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Changes in Chronic Medication Adherence in Older Adults with Cancer Versus Matched Cancer-Free Cohorts

Jennifer L. Lund, PhD[1,2,*], **Parul Gupta, PhD**[2], **Krutika B. Amin, PhD**[3], **Ke Meng, PhD**[2], **Benjamin Y. Urick, PharmD, PhD**[4], **Katherine E. Reeder-Hayes, MD, MBA**[2,5], **Joel F. Farley, PharmD, PhD**[6], **Stephanie B. Wheeler, PhD**[2,3], **Lisa Spees, PhD**[2,3], **Justin G. Trogdon, PhD**[2,3]

[1]Department of Epidemiology, Gillings School of Global Public Health, University of North Carolina at Chapel Hill, Chapel Hill, NC 27599

[2]Lineberger Comprehensive Cancer Center, University of North Carolina at Chapel Hill, Chapel Hill, NC 27599

[3]Department of Health Policy and Management, Gillings School of Global Public Health, University of North Carolina at Chapel Hill, Chapel Hill, NC 27599

[4]Division of Practice Advancement and Clinical Education, University of North Carolina at Chapel Hill, Chapel Hill, NC 27599

[5]Division of Hematology/Oncology, Department of Medicine, University of North Carolina at Chapel Hill, Chapel Hill, NC 27599

[6]Department of Pharmaceutical Care and Health Systems, University of Minnesota, Minneapolis, MN 55455

Abstract

[*]Corresponding author at: Department of Epidemiology, Gillings School of Global Public Health, University of North Carolina at Chapel Hill, McGavran-Greenberg Hall, CB #7435, Chapel Hill, NC 27599-7435, Jennifer.Lund@unc.edu.

Author contributions

Jennifer L. Lund: conceptualization, data curation, investigation, methodology, supervision, writing - original draft, and writing - review and editing.
Parul Gupta: data curation, formal analysis, methodology, project administration, writing - review and editing
Krutika B. Amin: data curation, formal analysis, methodology, project administration, writing - review and editing
Ke Meng: data curation, formal analysis, methodology, project administration, writing - review and editing
Benjamin Y. Urick: supervision, methodology, writing - review and editing
Katherine E. Reeder-Hayes: conceptualization, supervision, methodology, writing - review and editing
Joel F. Farley: conceptualization, supervision, methodology, writing - review and editing
Stephanie B. Wheeler: conceptualization, supervision, methodology, writing - review and editing
Lisa Spees: methodology, writing - review and editing
Justin G. Trogdon: conceptualization, data curation, funding acquisition, investigation, methodology, supervision, writing - review and editing.

Conflicts of Interest: Dr. Lund's spouse is a full-time, paid employee of GlaxoSmithKline who also holds stock in the amount of approximately $42,000. Dr. Lund also receives unrelated grant funding paid to her institution from AbbVie. Dr. Wheeler receives unrelated grant funding paid to her institution from Pfizer. All other co-authors have no potential conflicts of interest to report.

Objectives—A cancer diagnosis can influence medication adherence for chronic conditions by shifting care priorities or reinforcing disease prevention. This study describes changes in adherence to medications for treating three common chronic conditions – diabetes, hyperlipidemia, and hypertension – among older adults newly diagnosed with non-metastatic breast, colorectal, lung, or prostate cancer.

Methods—We identified Medicare beneficiaries aged ≥66 years newly diagnosed with cancer and using medication for at least one chronic condition, and similar cohorts of matched individuals without cancer. To assess medication adherence, proportion of days covered (PDC) was measured in six-month windows starting six-months before through 24 months following cancer diagnosis or matched index date. Generalized estimating equations were used to estimate difference-in-differences (DID) comparing changes in PDCs across cohorts using the pre-diagnosis window as the referent. Analyses were run separately for each cancer type-chronic condition combination.

Results—Across cancer types and non-cancer cohorts, adherence was highest for anti-hypertensives (90–92%) and lowest for statins (77–79%). In older adults with colorectal and lung cancer, adherence to anti-diabetics and statins declined post-diagnosis compared with the matched non-cancer cohorts, with estimates ranging from a DID of −2 to −4%. In older adults with breast and prostate cancer cohorts, changes in adherence for all medications were similar to non-cancer cohorts.

Conclusion—Our findings highlight variation in medication adherence by cancer type and chronic condition. As many older adults with early stage cancer eventually die from non-cancer causes, it is imperative that cancer survivorship interventions emphasize medication adherence for other chronic conditions.

