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Use of Psychotropic Medications by U.S. Cancer Survivors

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Abstract

Objectives—To describe national utilization of **psychotropic** medications by adult cancer survivors in the U.S. To estimate the extra use of **psychotropic** medications that is attributable to cancer survivorship.

Methods—Prescription data for 2001 to 2006 from the Medical Expenditure Panel Survey (MEPS) were linked to data identifying cancer survivors from the National Health Interview Survey (NHIS), the MEPS sampling frame. The sample was limited to adults 25 years of age and older. Propensity score matching was used to estimate the effects of cancer survivorship on utilization of **psychotropic** medications, by comparing cancer survivors and other adults in MEPS. Utilization was measured as any use during a calendar year and the number of prescriptions purchased (including refills). Analyses were stratified by gender and age, distinguishing adults younger than 65 from those 65 and older.

Results—Nineteen percent of cancer survivors under age 65 and 16% of survivors 65 and older used **psychotropic** medications. Sixteen percent of younger survivors used antidepressants; 7% used anti-anxiety medications. For older survivors, utilization rates for these two drug types were 11% and 7% respectively. The increase in any use attributable to cancer amounted to 4-5 percentage points for younger survivors ($p<.05$) and 2-3 percentage points for older survivors ($p<.05$), depending on gender.

Conclusion—Increased use of **psychotropic** medications by cancer survivors, compared to other adults, suggests that survivorship presents ongoing psychological challenges.

Keywords

cancer; survivorship; **psychotropic** medicines; oncology; utilization

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Introduction

Studies have shown that psychopharmacological agents are helpful in managing fatigue, nausea, anxiety and depression among cancer patients [1-4]. However, few studies have described the use of **psychotropic** medicines in oncology [5-8], and no national study has described the use of **psychotropic** medications in the growing American population of cancer survivors (which has now reached about 12 million) [9]. Accordingly, this study has two primary goals: (1) to describe national utilization of **psychotropic** medications by adult cancer survivors in the U.S. and (2) to estimate the extra use of **psychotropic** medications by U.S. cancer survivors that is attributable to cancer survivorship. Understanding national utilization patterns can be helpful to oncology professionals and cancer survivors in putting their own prescribing patterns and experiences in perspective. The dramatic improvement in cancer survival rates over recent decades has stimulated interest in the long-term consequences of cancer diagnosis and treatment, including needs for psycho-social services [10, 11]. Assessing the use of **psychotropic** medicines by cancer survivors compared to other adults is a new way of quantifying the ongoing psychological challenges of survivorship.

Methods

Data

Our data come from two large, nationally representative surveys, the Household Component of the Medical Expenditure Panel Survey (MEPS-HC) and the National Health Interview Survey (NHIS). MEPS-HC provides detailed information about annual health care utilization and expenditures for each person in the sample, including the number and types of prescriptions. Because the NHIS is the sampling frame for MEPS, data collected for individuals in each survey can be linked across surveys. For this study, questions systematically identifying cancer survivors that are asked in NHIS (but not in MEPS) are linked to the prescribed medicine data in MEPS to study **psychotropic** medicine use by people with and without a history of cancer.

Each year a new panel of MEPS households is selected from participants in the previous year's NHIS. Then data are collected for each MEPS panel for two calendar years. As a result, there are two years of data for most individuals in MEPS (e.g., the 2005 MEPS panel has 2005 and 2006 data for a sample drawn from the 2004 NHIS). By the same token, there are data from two panels for each calendar year (e.g., MEPS data for 2006 are collected from samples drawn from the 2004 and 2005 NHIS). This study pools annual data from 2000 to 2005 from NHIS [12], linked to MEPS data from 2001 to 2006 [13], to obtain a large enough sample of cancer survivors to make reliable utilization estimates and comparisons, including for survivor subgroups.

Use of **psychotropic** medicines is measured from the MEPS Prescribed Medicine files [14], which provide detailed information on household-reported prescriptions for each subject for the calendar year. Each record corresponds to a prescription and includes information about therapeutic class from Multnum Lexicon, which was used to identify prescriptions in the **psychotropic** class (TC1=242) and subclasses: antidepressants (TC1S1=249); antipsychotic

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(TC1S1=251); anxiolytics, sedatives, and hypnotics (TC1S1=67); CNS stimulants (TC1S1=71). Records associated with **psychotropic** medicines were counted for each person each year to determine the total number of **psychotropic** prescriptions, including refills, and to identify people with any use of **psychotropic** medications during the year.

