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Long-term use of lithium and risk of colorectal adenocarcinoma: a nationwide case–control study

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Background: Lithium accumulates in the colon and inhibits the enzyme GSK-3 β that possesses anti-carcinogenic effects. We therefore examined the association between lithium use and colorectal cancer risk in a nationwide study.

Methods: We used the Danish Cancer Registry to identify all patients diagnosed with incident colorectal adenocarcinoma during 2000–2012 ($n=36\,248$). Using a matched case–control approach, we estimated the association between long-term use (≥ 5 years) of lithium and risk of colorectal adenocarcinoma using conditional logistic regression.

Results: Long-term use of lithium was similar among cases (0.22%) and controls (0.20%), yielding an odds ratio of 1.13 (95% confidence interval (CI), 0.89–1.43) for colorectal adenocarcinoma. Dose–response, subgroup and other subanalyses returned neutral associations. However, ORs differed for colorectal subsites (proximal colon: 1.01 (95% CI, 0.66–1.55; distal colon: 1.52 (95% CI, 1.05–2.20); and rectum: 0.80 (95% CI, 0.50–1.30).

Conclusions: Lithium use was not associated with an overall increased risk of colorectal adenocarcinoma. The variation by subsite warrants further investigation.

Lithium is first-line therapy in bipolar affective disorder (Licht, 2012) and as adjuvant therapy in unipolar depression (Bauer *et al*, 2014; Bschor, 2014). The colonic epithelium is exposed to lithium as 10–20% of an oral dose is eliminated by faeces (Saran and Russell, 1976; Kersten *et al*, 1986). Lithium enters the colon epithelium through the Na⁺ channel ENaC (Diamond *et al*, 1983; Mall *et al*, 1999) and studies have demonstrated accumulation in the epithelium (Dolman and Edmonds, 1976; Dolman *et al*, 1976; Diamond *et al*, 1983).

It is unknown whether lithium induces proliferative changes in the colon as demonstrated in kidney and endometrial tissue (Christensen *et al*, 2006; Polotsky *et al*, 2009). Tumour cells from mice with adenomatous polyposis coli mutant-multiple intestinal

neoplasia (Min) express increased ENaC activity (Ousingsawat *et al*, 2008), and when treated with lithium these mice develop larger tumours (Gould *et al*, 2003). In addition, lithium inhibits glycogen synthase kinase-3 beta (GSK-3 β) in humans (Klein and Melton, 1996); an important part of the Wnt-signalling pathway that possesses anti-carcinogenic properties in many tissues, including the colorectum.

As colorectal cancer is common and has many established risk factors, any carcinogenic effect of lithium might remain unrecognized due to the low prevalence of lithium use. Identifying or disproving risks suggested to be associated with lithium use is instrumental in ensuring rational therapy with this drug. Recently, we examined the association between lithium use and risk of renal

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cancer based on a recent study showing a strong correlation between the two (Zaidan *et al*, 2014), finding a reassuring null association (Pottegård *et al*, 2015). This prompted us to examine the association between long-term use of lithium and risk of colorectal adenocarcinoma in an additional study using the Danish high-quality registry data.

MATERIALS AND METHODS

The study was a nationwide case–control study. We compared use of lithium among persons with colorectal cancer (cases) to that of cancer-free persons (controls) and estimated odds ratios (ORs) for colorectal adenocarcinoma associated with long-term use of lithium.

Data sources. We used the Danish Cancer Registry (Storm *et al*, 1997; Gjerstorff, 2011), the National Prescription Registry (Kildemoes *et al*, 2011), the National Patient Register (Lynge *et al*, 2011), registers in Statistics Denmark on educational level (Jensen and Rasmussen, 2011) and the Civil Registration System (Pedersen, 2011). Further details of the nationwide data sources, including codes and definitions are provided in the Supplementary Materials I–II.

All Danish citizens receive free tax-supported health care administered by the national health authorities, allowing population-based register linkage studies covering all inhabitants. Data were linked by the personal identification number assigned to all Danish residents (Pedersen, 2011).