Keywords

aging; cancer; chronic conditions; medication adherence

INTRODUCTION

As the population ages, patients and providers must increasingly manage multiple chronic conditions (or multimorbidity). The challenge of multiple chronic conditions is particularly notable within the cancer population. Cancer is primarily a disease of aging; by 2030 approximately 70% of all Americans diagnosed with cancer will be age 65 years or older.[1] Among Medicare beneficiaries diagnosed with cancer, more than 60% are living with three or more chronic conditions.[2] Often, cancer survivors receive inadequate care for their chronic conditions, including lower rates of checkups, screening and surveillance of diabetes symptoms, and prescriptions for cardiovascular risk factors.[3–6] However, little is known about how medication adherence for chronic conditions changes among older adults (age 65+ years) following a cancer diagnosis.[7–12]

Adherence to medications for chronic conditions in older adults is poor; about half of all Medicare beneficiaries dispensed antihypertensive medications stopped taking them within one year of the initial prescription.[13] For older patients, a diagnosis of cancer has the potential to affect medication adherence for other chronic conditions in a variety of ways, either by shifting the emphasis of medical care to the emerging cancer or by reinforcing the

importance of secondary prevention of existing chronic conditions. For example, cancer-related prescriptions (both treatment and symptom management) could add more cost and complexity to patients' existing medication burden, potentially decreasing adherence to medications for other chronic conditions. On the other hand, a cancer diagnosis may serve as a "wake-up call" encouraging healthy behaviors such as eating better, exercising, and taking medications on-time. It may also provide patients with increased provider contact to clarify medication taking instructions, request refills, or increase monitoring of treatment effects such as blood pressure measurement or blood glucose. In addition, the constellation of healthcare providers (e.g., primary care and specialists) that a patient interacts with changes following a cancer diagnosis, and the degree of coordination among the care team may influence medication adherence for other chronic conditions.[14]

Few studies have evaluated how a new cancer diagnosis influences how older adults take their medications for chronic conditions, with most focusing solely on women with breast cancer and comorbid diseases.[7–9,11,12,15] Furthermore, only one study has attempted to isolate the impact of a cancer diagnosis separately from age-related trends in medication adherence by comparing changes observed in older adults with cancer to those without.[10] In this study, we describe adherence to medications for hyperlipidemia, hypertension, and diabetes, three of the most common chronic conditions,[2] among Medicare beneficiaries newly diagnosed with one of the four most common cancer types (breast, colorectal, lung, or prostate cancer) and evaluate the impact of a new cancer diagnosis on medication adherence through comparison with matched non-cancer cohorts. Ultimately, these results will help identify subgroups of older adults with cancer who may be at high risk for medication non-adherence and could benefit from targeted survivorship interventions to improve medication adherence and reduce the occurrence of adverse chronic condition sequelae.

MATERIALS AND METHODS

Data sources

We used the linked Surveillance, Epidemiology, and End Results program (SEER) cancer registries and Medicare enrollment and claims data.[16] The SEER cancer registries collect demographic, tumor, initial treatment, and vital status data for incident cancers that arise in 21 specific SEER regions (e.g., the state of Connecticut). These SEER regions currently cover approximately 34% of the United States population. Medicare enrollment and claims data record longitudinal information about healthcare utilization for beneficiaries aged 65 and older who are enrolled in the fee-for-service health insurance benefits. Heath insurance benefits include Medicare Parts A (coverage for hospitalizations, long-term stays, and skilled nursing stays), B (coverage for outpatient care), and D (coverage for prescription drugs).

Setting and participants

We identified patients aged ≥66 with a first primary diagnosis of stage I-III breast, prostate, non-small cell lung, or colorectal cancer from July 1, 2008 – December 31, 2012 using the SEER registry data. These cancer types allow us to explore the influence of varying prognosis on medication adherence. Individuals diagnosed at autopsy or death were

excluded. To be included, individuals had to be enrolled in Medicare Parts A, B, and D health insurance benefits for the 18-months before through 24-months following the month of cancer diagnosis. Individuals who died or withdrew from Medicare Parts A, B, or D before 24-months from diagnosis were excluded from analysis.

Study design

We constructed cross-classified cohorts by cancer type and chronic condition (e.g., breast cancer and hypertension), identifying patients with cancer with at least one International Classification of Diseases, 9th Edition, Clinical Modification (ICD-9) diagnosis code for the chronic condition of interest and at least one prescription drug claim for an oral medication to manage that condition from −18 months to −7 months before cancer diagnosis. This approach resulted in twelve cross-classified cancer cohorts, although the same patient with cancer could be represented in up to three cohorts.

We then used a 5% random sample of Medicare beneficiaries identified within each SEER region to construct cross-classified cohorts of similar individuals without a history of cancer using exact matching[15] on age (in years), sex, race (White, Black, Asian, Hispanic, Native American Indian, Other), and SEER region. Among all eligible individuals without a diagnosis of cancer, up to five were selected with replacement (i.e., the same individual could be selected multiple times) and assigned an index date, based on the diagnosis date of the patient that they were matched to. As described above, this resulted in twelve cross-classified non-cancer cohorts, although patients could be in multiple cohorts.

Primary outcome variable - Medication adherence

The primary outcome was medication adherence, measured using the proportion of days covered (PDC), using the technical specifications from the Centers for Medicare and Medicaid Services (CMS) Star Ratings program.[17] The PDC is the number of days covered by a prescription drug divided by the total number of days in an observation window. The CMS specifications account for potential misclassification of medication exposure during hospitalizations and skilled nursing facility stays by removing this time from the denominator and carrying forward any days' supply which overlapped with a hospital or skilled nursing facility stay. Adherence was evaluated at the condition- (e.g., hypertension) level and switching within and across drug classes (e.g., switching from a thiazide diuretic to an ACE inhibitor for management of hypertension) was allowed.

