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Early Post-therapy Prescription Drug Usage among Childhood and Adolescent Cancer Survivors

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Abstract

Objective—To describe the patterns of prescription drug use among childhood and adolescent cancer survivors in the early post-therapy period as compared with matched peers without a cancer history.

Study design—Using the MarketScan commercial insurance claims database, we performed a retrospective cohort study identifying survivors of pediatric (0–21 years at diagnosis) leukemia, lymphoma, central nervous system (CNS), bone, or gonadal cancers who completed therapy from 2000–2011 and remained insured for three years post-therapy. Prescription fills during the first three years post-therapy were examined, categorized by drug class, and compared with age-, sex-, and region-matched individuals without cancer.

Results—We identified 1,414 survivors and 14,007 comparators. Compared with those without cancer, survivors had 1.5–4.5 times higher risk for filling opioids. Survivors of leukemia, lymphoma, CNS, and bone cancers had 2–5 times the risk for antidepressant and 3–7 times the risk for anxiolytic use. Survivors of leukemia, lymphoma, and bone tumors had 3–13 times the risk for angiotensin-converting enzyme (ACE) inhibitors by the third year post-therapy.

Conclusion—Compared with peers without cancer, childhood cancer survivors have higher rates of prescription use across many drug classes, suggesting higher medical morbidity. Survivors were more likely to use opioid, psychoactive, hormone, and cardiovascular medications. All general

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pediatricians and subspecialists should be aware of potentially emerging morbidities during the early post-therapy period to guide risk-based surveillance and survivorship care.

Keywords

Health insurance claims

Cancer remains the leading cause of disease-related death in children and adolescents[1], yet advancements in treatment have led to improved survival. The growing population of childhood cancer survivors in the United States will exceed 500,000 individuals by 2020.[2] However, improvements in survival have come with a cost. Because of cancer and its treatment, two-thirds of survivors will develop at least one chronic medical problem within 30 years of diagnosis.[3] Conditions such as cardiovascular disease, endocrinopathies, or psychiatric disorders[2–8] occur more commonly and often arise earlier among survivors, in comparison with the general population, leading to years of disability. It is important that pediatric providers are aware of these risks in order to provide optimal survivorship care.

Prescription drug use among childhood and adolescent cancer survivors can serve as an indicator for morbidity burden. Increased use of psychoactive medications[9–11] and treatments for risk factors of cardiovascular disease (antihypertensives, anti-hyperlipidemics, and antidiabetics)[12] have been reported. However, these studies focused on patients treated with older regimens,[9,10,12] primarily included patients who were more than 10 years from diagnosis,[9,10,12] and relied on patient report of medication use.[9,12] Building on these prior studies we sought to describe prescription drug use in the first three years post-therapy among cancer patients treated with contemporary regimens.

Using a commercial insurance claims database and an algorithm for cancer patient identification combining diagnosis and treatment codes,[13,14] we examined the patterns of prescription fills for all drug classes among survivors of childhood and adolescent leukemia, lymphoma, central nervous system (CNS) tumors, bone cancers, and gonadal cancers – five of the most common cancer types that span across this age group. We hypothesized that prescription drug usage is higher among survivors of childhood and adolescent cancers compared with age-, sex-, and region-matched children without a history of cancer. We sought to describe the class-specific patterns of use which may reflect chronic morbidities emerging in the early post-therapy period.

Methods

We identified children and adolescents (age ≤21 years at end of therapy [EOT]) treated for leukemia, lymphoma, CNS tumors, bone cancers, or gonadal cancers who completed therapy from January 1, 2000, to December 31, 2011, in the MarketScan Commercial Claims and Encounters Database.[15] This data source includes de-identified inpatient, outpatient, and pharmacy insurance claims data for over 50 million individuals and their dependents who are insured by commercial health plans in the United States. We identified children and adolescents with the aforementioned cancers using the Agency for Healthcare Research and Quality Clinical Classifications Software[16] matched to International Classification of Diseases, ninth revision codes for the diagnoses of interest (Table 1;

available at www.jpeds.com). These 5 cancer types were selected for inclusion as they represent 5 of the most common childhood and adolescent cancers and provide a study sample from across this population's developmental spectrum. Survivors were required to have at least 2 cancer-related visits. We further required that patients have claims for chemotherapy, surgery, or radiation therapy [Table 1]. EOT was defined as 30 days after the last observed treatment date. This included the date of the last inpatient or outpatient claim for chemotherapy or radiation therapy or the date at which an oral chemotherapy prescription would have concluded. We excluded patients with encounter diagnosis codes for two or more cancer types or who received a hematopoietic stem cell transplant. Patients were required to have three years of continuous health plan enrollment from EOT with no evidence of additional cancer treatment in order to provide a sufficient period of observation. Because data were available through 2015, subjects must have completed therapy before January 1, 2012, to allow for three years of observation. We selected comparators from children and adolescents in the database without claims for a cancer diagnosis at any time in which they were enrolled in the health plan. Comparators were individually matched for three-year continuous enrollment profile as determined by the matched survivor's end of treatment year, age, sex and geographic region. Separate comparator cohorts were created for each cancer type. Comparators were randomly sampled at approximately a 10:1 ratio.

The study design was reviewed by the University of North Carolina School of Medicine Institutional Review Board and classified as not human subjects research.

Measures

The primary study outcomes were (1) any prescription fill, by cancer type and year post-therapy and (2) drug class-specific use. Drug classes were defined using the Red Book classifications.17 The proportions of survivors and comparators with at least one fill per year post-therapy were determined. The number of fills of unique drug classes per person and the specific classes of these fills were also determined. Prescription fills among survivors were then categorized by therapeutic groups. Class-specific fills from the most commonly prescribed therapeutic groups among survivors (anti-infectives, CNS, hormonal, gastrointestinal, pulmonary, and cardiovascular agents) were compared with those among individuals without cancer.

Statistical Analyses

We compared the median number of prescriptions and unique drug classes filled by year between survivors and matched comparators using Wilcoxon rank-sum tests. The risk of class-specific prescription drug use by year for survivors and matched controls was estimated using unadjusted risk ratios and 95% confidence intervals. As a sensitivity analysis, risk ratios and 95% confidence intervals were determined using a Poisson regression model adjusting for age, sex, region, and year to account for residual confounding after matching. Minimal differences were noted between the unadjusted and adjusted risk ratios, so the unadjusted estimates are presented. Statistical analyses were performed using SAS Version 9.4 (Cary, North Carolina).

Results

Study sample

We identified 1,414 survivors of childhood cancers and 14,007 matched comparators (Figure 1; available at www.jpeds.com). Survivors of gonadal cancers (mean age 17.4 years [SD 3.4]) and lymphoma (15.6 years [SD 4.2]) were older than survivors of CNS tumors (10.1 years [SD 5.3]) and leukemia (9.3 years [SD 5.2]). There was a slight male predominance in the study sample (58%) with the highest sex differential among survivors of gonadal tumors (75% male). More patients were from the South and more were treated from 2009–2011, reflective of enrollment patterns for health plans included in the MarketScan database (Table 2).

Quantifying prescription fills among survivors and comparators

More survivors than comparators filled prescriptions. Across cancer types, 84–91% of survivors filled at least one prescription in the first year off therapy and this declined to 70–81% by the third year post-therapy. Approximately 60% of comparators filled at least one prescription per year. Throughout the study period, survivors were at 20–50% higher risk than comparators for having filled a prescription. This increase in prescription fills was present for survivors of all cancer types and across all three years of observation (Figure 2).

