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Screening pharmaceuticals for possible carcinogenic effects: initial positive results for drugs not previously screened

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Abstract

Objective—We screened commonly used prescription drugs for possible carcinogenic effects.

Methods—In a large health care program we identified 105 commonly used drugs, not previously screened. Recipients were followed for up to 12½ years for incident cancer. Nested case-control analyses of 55 cancer sites and all combined included up to ten matched controls per case, with lag of at least two years between drug dispensing and cancer. Positive associations entailed a relative risk (RR) of 1.50, with $p \leq 0.01$ and higher risk for three or more, than for one prescription. Evaluation included further analyses, searches of the literature, and clinical judgment.

Results—There were 101 associations of interest for 61 drugs. Sixty-six associations were judged to have involved substantial confounding. We found evidence that of the remaining 35, 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.

Conclusions—These preliminary findings suggest that further studies are indicated regarding sulindac, hyoscyamine, nortriptyline, oxazepam, fluoxetine, paroxetine, hydrochlorothiazide and nifedipine.

Many adults and children take medications regularly, yet relatively few drugs have undergone significant long-term post-marketing surveillance for adverse effects, including elevated cancer risk. In September 2006 the Institute of Medicine's Committee on the Assessment of the US Drug Safety System recommended substantial increases in safety studies of marketed drugs (1).

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We have been screening commonly used pharmaceuticals for possible carcinogenic effects for over 30 years, identifying drug recipients in an historical database consisting of prescriptions issued at the Kaiser Permanente San Francisco medical center to 143,574 persons during the years 1969 to 1973 (2–5). The International Agency for Research on Cancer (IARC) has issued several reports that reviewed world literature on drug carcinogenesis (6–12). The results of our previous screening studies were cited as providing data on 18 of the drugs evaluated and as the only source of data on humans for 9 of these.

With region-wide implementation achieved by August, 1994, the Kaiser Permanente Medical Care Program (KPMCP) in northern California employs a Pharmacy Information Management System (PIMS) that records all prescriptions dispensed to its subscribers, now numbering over 3 million. Drawing upon this newer resource and a region-wide cancer registry we have screened for possible carcinogenic effects 105 commonly used drugs that were not studied in the previous smaller database, mostly because they were introduced after 1973. We here present associations that are sufficiently strong and convincing, by both a few screening criteria and further evaluation, that more detailed study is suggested to help differentiate those that are causal from those that are due to unrecognized confounding or simply to chance, given the large number of possible associations generated.

Study population and methods

Setting

The KPMCP is an integrated prepaid health care delivery system that provides comprehensive inpatient and outpatient care, including pharmacy services, to over 3 million current members, who comprise about 30 percent of the residents of the areas served surrounding San Francisco Bay and in 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 (13).

Study cohort

Nested case-control analyses were conducted in a cohort of 6,608,681 subscribers to the KPMCP; drug coverage was identified and the subscribers were followed up starting as early as August 1994, when implementation of PIMS in all KPMCP pharmacies was completed. Entry to the study cohort began at the time of both joining the program and having drug coverage, if later than August, 1994. The ascertainment period for drug use was the same as that for incident cancer, ending on December 31, 2006. Follow-up ended earlier if a cancer of interest was diagnosed, or if the subject left KPMCP for any reason including death, whichever came first.

Pharmaceuticals

Ascertainment of pharmaceutical use was based on PIMS, which records all prescriptions dispensed to outpatients. Surveys of subscribers with drug coverage, i.e., at least partial payment for their prescriptions by KPMCP, indicate that they fill nearly 100% of their prescriptions at KPMCP pharmacies (14). The 105 drugs screened were drawn from 230 commonly used drugs with an arbitrarily selected cut-off number of at least 25,000 recipients in the PIMS database by the end of 2003.

Ascertainment of cancer

Occurrence of cancer was ascertained through KPMCP's Cancer Registry, which covers all subscribers and contributes to the local Surveillance, Epidemiology, and End Results (SEER) program (15). Persons first diagnosed with cancer before cohort entry were

excluded from the analysis of that cancer site. The index date was the date of first diagnosis of the cancer.

In 2000, the middle year of the total 1994–2006 study interval, the annual age-sex-adjusted (to the US census, 2000) incidence per 100,000 of cancer for all sites and both sexes in the KPMCP was 447.2, as compared to 456.4 in California (California Cancer Registry), and 482.8 in SEER (National) data (15).

Selection of controls

For each cancer case, ten risk-set matched controls (16) free of the cancer of interest were randomly selected from all of the program's subscribers of the same sex, same year of birth and same year of starting drug coverage. The index date for controls was the date in the same year as their matched case's diagnosis that provided equal follow-back time; all controls were still members on that date. Controls were not excluded if they developed the same cancer later and they could be included more than once for different cancer cases but not for the same case. Fewer than ten matched controls could be found for some very elderly cancer patients. For example, three women, age 99, 100, and 101 years at breast cancer diagnosis, could be matched with only 2, 8, and 3 controls, respectively.

Analytic methods

Conditional logistic regression was used to calculate odds ratios as estimates of the relative risk of cancer associated with each medication studied using the SAS system (17). The three comparisons made were: any use vs. no use before index date, any use vs. no use at least two years before index date to rule out pre-diagnostic prescribing for symptoms possibly related to cancer ("2-year lag"), and one, two, and at least three prescriptions dispensed vs. no use to ascertain possibly greater risk for longer use. All subjects were considered non-users of a drug until our records showed that it was dispensed to them.

Analyses were performed for 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) (18) except for non-melanoma skin cancers. We combined each subsite in the mouth and pharynx into one site for analysis except that cancers of the lip, salivary glands, and nasopharynx were each analyzed separately.

Because the screening of 105 drugs with 55 cancer sites plus all cancers combined, is so apt to produce nominally statistically significant associations just by chance, we here report only those that met the following criteria: odds ratio at least 1.50 for three or more dispensings in the 2-year lag analysis, $p < 0.01$ for difference from odds ratio 1.00, and odds ratio for three or more dispensings greater than odds ratio for one dispensing as an indication of dose-response. Occasional noteworthy findings that did not meet these criteria will be mentioned. P values were rounded to three decimal places for Tables 2 and 3; thus $p < 0.001$ indicates that p was less than 0.0005 because $p = 0.0005$ to 0.0009 were rounded up and shown as $p = 0.001$.

