Gabapentin and Cancer Risk: Updated Findings from Kaiser Permanente Northern California

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ABSTRACT

Context: Epidemiologic analyses of gabapentin use and cancer risk in Kaiser Permanente Northern California were previously carried out in a collaborative study and independently evaluated in a UK database.

Objective: To update these epidemiologic analyses with 7.5 more years of follow-up.

Design: Case-control analyses using conditional logistic regression to estimate relative risk by odds ratios using the prior collaboration's criteria for identifying positive drug-cancer associations and our more stringent criteria requiring stronger association, lower p values, and evidence of dose response. New associations were reanalyzed with additional control for limited measures of smoking and alcohol use.

Main Outcome Measures: Gabapentin-cancer associations.

Results: No previously found associations met our stringent criteria, but cancers of the mouth/pharynx, esophagus, liver, and vagina did. All odds ratios for 3 or more and 8 or more prescriptions were moderately reduced by control for smoking and alcohol. Substantial elevations of risk of mouth/pharynx, liver, and vaginal cancers were associated with only 1 prescription dispensed. Sensitivity analyses aimed at possible confounding and other biases did not change our conclusions but did reveal a markedly increased risk of vaginal cancer in gabapentin users with epilepsy compared with users without.

Conclusion: The reduced magnitude of relative risk with control for smoking and alcohol use suggests confounding by known risk factors. Biologically implausible elevated risk from just 1 prescription suggests confounding by indication. Either or both of these concerns applies to each of the 4 cancer sites associated with gabapentin use. Updated analyses show little if any evidence for carcinogenic effects of gabapentin.

INTRODUCTION

In 2011, we participated in a collaborative study, headed by Michael Irizarry, MD, MPH, of GlaxoSmithKline Corporation, Research Triangle Park, NC, regarding the relation of gabapentin use to the risk of cancer development.[1] High doses of gabapentin, an anticonvulsive and analgesic pharmaceutical drug, had been found to be associated with the development of pancreatic acinar cell tumors in male Wistar rats,[2] which prompted that study.

For that study, our previous case-control screening of pharmaceuticals for possible carcinogenicity in Kaiser Permanente Northern California (KPNC)[3] was used to identify possible gabapentin-cancer associations in humans, which were independently evaluated in the UK General Practice Research Database (GPRD).[1] This computerized database, now called the Clinical Practice Research Datalink, contained anonymized data from patient records in the UK collected since 1987. Compared with no dispensings, 3 or more dispensings of gabapentin were minimally associated (odds ratio [OR] > 1.0, $p < 0.05$) with 9 cancer sites in KPNC members. These cancers were of the breast, lung/bronchus, urinary bladder, kidney/renal pelvis, stomach, anus/anal canal/anorectum, penis, other nervous system, and any cancer.[1] Only 1 of these, kidney/renal pelvis cancer, would meet our stricter screening criteria for limiting false-positive results ($OR \geq 1.50$, $p \leq 0.01$, higher risk for ≥ 3 dispensings than for 1 dispensing), suggesting dose response.[3] We suggested that this was subject to likely confounding by cigarette smoking and hypertension, but this possibility was not confirmed in additional analyses. There were 2 statistically significant associations in the GPRD analyses: Pancreatic cancer and renal cancer, but for both cancer sites there was no evidence of dose response or evidence for protopathic bias (prescribed for symptoms of cancer before diagnosis).

We now have 7.5 more years of follow-up data (January 2007-June 2014) for cancer occurrence and conducted the present study of gabapentin solely within KPNC and completely independent of the previous collaborating investigators. Our goals were to reevaluate previous associations and evaluate those newly found.

METHODS

As approved by the institutional review board of the Kaiser Foundation Research Institute, we have screened pharmaceutical drugs for possible carcinogenic effects in a research database of KPNC, an integrated health care system that currently has approximately 4 million subscribers. Data include records of prescriptions dispensed from KPNC pharmacies, clinical and laboratory data, and a cancer registry that reports to the California Cancer Registry and the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) program.[4]

Case-control analyses using conditional logistic regression are conducted in a cohort of subscribers with at least partial coverage of prescription costs and with membership starting on or after January 1, 1996, and followed-up until they left membership for any reason or June 30, 2014, whichever came first. Almost 100% of this cohort obtained all their prescriptions from KPNC pharmacies.[5] The earlier collaborative study[1] also encompassed pharmacy records from August 1, 1994, through December 31, 1995, which were not included

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in the newer research database. Up to 50 individuals without cancer (controls) are selected for each patient with cancer (case) and matched for age, sex, and year that KPNC membership began. The index date is the date of diagnosis for cases and the same or nearby date for controls that gives them equal follow-back time for ascertainment of drug exposure. Because of their increased risk of several cancers, patients who are positive for HIV infection were excluded from the study cohort.[6] All analyses exclude subjects with previous cancers at any cancer site, include a 2-year lag (ignore prescriptions within the 2 years before the index date), and are controlled for race/ethnicity.

