Drug use and cancer risk: a drug-wide association study (DWAS) in Norway

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Abstract

Background

Population-based pharmacoepidemiological studies are used to assess post-marketing drug safety and discover beneficial effects of off-label drug use. We conducted a drug-wide association study (DWAS) to screen for associations between prescription drugs and cancer risk.

Methods

This registry-based nested case-control study, 1:10 matched on age, sex and date of diagnosis of cases comprises approximately 2 million Norwegian residents including their drug history from 2004-2014. We evaluated the association between prescribed drugs, categorized according to the Anatomical Therapeutic Chemical (ATC) classification system, and the risk of the 15 most common cancer types, overall and by histology. We used stratified Cox regression, adjusted for other drug use, comorbidity, county and parity, and explored dose-response trends.

Results

We found 145 associations among 1230 drug–cancer combinations on the ATC2-level and 77 of 8130 on the ATC4-level. Results for all drug–cancer combinations are presented in this paper and an online tool (https://pharmacoepi.shinyapps.io/drugwas/). Some associations have been previously reported, i.e. menopausal hormones and breast cancer risk, or are likely confounded, i.e. chronic obstructive pulmonary diseases and lung cancer risk. Other associations were novel, i.e. inverse association between proton pump inhibitors and melanoma risk, and carcinogenic association of propulsives and lung cancer risk.

Conclusions

This study confirmed previously reported associations and generated new hypotheses on possible carcinogenic or chemopreventive effects of prescription drugs. Results from this type of explorative approach need to be validated in tailored epidemiological and preclinical studies.

Impact

DWAS studies are robust and important tools to define new drug-cancer hypotheses.

Introduction

Safety monitoring of marketed pharmaceutical drugs mainly relies on the spontaneous reporting of adverse effects by health-care professionals and drug users. However, the importance of using the full spectrum of evidence, including observational studies, has long been acknowledged[1]. It may not be until hundreds of thousands of patients have used a medication that rare but possibly serious adverse events may appear, such as cancer. This, and a typically long induction period, is why population-based pharmacoepidemiological studies have been indicated as a powerful tool for post-marketing pharmacovigiliance [2].

Large, hypothesis-free, screening studies to detect associations between genes (GWAS-Genome-wide association studies), environmental variables (EWAS-environmental-wide association studies) or prescribed drugs (DWAS-Drug-wide association studies) and disease-related phenotypes have become feasible with advances in technology and data availability. In the Kaiser Permanente Medical Care Program [3], as well as in Danish [2] and Swedish [4] drug use-cancer risk screening studies, researchers identified several novel associations. Follow-up investigation of these signals may potentially reveal carcinogenic effects of prescription drugs [5, 6] or lead to eventual chemopreventive repurposing drugs [7].

We present a nationwide population- and registry-based nested case-control study comprising approximately 2 million people in Norway [8]. We searched for associations between prescription drugs and risk for the 15 most common cancer types. We focused on the interpretation of interesting signals in the light of potential confounding. We also present an easy-to-use interactive online tool (https://pharmacoepi.shinyapps.io/drugwas/) displaying modifiable figures and tables of results.

Material and Methods

Data sources and study design

Study design and methodological details have been published in the protocol[8]. Briefly, all adult subjects (aged 18-85) with a primary cancer diagnosis between January 1st 2007 and December 31st 2015 were selected from the Cancer Registry of Norway (CRN). For each cancer case, 10 cancer free controls matched on birth year, gender and index date (i.e. date of cancer diagnosis) were sampled from the Norwegian population. Thus, the study design is a nested case-control design with incidence density sampling, one case-control study for each cancer type [8]. Cancer information was obtained from the CRN. Prescription drugs, classified according to the Anatomical Therapeutic Chemical (ATC) classification system [9] were collected from the Norwegian Prescription Database which contains all drugs dispensed from pharmacies to patients in ambulatory care. The Norwegian Patient Registry provided information on comorbidities and the Medical Birth Registry of Norway on parity.

