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The effect of chemotherapy innovation on cancer survival, 1991-2003: state-level evidence from the SEER-Medicare Linked Database

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Abstract

This study investigates the effect of chemotherapy innovation and other factors on the hazard rate of cancer patients using longitudinal, state-level data on four major types of cancer (colorectal, lung, breast, and prostate) in nine states during the period 1991-2003. We estimate 3 types of models: difference-in-differences models for the four major cancer sites combined; difference-in-difference models, by major cancer site; and difference-in-differences-in-differences models, for the four major cancer sites combined.

Estimates of almost all of the models are consistent with the hypothesis of a significant impact of chemotherapy innovation on hazard rates, although they provide varying evidence about the lag structure, and we fail to detect a link for colorectal cancer. The two states with the largest increases in chemotherapy vintage had the largest reductions in hazard rates.

Life expectancy of cancer survivors in 1991 was about 8.2 years. Our estimates imply that the 12.7-year increase in chemotherapy vintage that occurred during the period 1991-2002 increased the life expectancy of cancer survivors by 8-12 months, or about 10%. In 2003 Medicare spent about $475 on chemotherapy per cancer survivor, so expected lifetime (undiscounted) chemotherapy expenditure per cancer patient was $4372. This includes the cost of old as well as new chemotherapy treatments. Hence $6246 is an upper bound estimate of the average cost per life-year gained from using newer chemotherapy drugs. This is a small fraction of some leading economists' estimates of the value of a U.S. statistical life-year.

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Many clinical studies have compared the effects of newer and older drugs on cancer survival rates.[1] The findings of these studies have been mixed. Some studies (e.g. Richardson et al (2005), Kantarjian et al (2005)) have found that use of newer cancer drugs increased survival rates. Other studies (e.g. von der Maase et al (2005)) have found that use of newer cancer drugs did not increase survival rates.

This study will seek to determine the effect of pharmaceutical innovation—the use of newer drugs—*in general* on the survival of breast, colorectal, lung and prostate cancer patients.[2] A reliable estimate of this effect can't be obtained by simply surveying previous clinical studies of specific drugs and cancer sites, for several reasons. First, there is considerable variation in the methodology and metrics used in these studies, rendering comparison and aggregation difficult. Second, these studies may not provide a complete or representative picture; there may be little or no published evidence about the survival impact of some drugs.[3]

Third, evidence from clinical trials cannot necessarily be extrapolated to real-world experience. As noted in the Harvard Mental Health Letter (2007), the issue often raised by the favorable outcome of a formal clinical trial is, will the treatment work in the real world? There may be a "gap between efficacy and effectiveness"—efficacy meaning proof in a carefully controlled trial, and effectiveness meaning success in the circumstances of everyday life. Wieringa et al (2000) examined discrepancies between co-morbidity of patients included in pre-marketing clinical trials of cardiovascular drugs and patients from daily practice, representing the actual users after marketing. Phase III trials testing cardiovascular drugs included patients with concomitant cardiovascular, endocrine and metabolic diseases, but discrepancies were present with patients in daily practice.

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[1] A PubMed search for ((("Survival Rate") AND ("Antineoplastic Agents")) AND ("Comparative Study")) yields 387 items.

[2] In principle, this approach could be applied to data on other cancer sites. We applied it to just four major cancer sites because our analysis is based on the National Cancer Institute (NCI)'s SEER-Medicare Linked Database, and it is the NCI's policy that "investigators may not request the entire data set." http://healthservices.cancer.gov/seermedicare/obtain/requirements.html

[3] Johnson et al (2003) reported that only one-fourth of the oncology drug marketing applications approved by the FDA during the period January 1, 1990 to November 1, 2002 were based on direct evidence of survival benefits; 75% of approvals were based on surrogate end points (e.g. reduction in tumor size).

Central hypothesis

We hypothesize that, in general and *ceteris paribus*, newer chemotherapy drugs are more effective than older drugs, and therefore that increases in the mean *vintage* of chemotherapy treatments will reduce the *hazard rate* of cancer patients. We define the vintage of a drug as the year in which it was first approved by the FDA. For example, the vintage of docetaxel is 1998 since it was first approved by the FDA on June 22 of that year.

Economists believe that the development of new products is the main reason why people are better off today than they were several generations ago. Grossman and Helpman (1993) argued that "innovative goods are better than older products simply because they provide more 'product services' in relation to their cost of production." Bresnahan and Gordon (1996) stated simply that "new goods are at the heart of economic progress." Jones (1998) argues that "technological progress [is] the ultimate driving force behind sustained economic growth" (p.2), and that "technological progress is driven by research and development (R&D) in the advanced world" (p. 89). Bils (2004) makes the case that "much of economic growth occurs through growth in quality as new models of consumer goods replace older, sometimes inferior, models."

The best way to measure utilization of medical innovations (embodied technological change) is to measure the mean *vintage* of medical goods and services used. We seek to test the hypothesis that, ceteris paribus, people using newer, or later vintage, medical goods and services will be in better health, and will therefore live longer. This hypothesis is predicated on the idea that these goods and services, like other R&D intensive products, are characterized by *embodied technological progress*.[4]

A number of econometric studies (Bahk and Gort (1993), Hulten (1992), Sakellaris and Wilson (2001, 2004)) have investigated the hypothesis that capital equipment employed by U.S. manufacturing firms embodies technological change, i.e.

[4] Solow (1960, p 91): argued that "many if not most innovations need to be embodied in new kinds of durable equipment before they can be made effective. Improvements in technology affect output only to the extent that they are carried into practice either by net capital formation or by the replacement of old-fashioned equipment by the latest models…" We hypothesize that innovations may be embodied in nondurable goods (e.g. drugs) and services as well as in durable equipment.

that each successive vintage of investment is more productive than the last. Equipment is expected to embody significant technical progress due to the relatively high R&D-intensity of equipment manufacturers. The method that has been used to test the equipment-embodied technical change hypothesis is to estimate manufacturing production functions, including (mean) vintage of equipment as well as quantities of capital and labor. These studies have concluded that technical progress embodied in equipment is a major source of manufacturing productivity growth.

Although most previous empirical studies of embodied technical progress have focused on equipment used in manufacturing, embodied technical progress may also be an important source of economic growth in health care. One important input in the production of health—pharmaceuticals—is even more R&D-intensive than equipment. According to the National Science Foundation, the R&D intensity of drugs and medicines manufacturing is 74% higher than the R&D intensity of machinery and equipment manufacturing. Therefore, it is quite plausible that there is also a high rate of pharmaceutical-embodied technical progress.