For the previous collaborative study,[1] gabapentin-cancer associations were identified simply if the OR was greater than 1.0 and $p < 0.05$. Although the 2-year medication lag was used, there was no control for race/ethnicity, and HIV-positive subjects were excluded only in the analysis of cancer of the anus/anal canal/anorectum. The 9 cancer sites that met these criteria (listed in the Introduction) were analyzed again using the same criteria. We also screened all 56 cancer sites using our more stringent criteria (OR ≥ 1.50, $p \leq 0.01$, higher risk for ≥ 3 prescriptions than for 1 prescription as an indication of dose-response). Because the 4 cancer sites that previously screened positive have cigarette smoking and alcohol use as established risk factors—mouth/pharynx,[7] esophagus,[8] liver,[9] and vagina (alcohol use possible)[10]—we conducted multivariable analyses adding these 2 variables to the models. On the basis of oral and written questionnaires used in clinical encounters (using the earliest available record), cigarette smoking was classified as current, former, unknown, and never (reference), and alcohol use was classified as unknown, used less than 3 drinks per day, used 3 or more drinks per day, used unknown amount, and none (reference).

We conducted several sensitivity analyses to examine other potential confounding or biasing factors. These included controlling for socioeconomic status (using 2 available measures: Census block of residence and educational level); omitting alcohol use from the multivariable model because of incompleteness of the data; controlling for use vs nonuse of other

Table 1. Minimal associations[a] in KPNC case-control screening used to guide General Practice Research Database evaluations (previous) and recalculated with additional years of follow-up (latest)

Cancer site	No. of gabapentin-exposed cases, previous/latest	Previous OR (95% CI)[b]	Latest OR (95% CI)[c]
Breast	352/628	1.19 (1.01-1.39)	1.02 (0.94-1.10)
Lung/bronchus	269/517	1.34 (1.13-1.60)	1.36 (1.24-1.48)
Urinary bladder	100/173	1.41 (1.07-1.87)	1.15 (0.99-1.34)
Kidney/renal pelvis	70/134	1.71 (1.18-2.47)	1.44 (1.21-1.72)
Stomach	27/58	1.64 (1.01-2.64)	1.28 (0.98-1.67)
Anus/anal canal/anorectum	9/20	2.70 (1.16-6.25)	1.48 (0.94-2.34)
Penis	3/5	6.68 (1.47-30.28)	3.43 (1.33-8.85)
Other nervous system	2/2	6.67 (1.11-39.90)	1.53 (0.36-6.50)
Any cancer	1678/3662	1.10 (1.02-1.18)	1.08 (1.04-1.11)

[a] Odds ratio > 1.0, $p < 0.05$.
[b] Surveillance of drugs and cancers, 1994-2006. Two-year lag, no covariates. Cases positive for HIV were excluded from analysis of cancer of anus/anal canal/anorectum.
[c] Surveillance of drugs and cancers, 1996-2014. Two-year lag; subjects excluded from all analyses if they had a history of prior cancer or were HIV positive. Adjusted for race/ethnicity.
CI = confidence interval; KPNC = Kaiser Permanente Northern California; OR = odds ratio.

Table 2. Relative risk of cancer at 4 sites that screened positive for association with gabapentin use[a]

Number of prescriptions by cancer site	Cases, no.	Controls, no.	Model 1, OR (95% CI)[b]	Model 2, OR (95% CI)[c]
Mouth/pharynx				
Total	3670	182,423		
0	3516	177,248	1.00 (reference)	1.00 (reference)
Only 1	52	1885	1.37 (1.03-1.81)	1.26 (0.95-1.67)
≥ 3	86	2526	1.62 (1.30-2.02)	1.48 (1.18-1.85)
≥ 8	38	1260	1.41 (1.02-1.96)	1.26 (0.91-1.76)
Esophagus				
Total	1601	79,534		
0	1524	76,746	1.00 (reference)	1.00 (reference)
Only 1	23	1002	1.14 (0.75-1.74)	1.05 (0.69-1.61)
≥ 3	45	1398	1.59 (1.18-2.16)	1.39 (1.02-1.89)
≥ 8	35	681	2.53 (1.78-3.58)	2.15 (1.51-3.07)
Liver				
Total	2877	142,850		
0	2710	137,729	1.00 (reference)	1.00 (reference)
Only 1	57	1885	1.56 (1.19-2.05)	1.38 (1.05-1.81)
≥ 3	90	2501	1.97 (1.59-2.45)	1.64 (1.32-2.05)
≥ 8	40	1243	1.82 (1.32-2.50)	1.45 (1.05-2.01)
Vagina				
Total	139	6919		
0	126	6659	1.00 (reference)	1.00 (reference)
Only 1	5	89	3.22 (1.27-8.20)	3.04 (1.19-7.76)
≥ 3	8	136	3.35 (1.57-7.16)	3.01 (1.40-6.48)
≥ 8	6	73	4.70(1.96-11.28)	4.08 (1.67-9.93)