A peer reviewer questioned whether, even for chronically used drugs, three or more prescriptions represented long term use. For all drug/cancer associations not readily attributable to confounding we examined the distribution of total days' supply dispensed before the cancer diagnosis to the exposed cases and here report the median duration, rounded to the nearest month (Table 3). For drugs with median duration less than 6 months, we repeated the analysis requiring a days' supply of over two years, looking for associations with odds ratio of 1.50 or greater and p less than 0.01.

Main efforts to evaluate confounding

Female hormones: Drug usage statistics and subscriber surveys indicated that use of some drugs was associated with use of estrogens, progestins and other female hormone preparations for birth control, menopausal hormone therapy and other indications. Therefore, use of hormones, which may increase the risk of breast or uterine cancer and of tamoxifen or raloxifene, which may reduce the risk of breast cancer, was controlled in analytic models by adding four indicator variables: oral contraceptives, menopausal hormone therapy, raloxifene/tamoxifen, and other hormones. Use was treated as time-varying and was defined as receiving at least two prescriptions for the particular category of hormones before the index date. Estrogens, progestins and oral contraceptives were not screened because they have been studied extensively with good control for confounding variables (12)

HIV infection: When increased risk was noted for the HIV-associated sites, anal cancer, non-Hodgkin lymphoma, or other skin which includes Kaposi's sarcoma, we repeated the analysis excluding subjects in the HIV registry maintained by KPMCP. Finding virtually no change in the associations with other skin cancers, we determined that they included no cases of Kaposi's sarcoma; the predominant histological types are listed in the tables. When oropharyngeal cancer was found associated with drugs used to treat or prevent oral thrush in HIV-positive patients, these analyses were also repeated in HIV-free patients. Since anal intercourse is a major risk factor for both anal cancer and HIV infection, reduction in an association of a drug with anal cancer in HIV-free subjects suggests that a life-style that frequently includes this form of sexual behavior may be an important confounder (19).

Other possible confounders: Lacking data for all subjects on important possible confounders such as cigarette smoking, race/ethnicity and body mass index, we evaluated each association for likely confounding based on clinical judgment and, in some cases, review of computer-stored medical records. The main clinical conditions we were concerned about were: 1) hypertension, a risk factor for renal cancer (20), 2) hyperthyroidism, a risk factor for thyroid cancer (21) and possibly treated with antihypertensive drugs, 3) diabetes mellitus, a risk factor for cancer of the corpus uteri, possibly due to their mutual association with obesity (22), 4) alcoholism, a risk factor for esophageal and liver cancer (23,24) and 5) cirrhosis of the liver, which also predisposes to liver cancer. Secondary analyses were performed for these cancers after excluding cases and controls with these risk factors or after controlling for them. Considering that cigarette smoking is so much more likely than any drug to have caused lung cancer, we chose to use increased lung cancer risk as a proxy for confounding by cigarette smoking in evaluating associations of drugs with other smoking-related sites such as esophagus, kidney and urinary bladder. In the tables, cigarette smoking will be referred to simply as smoking.

For associations that were not likely due to confounding we searched the literature for possible clinical or biological connections between the drug and risk of cancer.

This study was approved by the Kaiser Permanente Institutional Review Board.

Results

Of the 105 drugs screened, 61 met our criteria for possible increased cancer risk and 44 did not. These two groups are listed in Table 1 subdivided by drug category.

Drug-cancer associations that met the screening criteria but where confounding seemed a likely explanation are shown in Table 2. Drug-cancer associations not readily attributed to confounding are listed Table 3. Brief comments are presented in Tables 2 and 3, with further

evaluation of selected associations in the Discussion. For drugs with median days supply before diagnosis in the exposed cases of less than 6 months, reanalysis requiring over two years use yielded no associations with odds ratio at least 1.50 and p less than 0.01.

Discussion

We have screened 105 commonly used drugs for possible carcinogenic effects with follow-up of up to 12 ½ years. Sixty-one drugs had 101 positive associations that met our criteria for consideration. Of these 66 were judged to be likely due to or substantially accentuated by confounding. The factors that we judged to be the main sources of confounding were cigarette smoking, hypertension, and life-style. Cigarette smoking led to acute and chronic respiratory conditions treated by drugs that were associated with smoking-related cancers. Hypertension contributed to the need for cardiovascular drugs which were associated with renal cancer, either due to hypertension itself or to associated diuretic treatment (20). The frequent associations with anal cancer were likely due to a life-style that involved anal intercourse. Other less frequent likely confounders are noted in Table 2.

The 35 associations that we judged less attributable substantially to confounding could all be due merely to chance, given the large number of possible associations that were examined. We attempted to reduce the number of chance associations by requiring a relative risk of at least 1.50 in persons who received three or more prescriptions and a p value of 0.01 or less. Also to rule out confounding by indication due to treatment of symptoms of cancer before diagnosis, we employed a two-year lag whereby only drugs received at least two years before the cancer was diagnosed were counted. Further, we included a dose-response criterion, admittedly not precise, requiring the relative risk with three or more prescriptions to be greater than that with just one prescription. These criteria are arbitrary, based on an attempted balance between finding too many chance associations and missing real causal connections that are weak. The relatively short duration of use of the antibiotics with three or more dispensings was expected. In only four of the other drug/cancer associations not readily attributable to confounding was the median duration of use by the cases before diagnosis less than six months, and many such median durations were well over one year. We found it reassuring that the established association between a thiazide drug and renal cancer (20) was confirmed by this screening procedure.

Strengths of this study include the large numbers of drug recipients with complete cancer follow-up while they are members, often long-term, in a comprehensive health care system. We have objective data on the filling of prescriptions not subject to failure of recall or recall bias. Limitations include our lack of readily accessible information about use of the drugs of concern before August 1994 and follow-up that may not be long enough to detect effects that are early in the carcinogenic process. We were not able to control for important confounders directly. Accordingly, we emphasize the fact that these findings are the result of screening and not of definitive epidemiologic studies that include more detailed information about cancer risk factors.