Exposures and Outcome

Drug use

All drug exposure was based on prescriptions from January 1st 2004 up to one year prior to index date for cases and controls to reduce the possibility of reverse causation. All drug–cancer associations were analysed on the ATC2- and ATC4-level, as well as some associations on the ATC5-level. We used the ATC classification system 2017 version, where active substances are classified in a hierarchy with five different levels, according to anatomical/pharmacological (ATC1-level), therapeutic/pharmacological / chemical subgroups (ATC2- to ATC4-level) and active substance (ATC5-level) [10-12].

Drug use was categorized according to number of prescriptions filled up to one year before index date; non-use (0-1 prescription), intermediate use (2-7 prescriptions) and long-term use (≥8 prescriptions).

The main exposure was long-term use, corresponding to approximately two years of use assuming a duration of 3 months per prescription filled. When analysing long-term use of drugs on the ATC4-level, non-users of the particular drug class who had used other drugs within the same ATC2-level were put in a separate category to keep a clean reference category (non-use). Dose-response relationships for the ATC2- and ATC4-level were assessed for all drug and cancer type combinations with signals when comparing long-term use versus non-use (signal defined below).

Dose-response relationships

Dose response relationships for the ATC2- and ATC4-level were assessed for all signals from the drug use – cancer risk association testing (long-term use versus non-use). The ATC-level specific cumulative defined daily doses (DDDs) were categorized according to quintiles among the users with one additional category for the non-users. If not all quintiles could be uniquely defined (due to many equal cumulative DDDs) or if there were less than 100 users of the particular drug, the cumulative DDDs were categorized according to tertiles.

We classified dose-response relationships as *continuously increasing or decreasing* (in short: *dose-response relationships*) or *associations mainly independent of dose.* The criteria for detrimental or protective *dose-response relationships* was defined as at least one dose-response signal with an unadjusted p-value of less than 0.1 and that each hazard ratio (HR) was larger (detrimental associations) or smaller (protective associations) than the previous dose category. One single exception (a miss) from this rule was allowed, but the following estimate had to be larger/smaller than the estimate prior to the miss. The criteria for *associations mainly independent of dose* was defined as not being among *dose-response relationships* and that all HRs and HR=1 were included in a ±10% interval around the mean of all HRs (excluding non-user category). Some ATC-codes do not have a DDD, for instance A10BA02, and when cumulating DDD's over ATC2- or ATC4 levels these prescriptions were not included in the calculation of dose-response relationships.

Cancer outcome

Cancer cases were categorized by topography according to the International Classification of Disease Tenth Revision (ICD-10) as in the publication 'Cancer in Norway' [13]. We included the 15 most common cancer types in Norway (Table 1). This choice ensured at least 70% power for at least 80% of the ATC2-categories. We also categorized each cancer type by major histological subtype and reported results for the most common ones (≥20% of all cases out of all cancers of a certain type).

Covariates

For *comorbidities*, we used the Patient Registry Index (PRI) with 15 levels, a modified version of Charlson Comorbidity Index [14]. Long-term use of other medications (*other drug use*), defined as whether the patients are long-term users of drugs from other drug groups on the same ATC-level than the drug of interest, was set as a binary indicator. *County* of residence was categorized according to the four health regions in Norway (north, mid, south-east, west and unknown). *Parity* was defined for females at index date.

Statistical analysis

We used Cox regression models stratified by case-control sets to obtain hazard ratios (HR) with 95% confidence intervals (CI). We adjusted all estimates for comorbidity index (continuous variable), use of other drugs and county of residence. The estimates of drug associations with female cancers (breast, endometrial and ovarian) were additionally adjusted for parity (continuous variable).

The main analyses evaluated the associations between long-term drug use versus non-use and the risk of cancer (on topographical level and by histological subgroups). To assess dose-response associations, we analysed the cumulative defined daily dose (DDD), which was analysed as a factor with the lowest user category as the reference.

We required at least 10 cases and controls in the long-term user and non-user group for a drug–cancer combination to be analysed.

In order to quantify the effect of covariates on effect estimates, we calculated the change in HR estimates for all drug cancer combinations by comparing the HR estimates from the statistical models with and without adjustment.

All statistical analyses were performed using R version 3.4.4 (http://cran.r-project.org).