General approach

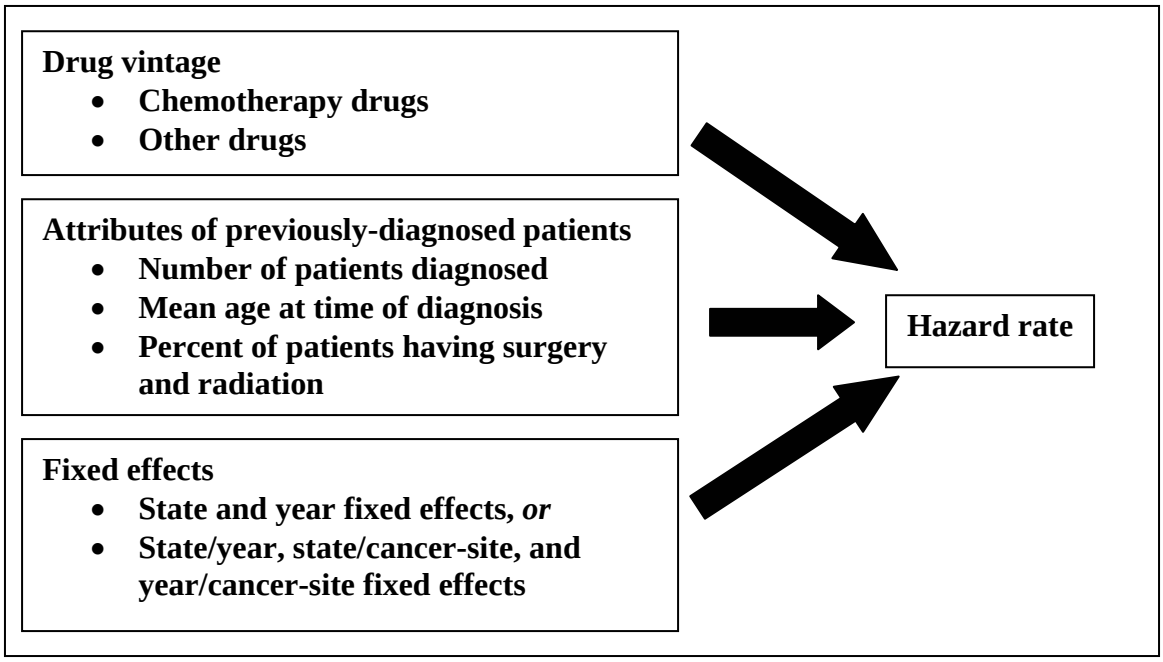
We will investigate the effect of chemotherapy innovation and other factors on the hazard rate of cancer patients using longitudinal, state-level data on four major types (primary sites) of cancer in nine states during the period 1991-2003.[5] While analysis at the individual level would be feasible with the available data, nonrandom assignment of drugs to patients may cause substantial biases at the individual level. Patients receiving newer treatments may be sicker (or healthier) than patients receiving older treatments.[6] Unobserved heterogeneity of illness severity is less likely to pose a problem at the state level than it is at the individual level. Whereas we have only a single observation on each individual, we have repeated observations on each state. This allows us to estimate models with state and year fixed effects, which control for unobserved determinants of

[5] Lichtenberg (2006) examined the effect of increased utilization of HIV drugs on the hazard rate of HIV/AIDS patients using aggregate U.S. time-series data.

[6] Duggan and Evans (2005) found that individuals with HIV/AIDS taking new antiretroviral drugs had substantially higher baseline mortality probabilities than did their counterparts who did not take the drugs.

cancer mortality (such as disease severity) that vary across states but not over time, or that change over time but don't vary across states.

Our research design is depicted by the following chart.



Our primary objective is estimation of the effect of chemotherapy vintage on the hazard rate of cancer survivors. The mean vintage of chemotherapy treatments administered to a group of patients in year t ($chemo\_vint_t$) is

$$chemo\_vint_t = \frac{\Sigma_a \, n\_chemo_{at} \, vint_a}{\Sigma_a \, n\_chemo_{at}}$$

where

n_chemo_{at} = the number of chemotherapy treatments administered to patients in year t that contained active ingredient a

$vint_a$ = the vintage (initial FDA approval year) of active ingredient a

The hazard rate is defined as the probability of dying during year t, conditional on surviving until the beginning of year t:

$$hazard_t = n\_died_t / n\_alive_t$$

$$= n\_died_t / \Sigma_{j=1}^{t-1} (n\_diag_j - n\_died_j)$$

where

n_died_t = the number of deaths during year t
n_alive_t = the number of people alive at the beginning of year t
n_diag_t = the number of people diagnosed during year t

Under certain assumptions (i.e., that the distribution of survival times is exponential, so that the hazard rate is constant), mean survival time (e.g. life expectancy at time of diagnosis) is equal to the reciprocal of the hazard rate. For example, if the hazard rate is 10%, life expectancy at time of diagnosis is 10 years. Under these assumptions, we can easily determine the effect of chemotherapy innovation on the life expectancy of cancer patients from estimates of the effect of chemotherapy innovation on hazard rates.

For this approach to be successful there must be nontrivial variation across states in the rate of increase in drug vintage. The summary data shown in Figure 1 suggest that this is indeed the case. In 1991, Connecticut's chemotherapy treatments were the oldest; in 2003 they were the newest. Hawaii had the newest treatments in 1995, and the oldest in 1997. Michigan ranked first in 1994 but ranked second to last in 2003.

This variation across states in the rate of increase in drug vintage may primarily be due to medical practice variation. Medical practice variation is a well-documented phenomenon: there are 2514 citations for this term in the PubMed database. The Dartmouth Atlas of Health Care Project (Wennberg (2006)) has demonstrated "glaring variations in how health care is delivered across the United States." Skinner and Staiger (2005) argue that medical practice variation may be partly due to variation in the frequency and likelihood of informational exchanges through networks or other social activities, which may in turn be related to both average educational attainment and other measures of social capital. They compared the adoption of several important innovations during the 20th century, ranging from advances at mid-century in hybrid corn and tractors, to medical innovations in the treatment of heart attacks at the end of the century. They found a very strong state-level correlation with regard to the adoption of new and effective technology, and this correlation held across a variety of industries and time periods. These results are suggestive of state-level factors associated with barriers to adoption. These barriers may be related to information or network flows, given that farmers, physicians, and individual computer users conduct their business in often small

and isolated groups, and therefore are most vulnerable to potential information asymmetries.