Comments on specific drug-cancer associations

To follow, listed in alphabetical order of drug, are comments about selected drug-cancer associations that need more consideration than could be provided in Tables 2 and 3. Of the associations not readily attributable to confounding (Table 3) there are a few for which evidence suggesting possible causality was found, and further study is recommended. The other associations should just be considered hypotheses, most or all of which may be due to chance. If they are found in other settings, it is helpful to know that they also appeared in our database. Also to follow are a few associations where possible confounding needs additional comment. Finally, recommendations for further study are summarized.

Amoxicillin/other skin cancer, Hodgkin lymphoma, monocytic leukemia—No clinical or biological link was found between this antibiotic and the three cancers. In one study the offspring, up to age 18 months, of women treated with amoxicillin during pregnancy had a reduced risk of leukemia (25).

Atorvastatin/testicular and renal cancer—In our previous study of recipients of all statins, of which atorvastatin accounted for only 1.5%, we found an increased risk of renal cancer with two-year lag in men only, but in corrected sensitivity analysis accounting for possible confounding by cigarette smoking, risk was not increased (25). In one laboratory study atorvastatin exhibited anti-proliferative and pro-apoptotic effects (26), which suggest possible preventive effects. In our study of statins risk of testicular cancer was not found (25). The drug also showed no harmful effects on the testes of beagle dogs and rats (26,27). Thus, there is little reason to pursue these associations.

Desipramine/non-Hodgkin lymphoma—No link of this drug with lymphoma was found. Initial concern about breast cancer has been allayed (28,29).

Diltiazem/other digestive organ cancer—The association of calcium channel blockers such as diltiazem has been subjected to considerable epidemiological study including control for confounders, mostly with negative results (30). A recent meta-analysis of randomized controlled trials found no increased risk for calcium channel blockers (31). Our screening does not contribute materially to this body of knowledge.

Fluoxetine/testicular cancer—Antidepressants including selective serotonin reuptake inhibitors (SSRIs) such as fluoxetine have been evaluated in laboratory experiments and epidemiologic studies with mixed results, including some findings of possible prevention (32). Attention in humans has been focused primarily on breast cancer and no relationship has been established (33,34). No human data concerning testicular cancer were found. The manufacturer (http://ehs.lilly.com/msds/msds_fluoxetine_hydrochloride_capsules_and_tablets.pdf) reported that in a juvenile toxicology study in rats, where the exposure period corresponds to human childhood and adolescence, administration of 30 mg/kg of fluoxetine hydrochloride (how many times not stated) resulted in skeletal muscle necrosis and irreversible degeneration and necrosis of the testis. The dosage to the rats was very large compared to the maximum recommended human dose of 80 mg. per day and the relevance of this experiment to testicular cancer in humans is not known. Further comment is below under paroxetine.

Hydrochlorothiazide/renal, lip and other skin cancer—The association between this antihypertensive diuretic and renal cancer has been found repeatedly but there is evidence that hypertension is the risk factor rather than the drugs used to treat it (20). It is reassuring regarding our methodology and data that this known association appeared in this screening. Hydrochlorothiazide was not distinguished from other thiazides in our previous screenings in a smaller cohort but elevated risk of renal cancer was detected for thiazides as a group (5). Data concerning 12,799 thiazide users in that cohort with follow-up through 2002, up to 33 years, showed a standardized morbidity ratio of 1.36 (95% confidence interval 1.03–1.77) based on 55 cases of renal cancer observed and 40.34 expected (Friedman and Habel, unpublished).

Hydrochlorothiazide is a photosensitizing drug and has been associated with increased risk of skin cancer (35). It is very possible that photosensitization could explain the link we found with cancers of the skin and lip (36).

Hyoscyamine/non-Hodgkin lymphoma—Five of the patients treated with this anti-spasmodic drug reported in Table 2 had ulcerative colitis and one had Crohn's disease in their computer-stored records. We considered the possibility that these auto-immune conditions might predispose to non-Hodgkin lymphoma but the evidence for their being substantially related to lymphoma risk is weak (37), more likely for Crohn's disease. An additional seven patients had nonspecific diagnoses of non-infectious gastroenteritis or colitis that might also include the auto-immune diagnoses. We did not find any diagnoses of celiac disease in these patients, a condition more clearly related to risk of non-Hodgkin lymphoma (37). Thus, this association is not easily explained away.

Lactulose/anal cancer—Lactulose is a laxative that is broken down by colorectal bacteria into substances with high osmotic pressure, thus bringing water into the bowel. It may be taken orally undiluted and rectally when diluted with water or saline. In the latter form it has been recommended for homosexual men to cleanse the rectum in preparation for anal intercourse. (http://gayspecies.blogspot.com/2007_07_01_archive.html). We are unable to determine how lactulose had been used by the anal cancer patients, but lifestyle confounding is a strong possibility.

Levothyroxine/myeloid leukemia—Exposure to ionizing radiation is known to cause both myeloid leukemia and thyroid cancer (21,38). Persons whose thyroid gland was removed because of cancer would likely receive levothyroxine for hormone replacement therapy. We were able to identify prior thyroid cancer in only one of the 115 patients presented in Table 2 but our access to long-term prior records of cancer is limited. Exposure to ionizing radiation could be a possible confounder. Also the fact the levothyroxine is a naturally occurring hormone produced by the thyroid gland would seem to make it an unlikely carcinogen.

Metoprolol/mouth-pharynx cancer—In randomized controlled trials and other studies, beta-adrenergic blockers such as this drug have not been found to increase cancer risk (32). One study found a reduced risk of prostate cancer (39). Laboratory data concerning metoprolol showed no evidence of chromosomal damage (40).

