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Research Paper

Identification of Associations Between Prescribed Medications and Cancer: A Nationwide Screening Study

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ABSTRACT

Purpose: We present a systematic screening for identifying associations between prescribed drugs and cancer risk using the high quality Danish nationwide health registries.
Methods: We identified all patients (cases) with incident cancer in Denmark during 2000–2012 (n = 278,485) and matched each case to 10 controls. Complete prescription histories since 1995 were extracted. Applying a two-phased case–control approach, we first identified drug classes or single drugs associated with an increased or decreased risk of 99 different cancer types, and further evaluated potential associations by examining specificity and dose–response patterns.
Findings: 22,125 drug–cancer pairs underwent evaluation in the first phase. Of 4561 initial signals (i.e., drug–cancer associations), 3541 (78%) failed to meet requirements for dose–response patterns and specificity, leaving 1020 eligible signals. Of these, 510 signals involved the use of single drugs, and 33% (166 signals) and 67% (344 signals) suggested a reduced or an increased cancer risk, respectively. While a large proportion of the signals were attributable to the underlying conditions being treated, our algorithm successfully identified well-established associations, as well as several new signals that deserve further investigation.
Conclusion: Our results provide the basis for future targeted studies of single associations to capture novel carcinogenic or chemopreventive effects of prescription drugs.

1. Introduction

Identification of unintended effects of drug therapy is an essential part of post-marketing drug surveillance (pharmacovigilance), as knowledge of rare side-effects is limited at the time of marketing of new medications (Strom et al., 2012). Unintended effects of drugs may involve an increase or a reduction in cancer risk (International Agency for Research on Cancer, 2012; Umar et al., 2012). Although systematic and comprehensive testing of genotoxicity and carcinogenicity is performed for any new drug prior to marketing (Brambilla and Martelli, 2009), both these laboratory assays and the premarketing phase-3 trials are disadvantaged by the typically long latency period of cancer development in humans (Umar et al., 2012; Burstein and Schwartz, 2008). For example, the excess risk of breast cancer induced by use of menopausal or contraceptive hormone therapy first becomes apparent after 5–10 years of continued use (Howell and Evans, 2011; Zhu et al., 2012), and the protective effect of aspirin against colorectal cancer requires at least five years of regular use (Chan et al., 2012; Cuzick et al., 2015). Traditional approaches in pharmacovigilance (based primarily on spontaneous reporting of adverse events) rarely detect drug–cancer associations, primarily due to the long induction time of most cancer types, which separate the use of the drug from the diagnosis by several years. As most individual cancer types are rare and have a long latency, pre-marketing clinical trials are unlikely to detect carcinogenic or chemopreventive effects of drugs due to the typically small size and short follow-up of these trials. Since neither spontaneous reporting nor clinical trials would be effective in capturing signals, the primary tool in surveillance of drugs for unintended carcinogenic or cancer preventive effects would be analyses of large administrative databases. Such studies have been instrumental in the identification of carcinogenic effects of several drugs, e.g., female hormone therapy and phenacetin (International Agency for Research on Cancer, 2012).

Denmark has a long history of establishing nationwide health care registries and databases with information on all Danish residents (Thygesen and Ersbøll, 2014). Two of the nationwide registries with the highest data quality, the Danish Prescription Registry (initiated in 1995 (Kildemoes et al., 2011)) and the Danish Cancer Registry (established in 1943 (Gjerstorff, 2011)), hold virtually complete data

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on drug prescriptions and incident cancer cases and thus provide a unique setting for active surveillance of cancer risk associated with the use of prescription drugs.

We established a system to screen for associations between prescription drug use and cancer risk, based on a multiple case–control design. In the present paper, we describe (i) the source population and data sources, (ii) the initial screening process, (iii) the strategy for internal validation of signals, and (iv) initial results from the nationwide screening.

2. Setting and Data Sources

2.1. Data Sources

The entire Danish population is provided free tax-supported medical care by the National Health Service (Thygesen and Ersbøll, 2014). For administration and maintenance of this health care system, numerous administrative and health registries have been established. In addition to supporting high quality service in the health care system, these registries allow population-based studies covering all residents in Denmark (approximately 5.6 millions).

The main data sources for our screening system include the Danish Cancer Registry (Gjerstorff, 2011), the Danish Prescription Registry (Kildemoes et al., 2011), the Danish National Patient Registry (Lynge et al., 2011), and the Danish Civil Registration System (Pedersen, 2011).

The Danish Cancer Registry (Gjerstorff, 2011) has recorded incident cancer cases on a nationwide basis since 1943 and has been shown to have accurate and almost complete ascertainment of cases (Gjerstorff, 2011; Statens Serum Institute and Danish Cancer Society, n.d.). Approximately 90% of cancer cases in the registry are histologically verified, while the remaining are mainly represented by brain tumours and cancers in very old and/or frail patients. Cancer diagnoses are recorded using the International Classification of Diseases, version 10 (ICD-10), and the ICD for Oncology (ICD-O-3).

