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HAS MEDICAL INNOVATION REDUCED CANCER MORTALITY?

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ABSTRACT

I analyze the effects of four types of medical innovation and cancer incidence on U.S. cancer mortality rates during the period 2000-2009, by estimating difference-in-differences models using longitudinal (annual) data on about 60 cancer sites (breast, colon, etc.). The outcome measure used is not subject to lead-time bias. I control for mean age at diagnosis, the stage distribution of patients at time of diagnosis, and the sex and race of diagnosed patients.

Under the assumption that there were no predated factors that drove both innovation and mortality and that there would have been parallel trends in mortality in the absence of innovation, the estimates indicate that there were three major sources of the 13.8% decline of the age-adjusted cancer mortality rate during 2000-2009. Drug innovation and imaging innovation are estimated to have reduced the cancer mortality rate by 8.0% and 4.0%, respectively. The decline in incidence is estimated to have reduced the cancer mortality rate by 1.2%. The social value of the reductions in cancer mortality attributable to medical innovations has been enormous, and much greater than the cost of these innovations.

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1. Introduction

The cost of cancer care is substantial, and increasing. In 2010, the direct cost of U.S. cancer care was $125 billion (almost $9000 per cancer patient). This figure does not include indirect costs, such as lost productivity, which add to the overall financial burden of cancer. According to researchers at the National Cancer Institute (Mariotto et al (2011), Yabroff et al (2008), National Cancer Institute(2013a, 2013b)), in the absence of any change in the cost per patient of cancer care, changes in the U.S. population alone will result in a real cost increase of 27%, to $155 billion, by 2020. However, if costs in the initial and final phases of care increase by 2% annually, e.g. due to advances in diagnostic technology and novel targeted treatments, the total cost of care in 2020 will be $173 billion, an increase of 40% from 2010. If costs increase by 5% annually, the total cost of care in 2020 will be $207 billion, an increase of 68% from 2010. Thus, medical innovation during the period 2010-2020 may increase the direct cost of U.S. cancer care by $52 billion in 2020. More generally, the Congressional Budget Office (2008, Preface) stated that "the largest single factor driving [healthcare] spending growth [is] the greatly expanded capabilities of medicine brought about by technological advances in medical science over the past several decades."[1]

As noted by the Australian Productivity Commission (2005), even if advances in medical technology drive increased healthcare expenditure, the critical question is whether the benefits outweigh the costs. In other markets, increased expenditure generally would indicate increased consumer benefits. But because the direct purchase of healthcare is mostly undertaken by third parties — governments and private health insurers — normal market tests for ensuring value for money generally do not apply. Although assessing the benefits of medical innovation—its impact on health outcomes—is as important as assessing the costs—its impact on health expenditure—the Commission (2005, p. 99) noted that "most formal studies…have focused on the expenditure impacts of medical technology, partly because costs are more easily identified and quantified than are benefits."

[1] However, this conclusion was based on studies that may have not fully accounted for spillovers across episodes of care or medical conditions. Such spillovers may be important: a recent study of a cohort of U.S. Medicare beneficiaries aged 65 years and older with a diagnosis of cataract found that patients who had cataract surgery had lower odds of hip fracture within 1 year after surgery compared with patients who had not undergone cataract surgery (Tseng et al (2012)). Also, Lichtenberg (2011) found that U.S. states that adopted new drugs and diagnostic imaging procedures more rapidly had larger gains in life expectancy during the period 1991-2004, but that they did not have larger increases in per capita medical expenditure, controlling for other factors.

In this paper, I will analyze the effects of medical innovation on U.S. cancer mortality rates. During the period I will study (1996-2009), the age-adjusted cancer mortality rate declined 19%; the age-adjusted cancer incidence rate declined by only 4%. Lakdawalla et al (2010) quantified the value of gains in cancer survival, and analyzed the distribution of value among various stakeholders. They estimated that, between 1988 and 2000, life expectancy for cancer patients increased by roughly four years, and the average willingness-to-pay for these survival gains was roughly $322,000. Improvements in cancer survival during this period created 23 million additional life-years and roughly $1.9 trillion of additional social value. However, Lakdawalla et al (2010) did not identify the source of these gains, or determine the extent to which they were due to innovation in cancer treatment.

A randomized clinical trial (RCT) undoubtedly provides the most reliable evidence about the impact of a specific treatment innovation (e.g. new drug or diagnostic procedure) on mortality or survival from a specific type of cancer. Therefore, to conduct an overall assessment of the impact of medical innovation on cancer mortality, one might consider performing a meta-analysis of data from RCTs. But that approach seems unlikely to be fruitful, for several reasons. The sheer number of studies that would need to be considered is overwhelming: PubMed contains over 29,000 articles that address both cancer mortality and just one type of cancer treatment: drug therapy.[2] The metrics used in these studies are likely to be quite heterogeneous. As Thaul (2012, p. 4) observes, a drug's "effectiveness"—how well it works in a real-world situation—may differ from its "efficacy"— whether a drug demonstrates a health benefit over a placebo or other intervention when tested in an ideal situation, such as a tightly controlled clinical trial. And the overall impact of medical innovation on cancer mortality depends on the extent to which various treatments are used, as well as on the effectiveness of each treatment.

Rather than performing a meta-analysis of RCTs, I will perform an original analysis of observational data on cancer treatment, incidence, and mortality. The data I will analyze—longitudinal (annual) data on about 60 cancer sites (breast, colon, etc.)—are aggregate data, rather than patient-level data. The patient-level datasets to which I have access do not include adequate information on both treatment and mortality.[3] Even if patient-level data on both

[2] The following PUBMED search yielded 29,699 results (articles): (((neoplasms[MeSH Major Topic])) AND ("drug therapy"[MeSH Subheading])) AND ("mortality"[MeSH Subheading]).

[3] The dataset I use to obtain treatment information (the MEDSTAT Marketscan database) includes only inpatient mortality data. The majority of deaths occur outside the hospital

treatment and mortality were available, Stukel et al (2007) argue that comparisons of outcomes between patients treated and untreated in observational studies may be biased due to differences in patient prognosis between groups, often because of unobserved treatment selection biases. I believe that difference-in-differences estimates based on aggregate panel data are much less likely to be subject to unobserved treatment selection biases than estimates based on cross-sectional patient-level data.[4]

Several previous studies have examined the overall impact of medical innovation on cancer mortality.[5] These studies were subject to several limitations. First, the outcome measure in all of these studies was the cancer survival rate—the proportion of patients alive at some point subsequent to the diagnosis of their cancer—and this measure may be subject to lead-time bias. Second, only one kind of medical innovation—chemotherapy innovation—was usually analyzed, and this was usually measured by the number of drugs potentially available to cancer patients, rather than by the drugs actually used by them.

This paper builds upon previous research in several ways. First, the outcome measure I use—the *unconditional* cancer mortality rate (the number of deaths, with cancer as the underlying cause of death, occurring during a year per 100,000 population)—is not subject to lead-time bias. Second, I analyze the effects of four important types of medical innovation—chemotherapy,[6] diagnostic imaging, radiotherapy, and surgical innovation —and cancer incidence rates on cancer mortality rates. Third, my measures of medical innovation are based on extensive data on treatments given to large numbers of patients with different types of cancer.

In Section 2, I will briefly review the history of several types of medical innovation, and discuss recent trends in cancer incidence and mortality. In Section 3, I will present the econometric model I will estimate to assess the impact of medical innovation on cancer

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(http://www.cdc.gov/nchs/data/dvs/Mortfinal2005_worktable_309.pdf). Moreover, if a person disenrolls from a health plan covered by Marketscan after he or she is treated, his or her death would not be observed, either inside or outside the hospital.

[4] Jalan and Ravallion (2001) argued that "aggregation to village level may well reduce measurement error or household-specific selection bias" (p. 10).

[5] Lichtenberg (2008, 2009a, 2009b) examined the effect of pharmaceutical innovation on relative cancer survival rates, controlling for variables likely to reflect changes in probability of diagnosis (e.g. age at diagnosis, cancer stage of diagnosis, and number of people diagnosed).

[6] I will analyze the impact of innovation in drugs administered by providers, not innovation in self-administered drugs, because provider-administered drug claims contain diagnosis codes, but self-administered drug claims do not. Data from MEDSTAT Marketscan and IMS Health's National Sales Perspectives indicate that about 70% of cancer drug expenditure is on drugs administered by providers. Only 10% of expenditure on other (non-cancer) drugs is on drugs administered by providers.

mortality. Data sources and descriptive statistics will be discussed in Section 4. Estimates of cancer mortality models will be presented in Section 5. The implications of the estimates will be discussed in Section 6.

2. Brief review of history of medical innovation, and recent trends in cancer incidence and mortality

In this section, I will first briefly review the history of three types of medical innovation: chemotherapy, diagnostic imaging, and radiation therapy. Then I will discuss recent trends in cancer incidence and mortality.

Chemotherapy. Chabner and Roberts (2005) and DeVita and Chu (2008) provide useful accounts of the history of chemotherapy. According to DeVita and Chu (2008), the use of chemotherapy to treat cancer began at the start of the 20th century with attempts to narrow the universe of chemicals that might affect the disease by developing methods to screen chemicals using transplantable tumors in rodents. It was, however, four World War II–related programs, and the effects of drugs that evolved from them, that provided the impetus to establish in 1955 the national drug development effort known as the Cancer Chemotherapy National Service Center. The ability of combination chemotherapy to cure acute childhood leukemia and advanced Hodgkin's disease in the 1960s and early 1970s overcame the prevailing pessimism about the ability of drugs to cure advanced cancers, facilitated the study of adjuvant chemotherapy, and helped foster the national cancer program. Today, chemotherapy has changed as important molecular abnormalities are being used to screen for potential new drugs as well as for targeted treatments.

Chabner and Roberts (2005) say that the beginnings of the modern era of chemotherapy can be traced directly to the 1942 discovery of nitrogen mustard as an effective treatment for cancer. Their history of chemotherapy timeline includes the following five milestones during the period 1975-2004:

- 1975: A combination of cyclophosphamide, methotrexate and fluorouracil (CMF) was shown to be effective as adjuvant treatment for node-positive breast cancer.
- 1978: The FDA approved cisplatin for the treatment of ovarian cancer, a drug that would prove to have activity across a broad range of solid tumors.
- 1992: The FDA approved paclitaxel (Taxol), which becomes the first 'blockbuster' oncology drug.

- 2001: Studies by Brian Druker led to FDA approval of imatinib mesylate (Glivec) for chronic myelogenous leukemia, a new paradigm for targeted therapy in oncology.
- 2004: The FDA approved bevacizumab (Avastin), the first clinically proven antiangiogenic agent, for the treatment of colon cancer.

The pace of chemotherapy innovation has increased sharply during the last two decades. Data from IMS Health indicate that, by the end of 2009, cancer drugs (EphMRA/PBIRG Anatomical Classification L: antineoplastic and immunomodulating agents) used in the U.S. contained 133 distinct molecules. Twenty of these drugs had been launched by the end of 1969, and 49 had been launched by the end of 1989. Thus, the number of new cancer molecules launched during 1990-2009 (84 = 133 – 49) was almost three times as large as the number of new cancer molecules launched during 1970-1989 (29 = 49 – 20).