Nifedipine/lip and larynx cancer—See comments regarding diltiazim, also a calcium channel blocker. There is evidence of photosensitivity associated with use of nifedipine, which could explain the increased risk of cancer of the lip, but not of the larynx. (41)

Nortriptyline/esophageal and liver cancer—Tricyclic antidepressants have been suspected to be carcinogenic but, as with fluoxetine, the experimental and epidemiologic evidence has been conflicting, including some findings of possible prevention. (32). An association with ovarian cancer has been reported (42) and our early screenings found a transient association of the related drug, amitriptyline, to liver cancer (4,43) possibly supporting our current finding. Although these two cancer sites suggest alcoholism as a confounder, this did not appear to be the case in our data. Nortriptyline and related tricyclic drugs would seem to merit further investigation.

Oxazepam/lung cancer—Confounding by smoking is possible but the drug caused benign and malignant liver tumors and thyroid adenomas in mice with evidence that it was a promoter of liver cancer development in mice and rats (9).

Paroxetine/testicular cancer—Experimental evidence has mainly pertained to the related SSRI, fluoxetine. (32). Similarly, attention in humans has been focused primarily on breast cancer. The evidence has been mixed (30,33,34,44). No human data concerning

testicular cancer were found. The manufacturer reported toxicity to testicular tissue in rats receiving 4 times the maximum recommended human dose for depression for two to 52 weeks (45). The relevance of this evidence to testicular cancer in humans is not known. Given the similar findings for the related drug, fluoxetine, further study would seem to be indicated.

Piroxicam/melanoma—Most evidence concerning nonsteroidal anti-inflammatory drugs (NSAIDs) such as piroxicam suggests that they have cancer-preventive properties, particularly regarding colorectal cancer (46,47). However, piroxicam did not show either cytostatic or cytotoxic effects on certain human skin melanoma cells, which were found for some other NSAIDs (48). Although no other studies of piroxicam and melanoma were found, large doses of this drug were found to inhibit proliferation and induce apoptosis in some canine cell lines (49), again supporting inhibition of cancer development. The positive association that we noted may well be due to chance.

Risperidone/Hodgkin lymphoma—We found no experimental or human evidence that would suggest carcinogenesis by this antipsychotic drug. Although some diseases are associated with increased risk of Hodgkin lymphoma, psychosis has not been reported to be one of them (50).

Rofecoxib/cancer of peritoneum-omentum-mesentery—Rofecoxib is a NSAID and like piroxicam, believed to have cancer-preventive properties. This likely chance finding has ceased to be of concern since this drug is no longer marketed.

Sulindac/gallbladder cancer and other leukemia—As noted (Table 3) the excretion of sulindac in bile (51,52) and the presence of its metabolites in gallstones (53) indicate a likely biological connection since gallstones predispose to gallbladder cancer (54). If this association is confirmed, questions needing to be answered are whether sulindac increases risk of gallstones, whether presence of sulindac metabolites in gallstones increases their carcinogenicity, or whether sulindac in bile increases risk of both stones and cancer without stones as a necessary intermediate step to cancer.

Of the five cases of Other Leukemia, the specific diagnoses in the Cancer Registry were: three “Leukemia, not otherwise specified”, one “Acute Leukemia, not otherwise specified” and one “Aggressive NK- (natural killer) cell leukemia”. There have been a few case reports of adverse effects on the bone marrow attributed to sulindac. These included aplastic anemia, erythroblastopenia, and progression of leucopenia to aplastic anemia and acute myeloid leukemia (55–57). The relevance of these to our observation is unknown, but they may add to the desirability of further studies of sulindac and cancer risk.

Verapamil/thyroid cancer—See comments regarding diltiazim. The one study of elderly patients in Rotterdam showing verapamil differing from other calcium channel blockers in being associated with increased risk of cancer may stimulate more interest in this drug but our screening data add little to the extensive literature on this class of drugs (58,59).

Suggestions for further study—Our preliminary findings plus the additional evidence cited above lead us to recommend further study of the following drugs for possible carcinogenic effects. Sulindac’s association with gallbladder cancer is especially provocative, given the enterohepatic circulation of this drug and its presence in gallstones. Its association with leukemia is also of interest. If there was more evidence that the autoimmune gastroenterological conditions often treated with hyoscyamine were more frequent in the patients who received it and that these conditions were associated with increased risk of non-Hodgkin lymphoma, our finding would be of less concern. Until then, we believe

further study of hyoscyamine is indicated. Nortriptyline is of interest in relation to cancer of the liver and perhaps to a lesser degree to other cancers. Although oxazepam's association with lung cancer raises suspicion of confounding by smoking, animal experiments provide further evidence of possible carcinogenicity and the advisability of further study. The fact that the two related drugs, fluoxetine and paroxetine were both associated with testicular cancer, with relatively little overlap in the patients receiving them, and testicular damage was produced by high doses in experimental animals, suggests the advisability of further study. Finally, our confirmation of increased risk of renal cancer with hydrochlorothiazide has already been amply confirmed but the question of drug vs. hypertension as the cause is still of interest. Given this drug's photosensitizing effects and association with skin cancer, its association with lip cancer deserves further attention, as does a possible link between the photosensitizing drug, nifedipine, and lip cancer.

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Table 1

List of drugs studied with number of recipients and indication as to whether any associations of interest were found.

	Number of recipients	Associations of interest *	
Drug		Yes	No
ANTI-INFECTIVE AGENTS			
Cephalosporins			
Cefaclor	92,501	x	
Cefixime	35,936		x
Cefpodoxime	122,048	x	
Cefuroxime	54,600	x	
Erythromycins and Related Macrolides			
Azithromycin	577,576	x	
Clarithromycin	57,161	x	
Penicillins			
Amoxicillin	2,473,795	x	
Sulfonamides and Related anti-infectives			
Trimethoprim (most with sulfamethoxazole)	1,360,973	x	
Tetracyclines			
Minocycline	79,679		x
Antifungals			
Fluconazole	230,255	x	
Ketoconazole	40,696	x	
Terbinafine	46,794		x
Quinolones			
Ciprofloxacin	721,010	x	
Levofloxacin	40,508		x
Moxifloxacin	91,190		x
Antiparasitic Agents			
Anthelmintics			
Mebendazole	28,995		x
Antimalarials			
Mefloquine	119,163		x
Antiviral Agents			
Acyclovir	310,973		x
Famciclovir	54,169		x
AGENTS FOR BLOOD FORMATION & COAGULATION			
Anticoagulants/Antiplatelet Agents			
Clopidogrel	62,146		x
Enoxaparin	52,949		x
CARDIOVASCULAR & RENAL AGENTS			
Antianginals			

