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PROJECT TITLE: Antihypertensive medications and cancer patient survival: A population-based retrospective cohort study.

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SUMMARY:

Rationale: The relationship between antihypertensive medications and cancer development has been widely studied. There is extensive *in vitro* evidence for a beneficial effect for beta-blocker drugs in particular. Population-based research has until recently focused on the associations between antihypertensive use and cancer incidence, and there is a need for further study of the influence of these drugs on cancer patient survival. **Hypotheses:** Antihypertensive use was expected to be associated with increased mortality relative to nonuse. Beta-blockers were expected to provide a survival benefit relative to other classes of antihypertensive. **Methods:** Patient information from the Manitoba Cancer Registry was linked with prescription information from Manitoba's Drug Product Information Network for patients diagnosed between 2004 and 2008 with new lung (n = 4241), colorectal (n = 3967), breast (n = 4019), prostate (n = 3355) and liver (n = 244) cancer primaries. Cox proportional-hazards regression analysis was used to evaluate all-cause mortality for users of four classes of medication (beta-blockers, calcium channel blockers, diuretics, and ACE inhibitors / ARBs) relative to nonusers. A separate set of analyses was then conducted on single drug category users to permit direct comparison between beta-blockers and other classes of antihypertensive. **Results:** Antihypertensive medication use was associated with increased cancer mortality. There is no significant evidence that beta-blocker use results in improved survival relative to other classes of antihypertensive. There is a significant association between calcium channel blocker use and improved lung cancer survival relative to beta-blocker users (HR = 0.79, 95% CI = 0.64, 0.98), warranting further study.

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INTRODUCTION

Antihypertensive Medications and Cancer Development

Antihypertensive medications include many subclasses of drugs with different mechanisms of action. These medications are widely used by a range of individuals comprising of many with other morbidities including cancer patients. Recently, antihypertensives have come under investigation due to interest in their potential influence on the development and progression of cancer.

There are many classes of antihypertensives with distinct ways of reducing blood pressure. Within each class there are differences in the exact properties of each drug, but the most widely prescribed medications can be divided into four main categories [1]. These include the beta-blockers, which target primarily beta-adrenoreceptors, the calcium channel blockers, the diuretics, and drugs acting on the renin-angiontensin system which include angiotensin-converting enzyme (ACE) inhibitors and angiotensin-receptor blockers (ARBs).

The impetus for research into the role of antihypertensive medications in cancer development and progression comes from *in vitro* work with cancer cell lines and in animal models. Beta-blockers in particular may be of benefit due to their anti-stress effects. Stress has been identified for many years as a factor in the development and progression of cancer, an effect that appears to be mediated at least in part by suppression of the immune system [2, 3]. However, recent evidence supports a more direct role for the hormones of the sympathetic nervous system in regulating tumor development and invasion [4, 5].

Norepinephrine (NE) is a catecholamine neurotransmitter associated with the sympathetic nervous system that is elevated in stress. There is extensive *in vitro* evidence for the role of NE as a cancer-promoting agent. NE promotes invasiveness in a concentration-dependent manner in pancreatic cell lines, and stimulates breast, colon and prostate cancer cell migration [6-10]. These properties appear to be mediated by activation of beta-adrenoreceptors present on the surface of malignant cells. Administering beta-blockers in conjunction with NE inhibits or reverses the promotion of metastasis and invasiveness normally induced by NE. This effect has been documented in hepatocellular, breast, prostate, lung, and colon cell lines, among others [7-9, 11].

ACE inhibitors and ARBs have shown similar promise in the lab when it comes to reducing tumor proliferation, angiogenesis, and metastasis [12, 13]. This effect appears to be mediated at least in part through inhibition of vascular endothelial growth factor (VEGF), an important factor in tumor-induced angiogenesis. This general mechanism could prove beneficial for the treatment of a broad range of solid tissue tumors, in contrast to the targeted nature of many current antiangiogenic drugs.

Conversely, concerns have been raised over calcium channel blockers. These drugs may promote tumor progression by inhibiting the normal process of apoptosis, which is dependent on regulation of intracellular calcium levels and necessary for the programmed death of

dysfunctional cells [14]. There is evidence both for and against a carcinogenic role for calcium channel blockers [15].