Cases and controls. From the Danish Cancer Registry, we identified all patients (cases) in Denmark with a first time diagnosis of colorectal cancer between 2000 and 2012. We restricted the case population to histologically verified adenocarcinoma. The date of cancer diagnosis was defined as the index date. Exclusion criteria were age outside 18–85 years at index date and any residency outside Denmark within 10 years prior to index date. We further excluded cases with previous cancer (except non-melanoma skin cancer) as well as subjects with inflammatory bowel disease, hereditary non-polyposis colon cancer or familial adenomatous polyposis.

Controls were selected by risk set sampling, applying the same exclusion criteria as for cases. For each case, we selected 10 cancer-free population controls of same gender and birth year. Index date for controls was identical to that of the corresponding case. Subjects were eligible for multiple control selection before they became cases. Thereby, the ORs provide unbiased estimates of the corresponding incidence rate ratios in the underlying source population.

Exposure definition. Ever use of lithium was defined as having filled two or more prescriptions (ATC code, N05AN01 (WHO Collaborating Centre for Drug Statistics Methodology)) of lithium prior to the index date. Long-term use of lithium was defined as cumulative treatment for ≥5 years.

The duration of each lithium prescription was defined as 90 days, that is, we considered the exposure period of one prescription to last 90 days after the date of purchase. In all analyses, we disregarded prescriptions redeemed within 1 year prior to the index date. This was done to reduce the possibility of reverse causation (Jørgensen *et al*; Csizmadl *et al*, 2007), and the improbability that very recent exposure would be associated with cancer development (Burststein and Schwartz, 2008).

Main analysis. We used multivariable conditional logistic regression to estimate ORs for colorectal cancer associated with long-term use of lithium, adjusting for potential confounders. In all analyses, non-use (less than two prescriptions) of lithium was the reference group.

Potential confounders included (i) use of aspirin, non-steroidal anti-inflammatory drugs, statins, antidepressants and hormone replacement therapy; (ii) history of type 2 diabetes, chronic

obstructive pulmonary disease and alcohol-related disease; and (iii) highest achieved education (as a crude measure of socioeconomic status). Details are presented in the Supplementary Material II. We disregarded the year before the index date for all covariates.

Pre-planned sub-analyses and sensitivity analyses. First, to explore the dose–response relationship between lithium use and colorectal cancer risk, we defined exposure according to various periods of cumulative use of lithium.

Second, we examined associations for colorectal cancer with lithium use stratified by gender, age, year of sampling and histories of diabetes or alcohol abuse.

Third, we estimated ORs for associations between long-term use of lithium and colorectal cancer risk stratified by colorectal subsite, that is, proximal colon, distal colon and rectum.

Finally, we stratified the analyses by localised or non-localised disease.

Other. All analyses were performed using Stata Release 13.1 (StataCorp, College Station, TX, USA). The study was approved by the Danish Data Protection Agency. According to Danish law, studies based solely on register data do not require approval from an ethics review board (Thygesen *et al*, 2011).

RESULTS

We identified 51 225 colorectal cancer cases. The exclusion criteria left 36 248 colorectal adenocarcinoma cases that were matched to 362 480 cancer-free population controls (for flowchart, see Supplementary Material III). Baseline characteristics of cases and controls are shown in Table 1.

Table 1. Characteristics of colorectal cancer cases and their matched controls

	Cases (n = 36 248)	Controls (n = 362 480)
Age, median (IQR, years)	70 (62–77)	70 (62–77)
Gender		
Males	19 868 (54.8%)	198 680 (54.8%)
Females	16 380 (45.2%)	163 800 (45.2%)
Cancer site		
Colon, proximal	9771 (27.0%)	NA
Colon, distal	11 753 (32.4%)	NA
Colon, unspecified	1708 (4.7%)	NA
Rectum	13 016 (35.9%)	NA
Use of lithium prior to index date		
Non-use	36 089 (99.6%)	360 909 (99.6%)
Ever use	159 (0.44%)	1571 (0.43%)
Long-term use (≥5 years)	78 (0.22%)	734 (0.20%)
Drugs		
Aspirin	9146 (25.2%)	91 517 (25.2%)
NSAID	17 350 (47.9%)	179 995 (49.7%)
Statins	7077 (19.5%)	69 082 (19.1%)
Antidepressants	5794 (16.0%)	61 925 (17.1%)
Hormone replacement therapy	6238 (17.2%)	65 106 (18.0%)
Diagnoses		
Diabetes, type 2	3353 (9.3%)	29 131 (8.0%)
COPD	2728 (7.5%)	24 255 (6.7%)
Alcohol-related disease	2308 (6.4%)	19 586 (5.4%)
Highest achieved education		
Short (7–10 years)	14 179 (39.1%)	141 774 (39.1%)
Medium (11–13 years)	12 104 (33.4%)	117 170 (32.3%)
Long (> 13 years)	5537 (15.3%)	58 813 (16.2%)
Abbreviations: IQR = inter-quartile range; NA = not applicable; NSAID = non-steroidal anti-inflammatory drugs.		