The Danish National Prescription Registry (Kildemoes et al., 2011) contains data on all prescription drugs dispensed to Danish residents since 1995. The data include the type of drug, date of dispensing, and quantity dispensed. Drugs are categorized according to the Anatomical Therapeutic Chemical (ATC) index, a hierarchical classification system developed by the WHO (WHO Collaborating Centre for Drug Statistics Methodology, 2014).

The Danish National Patient Register (Lynge et al., 2011) contains nationwide data on all non-psychiatric hospital admissions since 1977 and all outpatient specialist contacts in hospital setting since 1995. Discharge/contact diagnoses are coded using ICD-8 (1977–1993) and ICD-10 (1994–).

The Danish Civil Registration System (Pedersen, 2011) contains data on vital status (date of death) and migration to and from Denmark, allowing sampling of general population controls and complete tracking of study subjects.

2.2. Data Linkages

Data sources were linked by the civil registry number, a unique identifier assigned to all Danish residents since 1968 (Pedersen, 2011). Linkage was performed within Statistics Denmark, a governmental institution that collects and maintains electronic records for a broad spectrum of statistical and scientific purposes (Thygesen et al., 2011a).

2.3. Identification of Cancer Cases

From the Danish Cancer Registry, we identified all individuals in Denmark with incident cancers diagnosed between January 1, 2000 and December 31, 2012. We defined the index date as the date of diagnosis. Cases were restricted to histologically verified cancers (except for tumours of the central nervous system, of which some are based on clinical and imaging findings only, and haematological malignancies).

Exclusion criteria were age outside 18–85 years at index date and migration to or from Denmark anytime during the 10 years prior to index date. This ensured at least 10 years of complete follow-up prior to sampling for all study subjects and a minimum of five years of prescription data (available from 1995). We excluded the youngest since both drug use and cancer incidence are low among children and adolescents. We further excluded individuals with a previous history of cancer (except non-melanoma skin cancer) thus focusing on primary incident cancers.

Based on ICD-O topography and morphology codes for 34 cancer sites, we restricted the cancer outcomes to 99 cancer subtypes. For a complete list of the included cancers and their definitions within the Cancer Registry, see Appendix A.

2.4. Selection of Controls

Controls were selected using risk set sampling. For each case, we randomly selected 10 controls from all Danish citizens applying the same exclusion criteria as for cases and with the same sex and birth year as the case. Controls were assigned an index date identical to that of the corresponding case. Each subject was eligible for sampling as a control before becoming a case and could be sampled as a control more than once. Thereby, the calculated odds ratios (ORs) provide unbiased estimates of the corresponding incidence rate ratios (IRRs) that would have emerged from cohort studies conducted in the underlying source population (Rothman et al., 2008).

2.5. Approvals and Funding

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., 2011a). The study was funded by the Danish Council for Independent Research (grant 4004-00234B). The funder had no role in the study conduct, interpretation of data, or reporting of the findings.

3. Initial Screening Process

The process consisted of two stages. In the first stage, we identified potential signals, i.e., drug–cancer associations. Those associations meeting our strength criteria qualified for further evaluation of causation in the second stage (see “Evaluation of Signals” below).

3.1. Classification of Drug Exposures

For each cancer or cancer subtype in the screening process, we included all drugs and drug classes that either had 10 observed long-term users (defined as ≥8 prescriptions) among the cases or where 10 cases were expected to be long-term users based on drug exposure among the controls given no drug–cancer association. Single drugs were defined by the fifth level of the ATC-system (e.g., C07AB02, metoprolol), and drug classes were analysed at both the second (e.g., C07, all beta-blockers) and fourth level (e.g., C07AB, selective beta-blockers).

Exposure to a specific drug or drug class was assessed from prescription fills recorded in the Prescription Registry prior to the index date for cases and controls. We classified use as non-use (0–1 prescription), intermediate use (2–7 prescriptions), and long-term use (≥8 prescriptions). Eight prescriptions was chosen as a cut-off as drugs for chronic treatment are typically supplied for 3 months use for each dispensing in Denmark, whereby our definition of long-term use would correspond to two years' cumulative treatment.

In all assessments of primary drug exposures or confounders, we disregarded prescriptions redeemed within one year prior to the index date. This was done for two reasons. First, such recent exposure is unlikely to be associated with cancer development (International Agency for Research on Cancer, 2012; Umar et al., 2012). Secondly, drug use has been shown to increase in the year prior to cancer

diagnoses (Jørgensen et al., 2012), likely due to treatment of early symptoms of yet undiagnosed cancers. Such treatment patterns raise the possibility of reverse causation bias (Csizmadl et al., 2007).

3.2. First-level Screening

The analyses followed a conventional matched case–control approach using conditional logistic regression. We estimated odds ratios (OR) for each individual cancer outcome associated with the drug exposures by comparing long-term use (≥8 fills) to non-use (i.e., disregarding intermediate use). Potential confounding by gender, age, and calendar time was handled by the design (matching) and conditional analysis. We further adjusted for Charlson Comorbidity Index (CCI) score (Charlson et al., 1987; Thygesen et al., 2011b) (categorized as 0, 1, 2, 3 or 4+) using information on medical history recorded in the Patient Registry from 1977 up to one year prior to index date, and years of schooling (categorized into basic [≤10 years], short/medium [11–13 years], long [14+ years], or missing) (Dalton et al., 2008).