[a] Risk estimated by ORs listed according to the number of prescriptions dispensed. Note that ≥ 3 prescriptions includes ≥ 8 prescriptions.
[b] Adjusted for race/ethnicity. Two-year lag.
[c] Adjusted for race/ethnicity, smoker status, and alcohol use. Two-year lag.
CI = confidence interval; OR = odds ratio.

antiepileptic drugs; analyzing users of gabapentin with epilepsy (ascertained by clinical diagnosis or receipt of antiepileptic drugs) separately from other users of gabapentin, many of whom probably received it to control pain; analyzing by cumulative dose received rather than the number of prescriptions; and changing 2-year lag to no lag to include all prescriptions received up to the index date.

RESULTS

Reanalysis using the original weak criteria with 7.5 additional years of follow-up yielded reduced ORs and loss of statistical significance for cancers of the breast, urinary bladder, stomach, anus/anal canal/anorectum, and other nervous system. Cancers of the kidney/renal pelvis and the penis had lower but still statistically significant ORs with longer follow-up, and associations with lung cancer and all cancers combined showed very little change and remained significant (Table 1).

Findings with New Screening Criteria

None of the original 9 cancer sites met our more stringent screening criteria. Four other cancer sites did: Mouth/pharynx, esophagus, liver, and vagina. Table 2 shows the initial screening findings (Model 1) and multivariable analyses with cigarette smoking and alcohol use added (Model 2). Displayed are the main results: ORs for only 1 prescription, 3 or more prescriptions, and 8 or more prescriptions (included in ≥ 3 prescriptions) of gabapentin. ORs for mouth/pharynx were mildly elevated, with some evidence of dose response, when we compared 3 or more prescriptions with 1 prescription but not 8 or more prescriptions with 1 prescription. Adjustment for cigarette smoking and alcohol use reduced all ORs moderately. Esophageal cancer showed clearly elevated and statistically significant ORs for 3 or more and 8 or more prescriptions, with evidence of dose response, and moderate reductions in risk with control for cigarette smoking and alcohol use. Associations with liver cancer were all statistically significant, even with only 1 prescription. After adjustment for cigarette smoking and alcohol use, which reduced ORs moderately, dose response was suggested in a comparison of 3 or more but not 8 or more prescriptions with 1 prescription. ORs, including that for only 1 prescriptions, were all greater than 3.0 for vaginal cancer despite small numbers of cases with gabapentin use. As

Table 3. Sensitivity analyses: Results of modified multivariable analyses compared with original model for relative risk of cancer at 4 sites that screened positive for association with gabapentin use[a]

