Risk of cancer in patients exposed to gabapentin in two electronic medical record systems

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Abstract

Purpose—High doses of gabapentin were associated with pancreatic acinar cell tumors in male Wistar rats, but there is little published epidemiological data regarding gabapentin and carcinogenicity. We explored the association between gabapentin and cancer in a United States (US) medical care program, and followed up nominally significant associations in a United Kingdom (UK) primary care database.

Methods—In the US Kaiser Permanente Northern California (KPNC) health system, we performed nested case-control analyses of gabapentin and 55 cancer sites and all-cancer combined using conditional logistic regression. Up to ten controls were matched to each case on year of birth, sex, and year of cohort entry. No other covariates were included in models. Only dispensings for gabapentin 2 years or more prior to index date were considered. Nominally significant associations with an odds ratio > 1.00 and p < 0.05 for three or more dispensings versus no dispensings were followed up by similar nested-case control analyses in the UK General Practice Research Database (GPRD), adjusting for potential indications for gabapentin and risk factors for the specific cancers.

Results—The following analyses had OR>1.00 and p<0.05 for three or more dispensings of gabapentin versus no dispensing (2-year lag) in KPNC, and were also examined in the GPRD: all-cancer, breast, lung and bronchus, urinary bladder, kidney/renal pelvis, stomach, anus/anal canal/ anorectum, penis, and other nervous system. These cancers were not statistically significantly associated with gabapentin in the GPRD case-control studies (2-year lag). The GPRD and KPNC studies did not identify a statistically significant increased risk of pancreatic cancer with >2 prescriptions of gabapentin in 2-year lagged analyses.

Conclusions—The epidemiological data in a US cohort with up to 12 years of follow-up and a UK cohort with up to 15 years of follow up do not support a carcinogenic effect of gabapentin use. However, the confidence intervals for some analyses were wide, and an important effect cannot be confidently excluded.

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INTRODUCTION

Gabapentin was approved in the United States (US) as adjunctive therapy for partial seizures in December 1993 and for treatment of post-herpetic neuralgia (PHN) in May 2002. In the United Kingdom (UK), gabapentin was approved as adjunctive therapy for partial seizures on May 1993, and is also indicated for the treatment of peripheral neuropathic pain such as painful diabetic neuropathy (PDN) and PHN in adults. Gabapentin has also been prescribed off-label for other pain conditions,[1] and is considered an adjunctive therapy for cancer pain according to the World Health Organization (WHO) analgesic ladder.[2]

High doses of gabapentin were associated with pancreatic acinar cell tumors in male Wistar rats.[3] There is one published epidemiological study of gabapentin and cancer. The association of gabapentin with cancer was evaluated in a case-control screening study of the association of 105 drugs with 55 cancers in Kaiser Permanente Northern California (KPNC), 1994–2006.[4] The only cancer that met the screening criteria for possibly increased cancer risk with gabapentin exposure was renal (including renal pelvis) cancer. This association was judged to be likely due to or substantially accentuated by confounding by cigarette smoking and hypertension. The current paper reports the full results of the KPNC study for gabapentin and each cancer.

We also conducted a series of epidemiologic studies using the United Kingdom General Practice Research Database (GPRD) to assess the relationship between gabapentin and (1) pancreatic cancer, based on the rat findings; (2) renal cancer, based on the published KPNC findings; (3) and those cancers with OR>1.00 and p<0.05 for three or more dispensings of gabapentin versus no dispensing of gabapentin in the KPNC study.

METHODS

KPNC Study Population and Methods

The details of the case-control screening study of gabapentin with 55 cancers in Kaiser Permanente Northern California (KPNC), 1994–2006 were published.[4] The study was approved by the Kaiser Permanente Institutional Review Board. In brief, KPNC is an integrated health care plan (including comprehensive inpatient and outpatient care and pharmacy services), serving over 3 million current members, comprising about 30% of the residents in the San Francisco Bay area and the Central Valley of California. The membership is fairly representative of the local population except for some under-representation of both extremes of the economic spectrum.

The study design was a nested case-control study within a cohort of 6.6 million KPNC subscribers with drug coverage August 1994-December 31, 2006. Cohort entry began August 1994, or at the time of joining the program and having drug coverage if later than August 1994. Follow-up was through the earlier of (1) December 31, 2006, (2) diagnosis of the cancer of interest, or (3) leaving KPNC for any reason, including death.

Cancer categories were based on invasive cancers at each cancer site (plus non-invasive urinary bladder cancers) listed in the International Classification of Diseases for Oncology, Version 3 (ICD-O-3) except for non-melanoma skin cancers.[5] Cancer cases were risk set matched with up to 10 controls by year of birth, sex, and year of cohort entry. The index date was the date of incident cancer for cases. The index date for controls was chosen so as to give the controls equal follow-back time to that of the case for ascertainment of prior use of gabapentin. Conditional logistic regression calculated the odds ratio (OR) as the estimate of the relative risk of cancer associated with 1, 2, and ≥3 prescription dispensings versus no

use of gabapentin at least 2-years before the index date. The 2-year lag was defined *a priori* to control for prediagnostic prescribing for symptoms possibly related to cancer.[4, 6] These analyses were not adjusted for covariates other than the matching variables.

GPRD Study Population and Methods

Study Design—Nominally significant associations with OR>1.00 and p<0.05 for three or more dispensings versus no dispensings in KPNC were followed up by similar nested-case control analyses in the GPRD, adjusting for potential indications for gabapentin and the main risk factors for the specific cancers. Pancreatic cancer, though not significant in KPNC, was also evaluated in the GPRD.

GPRD study protocols were approved by the Independent Scientific Advisory Committee (ISAC) of the GPRD and posted to ClinicalTrials.gov prior to analysis (ClinicalTrials.gov Identifiers NCT01138124 and NCT01236053). The results reported herein are from the protocol-specified analyses. The pancreatic and renal studies were conducted initially (NCT01138124), and the additional cancers were subsequently assessed with modifications in the analysis (NCT01236053). The main modification was exclusion of cases and controls with a prior history of cancer before the index date in the analyses of the additional cancers, to limit misclassification of primary cancer diagnosis codes that may be recurrent or metastatic. In the analysis of the additional cancers, back pain was added as a covariate to further control for potential confounding by indication. However, supplemental analyses of gabapentin and the risk of pancreatic and renal cancers were also performed under these modifications (i.e. excluding those with prior history of other cancer before index date and further adjusting for back pain) to allow for comparability of study results.