Pharmaceuticals are more research-intensive than other types of medical care: in 2007, prescription drugs accounted for 10% of U.S. health expenditure (Center for Medicare and Medicaid Services, 2013: Table 2), but more than half of U.S. funding for biomedical research came from pharmaceutical and biotechnology firms (Dorsey et al, 2010). Moreover, new drugs often build on upstream government research (Sampat and Lichtenberg, 2011).

Diagnostic imaging. Bradley (2008) provides a useful survey of the history of medical imaging. He argues that computers really entered the world of medical imaging in the early 1970s with the advent of computed tomography (CT scanning) and then magnetic resonance imaging (MRI). CT was a major advance that first allowed multiple tomographic images (slices) of the brain to be acquired. Prior to the advent of CT in 1973, we had only plane films of the head (which basically just show the bones) or angiography (which only suggests masses when the vessels of the brain are displaced from their normal position). Basically there was no way to directly image the brain. Today's multidetector row CTs acquire multiple submillimeter spatial resolution slices with processing speeds measured in milliseconds rather than hours. MRI also evolved during the 1970s, initially on resistive magnets with weak magnetic fields, producing images with low spatial resolution. Even then, however, it was obvious that the soft tissue discrimination of MRI was superior to that of CT, allowing earlier diagnoses. MR also had the advantage that it did not require ionizing radiation like X-ray-based CT.

As stated by the National Cancer Institute (2010)

> imaging, by itself, is not a treatment, but can help in making better decisions about treatments. The same imaging technique can help doctors find cancer, tell how far a

> cancer has spread, guide delivery of specific treatments, or find out if a treatment is working… Imaging can be used to make cancer treatments less invasive by narrowly focusing treatments on the tumors. For instance, ultrasound, MRI, or CT scans may be used to determine exact tumor locations so that therapy procedures can be focused on the tumor, minimizing damage to surrounding tissue… Imaging can be used to see if a previously treated cancer has returned or if the cancer is spreading to other locations.

Radiation therapy. The American Society for Radiation Oncology (2013) provides a brief survey of the history of radiation therapy. It is clear from this that recent advances in radiation therapy have been facilitated or enabled by advances in diagnostic imaging. Medicine has used radiation therapy as a treatment for cancer for more than 100 years, with its earliest roots traced from the discovery of x-rays in 1895 by Wilhelm Röntgen. Emil Grubbe of Chicago was possibly the first American physician to use x-rays to treat cancer, beginning in 1896. The field of radiation therapy began to grow in the early 1900s largely due to the groundbreaking work of Nobel Prize–winning scientist Marie Curie (1867–1934), who discovered the radioactive elements polonium and radium in 1898. This began a new era in medical treatment and research. Radium was used in various forms until the mid-1900s, when cobalt therapy and cesium units came into use. Medical linear accelerators have been used too as sources of radiation since the late 1940s.

With Godfrey Hounsfield's invention of computed tomography (CT) in 1971, three-dimensional planning became a possibility and created a shift from 2-D to 3-D radiation delivery. CT-based planning allows physicians to more accurately determine the dose distribution using axial tomographic images of the patient's anatomy. Orthovoltage and cobalt units have largely been replaced by megavoltage linear accelerators, useful for their penetrating energies and lack of physical radiation source.

The advent of new imaging technologies, including MRI in the 1970s and positron emission tomography (PET) in the 1980s, has moved radiation therapy from 3-D conformal to intensity-modulated radiation therapy (IMRT) and to image-guided radiation therapy (IGRT) tomotherapy. These advances allowed radiation oncologists to better see and target tumors, which have resulted in better treatment outcomes, more organ preservation and fewer side effects.

Recent trends in cancer incidence and mortality. Data on rates of incidence of and mortality from all malignant cancers are shown in Figure 1. Cancer incidence and mortality were both

increasing between 1973 and the early 1990s, but have declined since then. The change in cancer mortality during the period 1996-2009 (the period covered by my econometric analysis) has varied considerably across cancer sites, whether or not we control for the change in incidence. Figure 2 presents data on the 1996-2009 log change in the mortality rates of the ten largest cancer sites (ranked by their average mortality rate during 1985-2009). The red bars show the simple log change in the mortality rate, i.e. $\ln(mort_{i,2009}/mort_{i,1996})$, where $mort_{it}$ is the age-adjusted mortality rate from cancer at site i in year t. The change in cancer mortality ranged between -39% (= exp(-0.49) - 1) for prostate cancer and +3% for pancreatic cancer. The blue bars show the residual from the simple regression of $\ln(mort_{i,2009}/mort_{i,1996})$ on $\ln(inc_{i,2009}/inc_{i,1996})$, where inc_{it} is the age-adjusted incidence rate of cancer at site i in year t.[7] The change in cancer mortality, adjusted for the decline in incidence, ranged between -25% for prostate cancer and +16% for pancreatic and urinary bladder cancers. Figure 3 shows annual data on the age-adjusted mortality rates of six major cancer sites during 1996-2009. In the next section, I will present an econometric model for testing the hypothesis that cancer sites experiencing more medical innovation tended to have larger reductions in mortality rates.

3. Econometric model to assess the impact of medical innovation on cancer mortality

To assess the impact of medical innovation on cancer mortality, I will estimate difference-in-differences models using longitudinal (annual) data on about 60 cancer sites (breast, colon, etc.). The dependent variable in these models will be $\ln(mort\_rate_{st})$, where $mort\_rate_{st}$ is the age-adjusted mortality rate from cancer at site s in year t. The explanatory variables will be current and lagged measures of the *vintage*[8] of drug, imaging, radiotherapy, and surgery treatments for cancer at site s in year t; current and lagged values of $\ln(inc\_rate_{st})$, where inc_rate_{st} is the age-adjusted incidence rate of cancer at site s in year t; and current and lagged values of several variables that should reflect case mix, illness severity, and cancer stage at time of diagnosis:

- mean age at diagnosis

[7] The coefficient on $\ln(inc_{i,2009}/inc_{i,1996})$ in this regression is 0.385 (t-statistic = 3.50; p-value = 0.0009). $R^2 = 0.1604$; N = 66. The equation was estimated by weighted least-squares, weighting by the cancer site's average mortality rate during 1985-2009.

[8] According to the Merriam Webster dictionary, one definition of vintage is "a period of origin or manufacture (e.g. a piano of 1845 vintage)". http://www.merriam-webster.com/dictionary/vintage

- stage distribution of patients at time of diagnosis: the fractions of patients with (1) in situ; (2) localized or regional; and (3) distant cancers. (The omitted category is unstaged cancers.)
- the fraction of diagnosed patients who were male
- the fraction of diagnosed patients who were white

I assume that there were no pre-dated factors that drove both vintage and mortality, and that there would have been parallel trends in mortality in the absence of innovation. Direct testing of this assumption (e.g. by comparing the pre-trends of early and late adopters or of deep/non-deep new technology implementers) is difficult, because, as shown below, medical innovation is a continuous process, not a discrete process.[9] Since I control for the current and lagged incidence rate and several variables that should reflect case mix, illness severity, and cancer stage at time of diagnosis, I believe that this assumption is very likely to be satisfied. Before describing the specific models I will estimate, I will provide justifications for my choices of dependent and explanatory variables.

Two types of statistics are often used to assess progress in the "war on cancer": survival rates and mortality rates. Survival rates are typically expressed as the proportion of patients alive at some point subsequent to the diagnosis of their cancer. For example, the observed 5-year survival rate is defined as follows:

5-year Survival Rate = Number of people diagnosed with cancer at time t alive at time t+5 / Number of people diagnosed with cancer at time t

= 1 – (Number of people diagnosed with cancer at time t dead at time t+5 / Number of people diagnosed with cancer at time t)

Hence, the survival rate is based on a *conditional* (upon previous diagnosis) mortality rate. The second type of statistic is the *unconditional* cancer mortality rate: the number of deaths, with cancer as the underlying cause of death, occurring during a year per 100,000 population.

The 5-year relative survival rate from cancer has increased steadily since the mid 1970s, from 49.1% for people diagnosed during 1975-1977 to 67.6% for people diagnosed during 2001-2008. Although this increase suggests that there has been significant progress in the war against

[9] When an intervention (or policy change) being analyzed is discrete, e.g. in Galiani et al's (2005) study of the impact of privatization of water services on child mortality in Argentina, analysis of pre-trends is feasible and appropriate.

cancer, it might simply be a reflection of (increasing) lead-time bias. Lead time bias is the bias that occurs when two tests for a disease are compared, and one test (the new, experimental one) diagnoses the disease earlier, but there is no effect on the outcome of the disease--it may appear that the test prolonged survival, when in fact it only resulted in earlier diagnosis when compared to traditional methods. Epidemiologists have argued that while 5-year survival is a perfectly valid measure to compare cancer therapies in a randomized trial, comparisons of 5-year survival rates across time (or place) may be extremely misleading. If cancer patients in the past always had palpable tumors at the time of diagnosis while current cancer patients include those diagnosed with microscopic abnormalities, then 5-year survival would be expected to increase over time even if new screening and treatment strategies are ineffective. Therefore, to avoid the problems introduced by changing patterns of diagnosis, progress against cancer should be assessed using unconditional mortality rates.[10]

The unconditional cancer mortality rate is essentially the unconditional probability of death from cancer (P(death from cancer)). The law of total probability implies the following:

$$P(\text{death from cancer}) = P(\text{death from cancer} \mid \text{cancer diagnosis}) * P(\text{cancer diagnosis}) + P(\text{death from cancer} \mid \text{no cancer diagnosis}) * (1 - P(\text{cancer diagnosis})) \quad (1)$$

If the probability that a person who has never been diagnosed with cancer dies from cancer is quite small ($P(\text{death from cancer} \mid \text{no cancer diagnosis}) \approx 0$), which seems plausible,[11] this reduces to

$$P(\text{death from cancer}) \approx P(\text{death from cancer} \mid \text{cancer diagnosis}) * P(\text{cancer diagnosis}) \quad (2)$$

Hence

$$\ln P(\text{death from cancer}) \approx \ln P(\text{death from cancer} \mid \text{cancer diagnosis}) + \ln P(\text{cancer diagnosis}) \quad (3)$$

[10] I will control for cancer incidence (by including it in the mortality equation), but in a completely unrestrictive manner. If changes in incidence are merely due to lead-time bias, the coefficient on incidence should be zero.
[11] The cancer incidence rate is 2.5 times as high as the cancer mortality rate: 2006 U.S. age-adjusted incidence and mortality rates were 456.2 and 181.1, respectively. Since the probability of dying from cancer is much lower than the probability of being diagnosed with cancer, P(death from cancer|no cancer diagnosis) is likely to be small.