Number of prescriptions by cancer site	Original model	Model with socioeconomic status added[b]	Model with alcohol use excluded[c]	Model with use vs nonuse of other antiepileptic drugs[d]	Model showing gabapentin users with or without epilepsy[e]		Model with no lag[f]
					Epilepsy	Nonepilepsy	
Mouth/pharynx							
0	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Only 1	1.26 (0.95-1.67)	1.26 (0.95-1.67)	1.28 (0.97-1.70)	1.25 (0.94-1.66)	0.69 (0.34-1.39)	1.48 (1.09-2.01)	1.13 (0.88-1.44)
≥ 3	1.48 (1.18-1.85)	1.47 (1.18-1.84)	1.50 (1.20-1.87)	1.46 (1.16-1.83)	1.44 (1.01-2.03)	1.51 (1.14-2.00)	1.52 (1.27-1.82)
≥ 8	1.26 (0.91-1.76)	1.26 (0.91-1.75)	1.28 (0.92-1.78)	1.25 (0.89-1.74)	1.05 (0.61-1.79)	1.44 (0.95-2.17)	1.50 (1.17-1.94)
Esophagus							
0	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Only 1	1.05 (0.69-1.61)	1.05 (0.69-1.60)	1.08 (0.71-1.65)	1.04 (0.68-1.59)	0.93 (0.38-2.28)	1.09 (0.68-1.75)	1.18 (0.84-1.66)
≥ 3	1.39 (1.02-1.89)	1.37 (1.01-1.87)	1.42 (1.04-1.93)	1.36 (0.99-1.87)	1.05 (0.61-1.80)	1.62 (1.12-2.35)	1.27 (0.97-1.66)
≥ 8	2.15 (1.51-3.07)	2.14 (1.50-3.04)	2.21 (1.55-3.14)	2.12 (1.48-3.03)	1.85 (1.05-3.28)	2.38 (1.53-3.70)	1.71 (1.23-2.36)
Liver							
0	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Only 1	1.38 (1.05-1.81)	1.37 (1.04-1.80)	1.45 (1.10-1.90)	1.35 (1.03-1.78)	1.26 (0.71-2.27)	1.41 (1.04-1.92)	1.22 (0.96-1.55)
≥ 3	1.64 (1.32-2.05)	1.63 (1.31-2.04)	1.78 (1.43-2.22)	1.58 (1.26-1.99)	1.39 (0.96-2.02)	1.81 (1.38-2.36)	1.46 (1.20-1.77)
≥ 8	1.45 (1.05-2.01)	1.44 (1.04-1.99)	1.59 (1.15-2.20)	1.39 (1.00-1.93)	1.35 (0.81-2.25)	1.53 (1.01-2.31)	1.48 (1.13-1.93)
Vagina							
0	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Only 1	3.04 (1.19-7.76)	3.12 (1.22-8.00)	3.26 (1.28-8.28)	2.96 (1.15-7.66)	6.21 (1.77-21.78)	1.76 (0.42-7.34)	2.50 (1.13-5.54)
≥ 3	3.01 (1.40-6.48)	3.05 (1.41-6.57)	3.27 (1.53-6.98)	2.88 (1.29-6.41)	6.71 (2.88-15.62)	0.61 (0.08-4.52)	2.92 (1.46-5.85)
≥ 8	4.08 (1.67-9.93)	4.18 (1.72-10.20)	4.49 (1.87-10.79)	3.91 (1.55-9.88)	7.91 (2.91-21.48)	1.16 (0.15-8.77)	3.91 (1.71-8.93)

[a] Risk estimated by odds ratios (and 95% confidence intervals) listed according to the number of prescriptions dispensed. Note that ≥ 3 prescriptions includes ≥ 8 prescriptions. All with 2-year lag except where indicated. Original model was adjusted for race/ethnicity, smoking status, and alcohol use.

[b] Adjusted for race/ethnicity, smoking status, alcohol use, census block of residence, and educational level.

[c] Adjusted for race/ethnicity and smoker status (alcohol use excluded from model).

[d] Adjusted for race/ethnicity, smoking status, alcohol use, and use vs nonuse of other antiepileptic drugs.

[e] Adjusted for race/ethnicity, smoking status, alcohol use, and gabapentin users classified to those with an epilepsy diagnosis or other antiepileptic drug use and those without an epilepsy diagnosis and without use of other antiepileptic drugs.

[f] Adjusted for race/ethnicity, smoking status, and alcohol use. Two-year lag eliminated.

with the other cancer sites, adjustment for cigarette smoking and alcohol use reduced ORs moderately.

The full models with results for 1, 2, 3, 4 to 7, and 8 or more prescriptions and for all categories of race/ethnicity, cigarette smoking, and alcohol use in relation to the risk of each of the 4 cancers are provided as Supplemental Tables 1 to 4, available at www.thepermanentejournal.org/files/2018/18-040-Suppl.pdf.

Although the previous collaborative study was prompted mainly by experimental evidence of an association of gabapentin use with pancreatic cancer in rats,[2] we again found no statistically significant association of gabapentin with this cancer site; the OR for 3 or more prescriptions vs none was 1.15 (95% confidence interval [CI] = 0.95-1.40) based on 109 cases and 4634 controls. One cancer site, rectum/rectosigmoid, met our analogous strict screening criteria for a negative association OR less than 0.67 for 3 or more prescriptions vs none and more negative than the OR for 1 prescription vs none. The findings for this cancer site were as follows: 3 or more vs 0 prescriptions: OR = 0.61 (95% CI = 0.46-0.82) based on 46 cases and 3650 controls; 1 vs 0 prescriptions: OR = 1.01 (95 CI = 0.78-1.31) based on 58 cases and 2782 controls. This negative association was not evaluated further.