Multiple testing

For each ATC-level, we adjusted for multiple testing based on the number of tested drug groups within each cancer type using Bonferroni [15], thus treating each nested case-control study as independent and the tests for the different drug groups as dependent. In the following, associations with adjusted p-values below 0.05 were considered to be *associations or signals*. Associations were considered as *detrimental* when HR > 1 and *protective* when HR < 1.

Comparison to other drug–cancer screening results

We evaluated how many of our signals were also found in the association screening studies performed previously[2, 4]. As the Swedish screening solely included associations between drugs (ATC4-level) and

breast, colon and prostate cancer (in addition to cancer overall), we only compared the results for these three cancer types and we relied solely on the results from the Cox regression. We compared the Danish screening results with ours by comparing results on the ATC4-level for histological subtypes.

Results

The total number of cases and controls included in this study as well as the distribution of sex, age, region, comorbidity and parity (for female cancers only) are presented in Table 1.

Long-term drug use

The first analysis evaluated the associations between combinations of all drugs and all 15 cancer types included in this study. The results are illustrated in Figure 1 (ATC2-level) and Supplementary figures 1A-V (ATC4-level). Although Figure 1 focuses on ATC2-level results, combinations for which ATC4-level signals (and *no* ATC2-level signal) were detected were highlighted by the ATC4 code. HRs, CIs, and p-values are presented in Supplementary Table 1 (ATC2-level) and Supplementary Table 2 (ATC4-level) as well as in our online interactive tool (https://pharmacoepi.shiny apps.io/drugwas/).

ATC2-level

On the ATC2-level, we investigated 15 cancer types against 82 drug classes (i.e. 1230 combinations), and found 145 (11.8%) signals (Figure 1; blue/red corresponding to protective/detrimental associations). These signals were unevenly distributed across cancer types, with most signals for lung cancer (22 detrimental, 9 protective). Lung and kidney cancer had the highest number of detrimental signals (22 and 21, respectively). Prostate cancer had the highest number of protective signals (9). The drug classes with the most signals were antibacterials for systemic use (J01) (8 detrimental, 1 protective), analgesics (N02) (6 detrimental, 2 protective) and antidiabetics (A10) (6 detrimental, 2

protective). As shown in Figure 1, the power was high (>90%) for about two third of all investigated ATC2 codes.

ATC4-level

On the ATC4-level, we investigated 15 cancer types against 542 drug classes (i.e. 8130 combinations, and found 77 (0.9%) signals (64 detrimental, 13 protective). The majority of the detrimental signals (39) were observed for lung cancer. Six combinations did not have an unadjusted signal on the corresponding ATC2 level and where thus marked with the ATC4 level codes in Figure 1.

Overall, we observed that the signals involving antibacterials for systemic use (J01) were mainly based on penicillins (J01CA/E), tetracyclines (J01AA), macrolides (J01FA) and trimethoprim/sulfonamides (J01EA/E). The statistical power was low to moderate for the majority of combinations assessed.

The ATC4-level signals resulting from drugs used in diabetes (A10) were mainly driven by intermediate-acting insulins (A10AC) and the blood glucose lowering drugs biguanides (A10BA) and sulfonyleras (A10BB). The signals for these drugs were mainly detrimental for stomach, colon, rectum, pancreas, kidney and endometrial cancer and protective for lung and prostate cancer. The power to detect associations was moderate to high.

For analgesics, the by far strongest ATC4-level signals were seen for lung cancer risk related to intake of natural opium alkaloids, phenylpiperidine and diphenylpropylamine derivatives (N02AA/B/C), opioids (plain or in combination with non-opioid analgesics N02AJ/X) and anilides (paracetamol N02BE). Most signals for other relevant cancer types were cumulative for opioids and anilides. The power for the corresponding ATC4 analyses was generally low, but moderate or high for opioids and anilides.

Dose-response analysis

We evaluated which signals from the long-term use analysis were confirmed in the dose-response analysis (Figure 1; arrow up/down corresponding to detrimental/protective dose-response

associations, square corresponding to an association mainly independent of dose). Among 145 signals, we identified 23 detrimental and 10 protective *dose-response relationships.* Additional 50 signals were classified as *associations mainly independent of dose* (33 detrimental, 17 protective associations).