The hazard and survival rates of cancer patients are likely to depend on a number of factors, including the intensity of cancer screening. The goal of screening is to diagnose a disease earlier than it would be without screening. Without screening, the disease may be discovered later once symptoms appear. Even if in both cases a person will die at the same time, because the disease was diagnosed early with screening, the survival time since diagnosis is longer with screening. No additional life has been gained (and indeed, there may be added anxiety as the patient must live with knowledge of the disease for longer). Looking at raw statistics, screening will appear to increase survival time (this gain is called *lead time*). If we do not think about what *survival time* actually means in this context, we might attribute success to a screening test that does nothing but advance diagnosis.

If increases in screening intensity were positively correlated across states with increases in chemotherapy vintage, then failure to control adequately for screening would result in overestimation of the effect of chemotherapy vintage on survival. We will attempt to control for screening intensity by including several characteristics of previously-diagnosed patients. The first is the number of patients diagnosed. States with greater increases in screening are likely to have larger increases in the number of people diagnosed. The second is mean age at time of diagnosis. States with greater increases in screening are likely to have smaller increases (or even declines) in mean age at time of diagnosis. We will also control for the percent of patients having surgery and radiation as part of their initial course of therapy; these variables may also be indicative of disease progression at time of diagnosis. For example, a patient whose cancer is localized at time of diagnosis may be more likely to undergo surgery than a patient whose cancer has metastasized.

Econometric model

We will estimate 3 types of models, all based on state-level data:

- difference-in-differences, four major cancer sites combined
- difference-in-differences, by major cancer site

- difference-in-differences-in-differences, four major cancer sites combined[7]

The first two models are of the form:

$$\log(\text{hazard}_{st}) = \beta\, \text{chemo\_vint}_{st} + \gamma\, Z_{st} + \alpha_s + \delta_t + \varepsilon_{st} \qquad (1)$$

where

hazard_{st} = the probability that patients previously diagnosed with cancer in state s (s = 1,…,9) died during year t (t = 1991,…, 2003), conditional on surviving until the beginning of year t

chemo_vint_{st} = the mean vintage of the active ingredients in chemotherapy treatments administered to cancer patients in state s in year t

Z_{st} = other potential determinants of the hazard rate in year t of people previously diagnosed with cancer in state s

α_s = a fixed effect for state s

δ_t = a fixed effect for year t

The third model is of the form:

$$\log(\text{hazard}_{ist}) = \beta\, \text{chemo\_vint}_{ist} + \gamma\, Z_{ist} + \alpha_{is} + \delta_{it} + \pi_{st} + \varepsilon_{ist} \qquad (2)$$

where

hazard_{ist} = the probability that patients previously diagnosed with cancer at site i (i = 1,…,4) in state s died during year t, conditional on surviving until the beginning of year t

chemo_vint_{ist} = the mean vintage of the active ingredients in chemotherapy treatments administered to patients with cancer at site i in state s in year t

Z_{ist} = other potential determinants of the hazard rate in year t of people previously diagnosed with cancer at site i in state s

α_{is} = a fixed effect for cancer site i in state s

δ_{it} = a fixed effect for cancer site i in year t

π_{st} = a fixed effect for state s in year t

All models will be estimated via weighted least-squares, weighting by the number of people previously diagnosed with cancer who have survived until the beginning of year t.

To simplify notation, the models specified above implicitly assume that the hazard rate depends solely on *contemporaneous* chemotherapy vintage. However, treatment innovations could reduce the *lagged* hazard rate, as opposed to (or in addition to) the current hazard rate. Also, due to delays in the establishment by CMS of procedure

[7] Dee et al (2005), Racine et al (1998), and Zavodny (2000) use difference-in-differences-in-differences estimators.

codes for new chemotherapy procedures, our measure of chemotherapy vintage is likely to be a "lagging indicator" of the true increase in chemotherapy treatment vintage. The following table shows the FDA approval dates and HCPCS code establishment dates for five cancer drugs approved by the FDA in 1996.

Drug	FDA approval date	HCPCS code establishment date	Lag (months)
daunorubicin liposomal	4/8/1996	1/1/1999	33
docetaxel	5/14/1996	1/1/1998	20
gemcitabine	5/15/1996	1/1/1998	20
topotecan	5/28/1996	1/1/1998	19
irinotecan	6/14/1996	1/1/1998	19

FDA, Listing of Approved Oncology Drugs with Approved Indications, http://www.fda.gov/cder/cancer/druglistframe.htm

CMS, 2007 Alpha-Numeric HCPCS File, http://www.cms.hhs.gov/HCPCSReleaseCodeSets/downloads/anweb07.zip

HCPCS codes for these five drugs were established 19-33 months after FDA approval. These drugs were administered to patients prior to the establishment of their HCPCS codes. The following table shows unpublished IMS Health data for four of these drugs on the number of "standard units" sold in the U.S. via retail and hospital channels in the years 1996-1998.

	1996	1997	1998
docetaxel	36,962	115,191	211,728
gemcitabine	185,237	508,379	763,405
topotecan	88,987	150,492	170,665
irinotecan	117,510	371,832	439,420

According to one Medicare carrier, "J9999 [not otherwise classified, antineoplastic drugs] is the code that should be used for chemotherapy drugs that do not already have an assigned code."[8] 16% of chemotherapy treatments for patients with colorectal cancer used code J9999 in 2004.

[8] http://www.palmettogba.com/palmetto/providers.nsf/44197232fa8516898525719600693 9dd/85256d580043e75485256db3004fe953

To account for the possibility that chemotherapy vintage may affect the lagged hazard rate, and that measured vintage may lag true vintage, we will estimate models in which the hazard rate depends on vintage in the following, current, and previous years. When several values of chemo_vint are included (e.g. $chemo\_vint_t$ and $chemo\_vint_{t-1}$), the *sum* of their coefficients is an estimate of the (long-run) effect of a sustained increase in chemotherapy vintage on the hazard rate.