Data Source—The GPRD, managed by the UK Medicines and Healthcare products Regulatory Agency (MHRA), comprises the entire computerized medical records of a sample of general practitioners (GPs) in England and Wales. All members of the population are registered with a single practice, which centralizes the medical information from GPs, specialist referrals, and hospital attendances. This study is based on data from about a 6% representative sample of the UK population. Data recorded in the GPRD includes demographic information, prescription details, clinical events, preventive care provided, specialist referrals, hospital admissions and their major outcomes. Data are retrieved by means of the Oxford Medical Information Systems (OXMIS) and READ codes.[7]

Study Cohort—Nested case-control analyses were conducted in a cohort of subjects in the GPRD 1993–2008. Entry into the study cohort began Jan 1, 1993 for all those who were registered in GPRD before that time, and at the time of registration if later than Jan 1, 1993. The ascertainment period for gabapentin use was from Jan 1, 1993 through Dec 31, 2008. The ascertainment period for incident cancers was from Jan 1, 1995 through Dec 31, 2008. Follow-up ended earlier if the respective cancer was diagnosed, or if the subject left the GPRD for any reason including death, whichever came first.

Case Definition—The cancer outcomes were defined by READ/OXMIS codes (Supplemental Table 1). The code list for all-cancer was derived from clinical review of all cancer, neoplasm, and oncology related READ/OXMIS codes by William T. Hamilton, MD, FRCP, FRCGP, chair of the early diagnosis subgroup within the UK National Cancer Research Institute, Primary Care Section. All-cancer included metastatic disease, carcinoma in situ, and non-melanotic skin cancers. The codes for specific cancers were reviewed by a physician (MCI). The specific cancers included carcinoma in situ, and excluded metastatic disease to those sites. The index date for the case was the earliest date of diagnosis of the respective cancer in the GPRD.

Control Selection—Patients with a first diagnosis of the respective cancer 1995–2008 were risk set matched with up to 10 controls within the same General Practice for age at cohort entry (within two years), sex, and year of entry into the study cohort (within one year). The index date for controls was set as the date at which the follow-up time from cohort entry was the same as the case. The index date was chosen so as to give the control equal follow-up time to that of the case for ascertainment of use of gabapentin. Cases and controls were required to have at least 2 years of follow-up in the study cohort before their index date. For pancreatic and renal cancer, cases and controls could have a prior diagnosis of another cancer. For the analyses of the other cancers (and supplemental analyses of pancreatic and renal cancer), cases were required to be free of other cancers prior to the index date for the specific cancer, and controls were required to be free of any cancer prior to the index date.

Gabapentin exposure—The exposure of interest was gabapentin use as defined by prescriptions recorded by the general practitioner (British National Formulary Codes). Data on gabapentin prescriptions were obtained for cases and controls from cohort entry to the index date. Exposure to gabapentin was assessed as ever/never, number of prescriptions, cumulative duration, and cumulative dose, from cohort entry to 2-years prior to the index date (2-year lagged exposure). The 2-year lagged exposure attempted to account for protopathic bias (gabapentin prescribing for cancer-related pain or worsening of neuropathic or non-neuropathic pain prior to clinical cancer diagnosis) and latency in carcinogenesis (non-etiological exposure to gabapentin in the period between cancer onset and cancer diagnosis). Tertiles of each exposure measure (prescription, cumulative duration, cumulative dose) for the pancreatic and renal analyses were based on the pooled pancreatic and renal controls; tertiles for the additional cancers were based on the all-cancer controls. Explicit indications for each gabapentin prescription were not recorded in the GPRD.

Covariates—The relevant potential confounders were the consistent risk factors for each cancer (defined *a priori*) as well as the major indications for gabapentin use in the UK (epilepsy, diabetes, neuropathic pain, back pain). Covariates were assessed up to the index date, unless otherwise specified. The following were controlled by either matching or covariate adjustment in all analyses: Age at cohort entry; sex; calendar year of cohort entry; body mass index (BMI); smoking, diabetes, epilepsy, and neuropathic pain. Covariates for pancreatic cancer included diabetes ≥2 years prior to index date and chronic pancreatitis ≥2 years prior to index date (the lag was incorporated since these can be also be early symptoms of neoplastic destruction of pancreatic tissue).[8–10] Covariates for renal cancer included history of hypertension and diuretic use.[11] Additional covariates for the other cancers were history of back pain and (1) all-cancer: alcohol consumption; (2) breast: previous hysterectomy, current (within 6 months of index date) or previous hormone replacement therapy; benign breast disease; alcohol consumption;[12] (2) lung and bronchus: chronic obstructive pulmonary disease (COPD); alcohol consumption; (3) urinary and bladder – no additional covariates;[13] (4) stomach: upper gastrointestinal disorders, acid-suppressing drugs up to 6 months before index date, alcohol consumption;[14] (5) anus, anal canal, and anorectum: human immunodeficiency virus (HIV) and human papilloma virus (HPV, anogenital warts, condylomas); (6) penis: HIV; HPV (anogenital warts, condylomas); phimosis/balanitis; (7) other nervous system (defined as malignant meningioma, spinal glioblastoma, and malignant tumors of cranial and peripheral nerves) – no additional covariates.

Analytic methods—Conditional logistic regression models for matched case and control data estimated the crude and multivariable adjusted relative risk (estimated by the odds ratio [OR]) for the respective cancer in relation to gabapentin exposure, conditional on the

matching factors. Separate analyses were performed for all-cancer and each individual cancer. Four exposure comparisons (ever versus never, number of prescriptions, duration of exposure, and cumulative exposure) were evaluated, with a 2 year lag from the index date. For the more common cancers (all-cancer, lung, and breast), longer exposures were also assessed (>1 y, >2 y, >3 y cumulative duration versus no exposure). The primary analyses were the multivariable adjusted 2-year lagged models. Adjustments were not made for multiple comparisons. Exploratory models with unlagged exposure (gabapentin usage up to the index date) were performed to gain insight into the extent of protopathic bias (reduction in effect estimates with 2-year lagged exposure compared to unlagged exposure) or sample size effects (widening of confidence intervals with lagged exposure compared to unlagged exposure).

For the comparison of highest tertile of exposure to no exposure in the 2-year lagged analysis, the studies were estimated to have an 80% power (2-sided $\alpha=0.05$) to detect ORs of 1.20 or greater for all-cancer; 1.62 for lung; 1.78 for breast; 2.34 for bladder; 2.60 for kidney, pancreas and stomach; 7.45 for anus; 10.49 for penis; and 23.45 for other CNS. This assumed a 0.6% overall gabepentin exposure rate and UK Office of National Statistics cancer incidence rates.

