

Barbiturates and lung cancer: a re-evaluation

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Background	Barbiturates, particularly phenobarbital, have been shown to be a tumour promoter in animal experiments and were found to be associated with increased risk of lung cancer in our cohort follow-up study to screen pharmaceuticals for possible carcinogenic effects. Sixteen more years of follow-up have accumulated permitting a more detailed evaluation of this association.
Methods	In all, 10 213 subscribers of the Kaiser Permanente Medical Care Program who received barbiturates between 1969 and 1973 from its San Francisco pharmacy were followed up through 1992 and their incidence of lung cancer at biennial intervals was compared with what was expected based on the experience of the entire pharmacy cohort (143 594). Smoking-habit data were available on about half of the barbiturate users and were used to adjust for cigarette smoking in both the observed/expected analysis and in Cox proportional hazards analysis.
Results	The initially elevated standard morbidity ratio of 1.55 (95% CI : 1.25–1.91) with 3–7 years of follow-up gradually decreased and stabilized at about 1.3 after 11–15 years of follow-up. This trend for diminishing relative risk over time was more pronounced among the never smokers but their initial excess risk was not statistically significant due to small numbers. A dose-response trend was observed, based on the number of prescriptions dispensed. Analytical control for cigarette smoking reduced but did not eliminate either the association or the dose-response trend. Most of the barbiturate-associated cases in never smokers were women and the predominant histological type was adenocarcinoma.
Conclusions	These findings from up to 23 years of follow-up are not conclusive because of the continuing small number of never smokers who developed lung cancer. However, they strengthen and refine previous observations of a barbiturate-lung cancer association, which is probably not fully explained by confounding by cigarette smoking. The diminution of excess risk over time is consistent with a tumour promoter effect. Findings among the never smokers suggest that this possible effect may be greatest on adenocarcinomas in women.
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In 1981, one of us published an article showing an elevated risk of lung cancer among people who received barbiturate prescriptions, as noted in the follow-up of a large cohort of subscribers of the Kaiser Permanente Medical Care Program who had received prescriptions in the Program's outpatient pharmacy in San Francisco, California, during the period July 1969–August 1973.¹ The relative risk for lung cancer being diagnosed by the end of 1976 was 1.7 (95% CI : 1.4–2.1). Although a later analysis showed increasing risk with increasing numbers of prescriptions dispensed,² investigation of medical charts did not reveal that lung cancer incidence was related to duration or

intensity of barbiturate use and a causal relationship could not be confirmed.¹ Of particular interest was the possibility of confounding by cigarette smoking. The most convincing evidence that this was not the explanation for the barbiturate-lung cancer association would have been persistence of the association when attention was restricted to those who had never smoked. Among this subgroup there were 4 observed and 2.7 expected cases of lung cancer among barbiturate users, so the association did not disappear, but the number of cases was too small to yield reliable conclusions. The possibility that barbiturate use increases the risk of developing lung cancer continues to be of great interest because of the demonstrated tumour-promoting effects of phenobarbital in experimental animals.³ Evidence from humans, however, is quite limited.^{3–7}

Sixteen more years of follow-up have been added to what was available for the initial report¹ and we have studied what

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happened to the barbiturate-lung cancer association over this period in the biennial analyses that have been conducted. In addition, greater efforts were made to control for cigarette smoking and the findings among the never smokers have been expanded.

Methods

The study to screen pharmaceutical drugs for possible carcinogenic effects has been described in detail in a series of reports covering increasing follow-up time.^{8–11} In brief, newly diagnosed cancers have been ascertained in the cohort of 143 574 pharmacy users mentioned above, by review of records of the Kaiser Permanente Medical Care Program and of the local Surveillance, Epidemiology and End Results (SEER) Program operated by the Northern California Cancer Center. Follow-up for a particular type of cancer is conducted on people free of that cancer at entry, in this case at their first recorded barbiturate dispensing, and ends at the earliest of the following events: end of the designated follow-up period, diagnosis of the cancer, or departure from the Program for any reason, including death. We compare the observed with the expected number of cases of cancer at each site and all sites combined that develop among those who received a prescription for one of the 215 commonly used drugs and drug groups routinely studied. The expected number is derived from the age- and sex-specific incidence rates for the entire pharmacy cohort as applied to the age-sex composition of the users of the drug under consideration. The observed number divided by the expected number yields a standard morbidity ratio (SMR). The 95% CI are based on application of the Poisson distribution to the observed number of cases.