	Number of recipients	Associations of interest *	
Drug		Yes	No
Calcium Channel Blockers			
Diltiazem	86,983	x	
Verapamil	121,403		
Nifedipine	190,554	x	
Antihypertensives			
Beta-Adrenergic Blockers			
Atenolol	497,815	x	
Metoprolol	140,853	x	
Antiadrenergics			
Clonidine	84,118	x	
Prazosin	64,648	x	
Terazosin	113,119		x
Angiotensin Converting Enzyme Inhibitors			
Lisinopril	630,311	x	
Angiotensin II Receptor Antagonist			
Losartan	105,665	x	
Antilipemics			
Atorvastatin	45,265	x	
Gemfibrozil	58,184	x	
Lovastatin	541,743		x
Simvastatin	179,291		x
Diuretics			
Thiazide & Related Diuretics			
Hydrochlorothiazide including combinations	267,125	x	
CENTRAL NERVOUS SYSTEM AGENTS			
Analgesics			
Non-Narcotic Analgesics			
Ibuprofen	1,955,551		x
Nabumetone	397,499		x
Narcotic Analgesics			
Fentanyl	38,465	x	
Anticonvulsants			
Anticonvulsants, Benzodiazepine			
Clonazepam	88,351		x
Anticonvulsants, Miscellaneous			
Carbamazepine	39,021	x	
Gabapentin	109,879	x	
Antimigraine Agents			
Rizatriptan	81,241		x
Sumatriptan	45,873		x
Psychotherapeutic Agents			

	Number of recipients	Associations of interest *	
Drug		Yes	No
Antidepressants			
Amitriptyline	238,044		x
Bupropion	211,547	x	
Citalopram	87,247		x
Doxepin	51,345		x
Fluoxetine	418,005	x	
Nortriptyline	172,844	x	
Paroxetine	253,165	x	
Sertraline	92,001	x	
Trazodone	269,380	x	
Venlafaxine	67,842	x	
Desipramine	25,271	x	
Antianxiety Agents			
Alprazolam	127,660		x
Buspirone	48,227		x
Lorazepam	276,492	x	
Oxazepam	85,870	x	
Antipsychotic Agents			
Olanzapine	35,996		x
Risperidone	41,289	x	
Sedative/Hypnotics			
Temazepam	253,078		x
Zolpidem	61,930		x
Skeletal Muscle Relaxants, Centrally-Acting Agents			
Cyclobenzaprine	674,629	x	
ANTIRHEUMATICS AND ANTIGOUT AGENTS			
Celecoxib	46,411		x
Etodolac	110,132		x
Meclofenamate	32,860		x
Naproxen	715,929		x
Piroxicam	65,080	x	
Rofecoxib	36,692	x	
Sulindac	112,292	x	
GASTROINTESTINAL AGENTS			
Antispasmodics, Single Entities			
Hyoscyamine	49,282	x	
Emetics and Antiemetics			
Antiemetics/Antivertigo Agents			
Ondansetron	30,878		x
Metoclopramide	134,022	x	
Laxatives and Cathartics			

Drug	Number of recipients	Associations of interest *	
		Yes	No
Docusate	338,250		x
Lactulose	67,946	x	
Antiulcer Products			
Cimetidine	393,883		x
Famotidine	331,248		x
Omeprazole	372,547		x
Pantoprazole	263,857	x	
Ranitidine	439,499	x	
HORMONES & SYNTHETIC SUBSTITUTES			
Adrenocorticosteroids			
Methylprednisolone	95,260		x
Oral Hypoglycemics			
Glipizide	59,025	x	
Glyburide	93,238	x	
Antihyperglycemic Agents			
Metformin	183,964	x	
Pioglitazone	46,515	x	
Thyroid Hormones			
Levothyroxine	255,788	x	
Hormones, Misc. Products			
Clomiphene	31,977		x
NUTRITIONAL & HOMEOSTATIC PRODUCTS			
Vitamins and derivatives			
Isotretinoin	29,867	x	
AGENTS FOR RESPIRATORY & ALLERGIC DISORDERS			
Sympathomimetics			
Albuterol	1,411,133	x	
Metaproterenol	27,343	x	
Salmeterol	67,381	x	
Xanthine Derivatives			
Theophyllin	35,926	x	
Antiasthmatics and Related Agents, Steroid			
Beclomethasone	520,600	x	
Fluticasone	203,798	x	
Misc. Respiratory Agents			
Ipratropium	183,032	x	
Antihistamine			
Terfenadine	45,591	x	
Fexofenadine	672,443		x
Loratadine	233,973		x
Expectorants			

Drug	Number of recipients	Associations of interest *	
		Yes	No
Guaifenesin	1,356,597		x
Antitussives			
Benzonatate	198,170		x
MISCELLANEOUS AGENTS			
Antispasmodics, Urinary			
Oxybutynin	110,350	x	
Bone Resorption Inhibitors			
Alendronate	93,809		x
Smoking Deterrents			
Nicotine	66,048	x	
Agents for Male Erectile Dysfunction			
Sildenafil	165,333		x

* Associations of interest: $RR \geq 1.50$, $p < 0.01$, RR for 3+ dispensings $>$ RR for 1 dispensing in 2 year lag analysis.

Table 2

Drug-cancer associations meeting positive criteria for which confounding could be the explanation. Results shown are for 3+ dispensings, 2 year lag.

