

# Antiepileptic Treatment and Risk for Hepatobiliary Cancer and Malignant Lymphoma

Jørgen H. Olsen,<sup>1</sup>Gabi Schulgen, John D. Boice, Jr., John Whysner, Lois B. Travis, Gary M. Williams, Frank B. Johnson, and James O'D. McGee

*Division for Cancer Epidemiology, Danish Cancer Society, DK-2100 Copenhagen Ø, Denmark [J. H. O.]; Institut für Medizinische Biometrie und Informatik der Albert Ludwigs Universität Freiburg, D-79104 Freiburg, Germany [G. S.]; Radiation Epidemiology Branch National Cancer Institute, Bethesda, Maryland 20892 [J. D. B., L. B. T.]; Division of Pathology and Toxicology, American Health Foundation, Valhalla, New York 10595 [J. W., G. M. W.]; Department of Chemical Pathology, Armed Forces Institute of Pathology, Washington, DC [F. B. J.]; and Nuffield Department of Pathology and Bacteriology, John Radcliff Hospital University of Oxford, Headington, Oxford OX3 9DU, United Kingdom [J. O. M.]*

## ABSTRACT

The possible influence of phenobarbital and phenytoin treatment on cancer risk was investigated in a case-control study nested in a cohort of 8004 epileptic patients in Denmark. Information on anticonvulsive treatments was abstracted for 95% of 60 patients with cancers of the liver and biliary tract or malignant lymphoma and for 94% of 171 cancer-free control patients. Use of anticonvulsive drugs was correlated with angiographic procedures that used Thorotrast, a well-known human liver carcinogen. After exclusion of study subjects exposed to Thorotrast, no association was seen between treatment with phenobarbital and cancer of the liver (odds ratio, 1.0; 95% confidence interval, 0.1-8.0) or biliary tract (odds ratio, 0.8; 95% confidence interval, 0.1-4.2). Furthermore a histopathological evaluation of slides from 7 of 9 liver cancer patients not treated with Thorotrast revealed that 3 of the 4 cases of hepatocellular carcinoma involved cirrhosis of the liver, which suggested an etiological role for alcohol or viral hepatitis. A possible link was observed between use of phenytoin and risk for non-Hodgkin's lymphoma (1.8; 0.5-6.6), with a rising trend in risk with increasing dose. Our results suggest that the increased risk for cancers of the liver and biliary tract among Danish epileptic patients is likely to be due to Thorotrast administration and factors associated with cirrhosis of the liver rather than to anticonvulsive treatment.

## INTRODUCTION

Our survey of cancer incidence among 8004 patients with epilepsy in Denmark revealed a significant 4.7-fold excess of cancers of the liver and a nonsignificant 1.5-fold excess of non-Hodgkin's lymphoma (1, 2). Although many of the liver cancers were caused by Thorotrast (a contrast medium used during cerebral angiography in 140 of the patients), excesses were also observed in a subgroup of 7864 epileptics presumed not to have received this radioactive substance, with a significant 2.9-fold increased risk in patients who were followed for 30 years or more (1). Phenobarbital, which is one of the main drugs used in the treatment of epilepsy, can cause benign and malignant liver tumors in mice and benign liver tumors in various strains of rats (3). Phenytoin (5,5-diphenylhydantoin or Dilantin), another commonly used anticonvulsant drug, can cause benign lymphadenopathy in humans and has been linked with malignant lymphoma in small surveys (4-6).

In order to investigate the influence of long-term treatment with phenobarbital and phenytoin on the risks for liver cancer, cancer of the biliary tract, and malignant lymphoma, a nested case-control study was carried out among Danish epileptics.

## MATERIALS AND METHODS

**Case-Control Study.** The earlier Danish cohort study of 8004 epileptic patients identified 26 primary liver cancers, 14 biliary tract cancers, 17 non-Hodgkin's lymphoma, and 6 cases of Hodgkin's disease (Table 1) (1). Patients had been treated at the Philadelphia epilepsy center between 1932 and 1962 and were followed for cancer incidence through 1984. Two controls were matched individually to each case of liver or biliary tract cancer and five controls were matched to each case of lymphoma on the basis of sex, year of birth ( $\pm 1$  year), and survival time. Three cases (4.8%) and 12 controls (6.2%) were excluded because medical records were missing; an additional 12 controls who were no longer matched to a case were excluded, leaving 60 cases and 171 controls for study (Table 1).