For these analyses we added users of two barbiturate mixtures—of butabarbital, phenobarbital and secobarbital, and of amytal and secobarbital—to the users of the three barbiturates initially studied—pentobarbital sodium, phenobarbital and secobarbital sodium. This increased the number of users from 9816 to 10 213. Some numbers in this report differ slightly from those in the two previous reports^{1–2} because of the later discovery of pre-existing lung cancers in a few subjects, which removed them from the population at risk, and other corrections in the data.

We examined the evolution of the barbiturate-lung cancer association as successive 2-year extensions of follow-up were added between 1976 and 1992. We also conducted a more extensive look at dose-response than our previous comparison of one-or-more with two-or-more and three-or-more dispensings² by determining the effects of focusing on people with larger numbers of barbiturate dispensings in the 1969–1973 period of ascertainment. To take cigarette smoking into account we used data from multiphasic health checkups¹² in which smoking habits were ascertained by self-administered questionnaires.¹³ These were available for about half of the barbiturate users and if a person had more than one check-up, the last between July 1964 and August 1973 was used. Adequate data were available to identify 19 214 members of the pharmacy cohort as current cigarette smokers of whom 1882 were barbiturate users. The numbers of cohort members and barbiturate users who were ex-cigarette smokers were 10 342 and 1100, and never smokers, 20 261 and 2082, respectively. Calculations of smoking-specific

expected numbers of lung cancer cases among barbiturate users were based on the incidence of lung cancer among all identified members of the smoking category. To adjust for cigarette smoking in the analysis of lung cancer risk, the observed and expected numbers of cases among barbiturate users were calculated separately and then summed over the following six strata: never smokers, former smokers, current smokers of <1 pack per day, 1–2 packs per day, >2 packs per day and amount unknown. When barbiturate use was subdivided according to number of prescriptions dispensed, follow-up began with the last dispensing instead of the first. Starting follow-up in September 1973, after pharmacy data collection ended, made virtually no difference in the findings.

To accomplish even tighter control ('maximal adjustment') for cigarette smoking we formed all 64 possible subcategories based on current versus ex-smoker, quantity smoked (<1, 1–2, >2 packs/day, unknown), duration (<10, 10–20, >20 years, unknown), and inhalation (yes, no—unknown was apparently combined with no). For example, one such subcategory was people who reported currently smoking <1 pack per day for 10–20 years and who inhaled. With never cigarette smokers as a reference group, each of the 27 subcategories with at least 30 barbiturate users plus an 'other' subcategory containing the remaining 185 barbiturate users was entered as a categorical variable into a Cox proportional hazards model, which also included use versus non-use of barbiturates, age at start of follow-up, sex, and skin colour (white, black, yellow, other and unknown) as independent variables. The outcome variable was, of course, the diagnosis of lung cancer and follow-up began with the first computer recorded barbiturate prescription for the yes-versus-no barbiturate analysis and with the last of these barbiturate prescriptions when their number was considered in the analysis.

We also assessed barbiturate use by the questionnaire item in the 1964–1972 multiphasic health check-ups, 'In the past year have you often taken any phenobarbital or barbiturates?' People who were free of lung cancer and who responded 'yes' to this item during their first check-up during the 8-year period were compared to those who responded 'no' with respect to the incidence of lung cancer through 1996. Relative risks were calculated using the Mantel-Haenszel method for cohort studies¹⁴ with adjustment for age in 5-year age categories. There was no association of a 'yes' answer with risk of lung cancer but there was poor concordance of these questionnaire responses with pharmacy data among those who used the pharmacy. For example, of 1749 who answered 'yes' and used the pharmacy, only 594 (34%) had received a barbiturate prescription during the previous year. We therefore decided to rely on the more objective drug-dispensing data to assess barbiturate use. The questionnaire-related findings are available from the authors on request.

Results

For all barbiturate users the strength of the association decreased slightly with increasing length of follow-up, but between a maximum follow-up of 15–23 years the standard morbidity ratio stabilized at about 1.3 (Table 1). As indicated by the CI, chance variation was a very unlikely explanation for the increased risk of lung cancer.