Sample

We identified our sample of cancer survivors in keeping with a definition of survivorship, adopted by the National Cancer Institute's Office of Cancer Survivorship (OCS) and others, that equates the population of survivors with cancer prevalence. According to OCS (2010), "An individual is considered a cancer survivor from the time of diagnosis through the balance of his or her life." The questions used to identify cancer survivors are from a section of the NHIS questionnaire that is administered to one randomly-sampled adult per household. The sequence begins, "Has a doctor or other health provider EVER told you that you have a cancer or malignancy of any kind?" Anyone answering "yes" is shown a flashcard enumerating 29 cancer sites and is asked, "What kind of cancer was that?"

Although we mainly identified cancer survivors in this study from NHIS, we relied on MEPS medical condition files [15] to identify survivors who were diagnosed after they were interviewed in NHIS. Whenever care is reported in MEPS, the respondent is asked, "Was this visit for any specific health condition or were any conditions discovered during this visit? …What condition was that?" Similar questions are asked about restricted activity days, and respondents are also asked about health problems that bothered them. For all conditions identified in these ways, the MEPS condition files provide "Clinical Classification" codes developed by AHRQ and assigned from text survey responses coded by trained professionals into the *International Classification of Diseases*, Ninth Revision (ICD-9). We used clinical classification codes 11 to 46, excluding code 23 (non-melanoma skin cancer) and code 44 (unclassified neoplasm) to identify subjects with cancer.

Our sample was limited to MEPS respondents with data from NHIS. Considering the cancer diagnoses from NHIS, along with cancers and beginning dates in the MEPS condition files, we classified each subject in each survey year as (1) a newly diagnosed cancer survivor (in that calendar year), (2) a previously diagnosed survivor (in a prior calendar year), or (3) not a survivor. Skin cancers other than melanoma were ignored. This procedure yielded a final sample of 531 observations for newly diagnosed survivors, 3774 for previously diagnosed survivors and 52,262 for adults who were not survivors. There were two years of data for most individuals.

To produce nationally-representative estimates from the linked sample, we modified the person-level annual weights on the MEPS public use files. The first step was to adjust the original weights for differences in the probability of selection for NHIS sampled adults in different sized families. For each sampled adult over 25 years of age with a positive MEPS survey weights, an adjustment factor was defined as the inverse of the weighted proportion of household adults represented by the sampled adult. To avoid very large adjustments in the weights of some individuals, the factor was capped at 4.25 (the 99 percentile of unconstrained values).

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Next we used a "raking" procedure to adjust the weights by calendar year to population control totals from the full MEPS sample by age, sex, race/ethnicity, family income as a percent of poverty, region, and metropolitan location (yes or no). The new weights for the 6 MEPS samples pooled for analysis, which summed to about 6 times the U.S. population, were rescaled to sum to the U.S. population in 2006. Applying the rescaled weights to the pooled, linked adult sample yielded a national estimate of 12,150,000 ± 817,948 adult cancer survivors at the start of 2006 and 1,650,000 ± 194,910 new cancer cases diagnosed in 2006. These estimates are consistent with national prevalence estimates based on SEER (11.3 million adults at the beginning of 2006) [9] and the American Cancer Society's estimates of annual incidence (1.4 million in 2005) [16]. Because 2006 decedents are included, the combined total of 13,700,000 survivors (12,150,000 + 1,650,000) corresponds to the number ever alive in 2006, not the prevalence of cancer at the end of 2006.

Analysis

Descriptive sample statistics and weighted population estimates were tabulated by cancer status (cancer survivor, other adults) and age group. Confidence intervals and Z-tests involving weighted national estimates were adjusted for the complex survey design, using survey estimation procedures in SAS 9.1 and Stata 11.

To estimate the increases in utilization attributable to cancer, we adjusted for observable differences between cancer survivors and other adults using a variant of propensity score matching known as kernel matching. The propensity score is the predicted probability of being in the "treatment group," which in our application corresponds to being a previously diagnosed cancer survivor, conditional on observed characteristics. Propensity score matching can be used to estimate the "average effect of treatment on the treated" (ATT) if the following two conditions are met:

- For each value of the propensity score in the treatment group, there are some individuals in the comparison group with the same score. This assumption is known as "common support."
- Selection into treatment (having survived cancer) is independent of the untreated outcome (prescription drug utilization in the absence of cancer), conditional on observable characteristics, as summarized by the propensity score [17].