I hypothesize that the conditional mortality rate (P(death from cancer | cancer diagnosis)) is inversely related to the average (current and lagged) *quality* of medical procedures.[12] The quality of procedures is not directly observable. However, I also hypothesize that, in general, the average quality of newer (later vintage) procedures is higher than that of older (earlier vintage) procedures. The hypotheses that vintage has a positive effect on quality, and that quality has a negative effect on mortality, imply that vintage has a negative effect on mortality, i.e. that $\beta < 0$ in the following equation:

$$\ln P(\text{death from cancer} \mid \text{cancer diagnosis}) = \beta \, \text{treatment\_vintage} \qquad (4)$$

Robert Solow (1960) introduced the concept of vintage into economic analysis. This was one of the contributions to the theory of economic growth that the Royal Swedish Academy of Sciences cited when it awarded Solow the 1987 Alfred Nobel Memorial Prize in Economic Sciences:

> Solow's basic idea was that technical progress is "built into" machines and other capital goods and that this must be taken into account when making empirical measurements of the role played by capital.[13] This idea then gave birth to the "vintage approach"…Solow's empirical results naturally gave the formation of capital a markedly higher status in explaining the increase in production per employee…the vintage capital concept …is no longer solely employed in analyses of the factors underlying economic growth [and] has proved invaluable, both from the theoretical point of view and in applications..." (Nobelprize.org (2013)).

Subsequently, Grossman and Helpman (1991) argued that "almost every product exists on a *quality ladder*, with variants below that may already have become obsolete and others above that have yet to be discovered," and that "each new product enjoys a limited run at the technological frontier, only to fade when still better products come along." Harper (2007, p. 103) argued that "new improved models of high-tech equipment that embody improvements are frequently introduced and marketed alongside older models."

Substituting (4) into (3),

$$\ln P(\text{death from cancer}) \approx \beta \, \text{treatment\_vintage} + \ln P(\text{cancer diagnosis}) \qquad (5)$$

[12] The average quality of imaging procedures may also affect the probability of diagnosis.

[13] Solow assumed that technical progress is embodied in machines because machine manufacturers perform R&D. Since the medical substances and devices industry is much more research-intensive than the machinery industry (National Science Foundation, 2013), new medical treatments may embody even more technical progress than new machines.

I will estimate difference-in-difference (DD) versions of eq. (5), generalized to include four different types of treatment, using longitudinal, cancer-site-level data on over 60 cancer sites.[14, 15] The equations will be of the following form:

$$\ln(\text{mort\_rate}_{st}) = \Sigma_{k=0}^{4} [\beta_{1k}\,\text{drug\_vintage}_{s,t-k} + \beta_{2k}\,\text{imaging\_vintage}_{s,t-k} + \beta_{3k}\,\text{radiation\_vintage}_{s,t-k} + \beta_{4k}\,\text{surgery\_vintage}_{s,t-k} + \gamma_k \ln(\text{inc\_rate}_{s,t-k}) + \delta_{1k}\,\text{age\_diag}_{s,t-k} + \delta_{2k}\,\%\text{in\_situ}_{s,t-k} + \delta_{3k}\,\%\text{loc\_reg}_{s,t-k} + \delta_{4k}\,\%\text{distant}_{s,t-k} + \delta_{5k}\,\%\text{male}_{s,t-k} + \delta_{6k}\,\%\text{white}_{s,t-k})] + \alpha_s + \delta_t + \varepsilon_{st} \quad (6)$$

where

mort_rate_{st}	= the age-adjusted mortality rate from cancer at site s (s = 1,…, 60) in year t (t=1991,…,2006)
$\text{drug\_vintage}_{s,t-k}$	= index of the vintage of drug procedures associated with cancer at site s in year t-k (k = 0,1,…,4)
$\text{imaging\_vintage}_{s,t-k}$	= index of the vintage of imaging procedures associated with cancer at site s in year t-k
$\text{radiation\_vintage}_{s,t-k}$	= index of the vintage of radiation procedures associated with cancer at site s in year t-k
$\text{surgery\_vintage}_{s,t-k}$	= index of the vintage of surgical procedures associated with cancer at site s in year t-k
$\text{inc\_rate}_{s,t-k}$	= the age-adjusted incidence rate of cancer at site s in year t-k
$\text{age\_diag}_{s,t-k}$	= mean age of patients diagnosed with cancer at site s in year t-k
$\%\text{in\_situ}_{s,t-k}$	= fraction of patients diagnosed with cancer at site s in year t-k whose cancer was in situ
$\%\text{loc\_reg}_{s,t-k}$	= fraction of patients diagnosed with cancer at site s in year t-k whose cancer was localized or regional
$\%\text{distant}_{s,t-k}$	= fraction of patients diagnosed with cancer at site s in year t-k whose cancer was distant
$\%\text{male}_{s,t-k}$	= fraction of patients diagnosed with cancer at site s in year t-k who were male
$\%\text{white}_{s,t-k}$	= fraction of patients diagnosed with cancer at site s in year t-k who were white
α_s	= a fixed effect for cancer site s
δ_t	= a fixed effect for year t

[14] The cancer sites are those included in the National Cancer Institute's SEER Cause of Death Recode.

[15] Galiani et al (2005) used a difference-in-differences model to assess the impact of privatization of water services on child mortality in Argentina. They estimated their model using data classified by region and year, whereas the data I will use are classified by disease and year. Their "treatment variable" (whether water services were publicly or privately provided) was discrete, whereas my treatment variables (vintage indexes) are continuous.

ε_{st} = a disturbance

In eq. (6), the cancer mortality rate is postulated to be an unrestricted distributed lag function of the cancer incidence rate and the vintages of the four types of medical procedures in the current year and the four previous years. Eq. (6) includes lagged values of the explanatory variables, since it may take several years for medical innovation to have its peak effect on mortality rates. In this model, the long-run effect of a variable on ln(mort_rate) is the *sum* of the coefficients on the current and lagged values of the variable,[16] e.g. the long-run effect of drug vintage is $\Sigma_{k=0}{}^{4}\ \beta_{1k}$. A finding that $\Sigma_{k=0}{}^{4}\ \beta_{1k} < 0$ would signify that cancer sites that had above-average rates of drug innovation (increases in drug vintage) had above-average reductions in the age-adjusted mortality rate, *ceteris paribus*. The estimation procedure will account for clustering of disturbances within cancer sites.

Eq. (6) will be estimated via weighted least-squares, weighting by the mean mortality rate of cancer site s during the period 1985-2009. Since the dependent variable is the log of the mortality rate, I am analyzing percentage changes in the mortality rate. As shown in Figure 4, the data exhibit heteroskedasticity: cancer sites with low average mortality rates exhibit much larger positive and negative percentage changes in mortality rates than cancer sites with high average mortality rates. Weighted least squares is appropriate in the presence of heteroskedasticity.

The four treatment vintage (innovation) measures will all be defined as follows:

$$\text{treatment\_vintage}_{st} = \frac{\Sigma_p\ \text{n\_proc}_{pst}\ \text{new}_p}{\Sigma_p\ \text{n\_proc}_{pst}} \qquad (7)$$

where

n_proc_{pst} = the number of times procedure p was performed in connection with cancer diagnosed at site s in year t

new_p = 1 if procedure p is a "new" procedure

= 0 if procedure p is an "old" procedure

[16] Wooldridge (2009), p. 344.

However, as shown in Table 1, the definition of new_p will vary across treatment categories. Hence, $drug\_vintage_{st}$ is defined as the fraction of drug procedures (performed in connection with cancer diagnosed at site s in year t) that utilized drugs approved by the FDA after 1995;[17] $imaging\_vintage_{st}$ is defined as the fraction of imaging procedures that were advanced procedures; $radiation\_vintage_{st}$ is defined as the fraction of radiation procedures that had codes established by the AMA after 1995; and $surgical\_vintage_{st}$ is defined as the fraction of surgical procedures that had codes established by the AMA after 1995.

I believe that drug_vintage and imaging_vintage are good indicators of the diffusion of drug and imaging innovations, respectively, but I am less confident that radiation_vintage and surgical_vintage are good indicators of the diffusion of radiation and surgical innovations, respectively. Although the AMA (2013) says that establishment of a new CPT code requires that the "procedure or service [be] clearly identified and distinguished from existing procedures and services already in CPT," it seems that in some cases procedures that are assigned new codes had already been performed under different, existing codes. For example, several psychotherapy procedure codes were retired at the end of 2012, and the procedures were reassigned to new codes.[18] In the case of radiation and surgical innovations, there may therefore be substantial measurement error in the variable new_p in eq. (7).

The variable new_p is subject to little or no error in the case of drug and imaging innovations, but delays in the establishment by CMS or the AMA[19] of codes for new procedures introduce another source of error in eq. (7): n_proc_{pst} may be positive but reported as zero during the first few years of a procedure's existence. Consequently, drug_vintage is likely to be a "lagging indicator" of the true diffusion of pharmaceutical innovations. Table 2 shows the FDA approval dates and HCPCS code establishment dates for five cancer drugs approved by the FDA in 1996. 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.

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[17] I performed analyses using alternative measures of drug $vintage_{st}$, e.g. the fraction of drug procedures that utilized drugs approved by the FDA after 1990 (rather than 1995); this had very little effect on the estimates.

[18] CPT code 90801 (psychiatric diagnostic interview examination) was replaced by code 90791 (diagnostic evaluation without medical services), and code 90804 (20-30 minutes psychotherapy) was replaced by code 90832 (30 minutes). Source: http://thriveworks.com/blog/2013-cpt-code-revisions-what-the-changes-mean-for-counselors/

[19] Codes for chemotherapy procedures (and other procedures involving equipment and supplies)—Level II HCPCS codes—are established and maintained by CMS. Codes for other medical services and procedures furnished by physicians and other health care professionals)—CPT codes or Level I HCPCS codes—are established and maintained by the AMA. (Center for Medicare and Medicaid Services (2013))

Table 3 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. 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."[20] 16% of chemotherapy treatments for patients with colorectal cancer used code J9999 in 2004.

4. Data sources and descriptive statistics

Cancer incidence and mortality rates. Data on age-adjusted cancer incidence and mortality rates, by cancer site and year, were obtained from the National Cancer Institute's Cancer Query Systems (http://seer.cancer.gov/canques/index.html). Mortality data are based on a complete census of death certificates and are therefore not subject to sampling error, although they are subject to other errors, i.e. errors in reporting cause of death and age at death.[21] Cancer incidence rates are based on data collected from population-based cancer registries, which currently cover approximately 26 percent of the US population; incidence rates are therefore subject to sampling error.

Medical procedure innovation. Data on the number of medical procedures, by CPT or HCPCS code[22], principal diagnosis (ICD9) code, and year (n_proc_{pst}) were obtained from MEDSTAT MarketScan Commercial Claims and Encounters Database produced by Thomson Medstat (Ann Arbor, MI).[23] Each claim in this database includes information about the procedure performed (CPT code), the patient's diagnosis (ICD9 code), and the date of service. I extracted data on one

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

[21] During the period 1979-1998, cause of death was coded using ICD9 codes. Since 1999, cause of death has been coded using ICD10 codes. An advantage of the National Cancer Institute's Cancer Query Systems is that the mortality data from the two periods have been linked together.

[22] According to the American Medical Association's *CPT Assistant Archives*, procedures with CPT codes between 70010 and 75893 are diagnostic imaging procedures.