The PDC was measured in 6-month time windows from 6-months before the diagnosis or index date (the pre-index or reference window) through 24 months after diagnosis or index date, resulting in five consecutive 6-month windows of observation (one pre-diagnosis and four post-diagnosis). These windows were then further classified as: (1) pre-diagnosis (months −6 to −1 months), (2) initial treatment (months 0 to 11) and (2) survivorship (months 12 to 23) phases. Figure 1 illustrates the main features of our study design, including the windows for PDC measurement. For the analysis of antidiabetics, we excluded all patients that initiated insulin at any point during follow-up. PDC calculations are unreliable for insulin, and removal of patients who initiate insulin is consistent with CMS

specifications.[17] The PDC was analyzed as a continuous variable and dichotomized at ≥80% (adherent) versus <80% (non-adherent) in secondary analyses.

Statistical analysis

We summarized patient characteristics for cancer cohorts using descriptive statistics. Mean PDCs and the proportion of patients classified as adherent were averaged over three phases of care for cancer and non-cancer cohorts by site and chronic condition combination.

We then implemented a difference-in-difference (DID) analysis.[18] DID is a quasi-experimental study design that uses longitudinal pre-post data from an index group (i.e., those with cancer) and a comparison group (i.e., those without cancer) to obtain a valid counterfactual to estimate a causal effect of interest. In this study, we calculated the mean differences in PDCs in the initial treatment and survivorship phase compared with the pre-diagnosis phase (referent period) separately for the cancer and non-cancer cohorts. Then, we took the difference of those differences as a way to estimate the "effect of a cancer diagnosis on changes in medication adherence."

Analyses were conducted separately by cancer type and chronic condition combination (i.e., 12 distinct analyses). Weighted generalized estimated equations for repeated observations were run, accounting for the matching,[19] using an exchangeable working correlation matrix. Mean differences in PDCs were estimated with 95% confidence intervals. Effect measure modification (i.e., variation in subgroup effects) was explored by American Joint Commission on Cancer, 6th Edition (AJCC) stage (I, II, and III) for the breast, colorectal, and lung cancer analyses and by Gleason score (1–6, 7, 8–10) for the prostate cancer analyses. Secondary analyses of the proportion of adherent patients were also conducted. All statistical analyses were performed using SAS version 9.4 (Cary, NC). This study was approved by the University of North Carolina at Chapel Hill Institutional Review Board.

RESULTS

Table 1 reports the characteristics of older adults diagnosed with breast, colorectal, lung, and prostate cancer contributing to at least one of the chronic condition analyses, including 34,395 individuals. The total number of older adults with cancer and matched patients without cancer eligible for each chronic condition analysis are presented in Supplemental Figure 1. As the non-cancer sample was exact matched on each of these characteristics, their data are not presented. Overall, patients with colorectal cancer were the oldest with a mean age at diagnosis of 78 years. The distribution of conditions was similar across cancer types with 8–9% of patients with cancer having all three conditions. Descriptive characteristics of each of the 12-cancer type by condition cohorts are presented in Supplemental Table 1.

Figures 2A–C show the mean PDC for medications used to treat diabetes (A), hyperlipidemia (B), and hypertension (C), comparing the four cancer cohorts with their matched non-cancer comparators by phase of care (data provided in Supplemental Table 2). Across all cohorts in the pre-diagnosis period, the mean PDC was highest for anti-hypertensives, ranging from 90–92% in both the cancer and non-cancer cohorts, and lowest for statins, ranging from 77–79%. For both anti-diabetics and statins, the mean PDC

appeared to decline during the initial treatment and survivorship windows for both cancer and non-cancer populations, except for the prostate cancer cohort, where adherence remained steady over time. Similar patterns for the outcome of the proportion of adherent individuals were observed (Supplemental Figures 2A–C, Supplemental Table 2).

Results from the difference-in-difference models comparing changes in mean PDCs in the initial and survivorship phases versus the pre-diagnosis phase are presented in Table 2. For the breast, colorectal, and prostate cancer cohorts, declines in mean anti-hypertensive PDC in the initial or survivorship phases versus the pre-diagnosis phase were similar or smaller compared with the matched non-cancer cohorts. However, in the lung cancer cohort there was a notably larger decline in mean anti-hypertensive PDC during the survivorship window versus the pre-diagnosis window compared with the matched non-cancer cohort (−1.88%, 95% CI: −3.13%, −0.64%). In analyses of anti-diabetic and statin medication adherence, declines in adherence post-diagnosis were similar between older adults with breast and prostate cancer and matched non-cancer cohorts. In contrast, older adults with lung and colorectal cancer experienced larger declines in mean PDC than the matched non-cancer cohorts (difference-in-difference estimates ranging from −1.94% to −4.46% for non-insulin anti-diabetics and −1.35% to −3.44% for statins).