The ATT is similar to the average treatment effect, but represents a more conservative approach to inference because the ATT isn't presumed to generalize beyond the "treated" population (current cancer survivors in our study) [17].

Propensity score matching offers two advantages over parametric approaches to covariate adjustment, such as regression. First, because the ATT is based on averaged differences across matched individuals with similar characteristics, no assumption regarding the functional relationship between the outcome variable and covariates is required. Second, when the common support condition is imposed, matching ensures that only comparable individuals are compared. For additional information on matching and other methods based on the propensity score, see Harder et al. (2010) and D'Agostino (1998) [17, 18].

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Kernel matching is conceptually similar to nearest neighbor (NN) matching, since both use observations from an untreated comparison group to estimate each treated individual's outcome in the absence of treatment. Whereas NN matching constructs counterfactual outcomes by selecting the single observation from the comparison group with the propensity score most similar to each of the treated observations, kernel matching estimates the same counterfactual using a distance-weighted mean of the comparison group observations [19]. Kernel matching performs well in settings, such as ours, where the ratio of comparison to treated observations is 4:1 or better [20]. Kernel matching has the additional advantage of allowing the use of bootstrapped standard errors that incorporate the estimation error in the scores. Abadie and Imbens (2008) show that bootstrapping may not produce valid standard errors for "nonsmooth" matching estimators, such as the NN estimator, but should lead to valid inferences for "smooth" estimators, such as kernel matching [21].

The first step in our matching analysis was to estimate separate propensity scores for each age-gender subsample (females 65+, males 65+, females < 65, and males < 65) and for two model specifications, described below. All propensity scores were estimated as Probits using the PSMATCH2 program in Stata [22] and all person-years of MEPS data for previously diagnosed survivors and other adults with no history of cancer. We limited the matching analyses to previously diagnosed survivors because our calendar-year utilization measures reflect less than a full year of cancer experience for individuals diagnosed during the year, diluting the cancer effect when newly diagnosed cases are included. Because the few prior studies of **psychotropic** medications in oncology focused more on patients in primary treatment than survivors, our study contributes more to the literature by concentrating on previously diagnosed survivors. We limited the analyses to individuals aged 40-64 because it was difficult to achieve close matches for the small number of survivors aged 25-40.

The covariates in the propensity score models included indicators for each year of age, race/ethnicity, education, marital status, Census region, metro location, and each survey year. One model included indicators for specific chronic conditions: arthritis, asthma, diabetes, emphysema, heart disease, hypertension, and stroke. These conditions, which may sometimes result from a person's cancer history, were excluded from a second model. For example, anthracycline-based chemotherapy sometimes causes heart problems, premature menopause can alter a woman's health risks in many ways, and chest radiation carries a risk of lung damage [10]. Matching the cancer and non-cancer samples on co-morbidities removes the effect of comorbidities from the comparison, an approach that is appropriate only if the higher rate of comorbidities in the cancer sample is entirely unrelated to cancer. Ignoring co-morbidities in matching the samples fully incorporates their effect into the comparison, which is only appropriate if the higher rate of co-morbidities in the cancer sample is entirely related to cancer. When considered together, the two approaches have the advantage of bracketing the potential effect of cancer-related co-morbidities on utilization differences.

In comparing a variety of matching estimators to experimental estimates based on randomization, Heckman, Ichimura, and Todd (1997) find that violating the common support condition accounts for a substantial portion of the bias arising from the use of non-experimental estimators [19]. Thus, to ensure that only comparable individuals were

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compared, we imposed the common support condition prior to matching, using a “trimming” procedure that removed 2% of the cancer observations whose corresponding control observations had propensity scores with relative frequencies below an endogenously-determined cut-off [19].

After matching on the propensity scores, we performed balancing tests (standard *t*-tests for equality of means in the cancer and non-cancer groups) on every covariate, separately for each model and age-gender subsample, using the PSTEST procedure in PSMATCH2. The rejection rates on these tests varied from 0% to 5% across all age-gender subsamples and all models, which is within the expected range given a Type I error rate of 0.05.