RESULTS

Kaiser Permanente Northern California

There were 109,879 exposures to gabapentin in the cohort of 6,608,681 subscribers to KPNC.[4] Table 1 reports the ORs of all-cancer and the 55 individual cancers for 1-;, 2-, and ≥3 dispensings of gabapentin versus no dispensing in the 2-year lagged analysis. The following analyses, with adjustment for matching variables only, had OR>1.00 and p<0.05 for three or more dispensings of gabapentin versus no dispensing, and were followed up in the GPRD: 1) all-cancer, OR 1.10 (95% CI 1.02–1.18); 2) breast, OR 1.19 (1.01–1.39); 3) lung and bronchus, OR 1.34 (1.13–1.60); 4) urinary bladder, OR1.41 (1.07–1.87); 5) kidney/ renal pelvis, OR 1.71 (1.18–2.47); 6) stomach, OR 1.64 (1.01–2.64); 7) anus, anal canal, and anorectum, OR 2.70 (1.17–6.25); 8) penis, OR 6.68 (1.47–30.28); 9) and other nervous system, OR 6.67 (1.11–39.90).

General Practice Research Database

Pancreatic Cancer—3,149 pancreatic cancer cases were risk set matched to 30,026 controls, with mean duration of follow up from cohort entry of 9.0–9.1 years (Table 2). 1.8% (n=56) of pancreatic cancer cases were exposed to gabapentin, relative to 0.8% (n=253) of the controls. The distribution of time from first gabapentin prescription to index date for the gabapentin-exposed pancreatic cancer cases and controls demonstrates that the first gabapentin prescription in the cancer cases was skewed toward exposure within the 100 days prior to the specific diagnosis code for cancer (Figure 1). In the 2-year lagged exposure window, 0.8% (n=24) of pancreatic cancer cases were exposed to gabapentin, relative to 0.5% (n=143) of the controls (Supplemental Table 2). The OR of pancreatic cancer with gabapentin exposure was sensitive to modeling assumptions (Table 3). Although ever exposure was associated with a significantly increased risk of pancreatic cancer in the unlagged analysis (multivariable adjusted OR 1.82 [95% CI 1.34, 2.46]), the OR was attenuated and not significant in the 2-year lagged exposure analysis (adjusted OR 1.33 [95% CI 0.85, 2.08])(Supplemental Table 3). There was no evidence of a positive dose-response relationship with increasing number of prescriptions, duration of exposure, or cumulative dose; point estimates were consistently lower for the highest exposure tertiles (adjusted ORs 0.87–1.17 relative to no exposure) than the lowest exposure tertiles (adjusted ORs 1.95–2.88), even in the 2-year lagged analysis.

Renal Cancer—1,981 renal cancer cases were risk set matched to 19,046 controls, with mean duration of follow up from cohort entry of 9.4–9.5 years (Table 4). 1.6% (n=32) of renal cancer cases were exposed to gabapentin, relative to 0.9% (n=166) of the controls. Similar to the gabapentin-exposed pancreatic cancer cases, the distribution of gabapentin exposure was skewed toward exposure within the 100 days prior to the specific diagnosis code for renal cancer (Figure 1). In the 2-year lagged exposure window, 0.7% (n=13) of renal cancer cases were exposed to gabapentin, relative to 0.4% (n=76) of the controls (Supplemental Table 4). The OR of renal cancer with gabapentin exposure was sensitive to modeling assumptions, particularly given the low numbers of gabapentin exposed cases and controls in the tertile analyses (Table 5). Ever exposure was associated with a significantly increased risk of renal cancer in the unlagged analysis (adjusted OR 1.68 [95% CI 1.13, 2.49]); the point estimate was similar in the 2-year lagged analysis (adjusted OR 1.63 [0.89, 2.97])(Supplemental Table 5). Dose-response estimates were limited by the low numbers of exposed cases, especially in the 2-year lagged exposure analyses.

Other Cancers—The additional cancers in the KPNC study nominally (p<0.05) associated with gabapentin were not statistically significantly associated with gabapentin in the GPRD case-control studies. The results based on ever/never exposure and tertiles of duration of exposure (2-year lag) are shown in Table 6; the results were similar for tertiles of number of prescriptions and of cumulative dose (supplementary results available at GSK Clinical Study Register[15] and Supplemental Tables 6–15). There was a trend (p=0.054) for association of the highest tertile of gabapentin cumulative duration (>5.56 months 2-year lagged exposure) with breast cancer (OR 1.49, 95% CI 0.99–2.04). Longer cumulative durations of gabapentin exposure were assessed (>1 y, >2 y, or >3 y) for the more common cancers—all cancer, lung, and breast; long durations of gabapentin exposure were not significantly associated with increased risk of these cancers. The results for breast cancer were OR 1.48 (95% CI 0.92, 2.39) for >1y duration, OR 1.62 (95% CI 0.79, 3.29) for >2y duration, and OR 0.76 (95% CI 0.18, 3.21) for >3y duration.

Supplemental analyses of pancreatic and renal cancer were reported for comparability (Table 6). The numbers of incident pancreatic and renal cancer cases were reduced by approximately 1/3 after excluding those with prior history of other cancers or non-specific cancer codes before their index date. Ever exposure to gabapentin (2-year lag) was marginally associated with an increased risk of pancreatic cancer (adjusted OR 1.68 [95% CI 1.00, 2.82] relative to no exposure). The highest tertiles of gabapentin exposure were not significantly associated with risk of pancreatic cancer (point estimates of OR 1.00–1.36 relative to no exposure). Ever exposure to gabapentin and the highest tertiles of exposure were not significantly associated with renal cancer.

DISCUSSION

Gabapentin was approved in the US and UK in 1993. Despite being prescribed for epilepsy and pain, the exposure rate in the general population is low (<1%).[4] Therefore, large population-based studies are required to accrue sufficient exposure and outcomes for safety studies, especially for rare outcomes such as pancreatic cancer. The GPRD and KPNC cohorts are well suited to study gabapentin and carcinogenicity. These data sources include large numbers of drug recipients with complete cancer follow-up, often long-term, in a comprehensive health care system. They contain objective data on the prescribing or dispensing of prescriptions, without recall bias.