Additionally, survivors were more likely than comparators to fill prescriptions from multiple drug classes. Although survivors filled prescriptions from 4–8 drug classes per person in year 1, and 2–6 classes in years 2 and 3, comparators typically filled drugs in 1 class per year (Table 3). Survivors of CNS tumors filled prescriptions from the most drug classes (6–8 classes/person-year) and survivors of gonadal tumors filled prescriptions from the fewest number of classes (2–4 classes/person-year).

Nearly one-third of all prescriptions filled by survivors were for anti-infectives (antibacterials, antifungals, antivirals). Compared with individuals without a history of cancer, survivors of all cancer types were at increased risk for filling antibacterial prescriptions in all three years of the study period (Figure 3, A and Table 4 [available at www.jpeds.com]). Although approximately 40% of comparators filled an antibacterial prescription each year, 50–60% of survivors did so. Survivors of leukemia, lymphoma, and CNS tumors were also more likely to persistently fill antiviral and antifungal prescriptions (Table 4).

Nearly one-fourth of prescriptions filled by survivors were for CNS agents (opioids, antidepressants, anxiolytics, anticonvulsants). Fills for opioid pain medications were common among both survivors and comparators (12–46% of survivors and 7–13% of comparators) (Table 4). Versus comparators, risks for filling opioid prescriptions were 2.5 times higher for survivors of lymphoma (29 v 13%, RR 2.3 [95% CI 1.96–2.80]) to over 4 times higher for survivors of leukemia (31 v 7%, RR 4.3 [3.66–5.14]) during the first year off therapy. The risks declined with time but remained significantly higher among survivors even into the third year post therapy (Figure 3, B). Survivors were also at increased risk for receiving prescriptions of many psychoactive medications. Survivors experienced 2–5 times the risk for antidepressant use as comparators (leukemia: 6 v 2%, RR 3.0 [1.95–4.52];

lymphoma: 10 v 5%, RR 2.0 [1.43–2.83]; CNS 11 v 2% RR 5.3 [3.47–8.25]; bone 10 v 4%, RR 2.5 [1.48–4.07]; gonadal 12 v 6%, RR 1.9 [1.12–3.19] in year 1), a trend that persisted among survivors of leukemia, lymphoma, and CNS cancers through year 3 (Figure 3, C). A 2- to 7-fold increase in risk for anxiolytic use was observed among survivors of leukemia, lymphoma, CNS tumors, and bone cancers. Approximately 10% of CNS and bone tumor patients filled a prescription for an anxiolytic in year 3. Stimulant prescriptions were overall not increased among survivors. Only among CNS tumor survivors and in the third year post-therapy did an increased risk for receiving a stimulant reach statistical significance (9 v 5%, RR 1.6 [1.08–2.51] in year 3).

Among survivors 17% of prescription fills were for hormonal medications. Estrogen and progesterone containing agents were one of the most commonly filled classes among older female survivors and comparators (lymphoma 32 v 32%, RR 1.0 [0.79–1.28]; gonadal 31 v 27%, RR 1.2 [0.68–2.03] in year 3). However, an increased risk for these medications was noted among female survivors of CNS tumors (17 v 7%, RR 2.4 [1.52–3.66] in year 3). CNS survivors were also at twice the risk for receiving adrenal hormones (20 v 9%, RR 2.2 [1.69–2.88] in year 3). By year three, a higher percentage of male leukemia, lymphoma, CNS tumor, and gonadal cancer survivors received testosterone than matched comparators (Table 4). Additionally, fills of thyroid hormone prescriptions were higher among survivors of CNS tumors, bone cancers, lymphoma, and leukemia (Figure 3, C and Table 4) throughout the 3-year study period.

The risks for use of certain pulmonary and cardiovascular medications were also higher among survivors (Figure 3, E and F]. Notably, higher risks for inhaled bronchodilators were observed among survivors of leukemia and lymphoma beginning in the first post-therapy year and among survivors of gonadal tumors by the third year off therapy (leukemia 15 v 10%, RR 1.5 [1.20–1.91] in year 1; lymphoma 13 v 7%, RR 1.8 [1.33–2.36] in year 1; gonadal 10 v 6%, RR 1.8 [1.03–3.16] in year 3). In addition, between 2–3% of bone tumor survivors filled prescriptions for angiotensin-converting enzyme (ACE) inhibitors which represented over a10-fold increase in risk (3 v 0.2%, RR 13.3 [3.00–58.86] in year 3). Survivors of leukemia and lymphoma were also more likely to receive an ACE inhibitor with 3 to 8 times the risk of comparators (leukemia: 0.8 v 0.2%, RR 4.4 [1.36–14.23]; lymphoma: 1 v 0.4%, RR 3.3 [1.20–9.01] in year 3).

Discussion

We provide an objective assessment of prescription drug use for more than 1,400 childhood and adolescent cancer survivors and 14,000 matched comparators. We have shown that survivors fill significantly more prescriptions than general pediatric comparators, which we suggest may reflect their higher burden of medical morbidities due to cancer and its treatment. Survivors of all five cancer types considered in this study (leukemia, lymphoma, CNS tumors, bone cancers, and gonadal cancers) were at greater risk of filling prescriptions in the first three years following completion of therapy and filled prescriptions from more drug classes than comparators. Survivors were more likely to receive anti-infective, hormonal, cardiovascular, and pulmonary medications. Importantly, as the cancer patients in this study underwent treatment in the 2000s (many between 2009–2011), this pattern of

prescription drug use reflects the therapy-associated medical problems faced by childhood cancer survivors who have been treated with contemporary regimens.

Although a portion of these prescriptions were likely being used to treat or prevent acute post-therapy conditions (eg, infections), 2 observed patterns of prescription use suggest emerging chronic, treatment-related morbidities. First, the higher risk for many specific drug classes persists throughout all three years of the study period. Second, the risk associated with several classes of drugs appear to increase over time including thyroid hormone among survivors of leukemia and lymphoma; pituitary and gonadal hormones among survivors of CNS tumors; bronchodilators among survivors of gonadal tumors; and ACE inhibitors among survivors of lymphoma. These observations, coupled with prior reports of increased use of pain medications[9] and antihypertensives[12] among long-term survivors, suggest that we are observing the emergence of chronic medical morbidities in the early post-therapy period. This is further suggested by our prior observation that the leukemia and lymphoma survivors experienced increased rates of hospitalizations during this same time period as compared with matched controls.[18]

Our findings support those of prior studies demonstrating increased prescription use among survivors. Although these earlier studies have generally focused on psychoactive medications and long-term survivors, [9–11] our current work examined multiple drug classes and patients who have been treated with current regimens. Similar to previous reports,[10,11] we observed increased risks for use of antidepressants and anxiolytics for survivors of all cancer types. A prior study using the Childhood Cancer Survivor Study (CCSS) data comparing survivors to siblings did not observe an increased risk for antidepressant use among survivors; however, increased risks for anxiolytic, anticonvulsant, and opioid pain medications were noted.[9]

In our analysis, antidepressant use among comparators was consistent with the known age-appropriate prevalence of depression (3–4% in pre-pubertal and 6% in the post-pubertal).[19] The percent of survivors filling an antidepressant prescription was 2–4 times that of children without cancer. This increased risk persisted for antidepressant prescriptions among survivors of most cancer types into the third year post-therapy—a similar pattern to anxiolytic medication fills.