Having verified that our estimated propensity scores successfully balanced observable characteristics in the treatment and control groups, we estimated the ATT parameter for each subsample and model using kernel matching. The PSMATCH2 program does not accommodate the use of survey weights, because there is no consensus in the literature about how to use weights in matching [22]. As a result, our matching estimates were generated without survey weights.

The final step was to compute standard errors for the ATT estimates that incorporated the estimation error in the propensity scores. This was done using a bootstrap based on 200 replications of the combined propensity score – matching procedure, clustering by person to account for multiple observations on each individual.

Results

Weighted survey tabulations showed that cancer survivors were older and disproportionately female and non-Hispanic whites compared to other adults (Table 1). For example, 38% of survivors under age 65 were 55-64 years old, compared to 19% of other adults in that age group. Higher percentages of cancer survivors had chronic conditions such as arthritis, asthma, diabetes, chronic heart disease and stroke than other adults.

About 17% of survivors younger than 65 and 15% of survivors 65 and older purchased at least one **psychotropic** medication in a year (Table 2). The mean number of purchases was 2.0 per survivor in the younger age group and 1.5 per survivor in the older age group, implying that survivors using **psychotropic** medications averaged about 12 purchases per year in the younger age group (dividing 2.0 by .17) and 10 per year in the older age group (dividing 1.5 by .15). Male survivors used the medications about half as often as female survivors. Calendar-year utilization by newly diagnosed survivors was slightly lower than utilization by previously diagnosed survivors, but calendar-year statistics do not reflect a full year of cancer experience for individuals newly diagnosed in the year.

Among cancer survivors under age 65, 30% were gynecological cancer survivors and 21% were breast cancer survivors. In this age group, prostate cancer was the only cancer type associated with significantly different rates of utilization compared to survivors in the reference group, the residual group of “other” cancer types. Among cancer survivors older than 65, 24% were breast cancer survivors, 23% were prostate cancer survivors, and 14%

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were colorectal cancer survivors. In the older age group, prostate and lung cancer survivors used **psychotropic** medications less than the "other" cancer types.

Four out of five survivors under age 65 who used **psychotropic** medications were on anti-depressants (Table 3). Anti-anxiety agents were the next most frequent drug type. Compared to other adults, rates of any use were significantly higher for cancer survivors for all **psychotropic** medications and anxiolytics in both age groups, and for antidepressants in the age group under age 65.

Comparing previously diagnosed cancer survivors to other adults in the age group from 40 to 64 with propensity score matching (Table 4), rates of any use of **psychotropic** medications remained significantly higher for survivors (regardless of gender). Differences in the mean number of purchases were also statistically significant in the younger age group after matching. The effects of cancer survivorship on utilization by male and female survivors were fairly similar. Matching on chronic conditions had relatively little effect on the estimates, reducing the estimated effect of cancer on the utilization rate by about a percentage point and the mean number of medication purchases by about 0.15 per year.

After matching, the difference in utilization attributable to cancer was smaller in the older age group compared to the younger age group. For example, after matching, the cancer-related increase in any use of **psychotropic** medications was 2.6 percentage points for older females compared to 6.1 percentage points for younger females.

Discussion

To the best of our knowledge, this is the first study to provide national estimates of **psychotropic** medications used by U.S. cancer survivors or to compare utilization between survivors and the general population. One out of six cancer survivors under age 65, and one out of seven survivors age 65 and older, took **psychotropic** medications during a year. Antidepressants were the most common drug type (used by 14% of younger survivors and 10% of older survivors), followed by anti-anxiety medications. The increased use of **psychotropic** medications attributable to cancer amounted to 3-6 percentage points for younger survivors, depending on gender, compared to 2-4 percentage points for older survivors.

Many studies have compared the mental health of cancer survivors and other adults, but this research has not reached definitive conclusions about the longer term psychological effects of cancer. Some studies have found a significant negative effect of survivorship on mental health over the medium to long term [23-25]; others have not [26-28]. Moreover, benefit-finding is a common reaction to the survivorship experience [29, 30]. Our discovery that cancer survivors are significantly more likely to use **psychotropic** medications than other adults suggests that cancer does have lasting psychological effects on survivors. Assuming that these drugs are effective in treating the psychological consequences of cancer, their use may help to explain why many researchers have found that the mental health of cancer survivors and other adults is similar over the long run.