[23] The MarketScan Databases capture person-specific clinical utilization, expenditures, and enrollment across inpatient, outpatient, prescription drug, and carve-out services from a selection of large employers, health plans, and government and public organizations. The MarketScan Databases link paid claims and encounter data to detailed patient information across sites and types of providers, and over time. The annual medical databases include private sector health data from approximately 100 payers. Historically, more than 500 million claim records are available in the MarketScan Databases. The Commercial Claims and Encounters Database provides data on the medical experience of active employees, early retirees, COBRA continues, and their dependents insured by employer-sponsored plans (i.e., non-Medicare eligibles). I am grateful to the National Bureau of Economic Research for making these data available to me.

million outpatient procedures and one million inpatient procedures in which the principal diagnosis was cancer in each year during the period 1996-2009.[24]

The MEDSTAT Marketscan database is not based on a nationally representative sample of Americans. Moreover, the database I use contains data on medical care used by active employees, early retirees, COBRA continues, and their dependents insured by employer-sponsored plans. Medical care used by people eligible for Medicare is not covered.[25] The majority of cancer patients are enrolled in Medicare. Nevertheless, there is likely to be a strong positive correlation across cancer sites between innovations in treatment of nonelderly and elderly patients. If there was more treatment innovation for cancer type A than for cancer type B among nonelderly patients, there was likely to have been more treatment innovation for cancer type A than for cancer type B among elderly patients.

Measurement of new$_p$, by treatment category. In the case of drugs, new$_p$ is a dummy variable equal to 1 if the active ingredient was approved by the FDA after 1995, and otherwise equal to zero. To measure new$_p$ for each chemotherapy procedure, I used three databases. The first database, Noridian's NDC to HCPCS Crosswalk, provides a link between (HCPCS) procedure codes and drug product codes (NDCs: National Drug Codes). The second database, the FDA's National Drug Code Directory, provides a link between NDCs and New Drug Application (NDA) numbers, which are assigned by FDA staff to each application for approval to market a new drug in the United States.[26] The third database, the Drugs@FDA database, provides a link between NDA numbers and active ingredients, and allows me to determine the date when each active ingredient was first approved by the FDA.

In the case of imaging procedures, new$_p$ is a dummy variable equal to 1 if the procedure is designated as an "advanced imaging" procedure by CMS, and otherwise equal to zero. To

[24] More than half of these procedures were diagnostic lab and physician attendance procedures.

[25] I do not have access to a separate MEDSTAT database that covers Medicare-eligible retirees with employer-sponsored Medicare Supplemental plans. The National Cancer Institute publishes data (http://healthservices.cancer.gov/seermedicare/aboutdata/hcpcs.html) on the number of patients in the Patient Entitlement and Diagnosis Summary File (PEDSF) receiving each procedure in each year (1991-2009) by cancer site, but only for four cancer sites (breast, colorectal, lung, and prostate). NCI informed me that, due to budget constraints, it is not able to support the significant amount of programming that would be required to provide similar data for other cancer sites.

[26] The National Drug Code Directory also includes Abbreviated New Drug Application (ANDA) numbers, which are assigned by FDA staff to each application for approval to market a generic drug in the United States, and Biologic License Application (BLA) numbers, which are assigned by FDA staff to each application for approval to market biological products under the provisions of the Public Health Service (PHS) Act.

measure new_p for each imaging procedure, I used CMS' 2013 Berenson-Eggers Type of Service (BETOS) file.

In the case of radiation and surgical procedures, new_p is a dummy variable equal to 1 if the CPT code for the procedure was established by the AMA after 1995, and otherwise equal to zero. To measure new_p for each of these procedures, I used the AMA's CPT Assistant Archives database, which indicates the year in which each CPT code was added, revised, or deleted.

Other explanatory variables. Data on mean age and cancer stage at time of diagnosis, and on the sex and race of cancer patients were calculated from the National Cancer Institute's SEER 9 Research Data file (http://seer.cancer.gov/data/). This stage distribution corresponds to "SEER historic stage A" in the *SEER Research Data Record Description: Cases Diagnosed in 1973–2010*, http://seer.cancer.gov/data/seerstat/nov2012/TextData.FileDescription.pdf. The SEER 9 Research Data file does not include other measures of socioeconomic status, such as income or educational attainment.

Descriptive statistics. Data on the number of sample procedures, and on new procedures as a percent of the total number of procedures, by treatment type and year (1996-2009), are shown in Table 4. My sample includes data on about 1.5 million drug procedures, 1.0 million imaging procedures, 1.1 million radiation procedures, and 1.6 million surgical procedures. The fraction of drug procedures that were post-1995 procedures increased from 1% in 1996 to 26% in 2009. The fraction of radiation and imaging procedures that were post-1995 procedures increased by similar amounts: 27 and 23 percentage points, respectively. The large jump between 1999 and 2000 in the fraction of radiation procedures that were post-1995 procedures looks suspicious, however. The fraction of imaging procedures that were advanced procedures increased from 40% in 1996 to 60% in 2009.

Table 5 shows data on mortality, incidence, and treatment in 1996 and 2009, by cancer site, for the top 16 cancer sites (ranked by average mortality rate during 1985-2009).[27] It illustrates that the rate of diffusion of medical innovations varied across cancer sites and treatment types. For example, the fraction of drug procedures that were post-1995 procedures increased by almost twice as much for breast cancer (30%) as it did for stomach cancer (16%). But the fraction of imaging procedures that were advanced procedures increased much less for breast cancer (14%) than it did for prostate cancer (37%).

[27] Appendix Table 1 shows similar data for the 50 cancer sites not shown in Table 5.

Figure 5 provides data about the ten drugs with the largest 1996-2009 increase in share of all cancer drug procedures. These ten drugs accounted for only 2% of drug procedures in 1996, and 25% of procedures in 2009. Seven of the ten drugs were approved by the FDA after 1995. Figure 6 shows annual data on the fraction of drug procedures that were post-1995 drug procedures for 6 major cancer sites during 1996-2009.

Figure 7 provides data about the ten imaging procedures with the largest 1996-2009 increase in share of all cancer imaging procedures. These ten procedures accounted for 19% of imaging procedures in 1996, and 45% of procedures in 2009. Figure 8 shows annual data on the fraction of imaging procedures that were advanced imaging procedures for 6 major cancer sites during 1996-2009.

5. Estimates of cancer mortality models

Weighted least-squares estimates of six versions of the model of the age-adjusted mortality rate (eq. (6)) are presented in Table 6. All models include cancer-site fixed effects and year fixed effects, and were estimated using annual data during the period 2000-2009. To conserve space, estimates of cancer-site fixed effects are not reportedAlso to conserve space, only estimates of the *sums* of coefficients of current and lagged values of variables (e.g. $\Sigma_{k=0}{}^{4}$ β_{1k}) are reported in Table 6.[28] As discussed earlier, sums of coefficients are estimates of long-run effects.

Models 1-4 each includes one of the four treatment vintage (innovation) measures. Model 1 includes current and lagged values of drug vintage (post-1995 drug procedures as a percentage of all drug procedures). The sum of the drug vintage coefficients is negative (-0.3807) and highly significant (p-value = .0007), indicating that mortality rates declined more for cancer sites subject to more pharmaceutical innovation, controlling for the change in incidence. The sum of the cancer incidence coefficients is 0.3923 (p-value < .0001): cancer sites with larger declines in incidence had larger declines in mortality. However, the coefficient is much smaller than one. This is consistent with the view that some changes in measured incidence are due to changes in the probability of diagnosis, as opposed to changes in true incidence. The sum of the age_diag (mean age at diagnosis) coefficients is positive, as one might expect—earlier diagnosis (lower mean age at diagnosis) is associated with lower mortality—but not significant (p-value =

[28] Estimates of all of the parameters of one model (model 5) are shown in Appendix Table 2.

0.0921). The sums of the coefficients on the stage distribution and %white variables are insignificant.[29] The sum of the %male coefficients is positive, as one might expect—men have higher age-adjusted mortality rates—and marginally significant (p-value = 0.0572).

Model 2 includes current and lagged values of imaging vintage (advanced imaging procedures as a percentage of all imaging procedures). The sum of the imaging vintage coefficients is negative (-0.2438) and significant (p-value = .046), indicating that mortality rates also declined more for cancer sites subject to more imaging innovation, controlling for the change in incidence and other included variables.

Model 3 includes current and lagged values of radiation vintage (post-1995 radiation procedures as a percentage of all radiation procedures). The sum of the radiation vintage coefficients is negative (-0.1565) but not significant (p-value = .1532). Model 4 includes current and lagged values of surgery vintage (post-1995 surgery procedures as a percentage of all surgery procedures). The sum of the surgery vintage coefficients is also insignificant (p-value = .8297). The insignificance of the radiation and surgical innovation measures may be attributable to substantial errors of measurement of radiation and surgical innovation.

Model 5 includes all four treatment vintage (innovation) measures. The coefficients on the measures in this model are not very different from the corresponding coefficients in models 1-4, suggesting that the four treatment vintage measures are not highly collinear. Model 6 also includes all four treatment vintage (innovation) measures, but excludes current and lagged incidence rates. The sums of the coefficients on the drug and imaging innovation measures are over 50% larger in model 6 than they are in model 5: controlling for incidence reduces the estimated effects of drug and imaging innovation. But since eq. (3) indicates that the incidence rate should be included in the mortality rate equation (and also to obtain conservative estimates of the effects of drug and imaging innovation), I will use the estimates of model 5 to assess the contributions of medical innovation and changes in incidence to the recent decline in cancer mortality.

During the period 2000-2009, the age-adjusted cancer mortality rate declined by 13.8%. If the distribution of cancer deaths by cancer site had not changed, the mortality rate would have

[29] The insignificance of the stage distribution variables is consistent with the "stage migration" hypothesis (Feinstein et al (1985)). Measured changes in the stage distribution may be due to improvements in diagnostic imaging—metastases that had formerly been silent and unidentified are now identified—rather than a true change in the disease distribution.

declined slightly more, by 14.3%. To calculate the contribution of each factor to the decline in cancer mortality, I multiply the estimated long-run effect of that variable by the long-run change in the variable: the difference between the average value of the variable during 2005-2009 and its average value during 1996-2000. These calculations are shown in Table 7. I calculate the contribution of each factor using the 95% lower and upper bound estimates of long-run effects as well as the mean estimates shown in Table 6 (for model 5). The mean estimates imply that there were three major sources of decline in the cancer mortality rate. Drug innovation was the largest source: it is estimated to have reduced the cancer mortality rate by 8.0%. Imaging innovation is estimated to have reduced the cancer mortality rate by 4.0%. The 3% decline in the cancer incidence rate is estimated to have reduced the cancer mortality rate by just 1.2%. Surgical innovation is estimated to have had almost no effect on cancer mortality. The magnitude of the sum of the estimated contributions (13.2%) is only slightly smaller than the observed decline in mortality.. Drug and imaging innovation and (to a much lesser extent) declining incidence explain almost the entire decline in cancer mortality.