Detailed drug use was abstracted from medical records at the epilepsy center. Exposure to Thorotrast was determined from information on cerebral angiography and through record linkage with files from the Danish Thorotrast study (2,7). Phenobarbital in daily doses of 100-300 mg was frequently prescribed to prevent seizures (8). Phenytoin (100-400 mg/day) came in to use in the 1940s. Cumulative doses were computed by assuming that treatment continued daily at the prescribed dose after each discharge until the date of cancer diagnosis (or equivalent date for matched controls) or the end of 1964, whichever occurred first. After the mid-1960s, many new anticonvulsants became available, and credible assumptions about continuation of previous treatments after discharge were not possible. A patient was classified as exposed if he or she received more than 5 g (50 tablets) of phenobarbital or phenytoin or more than 10 g (40 tablets) of primidone lifelong. A median cumulative dose of 750 g was chosen to separate low from high exposures to phenobarbital and phenytoin.

The effect of the anticonvulsants was assessed by means of conditional logistic regression for matched sets (9). Crude and adjusted risk estimates (OR)<sup>2</sup> and associated 95% confidence intervals were calculated. Adjustment was undertaken for other anticonvulsant treatments whenever possible by inclusion of a 0/1 variable for each treatment in the conditional logistic regression. Because of a strong effect of Thorotrast exposure on liver cancer risk (17 exposed cases; 1 exposed control), results are presented for matched sets with and without Thorotrast exposure separately. The supplementary unmatched results in the non-Thorotrast-exposed group were derived by logistic regression analysis.

**Histopathological Review.** Slides of tumor tissue were obtained from seven of the nine liver cancer patients who had no documented exposure to Thorotrast, and diagnoses were determined independently by two pathologists (G. M. W. and J. O'D. M.). These slides and slides from two patients with known Thorotrast exposure (positive controls) were also examined for thorium by X-ray analysis, by remounting sections from the slides on spectrographic grade carbon discs, and by using a Kevex 800 X-ray energy analytical system with a Quantum detector (10). The two positive controls for Thorotrast were identified without difficulty.

## RESULTS

Among control patients, phenobarbital was the most commonly prescribed antiseizure drug (71%), followed by phenytoin (52%) and primidone (27%). Linkage with the files of the Danish Thorotrast study showed that Thorotrast had been given to 17 (65%) of the liver

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<sup>1</sup>To whom requests for reprints should be addressed.

<sup>2</sup>The abbreviations used are: OR, odds ratio; RR, relative risk.

Table 1 Relative risks of developing liver and biliary tract cancers and lymphomas observed in the Danish epilepsy study, and numbers included in the care-control analysis<sup>a</sup>

Cancer	Epilepsy cohort <sup>b</sup>			Case-control study	
	n	RR	95% CI	Cases (n)	Controls (n)
Liver	26	4.7	3.2-6.8	26	49
Biliary tract	14	2.2	1.2-3.5	13	24
Non-Hodgkin's lymphoma	17	1.5	0.9-2.3	15	69
Hodgkin's disease	6	0.9	0.4-2.0	6	29

<sup>a</sup>Unadjusted for Thorotrast exposure; general population used for comparison.

<sup>b</sup>Sources: Refs. 1 and 2.

<sup>c</sup>CI, confidence interval.

cancer patients, 3 (23%) of the patients with biliary tract cancer, 1 (5%) of the lymphoma patients, and 3 (2%) of the control patients, demonstrating how strongly administration of Thorotrast is associated with cancers of the liver and biliary tract. Administration of Thorotrast revealed a slight positive correlation with the use of anticonvulsive treatment in study subjects, with correlation coefficients of 0.2 and 0.1 for phenobarbital and phenytoin, respectively.