Secondary analyses evaluating the changes in the proportion of older adults that were adherent (rather than changes in mean PDC) using difference-in-difference models yielded similar findings (Supplemental Table 3). Finally, stratified analyses by stage or Gleason score (Table 3) further underscore the main findings in the colorectal and lung cohorts. Across all AJCC stages and cardiometabolic conditions, difference-in-difference estimates indicated larger declines in mean PDCs for older adults with colorectal and lung cancer compared with their respective matched non-cancer cohorts. However, a slightly different picture emerged for the breast and prostate cancer analyses. Across all stages and cardiometabolic conditions among older adults with prostate cancer, mean PDCs were unchanged or improved compared with the matched non-cancer cohorts. In contrast, mean PDCs appeared to decrease for statins in stage II, and statins and non-insulin anti-diabetics in stage III breast cancer cohort compared with the non-cancer comparison women, although estimates were imprecise.

DISCUSSION

In this study, overall adherence to medications to treat chronic conditions varied among older adults with and without cancer, with the highest adherence observed for anti-hypertensive medications followed by non-insulin anti-diabetics and statins. Changes in medication adherence post-diagnosis further varied by cancer type and phase of care relative to matched non-cancer cohorts. The largest relative decreases were observed during the survivorship phase in the colorectal, lung, and higher stage breast cancer cohorts.

Most existing research has focused on women with breast cancer and chronic disease. Consistent with our findings, several studies report that medication adherence was high prior to a breast cancer diagnosis, with PDCs for antidiabetic medications ranging from 63–86%, for antihypertensives from 70–91%, and for statins from 75–83%.[7–9,11,12,15] Medication

adherence following cancer diagnosis declined to varying degrees across these studies, as in our study with the exception of adherence to antihypertensives which increased following breast cancer diagnosis.

Some of the variation across studies is likely attributable to differences in measures used to define adherence (e.g., medication possession ratio versus PDC[20]), their operationalizations (e.g., proportion of patients with 80% and higher adherence versus a mean measure of adherence, adjustment for hospitalizations), and the time windows used for assessment (e.g., 6-months versus three years following cancer diagnosis). Furthermore, differences in study populations also likely drive differences in adherence observed across studies. While some studies, like ours, only included patients 65 and older enrolled in Medicare,[9,10] others including patients <65 years generally found that younger women were more likely to be non-adherent following a cancer diagnosis than older women.[15]

Our study also evaluated changes in medication adherence for individuals diagnosed with lung, colorectal, and prostate cancers, as well as matched individuals without a history of cancer. This expansion of scope provided an opportunity to generate additional hypotheses about why medication adherence patterns might vary across cancer types and over time and whether these changes are in excess of what would be expected in similar individuals without cancer. Only one prior study included multiple cancer types and matched cancer-free individuals in their investigation of changes in cardiometabolic medication adherence before and after a cancer diagnosis,[10] but was notably limited by a lack of cancer registry data. The authors reported particularly marked declines for antihypertensives, driven by patients with a shorter survival time, where discontinuation of preventive therapies might be indicated.[21] Our findings are more comparable to the longer survival population, where declines in PDC (compared to patient without cancer) resulted in mean difference-in-difference estimates in the range of −2 to −4% following a cancer diagnosis.

Interestingly, our findings add to that of Stuart et al highlighting notable variation in chronic medication adherence across cancer types and over time. First, the largest declines in mean PDC (relative to the non-cancer population) were observed in the lung (−1 to −4%) and colorectal (−1 to −3%) cohorts, increasing over time from the initial treatment to survivorship phase, and mostly driven by patients with more advanced (stage II and III) disease. This result may point to: (1) the appropriate discontinuation of preventive therapies that may require a long lag-time for benefit[21] or (2) that more complex cancer treatments (e.g., surgical resection and adjuvant chemotherapy) could either complicate, deprioritize, or make medically unnecessary continued use of these medications. However, changes in PDCs (relative to the non-cancer population) for chronic conditions either remained stable or increased over time in the breast and prostate cohorts, specifically for non-insulin antidiabetics and antihypertensives. While some decreases in PDC were observed in the stage II and III breast cancer cohorts, similar patterns were not observed in the prostate cohorts. Future studies investigating specific drivers of these differences are warranted.

Notably, mean PDCs for antihypertensives in both older adults with cancer and the matched non-cancer cohorts were high over all phases of care ranging from 90–93%. This high level of sustained adherence may be partly due to the routine monitoring of blood pressure during

frequent visits for cancer care, and the opportunity to discuss and reinforce the importance of antihypertensive adherence. Monitoring of lipid-levels or glycemic control are not routinely performed by oncologists, which could partly explain the lower adherence over time in these medication classes. While oncologists may be pressed into the role of managing chronic health concerns if patients are unable to see other healthcare providers during cancer treatment or must divert financial or social support resources to pay for and participate in cancer care, such lack of care coordination may result in suboptimal outcomes. One study within the Veterans' Administration[22] found that adherence to antihypertensives and statins decreased as the number of prescribers of those medications increased. Thus, investigations are needed to explore how care for patients with cancer and chronic conditions is coordinated among oncologists, primary care physicians, and other specialists and whether better coordination improves medication adherence.