All analyses were performed using Stata Release 13.0 (StataCorp, College Station, TX, USA).

3.3. Definition of Signals

Following the initial analysis, we identified all drug–cancer pairs meeting our criteria for strength of association. Signals were defined as drug–cancer associations with an OR greater than 1.5 or less than 0.67, or a lower limit of the 95% confidence interval above 1.2 or a higher limit below 0.83.

4. Evaluation of Signals

All signals identified in the initial screening procedure were examined further according to two additional criteria: (i) specificity and (ii) dose–response relationship.

4.1. Outcome Specificity

Signals were tested for specificity, i.e., whether the drug was associated with a particular cancer types or with cancer overall. No drug is known to increase the risk of all cancer types, and absence of specificity of the signals thus suggests the existence of bias, e.g., residual confounding by smoking or other factors such as surveillance. In the test for specificity of a given signal, we compared the point estimate for any drug–cancer association with the particular drug's association with cancer overall. To meet the criteria for specificity, we required that the ratio of the OR for the signal to the overall OR was outside the range of 0.83–1.20.

4.2. Dose–Response Pattern

We tested each signal for presence of a dose–response relationship. We first restricted the data to ever-users of the drug of interest and then estimated the incremental OR per prescription among the remaining users, while capping exposure at 50 prescriptions. This incremental OR corresponds to the slope of the dose–response curve. To evaluate whether a dose–response relationship was present, we tested the null hypothesis that the slope of the dose–response curve was zero. We arbitrarily selected a cutoff of $p < 0.10$.

5. Results

Following exclusions, the final study population consisted of 278,485 incident cancer cases. The most frequent cancers were ductal adenocarcinoma of the breast among females (n = 36,805), prostate adenocarcinoma among men (n = 34,443), and colon adenocarcinoma in both genders (n = 24,557). In the initial screening process, 22,125 drug–cancer pairs underwent evaluation. For the majority of cancer types (61 of 99), more than 100 drug–cancer pairs underwent evaluation.

A total of 4561 signals (i.e., drug–cancer pairs meeting criteria for strength of association) were identified in the initial screening process, most frequently for cancers of the lung (196 signals for squamous cell carcinoma, 178 for small cell carcinoma and 176 for other adenocarcinomas). For five of the 99 cancer types, we found no signals in the initial screening process (Table 1).

Of the signals identified in the initial screening stage, 3464 (75.9%) failed to meet the criteria for dose–response relationship, 12 (0.2%) failed the test for outcome specificity, while 65 (1.4%) failed both criteria; thus leaving 1020 signals. The signals most commonly disqualified because of the specificity criterion were drug–cancer pairs involving squamous cell carcinoma of the pharynx and various types of lung cancer. An overview of the total number of cases, drug–cancer pairs undergoing evaluation, and final signals are displayed in Table 1.

Of the final 1020 signals, 159 were observed among drug classes at the second level of the ATC-system, 351 among drug classes at the fourth level, and 510 for single agents (fifth level).

Table 2 displays all signals indicating a reduced cancer risk associated with long-term use of a drug class (at second ATC level), among associations based on more than 100 exposed cases or 1000 exposed controls. Table 3 displays signals suggesting an increased risk with a similar restriction. The full list of all 1020 signals for drug classes at the second or fourth level of the ATC-system and for single drug substances are provided in Supplementary Results I–II, III–IV, and V–VI, respectively.

6. Discussion

In this large-scale nationwide screening study, we evaluated 22,125 drug–cancer pairs and identified 1020 signals (i.e., drug–cancer associations) that met the criteria for strength of association, specificity, and dose–response pattern. The majority of the identified signals (703 signals) indicated an increased cancer risk associated with the specific prescription drugs, while a smaller proportion (317 signals) were inverse associations indicative of a potential chemopreventive effect. Our findings constitute a broad basis for future comprehensive studies of signals suggesting a potential causal relationship between the specific drugs and cancer types. The public health importance of identifying carcinogenic effects of drugs is evident, since even small carcinogenic effects of widely used drugs will translate into numerous drug-induced cancer cases. Moreover, neutral associations have important value by reassuring prescribers and patients of the safety of drugs, which will promote their appropriate use. Lastly, identification of potential chemopreventive drug effects may provide a clue to development of new compounds for cancer prophylaxis and treatment.

The primary strength of our study is the use of the Danish nationwide health registries, ensuring a prescription history of up to 17 years and virtually complete ascertainment of cancer cases. The large study population also allowed evaluation of drug exposure in relation to risk of more rare cancers. The quality of the data in the Danish Prescription Registry (Kildemoes et al., 2011) and the Danish Cancer Registry (Gjerstorff, 2011) has been found to be high (Kildemoes et al., 2011; Gjerstorff, 2011; Statens Serum Institute and Danish Cancer Society, n.d.). Lastly, the detailed stratification according to cancer histology avoided lumping of cancer types with markedly different histology. For example, lung cancer consists of squamous cell carcinoma, adenocarcinoma, small cell carcinoma, large cell carcinoma and carcinoids, among others. As these cancer subtypes have markedly different biology, it is unlikely that their development would be similarly affected by the same drugs.