Population-Based Findings

Given the potential for both benefit and harm stemming from the choice of antihypertensive medication, there has been extensive research into the associations between different classes of medication and the incidence of various cancers. Findings from these studies have been mixed, in part due to differences in control group composition and study methodology. More recently, meta-analyses have concluded that there is no convincing evidence that any of the four major classes of antihypertensive medications (beta-blockers, calcium channel blockers, diuretics, and ACE inhibitors / ARBs) are associated with an increased or reduced risk of developing cancer [1, 16].

The focus of research has recently shifted from cancer incidence to cancer patient mortality. Beta-blockers have shown very promising effects on breast cancer in particular *in vitro* and at least one study has found significantly reduced distant metastasis and improved survival in breast cancer patients who use beta-blockers relative to those on non-beta-blocker antihypertensives [17].

Beta-blockers have also been investigated more broadly in a retrospective cohort study for their relationship with cancer patient mortality [18]. Participating cancer patients were divided into beta-blocker users and non-beta-blocker antihypertensive users and evaluated for all-cause mortality. Contrary to expectations there was found to be an overall higher mortality rate for beta-blocker users. This effect was explained by the increased mortality rates observed in the pancreatic and prostate cancer patients who were prescribed beta-blockers.

One hypothesis for the conflicting results regarding the relationship between beta-blockers and tumor progression has been that not all beta-blockers are equally effective at limiting tumor spread. Certain beta-blockers are selective for beta-1 receptors, while others target both beta-1 and beta-2 receptors and are referred to as nonselective beta-blockers. The beta-2 receptor has been proposed to play a more important role in limiting tumor spread based on *in vitro* work [19]. However, this effect was not found to hold true in the population for cancer patient mortality when selective and nonselective beta-blockers were analyzed separately [18].

A complicating factor in the field has been the potential influence of both treated and untreated hypertension and their associated morbidities on both cancer-related and all-cause mortality. Hypertension has been found to be associated with increased risk of cancer in men and women [20, 21]. Meta-analysis has indicated that subjects with hypertension also experience an increased rate of cancer-related mortality [22]. Even treated hypertension has been associated with increased risk of breast cancer and breast cancer mortality [23].

Role of the Current Study

A recurring issue when evaluating population-based research on antihypertensive medications and cancer incidence and mortality is an inconsistency in the definitions of drug users and

nonusers and in the control groups used when evaluating a particular drug category. The major classes of antihypertensive have very different mechanisms of action and all have been postulated to influence cancer development and progression one way or the other [1]. Combining these classes of medication to form a single control group is therefore problematic and may mask important effects. The reverse problem is the need to define drug categories that are broad enough to permit sample sizes large enough to generate sufficient statistical power.

There are many factors influencing cancer patient mortality. While data on some of these factors is not easily available, demographic and cancer staging information should be included where possible in population-based analysis. Cancer sites for the current study were selected based on *in vitro* evidence and cancer patient population size to include lung, breast, prostate, liver, and colorectal cancer.

The current project aimed to add to our presently limited knowledge of the relationship between antihypertensive medications and cancer patient mortality. Rather than comparing a particular class of medication of all other antihypertensives we chose to consider each of the four major classes separately. Given recent findings indicating no added survival benefit to nonselective beta-blockers, these were considered together with selective beta-blockers [18].

The primary goal of the project was an exploratory analysis of each class of drug where drug user mortality was compared with nonuser mortality. This was done through a population-based retrospective cohort design. It was expected that drug user mortality would overall be higher based on the relationship between hypertension and both cancer-related and all-cause mortality, but that this trend would be attenuated for beta-blockers and ACE inhibitors / ARBs based on *in vitro* findings.

While the one existing broad population-based investigation of beta-blockers and cancer mortality did not find a significant benefit to beta-blocker therapy, the evidence for a potential benefit to cancer patients is sufficiently strong, particularly for breast cancer, that it warranted further investigation [24, 25]. In contrast to previous research, we chose to create a subpopulation of single-drug users to avoid the influence of multiple drug interactions and compare each class of antihypertensive individually to beta-blocker users for each cancer site. We hypothesized that beta-blocker use would be associated with reduced mortality overall, but that this relationship might be complicated in some manner that led to a masking of benefit when all other antihypertensives were considered as a single group.