These findings underscore the importance for mental health screening among survivors even during the early post-therapy period. Nearly 10% of CNS and bone tumor survivors (patients often treated with highly complex and intense multi-modal regimens) continued to fill prescriptions for anxiolytics into the third year post-therapy; over 4 times the risk of comparators. It is possible that survivors experience higher rates of anxiety and depression as sequelae of more intensive therapy. Indeed, we observed an overall trend for increased risk of medication use among survivors of CNS and bone cancers compared with survivors of gonadal cancers. This may be the result of more intensive therapy among those treated for brain and bone cancers (often multimodal including surgery, chemotherapy, and radiation) versus those treated for gonadal cancers (frequently treated with surgery alone). However, as the exact indication for prescription use is not ascertainable with this data source, the

increased use of these drugs could also reflect other morbidities in these populations (eg, seizures in the CNS tumor survivors or neuropathic pain in the bone cancer survivors).

With increasing concern regarding opioid prescribing trends, we were particularly interested in understanding the patterns of opioid use with time from EOT. Consistent with reports from the CCSS,[9] cancer survivors in our analysis had an increased risk for receiving opioids in each year observed. In the third post-therapy year nearly 30% of bone cancer survivors, 20% of lymphoma and gonadal cancer survivors, and 10% of leukemia and CNS tumor survivors received an opioid medication in contrast to 7–13% of comparators. Our observed percentage of comparators with an opioid fill is higher than a previous report for children without cancer from the same time period that used data from the Medical Expenditure Panel Surveys. That study reported that annually 3% of a population-based sample of children and adolescents without cancer had filled an opioid prescription,[20] a lower rate that may be due to underestimation from survey data.

Nevertheless, these findings indicate that chronic pain remains a significant morbidity among survivors even three years off therapy. Interestingly, a prior survey-based study of adolescent survivors of childhood cancers reported that survivors were less likely than peers to use alcohol, tobacco, and illicit drugs except for the non-medical use of pain relievers. Survivors within 5 years of diagnosis were the most likely to participate in such use.[21] In light of these findings, with time from completion of therapy, it may be important for providers to consider methods other than opioids for treatment of chronic pain in this population.

Our findings must be interpreted in the context of certain limitations. The indication for medication use is not assessable through insurance claims data, yet an understanding of likely indication for use can be inferred by examining cancer-specific (and thus therapy-specific) patterns of use. This is particularly an issue during the *first year post therapy* when prescriptions for medications such as anti-infectives, pain medications, and anxiolytics may reflect ongoing prophylaxis or use in planned off-therapy procedures (line removal). However, the use of drugs from many classes (antihypertensives, thyroid hormone, and antidepressants) is increased among survivors in the first year off therapy and the increased use of anti-infectives, pain medications, and anxiolytics persist into the third year post-therapy. Additionally, providers may be biased in prescribing more medications to cancer survivors (antibiotics, pain medications), or cancer survivors are prescribed more medications simply due to higher engagement with the healthcare system. Althoguh we are unable to clarify this, and likely no study would be able, the fact remains that survivors fill more prescriptions than their peers and the increased burden of healthcare use is clear.

Our data source could be limited in identifying the EOT for certain subsets of patients. For instance, a patient who transitioned to palliative therapy from active therapy may have been misclassified as a survivor. Among these patients, opioids may have been used for palliation of ongoing cancer symptoms as opposed to the treatment of therapy-related comorbidities. A lthough this is possible, it would be a rare and unlikely event as few childhood and adolescent cancer patients would survive for three years with palliative care alone and no further salvage therapy. Restricting our analysis to survivors with three years of continuous

enrollment following the EOT limits the size of the study sample; however, that restriction allows us to say with confidence that survivors identified for this study did not have subsequent claims for chemotherapy, radiation therapy, or surgery that would be associated with active treatment. Although death is not recorded in claims, our requirement that individuals be continuously enrolled during the three years following EOT should exclude those who died during the follow-up period. Last, our study sample is restricted to privately insured children, and prescription drug use among children without insurance or with other sources of insurance may differ. However, prior work has shown increased odds for prescription fills among survivors whose family income is less than $20,000[9] suggesting that survivors with publicly funded insurance are more likely to fill prescriptions than those with private insurance. Therefore, our estimates may be conservative.

Overall, our findings demonstrate increased prescription drug use among childhood and adolescent cancer survivors and suggest the emergence of chronic medical morbidities in the early post-therapy period. As cancer treatment regimens evolve and the number of survivors continues to increase, up-to-date assessments of treatment-associated morbidities will be necessary to provide optimal risk-based survivorship care. General pediatricians and subspecialists alike must be aware of the significant psychiatric and medical morbidities faced by cancer survivors even during the early-post therapy period, a period of significant transition with potential for missed opportunities in care.

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Abbreviations

CNS	central nervous system
ACE	angiotensin converting
enzyme EOT	end of treatment
SD	standard deviation
RR	risk ratio
CI	confidence interval
IQR	inter-quartile range
CCSS	Childhood Cancer Survivor Study

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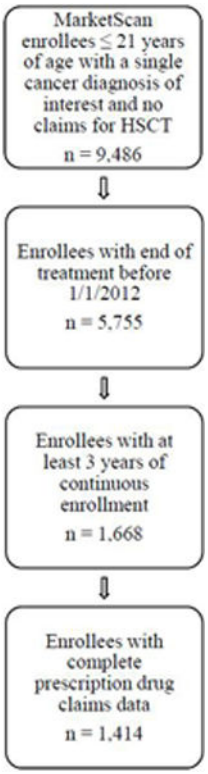

Figure 1.
Selection of cancer survivor cohort. HSCT: hematopoietic stem cell transplant

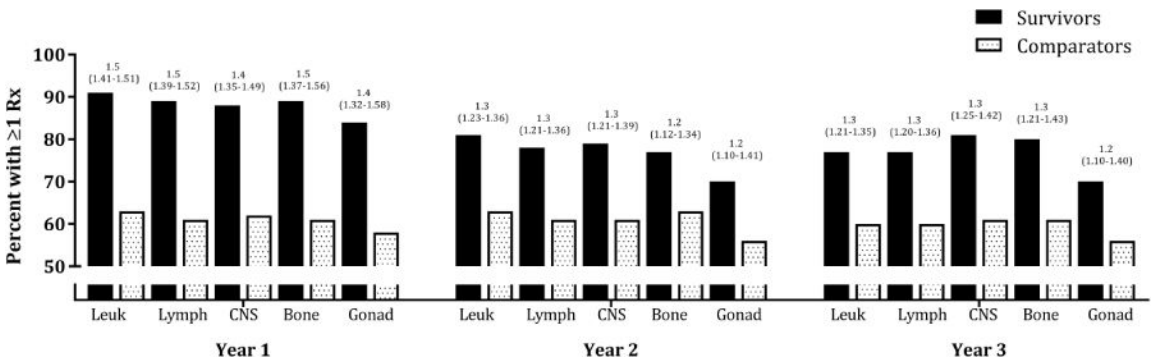

Figure 2.