Table 1 The association of barbiturate use and subsequent lung cancer among all who received barbiturate prescriptions and those who reported having never smoked cigarettes. Successive analyses with follow-up increasing by 2 years to a maximum of 23 years

Last year of follow-up	Maximum duration of follow-up (years)	All barbiturate users (n = 10 213)			Barbiturate users identified as never smokers (n = 2082)		
		Lung cancer cases			Lung cancer cases		
		Observed	Expected	SMR ^a (95% CI)	Observed	Expected	SMR ^a (95% CI)
1976	7	88	56.6	1.55 (1.25–1.91)	4	2.27	1.76 (0.48–4.51)
1978	9	108	69.8	1.55 (1.27–1.87)	6	3.37	1.78 (0.65–3.88)
1980	11	122	84.3	1.45 (1.20–1.73)	7	3.92	1.78 (0.72–3.68)
1982	13	137	96.9	1.41 (1.19–1.67)	7	4.73	1.48 (0.59–3.05)
1984	15	142	110.4	1.29 (1.08–1.52)	8	6.42	1.25 (0.54–2.46)
1986	17	158	121.9	1.30 (1.10–1.51)	8	6.58	1.22 (0.52–2.40)
1988	19	172	133.2	1.29 (1.11–1.50)	8	7.25	1.10 (0.48–2.17)
1990	21	186	143.7	1.29 (1.12–1.49)	8	7.97	1.00 (0.43–1.98)
1992	23	203	156.1	1.30 (1.13–1.49)	9	8.73	1.03 (0.47–1.96)

^a Standard morbidity ratio.

Table 2 Distribution of cigarette smoking status and quantity smoked among cigarette smokers according to number of barbiturate prescriptions (Rx) received, 1969–1973. Percentages may not total 100.0% due to rounding

No. of barbiturate Rx	Cigarette smoking status ^a				Current smokers: packs/day ^a				
	No. (100%)	Current	Former	Never	No. (100%)	<1	1–2	>2	Unknown
1	2625	38.5%	20.9%	40.6%	1010	42.0%	45.6%	12.2%	0.2%
2–4	1410	37.8	22.6	39.6	533	43.7	42.2	13.5	0.6
5–19	856	32.5	22.5	45.0	278	38.5	40.3	20.5	0.7
20+	173	35.3	22.5	42.2	61	39.3	42.6	18.0	0.0
5+	1029	32.9	22.5	44.5	339	38.6	40.7	20.1	0.6

^a At last multiphasic health check-up, 1964–1973.

Association among never smokers

Among the never smokers the SMR appeared somewhat higher than that for all barbiturate users in the first three follow-up intervals and decreased to near unity in the last three (Table 1). However, the numbers of cases were quite small and the CI were wide. Lung cancer develops so infrequently among non-smokers that, even with extended follow-up, no firm conclusions can be drawn among the never smoking group.

Lag analyses

More detailed analysis of the findings with follow-up through 1992 revealed, first, that incorporating a one- or two-year lag into the analysis (that is, ignoring cases that occurred during the first one or two years after the first barbiturate dispensing) had little effect. The SMR was 1.30 (95% CI: 1.13–1.49) with no lag, 1.24 (95% CI: 1.07–1.44) with a one-year lag and 1.24 (1.06–1.44) with a two-year lag. Thus, the association is not primarily attributable to use of barbiturates to treat symptoms of lung cancer before it was diagnosed.

Relation of barbiturate use to cigarette smoking

We attempted to determine whether high levels of barbiturate use might be a proxy for a higher prevalence of cigarette smoking, or among smokers, for a greater quantity of cigarettes smoked. As the number of barbiturate prescriptions increased,

the distribution of smokers, ex-smokers and never smokers varied little, but the proportion of smokers of >2 packs per day increased moderately; this association was not statistically significant overall (Spearman correlation for categories of number of barbiturate prescriptions versus quantity of cigarettes smoked per day = 0.036, $P = 0.12$) (Table 2).