METHODS

Data Collection

This study was approved by the Health Research Ethics Board at the University of Manitoba, the CancerCare Manitoba Research Resource Impact Committee, and the Manitoba Health Information Privacy Committee. Individuals were selected for inclusion using the Manitoba Cancer Registry, a comprehensive database of all non-melanoma cancer diagnoses from 2004 onwards. The specific cancer sites of interest were breast, colorectal, lung, prostate, and liver.

Cancer site was specified using ICD-10 code (Colorectal C18.0-C18.9, C19, and C20; Liver C22.0 and C22.9; Lung C34.0-C34.9; Breast C50.0-C50.9; Prostate C61).

The full study cohort included all patients with a diagnosis date during the period of 2004 to 2008 at one of these sites. If an individual was diagnosed twice with the same site of primary tumor during the study period, only the first cancer was used for the analysis. If an individual was diagnosed with different sites of primary tumor, both cancers were analyzed in their respective regression models.

Antihypertensive medications were included from four categories based on their Anatomical Therapeutic Chemical Classification System (ATC) code: Beta-blockers (ATC groups C07AA, C07AB, and C07AG), ACE inhibitors and ARBs (ATC groups C09AA and C09CA), calcium channel blockers (ATC groups C08CA, C08DA, and C08DB), and diuretics (ATC groups C03AA, C03BA, C03CA, C03CC, C03DA, C03DB, and C03EA). Products were selected if hypertension was included in drug indications based on the WHO ATC index or the product monographs available through Health Canada.

Specific drug products were selected for inclusion using the Health Canada Drug Product Database (DPD). For each ATC category, we searched for all active and discontinued oral agents and collected the associated Canadian Drug Identification Numbers (DINs). This list, along with the list of individuals with qualifying cancer diagnoses, was sent to Manitoba Health. Here the data was cross-referenced with prescription information from the Drug Product Information Network (DPIN), Manitoba's point-of-sale drug database. The information from the Manitoba Cancer Registry and DPIN was linked using scrambled Personal Health Identification Numbers (PHINs).

This newly created database contained information regarding birth date, gender, mortality data up to December 31st, 2010, date of cancer diagnosis, site of diagnosed cancer, AJCC (TNM) stage at diagnosis, date of death (all-cause mortality), area of residence, previous history of cancer, and antihypertensive prescription information from 1996 to 2010. Gleason score at diagnosis was recorded for patients with prostate cancer diagnoses. Gleason scores are used specifically to grade prostate tumors and are a strong prognostic factor for cancer-specific survival in prostate cancer and commonly used in research in place of AJCC staging [26]. Prescription information included DIN, drug category (beta-blocker, calcium channel blocker, diuretic, or ACE inhibitor / ARB), date of prescription dispensation, and quantity dispensed.

Analysis

Analysis for the project was divided into two components, the first involving the full cohorts and the second involving a subpopulation. Both parts used a retrospective cohort design. The full cohorts were used to investigate the impact of each class of antihypertensive medication by comparing drug users to drug nonusers for each category of antihypertensive. Then, to permit comparison between beta-blockers and the other drug categories, a subpopulation of single drug category users was created by reducing the cohorts to those who had at least one prescription of beta-blockers, calcium channel blockers, diuretics, or ACE inhibitors / ARBs during the year prior to diagnosis and then further reducing the cohorts to individuals who only had one of the

four types of prescription in the year prior to diagnosis. All analysis was conducted using SAS 9.2 statistical software.

For both sets of analysis, individuals were defined as users of a particular drug category if they had at least one drug dispensed from that category in the year prior to diagnosis. This one-year window reflects the need for drug administration to be sufficiently recent to have had a potential effect on tumor progression and is based on evidence that advanced cancers take less than two years to acquire the ability to metastasize [27]. Each cancer site was analyzed separately because of differences in survival profiles.

For the full cohorts, DPIN prescription information was used to define each individual as a user or nonuser of each of the four drug categories. For this stage of analysis individuals with multiple types of drug prescription and individuals with no antihypertensive prescriptions in the year prior to diagnosis were included along with single drug category users in Cox proportional hazard regression models to isolate the impact of individual variables. Age, stage at diagnosis (or Gleason score for prostate cancer), gender, history of previous cancer, and rural residence were included as covariates in the regression model. The outcome of interest was all-cause mortality. For these full cohorts, users from each category of antihypertensive were compared to nonusers for that particular category while controlling for the impact of the other drugs.