6. Discussion

Although randomized clinical trials (RCTs) undoubtedly provide the most reliable evidence about the impacts of specific treatment innovations (e.g. new drugs or diagnostic procedures) on mortality or survival from a specific type of cancer, it would be exceedingly difficult to assess the overall impact of medical innovation on cancer mortality from a meta-analysis of RCTs. An alternative approach is to perform well-designed econometric analyses of observational data on cancer treatment and outcomes. Several previous econometric studies were subject to several limitations. The outcome measure used in those studies—the cancer survival rate—was potentially subject to lead-time bias. Only one kind of medical innovation—chemotherapy innovation—was usually analyzed, and this was usually measured by the number of drugs potentially available to cancer patients, rather than by the drugs actually used by them.

This paper has built upon previous research in several ways. The outcome measure used—the *unconditional* cancer mortality rate—is not subject to lead-time bias. I analyzed the effects of four important types of medical innovation—chemotherapy, diagnostic imaging, radiotherapy, and surgical innovation —and cancer incidence rates on cancer mortality rates.

My measures of medical innovation were based on extensive data on treatments given to large numbers of patients with different types of cancer. I allowed there to be a relationship between incidence and mortality, but did not impose a relationship. I also controlled for mean age at diagnosis, the stage distribution of patients at time of diagnosis; and the sex and race of diagnosed patients.

During the period 2000-2009, the age-adjusted cancer mortality rate declined by 13.8%. Under the assumption that there were no pre-dated factors that drove both vintage and mortality, and that there would have been parallel trends in mortality in the absence of innovation, the estimates imply that there were three major sources of decline in the cancer mortality rate. Drug innovation was the largest source: it is estimated to have reduced the cancer mortality rate by 8.0%. Imaging innovation is estimated to have reduced the cancer mortality rate by 4.0%. Estimates of the effects of radiation and surgical innovation were not significant, but these types of innovation are more difficult to measure than drug and imaging innovation. The 3% decline in the cancer incidence rate is estimated to have reduced the cancer mortality rate by just 1.2%. Drug and imaging innovation and (to a much lesser extent) declining incidence explain almost the entire decline in cancer mortality.

Murphy and Topel (2006) estimated that a "1 percent reduction in cancer mortality would be worth nearly $500 billion." This implies that the social value of the reductions in cancer mortality attributable to medical innovations has been enormous, and much greater than the cost of these innovations. For example, the value of the mortality reduction resulting from cancer drug innovation would be $4.2 trillion (= 8.4 * $500 billion). Data from IMS Health indicate that total U.S. expenditure on cancer drugs in 2009 was $40.5 billion; 76% ($31.0 billion) of this expenditure was on drugs launched after 1995. If Murphy and Topel's and my calculations are correct, the cost of new cancer drugs is less than 1% of the value of the mortality reduction they yielded. This implication is broadly consistent with the findings of Lakdawalla et al (2010). They found that, between 1988 and 2000, health care providers and pharmaceutical companies appropriated 5-19% of the value of gains in cancer survival, with the rest accruing to patients, and that the share of value flowing to patients has been rising over time.

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Figure 1

Age-adjusted cancer incidence and mortality rates, 1973-2009

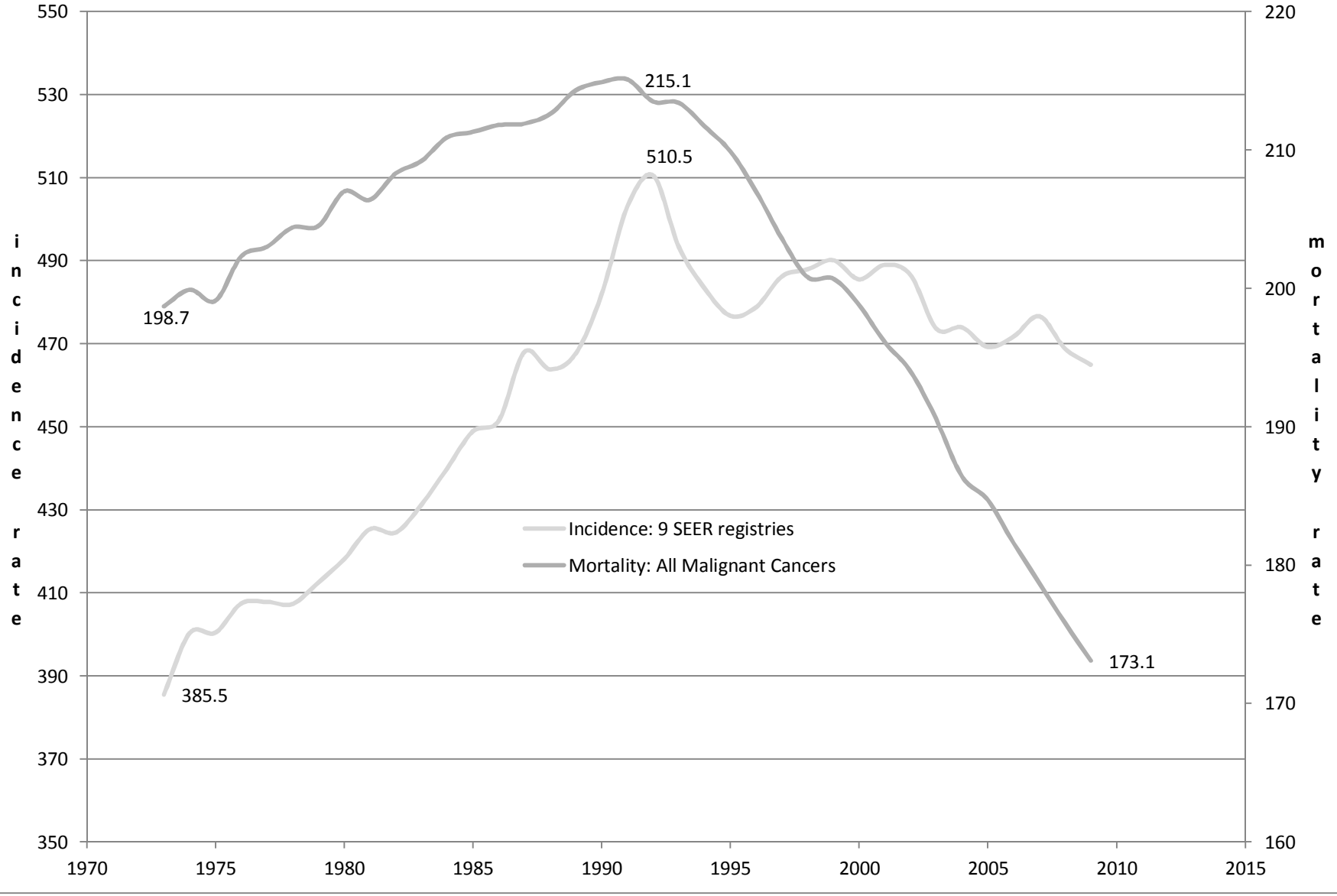

Figure 2
Log change in age-adjusted mortality rate, 1996-2009,
top 10 cancer sites (ranked by average mortality rate)

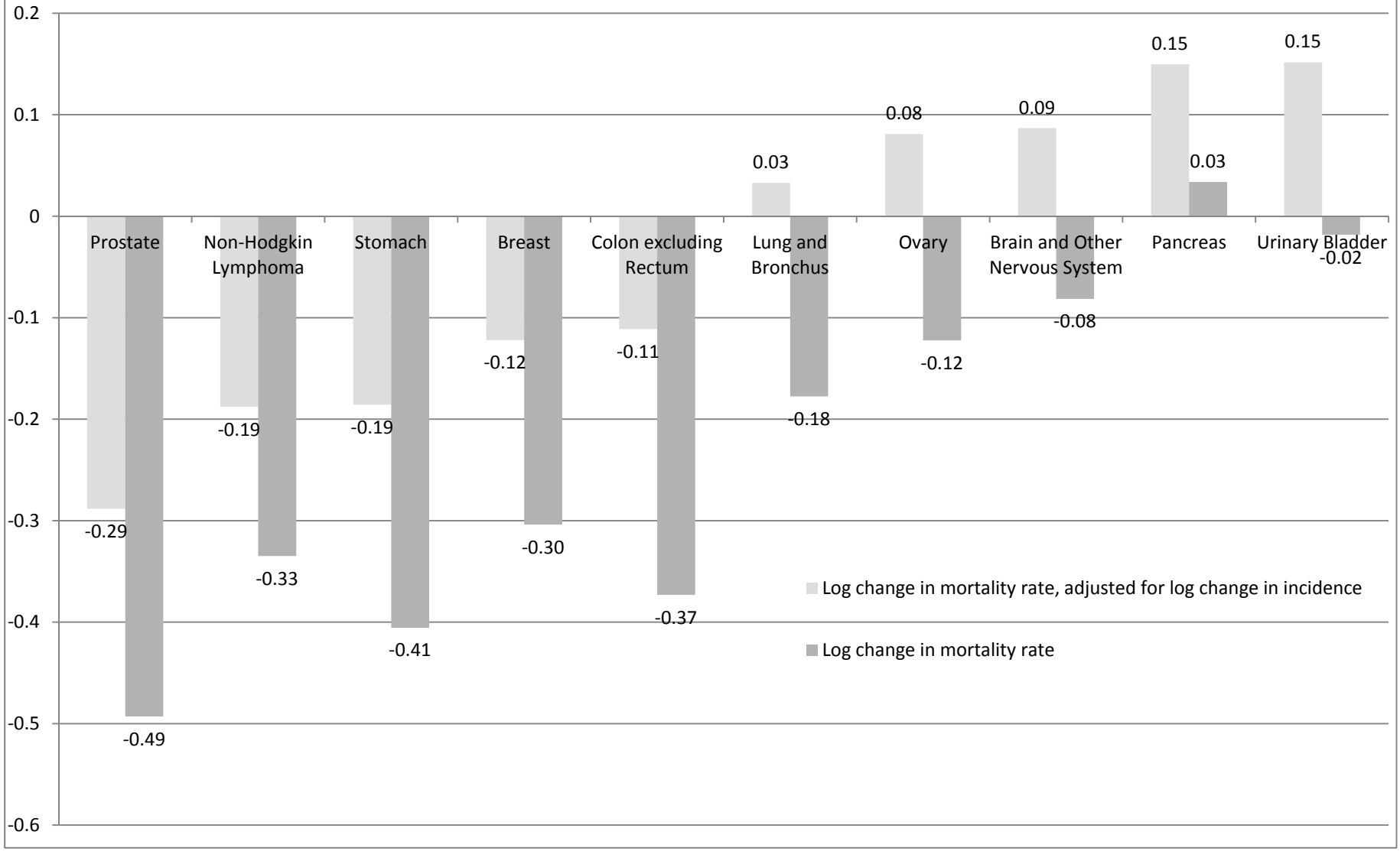

Figure 3
Age-adjusted mortality rate,
six major cancer sites, 1996-2009
(index: 1996 = 1.00)