Pancreatic and Renal Cancer

The relationship between gabapentin and pancreatic and renal cancer was sensitive to modeling assumptions. Increased risks of cancer were observed with lower exposures, or shorter duration of exposures, and closer to the index diagnosis of cancer. Relative risks were attenuated toward unity with the lag analysis, and there was no evidence of a dose response relationship with increasing numbers of prescriptions, cumulative dose, or duration of use. The pattern of increasing OR for cancer with very short gabapentin exposures (<2 months), lack of a positive dose response, and decreasing OR with longer exposures is not a pattern consistent with a mutagenic or non-mutagenic carcinogen.[16] The decreasing ORs with lagged analysis and with increasing exposure suggests that protopathic bias is inflating the OR.[17, 18] Protopathic bias (reverse causation) occurs when a pharmaceutical agent is prescribed for an early manifestation of a disease that has not yet been diagnostically detected or formally recorded in the medical record.[19, 20] Elements of protopathic bias were observed in studies of proton pump inhibitors and H2-antagonists with risk of gastric cancer, and of acetaminophen with cancer mortality.[17, 18, 21] In these examples, elevations in cancer risk diminished with duration of follow-up, returning to baseline with long-term use of the drug.

A plausible explanation is that individuals are prescribed gabapentin for cancer-related pain or worsening of other non-neuropathic or neuropathic pain in the context of pancreatic cancer, prior to the specific cancer diagnosis being recorded in the GPRD. Gabapentin is considered an adjunctive treatment for cancer pain in the World Health Organization (WHO) analgesic ladder.[2] Indeed, the first gabapentin prescription in the cancer cases was skewed toward exposure within the 100 days prior to the specific diagnosis code for cancer (Figure 1). Excluding exposure in the time period before the index date (lagged exposure) can control for protopathic bias, but misspecification of the lag period may result in spurious association from residual protopathic bias, or reduce power for detecting associations. A 2-year lagged exposure was incorporated in all analyses *a priori* based on recommendations for addressing protopathic bias for drugs that may be used to treat early symptoms of cancer, and for comparability of the results across cancers in GPRD and KPNC;[6] however, the optimal specification of the lag period is likely to vary across cancer types based on different symptoms, pain characteristics, time courses, and treatment patterns.[18] For instance, retroperitoneal cancers such as pancreatic or renal may be more likely to present as back pain that would serve as the protopathic stimulus for gabapentin treatment.[22]

Taken together, the GPRD and KPNC studies did not identify a statistically significant increased risk of pancreatic cancer with >2 prescriptions of gabapentin in 2-year lagged analyses.

Other cancers

The additional cancers in the KPNC study nominally associated with gabapentin (p<0.05) were not statistically significantly associated with gabapentin in the 2-year lag analysis of the GPRD case-control studies. There was a suggestion of association between gabapentin and breast cancer based on the OR point estimates. In the KPNC, the OR of breast cancer for ≥3 dispensings versus no dispensing of gabapentin was 1.19 (1.01–1.39), p=0.03. In the GPRD, the adjusted OR of breast cancer for 3–10 prescriptions versus no prescriptions was OR 1.17 (0.76, 1.81), p = 0.47; for >10 prescriptions the OR was 1.36 (0.95, 1.96) p = 0.09.

Given the low overall gabapentin exposure frequency, statistical power was limited for the evaluation of the effect of long durations or very high cumulative exposures, especially for the less common cancers such as anal cancer, penile cancer, and other nervous system

cancers. Nonetheless, ever exposure to gabapentin was not statistically significantly associated with these less common cancers.

Strengths and limitations

The study should be interpreted in the context of its strengths and limitations. Many strengths of the study are methodological, including the nesting of the case-control study within a population-based cohort of patients in KPNC and the GPRD. In KPNC, occurrence of cancer was ascertained through KPNC's Cancer Registry, which covers all subscribers and contributes to the local Surveillance, Epidemiology, and End Results (SEER) program. The accuracy of clinical data and cancer diagnoses was good in previous validation studies in the GPRD.[23–25] However, the index date of cancer based on the record of a specific diagnostic code by the general practitioner generally occurs after cancer symptoms, and may also be recorded after diagnosis by a specialist. This raises the possibility of protopathic bias —gabapentin prescription for cancer-related pain prior to the formal diagnosis in the GPRD.[2]

Imprecision in the measurement of potential confounders and unmeasured confounders (e.g. alcohol use) may result in residual confounding; this includes missing data in BMI and smoking, and the parameterization of smoking status, hypertension, and diuretic usage. Given the low overall gabapentin exposure frequency, statistical power was limited for the evaluation of the effect of long durations or very high cumulative exposures. Follow-up may not be long enough to detect a carcinogenic effect with a latency of more than a few years. Misclassification of exposure was possible for analyses of cumulative duration or cumulative dosage given missing data on daily dose or quantity dispensed; misclassification was likely to be non-differential with respect to cases and controls, and could weaken our ability to detect associations.

Conclusion

Studies in two large healthcare systems—KPNC in the US with up to 12 years of follow-up and GPRD in the UK with up to 15 years of follow-up—do not support a statistically significant association of >2 prescriptions of gabapentin and pancreatic cancer in the 2-year lag analyses. Furthermore, the nominal gabapentin associations with other cancers in the KPNC study were not statistically significant in the GPRD study in the 2-year lag analyses. However, the confidence intervals for some analyses were wide, and an important effect cannot be confidently excluded.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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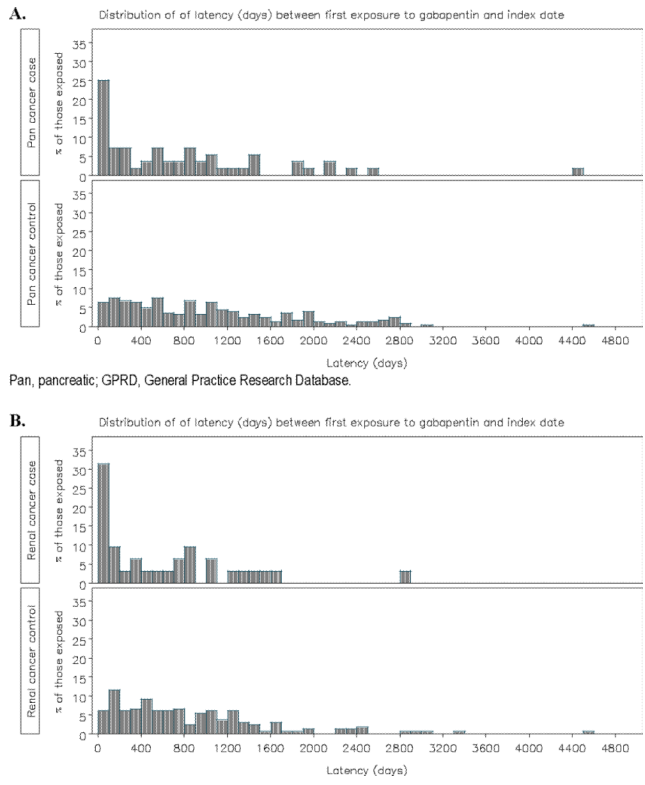
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Key Points

- Studies in two large healthcare systems—Kaiser Permanente Northern California (KPNC) in the United States and the General Practice Research Database (GPRD) in the United Kingdom—do not support a statistically significant association between gabapentin exposure (>2 prescriptions with a 2-year lag) and pancreatic cancer.