Drug	Site	No. of exposed cases	RR (95% CI)	P	Comment
Anti-infectives					
Azithromycin	Anus, anal canal, anorectum	7	3.12 (1.32–7.35)	0.009	RR somewhat lower in HIV-free cohort: 2.36 (0.89–6.29). May involve life-style confounder(s).
	Lung and bronchus	87	1.77 (1.40–2.22)	<0.001	Use for lower respiratory tract infections suggests confounding by smoking.
	Urinary bladder	32	1.73 (1.18–2.53)	0.005	Confounding by smoking is possible as for lung.
Cefpodoxime	Lung, bronchus	73	2.93 (2.26–3.80)	<0.001	Use for lower respiratory tract infections suggests confounding by smoking.
Ciprofloxacin	Anus, anal canal, anorectum	20	2.62 (1.56–4.40)	<0.001	RR somewhat lower in HIV-free cohort: 1.53 (0.83–2.82). May involve life-style confounder(s).
	Prostate	586	1.51 (1.38–1.65)	<0.001	Frequent use for urinary tract infections and by urologists, such as for infection prophylaxis with prostate biopsy, suggests diagnostic bias and confounding by indication.
	Penis	3	10.24 (2.06–50.89)	0.005	
	Kidney/renal pelvis	98	1.65 (1.30–2.06)	<0.001	
	Ureter	11	3.16 (1.51–6.62)	0.002	
Clarithromycin	Anus, anal canal, anorectum	10	50.34 (11.03–229.76)	<0.001	RR markedly reduced to 10.00 (1.41–70.99) based on 2 cases in HIV-free cohort suggesting life-style confounder(s).
	Lung, bronchus	23	1.95 (1.25–3.05)	0.004	Use for lower respiratory tract infections suggests confounding by smoking.
	Non-Hodgkin lymphoma	10	2.52 (1.26–5.06)	0.009	RR markedly reduced to 1.59 (0.67–3.76) based on 6 cases in HIV-free cohort, suggesting confounding by HIV infection.
Fluconazole	Anus, anal canal, anorectum	14	9.41 (4.46–19.87)	<0.001	RR markedly reduced to 1.20 (0.27–5.35) based on 2 cases in HIV-free cohort, suggesting life-style confounder(s).
	Vulva	5	5.98 (1.92–18.65)	0.002	Use for vaginal candidiasis suggests diagnostic bias and confounding by indication.
Trimethoprim (most with sulfamethoxazole)	Salivary glands	30	1.81 (1.17–2.78)	0.007	Lung also elevated, RR 1.48 (1.38–1.59), and lung met other screening criteria, suggesting at least partial confounding by smoking.
	Anus, anal canal, anorectum	42	2.20 (1.53–3.16)	<0.001	RR markedly reduced to 1.13 (0.71–1.80) in HIV-free cohort suggesting confounding by life-style factor(s).
Cardiovascular Agents					
Clonidine	Kidney, renal pelvis	71	1.82 (1.41–2.35)	<0.001	Used to treat hypertension, a risk factor for renal cancer.
Diltiazem	Kidney, renal pelvis	108	1.65 (1.34–2.03)	<0.001	Used to treat hypertension, a risk factor for renal cancer.
Gemfibrozil	Kidney, renal pelvis	56	1.54 (1.16–2.05)	0.003	51 of the cases had prior hypertension. RR on repeat analysis controlling for presence of hypertension was 1.26 (0.95–1.68).
Hydrochlorothiazide	Kidney, renal pelvis	537	1.71 (1.54–1.91)	<0.001	Used to treat hypertension, a risk factor for renal cancer, but this drug possibly also independently related. (See Discussion)

Drug	Site	No. of exposed cases	RR (95% CI)	p	Comment
Lisinopril	Kidney, renal pelvis	572	1.80 (1.62–2.00)	<0.001	Used to treat hypertension, a risk factor for renal cancer.
Losartan	Corpus uteri	69	1.55 (1.19–2.01)	0.001	Used to treat diabetic nephropathy and diabetes is a known risk indicator of endometrial cancer, possibly due to underlying obesity. Control for hormone use had almost no effect on RR.
Verapamil	Kidney, renal pelvis	199	1.73 (1.48–2.03)	<0.001	Used to treat hypertension, a risk factor for renal cancer.
Central Nervous System Agents					
Bupropion	Mouth, pharynx	31	1.88 (1.28–2.78)	0.001	Used in smoking cessation therapy. Lung cancer was associated but did not meet the dose-response criterion that 3+ dispensed RR 2.90 (2.54–3.30) > 1 dispensed RR 3.90 (3.45–4.41) criterion. Likely confounding by smoking.
	Larynx	13	2.61 (1.41–4.82)	0.002	
	Urinary bladder	79	2.15 (1.68–2.74)	<0.001	
	Ill-defined, unspecified	39	1.60 (1.14–2.26)	0.007	
Carbamazepine	Brain	11	2.84 (1.45–5.56)	0.002	Anticonvulsant likely used to treat seizures due to brain tumor over two years before diagnosis, as previously noted for diphenhydantoin (2).
Fentanyl	Esophagus	3	10.00 (2.02–49.55)	0.005	Confounding by smoking is possible for esophagus, likely for lung. Exclusion of subjects with an alcoholism diagnosis reduced the esophageal cancer RR to 6.67 (1.11–39.90) suggesting additional confounding by alcohol use.
Gabapentin	Lung, bronchus	20	2.25 (1.39–3.65)	0.001	
	Kidney, renal pelvis	34	1.71 (1.18–2.47)	0.004	Lung cancer somewhat elevated, RR 1.34 (1.13–1.60) suggesting partial confounding by smoking. 29 of the cases had prior hypertension. RR was still elevated on repeat analysis controlling for presence of hypertension: 1.56 (1.08–2.26).
Lorazepam	Kidney, renal pelvis	73	1.63 (1.26–2.09)	<0.001	Lung cancer somewhat elevated, RR 1.31 (1.18–1.47) suggesting partial confounding by smoking. 61 of the cases had prior hypertension. RR on repeat analysis controlling for presence of hypertension was still elevated: 1.49 (1.15–1.92).
Sertraline	Anus, anal canal, anorectum	12	4.08 (2.09–7.98)	<0.001	Three fewer cases and RR somewhat lower 3.37 (1.58–7.16) in HIV-free cohort suggesting possible confounding by life-style
Trazodone	Larynx	19	2.06 (1.25–3.39)	0.005	Lung also elevated (RR 1.40 (1.25–1.57) suggesting at least partial confounding by smoking.
Gastrointestinal Agents					
Lactulose	Liver, intrahepatic bile ducts	21	4.97 (2.94–8.39)	<0.001	Used to treat hepatic encephalopathy with liver cirrhosis, which predisposes to liver cancer
	Anus, anal canal, anorectum	4	6.69 (1.76–25.35)	0.005	Findings virtually unchanged in HIV-free subjects. However life-style confounding is likely; see Discussion.
Pantoprazole	Esophagus	34	1.68 (1.15–2.46)	0.008	Used to treat GERD and esophagitis, precursors of esophageal cancer, and gastric symptoms and H. pylori infection, precursors of stomach cancer. Confounding by indication.
	Stomach	66	1.72 (1.30–2.26)	<0.001	
Ranitidine	Esophagus	64	1.52 (1.15–2.00)	0.003	Used to treat GERD and esophagitis, precursors of esophageal cancer. Confounding by indication.
Hormones and Related Agents					
Glipizide	Corpus uteri	35	2.32 (1.60–3.35)	<0.001	Used to treat diabetes mellitus, a known risk indicator of endometrial cancer, possibly due to underlying obesity. Control for hormone use had almost no effect on RR.