For the single drug user subpopulation, liver cancer was dropped from the analysis due to insufficient numbers. For this portion of the analysis there was no overlap between categories of drug user, permitting direct comparison. Cox proportional hazard regression models were used again with the same covariates as the full cohort analysis. In these models, beta-blockers were used as a reference category relative to the other three drug categories. Again, the outcome of interest was all-cause mortality.

RESULTS

Results for the Full Study Cohorts

Sample characteristics for each of the cancer site cohorts are presented in Table 1. Data was collected for 4019 breast cancer patients, 3967 colorectal cancer patients, 4241 lung cancer patients, 3355 prostate cancer patients, and 244 liver cancer patients. The prevalence of beta-blocker use varied by site from 13.2% (531/4019) in breast cancer patients to 19.7% (48/244) in liver cancer patients. The other categories of antihypertensive were more widely prescribed with up to 46.7% (114/244) of liver cancer patients using diuretics. Liver cancer had the highest proportion of patients on antihypertensives, while breast cancer patients had the lowest proportion.

The majority of patients were from urban centers (Winnipeg or Brandon). History of previous cancer ranged in prevalence between 21.0% (705/3355) for prostate cancer and 28.3% (1123/3967) for colorectal cancer. Individuals were stratified by age at diagnosis, which varied widely between cancer sites with 54.5% (2192/4019) of breast cancer patients under the age of 65 at diagnosis, but only 28.9% (1227/4241) of lung cancer patients. Stage at diagnosis showed similar variability between sites with 41.8% (1772/4241) of lung cancer patients being

diagnosed with advanced Stage IV disease and only 5.6% (226/4019) of breast cancer patients presenting with Stage IV disease.

Results from the Cox regression analysis are presented in Table 2. Significant results ($p < .05$) are bolded. Individuals who were prescribed calcium channel blockers demonstrated significantly increased mortality rates relative to nonusers for breast cancer (HR = 1.23, 95% CI 1.02, 1.47). Individuals who were prescribed diuretics demonstrated increased mortality rates relative to nonusers for colorectal (HR = 1.28, 95% CI 1.15, 1.42), lung (HR = 1.10, 95% CI 1.01, 1.19), and prostate cancer (HR = 1.41, 95% CI 1.20, 1.65). ACE inhibitor / ARB use was associated with increased mortality in breast (HR = 1.22, 95% CI 1.04, 1.44) and lung cancer (HR = 1.11, 95% CI 1.03, 1.21). No significant results were observed for beta-blocker use. There appeared to be a tendency towards increased mortality for antihypertensive users relative to nonusers.

Age and stage at diagnosis were significantly associated with increased mortality for all cancer sites. History of cancer was significantly associated with mortality in breast, colorectal, and lung cancer. Male gender was associated with increased mortality risk in lung cancer. There was no significant associations between rural or urban residence and mortality.

Results for the Single Drug Category User Subpopulation

Sample characteristics for each cancer site for the reduced single drug user cohorts are presented in Table 3. Reducing the cohorts to individuals with prescriptions from a single drug category in the year prior to diagnosis left 785 breast cancer patients, 888 colorectal cancer patients, 1048 lung cancer patients, and 760 prostate cancer patients. Liver cancer patients were not included in the analysis.

As in the larger cohorts, beta-blockers were the least widely prescribed drugs. Relative to the full cohorts, single drug category users trended towards being older with slightly less advanced disease at diagnosis but were otherwise very similar in demographics.

Results from this second set of Cox regression analyses are presented in Table 4. Calcium channel blockers, diuretics, and ACE inhibitor / ARB users are evaluated relative to beta-blocker users. There was an overall increase in mortality in non-beta-blocker users relative to beta blocker users, but this findings was nonsignificant.

In lung cancer patients, calcium channel blockers are associated with reduced risk of mortality (HR 0.79, 95% CI 0.64, 0.98) relative to beta-blockers. This association does not carry over to other cancer sites. Kaplan-Meier survival curves for each cancer site are presented in Figure 1.