As indicated, the models we estimate will control for other potential determinants of the hazard rate (Z). These other determinants are:

- the mean vintage of the active ingredients in other (non-chemotherapy) drug treatments (other_drug_vint)
- the log of the number people diagnosed in year t-5 ($\log(n\_diag_{t-5})$)
- the mean age of people diagnosed in year t-5 (age_diag_{t-5})
- the percent of people diagnosed in year t-5 whose initial course of treatment included surgery ($surgery\%_{t-5}$)
- the percent of people diagnosed in year t-5 whose initial course of treatment included radiation ($radiation\%_{t-5}$)

Data construction and sources

We will make use of the following definitions:

$hazard_{ist}$ = n_died_{ist} / n_alive_{ist} = the probability of dying during year t, conditional on surviving until the beginning of year t

n_died_{ist} = the number of deaths in year t of people previously diagnosed with cancer at site i in state s

n_alive_{ist} = $\Sigma_{j=1}^{t-1} (n\_diag_{isj} - n\_died_{isj})$ = the number of people diagnosed with cancer at site i in state s before year t who survived until the beginning of year t

n_diag_{ist} = the number of people diagnosed with cancer at site i in state s in year t

$chemo\_vint_{ist}$ = $\dfrac{\Sigma_a \, n\_chemo_{aist} \, vint_a}{\Sigma_a \, n\_chemo_{aist}}$

n_chemo_{aist} = $\Sigma_p \, n\_proc_{pist} \, d_{pa}$ = the number of chemotherapy treatments administered to patients with cancer at site i in state s in year t that contained active ingredient a

n_proc_{pist} = the number of times chemotherapy treatment p was administered to patients with cancer at site i in state s in year t

d_{pa} = 1 if chemotherapy treatment p contains active ingredient a
= 0 if chemotherapy treatment p does not contain active ingredient a[9]

[9] $\Sigma_a \, d_{pa} = 1$ if chemotherapy treatment p contains a single ingredient; $\Sigma_a \, d_{pa} > 1$ if it contains multiple ingredients.

$vint_a$ = the vintage (initial FDA approval year) of active ingredient a
Z_{ist} = other potential determinants of the hazard rate in year t of people previously diagnosed with cancer at site i in state s

The 1973-2003 SEER 9 Public Use File[10] was used to calculate the following variables: n_died, n_diag, mean age at time of diagnosis, and the percent of patients having surgery and radiation. We selected all records for colorectal (21041 $\leq$ site recode $\leq$ 21052), lung & bronchus (site recode=22030), breast (site recode=26000), and prostate (site recode=28010) cancer.

We used the SEER 9 Public Use File (PUF) rather than the Patient Entitlement and Diagnosis Summary File (PEDSF) because the latter is censored—it contains diagnosis and treatment data only for those patients who had Medicare claims during the period 1991-2004—while the former is not. Cancer survivors of all ages will be included in our sample. The NCI estimates that in 2003, 60% of cancer survivors were at least 65 years old.[11] Moreover, data from MEDSTAT indicate that chemotherapy treatments administered to non-Medicare patients (employees and their dependents) are generally similar to those administered to Medicare patients.[12]

The variable n_proc was calculated using data in the NCH 100% physician/supplier data file in the SEER-Medicare Linked Database.[13] Since 1991, CMS has collected physician/supplier (Part B) bills for 100 percent of all claims. These bills, known as the National Claims History (NCH) records, are largely from physicians although the file also includes claims from other non-institutional providers such as physician assistants, clinical social workers, nurse practitioners, independent clinical laboratories, ambulance providers, and stand-alone ambulatory surgical centers. The claims are processed by carriers working under contract to CMS. Each carrier claim must include a Health Care Procedure Classification Code (HCPCS) to describe the nature of the billed service.

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[10] http://seer.cancer.gov/publicdata/ The SEER 9 registries are Atlanta, Connecticut, Detroit, Hawaii, Iowa, New Mexico, San Francisco-Oakland, Seattle-Puget Sound, and Utah. In this data set, cases diagnosed from 1973 through 2003 are available for all registries except Seattle-Puget Sound (1974+) and Atlanta (1975+). The database contains one record for each of 3,260,176 tumors.
[11] http://cancercontrol.cancer.gov/ocs/prevalence/prevalence.html#age
[12] Unfortunately, state-level data on chemotherapy treatments administered to non-Medicare patients are not available.
[13] http://healthservices.cancer.gov/seermedicare/medicare/claims.html

The HCPCS is divided into two principal subsystems, referred to as level I and level II of the HCPCS. Level I of the HCPCS is comprised of CPT (Current Procedural Terminology), a numeric coding system maintained by the American Medical Association (AMA). The CPT is a uniform coding system consisting of descriptive terms and identifying codes that are used primarily to identify medical services and procedures furnished by physicians and other health care professionals. These health care professionals use the CPT to identify services and procedures for which they bill public or private health insurance programs. Decisions regarding the addition, deletion, or revision of CPT codes are made by the AMA. The CPT codes are republished and updated annually by the AMA. Level I of the HCPCS, the CPT codes, does not include codes needed to separately report medical items or services that are regularly billed by suppliers other than physicians.

Level II of the HCPCS is a standardized coding system that is used primarily to identify products, supplies, and services not included in the CPT codes, such as ambulance services and durable medical equipment, prosthetics, orthotics, and supplies (DMEPOS) when used outside a physician's office. Because Medicare and other insurers cover a variety of services, supplies, and equipment that are not identified by CPT codes, the level II HCPCS codes were established for submitting claims for these items. The development and use of level II of the HCPCS began in the 1980's. Level II codes are also referred to as alpha-numeric codes because they consist of a single alphabetical letter followed by 4 numeric digits, while CPT codes are identified using 5 numeric digits.

Each HCPCS code on the carrier bill must be accompanied by an ICD-9 diagnosis code, providing a reason for the service. In addition each bill has the fields for the dates of service, reimbursement amount, encrypted provider numbers (e.g., UPIN), and beneficiary demographic data. For every billed procedure (using a HCPCS code), there should be a corresponding ICD-9 diagnosis code (often called the line item diagnosis) that provides the reason for the billed service.

We extracted all claims in the NCH 100% physician/supplier data file where the Berenson-Eggers Type of Service (BETOS) code[14] was O1D (chemotherapy) or O1E

[14] The BETOS coding system was developed primarily for analyzing the growth in Medicare expenditures. The coding system covers all HCPCS codes; assigns a HCPCS code to only one BETOS code; consists of

(other drugs), and where the first 3-digits of the beneficiary's principal diagnosis code (pdgns_cd) were 153 or 154 (colorectal cancer), 162 (lung & bronchus), 174 (breast), or 185 (prostate). Table 1 shows the top chemotherapy treatments in 2004, by cancer site.

The Medicare data are subject to certain limitations. Prior to January 2006, Medicare did not cover most oral prescription drugs. The Medicare claims data do not include claims for HMO enrollees, claims for care provided in other settings, such as the Veterans Administration, and (in some cases) claims for care for persons with Medicare as the secondary payer.