Results from this study should be viewed considering several limitations. First, medication adherence is evaluated using dispensed prescriptions and we cannot assume that all filled medications were consumed. Second, this study was restricted to adults age 66 and older with continuous Medicare fee-for-service and Part D coverage who also survived two years following their cancer diagnosis (or index date). As such, our findings may not be generalizable to those with Medicare Advantage or without prescription drug or other healthcare insurance, the population 65 years and under, or patients with a short life expectancy. Third, we matched cancer and non-cancer cohorts on a limited set of potential confounding variables. To the extent that other factors (e.g., prevalence of other comorbidities) differs between the two groups and leads to non-parallel trends in adherence in the pre-diagnosis window, our estimates may be biased. Finally, this was a descriptive, hypothesis-generating study and we were not able to isolate the specific causes of variation in medication adherence across cancer types. Future qualitative and analytic research to examine competing explanations for the observed patterns, including the role of cancer prognosis, treatment complexity, behavioral changes, and care coordination, are needed.

Chronic conditions are common among older adults with cancer and their management alongside a new cancer diagnosis can be complex. Our findings highlight particularly large decrements in chronic medication adherence over time among patients with cancer with worse cancer prognoses or more complex and burdensome treatment, including older adults diagnosed with lung, colorectal, and stage II-III breast cancers. As many of these patients will become long-term survivors, further research is needed to understand the aspects of cancer care that may adversely impact medication adherence for other chronic conditions. These patient subgroups may also be high priority for interventions to support medication adherence across the care continuum, saving resources for our healthcare system and turning the complex journey of cancer treatment into an opportunity to positively impact long-term, overall health among survivors.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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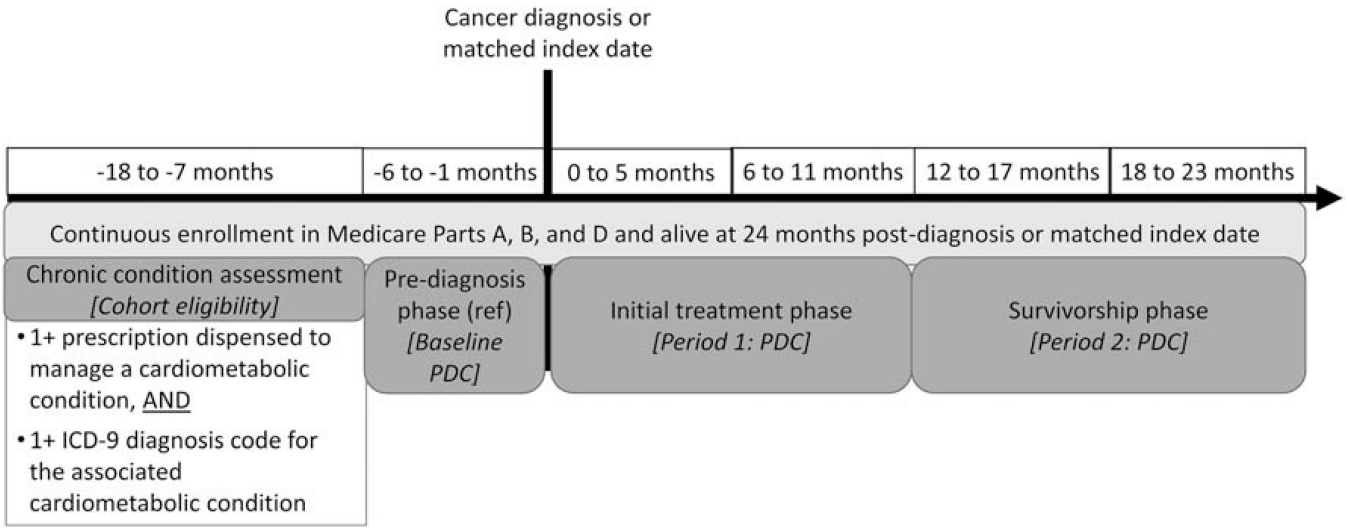
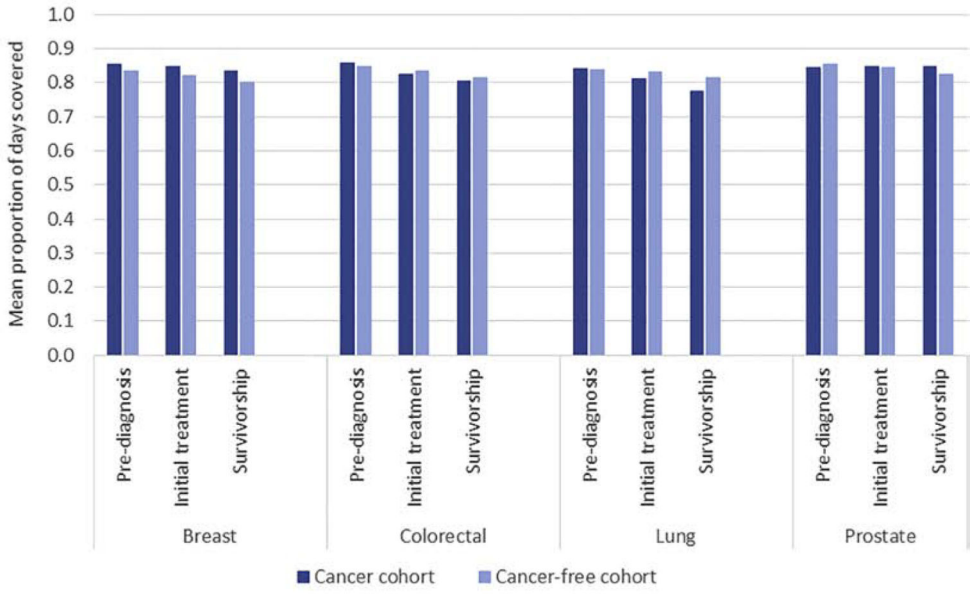