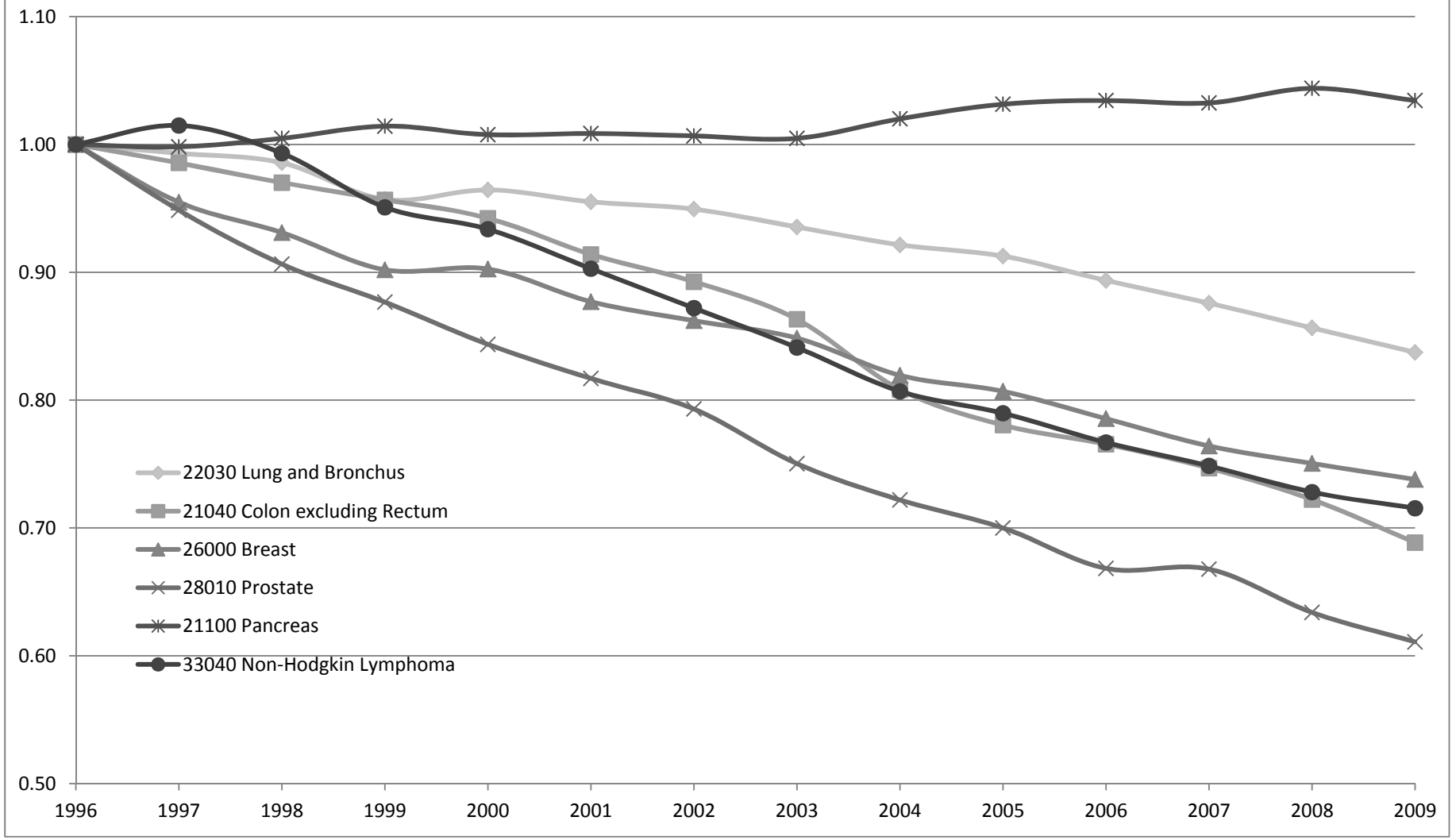

Figure 4

Heteroskedasticity: relationship across cancer sites between average mortality rate and log change in mortality rate

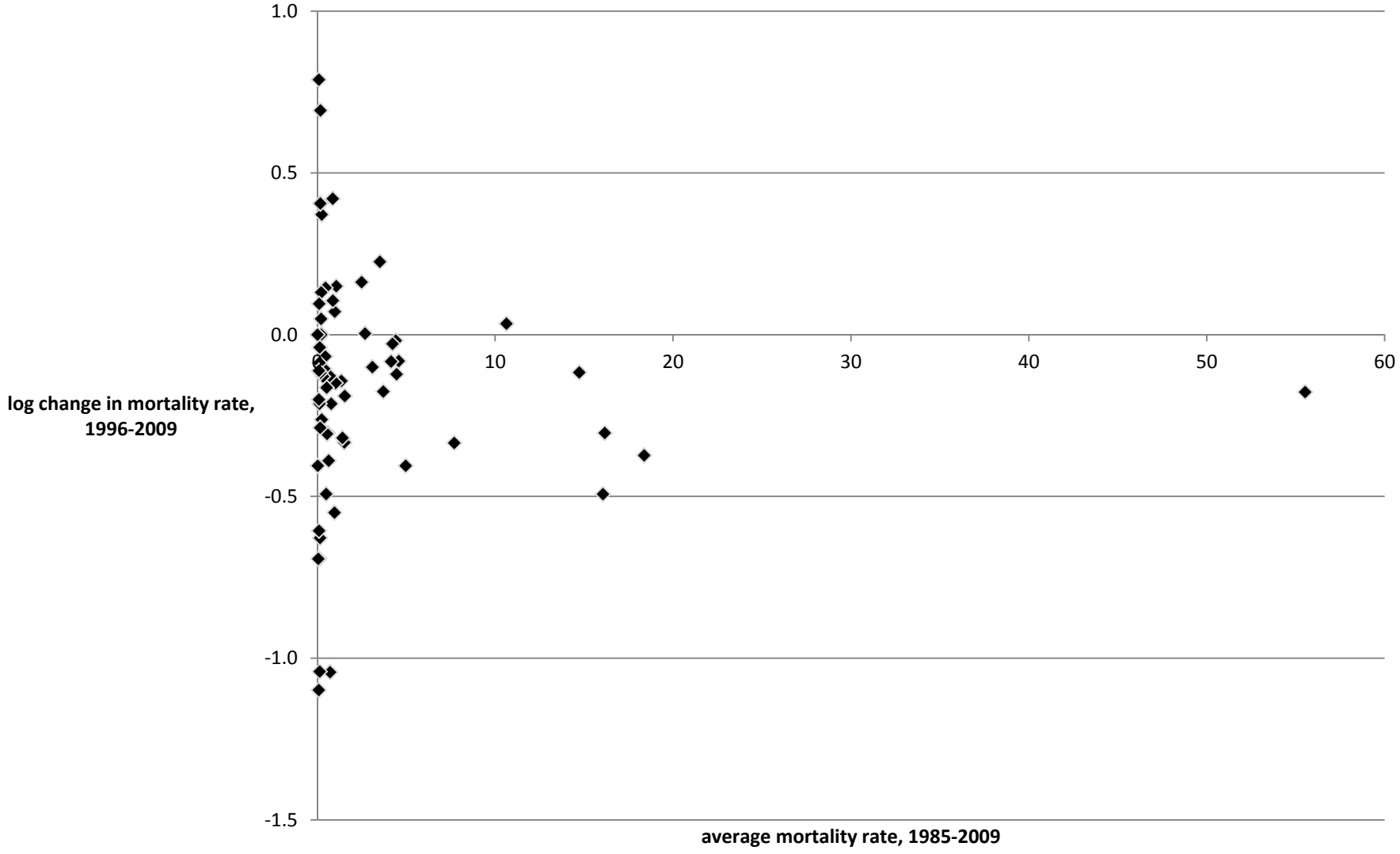

Figure 5

Ten drugs with the largest 1996-2009 increase in share of all cancer drug procedures

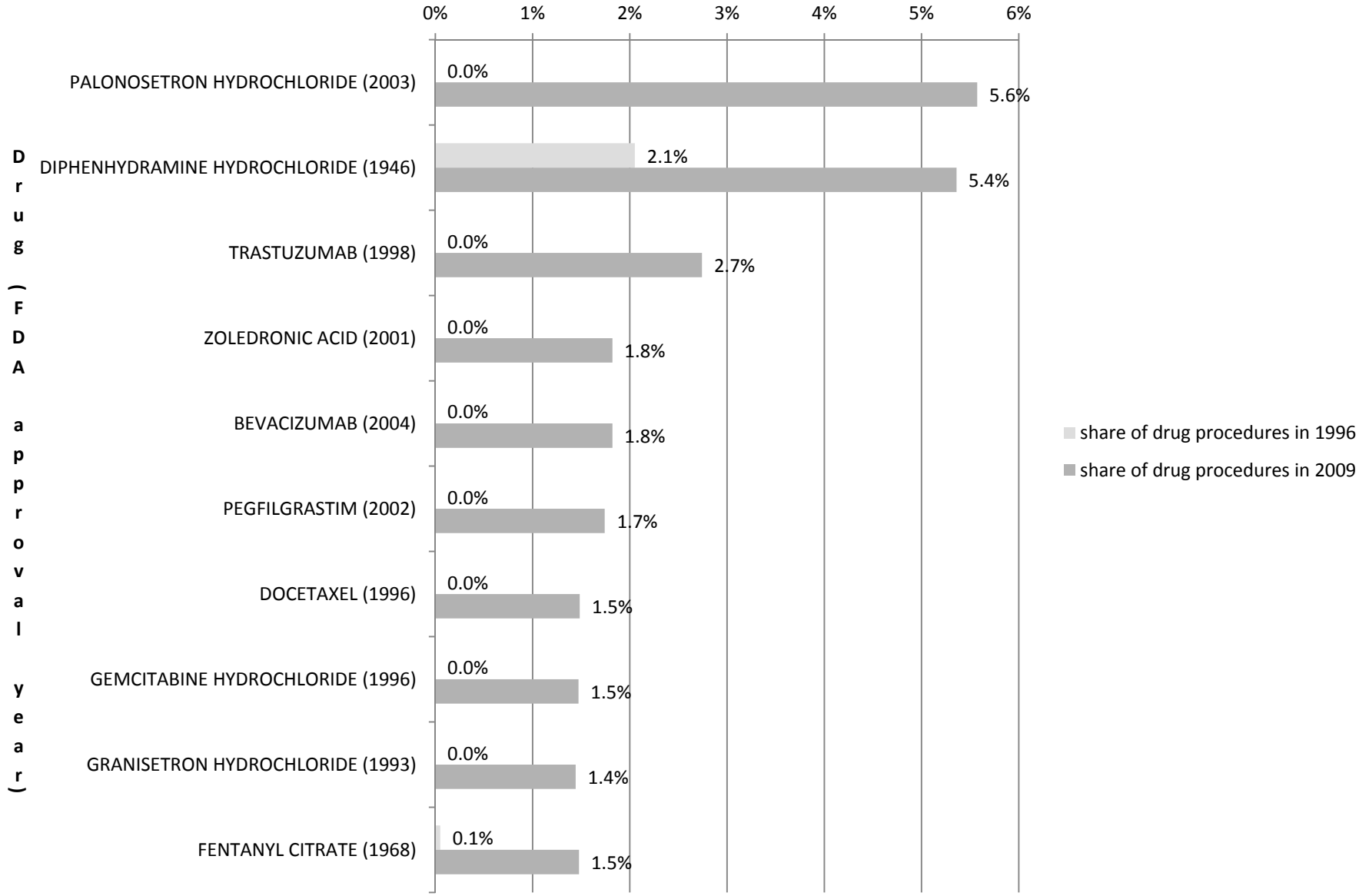

Figure 6
Fraction of drug procedures that were post-1995 drug procedures ,
6 major cancer sites, 1996-2009