The principal weakness of the study is the lack of adjustment for potential confounding from life-style factors. Although we adjusted for education and a measure of comorbidity, our analyses would benefit from adjustment for life-style factors, such as obesity, alcohol

Table 1
Overview of cancer cases and number of signals according to the screening phases, i.e., evaluation in the first stage of the algorithm, initial screening, and the second stage, internal validation.

No	Cancer	Cancer cases	Drug–cancer pairs evaluated	Signals passed stage 1	Signals passed stage 2
1	Lip (Squamous cell carcinoma)	491	113	19	3
2	Lip (Other)	31	0	0	0
3	Oral cavity (Squamous cell carcinoma)	3304	408	134	27
4	Oral cavity (Other)	272	63	19	1
5	Salivary glands (Adenocarcinoma)	368	77	15	2
6	Salivary glands (Other)	180	39	7	0
7	Pharynx (Squamous cell carcinoma)	3358	376	135	20
8	Pharynx (Other)	240	52	24	3
9	Oesophagus (Squamous cell carcinoma)	1889	296	101	24
10	Oesophagus (Adenocarcinoma)	1925	328	79	20
11	Oesophagus (Other)	412	107	25	7
12	Stomach (Adenocarcinoma)	4775	463	51	11
13	Stomach (Other)	412	97	15	2
14	Small intestine (Adenocarcinoma)	373	102	13	2
15	Small intestine (Carcinoid)	239	65	20	5
16	Small intestine (Other)	147	43	18	1
17	Colon (Adenocarcinoma)	24,557	809	66	14
18	Colon (Carcinoid)	386	84	9	1
19	Colon (Other)	283	77	15	4
20	Rectum (Adenocarcinoma)	13,445	654	94	21
21	Rectum (Other)	249	70	14	1
22	Liver (Hepatocellular carcinoma)	1382	301	121	39
23	Liver (Adenocarcinoma)	329	94	21	4
24	Liver (Bile duct carcinoma)	231	71	35	5
25	Liver (Other)	336	107	44	15
26	Gallbladder and biliary tract (Adenocarcinoma)	1129	253	46	13
27	Gallbladder and biliary tract (Bile duct carcinoma)	111	28	8	2
28	Gallbladder and biliary tract (Other)	128	49	18	3
29	Pancreas (Adenocarcinoma)	5522	500	64	10
30	Pancreas (Other)	1245	268	44	13
31	Larynx (Squamous cell carcinoma)	2630	351	110	20
32	Larynx (Other)	108	31	17	1
33	Lung (Adenocarcinoma)	14,363	707	176	55
34	Lung (Squamous cell carcinoma)	8526	619	196	66
35	Lung (Small cell carcinoma)	6745	564	178	62
36	Lung (Other (non-small cell))	3829	444	125	31
37	Lung (Carcinoid)	783	198	66	14
38	Lung (Large cell carcinoma)	840	184	55	9
39	Lung (Other)	3609	436	113	30
40	Bones, joints and cartilage (Chondrosarcoma)	211	40	9	4
41	Bones, joints and cartilage (Osteosarcoma)	83	3	0	0
42	Bones, joints and cartilage (Ewing sarcoma)	42	0	0	0
43	Bones, joints and cartilage (Other)	82	4	3	0
44	Skin (Melanoma)	16,331	708	82	14
45	Skin (Other)	49	3	1	0
46	Mesothelium and connective tissue (Sarcomas)	1404	229	28	5
47	Mesothelium and connective tissue (Mesothelioma)	1125	206	38	7
48	Mesothelium and connective tissue (Other)	432	112	33	11
49	Breast (female) (Adenocarcinoma, Ductal carcinoma)	36,805	899	75	11
50	Breast (female) (Adenocarcinoma, other)	5275	525	58	14
51	Breast (female) (Adenocarcinoma, Lobular carcinoma)	5514	516	62	20
52	Breast (female) (Other)	723	178	27	1
53	Breast (male) (Other)	287	74	16	2
54	Vulva and vagina (Squamous cell carcinoma)	815	205	34	5
55	Vulva and vagina (Other)	225	79	18	3
56	Cervix uteri (Squamous cell carcinoma)	3208	354	96	23
57	Cervix uteri (Adenocarcinoma)	725	121	18	4
58	Cervix uteri (Other)	391	80	28	2
59	Corpus uteri (Adenocarcinoma, endometrioid)	5130	525	161	48
60	Corpus uteri (Adenocarcinoma, other)	940	208	52	7
61	Corpus uteri (Sarcomas)	574	147	37	8
62	Corpus uteri (Adenocarcinoma, serous)	420	131	39	7
63	Corpus uteri (Other)	538	138	42	4
64	Ovary (Adenocarcinoma, serous)	3002	396	62	18
65	Ovary (Adenocarcinoma, other)	916	231	38	6
66	Ovary (Adenocarcinoma, endometrioid)	527	117	21	4
67	Ovary (Adenocarcinoma, mucinous carcinoma)	482	101	20	5
68	Ovary (Adenocarcinoma, clear cell)	257	67	15	1
69	Ovary (Other)	591	141	32	2
70	Prostate (Adenocarcinoma)	34,443	800	126	34
71	Prostate (Other)	256	70	16	3
72	Testis (Seminoma)	2073	134	33	4
73	Testis (Teratoma)	586	21	5	1
74	Testis (Embryonal carcinoma)	468	17	9	0