Sensitivity Analyses

The addition of indicators related to socioeconomic status yielded ORs virtually identical to those absent of this change (Table 3). Exclusion of alcohol use from the model resulted in slightly higher ORs for all number-of-prescription categories for all 4 cancer sites (Table 3). The opposite was true when use vs nonuse of other antiepileptic drugs was added to the model, with slight decreases in all number-of-prescription categories for all 4 cancer sites (Table 3).

About 30% of gabapentin-using cases had a diagnosis of epilepsy or used another drug for treatment of epilepsy. For example, of the 154 gabapentin recipients among cases of the most frequent cancer site, mouth/pharynx, 49 (31.8%) had a diagnosis or other drug for epilepsy (epilepsy subgroup), and 105 (68.2%) did not (nonepilepsy subgroup). These 2 subgroups of gabapentin users were entered separately into the multivariable analysis. For mouth/pharynx cancer, ORs were somewhat lower in the epilepsy subgroup than in the nonepilepsy subgroup for only 1 and for 8 or more prescriptions. This was also the case for 3 or more and 8 or more prescriptions in relation to esophageal cancer and for all 3 prescription categories in relation to liver cancer.

Regarding vaginal cancer, the subgroups differed markedly. The nonepilepsy subgroup showed no statistically significant increases in risk and the users of only 1 prescription had the highest OR, 1.76 (95% CI = 0.4 2-7.34). The smaller subgroup, those with epilepsy, had high and statistically significant ORs ranging from 6.21 (95% CI = 1.77-21.78) for only 1 prescription to 7.91 (95% CI = 2.91-21.48) for ≥ 8 prescriptions. Because of small numbers, all CIs were wide, and there was considerable overlap of the CIs between the epilepsy and nonepilepsy subgroups, reducing confidence that they truly differ (Table 3).

ORs from the multivariable analysis by cumulative dose (Table 4, Model 2) are best compared with multivariable analysis by number of prescriptions (Table 2, Model 2), both controlled for cigarette smoking and alcohol use. ORs in the

Table 4. Sensitivity analyses based on cumulative dose: Relative risk of cancer at 4 sites that screened positive for association with gabapentin use[a]

Cumulative dose (in grams) by cancer site	Cases, no.	Controls, no.	Model 1[b]	Model 2[c]	Model 3[d]
Mouth/pharynx					
Total	3670	182,423			
0	3516	177,248	1.00 (reference)	1.00 (reference)	1.00 (reference)
> 0 to < 30	30	1250	1.18 (0.82-1.70)	1.12 (0.77-1.61)	1.02 (0.74-1.41)
30 to < 60	26	1057	1.22 (0.82-1.80)	1.10 (0.75-1.64)	1.27 (0.93-1.73)
60 to < 150	35	1057	1.61 (1.15-2.27)	1.48 (1.05-2.08)	1.36 (1.03-1.82)
≥ 150	63	1811	1.65 (1.27-2.13)	1.49 (1.15-1.93)	1.49 (1.20-1.84)
Esophagus					
Total	1601	79,534			
0	1524	76,746	1.00 (reference)	1.00 (reference)	1.00 (reference)
> 0 to < 30	13	663	0.97 (0.56-1.69)	0.89 (0.51-1.55)	0.96 (0.61-1.53)
30 to < 60	11	521	1.06 (0.58-1.94)	1.00 (0.55-1.83)	1.14 (0.71-1.83)
60 to < 150	18	582	1.55 (0.97-2.49)	1.34 (0.83-2.17)	1.19 (0.78-1.81)
≥ 150	35	1022	1.68 (1.19-2.37)	1.44 (1.02-2.04)	1.36 (1.01-1.84)
Liver					
Total	2877	142,850			
0	2710	137,729	1.00 (reference)	1.00 (reference)	1.00 (reference)
> 0 to < 30	41	1210	1.74 (1.27-2.39)	1.53 (1.11-2.11)	1.24 (0.92-1.68)
30 to < 60	30	1044	1.51 (1.04-2.18)	1.35 (0.93-1.96)	1.35 (0.98-1.85)
60 to < 150	39	1082	1.94 (1.40-2.68)	1.74 (1.26-2.42)	1.53 (1.15-2.02)
≥ 150	57	1785	1.77 (1.35-2.32)	1.45 (1.10-1.90)	1.39 (1.11-1.75)
Vagina					
Total	139	6919			
0	126	6659	1.00 (reference)	1.00 (reference)	1.00 (reference)
> 0 to < 30	2	57	2.00 (0.48-8.39)	1.87 (0.44-7.89)	1.53 (0.47-4.96)
30 to < 60	1	58	0.96 (0.13-7.01)	0.84 (0.11-6.24)	0.67 (0.09-4.91)
60 to < 150	1	55	1.05 (0.14-7.75)	0.99 (0.13-7.39)	2.05 (0.61-6.85)
≥ 150	9	90	5.88 (2.80-12.32)	5.36 (2.53-11.36)	4.80 (2.42-9.50)