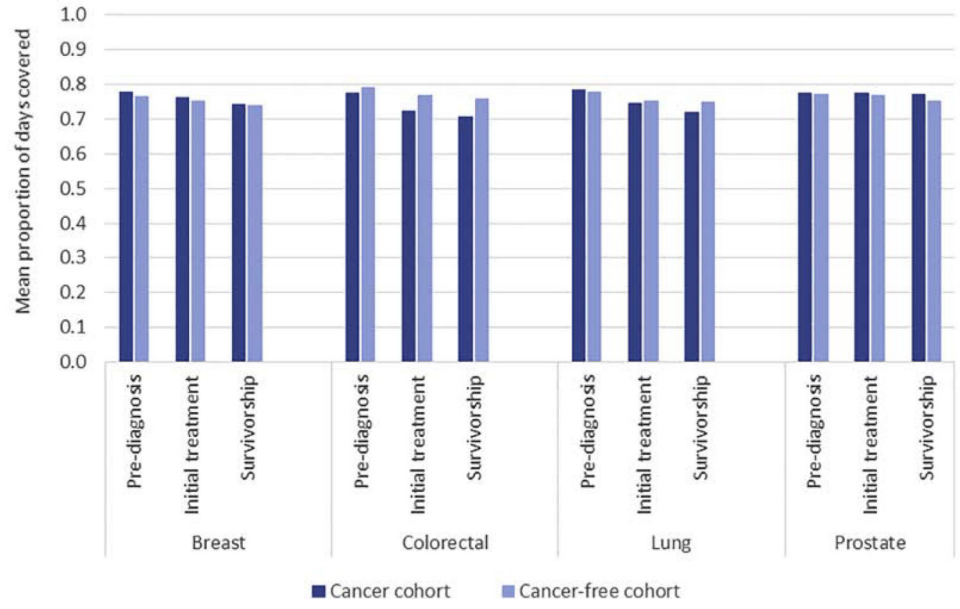
Figure 1. Illustration of study design and analytic definitions.

The schematic indicates what periods are used to determine cohort eligibility and periods to measure medication adherence using the proportion of days covered (PDC). Period 1 refers to the initial treatment phase and period 2 refers to the survivorship phase.