Table 1 (*continued*)

No	Cancer	Cancer cases	Drug–cancer pairs evaluated	Signals passed stage 1	Signals passed stage 2
75	Testis (Choriocarcinoma)	109	1	0	0
76	Testis (Other)	99	1	0	0
77	Kidney (Adenocarcinoma, clear cell)	5083	496	120	21
78	Kidney (Adenocarcinoma, other)	385	105	31	7
79	Kidney (Other)	177	48	9	0
80	Renal pelvis and ureter (Urothelial carcinoma)	713	177	35	5
81	Renal pelvis and ureter (Other)	106	30	7	0
82	Bladder (Urothelial carcinoma)	7611	565	79	13
83	Bladder (Adenocarcinoma)	425	101	27	5
84	Bladder (Squamous cell carcinoma)	233	72	22	11
85	Bladder (Other)	277	90	20	4
86	Eye (Melanoma)	307	56	5	0
87	Eye (Other)	50	10	5	1
88	Brain and meninges (Glioma)	3669	391	55	15
89	Brain and meninges (Meningioma)	2045	307	51	10
90	Brain and meninges (Other)	653	104	17	5
91	Thyroidea (Adenocarcinoma, Papillary carcinoma)	1260	191	56	11
92	Thyroidea (Follicular carcinoma)	339	80	32	6
93	Thyroidea (Other)	399	91	18	6
94	Hodgkin (Other)	1346	184	59	8
95	Non-Hodgkin (Other)	9002	607	83	17
96	Multiple myeloma (Other)	3257	412	52	13
97	Leukaemia (Lymphatic)	3494	405	51	12
98	Leukaemia (Myeloid)	2719	354	55	5
99	Leukaemia (Other)	615	139	28	6
	TOTAL	278,485	22,125	4561	1020

consumption, and smoking. However, this information is not available in the Danish health registries. Moreover, a generic confounder adjustment relevant to all cancers is difficult as no universal confounders exist, which emphasizes the need for tailored analyses of our individual signals.

Under the null hypotheses and with the traditional α of 0.05, evaluation of 22,000 associations is expected to result in approximately 1100 false positive associations. Importantly, this pertains to the initial signals (n = 4561) before dose–response and specificity requirements. One way to handle this would be to adjust for multiple testing, e.g. Bonferroni correction (Rice et al., 2008). Although such adjustment reduces the number of false positive associations, it also reduces the likelihood that a true association will be captured. Given the explorative nature of our screening study, we should not reject signals before they can be subjected to rigorous evaluation. Thus, we did not include any correction for multiple testing, as also recommended by others (Rothman, 1990).

Some of the identified signals can be attributed to confounding by indication. This is most notable for the observed associations with lung cancers. As an example, drugs used to treat obstructive lung diseases exhibited a strong association with squamous cell carcinoma of the lung (OR, 2.61), which is likely explained by these drugs being used for chronic obstructive pulmonary disease (COPD), which is caused primarily by smoking (Supplementary Results I). Nevertheless, our algorithm succeeded in identifying established or previously reported associations, such as the association between use of female hormone therapy and risk of ductal and lobular adenocarcinomas (International Agency for Research on Cancer, 2007) (OR 1.92 and 2.65, respectively, Supplementary Results V), and the association between the antihypertensive drug hydrochlorothiazide and lip cancer (Friedman et al.,

Table 2
16 signals (drug–cancer associations) indicative of a decreased cancer risk associated with drug classes at second ATC-level restricted to signals with more than 100 long-term users among cancer cases or 1000 among controls for the given drug exposure.