Proportion of survivors and comparators with ≥ 1 prescription fill by survivor-defined post-therapy year. Risk ratios (95%CIs) compare each survivor-comparator pair. Rx: prescription, Leuk: leukemia, Lymph: Lymphoma, CNS: central nervous system

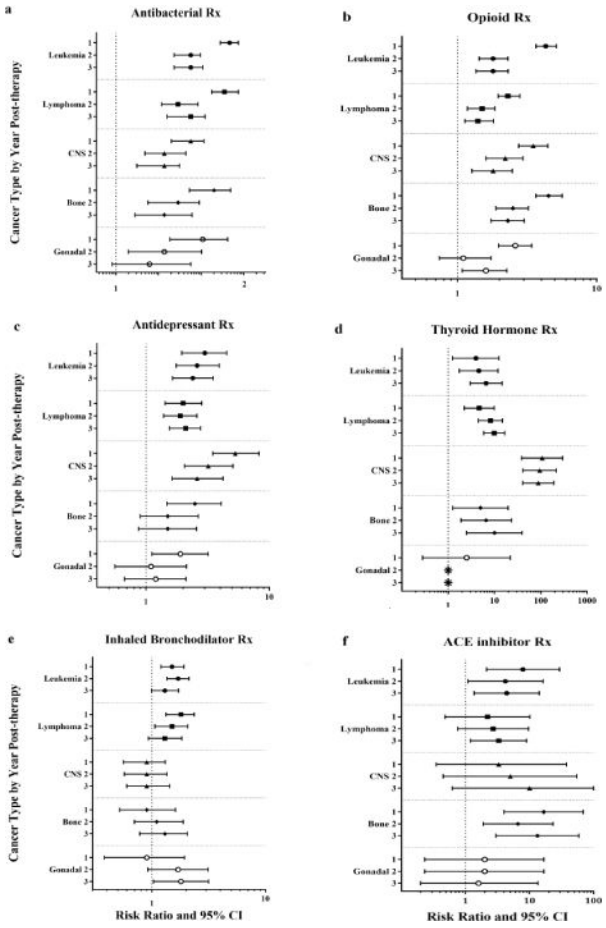

Figure 3.

Unadjusted risk ratios (95% confidence intervals) for class-specific prescription fills among survivors versus comparators by year post-therapy. * Unable to calculate, Rx: prescription, CNS: central nervous system, ACE: angiotensin-converting enzyme

Table 1

Clinical classification codes for cancer diagnoses of interest. Chemotherapy, radiation therapy, and surgical billing codes for cancer treatment.

AHRQ Clinical Classifications Software Codes for Cancer Diagnoses of Interest	
39	Leukemia
37,38	Lymphoma
35	Central nervous system (CNS) cancers
21	Bone cancers
27,30	Gonadal cancers
Health Care Common Procedure Coding System Chemotherapy Codes	
6-Mercaptopurine	S0108
Alemtuzumab	J9010
Andelsleukin	J9015
Arsenic	J9017
Asparaginase	J9019, J9020, J9266, C9289
Azacitidine	J9025
Belinostat	J9032, C9442
Bevacizumab	J9035, C9257
Bleomycin	J9040
Blinatumomab	J9039, C9449
Bortezomib	J9041
Brentuximab	J9042, C9287
Busulfan	C1178, J0594, J8510
Carboplatin	J9045
Carmustine	J9050, C9437
Chlorambucil	S0172
Cisplatin	J9060
Cladribine	J9065
Clofarabine	J9027
Crizotinib	J8999
Cyclophosphamide	J8530, J9070, J9080, J9090, J9091, J9092, J9093, J9094, J9095, J9096, J9097
Cytarabine (IT/IV)	J9098, J9100, J9110
Dacarbazine	J9130, J9140
Dactinomycin	J9120
Dasatinib	J8999
Daunorubicin	J9150, J9151
Decitabine	J0894
Dexamethasone (po)	J8540
Docetaxel	J9171
Doxorubicin	Q2048, Q2049, Q2050, J9000, J9001, J9002
Epirubicin	J9178
Eribulin	J9179, C9280

AHRQ Clinical Classifications Software Codes for Cancer Diagnoses of Interest	
Etoposide	J8560, J9181, J9182
Everolimus	J8561
Fludarabine	J8562, J9185
Fluorouracil	J9190
Gemcitabine	J9201
Gemtuzumab	J9300
GM-CSF	J2820
Idarubicin	J9211
Ifosfamide	J9208
IL-2	J9015
Imatinib	S0088
Irinotecan	J9206
Lomustine	S0178
Mechlorethamine	J9230
Melphalan	J8600, J9245
Methotrexate (IV)	J9250, J9260
Methotrexate (po)	J8610
Mitoxantrone	J9293
Nelarabine	J9261
Neulasta	J2505
Neupogen	J1440, J1441
Nilotinib	J8999
Oxaliplatin	J9263
Paclitaxel	J9264, J9265, J9267
Prednisone	J7506
Procarbazine	S0182
Rituximab	J9310
Sorafenib	J8999
Streptozocin	J9320
Temozolomide	J8700, J9328, C9253
Temsirolimus	J9330
Teniposide	Q2017
Thiotepa	J9340
Topotecan	J8705, J9351
Vinblastine	J9360
Vincristine	J9370, J9375, J9380
Vinorelbine	J9390
Current Procedural Terminology (CPT) Radiation Therapy Codes	
77280	Therapeutic radiology simulation-aided field setting; simple
77285	Therapeutic radiology simulation-aided field setting; intermediate
77290	Therapeutic radiology simulation-aided field setting; complex
77295	Three-dimensional radiotherapy plan

AHRQ Clinical Classifications Software Codes for Cancer Diagnoses of Interest	
77372	Under Stereotactic Radiation Treatment Delivery
77373	Stereotactic body radiation therapy, treatment delivery
77401	Radiation treatment delivery, superficial and/or ortho voltage, per day
77402	Radiation treatment delivery, 1 area, ≤5 MeV; simple
77403	Radiation treatment delivery, 1 area, 6–10 MeV; simple
77404	Radiation treatment delivery, 1 area, 11–19 MeV; simple
77406	Radiation treatment delivery, 1 area, ≥ 20 MeV; simple
77407	Radiation treatment delivery, 2 areas ≤5 MeV; intermediate
77408	Radiation treatment delivery, 2 areas, 6–10 MeV; intermediate
77409	Radiation treatment delivery, 2 areas, 11–19 MeV; intermediate
77411	Radiation treatment delivery, 2 areas, ≥ 20 MeV; intermediate
77412	Radiation treatment delivery, ≥ 3 areas, ≤5 MeV; complex
77413	Radiation treatment delivery, ≥ 3 areas, 6–10 MeV; complex
77414	Radiation treatment delivery, ≥ 3 areas, 11–19 MeV; complex
77416	Radiation treatment delivery, ≥ 3 areas, ≥ 20 MeV; complex
77421	Stereoscopic x-ray guidance for delivery of radiation therapy
77435	Stereotactic body radiation management
Current Procedural Terminology (CPT) Surgical Codes	
19260	Excision of chest wall tumor including ribs
19271	Excision of chest wall tumor involving ribs, w plastic reconstruction; w/o med lad
19272	Excision of chest wall tumor involving ribs, w plastic reconstruction; w med lad
21011	Excision, tumor, soft tissue of face or scalp, subcutaneous; less than 2 cm
21012	Excision, tumor, soft tissue of face or scalp, subcutaneous; 2 cm or greater
21013	Excision, tumor, soft tissue of face and scalp, subfascial; less than 2 cm
21014	Excision, tumor, soft tissue of face or scalp, subfascial; 2 cm or greater
21015	Radical resection of tumor (eg, sarcoma), soft tissue of face or scalp; less than 2 cm
21016	Radical resection of tumor (eg, sarcoma), soft tissue of face or scalp; 2 cm or greater
21029	Removal by contouring of benign tumor of facial bone
21034	Excision of malignant tumor of maxilla or zygoma
21044	Excision of malignant tumor of the mandible
21045	Excision of malignant tumor of the mandible; radical resection
21552	Excision, tumor, soft tissue of neck or anterior thorax, subcutaneous; 3 cm or greater
21554	Excision, tumor, soft tissue of neck or anterior thorax, subfascial; 5 cm or greater
21555	Excision, tumor, soft tissue of neck or anterior thorax, subcutaneous; less than 3 cm
21556	Excision, tumor, soft tissue of neck or anterior thorax, subfascial; less than 5 cm
21557	Radical resection of tumor soft tissue of neck or anterior thorax; less than 5 cm