Histological subtypes

We evaluated the risk of drugs for specific histological subtypes and illustrated the results in Supplementary Figure 2 (ATC2-level) and 3A-V (ATC4-level) as well as in our online tool. HRs, CIs and p-values are presented in Supplementary Tables 3 (ATC2-level) and 4 (ATC4-level).

The role of covariates as potential confounders

Observed and modelled confounders in our dataset are county of residence, other drug use, comorbidity and parity (for female cancers only). The distribution of observed potential confounders is presented in Table 1. The impact of county of residence on cancer risk is most obvious when investigating drug use related to melanoma, stomach and leukemia. Table 1 also indicates that there is no difference between cases and controls with respect to underlying comorbidities, except for smoking-related cancers, i.e. lung, bladder and kidney cancer. For female cancers, it can be seen that cases had lower parity than controls.

Proof of concept

We first verified that well-known associations emerged in our study. As expected, we found a protective association between aspirin use and colorectal cancer[16] (ATC code B01AC06; HR=0.91, CI: 0.84-0.97). We also observed an association between use of menopausal hormone therapy and increased risk of breast cancer, both for estrogens only (G03C; HR=1.16; CI:1.04-1.31) and progestines and estrogens in combination (G03F; HR=2.07; CI:1.82-2.35), consistent with randomized and observational studies [17].

Second, we evaluated the agreement between our results and those from two other recent studies based on data from Sweden [4] and Denmark [18] (Table 2): 8 out of our 10 signals in breast, colon-

and prostate cancer on the ATC4-level, were also found in the Swedish study. The Danish study was based on histological subtypes and ATC4-level: of the 95 signals in both datasets with matching drug–histologic subtype cancer risk combination, 25 of these had concordant results. Additional 7 signals show up when allowing signals on the same ATC3-level to replicate a particular finding on the ATC4-level.

Unexpected signals

Some unexpected associations emerged from our analyses, which had not been reported in earlier epidemiological studies. We report here three examples: A) a protective association between drugs that decrease the production of stomach acid (H2-receptor antagonists (A02BA) and proton pump inhibitors (A02BC)) and melanoma risk, B) a possible protective association between anticholinesterases (N06DA), a class of anti-dementia drugs, and lung, colon and particularly prostate cancer and C) an association between use of propulsives (A03FA), a type of drug used to reduce nausea and vomiting, and increased risk of lung cancer.

Discussion

We have presented the results of a population-based nested case-control study [8] involving approximately 2 million residents in Norway, and evaluated associations between prescribed drugs and cancer risk for the 15 most common cancer types and corresponding histological subtypes.

Discussion of results

As for the analysis on the ATC2-level, the majority of the detrimental associations (39) were observed in for lung cancer. This is not surprising, as lung cancer is heavily associated with smoking, which also causes numerous other diseases related to lung function, such as COPD [19] and inflammations [20]. The drug classes with most signals were antibacterials for systemic use, analgesics and drugs used in diabetes. Confounding by indication might also explain a substantial proportion of these other findings. For example, diabetes and obesity are risk factors for several cancer types [21] and extensive

antibiotics use might be related to inflammations [22] and bacterial infections [23], associated directly with cancer development. Confounders, observed and unobserved, known and unknown, thereby play an important role when interpreting the results of our study. This concerns in particular life-style variables, including smoking, alcohol intake or BMI[24, 25]. As an example, obesity and other related life-style factors represent essential confounders of the observed detrimental associations between drugs used in diabetes (A10) and the risk of colon, endometrial, kidney, pancreas, rectum and stomach cancer [21]. The protective association between the intake of antidiabetic drugs and the risk of prostate cancer may also rely on confounding by indication as diabetes has been shown to be associated with a lower risk of prostate cancer [26]. The largest risk related to the use of antibacterials was observed for bladder and urinary tract cancer and suffers from a confounding by indication bias as the indication (urinary tract infection) for taking the actual drug (antibiotics) is a strong risk factor for some subtypes of bladder cancer [27-29].