Overall, 78 (0.22%) of cases had used lithium for ≥ 5 years compared with 734 (0.20%) among controls. This yielded an adjusted OR of 1.13 (95% confidence interval (CI) 0.89–1.43) for colorectal adenocarcinoma associated with long-term use of lithium (Table 2).

Analyses defining lithium use according to duration of use yielded ORs close to unity (Table 2). Likewise, analyses stratified by age, gender or selected morbidity revealed no specific patterns in the ORs. In contrast, we found substantial risk variation for colorectal subsites, with ORs for proximal colon, distal colon and rectum of 1.01 (95% CI 0.66–1.55), 1.52 (95% CI 1.05–2.20) and 0.80 (95% CI 0.50–1.30), respectively (Table 3). We also observed variation in ORs for localised or non-localised cancer (1.44 (95% CI 1.01–2.04) vs 1.06 (95% CI 0.75–1.49)).

Post hoc analyses of the anatomical distribution of the colorectal tumours confirmed a slightly skewed distribution towards those of the distal colon among long-term users of lithium (Supplementary Material IV). When restricting analyses to this sub-set of cases, we observed a suggestive dose–response pattern, however, the

statistical precision of the individual point estimates was limited (Supplementary Material V). Last, we evaluated the influence of timing of lithium use by stratifying the results for long-term use into initiation of use (defined as first prescription) < 10 years or ≥ 10 years, respectively, prior to the index date (< 10 years: OR 1.33, 95% CI 0.94–1.90; ≥ 10 years: OR 0.98, 95% CI 0.72–1.35).

DISCUSSION

In our nationwide case–control study, we found no association between long-term use of lithium and overall risk of colorectal adenocarcinoma. Findings were consistent between patient subgroups and when applying different definitions of lithium use. In analyses stratified by colorectal subsite, the associations deviated substantially, including a statistically significant increased OR for distal colon cancer associated with long-term lithium use.

The main strength of our study is the use of nationwide, comprehensive, high-quality registry data on drug use, cancer outcomes and potential confounders. The weakness of the study is the lack of data on life-style habits, including smoking, obesity and alcohol consumption. Patients with psychiatric diseases have on average higher consumption of tobacco and alcohol than the general population (Lasser *et al*, 2000; Heffner *et al*, 2011; McDonald and Meyer, 2011), and both smoking and alcohol are known to induce colorectal cancer (Baan *et al*, 2007; Secretan *et al*, 2009). This might have biased our risk estimates slightly upwards. Last, adjustment for the underlying psychiatric indication (i.e., bipolar disorder, severe depression or other) were not feasible due to the possibility of introducing collinearity (as lithium use is closely correlated with the main diagnosis of BPD), lack of information on indications in the Prescription Registry and questionable proxies in the Patient Registry for the relevant conditions.

An unexpected observation was the risk variation by colorectal subsite. Differences in risk estimates between proximal and distal colon tumours have been reported for other drugs (Elsaleh *et al*, 2000). This is compatible with the different embryological origins and physiology of proximal and distal tumours (Iacopetta, 2002) as well as with differences in molecular and genetic characteristics

Table 2. Association between lithium use and risk of colorectal adenocarcinoma, specified by pattern of use within the entire exposure period, excluding the last year prior to the index date