AHRQ Clinical Classifications Software Codes for Cancer Diagnoses of Interest	
21558	Radical resection of tumor soft tissue of neck or anterior thorax; 5 cm or greater
21930	Excision, tumor, soft tissue of back or flank, subcutaneous; less than 3 cm
21931	Excision, tumor, soft tissue of back or flank, subcutaneous; 3 cm or greater
21932	Excision, tumor, soft tissue of back or flank, subfascial; less than 5 cm
21933	Excision, tumor, soft tissue of back or flank, subfascial; 5 cm or greater
21935	Radical resection of tumor, soft tissue of back or flank; less than 5 cm
21936	Radical resection of tumor, soft tissue of back or flank; 5 cm or greater 22900
Excision, tumor, soft tissue of abdominal wall, subfascial; less than 5 cm 22901	
Excision, tumor, soft tissue of abdominal wall, subfascial; 5 cm or greater 22902	
Excision, tumor, soft tissue of abdominal wall, subcutaneous; less than 3 cm 22903	
Excision, tumor, soft tissue of abdominal wall, subcutaneous; 3 cm or greater 22904	
Radical resection of tumor, soft tissue of abdominal wall; less than 5 cm 22905	
Radical resection of tumor, soft tissue of abdominal wall; 5 cm or greater 23071	
Excision, tumor, soft tissue of shoulder area, subcutaneous; 3 cm or greater 23073	
Excision, tumor, soft tissue of shoulder area, subfascial; 5 cm or greater 23075	
Excision, tumor, soft tissue of shoulder area, subcutaneous; less than 3 cm 23076	
Excision, tumor, soft tissue of shoulder area, subfascial; less than 5 cm	
23077	Radical resection of tumor, soft tissue of shoulder area, subfascial; less than 5 cm
23078	Radical resection of tumor, soft tissue of shoulder area, subfascial; 5 cm or greater
23200	Radical resection of tumor, clavicle
23210	Radical resection of tumor, scapula
23220	Radical resection of tumor, proximal humerus
24071	Excision, tumor, soft tissue of upper arm or elbow area, subcutaneous; 3 cm or greater
24073	Excision, tumor, soft tissue of upper arm or elbow area, subfascial; 5 cm or greater
24075	Excision, tumor, soft tissue of upper arm or elbow area, subcutaneous; less than 3 cm
24076	Excision, tumor, soft tissue of upper arm or elbow area, subfascial; less than 5 cm
24077	Radical resection of tumor, soft tissue of upper arm or elbow area; less than 5 cm
24079	Radical resection of tumor, soft tissue of upper arm or elbow area; 5 cm or greater
24150	Radical resection of tumor, shaft or distal humerus
24152	Radical resection of tumor, radial head or neck
24900	Amputation, arm through humerus; with primary closure
24920	Amputation, arm through humerus; open, circular (guillotine)
24930	Amputation, arm through humerus; re-amputation
24931	Amputation, arm through humerus; with implant
25900	Amputation, forearm, through radius and ulna
25909	Amputation, forearm, through radius and ulna; re-amputation
25927	Transmetacarpal amputation

AHRQ Clinical Classifications Software Codes for Cancer Diagnoses of Interest	
27590	Amputation, thigh, through femur
27592	Amputation, thigh, through femur; open, circular (guillotine)
27880	Amputation leg, through tibia and fibula
27882	Amputation leg, through tibia and fibula; open, circular (guillotine)
28800	Amputation, foot; midtarsal (eg, Chopart type procedure)
28805	Amputation, foot; transmetatarsal
28810	Amputation, metatarsal; with toe, single
28820	Amputation, toe; metatarsophalangeal joint
28825	Amputation, toe; interphalangeal joint
25071	Excision, tumor, soft tissue of forearm/wrist area, subcutaneous; 3 cm or greater
25073	Excision, tumor, soft tissue of forearm/wrist area, subfascial; 3 cm or greater
25075	Excision, tumor, soft tissue of forearm/wrist area, subcutaneous; less than 3 cm
25076	Excision, tumor, soft tissue of forearm/wrist area, subfascial; less than 3 cm
25077	Radical resection of tumor, soft tissue of forearm/wrist area, subcut; less than 3 cm
25170	Radical resection of tumor, radius or ulna
26117	Radical resection of tumor, soft tissue of hand or finger; less than 3 cm
26250	Radical resection of tumor, metacarpal
26260	Radical resection of tumor, proximal or middle phalanx of finger
26262	Radical resection of tumor, distal phalanx of finger
27043	Excision, tumor, soft tissue of pelvis and hip area, subcutaneous; 3 cm or greater
27045	Excision, tumor, soft tissue of pelvis and hip area, subfascial; 5 cm or greater
27047	Excision, tumor, soft tissue of pelvis and hip area, subcutaneous; less than 3 cm
27048	Excision, tumor, soft tissue of pelvis and hip area, subfascial; less than 5 cm
27049	Radical resection of tumor, soft tissue of pelvis and hip area; less than 5 cm
27059	Radical resection of tumor, soft tissue of pelvis and hip area; 5 cm or greater
27075	Radical resection of tumor; wing of ilium, 1 pubic or ischial ramus or symphysis pubis
27076	Radical resection of tumor; ilium, both pubic rami, or ischium and acetabulum
27077	Radical resection of tumor; innominate bone, total
27078	Radical resection of tumor; ischial tuberosity and greater trochanter of femur
27327	Excision, tumor, soft tissue of thigh or knee area, subcutaneous; less than 3 cm
27328	Excision, tumor, soft tissue of thigh or knee area, subfascial; less than 5 cm
27329	Radical resection of tumor, soft tissue of thigh or knee area; less than 5 cm
27337	Excision, tumor, soft tissue of thigh or knee area, subcutaneous; 3 cm or greater
27339	Excision, tumor, soft tissue of thigh or knee area, subfascial; 5 cm or greater
27364	Radical resection of tumor, soft tissue of thigh or knee area; 5 cm or greater
27365	Radical resection of tumor; femur or knee
27615	Radical resection of tumor, soft tissue of leg or ankle area; less than 5 cm