DISCUSSION

Findings From the Full Study Cohort

The primary goal of the project was to complement the extensive literature on antihypertensive medications and cancer incidence by using a broad, population-based approach to investigate

antihypertensive medications and cancer mortality. While there is some evidence that beta-blockers may provide a survival benefit for certain cancers, this evidence is limited and so for the initial analysis, users for each major category of antihypertensive were compared to nonusers while adjusting for other antihypertensive use, age, gender, rural residence, history of cancer and stage at diagnosis [17].

The results of this analysis highlight the importance of analyzing each cancer and each class of antihypertensive separately. Combining classes of antihypertensive with very different mechanisms of action into a single control group, as many past investigations have done, may mask important effects.

No single class of antihypertensive demonstrated a consistent, significant relationship across all cancer sites. Calcium channel blockers, diuretics, and ACE inhibitors / ARBs all showed at least one significant association with increased mortality whereas no significant relationship was found for beta-blockers. This is in line with the study's hypothesis that the association between antihypertensive use and mortality would be attenuated for beta-blocker users. However, the lack of significant results may be due to the relatively lower number of beta-blocker users.

This exploratory investigation was expected to show an overall trend towards increased mortality for all antihypertensive users. While this was found to be true, there were a few nonsignificant but noteworthy exceptions. For both liver cancer and lung cancer, there was a trend towards decreased mortality for calcium channel blocker users. This is of particular interest given the survival advantage for lung cancer patients who were prescribed calcium channel blockers that was found in the second part of the analysis.

Findings from Comparison Between Beta-Blockers and Other Antihypertensives

The second goal of the present study was to determine whether there is a significant survival advantage to beta-blocker use relative to other antihypertensive medications. Given the limited literature available on beta blockers and cancer mortality a broad approach was taken, comparing beta-blocker users to individuals using other classes of antihypertensive medication for four common cancer sites.

Previous population-based research comparing beta-blockers to other antihypertensives did not divide the other antihypertensive medications into subcategories [18]. The current study offers some further insight into the relative mortality risks associated with the use of each of the four main categories of antihypertensive medications. Specifically, calcium channel blockers appear protective in lung cancer patients relative to beta-blockers, but this relationship does not carry over to other cancer sites and neither diuretics nor ACE inhibitors / ARBs are associated with a similar reduction in mortality relative to beta-blocker users with lung cancer.

This relationship between calcium channel blockers and lung cancer is surprising given that past research indicates that there may be an increase in lung cancer incidence with calcium channel blocker use given their potential effect on the calcium channels necessary for normal apoptosis [14, 15]. However, the finding may be in line with recent findings that certain

calcium channel blockers promote sensitivity of multidrug resistant lung cancer cells to chemotherapy [28].

No other significant differences were found between beta-blocker user mortality and mortality for other classes of antihypertensive. Contrary to past research, there was no significant increase in mortality for beta blocker users with prostate cancer [18]. There was an overall tendency towards reduced mortality for beta-blocker users in breast cancer and increased mortality for diuretics users that may warrant follow-up study.

Limitations

The present study had certain limitations. First, it was constrained by being retrospective in nature. However, the retrospective design permitted a larger sample size and a faster turnaround to determine whether there was justification for a longer-range prospective study. Second, it is difficult to make firm conclusions regarding cause and effect due to the potential influence of other variables. Although covariates including age, stage at diagnosis, and gender were included in the regression analysis, there are many potential confounding variables where information was not available for the study populations

The most obvious potential confounding variable in the current study is differences between the patients who are prescribed each category of antihypertensive medication. There are two ways in which this could happen. First, there could be relevant differences between patients that would lead physicians to prescribe one antihypertensive over another. Second, patients could be taking medications for indications other than hypertension that are associated with increased morbidity. An example of this would be a liver cancer patient with advanced liver disease taking a diuretic to manage their ascites. To address this issue, additional information would need to be collected on patient comorbidities. All-cause mortality was selected as the outcome of interest, which could be an issue if there are differences in cancer-specific death between the users of different classes of medication.

Total exposure to medications was not included in the analysis. As a result, the potential impact of continuous versus interrupted use of drugs and any dose-response relationships were not taken into account.