[a] Risk estimated by odds ratios (and 95% confidence intervals) listed according to cumulative dose with a 2-year lag (Models 1 and 2) and without a 2-year lag (Model 3).
[b] Adjusted for race/ethnicity. Two-year lag in cumulative dose.
[c] Adjusted for race/ethnicity, smoker status, and alcohol use. Two-year lag in cumulative dose.
[d] Adjusted for race/ethnicity, smoker status, and alcohol use. No lag in cumulative dose.

highest categories of cumulative dose, 60 g to 149 g and 150 g or more, were very similar to those for 3 or more gabapentin prescriptions for association with cancers of the mouth/pharynx, esophagus, and liver. For vaginal cancer, the OR for a cumulative dose of 60 g to 149 g was lower (but based on only 1 exposed case) and for 150 g or more was higher, but the CIs for both of these cumulative dose levels were wide and clearly encompassed the OR for 3 or more prescriptions. The findings for differences between gabapentin users with and without epilepsy on the basis of cumulative dose (data not shown, available from the authors on request) were similar to those based on number of prescriptions. Notable was this difference for risk of vaginal cancer among those who had received at least 150 g of gabapentin: OR with epilepsy of 11.32 (95% CI = 4.93-25.99); without epilepsy, OR of 0.99 (95% CI = 0.13-7.44).

A change from a 2-year lag to no lag between ascertainment of gabapentin use and the index date had variable but little effect on ORs on the basis of number of prescriptions (Table 3). For cancer of the mouth/pharynx, the OR was somewhat lower for only 1 prescription and somewhat higher for 8 or more prescriptions, the latter becoming statistically significant. For esophageal cancer, the OR was somewhat higher for only 1 prescription and somewhat lower for 3 or more and 8 or more prescriptions, with loss of statistical significance for the former. For liver cancer, ORs for only 1 and for 3 or more prescriptions were somewhat lower and very slightly higher for 8 or more prescriptions. All were somewhat lower for vaginal cancer, the largest reduction for only 1 cancer. Removal of 2-year lag had little effect on the findings for cumulative dose (Table 4). CIs were narrowed for all no-lag analyses because of increased numbers of gabapentin users in all categories.

DISCUSSION

Findings with 7.5 additional years of follow-up confirmed only the weak associations for lung cancer and all cancers combined found earlier,[1] and none met the stricter criteria[3] that we now use for screening drugs for possible carcinogenic effects. Four cancer sites screened positive by our stricter criteria.

We believe that it is important to look carefully at the findings when patients fill only 1 prescription for a drug. They include persons who did not take the drug or took very little of it because of side effects or perceived lack of benefit. Because most prescriptions in our setting are for 100 days or less, we doubt that such short-term use has biological plausibility in causing cancer. Thus, a notable positive association involving just 1 prescription probably represents confounding by indication where the condition that led to prescribing the drug is more likely associated with cancer risk than the drug itself. This would appear to be especially true if the relative risk for 1 prescription is similar to those observed for several prescriptions. Viewed in this way, the large multivariable relative risk of 1 prescription of gabapentin for vaginal cancer and the similarity of the 1-prescription and 8-or-more-prescription multivariable relative risks for mouth/pharynx and for liver cancer likely represent confounding by indication.

Our measurements of cigarette smoking and alcohol consumption were clearly crude. For example, cancer of the mouth/pharynx was the most frequent cancer site studied, with 3670 cases (Supplemental Table 1, available at www.thepermanentejournal.org/files/2018/18-040-Suppl.pdf). Of these, 767 (21%) had unknown smoking status, and no quantity and duration were specified for current and former smokers. Alcohol use was even less clear, with 2872 cases (78%) with unknown consumption, and an additional 248 (7%) who drank alcohol but the amount was unknown. Thus, they provide very limited control in Model 2 for these important risk factors for cancer of the mouth/pharynx, esophagus, and liver. Nevertheless, the fact that ORs were consistently reduced when they were added to the model suggests that these exposures, if more accurately measured, could account for much of the apparent associations of gabapentin use with these cancers. Even the notably incomplete data regarding alcohol use appeared to indicate confounding by alcohol use, as evidenced by slightly less attenuation of relative risk when this variable was excluded in a sensitivity analysis. Lacking clear evidence for confounding by indication for esophageal cancer, we suggest that associations with cigarette smoking and alcohol might be more important in explaining this cancer's association with gabapentin use. The ORs for vaginal cancer were also moderately reduced when these variables were added. The most important known risk factors for vaginal cancer appear to be mother's use of diethylstilbestrol (DES) during pregnancy and human papillomavirus infection.[10] We did not have information about these risk factors.