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The size and statistical significance of the increase in drug utilization that we have attributed to cancer is not particularly sensitive to alternative assumptions about the elevated rate of other chronic conditions in the cancer sample, as demonstrated by two estimation approaches that bracket the potential effect of co-morbidities on cancer-related medication use. Although MEPS does not reliably distinguish co-morbidities that originated before and after a cancer diagnosis, this limitation is not very important for our study. Limited sample sizes by type of cancer, and the lack of information about stage at diagnosis and treatment modalities, did hamper investigation of differences in medication use within the cancer survivor sample in MEPS. Since it is difficult to distinguish mental health conditions that originated before and after the cancer diagnosis, we could not account for mental health history. Although we compared counts of medication purchases (including refills) for survivors and other adults, differences in drug utilization are difficult to quantify, especially in patient surveys. In particular, the number of fills does not capture differences in pill counts or dosage.

We could not assess the appropriateness of the increased use of **psychotropic** medications by cancer survivors that we observed. Nevertheless, national benchmarks should be helpful to individual clinicians and cancer centers in evaluating their own prescribing patterns. Given the elevated use of **psychotropic** medications by cancer survivors, the development of an evidence base to guide prescribing in this population is warranted. In addition, national statistics should give cancer survivors a helpful perspective on their personal challenges and experiences. Increased use of anti-depressant and anti-anxiety drugs is the norm and likely improves the mental health of cancer survivors.

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Table 1

Sample characteristics by age group (United States, 2006)

Characteristics	25-64		65 and older	
	Cancer (N=2,149)	Non-cancer (N=41,560)	Cancer (N=2,138)	Non-cancer (N=10,702)
Weighted population (millions)	**7.1**	**145.9**	**6.5**	**29.9**
	100.0%	**100.0%**	**100.0%**	**100.0%**
Sex [a, b]				
Male	30.2	49.4	48.7	43.0
Female	69.8	50.6	51.3	56.9
Age [a, b],				
25-34	11.4	24.4	----	----
35-44	19.9	29.4	----	----
45-54	30.3	27.3	----	----
55-64	38.3	18.9	----	----
65-74	----	----	45.0	54.2
75+	----	----	54.9	45.7
Race/Ethnicity [a, b]				
Hispanic	6	13.0	3.1	7.4
Black, not Hispanic	8	11.5	5.5	9.1
White, not Hispanic	70.9	59.0	76.1	67.0
Other, not Hispanic	15.0	16.4	15.2	16.4
Marital status				
Married	60.6	65.4	58.7	54.5
Widowed	4.0	2.0	28.9	31.4
Divorced/separated	21.3	15.2	9.5	10.5
Never married	14.0	17.3	2.9	3.6
Education [b]				
LT high school	13.0	14.2	24.8	31.0
High school	33.2	31.1	34.7	34.0
Some college	24.4	23.4	17.2	16.0
College graduate	16.8	18.7	12.3	10.7
Post graduate	12.6	12.6	10.9	8.2
Chronic conditions				
Arthritis [a, b]	32.2	17.3	54.3	50.3
Asthma [a]	14.9	9.0	10.3	9.6
Diabetes [a]	8.3	5.9	18.9	17.7
Emphysema [a, b]	2.5	0.8	7.1	4.4
Heart disease [a, b]	12.1	6.8	36.7	30.2

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Characteristics	**25-64**		**65 and older**	
	Cancer (N=2,149)	**Non-cancer (N=41,560)**	**Cancer (N=2,138)**	**Non-cancer (N=10,702)**
Weighted population (millions)	**7.1**	**145.9**	**6.5**	**29.9**
	100.0%	**100.0%**	**100.0%**	**100.0%**
Hypertension [a, b]	30.0	19.1	56.9	53.1
Stroke [a, b]	2.8	1.3	11.2	9.1
MSA	81.5	84.5	77.6	78.1
Non-MSA	18.5	15.5	22.4	21.9

[a] Cancer and non-cancer individuals younger than 65 are significantly different at p=0.05 level

[b] Cancer and non-cancer individuals 65 and older are significantly different at p=0.05 level

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Table 2

Use of psychotropic medications by cancer survivors, according to survivor characteristics (United States, 2006)