An additional limitation was that we were unable to determine compliance with medications. There is some evidence that compliance with thiazide diuretics is reduced compared to other classes of antihypertensives, however, compliance with calcium channel blockers, beta blockers, and ACE inhibitors does not appear to be significantly different [29]. A final concern would be differences in side effects from different classes of drugs masking cancers, as in the case of the classic ACE inhibitor induced cough masking a developing lung cancer. We addressed this concern by separating our analysis into individual cancers for each of the classes of medication.

Conclusions and Future Directions

The exploratory portion of the study supported an overall increase in mortality for patients who were prescribed antihypertensive medications relative to nonusers. It also demonstrates the

importance of considering distinct classes of medication and cancer sites separately from one another.

A possible association between diuretics and increased mortality deserves further consideration but could be due to a number of factors. The link, if found consistently, may be due to benefits of the other comparison categories of medication, or harm from the diuretics. A more likely explanation may be that diuretics are prescribed to sicker patients, whether to avoid potential side effects from other classes of antihypertensive or for morbidities other than hypertension such as renal failure or advanced liver disease.

The current study did not confirm the potential benefit of beta-blocker prescriptions in cancer patient mortality. The relationship between beta blockers and breast cancer warrants further study but a more rigorous approach may be needed to determine the exact nature of the relationship between beta-blockers and breast cancer and the potential role of covariates. Separate consideration of selective and nonselective beta-blockers may also prove instructive.

The link between calcium channel blockers and lung cancer survival warrants follow-up study especially given recent discoveries regarding the potential role of calcium channel blockers in promoting lung cancer cell sensitivity to chemotherapy.

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Table 1. Characteristics of the full study cohorts

		Breast (N = 4019)		Colorectal (N = 3967)		Lung (N = 4241)		Prostate (N = 3355)		Liver (N = 244)	
		N	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**
Drug use in previous year	**Beta-blockers**	531	13.2	722	18.2	767	18.1	574	17.1	48	19.7
	Calcium channel blockers	567	14.1	726	18.3	854	20.1	573	17.1	52	21.3
	Diuretics	1005	25.0	1189	30.0	1259	29.7	805	24.0	114	46.7
	ACE inhibitors / ARBs	880	21.9	1187	29.9	1256	29.6	956	28.5	89	36.5
Age	**Under 65**	2192	54.5	1305	32.9	1227	28.9	1099	32.8	97	39.8
	65 and older	1827	45.5	2662	67.1	3014	71.1	2256	67.2	147	60.2
AJCC Stage	**I/II**	3150	78.4	1864	47.0	1154	27.2	.	.	106	43.4
	III	533	13.3	1089	27.5	1074	25.3	.	.	52	21.3
	IV	226	5.6	813	20.5	1772	41.8	.	.	49	20.1
	Unknown	110	2.7	201	5.1	241	5.7	.	.	37	15.2
Gleason score	**2 - 6**	.	.	.	.	.	.	1045	31.1	.	.
	7	.	.	.	.	.	.	1320	39.3	.	.
	8 - 10	.	.	.	.	.	.	730	21.8	.	.
	Unknown	.	.	.	.	.	.	261	7.8	.	.
History of cancer	**None**	3082	76.7	2844	71.7	2917	68.8	2650	79.0	192	78.7
	Positive	937	23.3	1123	28.3	1324	31.2	705	21.0	52	21.3
Residence	**Rural**	1394	34.7	1506	38.0	1560	36.8	1277	38.1	69	28.3
	Urban	2625	65.3	2461	62.0	2681	63.2	2078	61.9	175	71.7
Gender	**Female**	4019	100	1833	46.2	2022	47.7	.	.	70	28.7
	Male	.	.	2134	53.8	2219	52.3	3355	100	174	71.3

STUDENT NAME: *Signy Holmes*

Table 2. Covariate-adjusted Cox regression model results for the full study cohorts: For each category of antihypertensive, past-year users are evaluated relative to nonusers of that drug category