A) Non-insulin anti-diabetics



B) Statins



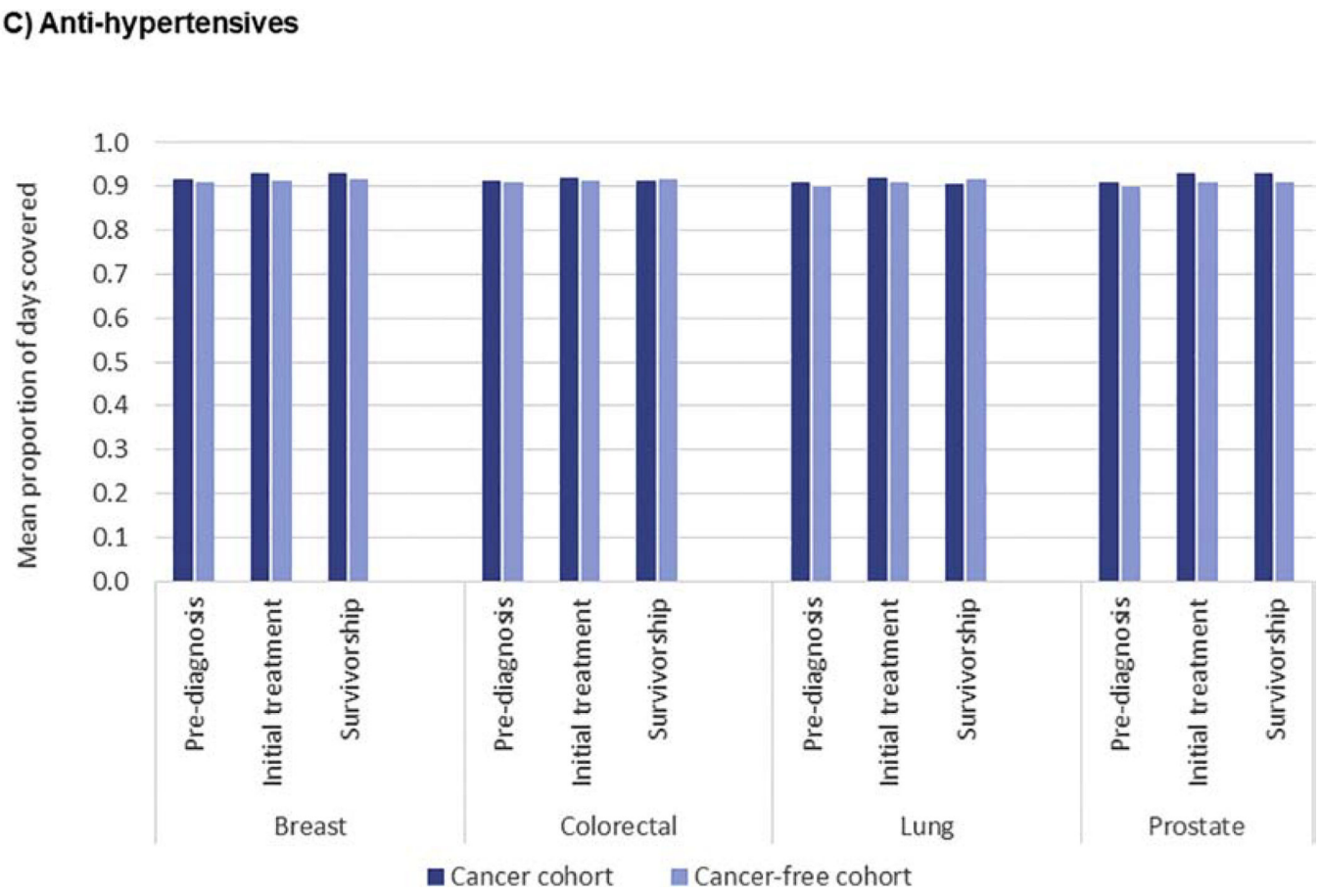


Figure 2A-C. Mean proportion of days covered by cardiometabolic condition cohort, cancer type, and phase of care.

Results regarding noninsulin anti-diabetics (A), statins (B), and anti-hypertensives (C) are reported.

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Table 1.

Characteristics of study populations by cancer type, 2008–2013[a]

Characteristics	Breast		Colorectal		Lung		Prostate	
	n=11831	%	n=6580	%	n=4105	%	n=11879	%
Cardiometabolic condition profile								
Hyperlipidemia only	1193	10	610	9	435	11	1,668	14
Diabetes only	193	2	154	2	49	1	252	2
Hypertension only	4552	38	2,483	38	1,415	34	3,751	32
Hyperlipidemia and diabetes	138	1	96	1	51	1	199	2
Hyperlipidemia and hypertension	4114	35	2,254	34	1,631	40	4,323	36
Diabetes and hypertension	612	5	384	6	186	5	600	5
Hyperlipidemia, diabetes, and hypertension	1029	9	599	9	338	8	1,086	9
Number of cardiometabolic conditions								
1	5,938	50	3,247	49	1,899	46	5,671	48
2	4,864	41	2,734	42	1,868	46	5,122	43
3	1,029	9	599	9	338	8	1,086	9
Age (mean, std)	76.38	6.7	77.65	7.0	75.1	6.0	73.42	5.2
66–69 years	2,122	18	877	13	838	20	3,203	27
70–74 years	3,138	27	1,615	25	1,240	30	4,401	37
75–79 years	2,791	24	1,490	23	1,041	25	2,610	22
80+ years	3,780	32	2,598	39	986	24	1,665	14
Female (except Prostate, Male)	11,742	99	4,079	62	2,548	62	11,879	100
Race/ethnicity								
White	9,871	83	5,234	80	3,426	83	9,576	81
Black	1,008	9	512	8	312	8	1,073	9
Asian	424	4	454	7	231	6	519	4
Hispanic	245	2	154	2	51	1	308	3
Native American Indian/Other[b]	283	2	226	3	85	2	403	3
AJCC stage or Gleason for Prostate								
I (or ≤6 Gleason)	6,841	58	2,285	35	2,639	64	4,536	39

Characteristics	Breast		Colorectal		Lung		Prostate	
	n=11831	%	n=6580	%	n=4105	%	n=11879	%
II (or 7 Gleason)	4,010	34	2,403	37	371	9	4,957	43
III (or 8–10 Gleason)	980	8	1,892	29	1,095	27	2,150	18

[a] Characteristics of the non-cancer comparison cohorts are not included because these characteristics were exact matched and thus are identical to those reported for the cancer cohorts.

[b] Native American Indian and Other were combined due to small cell sizes.

Table 2.