- Nominal gabapentin associations with other cancers in KPNC were not statistically significant in the GPRD.

- Evidence of protopathic bias (gabapentin prescribing for cancer-related pain prior to the formal diagnostic record of cancer) was observed for pancreatic and renal cancer in the GPRD.

A. Distribution of of latency (days) between first exposure to gabapentin and index date

Pan, pancreatic; GPRD, General Practice Research Database.

B. Distribution of of latency (days) between first exposure to gabapentin and index date

Figure 1.
Distribution of time from first gabapentin prescription (in days) to index date in gabapentin-exposed pancreatic cancer (A) and renal cancer (B) cases and controls in the GPRD

Table 1

Risk of cancer with 1-, 2-, and ≥3 dispensings of gabapentin versus no dispensing in KPNC

Cancer Site (alphabetical after "Any Cancer")	GP exposed cases (N)	OR (95%CI) and p-value for 1-, 2-, and ≥3 dispensings of gabapentin versus no dispensings (2-year lag)		
		1 dispensing vs none	2 dispensings vs none	≥3 dispensings vs none
Any Cancer	1678	1.05 (0.96–1.14) p=0.276	1.20 (1.06–1.36) p=0.005	1.10 (1.02–1.18) p=0.009[**]
Anus/anal canal/Anorectum	9	0.41 (0.06–3.03) p=0.382	1.42 (0.17–11.52) p=0.744	2.70 (1.17–6.25) p=0.021[*]
Biliary	7	Inestimable	3.35 (1.06–10.57) p=0.040	0.81 (0.25–2.63) p=0.726
Bones/joints	4	4.30 (1.11–16.62) p=0.035	Inestimable	1.29 (0.16–10.30) p=0.812
Brain	21	1.84 (0.93–3.65) p=0.079	0.87 (0.20–3.73) p=0.851	1.16 (0.58–2.32) p=0.673
Breast	352	1.09 (0.90–1.31) p=0.375	1.35 (1.03–1.78) p=0.032	1.19 (1.01–1.39) p=0.038[*]
Cervix uteri	6	0.60 (0.14–2.50) p=0.481	1.41 (0.32–6.22) p=0.647	0.49 (0.12–2.01) p=0.320
Colon excl. Rectum	145	1.13 (0.85–1.50) p=0.391	1.13 (0.73–1.74) p=0.586	0.96 (0.75–1.24) p=0.768
Comb mouth-pharynx[1]	9	0.91 (0.28–2.96) p=0.874	Inestimable	1.14 (0.49–2.68) p=0.760
Corpus uteri	36	0.39 (0.20–0.76) p=0.006	0.60 (0.28–1.29) p=0.189	0.64 (0.40–1.00) p=0.052
Esophagus	17	0.82 (0.30–2.28) p=0.707	2.67 (0.89–8.05) p=0.081	1.24 (0.62–2.48) p=0.550
Eye and orbit	0	Inestimable	Inestimable	Inestimable
Gallbladder	3	1.84 (0.40–8.46) p=0.433	Inestimable	0.55 (0.07–4.17) p=0.563
Heart/soft tissue	12	1.19 (0.42–3.38) p=0.748	2.31 (0.66–8.12) p=0.190	0.99 (0.39–2.48) p=0.978
Hodgkin lymphoma	10	1.93 (0.66–5.63) p=0.228	2.95 (0.61–14.19) p=0.178	1.96 (0.67–5.75) p=0.222
Kidney/renal pelvis	70	1.20 (0.75–1.94) p=0.450	2.48 (1.46–4.24) p=0.001	1.71 (1.18–2.47) p=0.004[*]
Larynx	10	1.35 (0.53–3.46) p=0.531	2.71 (0.76–9.72) p=0.126	0.49 (0.12–2.05) p=0.331
Lip	8	1.11 (0.39–3.15) p=0.841	0.67 (0.09–5.08) p=0.695	1.11 (0.34–3.69) p=0.861
Liver/intrahep.bile duct	36	2.19 (1.29–3.72) p=0.004	0.69 (0.17–2.90) p=0.614	1.65 (0.98–2.77) p=0.058
Lung and bronchus	269	0.87 (0.68–1.11) p=0.250	1.50 (1.11–2.02) p=0.008	1.34 (1.13–1.60) p=0.001[**]
Lymphocytic leukemia	19	1.48 (0.67–3.29) p=0.337	1.68 (0.58–4.85) p=0.335	1.14 (0.55–2.39) p=0.727
Melanoma	73	0.97 (0.63–1.51) p=0.896	1.15 (0.62–2.14) p=0.665	1.11 (0.80–1.54) p=0.534
Monocytic leukemia	0	Inestimable	Inestimable	Inestimable
Multiple myeloma	27	1.46 (0.81–2.63) p=0.211	0.32 (0.04–2.30) p=0.255	1.11 (0.62–1.97) p=0.730
Myeloid leukemia	16	0.48 (0.15–1.53) p=0.216	0.54 (0.13–2.26) p=0.399	1.64 (0.86–3.12) p=0.134
Nasopharynx	0	Inestimable	Inestimable	Inestimable
Non-hodgkin lymphoma	87	1.17 (0.82–1.69) p=0.391	1.06 (0.57–1.98) p=0.848	1.16 (0.85–1.60) p=0.356
Nose/nasal cavity/middle ear	2	1.01 (0.13–7.88) p=0.994	Inestimable	1.43 (0.18–11.62) p=0.739
Other digestive organs	6	2.86 (0.59–13.75) p=0.190	6.67 (1.11–39.90) p=0.038	4.33 (0.78–24.07) p=0.094
Other endocrine	1	Inestimable	Inestimable	2.50 (0.28–22.37) p=0.413
Other female genital	1	Inestimable	Inestimable	1.24 (0.15–9.88) p=0.842
Other leukemia	3	Inestimable	Inestimable	1.86 (0.54–6.44) p=0.33
Other male genital	1	3.33 (0.35–32.05) p=0.297	Inestimable	Inestimable
Other nervous system	2	Inestimable	Inestimable	6.67 (1.11–39.90) p=0.038[*]