**Liver and Biliary Tract Cancer.** Overall, administration of phenobarbital was associated with nonsignificantly increased risks for cancers of the liver (OR, 2.0) and biliary tract (OR, 1.5) (Table 2). Moreover, the risks increased with increasing dose of the drug. Owing to the particularly high prevalence of Thorotrast administration among the cases, we performed a separate, but unadjusted, matched analysis of the subgroup of patients not exposed to Thorotrast (Table 2). This analysis revealed no elevation of risk for liver cancer (OR, 1.0) or for biliary tract cancers (OR, 0.8). The risk estimates associated with each tumor type were, however, highly unstable, as reflected in the width of the associated 95% confidence intervals. Breaking the matching

and using all 48 non-Thorotrast controls for liver cancer patients (not shown in the table) narrowed the confidence intervals but did not change the risk estimates markedly. Thus, following any exposure to phenobarbital, liver cancer was associated with an odds ratio of 1.1 (95% confidence interval, 0.2-5.2). Following cumulative exposure to 750 g or more of phenobarbital, the corresponding odds ratio was 2.4 (95% confidence interval, 0.5-12).

The matched analysis of matched sets with at least one individual exposed to Thorotrast showed a significant association between phenobarbital given in highest dose category and liver cancer; however, the effect of phenobarbital and Thorotrast could not be separated in this particular subgroup due to just 1 control subject but all 17 cases being exposed to Thorotrast.

The relative risk for cancers of the liver and biliary tract was close to unity among patients ever treated with phenytoin (OR, 1.2; 95% confidence interval, 0.5-3.1) or primidone (0.9; 95% confidence interval, 0.4- 2.3).

Table 3 gives further details on the nine cases of liver cancer presumed to have had no exposure to Thorotrast on the basis of records and the absence of thorium in the seven tissue specimens available for X-ray analysis. The consensus diagnoses reached during pathological reevaluation of the seven tissue samples were six cases of primary liver tumors (four hepatocellular carcinomas (three with cirrhosis) and two cholangiocarcinomas) and a probable metastasis from a gastrointestinal tract cancer. None of the patients with cirrhosis had received significant doses of phenobarbital (Table 3).

**Malignant Lymphoma.** A slight nonsignificantly increased risk of 1.6 was observed for malignant lymphomas in epileptic patients ever given phenytoin (Table 4), highest for the subgroup of non-Hodgkin's lymphoma (OR, 1.8; 95% confidence interval, 0.5-6.6) and increas-

Table 2 Odds ratio<sup>a</sup> and 95% confidence intervals for cancers of the liver and biliary tract associated with exposure to phenobarbital

Site with phenobarbital	Matched sets included in analysis								
	All			No Thorotrast			Any Thorotrast		
	Cases/controls	OR	95% CI <sup>b</sup>	Cases/controls	OR	95% CI	Cases/controls	OR	95% CI
Liver									
None (<5 g)	7/20	1		3/5	1		4/15	1	
Ever exposed	19/29	2.0	0.5-7.2	6/11	1.0 <sup>c</sup>	0.1-8.0	13/18	3.5	0.7-18
5-749 g	5/16	0.4	0.1-3.4	1/5	0.4 <sup>c</sup>	0.0-5.9	4/11	1.0	0.1-14
>=750 g	14/13	3.2	0.7-14	5/6	2.8 <sup>c</sup>	0.2-39	9/7	6.2	1.0-39
Biliary tract									
None (<5 g)	3/8	1		3/5	1		0/3	1 <sup>d</sup>	—
Ever exposed	10/16	1.5 <sup>c</sup>	0.4-6.7	7/14	0.8 <sup>c</sup>	0.1-4.2	3/2	—	—
5-749 g	5/9	1.3 <sup>c</sup>	0.3-7.0	4/8	0.8 <sup>c</sup>	0.1-4.7	1/1	—	—
>=750 g	5/7	1.6 <sup>c</sup>	0.3-8.9	3/6	0.8 <sup>c</sup>	0.1-6.1	2/1	—	—

<sup>a</sup>Matched analysis adjusted for other anticonvulsant therapy.

<sup>b</sup>CI, confidence interval.