The most striking finding of all the sensitivity analyses was the marked difference in relative risk of vaginal cancer between gabapentin users with and without epilepsy—high risk for the epilepsy subgroup and virtually absent for the nonepilepsy subgroup. This finding was markedly different from this comparison for the other 3 cancer sites, which were mildly in the opposite direction. The difference in risk for vaginal cancer between the 2 indications for gabapentin should be verified in larger numbers of patients. Because epilepsy is not a likely risk factor for vaginal cancer, further study of women with epilepsy in whom vaginal cancer develops may explain our finding.

Other antiepileptic drugs were considered as possible confounders. A variety of evidence suggests that phenobarbital and phenytoin are possibly carcinogenic.[11] Varying slightly with cancer site, phenobarbital was received by approximately 10% of users of other antiepileptic drugs and phenytoin by about 18%. Valproate (used by about 16%) has been suggested as possibly preventive because of its antiproliferative effect on cell lines.[11] We participated in a collaborative study with outside investigators who hypothesized prevention of breast cancer in humans by valproate, but a negative association was not confirmed (unpublished written data). In a sensitivity analysis, we controlled for use vs nonuse of antiepileptic drugs other than gabapentin. The increase in ORs went in the direction expected with negative confounding (ie, not contributing to increased risk), and the changes were minimal. The 3 drugs (phenobarbital, phenytoin, and valproate) were each received by a relatively small proportion

of other-antiepileptic drug users. Benzodiazepines were by far the most commonly received, accounting for about 45% of the other antiepileptic drugs.

We did not see evidence that socioeconomic status might be an important confounder. When we added as a sensitivity analysis the 2 available indicators of this characteristic to our multivariable analysis, changes in ORs were negligible. Sensitivity analyses based on cumulative dose and on elimination of the 2-year lag did not importantly affect our findings. We have routinely included a 2-year lag in screening pharmaceuticals for possible carcinogenesis because short-term associations have less biological plausibility. Also, a 2-year lag helps to avoid protopathic bias caused by the drug being given for symptoms of cancer before it is diagnosed, thus falsely appearing to precede the cancer. Pertinent to this study, if gabapentin is prescribed for pain caused by cancer, it seems unlikely that the cancer will not be detected for at least 2 years.

CONCLUSION

In an updated analysis, we find little if any epidemiologic evidence of a carcinogenic effect of gabapentin. ❖

Disclosure Statement

The author(s) have no conflicts of interest to disclose.

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Cancer

… an uneven swelling, rough, unseemly, darkish, painful, and sometimes without ulceration … if operated on, it becomes worse … . It has the veins stretched on all sides as the animal the crab (cancer) has its feet, whence it derives.

— Paul of Aegina, 625-690, 7th-century Byzantine Greek physician known as the father of early medical books

Supplemental Table 1. Relative risk of mouth/pharynx cancer, multivariable analysis			
Variable	**Cases (N = 3670)**	**Controls (N = 182,423)**	**Odds ratio (95% confidence interval)**
Race/ethnicity			
White	2725	109,582	1.00 (reference)
African American	216	11,875	0.69 (0.60-0.80)
Asian/Pacific Islander	272	21,622	0.55 (0.48-0.62)
Hispanic	286	20,047	0.58 (0.51-0.66)
Multiple/other	170	8194	0.86 (0.73-1.00)
Unknown	1	11,103	0.002 (< 0.001-0.02)
Smoker status			
Never	892	74,404	1.00 (reference)
Current	971	28,349	2.85 (2.60-3.13)
Former	1040	48,937	1.74 (1.59-1.91)
Unknown	767	30,733	2.79 (2.51-3.10)
Alcohol use			
Never	356	17,359	1.00 (reference)
Yes, < 3 drinks/d	184	6548	1.17 (0.98-1.41)
Yes, ≥ 3 drinks/d	10	143	2.43 (1.26-4.68)
Yes, unknown amount	248	9826	1.11 (0.94-1.31)
Unknown	2872	148,547	0.78 (0.68-0.89)
No. of prescriptions			
0	3516	177,248	1.00 (reference)
1	52	1885	1.26 (0.95-1.67)
2	16	764	0.94 (0.57-1.55)
3	13	448	1.29 (0.74-2.24)
4-7	35	818	1.94 (1.38-2.74)
≥ 8	38	1260	1.26 (0.91-1.76)