Changes in mean adherence over time comparing patients with cancer to matched patients without cancer by cancer type, chronic condition, and phase of care[a]

	Cancer Type							
	Breast		Colorectal		Lung		Prostate	
Condition	Initial vs. pre-diagnosis phase	Survivorship vs. pre-diagnosis phase	Initial vs. pre-diagnosis phase	Survivorship vs. pre-diagnosis phase	Initial vs. pre-diagnosis phase	Survivorship vs. pre-diagnosis phase	Initial vs. pre-diagnosis phase	Survivorship vs. pre-diagnosis phase
Diabetes mellitus	1.05 (−0.25, 2.36)	1.45 (−0.42, 3.31)	−1.94 * (−3.71, −0.18)	−2.05 (−4.60, 0.51)	−2.31 (−5.22, 0.60)	−4.46 * (−8.62, −0.31)	1.29 (−0.03, 2.62)	3.1 ** (1.22, 4.98)
Hyperlipidemia	−0.38 (−1.44, 0.69)	−0.95 (−2.35, 0.45)	−2.7 ** (−4.50, −0.90)	−3.28 ** (−5.29, −1.26)	−1.35 (−3.31, 0.60)	−3.44 ** (−5.86, −1.03)	0.65 (−0.33, 1.62)	1.77 ** (0.46, 3.08)
Hypertension	0.91 ** (0.27, 1.56)	0.56 (−0.32, 1.43)	0.28 (−0.64, 1.20)	−0.82 (−1.95, 0.32)	0.23 (−0.89, 1.36)	−1.88 ** (−3.13, −0.64)	0.95 ** (0.35, 1.56)	0.98 (−0.02, 1.98)

Abbreviations: CI=confidence interval

**: P<0.01

*: P<0.05

[a]All point estimates and 95% confidence intervals are multiplied by 100 to represent percentages.

Table 3.

Changes in mean adherence overtime comparing patients with cancer to the matched patients without cancer by cancer type, stage, chronic condition, and phase of care[a]

	Cancer Type							
	Breast		Colorectal		Lung		Prostate	
Condition/ stage	Initial vs. pre-diagnosis phase	Survivorship vs. pre-diagnosis phase	Initial vs. pre-diagnosis phase	Survivorship vs. pre-diagnosis phase	Initial vs. pre-diagnosis phase	Survivorship vs. pre-diagnosis phase	Initial vs. pre-diagnosis phase	Survivorship vs. pre-diagnosis phase
Stage I/Gleason≤6								
Diabetes mellitus	1.19 (−0.18, 2.55)	1.01 (−0.82, 2.84)	−1.75 (−4.00, 0.5.10)	−2.18 (−5.22, 0.86)	−1.04 (−3.51, 1.44)	−1.37 (−4.83, 2.09)	0.86 (−0.70, 2.42)	2.03 (−0.06, 4.12)
Hyperlipidemia	−0.27 (−1.10, 0.57)	0.07 (−1.03, 1.17)	−2.77** (−4.40, −1.15)	−2.65* (−4.70, −0.61)	−2.31** (−3.65, −0.98)	−1.60 (−3.33, 0.13)	1.24* (0.27, 2.20)	1.61* (0.38, 2.84)
Hypertension	0.79** (0.35, 1.22)	0.71* (0.14, 1.28)	0.84* (0.022, 1.66)	0.0043 (−1.06, 1.07)	0.85* (0.054, 1.66)	−0.52 (−1.56, 0.52)	1.17** (0.58, 1.76)	0.92* (0.16, 1.68)
Stage II / Gleason=7								
Diabetes mellitus	−0.05 (−1.80, 1.70)	0.48 (−1.86, 2.82)	−2.51 (−5.08, 0.06)	−1.45 (−4.76, 1.86)	−2.02 (−8.43, 4.39)	−5.58 (−15.18, 4.02)	1.37 (−0.16, 2.90)	1.32 (−0.75, 3.40)
Hyperlipidemia	−1.18 (−2.36, 0.001)	−1.88* (−3.43, −0.33)	−3.26** (−4.91, −1.61)	−2.63* (−4.71, −0.55)	−2.21 (−5.83, 1.42)	−3.94 (−9.02, 1.14)	0.45 (−0.48, 1.38)	1.25* (0.10, 2.40)
Hypertension	0.72* (0.11, 1.32)	0.659 (−0.12, 1.43)	−0.125 (−1.01, 0.76)	−0.427 (−1.56, 0.71)	2.362 (−0.05, 4.78)	0.347 (−2.59, 3.28)	1.23** (0.65, 1.81)	0.511 (−0.25, 1.27)
Stage III/Gleason 8–10								
Diabetes mellitus	−0.52 (−4.19, 3.14)	−1.94 (−6.83, 2.96)	−2.23 (−4.92, 0.45)	−4.83* (−8.59, −1.06)	−4.75* (−8.82, −0.69)	−10.5** (−16.21, −4.80)	−0.01 (−2.19, 2.16)	1.96 (−1.00, 4.91)
Hyperlipidemia	−1.72 (−4.11, 0.67)	−2.56 (−5.74, 0.62)	−6.67** (−8.47, −4.88)	−6.81** (−9.28, −4.35)	−5.29** (−7.51, −3.07)	−9.65** (−12.65, −6.64)	0.596 (−0.90, 2.09)	1.293 (−0.65, 3.24)
Hypertension	0.74 (−0.48, 1.97)	0.34 (−1.35, 2.02)	−0.38 (−1.38, 0.62)	−1.47* (−2.80, −0.14)	−1.70* (−3.00, −0.39)	−4.69** (−6.50, −2.88)	1.77** (0.91, 2.62)	1.30* (0.17, 2.43)

** : P<0.01

* : P<0.05

[a]All point estimates and 95% confidence intervals are multiplied by 100 to represent percentages.