AHRQ Clinical Classifications Software Codes for Cancer Diagnoses of Interest	
27618	Excision, tumor, soft tissue of leg or ankle area, subcutaneous; less than 3 cm
27619	Excision, tumor, soft tissue of leg or ankle area, subfascial; less than 5 cm
27632	Excision, tumor, soft tissue of leg or ankle area, subcutaneous; 3 cm or greater
27634	Excision, tumor, soft tissue of leg or ankle area, subfascial; 5 cm or greater
27635	Excision or curettage of bone cyst or benign tumor, tibia or fibula
27637	Excision or curettage of bone cyst or benign tumor, tibia or fibula with autograft
27638	Excision or curettage of bone cyst or benign tumor, tibia or fibula with allograft
27645	Radical resection of tumor; tibia
27646	Radical resection of tumor; fibula
27647	Radical resection of tumor; talus or calcaneus
28039	Excision, tumor, soft tissue of foot or toe, subcutaneous; 1.5 cm or greater
28041	Excision, tumor, soft tissue of foot or toe, subfascial; 1.5 cm or greater
28043	Excision, tumor, soft tissue of foot or toe, subcutaneous; less than 1.5 cm
28045	Excision, tumor, soft tissue of foot or toe, subfascial; less than 1.5 cm
28046	Radical resection of tumor, soft tissue of foot or toe; less than 3 cm
28047	Radical resection of tumor, soft tissue of foot or toe; 3 cm or greater
28171	Radical resection of tumor, tarsal
28173	Radical resection of tumor, metatarsal
28175	Radical resection of tumor, phalanx of toe
31300	Laryngotomy; with removal of tumor or laryngocele, cordectomy
31640	Bronchoscopy, rigid or flexible, including fluoroscopic guidance; with tumor excision
31785	Excision of tracheal tumor or carcinoma; cervical
31786	Excision of tracheal tumor or carcinoma; thoracic
32503	Resection of apical lung tumor, including chest wall resection, w/o reconstruction
32504	Resection of apical lung tumor, including chest wall resection, w/ reconstruction
32661	Thoracoscopy, surgical; with excision of pericardial cyst, tumor, or mass
32662	Thoracoscopy, surgical; with excision of mediastinal cyst, tumor, or mass
33050	Resection of pericardial cyst or tumor
33130	Resection of mediastinal cyst or tumor
38505	Lymph node needle biopsy/excision – superficial
38510	Open lymph node biopsy/excision – cervical
38520	Open lymph node biopsy/excision - cervical deep
38525	Open lymph node biopsy/excision - axillary deep
38530	Open lymph node biopsy/excision - internal mammary
38564	Limited lymphadenectomy - retroperitoneal, aortic, splenic
38562	Limited lymphadenectomy - pelvic, para-aortic
38700	Suprahyoid lymphadenectomy
38720	Cervical lymphadenectomy
38724	Cervical lymphadenectomy – modified

AHRQ Clinical Classifications Software Codes for Cancer Diagnoses of Interest	
38740	Axillary lymphadenectomy – superficial
38745	Axillary lymphadenectomy – complete
38746	Throacotomy with mediastinal and regional lymphadenectomy
38747	Abdominal lymphadenectomy - celiac, gastric, portal, peripancreatic
38760	Inguinofemoral lymphadenectomy – superficial
38765	Inguinofemoral lymphadenectomy with pelvic lymphadenectomy
38770	Pelvic lymphadenectomy
38780	Retroperitoneal total abdominal lymphadenectomy
39220	Tumor Resection
43611	Tumor Resection
54520	Testicular Resection
54522	Testicular Resection
54530	Testicular Resection
54535	Testicular Resection
54690	Testicular Resection
58720	Oophorectomy
58940	Oophorectomy
58943	Oophorectomy
61500	Craniectomy with tumor excision
61510	Craniectomy with tumor excision
61518	Craniectomy with tumor excision
61546	Craniectomy with tumor excision
69970	Craniectomy with tumor excision
78800	Retroperitoneal Tumor Removal
78801	Retroperitoneal Tumor Removal
78802	Retroperitoneal Tumor Remova

Table 2

Survivor and comparator characteristics

Patient Characteristics		Leukemia		Lymphoma		CNS		Bone		Gonadal	
		Surv n=474	Comp n=4690	Surv n=374	Comp n=3695	Surv n=269	Comp n=2678	Surv n=168	Comp n=1674	Surv n=129	Comp n=1270
Age	Mean	9.3	9.3	15.6	15.6	10.1	10.1	13.4	13.4	17.4	17.4
	(SD)	(5.15)	(5.15)	(4.18)	(4.18)	(5.31)	(5.30)	(5.19)	(5.18)	(3.41)	(3.39)
Sex (%)	Male	54	54	59	59	54	54	62	62	75	75
	Female	46	46	41	41	46	46	38	38	25	25
Region (%)	Northeast	16	16	10	10	11	11	13	13	14	14
	South	40	40	36	36	38	38	31	31	35	35
	Midwest	24	24	30	30	35	35	24	24	33	33
	West	20	20	24	24	16	16	31	31	18	18
Year of EOT (%)	2000–2002	5	5	4	4	8	8	8	8	7	7
	2003–2005	19	19	19	19	17	17	22	22	18	18
	2006–2008	28	28	27	27	27	27	32	32	24	24
	2009–2011	48	48	50	50	48	48	38	38	51	51

Surv: survivors, Comp: comparators, CNS: central nervous system, SD: standard deviation, EOT: end of treatment

Table 3

Median number of unique prescription classes per person

	n	Year 1 Median # Rx (IQR)^	Year 2 Median # Rx (IQR)^	Year 3 Median # Rx (IQR)^
Leukemia	474	7 (3–15)	3.5 (1–10)	3 (1–9)
Comparators	4690	1 (0–4)	1 (0–4)	1 (0–4)
Lymphoma	374	5 (2–11)	4 (1–9)	3 (1–9)
Comparators	3695	1 (0–5)	1 (0–5)	1 (0–5)
CNS Cancers	269	8 (2–22)	6 (1–15)	6 (1–16)
Comparators	2678	1 (0–4)	1 (0–4)	1 (0–4)
Bone Cancers	168	7 (3–15)	3 (1–9)	4 (1–9)
Comparators	1674	1 (0–5)	1 (0–5)	1 (0–5)
Gonadal Cancers	129	4 (1–10)	2 (0–7)	2 (0–7)
Comparators	1270	1 (0–4)	1 (0–5)	1 (0–5)

^Median # of Rx determined as the number of unique class prescriptions per individual for the specified time period among all individuals. All comparisons made using Wilcoxon rank-sum tests with $p<0.01$. Rx: prescription, IQR: interquartile range, CNS: central nervous system

Table 4

Unadjusted risks, risk ratios (RR), and 95% confidence intervals for class-specific prescription fills by cancer type and year post-therapy. Red items indicate a statistically significant increase in risk for fills among survivors versus comparators.