Supplemental Table 2. Relative risk of esophagus cancer, multivariable analysis			
Variable	**Cases (N = 1601)**	**Controls (N = 79,534)**	**Odds ratio (95% confidence interval)**
Race			
White	1192	50,560	1.00 (reference)
African American	95	5045	0.72 (0.58-0.88)
Asian/Pacific Islander	112	8470	0.62 (0.51-0.76)
Hispanic	139	8305	0.74 (0.62-0.88)
Multiple/other	62	3859	0.72 (0.56-0.94)
Unknown	1	3295	0.01 (< 0.001-0.05)
Smoker status			
Never	194	28,872	1.00 (reference)
Current	396	11,113	5.49 (4.61-6.55)
Former	455	26,267	2.59 (2.18-3.08)
Unknown	556	13,282	10.05 (8.41-12.01)
Alcohol use			
Never	173	8028	1.00 (reference)
Yes, < 3 drinks/d	90	3077	1.20 (0.92-1.57)
Yes, ≥ 3 drinks/d	6	54	3.59 (1.49-8.68)
Yes, unknown amount	113	4240	1.14 (0.89-1.45)
Unknown	1219	64,135	0.67 (0.55-0.82)
No. of prescriptions			
0	1524	76,746	1.00 (reference)
1	23	1002	1.05 (0.69-1.61)
2	9	388	1.00 (0.51-1.96)
3	7	259	1.13 (0.53-2.42)
4-7	3	458	0.30 (0.10-0.94)
≥ 8	35	681	2.15 (1.51-3.07)

Supplemental Table 3. Relative risk of liver cancer, multivariable analysis		
Variable	Cases (N = 2877)	Odds ratio (95% confidence interval), Controls (N = 142,850)
Race		
White	1323	1.00 (reference) 86,899
African American	241	1.53 (1.33-1.76) 9184
Asian/Pacific Islander	641	2.75 (2.49-3.03) 17,056
Hispanic	532	2.28 (2.06-2.54) 15,664
Multiple/other	139	1.44 (1.21-1.72) 6518
Unknown	1	0.004 (< 0.001-0.03) 7529
Smoker status		
Never	533	1.00 (reference) 58,981
Current	648	3.83 (3.40-4.31) 22,039
Former	717	2.18 (1.94-2.45) 42,044
Unknown	979	10.02 (8.91-11.26) 19,786
Alcohol use		
Never	551	1.00 (reference) 16,129
Yes, < 3 drinks/d	105	0.56 (0.45-0.69) 6224
Yes, ≥ 3 drinks/d	6	1.35 (0.58-3.12) 113
Yes, unknown amount	169	0.57 (0.47-0.68) 8912
Unknown	2046	0.41 (0.36-0.47) 111,472
No. of prescriptions		
0	2710	1.00 (reference) 137,729
1	57	1.38 (1.05-1.81) 1885
2	20	1.38 (0.88-2.17) 735
3	16	1.72 (1.03-2.88) 413
4-7	34	1.89 (1.33-2.70) 845
≥ 8	40	1.45 (1.05-2.01) 1243

Supplemental Table 4. Relative risk of vagina cancer, multivariable analysis			
Variable	Cases (N = 139)	Controls (N = 6919)	Odds ratio (95% Confidence interval)
Race			
White	82	4292	1.00 (reference)
African American	15	469	1.59 (0.90-2.82)
Asian/Pacific Islander	19	747	1.52 (0.89-2.58)
Hispanic	17	780	1.26 (0.73-2.18)
Multiple/other	6	340	0.97 (0.42-2.26)
Unknown	0	291	—
Smoker status			
Never	53	3477	1.00 (reference)
Current	19	875	1.49 (0.87-2.57)
Former	30	1467	1.43 (0.90-2.28)
Unknown	37	1100	3.50 (2.14-5.71)
Alcohol use[a]			
Never	33	950	1.00 (reference)
Yes, < 3 drinks/d	8	210	1.25 (0.56-2.82)
Yes, unknown amount	6	326	0.60 (0.24-1.47)
Unknown	92	5433	0.19 (0.10-0.38)
No. of prescriptions			
0	126	6659	1.00 (reference)
1	5	89	3.04 (1.19-7.76)
2	0	35	—
3	0	23	—
4-7	2	40	2.77 (0.64-11.88)
≥ 8	6	73	4.08 (1.67-9.93)

[a] There were no cases or controls who reported drinking ≥ 3 alcoholic drinks per day.