Cancer Site (alphabetical after "Any Cancer")	GP exposed cases (N)	OR (95%CI) and p-value for 1-, 2-, and ≥3 dispensings of gabapentin versus no dispensings (2-year lag)		
		1 dispensing vs none	2 dispensings vs none	≥3 dispensings vs none
Other skin	11	2.29 (0.92–5.66) p=0.074	Inestimable	1.49 (0.57–3.85) p=0.416
Other urinary	1	Inestimable	Inestimable	Inestimable
Ovary	23	0.94 (0.49–1.80) p=0.849	0.62 (0.19–2.00) p=0.426	0.77 (0.40–1.46) p=0.417
Pancreas	46	0.74 (0.41–1.34) p=0.318	0.24 (0.06–0.96) p=0.043	1.23 (0.85–1.78) p=0.282
Penis	3	Inestimable	Inestimable	6.68 (1.47–30.28) p=0.014[*]
Peritoneum/Omentum/Mesentery	7	2.86 (0.76–10.7) p=0.119	Inestimable	1.68 (0.58–4.91) p=0.341
Pleura	1	Inestimable	Inestimable	Inestimable
Prostate	246	1.10 (0.89–1.36) p=0.379	1.03 (0.74–1.43) p=0.855	0.78 (0.64–0.94) p=0.011[†]
Rectum/Rectosigmoid	30	0.70 (0.39–1.26) p=0.236	1.03 (0.52–2.06) p=0.925	0.41 (0.21–0.80) p=0.009[††]
Retroperito-neum	1	1.64 (0.19–14.30) p=0.652	Inestimable	Inestimable
Salivary glands	8	2.55 (0.72–9.06) p=0.147	Inestimable	1.67 (0.64–4.36) p=0.298
Small intestine	8	0.82 (0.19–3.48) p=0.789	3.00 (0.82–10.88) p=0.096	2.05 (0.58–7.33) p=0.268
Stomach	27	0.65 (0.30–1.41) p=0.276	Inestimable	1.64 (1.01–2.64) p=0.045[*]
Testis	3	Inestimable	Inestimable	1.82 (0.40–8.20) p=0.437
Thyroid	26	1.06 (0.46–2.48) p=0.886	2.16 (0.90–5.22) p=0.087	1.51 (0.86–2.66) p=0.155
Trachea	0	Inestimable	Inestimable	Inestimable
Unspecified	75	1.65 (1.12–2.42) p=0.011	1.55 (0.86–2.78) p=0.143	1.20 (0.82–1.74) p=0.349
Ureter	4	2.02 (0.44–9.22) p=0.366	3.40 (0.35–32.69) p=0.290	0.74 (0.10–5.68) p=0.771
Urinary bladder	100	1.20 (0.84–1.71) p=0.309	0.70 (0.34–1.43) p=0.325	1.41 (1.07–1.87) p=0.015[*]
Uterus	2	4.83 (0.44–53.25) p=0.199	5.00 (0.45–55.14) p=0.189	Inestimable
Vagina	3	1.70 (0.20–14.12) p=0.624	Inestimable	2.49 (0.53–11.73) p=0.249
Vulva	3	0.54 (0.07–4.14) p=0.554	Inestimable	1.11 (0.25–4.84) p=0.895

KPNC, Kaiser Permanente Northern California; GP, gabapentin; OR, odds ratio; CI, confidence interval; vs, versus; excl, excluding; intrahep, intrahepatic; comb, combined.

Inestimable – no gabapentin-exposed cancer cases or no gabapentin-exposed non-cases at the exposure level, p > 0.97.

[1] Excludes lip, salivary glands and nasopharynx

[*] p<.05, OR>1 for ≥3 dispensings vs no dispensings

[**] p<.01, OR>1 for ≥3 dispensings vs no dispensings

[†] p<.05, OR<1 for ≥3 dispensings vs no dispensings

[††] p<.01, OR<1 for ≥3 dispensings vs no dispensings

Table 2

Characteristics of pancreatic cancer cases and controls in the GPRD

Characteristic	Level	Cases (N) N=3,149	Cases (%)	Controls (N)[4] N=30,026	Controls (%)
Age at Index Date (y)	Mean (SD)	71.9 (11.51)		71.5 (11.47)	
Gender	Female	1,603	50.9	15,316	51.0
	Male	1,546	49.1	14,710	49.0
Duration of follow-up from registration to index date (y)	Mean (SD)	21.2 (15.38)		21.9 (15.33)	
Duration of follow-up from cohort entry to index date (y)[3]	Mean (SD)	9.0 (3.90)		9.1 (3.90)	
Body mass index (kg/m2)[1]	Mean (SD)	26.8 (4.97)		27.0 (4.94)	
	BMI: Missing	1,917	60.9	19,419	64.7
Smoking Status	Current smoker	731	23.2	4,857	16.2
	Ex-smoker	768	24.4	6,626	22.1
	Never smoked	1,385	44.0	15,249	50.8
	Unknown	265	8.4	3,294	11.0
Comorbidities	Diabetes[2]	363	11.5	2,137	7.1
	Epilepsy	53	1.7	458	1.5
	Neuropathic Pain	737	23.4	6,616	22.0
	Chronic Pancreatitis[2]	13	0.4	17	0.1

y, year; SD, standard deviation; BMI, body mass index; GPRD, General Practice Research Database.

[1] 1–3 years prior to index date.

[2] 2 years prior to index date.

[3] Entry into the study cohort began Jan 1,1993 for all those who were registered in GPRD before that time, and at the time of registration if later than Jan 1,1993.

[4] NOTE: 2,868 (91.1%) of the 3,149 matched cases were 1:10 matched; 181 (5.7%) were 1:4 to 1:9 matched; 100 (3.2%) were 1:1 to 1:3 matched. N= 12 of the GPRD pancreatic cancer cases were unable to be matched.

Pharmacoepidemiol Drug Saf. Author manuscript; available in PMC 2013 February 1.