Evidence regarding dose-response and effect of adjustment for cigarette smoking

When increasingly greater numbers of barbiturate prescriptions were received, the SMR increased, supporting a dose-response relationship for all barbiturate users. This was observed both before and after adjustment for cigarette smoking and seemed also to be true among never smokers but small numbers of cases render the findings in the latter group unreliable (Table 3). A χ^2 test for trend among the never smokers indicated borderline statistical significance ($\chi^2 = 2.68$, $P = 0.10$). In comparison with the SMR unadjusted for cigarette smoking, the excess risk was reduced but not eliminated in the smoking-adjusted values, and the pattern of positive dose-response persisted. The lower confidence limits of the smoking-adjusted SMR for the entire group, the ≥ 5 dispensing and the ≥ 20 dispensing subgroups were just below 1.0, indicating borderline statistical significance. Maximal adjustment for cigarette smoking in the Cox model gave virtually the same results as the simpler adjustment which did not

Table 3 Relation of number of recorded barbiturate dispensings to risk of developing lung cancer among all barbiturate users, those with smoking habits reported at multiphasic health check-ups, adjusted for cigarette smoking, and those who reported never smoking. Follow-up began with the first reported barbiturate dispensing for the total (1+) group and with the last for the specific categories

	No. of barbiturate dispensings					
	1	2-4	5-19	20+	5+	1+ (all)
Barbiturate users, adjusted for age, sex						
No. at risk	5606	2563	1635	301	1936	10 213
New cases observed	74	47	42	17	59	203
New cases expected	72.6	40.2	28.4	5.1	33.4	156.1
Standard morbidity ratio (SMR)	1.02	1.17	1.48	3.36	1.76	1.30
95% CI of SMR	0.80-1.28	0.86-1.56	1.07-2.00	1.96-5.38	1.34-2.28	1.13-1.49
Barbiturate users with smoking habit data: SMR also adjusted for cigarette smoking						
No. at risk	2606	1400	842	171	1013	5030
New cases observed	42	30	23	8	31	114
New cases expected	44.0	26.8	17.6	3.7	21.3	97.4
Standard morbidity ratio (SMR)	0.95	1.12	1.30	2.19	1.46	1.17
95% CI of SMR	0.69-1.29	0.76-1.60	0.83-1.96	0.95-4.31	0.99-2.07	0.97-1.41
Barbiturate users with smoking habit data: Cox model: Rate ratios (RR) maximally adjusted for cigarette smoking						
Rate ratio (RR)	0.97	1.14	1.29	2.13	1.44	1.19
95% CI of RR	0.71-1.33	0.78-1.65	0.85-1.98	1.05-4.31	0.99-2.08	0.97-1.46
Barbiturate users identified as never smokers						
No. at risk	1066	556	385	73	458	2082
New cases observed	2	3	2	1	3	9
New cases expected	3.8	2.2	1.9	0.4	2.3	8.7
Standard morbidity ratio (SMR)	0.53	1.36	1.04	2.76	1.31	1.03
95% CI of SMR	0.06-1.91	0.28-3.97	0.13-3.76	0.07-15.39	0.27-3.84	0.47-1.96

consider duration of smoking or inhalation but the lower confidence limit of the rate ratio for the ≥ 20 dispensing subgroup slightly exceeded 1.0.

Other smoking groups

Among the current smokers, there was a substantial association of barbiturate use with lung cancer that became weaker as follow-up increased. To illustrate, the SMR was 1.52 (95% CI: 1.05-2.14) based on 33 observed and 21.7 expected cases in follow-up of up to 7 years, and 1.25 (95% CI: 1.00-1.55) based on 84 observed and 67.1 expected cases in follow-up of up to 23 years. Among the ex-smokers there was never an appreciable association of barbiturate use with lung cancer; the corresponding SMR and observed/expected cases were 0.88 (95% CI: 0.32-1.91), 6/6.8 and 1.03 (95% CI: 0.64-1.58), 21/20.4.

Confirmation of smoking status and lung cancer diagnosis of never smoking barbiturate users

We reviewed the medical records of the nine barbiturate users who reported never smoking cigarettes and who developed lung cancer. Eight of them were women. All lung cancers were confirmed; however, one of these patients also had a breast cancer and it was not clear to the treating physicians whether the cancer was primary in the lung or metastatic from the breast. Tissue diagnoses were available for seven of these patients. Four of the lung cancers were adenocarcinomas, one was of broncho-alveolar cell type, one was considered either oat cell or undifferentiated, and one was a malignant mesenchymoma.

All nine subjects were confirmed as never smokers except one who gave inconsistent responses on her multiphasic questionnaires. The discharge summary of her hospitalization for lung cancer, in 1993 at age 75, indicated a 'two-pack-year history of smoking a long time ago'.