Characteristics	Percent distribution (weighted)	Psychotropic medications	
		Percent with any use (s.e.)	Mean number of purchases (s.e.)
	Ages 25-64 (7.1 million)		
Total	100.0%	16.8% (0.88)	2.0 (.17)
Timing of diagnosis			
Newly diagnosed	13.7	14.7 (1.95)	1.5 (.24)
Previously diagnosed	86.3	17.2 (1.00)	2.1 (.19)
Gender			
Male	30.2	12.2 (1.62)	1.4 (.22)
Female	69.7	19.3 (1.29)	2.4 (.26)
Cancer site [§]			
Breast	21.1	18.0 (2.13)	2.1 (.19)
Prostate	4.6	7.2 (2.90)	0.6 (.31)
Colorectal	5.3	16.6 (3.85)	2.1 (.56)
Lung	2.3	17.3 (6.23)	1.7 (.67)
Gynecological	30.2	20.6 (1.85)	2.4 (.33)
	65 and older (6.5 million)		
Total	100.0%	14.8 (0.86)	1.5 (.12)
Timing of diagnosis			
Newly diagnosed	10.2	12.4 (2.87)	1.4 (.47)
Previously diagnosed	89.8	15.0 (0.89)	1.5 (.13)
Gender			
Male	48.7	11.1 (1.12)	1.0 (.12)
Female	51.3	18.6 (1.29)	2.0 (.19)
Cancer site [§]			
Breast	24.2	18.5 (1.91)	1.8 (.29)
Prostate	22.9	11.1 (1.89)	1.2 (.28)
Colorectal	14.4	14.4 (2.55)	1.8 (.44)
Lung	4.4	11.0 (3.69)	0.9 (.36)
Gynecological	8.6	18.6 (3.00)	2.1 (.41)

[§]The reference group for cancer sites is the residual group of all cancer types other than breast, prostate, colorectal, lung and gynecological cancers.

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Table 3

Use of psychotropic medications by cancer survivors and other adults, according to age (United States, 2006)

Psychotropic medication	25-64		65 and older	
	Cancer	Non-cancer	Cancer	Non-cancer
Any medication[a,b]	16.8%	9.5%	14.7%	12.1%
Antidepressants [a]	13.7	7.7	9.8	8.6
Antipsychotics [a]	1.7	0.9	0.9	1.0
Anti-anxiety [a,b]	5.9	2.8	6.7	4.8
CNS stimulants	0.9	0.4	0.1	0.4

[a] Cancer and non-cancer individuals younger than 65 significantly different at $p<0.05$ level

[b] Cancer and non-cancer individuals 65 and older are significantly different at $p<0.05$ level

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Table 4

Effects of cancer on psychotropic medication use

	Ages 40 to 64		65 and older	
	Females	**Males**	**Females**	**Males**
	N	**N**	**N**	**N**
Cancer Survivors	1,060	414	1,164	768
Other Adults	14,193	11,164	6,917	3,785
Percent with any use	%	%	%	%
Cancer survivors (1)	20.3	11.7	18.6	11.2
Other adults (2)	14.7	7.5	15.2	8.1
Unadjusted difference: (1)-(2) (SE)	5.6** (1.5)	4.2** (1.6)	3.4** (1.3)	3.1** (1.2)
Cancer-related difference	Means (SE)	Means (SE)	Means (SE)	Means (SE)
Matching without chronic Conditions	6.1** (1.1)	4.5** (1.7)	2.6** (1.1)	3.7** (1.3)
Matching with chronic Conditions	5.3** (1.2)	3.4** (1.7)	1.6 (1.2)	2.5** (1.2)
Mean number of purchases				
Cancer survivors (1)	2.6	1.4	2.0	1.0
Other adults (2)	1.9	0.9	1.7	0.8
Unadjusted difference: (1)-(2) (SE)	.7** (.3)	.5** (.3)	.3 (.2)	.2 (.1)
Cancer-related difference	Means (SE)	Means (SE)	Means (SE)	Means (SE)
Matching without chronic conditions	.7** (.3)	.6* (.3)	.1 (.2)	.3** (.2)
Matching with chronic conditions	.6** (.2)	.5 (.3)	−.1 (.2)	.3 (.2)

* Significantly different from 0 at p=0.10 level.

** Significantly different from 0 at p=0.05 level

Cancer-related difference= mean(cancer survivors) - mean(matched controls)