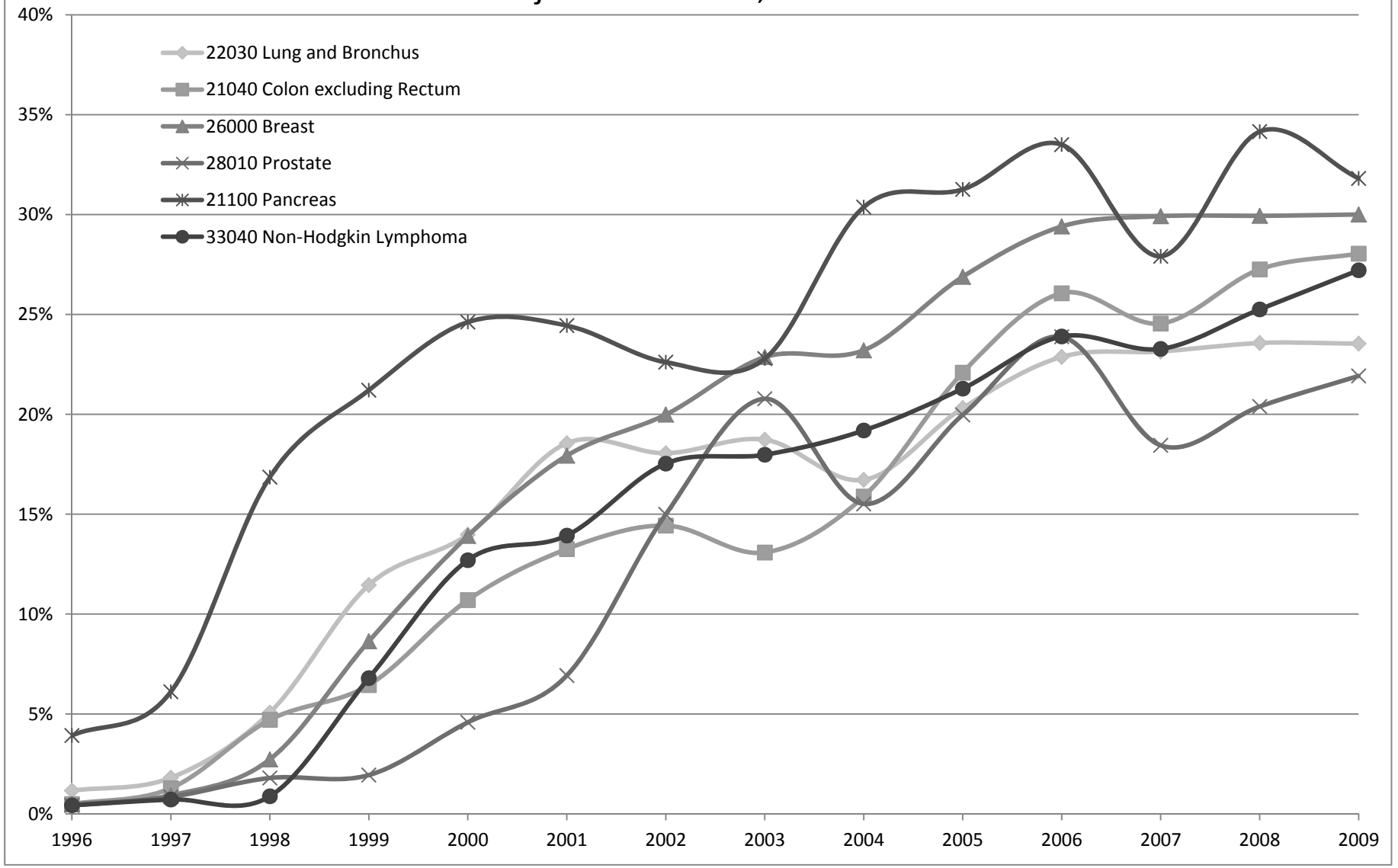

Figure 7
Ten imaging procedures with the largest 1996-2009 increase in share of all cancer imaging procedures

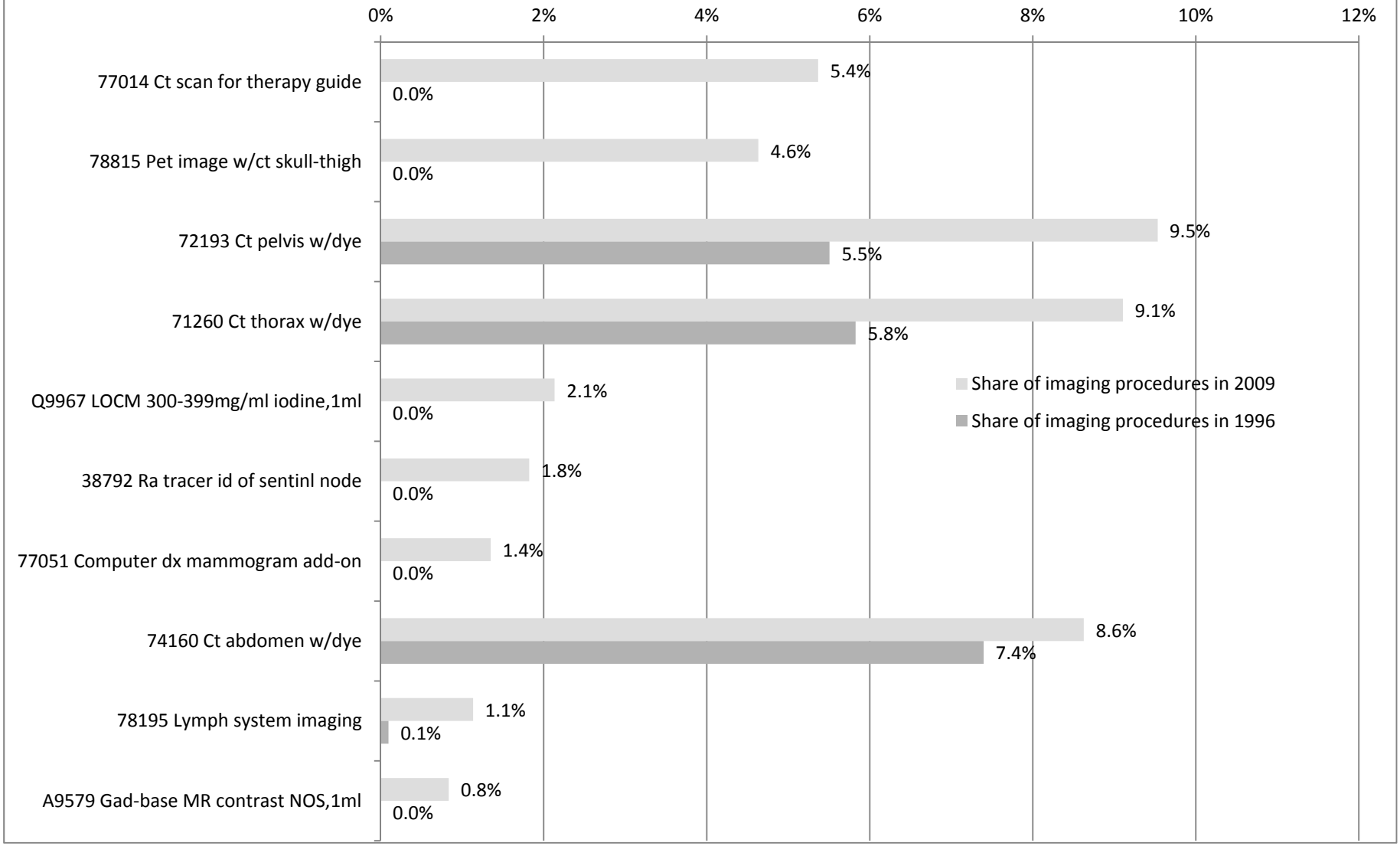

Figure 8
Fraction of imaging procedures that were advanced imaging procedures,
6 major cancer sites, 1996-2009

