 = 1, 2$, $R = 20$, $K - 1 = 4, 5$, $L = 5$. Aggregate method uses Swartz smoking submodel with $S' = 15$, GB(2) estimates of cigarettes per smoker, TMA estimates of tar per cigarette and square root correction. Individual method uses individual cigarettes per smoker and tar per cigarette, and square root correction.

changes (depending on the multistage parameters chosen), but this discrepancy too was virtually eliminated using individual histories.

Possible sources of bias include the following:

Changes in diagnostic standards

Although diagnosis of LC is inaccurate, we follow others in assuming detection rates are materially unchanged since 1955.¹²

Inadequacy of recalled smoking data

Although recalled data are doubtless imperfect, reliance on retrospective data should not have led to spurious time trends in predicted LC rates (submitted data). Any effect of differential smoker/non-smoker mortality in estimating past smoking prevalence is probably minor up to age 70 at interview (submitted data). Discrepancies between observed and predicted changes are larger for age 35–44 (who, for predictions in 1955, were aged approximately 60–69 in AHIP or 65–74 in HALS) than for other age groups suggesting they cannot be explained by differential mortality.

Changes in tar delivery

We present predictions assuming “dose” to a smoker is (a) independent of tar, (b) directly proportional to tar or (c) proportional to the square root of tar. As substantial epidemiological evidence shows tar reduction is associated with less LC risk,⁴³ (a) is implausible, though evidence^{39, 40} that smokers “compensate” to some extent for reduced yield implies predictions from (b) are probably also incorrect; (c) may predict better. In the analyses using individual smoking histories, we only had data on variation in tar over the past 10 years. As this only minimally affected predictions, lack of earlier data probably had no serious effect. While conceivable that the carcinogenic poten-

tial of tar per mg might have changed over time, no reliable evidence supports this conjecture.

Other tobacco products

Our analyses suggest pipe or cigar smoking cannot explain the pronounced discrepancy between observed and cigarette consumption predicted LC trends.

Smoking by children

With the aggregate method, smoking before S' is ignored. Although the value $S' = 21$ Swartz⁷ used seems unnecessarily high, the small difference between predictions using $S' = 12$ or $S' = 15$ suggests using $S' = 15$ in our main analyses did not lead to material error.

With the individual method, age of starting to smoke is fully accounted for. However amounts assumed to be smoked by child smokers (20/day in the constant dose analyses, or amount smoked at age 16 in the variable dose analyses) may have been overestimates. This may partly explain why predictions using the individual and aggregate methods differed more for younger ages, where childhood exposure contributes more.

ETS exposure

Without individual data, ETS exposure was assumed equal for everyone, irrespective of active smoking status but variable over time proportional to national cigarette consumption. While not unreasonable to assume the dose from a cigarette smoked passively is constant over time, because tar reduction has predominantly affected mainstream not side-stream smoke levels,⁴⁴ exposure may have been affected by changing ventilation of buildings and social patterns. Nevertheless, the modest effect on predictions of allowing for a clearly implausibly high ETS effect ($F = 0.2$) strongly suggests incomplete allowance for ETS could not have affected our general conclusions.

Use of inappropriate predictors of LC risk

The multistage model can only approximate the truth. Nevertheless its predictions align with much evidence¹⁵ and it is flexible, allowing for differing assumptions concerning relative importance of early and late exposure. As conclusions were similar from multistage predictions using a variety of parameters and from predictions based on various simpler predictors not entailing multistage assumptions (results not shown), our conclusions cannot be an artefact of our model. More crucial to predictions is not the decision to use the multistage model but the decision to use parameter values making smoking throughout life relevant to risk. Although, in men, the discrepancy would have been eliminated, or even reversed, had one assumed smoking affects very predominantly the early stage of the process, this is inconsistent with epidemiological data for ex-smokers.¹⁵ Mathematical modelling^{32–34} suggests the effect is, if anything, stronger on the later than the earlier stage, implying use of an inappropriate predictor cannot explain our findings.

Considering all these points we conclude cigarette consumption trends cannot fully explain trends in British LC rates, and that the discrepancies observed cannot be attributed to changes in ETS exposure or smoking pipes or cigars.

Our conclusions align with an age-period-cohort analysis,^{45–46} using mortality data for 1941–85, and estimates of cumulative constant tar cigarette consumption (CCTCC). That analysis showed similarity, in both sexes, between the timing of cohort peaks for CCTCC and for mortality from LC, emphysema, and chronic obstructive lung disease (COLD), but also noted “downward trends in the younger age groups are too large and too early to be explained in terms of changes in the frequency or type of cigarettes smoked.”

Our findings also apparently align with analyses⁴⁷ of male LC mortality for 1941–75 based on a simple model allowing for variation in CCTCC. Although “88% of total male deaths during the study period could be attributed to smoking,” the fitted model notably involved a pronounced decline in risk in non-smokers between 1951 and 1971. Except for analyses incorporating ETS effects, which were generally unimportant, our modelling assumes LC risk in non-smokers is invariant over time. This assumption is consistent with the similarity of age adjusted LC rates in male never smoking British doctors in 1951–71 and 1971–91,⁴⁸ but leads to being unable to fit the LC trend data adequately in terms of cigarette consumption.

Further evidence of discrepancies for the USA is presented elsewhere (submitted data), strengthening our major conclusion that factors other than cigarette smoking contribute importantly to overall LC risk.

Our secondary objective was to assess the value using aggregated data, in the form of age and sex specific smoking prevalence estimates at different times, as compared with using individual smoking histories. With non-linear models, using individual data is theoretically

KEY POINTS

- It is often held that time trends in British lung cancer rates merely reflect earlier trends in cigarette smoking habits.
- We tested this belief by using detailed cigarette smoking history data to predict lung cancer trends for 1955–1985.
- Although our modelling took all major aspects of cigarette smoking into account, it could not fully explain the trends.
- We found lung cancer rates declined considerably faster than explicable by cigarette smoking, particularly in younger men.
- We conclude that factors other than cigarette smoking contribute substantially to lung cancer trends and should be investigated more fully.

superior, but often only aggregated data are available. Our analyses suggest using aggregated data leads to quite similar conclusions to those based on individual data, suggesting aggregated data may be useful where individual data are unavailable.

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