When considering the observed potential confounders county of residence, other drug use, comorbidity and parity (for female cancers), these factors might either be confounders themselves, or they might act as a proxy for other confounders. For example, place of residency may reflect a different drug use and/or cancer risk pattern on the population level possibly capturing a combination of life-style related variables. County of residency had the largest impact when investigating drug use related to melanoma (related to sun exposure) and stomach cancer risk (related to H. pylori infection). Long-term use of other drugs (from other drug groups than the drug of interest) captures whether the effect observed for a specific drug group of interest might be due to the drug group itself or due to another drug group used in combination or supplemental. In this case, the *other drug use* might directly be associated to the drug under investigation, but may also impact cancer risk, thus acting as a confounder on the drug–cancer association. One example is non-steroid anti-inflammatory drugs (NSAID) which are often co-administered with proton pump inhibitors to reduce NSAID-induced gastrointestinal adverse events.

A comparison between our results and recent similar DWAS in Denmark and Sweden indicates concordance in 8 out of 10 (Denmark), and 25 out of 95 (Sweden) drug–cancer associations. These high proportions of agreement reveal a proof of concept, especially as these studies vary in study design and analytical methods. Another study from the Kaisers Permanente program [3] suggested that the following associations may not be due to chance: sulindac with gallbladder cancer and leukemia, hyoscyamine with non-Hodgkin lymphoma, nortriptyline with esophageal and hepatic cancer, oxazepam with lung cancer, both fluoxetine and paroxetine with testicular cancer, hydrochlorothiazide with renal and lip cancer, and nifedipine with lip cancer. Among the cancers we included in our study, we found detrimental associations between use of oxazepam (N05BA04) and lung cancer risk (HR= 1.90; unadjusted CI: 1.23-1.50) and a tendency for hydrochlorothiazide (C03AA03) and kidney cancer risk (HR = 1.52, unadjusted CI: 0.93-2.46), while the other drug–cancer combinations proposed by the Kaiser Permanente program had too few exposed cases in our study to allow replication.

We presented three examples of unexpected associations from our analyses. To our knowledge, they have not been reported previously in epidemiological studies. Some preclinical evidence exists for two of the examples. Histamine has been reported to be a growth factor for human cell lines from many cancers [30], including melanoma [31] and cancers from the gastrointestinal tract [32]. The picture is, however, complicated with divergent effects of histamine depending on the characteristics of the cancer cells [32], possibly explaining why solely melanoma showed a positive association with H2-receptor antagonists in our study. Proton pump inhibitors will decrease intracellular pH and was found to inhibit melanoma cell growth *in vitro* and in nude mice transplanted with human melanoma [33]. The only drug in the group of propulsives is metoclopramide, inhibitor of dopaminergic D2 receptors. Overexpression of D2 receptors was found to inhibit growth in non-small cell lung cancer cell lines [34], and D2-receptor agonists abrogated lung tumor progression in human xenograft murine models [35]. Moreover, pathological examination of human lung cancer tissue revealed a positive correlation between endothelial D2 receptor expression and tumor stage [35]. However, we did not find any preclinical evidence supporting our findings of a possible protective association between

anticholinesterases and a class of anti-dementia drugs, and lung, colon and particularly prostate cancer.

Discussion of Methods

Our use of p-values and thresholds may be criticised [36, 37]. However, in all types of statistical screening attempts, the challenge is to separate signals worth following up from irrelevant signals. The p-value can be used to quantify the strength of the association between a certain drug (or groups of drugs) and cancer risk [38]. Thus, we show the p-values together with the underlying effect estimates, the hazard ratio and the corresponding confidence intervals. Furthermore, we use a well-known (5%-adjusted and unadjusted), although arbitrary, threshold to illustrate the findings in the figures. As all effect estimates including confidence intervals are also shown, the readers can interpret the results in different ways based on own preferences. We acknowledge that our results reveal statistical associations only, not implying causal effects. However, a strong signal might be considered as hypothesis generating and worth further investigation at clinical, molecular or epidemiological levels.

Our study required a priori choices of thresholds to be made, which influences the interpretation of the data. For example, we removed all drug use within the past 12 month before cancer diagnosis (index date) to avoid signals due to reverse causation. There are different thresholds used in the literature as the length of this period is dependent on the disease or outcome of interest, and the detection time. A recent study suggested that 6 month lag was sufficient [39]. As we do not have any information on drug use before 2004, some of the non-users of drugs could in fact have been former-users, which potentially weakens the associations found in our study. We also defined chronic drug use as 8 or more prescriptions, which in most cases approximately corresponds to 2 years of drug use. The underlining assumption is that the subjects must be drug exposed over a longer period of time to affect cancer risk.