	Anti-infectives														
	% Surv	% Comp	RR (95%CI)	% Surv	% Comp	RR (95%CI)	% Surv	% Comp	RR (95%CI)	% Surv	% Comp	RR (95%CI)	% Surv	% Comp	RR (95%CI)
	Leukemia			Lymphoma			CNS			Bone			Gonadal		
Antibacterial															
Year 1	85	46		74	41		70	47		71	43		60	38	
Year 2	66	45		56	39		58	44		59	43		47	36	
Year 3	62	42		54	37		55	44		53	41		43	36	1.2 (0.98–1.50)
Antiviral															
Year 1	15	3		11	3		9	3		7	2		5	1	
Year 2	11	3		6	3		6	3		4	3	1.3 (0.55–2.93)	3	2	1.3 (0.47–3.67)
Year 3	8	3		4	3	1.6 (0.93–2.62)	5	3		2	3	0.9 (0.32–2.38)	3	2	1.4 (0.48–3.80)
Antifungal															
Year 1	19	3		10	3		12	3		11	3		9	4	
Year 2	7	3		7	4		5	3		4	4	1.0 (0.44–2.31)	4	3	1.1 (0.45–2.77)
Year 3	6	3		5	5	1.1 (0.69–1.73)	6	3		5	4	1.2 (0.63–2.41)	5	4	1.3 (0.55–2.88)
	Central Nervous System Agents														
	% Surv	% Comp	RR (95%CI)	% Surv	% Comp	RR (95%CI)	% Surv	% Comp	RR (95%CI)	% Surv	% Comp	RR (95%CI)	% Surv	% Comp	RR (95%CI)
	Leukemia			Lymphoma			CNS			Bone			Gonadal		
Anticonvulsants															
Year 1	6	1		4	2		16	0.9		10	1		5	2	
Year 2	4	1		2	2	0.9 (0.45–1.90)	10	1		7	2		2	3	0.9 (0.29–2.97)
Year 3	3	1		4	3	1.4 (0.78–2.35)	9	1		5	2		5	2	
Antidepressants															
Year 1	6	2		10	5		11	2		10	4		12	6	
Year 2	6	2		11	6		9	3		8	5	1.5 (0.90–2.66)	7	6	1.1 (0.56–2.13)
Year 3	7	3		13	6		7	3		8	6	1.5 (0.87–2.57)	9	8	1.2 (0.67–2.11)
Anxiolytics															
Year 1	8	2		9	3		16	2		15	3		13	3	

	Anti-infectives																	
	% Surv	% Comp	RR (95%CI)	% Surv	% Comp	RR (95%CI)	% Surv	% Comp	RR (95%CI)	% Surv	% Comp	RR (95%CI)	% Surv	% Comp	RR (95%CI)	% Surv	% Comp	RR (95%CI)
	Leukemia			Lymphoma			CNS			Bone			Gonadal					
Year 2	5	2		7	3		10	2		8	3		5	3	2.1 (0.94–4.63)			
Year 3	3	2	1.6 (0.95–2.79)	7	4		9	2		10	2		6	4	1.5 (0.75–3.18)			
	Stimulants																	
Year 1	3	4	0.6 (0.32–1.01)	5	5	1.0 (0.63–1.75)	5	5	1.0 (0.57–1.72)	5	6	0.8 (0.40–1.64)	4	5	0.8 (0.33–1.97)			
Year 2	4	5	0.8 (0.51–1.28)	6	5	1.1 (0.74–1.78)	6	5	1.2 (0.72–1.98)	4	6	0.7 (0.35–1.56)	5	5	0.9 (0.39–1.99)			
Year 3	5	6	0.9 (0.62–1.37)	5	5	1.1 (0.70–1.71)	9	5		6	5	1.1 (0.58–2.04)	4	5	0.8 (0.33–1.97)			
	Antipsychotics/Antimanics																	
Year 1	0	0.7	**	2	1	1.3 (0.59–2.79)	3	0.7		0	1	**	2	1	1.1 (0.26–4.66)			
Year 2	0.6	0.8	0.8 (0.26–2.67)	2	1	1.7 (0.87–3.51)	1	0.8	1.4 (0.41–4.51)	0	1	**	2	2	1.0 (0.23–4.02)			
Year 3	1	0.8	1.3 (0.50–3.20)	2	1	1.4 (0.63–3.03)	1	0.9	1.2 (0.36–3.93)	1	1	0.8 (0.19–3.34)	2	2	1.0 (0.24–4.40)			
	Opioids																	
Year 1	31	7		29	13		26	8		46	10		35	13				
Year 2	15	8		19	13		16	7		30	12		15	14	1.1 (0.74–1.74)			
Year 3	12	7		18	12		13	8		28	12		20	13				
	Non-Steroidal Anti-inflammatory Medications (NSAIDS)																	
Year 1	5	3		6	8	0.8 (0.51–1.19)	4	3	1.1 (0.60–2.15)	7	6	1.3 (0.71–2.27)	15	8				
Year 2	5	3		7	7	1.0 (0.69–1.45)	4	4	0.9 (0.47–1.65)	8	8	1.1 (0.63–1.82)	6	7	0.8 (0.42–1.70)			
Year 3	5	4	1.4 (0.89–2.07)	10	8	1.2 (0.89–1.68)	5	4	1.3 (0.74–2.20)	10	7	1.3 (0.79–2.13)	9	8	1.1 (0.60–1.99)			
	Hormonal Agents																	
	% Surv	% Comp	RR (95%CI)	% Surv	% Comp	RR (95%CI)	% Surv	% Comp	RR (95%CI)	% Surv	% Comp	RR (95%CI)	% Surv	% Comp	RR (95%CI)			
	Leukemia			Lymphoma			CNS			Bone			Gonadal					
	Thyroid Hormones																	
Year 1	0.8	0.2		3	0.6		16	0.1		2	0.4		0.8	0.3	2.5 (0.28–21.86)			
Year 2	1	0.3		5	0.6		21	0.2		2	0.4		0	0.2	**			
Year 3	2	0.3		7	0.7		23	0.3		2	0.2		0	0.2	**			
	Adrenal Hormones																	
Year 1	18	9		13	9		22	10		8	9	0.8 (0.48–1.43)	15	8				
Year 2	16	10		11	9	1.2 (0.90–1.67)	23	10		8	9	0.9 (0.53–1.52)	9	6	1.5 (0.82–2.60)			