Data on d_{pa} were obtained from the ndc_denorm table in the Multum Lexicon database (http://www.multum.com/Lexicon.htm). Data on $vint_a$ were obtained from the Drugs@FDA database, produced by the FDA Center for Drug Evaluation and Research (http://www.fda.gov/cder/drugsatfda/datafiles/default.htm). This database includes several tables. The product table enumerates properties of the products included in each application, including their active ingredient(s). The supplements table provides the approval history for each application, including dates of approval. We define $vint_a$ as the earliest approval date of any product that contains active ingredient a.

Descriptive statistics are shown in Table 2. All statistics are weighted by the number of surviving, previously-diagnosed sample patients. The hazard rate declined by about a third, from 12.3% in 1991 to 8.3% in 2003. The number of surviving, previously-diagnosed sample patients almost doubled, from 327 thousand in 1991 to 614 thousand in 2003. The mean vintage of chemotherapy treatments increased by 15.4 years, and the mean vintage of other drug treatments increased by 11.6 years. Mean age at diagnosis declined from 66.8 years to 65.6 years. The fraction of previously-diagnosed patients who had surgery declined, but the fraction who had radiation increased.

Empirical results

A. Difference-in-differences, four major cancer sites combined

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readily understood clinical categories (as opposed to statistical or financial categories); consists of categories that permit objective assignment; is stable over time; and is relatively immune to minor changes in technology or practice patterns. http://www.cms.hhs.gov/HCPCSReleaseCodeSets/20_BETOS.asp

Estimates of the difference-in-differences model (eq. (1)), for the four major cancer sites combined, are shown in Table 3. The first column shows the regression of the hazard rate on contemporaneous chemotherapy vintage and other variables. The chemotherapy vintage coefficient is not significantly different from zero. The second column shows the regression of the hazard rate on chemotherapy vintage in the previous year and other variables. The chemotherapy vintage coefficient is negative and highly significant (p-value = .0045). This is consistent with the hypothesis that above-average increases in chemotherapy vintage led to above-average declines in the hazard rate a year later. Figure 2 shows the relationship across the nine states between the 1991-2002 change in chemotherapy vintage and the 1992-2003 reduction in the hazard rate. The two states with the largest increases in chemotherapy vintage had the largest reductions in hazard rates.

As shown in Table 2, between 1991 and 2002 chemotherapy vintage increased by 12.7 years. The estimates imply that this increase in vintage reduced the log hazard rate by .081 (= .0064 * 12.7), which is 24% of the total observed 1992-2003 reduction in the log hazard rate (.338). This suggests that about a quarter of the increase in cancer survival was due to use of newer chemotherapy drugs.

The only other regressor whose coefficient is statistically significant is lagged incidence. States with larger increases in lagged incidence tended to have larger declines in the hazard rate of cancer survivors. As discussed earlier, this may merely reflect differential rates of growth of the intensity of cancer screening.

B. Difference-in-differences, by major cancer site

Estimates of the difference-in-differences model, by major cancer site, are shown in Table 4. We estimated two versions of the model for each cancer site. In the first version, we include chemotherapy drug vintage and other drug vintage in years t and t-1. In the second version, we include chemotherapy drug vintage and other drug vintage in years t+1 and t, to account for the fact that measured vintage is likely to lag actual vintage. To conserve space, we will report only estimates of the sums of the coefficients, which capture the long-run effects of drug vintage on hazard rates.

Estimates of the first version of the model indicate that use of newer chemotherapy drugs has reduced the hazard rate for lung and breast cancer, but not for colorectal and prostate cancer. They also indicate that use of newer non-chemotherapy drugs is associated with an *increased* hazard rate of lung cancer survivors.[15] Perhaps this reflects increased use of new palliative drugs in more advanced lung cancer cases.

Estimates of the second version of the model indicate that use of newer chemotherapy drugs has reduced the hazard rates for 3 of the 4 cancer sites: lung, breast and prostate cancer. States that had above-average increases in chemotherapy drug vintage had above-average declines in the hazard rates of lung, breast, and prostate cancer survivors, but not of colorectal cancer survivors. None of the non-chemotherapy drug vintage estimates are significant at the 5% level.

C. Difference-in-differences-in-differences, four major cancer sites combined

Estimates of the difference-in-differences-in-differences model (eq. (2)), for the four major cancer sites combined, are shown in Table 5. Once again, we estimated two versions of the model. In the first version, we include chemotherapy drug vintage and other drug vintage in years t and t-1. In the second version, we include chemotherapy drug vintage and other drug vintage in years t+1 and t.

In both versions, the sum of the chemotherapy vintage coefficients is negative and highly significant. The sum of the chemotherapy vintage coefficients in the first version is virtually identical to the chemotherapy vintage coefficient in column 2 of Table 3. Thus, the estimate of the long-run effect of chemotherapy vintage from the pooled DD model with a 1-year lag is virtually identical to the estimate from the pooled DDD model with contemporaneous and lagged vintage. However, in contrast to the DD model, the latter model implies that contemporaneous vintage matters more than lagged vintage.

Estimates of the second DDD model in Table 5 indicate that the hazard rate depends even more on measured chemotherapy vintage in the following year than it

[15] Lung cancer chemotherapy drug vintage increased more than lung cancer other drug vintage, so these estimates imply that, overall, use of newer drugs slightly reduced the lung cancer hazard rate.

depends on current measured chemotherapy vintage.[16] As discussed above, measured chemotherapy vintage is likely to lag true chemotherapy vintage by 1 or 2 years due to delays in assigning codes to new cancer drugs. The sum of the year t+1 and year t chemo_vint coefficients is almost 50% larger than the sum of the year t and year t-1 chemo_vint coefficients. The estimates of the second model in Table 5 imply that a 12.7-year increase in chemotherapy vintage (which occurred during the period 1991-2002) would reduce the log hazard rate by .119—35% of the observed decline in the hazard rate during that period. The estimates of the second model also indicate that the hazard rate is inversely related to lagged incidence and directly related to lagged mean age at diagnosis. The 1.24-year decline in mean age at diagnosis also reduced the log hazard rate, but by only 1/6 as much as the increase in chemotherapy vintage.