Indications for multiple barbiturate prescriptions

We arbitrarily selected the 23 people who had received either 22 or 23 prescriptions for phenobarbital and examined their relevant computer-stored diagnoses, available only for the period 1967-1973, starting about 2 years before the pharmacy was computerized. Ten had cardiovascular disease and/or hypertension, seven had a seizure disorder, four had anxiety, one had a gastrointestinal problem and one had no obvious reason recorded for receiving the drug. Seven of these patients had received phenobarbital predominantly from one particular physician, and three, two and two patients from three other physicians, respectively.

Discussion

To our knowledge, ours is the only study of the relationship of barbiturate use to risk of lung cancer that has included analytical control for cigarette smoking. Other epidemiological evidence has been based on elevated risk of lung cancer in follow-up of patients with epilepsy, many of whom have received phenobarbital for long-term anticonvulsant therapy.³⁻⁷ In these studies phenobarbital use was neither implicated nor ruled out as the reason for the excess of lung cancer cases. In an

attempt to control for cigarette smoking, Olsen *et al.*⁷ conducted a nested case-control study in one such cohort of epileptics in Denmark, but most of the lung cancer cases had died and could not complete questionnaires about their smoking habits. Because their control group reported a higher prevalence of cigarette smoking than the general Danish population, Olsen *et al.* concluded that this was the likely reason for the elevated lung cancer incidence among their epileptics.

With 16 years of follow-up added to those available for our first report on barbiturates and lung cancer,¹ the association still persists and is not attributable to the use of barbiturates to treat symptoms of lung cancer before it was diagnosed. Furthermore, there was an apparent dose-response relationship when dose was based on the number of prescriptions dispensed. The crucial question is whether the association is attributable to cigarette smoking. Although we did not arrive at a conclusive answer, we believe that our further investigation should be reported.

We did not find a strong relation of cigarette smoking to barbiturate use. Nevertheless analytical control for the smoking habit reduced the excess barbiturate-associated risk of lung cancer by about one-third to one-half as seen by comparing the SMR in the top two sections of Table 3. Even so, a weak barbiturate/lung cancer association was still present and there was a positive dose-response pattern with as good control for smoking as we could accomplish in these data.

Still, there could be some residual confounding by cigarette smoking if barbiturate users tended to smoke more than non-users within the broad smoking-quantity categories that were available, or with respect to unmeasured aspects of smoking such as depth of inhalation, butt length, or persistence of smoking during follow-up. The only way to rule out possible residual confounding in our data is to restrict attention to the never smokers. But because lung cancer develops infrequently in never smokers there were very few cases among these barbiturate users. In our first report,¹ with 7 years of follow-up there were four cases. Now, with 16 more years of follow-up only five were added.

What can be learned from the never smokers, acknowledging their small numbers? Among them the barbiturate/lung cancer association was present only in the early years of follow-up. This would fit with the idea that barbiturates are late-stage promoters of carcinogenesis and is consistent with the experimental data.³ There was an apparent dose-response trend and it was of borderline statistical significance. The 20+ dispensing group showed the highest risk but this barely deserves mention since they developed only one lung cancer case.

The never smokers who developed lung cancer were almost all women and the predominant histology was adenocarcinoma. Three of the four adenocarcinomas were diagnosed before 1980 when the largest increases in risk were observed. This suggests that the main suspicion concerning barbiturates, on which more attention should be focused, is that they increase risk of adenocarcinoma in women. However, only two of the four never smokers who developed adenocarcinoma received more than one prescription (4 and 23 respectively) for barbiturates during the drug ascertainment period whereas this was true of all three with other known histology (4, 12, 14) so the picture is not clear-cut.

In summary, an additional 16 years of follow-up has allowed us to study the barbiturate/lung cancer association in greater

depth. The modestly elevated SMR tended to decrease over time supporting a tumour-promoter effect. Control for smoking reduced but did not eliminate the association. Never smokers showed the association primarily during the early years of follow-up and exhibited a dose-response trend of borderline statistical significance. The number of cases of lung cancer among the never-smoking barbiturate users remained small and the barbiturate/lung cancer association among them involved mostly women and adenocarcinoma. Our study still cannot give a definitive answer as to whether barbiturate use can predispose to lung cancer but the characteristics of the association that we observed have become more clearly defined by the additional data that have accumulated.

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