Cancer	ATC	Drug class	Cases expo/nonexpo	Controls expo/nonexpo	OR (95%CI)[a]	Spec.[b]	p^{***}
Prostate (Adenocarcinoma)	A06	Drugs for constipation	63/34,062	1987/337,637	0.33 (0.26–0.43)	0.73	0.01
Pharynx (Squamous cell carcinoma)	C10	Lipid modifying agents	238/2953	3168/28,929	0.47 (0.40–0.54)	0.94	<0.01
Oral cavity (Squamous cell carcinoma)	C10	Lipid modifying agents	274/2866	3092/28,577	0.56 (0.49–0.65)	0.94	0.03
Oral cavity (Squamous cell carcinoma)	R01	Nasal preparations	78/3007	1244/29,426	0.58 (0.46–0.73)	0.97	<0.01
Lung (Other (non-small cell))	A10	Drugs used in diabetes	215/3571	2143/35,827	0.62 (0.53–0.72)	0.94	0.04
Lung (Adenocarcinoma)	A10	Drugs used in diabetes	691/13,562	7415/134,978	0.63 (0.58–0.69)	0.94	0.09
Lung (Small cell carcinoma)	D01	Antifungals for dermatological use	114/5849	1554/56,978	0.66 (0.54–0.80)	0.98	0.05
Larynx (Squamous cell carcinoma)	C09	Agents acting on the renin–angiotensin system	384/2117	4370/20,674	0.66 (0.58–0.75)	1.01	0.06
Pharynx (Squamous cell carcinoma)	C09	Agents acting on the renin–angiotensin system	419/2793	4572/27,633	0.67 (0.59–0.75)	1.01	0.05
Corpus uteri (Adenocarcinoma, endometrioid)	R03	Drugs for obstructive airway diseases	344/4395	4732/42,762	0.72 (0.64–0.81)	1.16	<0.01
Lung (Small cell carcinoma)	A10	Drugs used in diabetes	399/6262	3708/63,104	0.72 (0.64–0.81)	0.94	0.03
Cervix uteri (Squamous cell carcinoma)	G03	Sex hormones and modulators of the genital system	1187/1692	13,254/14,514	0.73 (0.67–0.81)	1.12	<0.01
Prostate (Adenocarcinoma)	N03	Antiepileptics	552/33,475	7698/332,407	0.74 (0.68–0.81)	1.01	<0.01
Lung (Squamous cell carcinoma)	C09	Agents acting on the renin–angiotensin system	1589/6490	16,324/64,287	0.76 (0.72–0.81)	1.01	0.01
Rectum (Adenocarcinoma)	N06	Psychoanaleptics	984/11,821	12,535/114,922	0.77 (0.71–0.82)	1.01	<0.01
Rectum (Adenocarcinoma)	N02	Analgesics	1603/9929	19,197/94,719	0.78 (0.74–0.83)	1.06	<0.01

Notes: OR = odds ratio; CI = confidence interval.
*** *p*-Value as obtained in the dose–response analysis.
[a] Adjusted for gender, age, and calendar time (by design) as well as Charlson Comorbidity Index (CCI) score and educational level.
[b] Specificity, i.e. the association (OR) between the drug and overall cancer risk.

Table 3
57 signals (drug–cancer associations) indicative of an increased cancer risk associated with drug classes at second ATC-level restricted to signals with more than 100 long-term users among cancer cases or 1000 among controls for the given drug exposure.