Now we will use the estimates of the chemo_vint coefficients in the hazard rate equations to estimate the increase in life expectancy of cancer survivors attributable to the increase in chemotherapy vintage that occurred during the period 1991-2002. The calculations are shown in the following table.

	lower estimate	higher estimate
$HAZARD_{1991}$	12.3%	12.3%
$LE_{1991} = 1 / HAZARD_{1991}$	8.2	8.2
$\ln(HAZARD_{1991})$	-2.098	-2.098
$chemo\_vint_{2002}$	1981.1	1981.1
$chemo\_vint_{1991}$	1968.5	1968.5
$\beta = \Delta \ln(HAZARD) / \Delta chemo\_vint$	-0.0064	-0.0094
$\ln(HAZARD_{2002}) = \ln(HAZARD_{1991}) + \beta (chemo\_vint_{2002} - chemo\_vint_{1991})$	-2.179	-2.217
$HAZARD_{2002}$	11.3%	10.9%
$LE_{2002} = 1 / HAZARD_{2002}$	8.8	9.2
Δ LE due to increase in chemotherapy vintage (in years)	0.7	1.0
Δ LE due to increase in chemotherapy vintage (in months)	8	12

[16] In a DDD regression of $\log(hazard_{ist})$ on $chemo\_vint_{ist}$, $chemo\_vint_{is,t+1}$, and $chemo\_vint_{is,t+2}$, the coefficient on $chemo\_vint_{is,t+2}$ is not significant, and the sum of the chemo_vint coefficients is virtually the same as it is in model 2 of Table 5.

The (baseline) hazard rate in 1991 was 12.3%. This implies that life expectancy of cancer survivors in 1991 was about 8.2 years. The lower estimate of the long-run effect of chemotherapy vintage on the hazard rate (Model 1 in Table 5) implies that the 12.7-year increase in drug vintage increased life expectancy by about 8 months. The higher estimate (Model 2 in Table 5) implies that the 1991-2002 increase in drug vintage increased life expectancy by about 12 months.

The National Cancer Institute estimates that there were about 6.25 million cancer survivors age 65 and over on January 1, 2003.[17] CMS reports that in calendar year 2003, Medicare payments for chemotherapy were $2.97 billion.[18] This means that in 2003 Medicare spent about $475 (= $2.97 billion / 6.25 million) on chemotherapy per cancer survivor. If the life expectancy of a cancer survivor were 9.2 years, expected lifetime (undiscounted) chemotherapy expenditure per cancer patient would be $4372 (= 9.2 * $475). This includes the cost of old as well as new chemotherapy treatments. Our lower estimate of the 1991-2002 increase in life expectancy attributable to use of newer chemotherapy treatments is 8 months (0.7 years). Hence $6246 (= $4373 / 0.7) is an upper bound estimate of the average cost per life-year gained from using newer chemotherapy drugs. This is a small fraction of some leading economists' estimates of the value of a U.S. statistical life-year (Murphy and Topel (2005), Nordhaus (2002)).

Summary

This study has investigated the effect of chemotherapy innovation and other factors on the hazard rate of cancer patients using longitudinal, state-level data on four major types of cancer (colorectal, lung, breast, and prostate) in nine states during the period 1991-2003. We estimated 3 types of models: difference-in-differences models for the four major cancer sites combined; difference-in-difference models, by major cancer site; and difference-in-differences-in-differences models, for the four major cancer sites

[17] Surveillance, Epidemiology, and End Results (SEER) Program (www.seer.cancer.gov). Prevalence database: "US Estimated Complete Prevalence Counts on 1/1/2003". National Cancer Institute, DCCPS, Surveillance Research Program, Statistical Research and Applications Branch, released April 2006, based on the November 2005 SEER data submission. http://srab.cancer.gov/prevalence/canques.html I assume that 50% of cancer survivors in the 60-69 year age group are 65 and over.

[18] CMS, Medicare Part B Physician/Supplier Data by BETOS, Calendar Year 2003, http://www.cms.hhs.gov/MedicareFeeforSvcPartsAB/Downloads/BETOS03.pdf

combined. Estimates of almost all of the models were consistent with the hypothesis of a significant impact of chemotherapy innovation on hazard rates, although they provided varying evidence about the lag structure, and we failed to detect a link for colorectal cancer. The two states with the largest increases in chemotherapy vintage had the largest reductions in hazard rates.

Life expectancy of cancer survivors in 1991 was about 8.2 years. Our estimates imply that the 12.7-year increase in chemotherapy vintage that occurred during the period 1991-2002 increased the life expectancy of cancer survivors by 8-12 months, or about 10%. In 2003 Medicare spent about $475 on chemotherapy per cancer survivor, so expected lifetime (undiscounted) chemotherapy expenditure per cancer patient was $4372. This includes the cost of old as well as new chemotherapy treatments. Hence $6246 is an upper bound estimate of the average cost per life-year gained from using newer chemotherapy drugs. This is a small fraction of some leading economists' estimates of the value of a U.S. statistical life-year.

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Figure 1
Mean vintage of chemotherapy treatments, by state, 1991-2003