Exposure group	Cases	Controls	Crude OR ^a	Adjusted OR ^b
Non-use	36 089	360 909	1.00 (ref.)	1.00 (ref.)
Ever use	159	1571	1.01 (0.86–1.19)	1.08 (0.92–1.28)
Long-term use (≥ 5 years)	78	734	1.06 (0.84–1.34)	1.13 (0.89–1.43)
Duration of use				
< 1 year	21	277	0.76 (0.49–1.18)	0.82 (0.53–1.28)
1–4.99 years	60	560	1.07 (0.82–1.40)	1.15 (0.88–1.50)
5–9.99 years	50	506	0.99 (0.74–1.33)	1.06 (0.79–1.41)
≥ 10 years	28	228	1.22 (0.83–1.81)	1.29 (0.87–1.91)

Abbreviation: OR = odds ratio.
^aAdjusted for age, calendar time and sex (by matched design).
^bFully adjusted model, see section 'Main analysis'.

Table 3. Associations between long-term use (≥ 5 years) of lithium and risk of colorectal adenocarcinoma, stratified by patient subgroups, subsite and stage

Subgroup	Cases exposed/unexposed	Controls exposed/unexposed	Crude OR ^a	Adjusted OR ^b
Gender				
Males	28/19 805	319/198 001	0.88 (0.60–1.29)	0.92 (0.62–1.35)
Females	50/16 284	415/162 908	1.21 (0.90–1.62)	1.29 (0.96–1.73)
Age				
< 50 years	0/1675	16/16 748	—	—
50–69 years	38/15 987	343/159 905	1.11 (0.79–1.55)	1.15 (0.82–1.61)
70+ years	40/18 427	375/184 256	1.07 (0.77–1.48)	1.16 (0.84–1.62)
Topography				
Colon, proximal	23/9725	233/97 258	0.99 (0.64–1.51)	1.01 (0.66–1.55)
Colon, distal	32/11 699	228/117 024	1.41 (0.97–2.04)	1.52 (1.05–2.20)
Colon, unspecified	5/1701	27/17 016	1.85 (0.71–4.81)	1.98 (0.76–5.16)
Rectum	18/12 964	246/129 611	0.73 (0.45–1.18)	0.80 (0.50–1.30)
Stage				
Localised	36/13 544	267/135 534	1.35 (0.95–1.92)	1.44 (1.01–2.04)
Non-localised	37/18 956	377/189 547	0.98 (0.70–1.38)	1.06 (0.75–1.49)
Unknown	5/3589	90/35 828	0.55 (0.22–1.36)	0.54 (0.22–1.34)
Medical history				
No history of type 2 diabetes	71/32 748	677/331 896	1.07 (0.84–1.37)	1.14 (0.89–1.46)
No history of alcohol abuse	73/33 800	636/341 563	1.15 (0.90–1.47)	1.24 (0.97–1.59)

Abbreviation: OR = odds ratio.
^aAdjusted for age, calendar time and sex (by design).
^bFully adjusted model, see section 'Main analysis'.

of the two segments (Iacopetta, 2002; Birkenkamp-Demtroder *et al*, 2005; Leopoldo *et al*, 2008). In the present context, ENaC displays a significant gradient of expression and activity towards distal colon in rodents (Epple *et al*, 2000; Greig *et al*, 2002). Whether a similar gradient is present in humans is unknown. Thus, we cannot exclude that the different risk estimates according to colorectal subsite represent true effects. However, the fact that the risk estimates did not increase or decrease uniformly from the proximal segment of colon to rectum also indicates that chance is a likely explanation.

The associations between long-term lithium and colorectal cancer risk also varied with gender, with women exhibiting higher risk estimates than men. A similar gender difference was found in a previous study, showing increased colon cancer mortality among women, but not men, with bipolar disorder (Crump *et al*, 2013). Last, we found a higher risk estimate for localised than for advanced colorectal cancer, which might result from increased medical surveillance among lithium users. These patients may have a lower threshold for health care contact and thereby may undergo earlier or more intensive diagnostic work-up compared with non-users of lithium. This might explain our observation of the highest risk estimates for localised disease, and the notion is also compatible with the higher risk estimate observed for distal colon cancer, as proximal colorectal cancers have been shown to present later than distal cancers (Hansen *et al*, 2015).

In conclusion, use of lithium was not associated with an overall increase in the risk of colorectal adenocarcinoma. The observed association between long-term lithium use and risk of distal colon cancer may warrant further investigation.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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