<sup>c</sup>Matched analysis unadjusted for other anticonvulsant therapy due to small numbers.

<sup>d</sup>—, not assessable.

Table 3 Primary liver cancers among epileptics with no evidence of Thorotrast exposure by histopathological examination and X-ray analysis for thorium residuals

Gender and yr of birth	Age at diagnosis (yr)	Source of verification	Original diagnosis	Results of reevaluation		Cumulative dose <sup>a</sup> of phenobarbital (g)
				Histocytological review	Comments	
F, 1899	65	Death certificate	Liver cancer	No tissue available		824
M, 1904	81	Death certificate	Liver cancer	No tissue available		647
M, 1905	61	Autopsy	Cholangiocarcinoma	Cholangiocarcinoma		1079
M, 1908	67	Autopsy	Hepatocellular carcinoma	Cholangiocarcinoma		1589
M, 1913	65	Autopsy	Hepatocellular carcinoma	Hepatocellular carcinoma	Tissue from a metastasis to the lung	22011
F, 1920	61	Biopsy	Hepatocellular carcinoma	Hepatocellular carcinoma	Cirrhosis present	3
F, 1920	59	Autopsy	Cholangiocarcinoma	Possibly secondary tumor		1065
M, 1925	59	Biopsy	Cholangiocarcinoma	Hepatocellular carcinoma	Cirrhosis present	0
F, 1926	58	Biopsy	Liver cancer, not otherwise specified	Hepatocellular carcinoma	Cirrhosis present	0

<sup>a</sup>Estimated as cumulative dose from date of initial treatment till end of 1964.

Table 4 Odds ratios<sup>a</sup> and 95% confidence intervals for malignant lymphomas associated with exposure to phenytoin

Subtype and lymphoma with phenytoin	Cases/controls	OR	95% CI <sup>b</sup>
All malignant lymphomas			
None	8/52	1	
Ever exposed	13/46	1.6	0.5-4.8
1-749 g	5/25	1.1	0.3-4.0
>=750 g	8/21	3.0	0.7-13
Non-Hodgkin's lymphoma			
None	6/35	1	
Ever exposed	9/34	1.8	0.5-6.6
1-749 g	3/18	1.0	0.2-4.9
>=750 g	6/18	3.1	0.6-15
Hodgkin's disease			
None	2/17	1	
Ever exposed	4/12	1.2	0.1-14
1-749 g	2/9	1.3	0.1-18
>=750 g	2/3	0.7	0.0-34

<sup>a</sup>Matched analysis adjusted for other anticonvulsant therapy,

<sup>b</sup>CI, confidence interval.

ing with dose. A modest increase in risk was seen in association with the treatment with the two other major anticonvulsive drugs, phenobarbital (1.5; 95% confidence interval, 0.5-5.0) and primidone (1.3; 95% confidence interval, 0.3-5.0).

**DISCUSSION**

Although studies on mice and rats have demonstrated that phenobarbital has a marked tumor-promoting effect in liver (11-13), our epidemiological study and pathological review of liver cancer indicate that any excess risk in humans treated with the drug must be small.

This cohort of 8004 epileptic patients, of whom approximately two-thirds had been treated with phenobarbital, is the largest of the established cohorts (14). A total of 26 cases of primary liver cancer were observed on the basis of more than 200,000 person years of follow-up over a period of 52 years (1). Only nine of the cases occurred among epileptics not known to have received Thorotrast of whom six had been treated with phenobarbital, suggesting that the exposure frequency of phenobarbital among cases is similar to that seen in controls. However, the statistical power of the study to detect an association between phenobarbital and liver cancer in the absence of Thorotrast exposure is low, as also reflected in the size of the associated 95% confidence interval with an upper limit of 8.0 (Table 2).