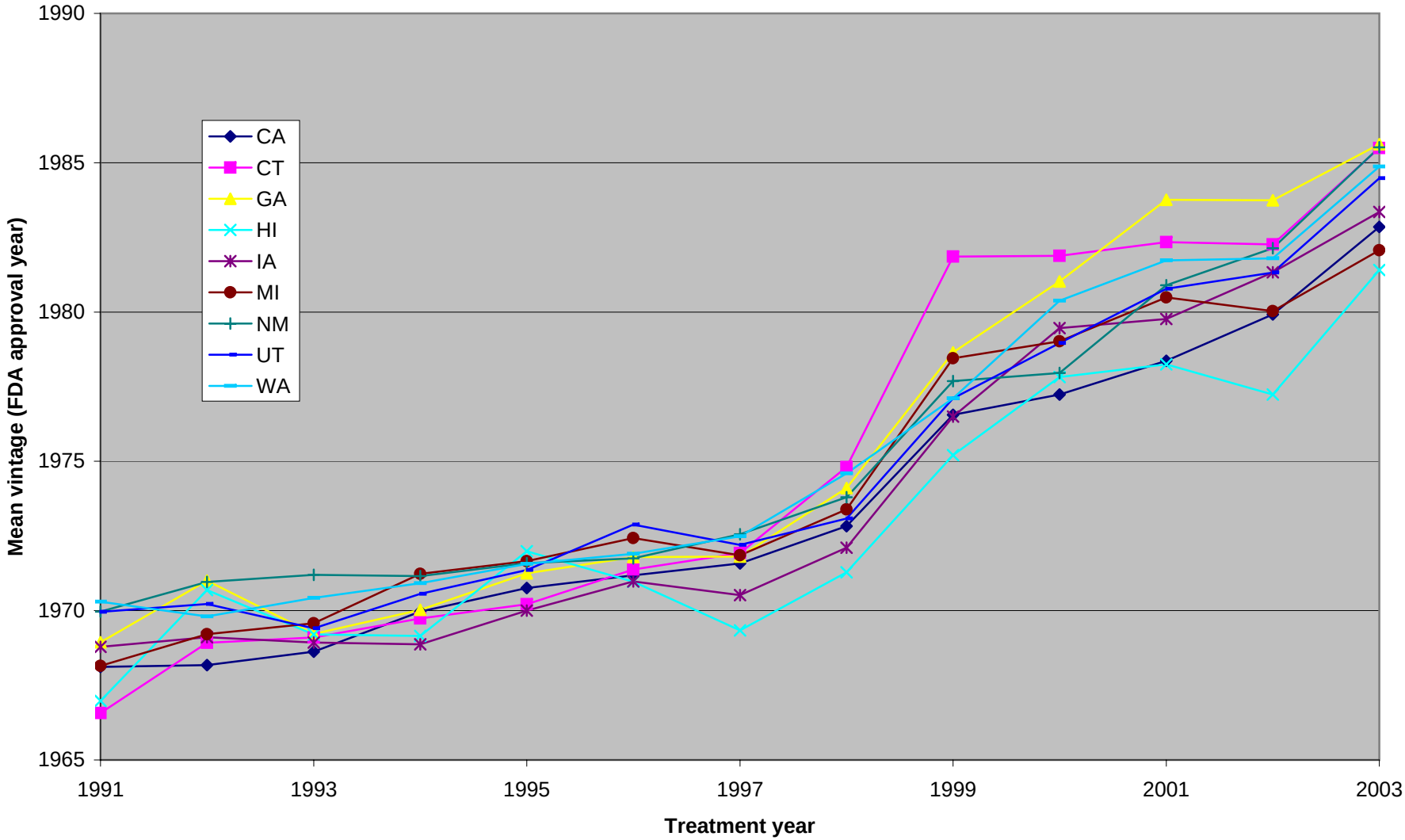

Figure 2
Relationship across states between the 1991-2002 increase in chemotherapy vintage and the 1992-2003 reduction in the log hazard rate

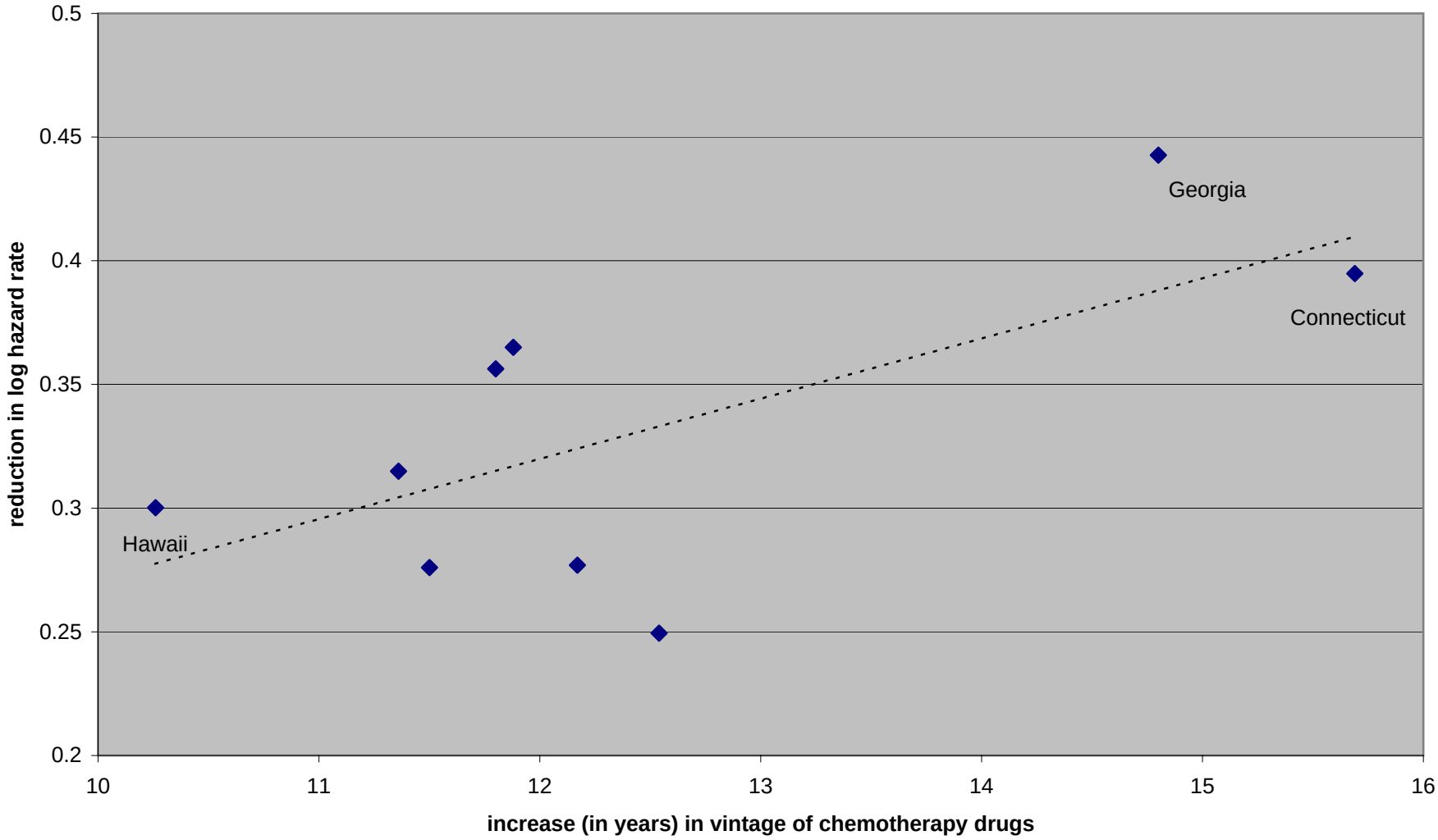

Table 1
Top chemotherapy procedures in 2004, by cancer site

breast (N = 29,562)	
J9170-Docetaxel	16%
J1260-Dolasetron Mesylate	15%
J9265-Paclitaxel Injection	14%
J9390-Vinorelbine Tartrate/10 Mg	12%
J9201-Gemcitabine HCl	11%
J9045-Carboplatin Injection	6%
J9190-Fluorouracil Injection	5%
colon & rectum (N = 57,203)	
J9190-Fluorouracil Injection	40%
J9999-Chemotherapy Drug	16%
J9206-Irinotecan Injection	14%
J9263-oxaliplatin injection/0.5 Mg	14%
J1260-Dolasetron Mesylate	11%
lung & bronchus (N = 31,274)	
J9201-Gemcitabine HCl	15%
J1260-Dolasetron Mesylate	15%
J9045-Carboplatin Injection	14%
J9265-Paclitaxel Injection	13%
J9390-Vinorelbine Tartrate/10 Mg	11%
J9170-Docetaxel	10%
prostate (N = 83,296)	
J9202-Goserelin Acetate Implant	52%
J9217-Leuprolide Acetate Suspnsion	30%
J9170-Docetaxel	7%

Source: author's calculations based on NCH 100% physician/supplier data file.