The scientific value of association studies has been questioned, given their lack of clinical, molecular and lifestyle data, as illustrated by the discussion between Patrignani/Dovizo and Pottegård et al, after the publication of the Danish screening results [40, 18]. However, the importance of using the full spectrum of evidence, including observational studies, has long been acknowledged [1].

A comparison of our results with other results from similar studies is not straightforward given differences in study design, statistical modelling methods, and criteria for statistical significance of a signal. We chose to compare our results with the Swedish and Danish DWAS [2, 4] by evaluating whether a signal found in our study also had been defined as a signal in the Swedish or Danish datasets respectively. This is a rather strict way to approach this, but there were still many replications. This does not necessarily imply that the corresponding associations are more likely to be causal. It rather means that even though there are many country- and dataset specific differences, several associations are robust, as suggested elsewhere [38].

The advantages of our study are the relatively large amount of data based on high quality registry data leading to the possibility of detecting associations of rare but possibly serious adverse events, such as cancer. Although our study has its limitations, as described above, it is superior to the general medicines' safety monitoring of marketed drugs based on the spontaneous reporting of suspected adverse reactions by health-care professionals, consumers and drug users [18], in particular for rare and long-term side effects.

In conclusion, this DWAS study verified some previously reported associations and also generated several new hypotheses for potential drug use – cancer risk associations. Some of these new findings are supported by previous preclinical results of hypothesized carcinogenic or chemopreventive effects. However, results of our study need to be validated in more tailored epidemiological studies. Moreover, preclinical studies could provide more insight in biological mechanisms.

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Tables

Table 1: Descriptive characteristics of cases and controls for each cancer type.

		N	Sex	Age	Region of residence				Comorbidity (PRI)			Parity		
			Male (%)	Median (IQR)	South-east n (%)	West n (%)	Mid n (%)	North n (%)	0 n (%)	1-2 n (%)	≥3 n (%)	0 n (%)	1-2 n (%)	≥3 n (%)
Stomach	**Cases**	3077	64%	69 (60, 78)	1501 (49%)	656 (21%)	495 (16%)	415 (13%)	2537 (82%)	345 (11%)	195 (6%)			
	Controls	30770			16855 (55%)	5901 (19%)	4411 (14%)	3049 (10%)	26494 (86%)	2835 (9%)	1441 (5%)			
Colon	**Cases**	16830	49%	71 (63, 78)	8989 (53%)	3512 (21%)	2508 (15%)	1758 (10%)	13992 (83%)	1888 (11%)	950 (6%)			
	Controls	168299			93051 (55%)	31650 (19%)	23732 (14%)	17208 (10%)	142824 (85%)	16969 (10%)	8506 (5%)			
Rectum	**Cases**	8841	60%	68 (60, 76)	4830 (55%)	1888 (21%)	1216 (14%)	888 (10%)	7682 (87%)	776 (9%)	383 (4%)			
	Controls	88410			48429 (55%)	16850 (19%)	12592 (14%)	8942 (10%)	76368 (86%)	8239 (9%)	3803 (4%)			
Pancreas	**Cases**	4716	52%	70 (62, 78)	2609 (55%)	851 (18)	709 (15%)	532 (11%)	3814 (81%)	573 (12%)	329 (7%)			
	Controls	47160			26054 (55%)	8811 (19%)	6695 (14%)	4812 (10%)	40245 (85%)	4635 (10%)	2280 (5%)			
Lung	**Cases**	19040	55%	69 (62, 76)	10782 (57%)	3588 (19%)	2525 (13%)	2061 (11%)	14387 (76%)	2888 (15%)	1765 (9%)			
	Controls	190400			105389 (55%)	35758 (19%)	26817 (14%)	19553 (10%)	162421 (85%)	18704 (10%)	9275 (5%)			
Bladder	**Cases**	9250	74%	70 (63, 78)	5094 (55%)	1702 (18)	1323 (14%)	1109 (12%)	7453 (81%)	1124 (12%)	673 (7%)			
	Controls	92499			50534 (55%)	17391 (19%)	13423 (15%)	9514 (10%)	77595 (84%)	9694 (10%)	5210 (6%)			
Kidney	**Cases**	5036	68%	65 (56, 73)	2770 (55%)	927 (18)	813 (16%)	519 (10%)	4133 (82%)	591 (12%)	312 (6%)			
	Controls	50360			27602 (55%)	9659 (19%)	6915 (14%)	5090 (10%)	43852 (87%)	4433 (9%)	2075 (4%)			
Melanoma	**Cases**	11964	50%	61 (50, 71)	7197 (60%)	2529 (21%)	1483 (12%)	708 (6%)	10623 (89%)	902 (8%)	439 (4%)			