However, some additional observations of biological relevance pointed to a lack of association. Only four of the nine observed liver cancers were of the hepatocellular subtype, which is the neoplasm associated with phenobarbital administration in the experimental rodent studies (15); however, in three cases the tumor originated from cirrhotic liver tissue from patients with almost no phenobarbital exposure, indicating that either alcoholic liver disease or viral hepatitis was the most likely etiology. Cirrhosis of the liver is the predominant risk factor associated with hepatocellular carcinomas in humans in Western countries (16, 17). Phenobarbital would be expected to produce a hepatocellular carcinoma without cirrhosis, as it does in mice (13). For the fourth case of hepatocellular carcinoma, only a metastasis to the lung was available for review therefore it was not possible to determine whether there was underlying liver disease. One of the nine cases was a metastatic tumor of probable gastrointestinal origin. The only tumors left to support an etiological consideration were, therefore, two cases of cholangiocarcinoma and two cases of unknown histology; cholangiocarcinomas are not, however, associated with phenobarbital in experimental studies (15).

The RR for liver cancer among epileptics exposed to Thorotrast (RR, 202; n = 17) (2) was higher but statistically compatible with that

observed in the Danish Thorotrast study (RR, 126; n = 79) (7) and comparable to that of a similar Thorotrast study in Germany (RR, 200; n = 396) (18). The possibility of some interaction between Thorotrast and phenobarbital, however, cannot be excluded on the basis of the present study.

While our study has limitations, such as the small numbers of specific types of cancers, there is little evidence of serious bias. Medical records were abstracted without knowledge of case-control status of study subjects; assumptions about cumulative exposure to drugs seem reasonable, given the extensive records available during hospitalizations and outpatient visits, although some uncertainty exists about drug use after discharge. The most serious concern was the effect of Thorotrast in overall analyses of the relationship between cancers of the liver and biliary tract and phenobarbital use. Although this problem was solved by restricting the analyses to patients not exposed to Thorotrast, the number of liver cancer cases available for analysis was further reduced, yielding even more unstable risk estimates. The absence in this study of a significant association between treatment with phenobarbital and human liver cancer is probably not due to inadequate exposure levels: 50% of the phenobarbital-treated epileptics received more than 750 g of the drug between first admission to the epilepsy treatment center (1933-1962) and the mid-1960s, which is equivalent to a daily dose of 200 mg for 10 years; some patients received up to 5 kg of the drug. In support of the findings of the present study is the fact that no case of liver cancer was found in cohort studies of epileptic patients in the United Kingdom (expected number, 0.6) or Minnesota (expected number, 0.2) (19, 20).

No relationship was observed between use of phenobarbital and risk for malignant lymphoma; however, the risks for lymphomas in phenytoin-treated patients were somewhat elevated, increasing with dose in the subgroup of non-Hodgkin's lymphoma patients. Only one case (a non-Hodgkin's lymphoma) and two lymphoma controls had been exposed to Thorotrast. Exclusion of these individuals from the analysis did not change meaningfully the point estimates of risk. Benign lymphadenopathy is a well-known clinical side effect of phenytoin treatment, but this condition regresses when treatment is stopped or changed, so that benign lymphadenopathy is not likely to explain the observed association. A number of cases of lymphomas have been reported among individuals treated with phenytoin, and there has been case reports of neuroblastomas in the fetal hydantoin syndrome, a constellation of birth defects seen among offspring of mothers who received phenytoin (3-6). In the mortality study of epileptic patients in the United Kingdom (19), 6 neoplasms of the lymphatic and hematopoietic tissues were observed, whereas 4.7 were expected (standardized mortality ratio, 1.3; nonsignificant); and in the United States incidence study (20), 3 lymphomas were seen, with 1.4 expected (RR, 2.1; nonsignificant). No analyses were performed to relate lymphomas to specific anticonvulsants.

In conclusion, our findings indicate that the increased risk for cancers of the liver and biliary tract among Danish epileptic patients are due to factors other than anticonvulsant treatment, including Thorotrast administration and conditions related to cirrhosis of the liver. Phenobarbital then appears to be of little importance in the etiology of these tumor types in humans. The study was large, and most patients treated with phenobarbital had been exposed during a significant part of their life to dose levels per body weight that are compatible to those used in studies of experimental animals. The risk for non-Hodgkin's lymphomas after long-term use of phenytoin may have been increased, but the association remains to be confirmed.

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