Cancer site:	**Previous year drug use:**	**Hazard Ratio (95% CI)** Relative to nonusers for that drug category
Breast	Beta-blockers	1.10 (0.92 – 1.32)
	Calcium channel blockers	**1.22 (1.02 – 1.47)**
	Diuretics	1.10 (0.94 – 1.30)
	ACE inhibitors and ARBs	**1.22 (1.04 – 1.44)**
Colorectal	Beta-blockers	1.05 (0.93 – 1.18)
	Calcium channel blockers	1.10 (0.98 – 1.24)
	Diuretics	**1.28 (1.15 – 1.42)**
	ACE inhibitors and ARBs	1.03 (0.93 – 1.15)
Lung	Beta-blockers	1.01 (0.93 – 1.11)
	Calcium channel blockers	0.95 (0.87 – 1.04)
	Diuretics	**1.10 (1.01 – 1.19)**
	ACE inhibitors and ARBs	**1.11 (1.03 – 1.21)**
Prostate	Beta-blockers	1.18 (0.99 – 1.40)
	Calcium channel blockers	1.08 (0.91 – 1.29)
	Diuretics	**1.41 (1.20 – 1.65)**
	ACE inhibitors and ARBs	1.06 (0.90 – 1.24)
Liver	Beta-blockers	1.34 (0.95 – 1.90)
	Calcium channel blockers	0.75 (0.53 – 1.06)
	Diuretics	1.19 (0.89 – 1.60)
	ACE inhibitors and ARBs	1.05 (0.79 – 1.41)

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Table 3. Characteristics of single drug class user subpopulation

		Breast (N = 785)		Colorectal (N = 888)		Lung (N = 1048)		Prostate (N = 760)	
		N	**%**	**N**	**%**	**N**	**%**	**N**	**%**
Drug use in previous year	**Beta-blockers**	123	15.7	152	17.1	196	18.7	163	21.4
	Calcium channel blockers	150	19.1	171	19.3	222	21.2	135	17.8
	Diuretics	264	33.6	262	29.5	333	31.8	190	25.0
	ACE inhibitors / ARBs	248	31.6	303	34.1	297	28.3	272	35.8
Age	**Under 65**	294	37.5	197	22.2	223	21.3	194	25.5
	65 and older	491	62.5	691	77.8	825	78.7	566	74.5
AJCC Stage	**I/II**	639	81.4	437	49.2	301	28.7	.	.
	III	82	10.4	229	25.8	280	26.7	.	.
	IV	36	4.6	181	20.4	403	38.5	.	.
	Unknown	28	3.6	41	4.6	64	6.1	.	.
Gleason score	**2 - 6**	.	.	.	.	.	.	241	31.7
	7	.	.	.	.	.	.	291	38.3
	8 - 10	.	.	.	.	.	.	173	22.7
	Unknown	.	.	.	.	.	.	55	7.2
History of cancer	**None**	574	73.1	587	66.1	678	64.7	581	76.4
	Positive	211	26.9	301	33.9	370	35.3	179	23.6
Residence	**Rural**	273	34.8	334	37.6	395	37.7	273	35.9
	Urban	512	65.2	554	62.4	653	62.3	487	64.1
Gender	**Female**	785	100	419	47.2	509	48.6	.	.
	Male	.	.	469	52.8	539	51.4	760	100

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Table 4. Covariate-adjusted Cox regression model results for single drug class user subpopulation: Beta-blockers are used as a reference category relative to the other three antihypertensive categories

Cancer site:	Previous year drug use:	**Hazard Ratio (95% CI)** Relative to Beta-Blockers
Breast	Calcium channel blockers	1.30 (0.77 – 2.20)
	Diuretics	1.24 (0.77 – 1.98)
	ACE inhibitors and ARBs	1.35 (0.85 – 2.15)
Colorectal	Calcium channel blockers	0.99 (0.71 – 1.37)
	Diuretics	1.24 (0.92 – 1.66)
	ACE inhibitors and ARBs	0.97 (0.72 – 1.31)
Lung	Calcium channel blockers	**0.79 (0.64 – 0.98)**
	Diuretics	1.06 (0.88 – 1.29)
	ACE inhibitors and ARBs	1.06 (0.87 – 1.29)
Prostate	Calcium channel blockers	1.05 (0.66 – 1.67)
	Diuretics	1.45 (0.97 – 2.17)
	ACE inhibitors and ARBs	1.14 (0.85 – 1.71)

Figure 1. Kaplan-Meier survival curves for the single drug class user subpopulation