Drug	Site	No. of exposed cases	RR (95% CI)	p	Comment
Glyburide	Corpus uteri	97	1.57 (1.27–1.96)	<0.001	Used to treat diabetes mellitus, a known risk indicator of endometrial cancer, possibly due to underlying obesity. Control for hormone use had almost no effect on RR.
Levothyroxine	Myeloid leukemia	115	1.61 (1.30–1.99)	<0.001	See Discussion concerning possible confounding by radiation exposure.
Metformin	Pancreas	116	1.58 (1.29–1.94)	<0.001	Used to treat diabetes mellitus, a known risk factor for pancreatic cancer (60)
Pioglitazone	Corpus uteri	23	2.11 (1.34–3.31)	0.001	Used to treat diabetes mellitus, a known risk indicator of endometrial cancer, possibly due to underlying obesity. Control for hormone use had almost no effect on RR.
Vitamin Derivatives					
Isotretinoin	Mouth, pharynx	4	9.08 (2.25–36.73)	0.002	Lung also elevated (RR 1.83 (0.86–3.89) suggesting at least partial confounding by smoking. Also used to treat leukoplakia in persons at high risk for these cancers, so confounding by indication likely.
Respiratory/Allergy Agents					
Albuterol	Esophagus	91	1.61 (1.27–2.04)	<0.001	Bronchodilator often used for smoking-related pulmonary disease. Confounding by smoking.
	Lung, bronchus	1984	2.52 (2.39–2.66)	<0.001	
Beclomethasone	Lung, bronchus	346	1.94 (1.72–2.18)	<0.001	Bronchodilator often used for smoking-related pulmonary disease. Confounding by smoking.
Fluticasone	Esophagus	23	1.87 (1.19–2.96)	0.007	Bronchodilator often used for smoking-related pulmonary disease. Confounding by smoking.
	Lung, bronchus	436	2.10 (1.89–2.34)	<0.001	
Ipratropium	Mouth, pharynx	66	2.53 (1.92–3.33)	<0.001	Bronchodilator often used for smoking-related pulmonary disease (e.g., COPD).
	Lung, bronchus	1111	4.18 (3.88–4.49)	<0.001	Confounding by smoking.
	Trachea, mediastinum, other respiratory	4	9.85 (2.49–38.96)	0.001	
	Urinary bladder	192	1.60 (1.37–1.87)	<0.001	
	Ill-defined, unspecified	129	1.80 (1.49–2.19)	<0.001	
	Any cancer	2797	1.55 (1.48–1.61)	<0.001	
	Ovary	46	1.56 (1.13–2.14)	0.006	Smoking associated with mucinous subtype of ovarian cancer (61)
Metaproterenol	Lung, bronchus	98	2.22 (1.78–2.76)	<0.001	Bronchodilator often used for smoking-related pulmonary disease. Confounding by smoking.
	Urinary bladder	30	1.77 (1.20–2.61)	0.004	
Salmeterol	Lung, bronchus	230	2.21 (1.91–2.55)	<0.001	Bronchodilator often used for smoking-related pulmonary disease. Confounding by smoking.
Theophyllin	Lung, bronchus	335	2.37 (2.10–2.67)	<0.001	Bronchodilator often used for smoking-related pulmonary disease. Confounding by smoking.
	Ill-defined, unspecified	55	1.54 (1.15–2.05)	0.003	
Miscellaneous Agents					
Nicotine	Lip	4	5.71 (1.67–19.49)	0.006	Used in smoking cessation therapy. Confounding by smoking.

Drug	Site	No. of exposed cases	RR (95% CI)	p	Comment
	Mouth, pharynx	12	2.30 (1.23–4.31)	0.009	
	Larynx	10	4.46 (2.12–9.38)	<0.001	
	Lung, bronchus	262	5.95 (5.11–6.94)	<0.001	
	Any cancer	619	1.71 (1.57–1.86)	<0.001	

Positive drug-cancer associations meeting positive criteria, not readily attributable to confounding. Results shown are for 3+ dispensings, 2 year lag.