	Anti-infectives																	
	% Surv	% Comp	RR (95%CI)	% Surv	% Comp	RR (95%CI)	% Surv	% Comp	RR (95%CI)	% Surv	% Comp	RR (95%CI)	% Surv	% Comp	RR (95%CI)	% Surv	% Comp	RR (95%CI)
	Leukemia			Lymphoma			CNS			Bone			Gonadal					
Year 3	13	9		9	9	1.1 (0.78–1.52)	20	9		13	9	1.4 (0.91–2.09)	12	8	1.5 (0.92–2.48)			
Pituitary Hormones																		
Year 1	0.2	0.4	0.5 (0.07–3.88)	0	0.2	**	10	0.5		0	0.2	**	0	0.2	**			
Year 2	0.8	0.3	2.6 (0.88–7.92)	0.3	0.3	0.8 (0.11–6.31)	16	0.5		0.6	0.2	3.3 (0.35–31.75)	0	0.08	**			
Year 3	1	0.3		0.3	0.3	1.0 (0.13–7.70)	20	0.5		0.6	0.2	2.5 (0.28–22.16)	0	0.08	**			
Testosterone[†]																		
Year 1	0.4	0.04	9.9 (0.62–157.51)	0.4	0.1	4.9 (0.45–54.05)	2	0.07		0	0.2	**	1	0	**			
Year 2	1	0.1		0.9	0.1		4	0.07		0	0.1	**	1	0.1	9.9 (0.62–156.49)			
Year 3	2	0.2		1	0.1		5	0	**	0	0.1	**	3	0	**			
Estrogens/Progesterone[^]																		
Year 1	6	6	1.0 (0.60–1.75)	27	24	1.1 (0.86–1.49)	7	5	1.4 (0.74–2.85)	12	13	1.0 (0.49–1.92)	28	15	1.9 (1.03–3.54)			
Year 2	7	7	1.0 (0.58–1.61)	34	28	1.2 (0.96–1.53)	13	7		9	17	0.6 (0.25–1.20)	19	25	0.7 (0.35–1.57)			
Year 3	9	8	1.0 (0.66–1.63)	32	32	1.0 (0.79–1.28)	17	7		17	19	0.9 (0.51–1.57)	31	27	1.2 (0.68–2.03)			
Antidiabetics																		
Year 1	0.2	0.3	0.6 (0.08–4.65)	1	0.7	1.5 (0.53–4.33)	0.4	0.2	2.0 (0.23–16.98)	0.6	0.4	1.7 (0.20–13.71)	0	0.5	**			
Year 2	0.2	0.4	0.6 (0.08–4.36)	1	0.8	1.7 (0.66–4.37)	0.4	0.3	1.4 (0.18–11.52)	0.6	0.3	2.0 (0.23–16.96)	0.8	0.3	2.5 (0.28–21.86)			
Year 3	0.4	0.4	1.1 (0.26–4.72)	1	1	1.3 (0.51–3.28)	1	0.3	3.3 (0.90–12.18)	0.6	0.5	1.2 (0.16–9.90)	0.8	0.3	2.5 (0.28–21.86)			
Pulmonary Agents																		
	% Surv	% Comp	RR (95%CI)	% Surv	% Comp	RR (95%CI)	% Surv	% Comp	RR (95%CI)	% Surv	% Comp	RR (95%CI)	% Surv	% Comp	RR (95%CI)			
	Leukemia			Lymphoma			CNS			Bone			Gonadal					
Bronchodilators																		
Year 1	15	10		13	7		8	9	0.9 (0.56–1.31)	7	8	0.9 (0.52–1.61)	5	5	0.9 (0.38–1.93)			
Year 2	16	9		10	6		8	9	0.9 (0.57–1.35)	10	8	1.1 (0.70–1.88)	9	5	1.7 (0.92–3.13)			
Year 3	11	9	1.3 (0.99–1.71)	9	7	1.3 (0.93–1.83)	8	8	0.9 (0.60–1.43)	10	8	1.3 (0.78–2.04)	10	6				
Gastrointestinal Agents																		
	% Surv	% Comp	RR (95%CI)	% Surv	% Comp	RR (95%CI)	% Surv	% Comp	RR (95%CI)	% Surv	% Comp	RR (95%CI)	% Surv	% Comp	RR (95%CI)			

	Anti-infectives																	
	% Surv	% Comp	RR (95%CI)	% Surv	% Comp	RR (95%CI)	% Surv	% Comp	RR (95%CI)	% Surv	% Comp	RR (95%CI)	% Surv	% Comp	RR (95%CI)	% Surv	% Comp	RR (95%CI)
	Leukemia			Lymphoma			CNS			Bone			Gonadal		
	Leukemia			Lymphoma			CNS			Bone			Gonadal		
Antiemetics																		
Year 1	12	1		10	2		22	0.8		20	1		11	0.9				
Year 2	6	2		4	2		7	1		7	2		6	2				
Year 3	5	2		5	3		5	1		5	2		5	2	2.4 (0.99–5.65)			
Antacids																		
Year 1	13	2		12	3		21	2		14	3		11	3				
Year 2	7	2		7	3		10	2		6	3		5	4	1.4 (0.64–2.98)			
Year 3	6	2		6	3		9	2		10	4		7	4	1.8 (0.93–3.67)			
Cardiovascular Agents																		
	% Surv	% Comp	RR (95%CI)	% Surv	% Comp	RR (95%CI)	% Surv	% Comp	RR (95%CI)	% Surv	% Comp	RR (95%CI)	% Surv	% Comp	RR (95%CI)			
	Leukemia			Lymphoma			CNS			Bone			Gonadal					
Alpha- and Beta-Blockers																		
Year 1	2	0.1		1	0.6	2.2 (0.86–5.89)	0	0.3	**	1	0.4	2.8 (0.60–13.59)	0	0.6	**			
Year 2	1	0.2		2	0.7	2.3 (0.94–5.50)	0	0.4	**	2	0.5		0.8	0.6	1.2 (0.16–9.76)			
Year 3	0.8	0.2		0.8	0.9	0.9 (0.27–2.82)	0	0.6	**	2	0.7	2.7 (0.77–9.64)	2	0.8	2.0 (0.44–8.89)			
Calcium Channel Blockers																		
Year 1	4	0.02		1	0.1		0.4	0.1	3.3 (0.35–37.79)	1	0.1		0.8	0.2	4.9 (0.45–53.92)			
Year 2	2	0.06		0.5	0.08		0.4	0.1	2.5 (0.28–22.19)	0	0.2	**	0.8	0.08	9.8 (0.62–156.47)			
Year 3	1	0.06		0.5	0.3	2.0 (0.43–8.98)	0.4	0.2	2.0 (0.23–16.98)	0	0.3	**	2	0.2				
ACE Inhibitors																		
Year 1	0.8	0.1		0.5	0.2	2.2 (0.48–10.12)	0.4	0.1	3.3 (0.35–37.79)	3	0.2		0.8	0.4	2.0 (0.23–16.72)			
Year 2	0.6	0.1		0.8	0.3	2.7 (0.76–9.62)	0.4	0.07	5.0 (0.45–54.72)	2	0.4		0.8	0.4	2.0 (0.23–16.72)			
Year 3	0.8	0.2		1	0.4		0.4	0.04	10.0 (0.62–158.71)	3	0.2		0.8	0.5	1.6 (0.20–13.52)			
Diuretics																		
Year 1	1	0.1		1	0.3		0.4	0.2	2.0 (0.23–16.98)	2	0.2		2	0.4	3.9 (0.77–20.09)			
Year 2	0.2	0.2	1.2 (0.16–9.87)	1	0.5	2.6 (0.98–6.92)	0.4	0.1	2.5 (0.28–22.19)	0.6	0.1	5.0 (0.45–54.66)	0.8	0.2	3.3 (0.34–31.32)			
Year 3	0.4	0.1	3.3 (0.67–16.30)	0.8	0.5	1.6 (0.46–5.25)	0	0.07	**	0.7	0.2	3.3 (0.35–31.75)	0.8	0.2	3.3 (0.34–31.32)			

	Anti-infectives														
	% Surv	% Comp	RR (95%CI)	% Surv	% Comp	RR (95%CI)	% Surv	% Comp	RR (95%CI)	% Surv	% Comp	RR (95%CI)	% Surv	% Comp	RR (95%CI)
	Leukemia			Lymphoma			CNS			Bone			Gonadal		
Antihyperlipidemics															
Year 1	0	0	**	1	0.2		1	0.2		0.6	0.1	5.0 (0.45–54.66)	0	0.2	**
Year 2	0.2	0.04	4.9 (0.45–54.46)	0.8	0.2	3.3 (0.90–12.11)	0.4	0.1	3.3 (0.35–31.79)	0.6	0.06	10.0 (0.63–158.58)	0.8	0.3	2.5 (0.28–21.86)
Year 3	0.4	0.1	4.0 (0.77–20.34)	0.8	0.2	3.3 (0.90–12.11)	0.4	0	**	0.7	0.2	5.0 (0.45–54.66)	0.8	0.2	3.3 (0.34–31.32)

** unable to calculate,

† among males only,

^ among females only; Surv: survivors, Comp: comparators