Table 2
Summary statistics, by year

year	n_alive_t	$hazard_t$	$chemo\_vint_t$	$other\_drug\_vint_t$	$log(n\_diag_{t-5})$	age_diag_{t-5}	$surgery\%_{t-5}$	$radiation\%_{t-5}$
1991	326,926	12.3%	1968.5	1959.6	2057.2	66.8	80%	23%
1992	353,170	11.7%	1969.4	1959.0	2058.6	66.9	79%	23%
1993	381,741	11.3%	1969.4	1965.4	2185.9	66.9	79%	25%
1994	406,309	10.9%	1970.2	1967.7	2367.2	66.9	78%	27%
1995	427,916	10.5%	1971.0	1966.8	2476.2	66.8	76%	29%
1996	448,831	10.2%	1971.7	1966.0	2396.6	66.6	75%	29%
1997	469,903	10.0%	1971.7	1966.6	2344.9	66.4	75%	30%
1998	493,020	9.8%	1973.5	1968.0	2360.5	66.2	74%	31%
1999	516,907	9.4%	1978.0	1966.8	2409.6	66.0	74%	33%
2000	542,299	9.2%	1979.5	1967.4	2527.7	66.0	73%	34%
2001	565,764	8.9%	1980.7	1968.1	2636.5	65.9	73%	37%
2002	590,201	8.7%	1981.1	1967.9	2708.3	65.7	73%	37%
2003	614,358	8.3%	1983.9	1971.1	2695.8	65.6	72%	38%

Table 3
Estimates of difference-in-differences model (eq. (1)), 4 cancer sites combined

	Model	
PARAMETER	**1**	**2**
$chemo\_vint_{st}$	-0.0026	
t-stat	-1.11	
p-value	0.2681	
$chemo\_vint_{s,t-1}$		-0.0064
t-stat		-2.92
p-value		0.0045
$other\_drug\_vint_{st}$	0.0002	
t-stat	0.11	
p-value	0.9139	
$other\_drug\_vint_{s,t-1}$		-0.0003
t-stat		-0.15
p-value		0.8778
$log(n\_diag_{s,t-5})$	-0.1469	-0.1787
t-stat	-2.7	-3.06
p-value	0.0082	0.003
$age\_diag_{s,t-5}$	-0.0074	-0.0057
t-stat	-0.76	-0.6
p-value	0.4493	0.5532
$surgery\%_{s,t-5}$	-0.1242	-0.0913
t-stat	-0.43	-0.31
p-value	0.6687	0.76
$radiation\%_{s,t-5}$	0.1730	0.2155
t-stat	1.22	1.6
p-value	0.2272	0.1125

The dependent variable is $log(hazard_{st})$.
Both models include state and year fixed effects.

Table 4

Estimates of selected parameters of difference-in-differences model (eq. (1)), by major cancer site

	sum of coefficients in year t and year t-1				**sum of coefficients in year t+1 and year t**		
cancer site	**ESTIMATE**	**T-VALUE**	**PROB>T**		**ESTIMATE**	**T-VALUE**	**PROB>T**
	chemotherapy drug vintage				**chemotherapy drug vintage**		
colon & rectum	0.0007	0.23	0.8177		0.0002	0.06	0.9547
lung & bronchus	-0.0096	-3.51	0.0007		-0.0063	-2.14	0.0356
breast	-0.0069	-2.87	0.0053		-0.0063	-2.40	0.0185
prostate	-0.0095	-1.04	0.3000		-0.0210	-2.08	0.0403
	other drug vintage				**other drug vintage**		
colon & rectum	-0.0039	-1.13	0.2630		-0.0014	-0.40	0.6924
lung & bronchus	0.0098	4.39	<.0001		0.0041	1.74	0.0861
breast	-0.0034	-1.38	0.1715		-0.0031	-1.16	0.2508
prostate	0.0020	0.95	0.3470		0.0033	1.42	0.1595

Table 5
Estimates of the difference-in-differences-in-differences model (eq. (2)), for four major cancer sites combined

	Model 1				Model 2		
PARAMETER	**ESTIMATE**	**T-VALUE**	**PROB>T**		**ESTIMATE**	**T-VALUE**	**PROB>T**
sum of chemo_vint	-0.0064	-3.22	0.0014		-0.0094	-4.45	<.0001
sum of other_drug_vint	-0.0023	-1.76	0.0797		-0.0019	-1.35	0.1789
$chemo\_vint_{is,t+1}$					-0.0066	-3.33	0.001
$chemo\_vint_{is,t}$	-0.0043	-2.31	0.0215		-0.0027	-1.42	0.1556
$chemo\_vint_{is,t-1}$	-0.0020	-1.13	0.2606				
$other\_drug\_vint_{is,t+1}$					-0.0014	-1.15	0.2494
$other\_drug\_vint_{is,t}$	-0.0014	-1.21	0.2288		-0.0005	-0.41	0.6852
$other\_drug\_vint_{is,t-1}$	-0.0009	-0.84	0.3999				
$\log(n\_diag_{is,t-5})$	-0.2530	-6.72	<.0001		-0.2279	-5.59	<.0001
$age\_diag_{is,t-5}$	0.0201	3.40	0.0008		0.0152	2.42	0.0164
$surgery\%_{is,t-5}$	0.0080	0.06	0.9533		-0.0956	-0.65	0.5137
$radiation\%_{is,t-5}$	0.0230	0.25	0.8004		-0.0869	-0.89	0.3723

These models include fixed effects for each cancer-site/year pair, each cancer-site/state pair, and each state/year pair.