Table 3

Drug	Cases who took drug					p	Comment
	Site	Number	Median months used ^a	RR (95% CI)			
Anti-infectives							
Amoxicillin	Other skin	66	2	1.50 (1.12–2.02)	0.007	Cases: 24 Merkel cell, 15 dermatofibrosarcoma, 8 sebaceous adenocarcinoma, 4 or fewer of 11 other types. No clinical or biological link found.	
	Hodgkin lymphoma	68	2	1.51 (1.13–2.03)	0.005	RR slightly lower in HIV-free cohort: 1.41 (1.04–1.90) analyzed because of Other skin association. No clinical or biological link found.	
	Monocytic leukemia	12	3	3.18 (1.49–6.79)	0.003	Findings virtually unchanged in HIV-free subjects. No clinical or biological link found. See Discussion.	
Cefaclor	Other skin	4	2	13.44 (3.01–60.04)	0.001	Cases: 2 Merkel cell, 1 each of dermatofibrosarcoma and sebaceous adenocarcinoma. No clinical or biological link found.	
Cefuroxime	Melanoma	13	1	2.84 (1.53–5.27)	0.001	No clinical or biological link found.	
Cardiovascular & Renal Agents							
Atenolol	Thyroid	118	41	1.54 (1.24–1.90)	<0.001	None of the cases had a prior diagnosis of hyperthyroidism. No clinical or biological link found.	
Atorvastatin	Testis	4	37	5.66 (1.66–19.33)	0.006	See Discussion	
	Kidney, renal pelvis	27	37	1.81 (1.19–2.73)	0.005	Lung cancer RR, 0.93 (0.73–1.19) not elevated so confounding by smoking unlikely. 23 of the cases had hypertension. RR on repeat analysis controlling for presence of hypertension was still elevated 1.54 (1.01–2.33). See Discussion.	
Diltiazem	Other digestive organs	9	56	4.43 (1.90–10.32)	0.001	Diagnoses were carcinoid, 4; adenocarcinoma, 3; sarcoma, 1; tumor, not specified, 1. See Discussion.	
Hydrochlorothiazide including combinations	Lip	147	58	2.29 1.84–2.86)	<0.001	Lung cancer only weakly related (RR 1.09 [0.04–1.15]) making confounding by smoking an unlikely explanation. See Discussion.	
	Other skin	95	43	1.56 (1.20–2.01)	0.001	Cases: 35 Merkel cell, 14 malignant fibrous histiocytoma, 8 dermatofibrosarcoma, 7 skin appendage carcinoma, and 5 or fewer of 14 other types. See Discussion.	

Drug	Site	Cases who took drug			RR (95% CI)	p	Comment
		Number	Median months used ^a				
Metoprolol	Mouth, pharynx	61	28		1.51 (1.15–2.00)	0.004	Lung cancer RR, 1.04 (0.94–1.15) minimally elevated so confounding by smoking unlikely. See Discussion.
Nifedipine	Lip	46	40		1.81 (1.30–2.52)	0.001	Lung cancer RR somewhat elevated 1.15 (1.06–1.24) but much less than lip or larynx suggesting only slight confounding by smoking. See Discussion.
	Larynx	39	50		1.60 (1.12–2.28)	0.009	
Prazosin	Thyroid	23	42		2.64 (1.64–4.26)	<0.001	Exclusion of two subjects with hyperthyroidism gave almost identical RR: 2.76 (1.67–4.59) No clinical or biological link found.
Verapamil	Vagina	10	51		3.63 (1.64–8.06)	0.002	No clinical or biological link found. See Discussion.
	Thyroid	55	39		1.52 (1.13–2.03)	0.006	Exclusion of ten subjects with hyperthyroidism gave almost identical RR: 1.46 (1.06–2.01). See Discussion.
Central Nervous System Agents							
Cyclobenzaprine	Thyroid	43	3		1.57 (1.13–2.19)	0.007	Exclusion of subjects with hyperthyroidism gave similar results: RR 1.54 (1.07–2.20). No clinical or biological link found.
Desipramine	Non-Hodgkin lymphoma	29	10		2.44 (1.62–3.67)	<0.001	Little reduction of RR in HIV-free cohort (2.12 [1.38–3.27]) See Discussion.
Fluoxetine	Testis	14	10		2.51 (1.39–4.53)	0.002	Three of the 14 cases were among the 11 paroxetine cases. Relatively small overlap. See Discussion.
Nortriptyline	Esophagus	12	9		2.56 (1.34–4.88)	0.004	Lung cancer weakly related, RR 1.15 (0.96–1.38) so confounding by smoking is not a likely explanation, even though this drug is sometimes used in smoking cessation therapy. RR somewhat higher 2.90 (1.42–5.95) when subjects with alcoholism-related diagnoses excluded. See Discussion.
	Liver, intrahepatic bile ducts	19	14		2.21 (1.33–3.66)	0.002	Exclusion of subjects with liver cirrhosis and alcoholism diagnoses (10 of the 19 cases) resulted in a similar RR with wider confidence interval: 2.24 (1.08–4.67). See Discussion.
Oxazepam	Lung, bronchus	117	9		1.54 (1.26–1.87)	<0.001	See Discussion.
Paroxetine	Testis	11	10		2.44 (1.25–4.74)	0.009	Three of the 11 cases were among the 14 fluoxetine cases. Relatively small overlap. See Discussion.
Risperidone	Hodgkin lymphoma	4	25		5.71 (1.67–19.52)	0.005	No clinical or biological link found. See Discussion.

Drug	Site	Cases who took drug			RR (95% CI)	p	Comment
		Number	Median months used ^a				
Venlafaxine	Melanoma	36	15		1.92 (1.34–2.76)	<0.001	No clinical or biological link found.
Anti-Rheumatic Agents							
Piroxicam	Melanoma	43	9		1.56 (1.13–2.16)	0.001	See Discussion.
Rofecoxib	Peritoneum, omentum, mesentery	3	10		10.75 (2.15–53.73)	0.004	See Discussion.
Sulindac	Gallbladder	9	6		2.88 (1.34–6.19)	0.007	See Discussion
	Other leukemia	5	6		5.78 (1.88–17.78)	0.002	
Gastrointestinal Agents							
Hyoscyamine	Non-Hodgkin lymphoma	23	4		2.45 (1.55–3.87)	<0.001	Findings virtually unchanged in HIV-free subjects. See Discussion.
Metoclopramide	Myeloid leukemia	13	3		2.68 (1.45–4.93)	0.002	No clinical or biological link found.
Pantoprazole	Hodgkin lymphoma	11	36		2.63 (1.29–5.34)	0.008	No clinical or biological link found.
Respiratory/Allergic Agents							
Terfenadine	Peritoneum, omentum, mesentery	7	4		5.02 (2.02–12.43)	0.001	No clinical or biological link found. This drug was removed from the market in 1998.
Miscellaneous Agents							
Oxybutynin chloride	Other skin	12	18		2.34 (1.24–4.42)	0.009	Cases: 5 Merkel cell carcinoma, 2 or fewer of 6 other types. No clinical or biological link found.

^aMedian total days supply dispensed before diagnosis to cases who receive three or more prescriptions divided by 365/12 = 30.4167, rounded to nearest number of months.