Table 3

Risk of pancreatic cancer with gabapentin exposure in the GPRD

Exposure Model	Without 2 year lag		With 2 year lag	
	Unadjusted OR (95% CI)	Adjusted OR (95% CI)[1]	Unadjusted OR (95% CI)	Adjusted OR (95% CI)[1]
Gabapentin (Ever vs Never)	2.04 (1.51, 2.75)	1.82 (1.34, 2.46)	1.52 (0.98, 2.36)	1.33 (0.85, 2.08)
Gabapentin Prescriptions [2,3]				
Tertile1 vs Never	2.82 (1.86, 4.28)	2.53 (1.66, 3.85)	2.75 (1.51, 5.03)	2.44 (1.32, 4.49)
Tertile2 vs Never	1.80 (0.97, 3.36)	1.65 (0.87, 3.11)	0.55 (0.17, 1.78)	0.48 (0.15, 1.57)
Tertile3 vs Never	1.35 (0.76, 2.42)	1.17 (0.65, 2.11)	1.31 (0.58, 2.97)	1.11 (0.48, 2.57)
Duration of exposure (mo) [4,5]				
Tertile1 vs Never	3.15 (2.04, 4.86)	2.88 (1.85, 4.46)	2.75 (1.47, 5.13)	2.45 (1.31, 4.62)
Tertile2 vs Never	1.68 (0.94, 2.99)	1.50 (0.83, 2.69)	0.82 (0.29, 2.28)	0.72 (0.26, 2.01)
Tertile3 vs Never	1.34 (0.75, 2.39)	1.15 (0.64, 2.07)	1.11 (0.49, 2.51)	0.94 (0.41, 2.15)
Cumulative Exposure (g) [6,7]				
Tertile1 vs Never	2.90 (1.88, 4.47)	2.65 (1.71, 4.11)	2.19 (1.12, 4.25)	1.95 (0.99, 3.81)
Tertile2 vs Never	1.87 (1.05, 3.32)	1.64 (0.92, 2.95)	1.42 (0.64, 3.16)	1.21 (0.54, 2.72)
Tertile3 vs Never	1.34 (0.75, 2.39)	1.15 (0.64, 2.08)	1.01 (0.42, 2.41)	0.87 (0.36, 2.12)

OR, odds ratio; CI, confidence interval; vs, versus; mo, months; g, grams; GPRD, General Practice Research Database.

[1] Adjusted for smoking, body mass index, diabetes, chronic pancreatitis, neuropathic pain, epilepsy

[2] The tertiles for number of prescriptions in the analysis without 2 year lag are: Tertile 1 (1–2). Tertile 2 (3–8). Tertile3 (9–218).

[3] The tertiles for number of prescriptions in the analysis with 2 year lag are: Tertile 1 (1–2). Tertile 2 (3–10). Tertile 3(11–191).

[4] The tertiles for cumulative duration in the analysis without 2 year lag are: Tertile 1 (0.01 – 1.55 mo). Tertile 2 (1.56 – 6.44 mo). Tertile 3 (6.45 – 78.36 mo).

[5] The tertiles for cumulative duration in the analysis with 2 year lag are: Tertile 1 (0.01 – 1.78 mo). Tertile 2 (1.79 – 7.20 mo). Tertile 3 (7.21 – 64.13 mo)

[6] The tertiles for cumulative dose in the analysis without 2 year laq are: Tertile 1 (0.01 – 33.6 g). Tertile 2 (33.7 – 185.0 g). Tertile 3 (185.1 – 7500.2 g).

[7] The tertiles for cumulative dose in the analysis with 2 year lag are: Tertile 1 (0.01 – 39.0 g) Tertile 2 (39.1 – 210.0 g). Tertile 3 (210.1 – 5623.8 g).

Table 4

Descriptive characteristics of renal cancer cases and controls in the GPRD

Characteristic	Level	Cases (N) N=1,981	Cases (%)	Controls (N) [3] N=19,046	Controls (%)
Age at Index Date (y)	Mean (SD)	67.1 (12.68)		66.7 (12.67)	
Gender	Female	759	38.3	7,273	38.2
	Male	1,222	61.7	11,773	61.8
Duration of follow-up from registration to index date (y)	Mean (SD)	21.3 (15.44)		21.3 (14.91)	
Duration of follow-up from cohort entry to i index date (y) [2]	Mean (SD)	9.4 (4.10)		9.5 (4.09)	
Body mass index (kg/m2) [1]	Mean (SD)	27.8 (5.29)		27.3 (4.92)	
	BMI: Missing	1,150	58.1	11,989	62.9
Smoking Status	Current smoker	476	24.0	3,555	18.7
	Ex-smoker	524	26.5	4,589	24.1
	Never smoker	867	43.8	9,121	47.9
	Unknown	114	5.8	1,781	9.4
Comorbidities	Hypertension	1,159	58.5	9,113	47.8
	Diuretic use	875	44.2	6,396	33.6
	Diabetes	240	12.1	1,598	8.4
	Epilepsy	33	1.7	303	1.6
	Neuropathic Pain	428	21.6	4,018	21.1

y, year; SD, standard deviation; BMI, body mass index; GPRD, General Practice Research Database.

[1] 1–3 years prior to index date.

[2] Entry into the study cohort began Jan 1, 1993 for all those who were registered in GPRD before that time, and at the time of registration if later than Jan 1, 1993.

[3] NOTE: 1,821 (91.9%) of the 1,981 matched cases were 1:10 matched; 107 (5.4%) were 1:4 to 1:9 matched; 53 (2.7%) were 1:1 to 1:3 matched. N=7 of the overall renal cancer cases were unable to be matched.

Table 5

Relative risk of renal cancer with gabapentin exposure in the GPRD

Exposure Model	Without 2 year lag		With 2 year lag	
	Unadjusted OR (95% CI)	Adjusted OR (95% CI)[1]	Unadjusted OR (95% CI) p-value	Adjusted OR (95% CI)[1]
Gabapentin (Ever vs Never)	1.79 (1.22, 2.63)	1.68 (1.13, 2.49)	1.65 (0.91, 2.99)	1.63 (0.89, 2.97)
Gabapentin Prescriptions[2,3]				
Tertile1 vs Never	2.53 (1.44, 4.44)	2.34 (1.32, 4.14)	2.18 (0.90, 5.32)	2.14 (0.87, 5.28)
Tertile2 vs Never	1.89 (0.98, 3.63)	1.77 (0.92, 3.43)	1.40 (0.49, 4.01)	1.39 (0.48, 4.02)
Tertile3 vs Never	0.87 (0.35, 2.19)	0.83 (0.33, 2.11)	1.32 (0.39, 4.47)	1.30 (0.38, 4.47)
Duration of exposure (mo)[4,5]				
Tertile1 vs Never	3.24 (1.79, 5.85)	2.90 (1.59, 5.28)	2.54 (1.03, 6.25)	2.40 (0.96, 5.98)
Tertile2 vs Never	1.35 (0.69, 2.65)	1.33 (0.68, 2.63)	0.95 (0.29, 3.12)	0.99 (0.30, 3.29)
Tertile3 vs Never	1.19 (0.54, 2.63)	1.10 (0.50, 2.45)	1.70 (0.58, 4.96)	1.63 (0.55, 4.84)
Cumulative Exposure (g)				
Tertile1 vs Never	1.89 (0.92, 3.88)	1.75 (0.85, 3.63)	2.03 (0.78, 5.34)	2.05 (0.77, 5.46)
Tertile2 vs Never	2.44 (1.42, 4.22)	2.34 (1.35, 4.07)	1.78 (0.68, 4.69)	1.70 (0.64, 4.53)
Tertile3 vs Never	0.99 (0.42, 2.29)	0.91 (0.39, 2.13)	1.15 (0.35, 3.82)	1.15 (0.34, 3.86)

OR, odds ratio; CI, confidence interval; vs, versus; mo, months; g, grams; GPRD, General Practice Research Database.