	Controls	119638			65555 (55%)	23020 (19%)	16457 (14%)	11769 (10%)	105903 (89%)	9488 (8%)	4247 (4%)				
Breast	**Cases**	23342	0%	60 (51, 68)	13565 (58%)	4507 (19%)	3186 (14%)	2037 (9%)	21244 (91%)	1493 (6%)	605 (3%)	6438 (28%)	12164 (52%)	4740 (20%)	
	Controls	233415			130567 (56%)	44880 (19%)	31970 (14%)	22826 (10%)	212112 (91%)	15550 (7%)	5753 (2%)	64038 (27%)	116157 (50%)	53220 (23%)	
Endometrial	**Cases**	5315	0%	67 (58, 73)	3107 (58%)	1030 (19%)	675 (13%)	493 (9%)	4745 (89%)	419 (8)%	151 (3%)	2050 (39%)	2453 (46%)	812 (15%)	
	Controls	53149			29712 (56%)	10028 (19%)	7536 (14%)	5293 (10%)	47122 (89%)	4375 (8%)	1652 (3%)	17280 (33%)	25900 (49%)	9969 (19%)	
Ovarian	**Cases**	3377	0%	64 (55, 72)	1994 (59%)	644 (19%)	414 (12%)	310 (9%)	3034 (90%)	253 (7%)	90 (3%)	1222 (36%)	1581 (47%)	574 (17%)	
	Controls	33770			18927 (56%)	6376 (19%)	4689 (14%)	3348 (10%)	30366 (90%)	2474 (7%)	930 (3%)	10739 (32%)	16214 (48%)	6817 (20%)	
Prostate	**Cases**	35441	100%	68 (63, 74)	19371 (55%)	7386 (21%)	5260 (15%)	3392 (10%)	30315 (86%)	3488 (10%)	1638 (5%)				
	Controls	354409			194071 (55%)	67009 (19%)	50414 (14%)	36996 (10%)	298220 (84%)	37031 (10%)	19158 (5%)				
CNS	**Cases**	7644	46%	59 (46, 69)	4140 (54%)	1630 (21%)	1055 (14%)	784 (10%)	6929 (91%)	509 (7%)	206 (3%)				
	Controls	76440			41972 (55%)	14577 (19%)	10289 (13%)	7361 (10%)	69754 (91%)	4754 (6%)	1932 (3%)				
NH-lymphoma	**Cases**	6369	55%	66 (57, 74)	3548 (56%)	1196 (19%)	926 (15%)	678 (11%)	5430 (85%)	649 (10%)	290 (5%)				
	Controls	63689			34943 (55%)	12117 (19%)	8956 (14%)	6418 (10%)	55561 (87%)	5547 (9%)	2581 (4%)				
Leukemia	**Cases**	6399	57%	67 (58, 76)	3808 (60%)	1269 (20%)	789 (12%)	509 (8%)	5303 (83%)	701 (11%)	395 (6%)				
	Controls	63990			35033 (55%)	12290 (19%)	8935 (14%)	6346 (10%)	55345 (86%)	5789 (9%)	2856 (4%)				