Cancer	ATC	Drug class	Cases expo/nonexpo	Controls expo/nonexpo	OR (95%CI)[a]	Spec.[b]	p^{***}
Lung (Squamous cell carcinoma)	R03	Drugs for obstructive airway diseases	1824/5947	7189/73,406	2.61 (2.45–2.78)	1.16	<0.01
Lung (Carcinoid)	R03	Drugs for obstructive airway diseases	147/563	635/6679	2.43 (1.96–3.00)	1.16	0.09
Lung (Other (non-small cell))	R03	Drugs for obstructive airway diseases	680/2843	3194/32,806	2.08 (1.89–2.29)	1.16	0.02
Oesophagus (Adenocarcinoma)	A02	Drugs for acid related disorders	366/1317	1976/15,268	2.07 (1.81–2.36)	1.07	<0.01
Pharynx (Squamous cell carcinoma)	N05	Psycholeptics	771/2129	4096/26,149	2.07 (1.89–2.28)	1.08	<0.01
Liver (Hepatocellular carcinoma)	A10	Drugs used in diabetes	301/1056	825/12,852	2.06 (1.72–2.46)	0.94	0.02
Lung (Other)	R03	Drugs for obstructive airway diseases	618/2685	2951/30,893	2.03 (1.83–2.24)	1.16	<0.01
Vulva and vagina (Squamous cell carcinoma)	D07	Corticosteroids, dermatological preparations	110/460	597/5457	1.99 (1.57–2.54)	1.02	<0.01
Hodgkin (Other)	D07	Corticosteroids, dermatological preparations	106/910	629/9999	1.93 (1.53–2.43)	1.02	0.05
Oral cavity (Squamous cell carcinoma)	N05	Psycholeptics	821/2030	4663/24,948	1.91 (1.73–2.10)	1.08	<0.01
Lung (Squamous cell carcinoma)	L04	Immunosuppressants	149/8296	588/84,152	1.87 (1.55–2.25)	1.13	0.04
Lung (Adenocarcinoma)	N07	Other nervous system drugs	228/13,549	1131/139,827	1.84 (1.59–2.13)	1.23	<0.01
Kidney (Adenocarcinoma, clear cell)	C09	Agents acting on the renin–angiotensin system	1287/3484	8107/40,331	1.82 (1.68–1.96)	1.01	<0.01
Lip (Squamous cell carcinoma)	C03	Diuretics	131/316	818/3662	1.80 (1.39–2.33)	1.05	<0.01
Larynx (Squamous cell carcinoma)	N05	Psycholeptics	610/1704	3552/20,101	1.79 (1.61–1.99)	1.08	<0.01
Kidney (Adenocarcinoma, clear cell)	C03	Diuretics	1147/3380	7528/39,297	1.78 (1.64–1.93)	1.05	0.05
Kidney (Adenocarcinoma, clear cell)	C08	Calcium channel blockers	879/3878	5250/43,226	1.77 (1.63–1.93)	1.04	<0.01
Lung (Small cell carcinoma)	R05	Cough and cold preparations	486/4974	2560/53,959	1.77 (1.59–1.97)	1.12	<0.01
Lung (Small cell carcinoma)	P01	Antiprotozoals	180/6136	889/62,483	1.69 (1.43–1.99)	1.14	<0.01
Larynx (Squamous cell carcinoma)	N02	Analgesics	505/1695	2866/19,793	1.68 (1.49–1.89)	1.06	<0.01
Liver (Hepatocellular carcinoma)	N02	Analgesics	359/784	1658/10,175	1.67 (1.42–1.96)	1.06	<0.01
Lung (Squamous cell carcinoma)	P01	Antiprotozoals	229/7765	1128/79,205	1.66 (1.43–1.93)	1.14	0.01
Stomach (Adenocarcinoma)	A02	Drugs for acid related disorders	757/3397	4903/37,921	1.65 (1.51–1.81)	1.07	<0.01
Liver (Hepatocellular carcinoma)	N05	Psycholeptics	373/823	2123/10,304	1.63 (1.40–1.89)	1.08	<0.01
Oral cavity (Squamous cell carcinoma)	N02	Analgesics	677/2085	3912/24,711	1.63 (1.47–1.81)	1.06	<0.01
Lung (Adenocarcinoma)	R03	Drugs for obstructive airway diseases	2100/11,087	11,905/122,450	1.63 (1.55–1.72)	1.16	<0.01
Breast (female) (Adenocarcinoma, Lobular carcinoma)	G03	Sex hormones and modulators of the genital system	2251/2622	16,711/31,474	1.62 (1.52–1.72)	1.12	<0.01
Lung (Squamous cell carcinoma)	J01	Antibacterials for systemic use	2537/2401	17,597/30,244	1.62 (1.51–1.75)	1.16	<0.01
Pharynx (Squamous cell carcinoma)	N03	Antiepileptics	134/3127	703/32,450	1.60 (1.32–1.95)	1.01	0.05
Lung (Squamous cell carcinoma)	R05	Cough and cold preparations	580/6456	3195/68,899	1.60 (1.45–1.76)	1.12	<0.01
Lung (Carcinoid)	J01	Antibacterials for systemic use	275/175	1987/2320	1.59 (1.25–2.01)	1.16	<0.01
Lung (Small cell carcinoma)	J01	Antibacterials for systemic use	2038/1831	14,794/22,787	1.58 (1.46–1.72)	1.16	<0.01
Bladder (Adenocarcinoma)	J01	Antibacterials for systemic use	114/111	856/1371	1.54 (1.12–2.13)	1.16	0.02
Lung (Squamous cell carcinoma)	M05	Drugs for treatment of bone diseases	230/8172	1400/83,177	1.53 (1.32–1.77)	0.98	0.09
Lung (Small cell carcinoma)	N02	Analgesics	1538/4,055	9975/47,049	1.53 (1.42–1.64)	1.06	<0.01
Lung (Adenocarcinoma)	P01	Antiprotozoals	335/12,924	1928/132,006	1.49 (1.32–1.68)	1.14	<0.01
Corpus uteri (Adenocarcinoma, endometrioid)	C03	Diuretics	1438/3135	11,378/34,576	1.48 (1.38–1.59)	1.05	<0.01
Lung (Adenocarcinoma)	J01	Antibacterials for systemic use	4541/3,529	35,295/44,294	1.48 (1.40–1.56)	1.16	<0.01
Larynx (Squamous cell carcinoma)	R05	Cough and cold preparations	131/2104	747/22,159	1.48 (1.21–1.80)	1.12	<0.01
Oesophagus (Squamous cell carcinoma)	N05	Psycholeptics	410/1249	2936/13,955	1.47 (1.30–1.67)	1.08	0.03
Hodgkin (Other)	J01	Antibacterials for systemic use	342/390	2679/4428	1.46 (1.20–1.78)	1.16	<0.01
Lung (Small cell carcinoma)	N05	Psycholeptics	1752/4204	12,313/47,245	1.46 (1.37–1.55)	1.08	<0.01
Pharynx (Squamous cell carcinoma)	N02	Analgesics	559/2255	3495/25,627	1.45 (1.30–1.62)	1.06	0.03
Lung (Squamous cell carcinoma)	N02	Analgesics	1876/5158	12,176/60,203	1.45 (1.36–1.55)	1.06	<0.01
Corpus uteri (Adenocarcinoma, endometrioid)	C09	Agents acting on the renin–angiotensin system	1055/3824	8204/40,669	1.45 (1.34–1.56)	1.01	<0.01
Liver (Hepatocellular carcinoma)	M01	Antiinflammatory and antirheumatic products	342/615	2393/7353	1.43 (1.22–1.69)	1.04	0.04
Lung (Other (non-small cell))	J01	Antibacterials for systemic use	1127/1070	8380/13,046	1.43 (1.29–1.59)	1.16	<0.01
Leukaemia (Lymphatic)	J01	Antibacterials for systemic use	836/1025	7235/12,145	1.40 (1.24–1.57)	1.16	0.04
Leukaemia (Myeloid)	J01	Antibacterials for systemic use	698/822	5684/9407	1.39 (1.22–1.59)	1.16	<0.01
Breast (female) (Adenocarcinoma, Ductal carcinoma)	G03	Sex hormones and modulators of the genital system	14,170/18,036	117,211/201,628	1.37 (1.34–1.40)	1.12	<0.01
Lung (Adenocarcinoma)	R05	Cough and cold preparations	864/10,808	5863/114,283	1.36 (1.26–1.47)	1.12	<0.01
Lung (Squamous cell carcinoma)	N05	Psycholeptics	2063/5489	15,025/60,826	1.36 (1.29–1.44)	1.08	<0.01
Lung (Other (non-small cell))	N02	Analgesics	816/2388	5636/26,768	1.35 (1.22–1.48)	1.06	<0.01
Lung (Adenocarcinoma)	N05	Psycholeptics	3435/9225	25,688/100,862	1.34 (1.28–1.40)	1.08	<0.01
Lung (Other (non-small cell))	N05	Psycholeptics	955/2406	7109/26,670	1.34 (1.23–1.46)	1.08	<0.01
Corpus uteri (Adenocarcinoma, endometrioid)	C07	Beta blocking agents	781/4068	6331/42,068	1.32 (1.21–1.43)	0.99	<0.01
Lung (Adenocarcinoma)	N02	Analgesics	2951/8915	21,622/99,702	1.32 (1.25–1.38)	1.06	<0.01