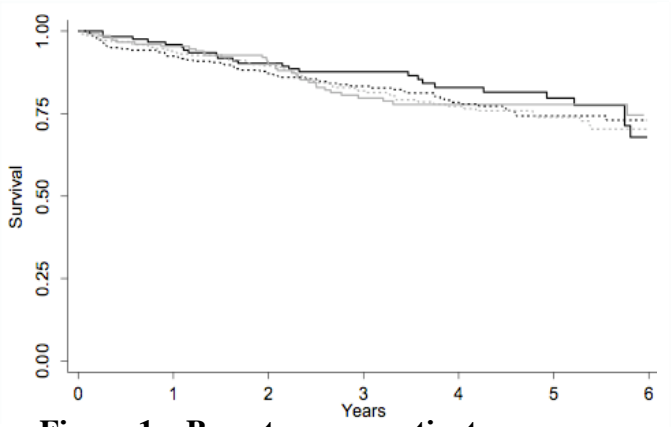

Figure 1a. Breast cancer patients

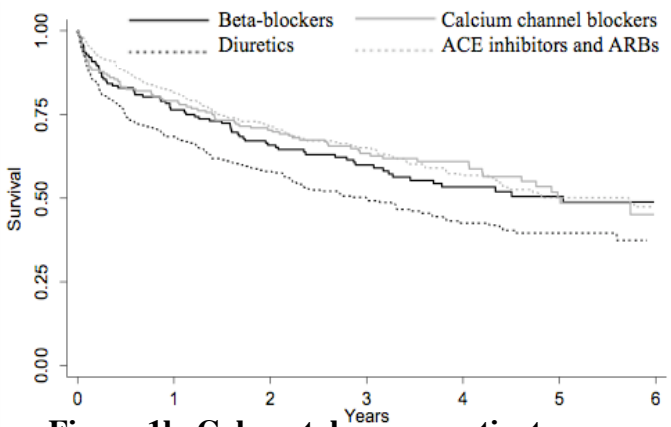

Figure 1b. Colorectal cancer patients

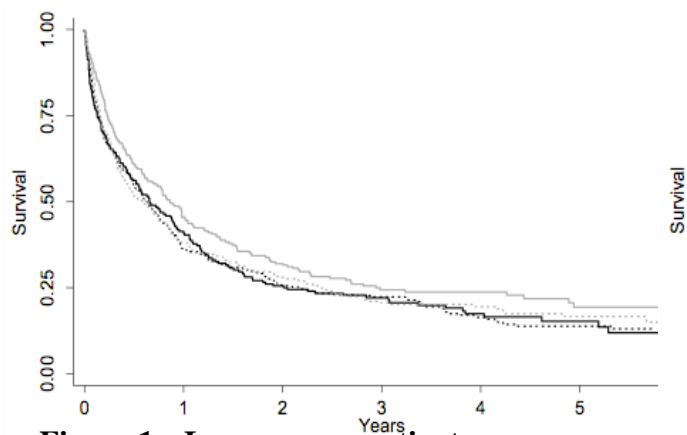

Figure 1c. Lung cancer patients

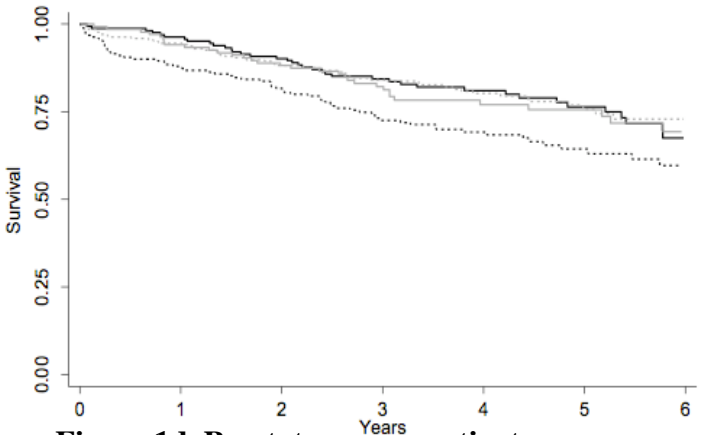

Figure 1d. Prostate cancer patients