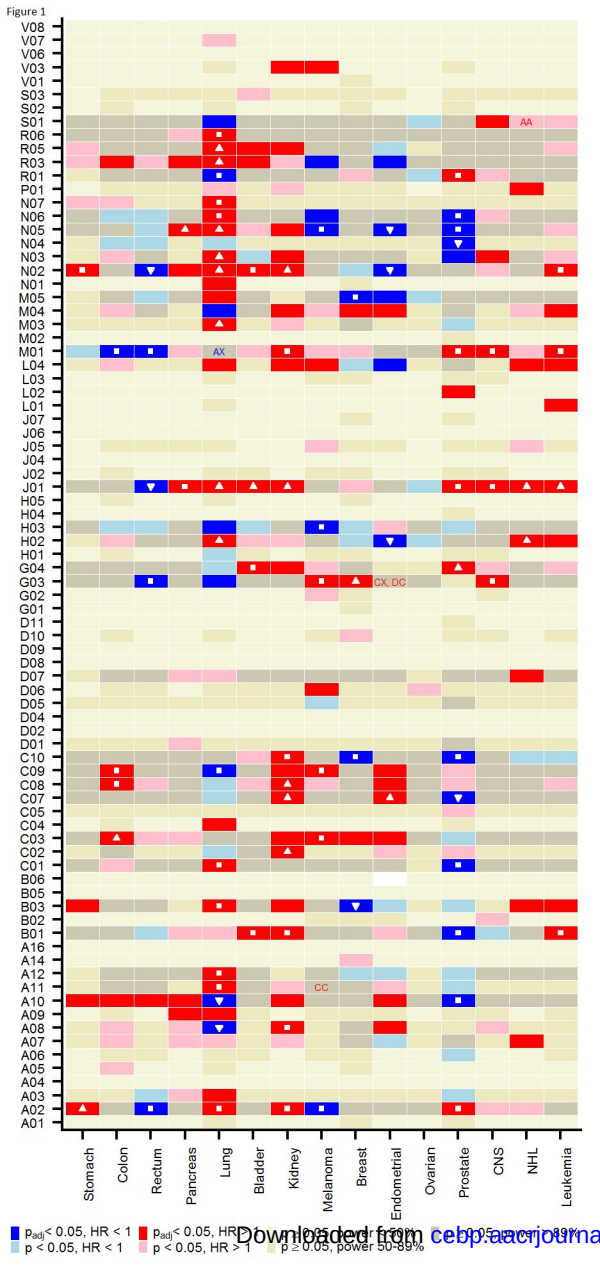
Table 2: Number of replicated findings with corresponding ATC4 codes in the Danish and Swedish studies.

	Denmark		Sweden	
Cancer Type	**Number of replicated findings**	**ATC4-codes**	**Number of replicated findings**	**ATC4-codes**
Prostate	1 out of 7	N06DA, N05AA (ATC3: N05AB/ N05AH), N03AF (ATC3: N03AA/N03AB)	4 out of 5	G04BE, G04CA, N05AA, N06DA
Colon	0 out of 1	M01AB (ATC3: M01AG)	0 out of 1	
Breast	1 out of 4	C10AA (ATC3: C10AD), G03FA, G03FB (ATC3:G03FA)	4 out of 4	G03FA, G03FB, C10AA, G03CX
Stomach	0 out of 1			
Bladder	2 out of 4	R03BB, J01CA		
Pancreas	0 out of 2			
Kidney	2 out of 9	A11CC,C08CA		
Melanoma	1 out of 4	G03AA		
CNS	0 out of 1			
NHL	0 out of 4	S01AA (ATC3: S01AX)		
Leukemia	0 out of 3	M01AE (ATC3: M01AB)		
Lung (Adenocarcinoma)	4 out of 13	J01FA, N05BA, N05CD, R03AC		
Lung (Squamous Cell Carcinoma)	9 out of 20	J01CE, J01FA, N02AX, N02BE, N05BA, N05CD, R03AC, R05CB, R05FA		
Lung (Other)	5 out of 22	J01CE, M03BA, N05BA, R03AC, R03BA		

Figure Legends

Figure 1: Heatmap of associations between prescribed drugs on ATC2 level and 15 cancer types. Cells marked with arrows indicate protective (arrow down) and detrimental (arrow up) dose-response relationships and cells marked with squares indicate associations mainly independent of dose. p_{adj} - multiple testing adjusted p-value, p – unadjusted p-value, HR – hazard ratio.

Figure 1



Cancer Epidemiology, Biomarkers & Prevention

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