Notes: OR = odds ratio; CI = confidence interval.
*** *p*-Value as obtained in the dose–response analysis.
[a] Adjusted for gender, age, and calendar time (by design) as well as Charlson Comorbidity Index (CCI) score and educational level.
[b] Specificity, i.e. the association (OR) between the drug and overall cancer risk.

2012) (OR 6.93, Supplementary Results V). Such findings provide assurance that our approach is capable of identifying true associations.

Some of the signals we have identified clearly warrant further investigation. For example, the two antibiotics pivmecillinam and sulfamethizole displayed odds ratios of about 13 and 6, respectively, for squamous cell carcinoma of the bladder (Supplementary Results V). Both drugs are used specifically to treat urinary tract infections and, as such, this signal might reflect a carcinogenic effect of inflammation due to recurrent infections. However, as both drugs are designed to accumulate in the bladder lumen and because the signal was very strong, this signal should be considered a candidate for future studies. Such studies should be designed specifically for the individual drug–cancer association, by

employing focused and comprehensive confounder adjustment and by focusing on etiologically relevant exposure windows for the specific cancer outcomes under study.

When deciding whether a given drug–cancer association is worthy of further study, i.e., prioritizing the many signals reported in this study, parameters other than the strength of the association should be considered. Thought should be given to the potential for confounding by indication or contraindication as discussed above, as well as biological plausibility, e.g., by considering the pharmacological mechanism of the drug and/or drawing upon findings in other studies, whether experimental, clinical or observational. In addition, the potential public health impact of a putative association should be considered, as reflected by the number of attributable cases, the aggressiveness of the cancer outcome and the age of those affected. Finally, several drugs evaluated by the International Agency for Research on Cancer (IARC) have been categorized as probably (Group 2 A) or possibly (Group 2B) carcinogenic to humans, because epidemiological evidence has not been definitive, or because carcinogenicity has been demonstrated only in experimental animals (International Agency for Research on Cancer, 2012; Friis et al., 2015). Additional studies and continued monitoring of the potential carcinogenicity of these drugs are of paramount importance.

Another valuable next step would be a full-scale replication of our study, a common approach in, e.g., genome-wide screening studies (NCI-NHGRI Working Group on Replication in Association Studies et al., 2007). This would require access to data sources comparable to the Danish registries, and should ideally hold data on potential lifestyle confounders or health-seeking behaviour. The combined results of the index and replication studies would help prioritize the signals that warrant further research.

In conclusion, we have presented an approach for nationwide screening of associations between the use of prescribed medications and cancer risk. The results of this screening should undergo external validation and the single drug–cancer associations should be subject to tailored analysis, in order to enhance our understanding of carcinogenic or chemopreventive effects of prescription drugs.

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.ebiom.2016.03.018.

Contributions

Anton Pottegård and Jesper Hallas were responsible for the initial concept and planning of the study. Statistical analyses and data management were performed by Anton Pottegård. All authors contributed significantly to the planning of the study and the subsequent reporting of the work described in the article. The manuscript was primarily drafted by Anton Pottegård, Jesper Hallas and Søren Friis. All authors have revised the manuscript for important intellectual content and approved the final version.

Declaration of Interests

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