[1] Adjusted for smoking, body mass index, hypertension, diuretic use, diabetes, neuropathic pain, and epilepsy.

[2] The tertiles for number of prescriptions in the analysis without 2 vearlaq are: Tertile 1 (1–2). Tertile 2 (3–8). Tertile 3. (9–218).

[3] The tertiles for number of prescriptions in the analysis with 2 yearlag are: Tertile 1 (1–2). Tertile 2 (3–10). Tertile 3 (11–191).

[4] The tertiles for cumulative duration in the analysis without 2 yearlag are: Tertile 1 (0.01 – 1.55 mo). Tertile 2 (1.56 – 6.44 mo). Tertile 3 (6.45 – 78.36 mo).

[5] The tertiles for cumulative duration in the analysis with 2 year lag are: Tertile 1 (0.01 – 1.78 mo). Tertile 2 (1.79 – 7.20 mo). Tertile 3 (7.21 – 64.13 mo).

[6] The tertiles for cumulative dose in the analysis without 2 yearlag are: Tertile 1 (0.01 – 33.6g). Tertile 2 (33.7 – 185.0 g). Tertile 3 (185.1 – 7500.2 g).

[7] The tertiles for cumulative dose in the analysis with 2 year lag are: Tertile 1 (0.01 – 39.0g) Tertile 2 (39.1 – 210.0 g). Tertile 3 (210.1 – 5623.8 g).

Table 6

OR of cancer with gabapentin exposure versus no exposure in the GPRD

Cancer	Cases, N Age, y (SD) GP exposed, N (%)	Controls, N Age, y (SD) GP exposed, N (%)	Adjusted OR (95% CI), for cancer based on cumulative duration of gabapentin exposure relative to never exposure to gabapentin (2-year lagged analysis)						
			Ever vs Never	Tertile 1 (0.01–1.38 mo) vs Never	Tertile 2 (1.39–5.56 mo) vs Never	Tertile 3 (>5.56 mo) vs Never	>1 y vs Never	>2 y vs Never	>3 y vs Never
All cancers[1,2]	179,138 66.3 (15.12) 804 (0.4%)	1,710,950 65.8 (15.07) 6,507 (0.4%)	1.07 (0.99,1.15)	1.03 (0.90,1.17)	1.10 (0.96,1.25)	1.07 (0.95,1.22)	1.09 (0.92,1.29)	1.16 (0.89,1.52)	1.05 (0.69,1.60)
Breast[1,2,3]	19,564 61.9 (14.04) 96 (0.5%)	188,924 61.4 (13.87) 725 (0.4%)	1.22 (0.99, 1.52)	1.08 (0.73, 1.59)	1.19 (0.82, 1.72)	1.42 (0.99, 2.04)	1.48 (0.92, 2.39)	1.62 (0.79, 3.29)	0.76 (0.18, 3.21)
Lung and bronchus[1,2,4]	10,855 70.8 (10.43) 55 (0.5%)	102,836 70.4 (10.38) 402 (0.4%)	0.94 (0.69, 1.27)	1.05 (0.64, 1.73)	0.93 (0.52, 1.66)	0.84 (0.50, 1.39)	0.79 (0.39, 1.58)	1.13 (0.37, 3.43)	1.87 (0.21, 16.86)
Urinary Bladder[1]	4,600 71.0 (11.59) 15 (0.3%)	43,559 70.6 (11.52) 144 (0.3%)	0.84 (0.49, 1.44)	0.80 (0.32, 2.05)	0.67 (0.24, 1.85)	1.06 (0.44, 2.52)			
Stomach[1,2,5]	1,877 73.5 (11.19) 5 (0.3%)	17,853 73.0 (11.06) 70 (0.4%)	0.54 (0.21, 1.34)	0.00 (no exposed cases)	1.07 (0.24, 4.84)	0.70 (0.21, 2.32)			
Anus, anal canal, anorectum[1,6]	212 65.1 (15.20) 4 (1.9%)	2,067 64.5 (14.86) 6 (0.3%)	3.39 (0.71, 16.17)	21.47 (1.78, 258.8)	1.00 (0.03, 32.21)	0.93 (0.06, 13.87)			
Penis[1,6,7]	148 63.6 (14.26) 1 (0.7%)	1,396 62.9 (14.04) 2 (0.1%)	2.90 (0.24, 34.69)	4.63 (0.28, 77.51)	Inestimable (no exposed cases or controls)	0.00 (no exposed cases)			
Other Nervous System Cancers[1]	38 58.5 (19.22) 0 (0%)	380 58.5 (19.08) 0 (0%)	Inestimable (no exposed cases or controls)	Inestimable (no exposed cases or controls)	Inestimable (no exposed cases or controls)	Inestimable (no exposed cases or controls)			
SUPPLEMENTARY ANALYSES									
Pancreas[1,8]	2,155 71.6 (11.52) 20 (0.9%)	20,382 71.1 (11.47) 86 (0.4%)	1.68 (1.00, 2.82)	3.25 (1.55, 6.83)	0.61 (0.14, 2.62)	1.32 (0.54, 3.21)			
Renal and renal pelvis[1,9]	1,272 65.8 (12.60) 9 (0.7%)	12,167 65.4 (12.59) 53 (0.4%)	1.33 (0.64, 2.75)	1.73 (0.49, 6.15)	1.10 (0.32, 3.75)	1.29 (0.37, 4.58)			

GP, gabapentin; mo, month; y, year; vs, versus; SD, standard deviation; OR, odds ratio; CI, confidence interval; GPRD, General Practice Research Database.

[1] Adjusted for body mass index, smoking, diabetes, epilepsy, neuropathic pain, back pain

[2] Additionally adjusted for alcohol consumption

[3] Additionally adjusted for previous hysterectomy, current or previous hormone replacement therapy, and benign breast disease

[4] Additionally adjusted for chronic obstructive pulmonary disease

[5] Additionally adjusted for upper gastrointestinal disorders and acid-suppressing drugs up to 6 months before index date

[6] Additionally adjusted for human immunodeficiency virus and human papilloma virus (anogenital warts, condylomas)

[7] Additionally adjusted for phimosis/balanitis

[8] Additionally adjusted for chronic pancreatitis > 2 years prior to index date

[9] Additionally adjusted for hypertension and diuretic use