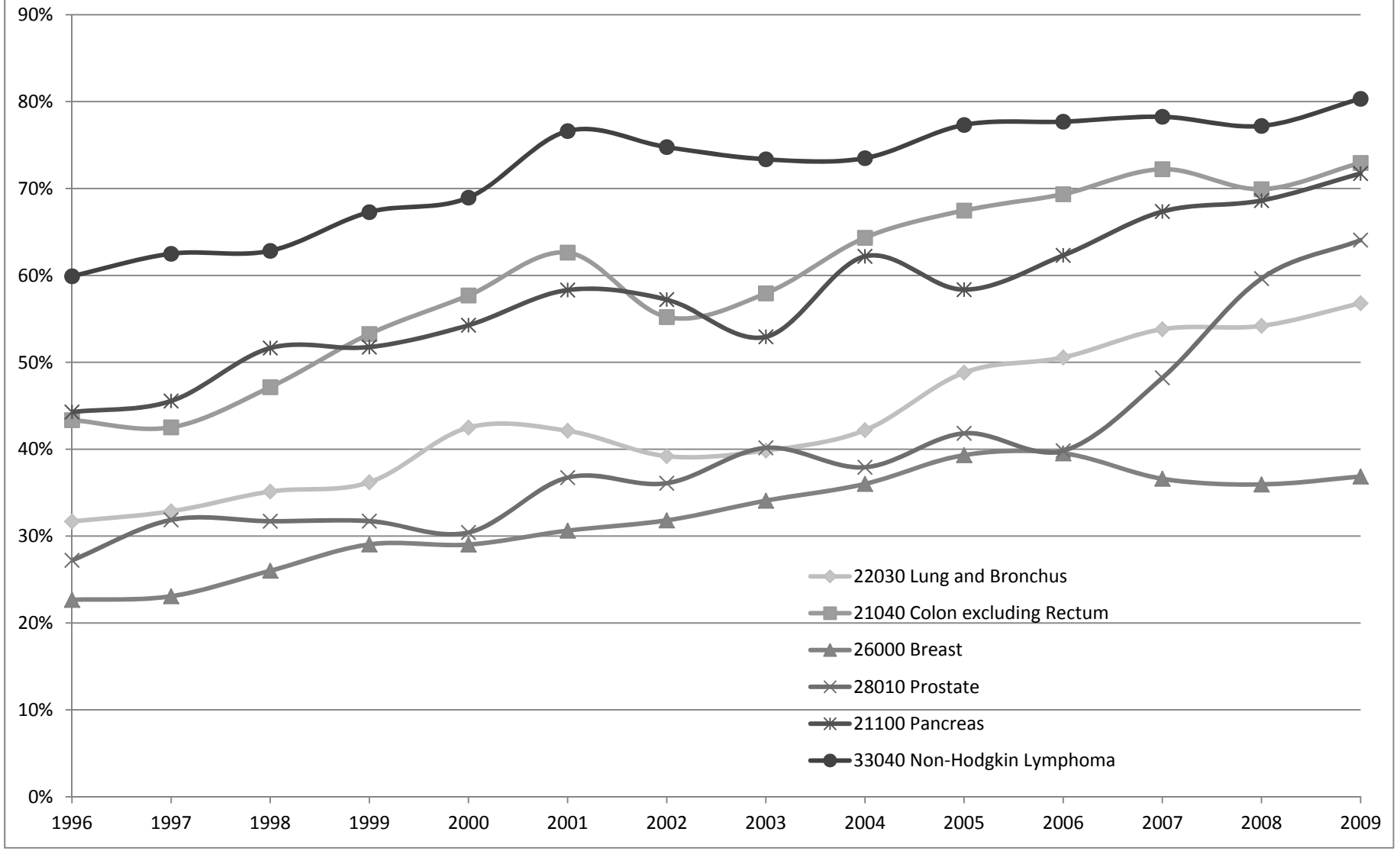

Table 1

Definition of new procedure indicator (new_p), by treatment category

Treatment category	**new_p definition**
Drug procedures	= 1 if the active ingredient was approved by the Food and Drug Administration (FDA) after 1995
	= 0 otherwise
Imaging procedures	= 1 if the procedure is designated as an "advanced imaging" procedure by the Center for Medicare and Medicaid Services (CMS)[1]
	= 0 if the procedure is designated as a "standard imaging" procedure by CMS
Radiation procedures	= 1 if the CPT code[2] for the procedure was established by the American Medical Association (AMA) after 1995
	= 0 otherwise
Surgical procedures	= 1 if the CPT code for the procedure was established by the American Medical Association after 1995
	= 0 otherwise

[1] "Advanced imaging" procedures are CAT/CT/CTA (CT Angiography) or MRI/MRA (MR Angiography) procedures, which are generally newer than "standard imaging" procedures.

[2] The Current Procedural Terminology (CPT) code set is maintained by the American Medical Association (AMA) through the CPT Editorial Panel. The CPT code set--copyright protected by the AMA-- describes medical, surgical, and diagnostic services and is designed to communicate uniform information about medical services and procedures among physicians, coders, patients, accreditation organizations, and payers for administrative, financial, and analytical purposes.

Table 2

FDA approval dates and HCPCS code establishment dates of 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,

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

Table 3

Number of “standard units” sold in the U.S. via retail and hospital channels in the years 1996-1998 of four cancer drugs approved by the FDA in 1996

	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

Table 4

Number of sample procedures, and new procedures as % of total number of procedures, by treatment type and year, 1996-2009

Year	total drug procedures	total imaging procedures	total radiation procedures	total surgical procedures
1996	52,682	58,156	63,857	90,012
1997	59,951	60,905	65,745	87,340
1998	81,961	59,062	68,016	83,431
1999	93,892	57,400	64,450	85,325
2000	102,044	57,202	80,644	86,440
2001	116,540	58,735	85,643	92,765
2002	118,860	66,928	82,068	119,204
2003	123,088	75,536	85,262	137,556
2004	124,002	77,552	86,508	131,290
2005	128,251	81,662	83,825	136,826
2006	128,149	84,569	79,288	136,435
2007	118,899	95,496	78,445	144,288
2008	117,227	99,564	83,614	150,522
2009	112,656	99,621	76,663	148,626
Total	1,478,202	1,032,388	1,084,028	1,630,060

Year	Post-1995 drug procedures/total drug procedures	advanced imaging procedures/total imaging procedures	Post-1995 radiation procedures/total radiation procedures	Post-1995 surgical procedures/total surgical procedures
1996	1%	40%	0%	5%
1997	1%	42%	0%	5%
1998	4%	44%	0%	7%
1999	9%	45%	0%	7%
2000	12%	47%	15%	8%
2001	15%	51%	16%	5%
2002	16%	51%	18%	8%
2003	18%	50%	18%	11%
2004	18%	53%	19%	17%
2005	22%	57%	21%	18%
2006	25%	57%	22%	19%
2007	25%	57%	23%	25%
2008	26%	58%	25%	27%
2009	26%	60%	27%	29%

Table 5

Data on mortality, incidence, and treatment in 1996 and 2009, top 16 cancer sites (ranked by average mortality rate during 1985-2009)

Cancer site	year	average mort. rate, 1985-2009	mort-ality rate	incid-ence rate	total drug procs.	post-1995 drug procs./total drug procs.	total imaging procs.	advanced imaging procs./total imaging procs.	total radiation procs.	post-1995 radiation procs./total radiation procs.	total surgical procs.	post-1995 surgical procs./total surgical procs.
22030 Lung and Bronchus	1996	55.5	57.9	66.4	81,619	1%	81,619	32%	7,406	0%	4,335	11%
22030 Lung and Bronchus	2009	55.5	48.5	58.8	101,013	24%	101,013	57%	5,561	18%	7,701	16%
21040 Colon excluding Rectum	1996	18.4	18.7	39.4	59,582	0%	59,582	43%	522	0%	3,811	5%
21040 Colon excluding Rectum	2009	18.4	12.9	30.5	79,826	28%	79,826	73%	306	14%	7,388	31%
26000 Breast	1996	16.2	16.8	73.3	256,945	0%	256,945	23%	20,345	0%	15,438	4%
26000 Breast	2009	16.2	12.4	69.8	275,753	30%	275,753	37%	27,277	18%	30,986	38%
28010 Prostate	1996	16.1	18.0	84.6	60,337	0%	60,337	27%	5,824	0%	5,447	6%
28010 Prostate	2009	16.1	11.0	76.0	82,238	22%	82,238	64%	12,230	53%	13,419	46%
37000 Miscellaneous Malignant Cancer	1996	14.7	14.4	11.4	73,249	1%	73,249	47%	6,775	0%	4,600	8%
37000 Miscellaneous Malignant Cancer	2009	14.7	12.9	7.3	101,921	28%	101,921	70%	10,421	17%	10,069	23%
21100 Pancreas	1996	10.6	10.5	11.3	14,344	4%	14,344	44%	881	0%	940	9%
21100 Pancreas	2009	10.6	10.8	12.8	28,360	32%	28,360	72%	654	33%	2,274	19%
33040 Non-Hodgkin Lymphoma	1996	7.7	8.8	19.4	69,308	0%	69,308	60%	1,568	0%	3,371	8%
33040 Non-Hodgkin Lymphoma	2009	7.7	6.3	20.2	88,030	27%	88,030	80%	1,317	19%	4,801	26%
21020 Stomach	1996	5.0	5.1	8.5	9,292	1%	9,292	35%	128	0%	669	2%
21020 Stomach	2009	5.0	3.4	7.3	15,132	17%	15,132	60%	497	44%	1,333	17%
31010 Brain and Other Nervous System	1996	4.6	4.7	6.7	24,967	1%	24,967	84%	2,802	0%	1,609	5%
31010 Brain and Other Nervous System	2009	4.6	4.4	6.6	36,554	31%	36,554	83%	2,366	34%	3,834	21%
27040 Ovary	1996	4.5	4.4	7.1	32,582	2%	32,582	51%	222	0%	2,530	10%
27040 Ovary	2009	4.5	3.9	6.4	33,969	23%	33,969	75%	97	11%	3,471	30%
29010 Urinary Bladder	1996	4.4	4.4	20.8	16,571	0%	16,571	27%	200	0%	3,286	4%
29010 Urinary Bladder	2009	4.4	4.3	20.5	16,488	18%	16,488	54%	81	16%	3,280	8%
21010 Esophagus	1996	4.2	4.3	4.8	10,280	0%	10,280	28%	1,166	0%	682	0%
21010 Esophagus	2009	4.2	4.2	4.6	19,221	21%	19,221	54%	1,189	39%	1,808	22%
29020 Kidney and Renal Pelvis	1996	4.2	4.3	11.4	15,336	2%	15,336	39%	285	0%	974	3%
29020 Kidney and Renal Pelvis	2009	4.2	3.9	15.0	27,087	33%	27,087	67%	133	16%	2,954	31%
34000 Myeloma	1996	3.7	3.9	5.8	22,130	1%	22,130	31%	753	0%	1,092	7%
34000 Myeloma	2009	3.7	3.3	6.1	46,619	43%	46,619	47%	496	14%	2,441	26%
21071 Liver	1996	3.5	3.6	4.6	3,940	2%	3,940	51%	130	0%	389	3%
21071 Liver	2009	3.5	4.5	7.1	10,763	21%	10,763	57%	53	13%	1,179	17%
21050 Rectum and Rectosigmoid Junction	1996	3.1	3.1	15.4	37,309	1%	37,309	45%	2,138	0%	2,836	2%
21050 Rectum and Rectosigmoid Junction	2009	3.1	2.8	12.2	40,340	27%	40,340	74%	1,889	23%	4,556	28%

Table 6

Estimates of six versions of the model of the age-adjusted mortality rate (eq. (6))

Model	1	2	3	4	5	6
ln(inc_rate)	**0.3923**	**0.3925**	**0.4837**	**0.3987**	**0.3645**	
Chi-Square (p-value)	**32.69 (<.0001)**	**27.54 (<.0001)**	**36.87 (<.0001)**	**24.01 (<.0001)**	**23.58 (<.0001)**	
drug_vintage	**-0.3807**				**-0.4124**	**-0.6347**
Chi-Square (p-value)	**11.41 (0.0007)**				**16.37 (<.0001)**	**25.35 (<.0001)**
imaging_vintage		**-0.2438**			**-0.2807**	**-0.4268**
Chi-Square (p-value)		**3.98 (0.046)**			**5.03 (0.0249)**	**13.15 (0.0003)**
radiation_vintage			-0.1565		-0.154	-0.1102
Chi-Square (p-value)			2.04 (0.1532)		2.53 (0.1116)	0.79 (0.3738)
surgery_vintage				0.0327	0.1676	0.1539
Chi-Square (p-value)				0.05 (0.8297)	1.43 (0.2311)	1.64 (0.1998)
mean age at diagnosis	0.0184	0.0172	0.0143	0.0176	0.0167	**0.023**
Chi-Square (p-value)	2.84 (0.0921)	2.53 (0.1117)	2.1 (0.1476)	2.61 (0.1064)	3.62 (0.0571)	**5.86 (0.0155)**
% in situ	0.0115	-0.1969	-0.0922	-0.0627	0.0893	0.2289
Chi-Square (p-value)	0 (0.9618)	0.48 (0.4902)	0.19 (0.6654)	0.06 (0.806)	0.16 (0.6869)	0.48 (0.4865)
% localized-regional	0.0568	0.0469	-0.0036	0.0406	0.0146	**0.1607**
Chi-Square (p-value)	1.02 (0.3135)	0.38 (0.5403)	0 (0.9529)	0.27 (0.6041)	0.07 (0.791)	**3.91 (0.0479)**
% distant	0.2521	0.3284	0.2714	0.3104	0.187	-0.1542
Chi-Square (p-value)	2.25 (0.1338)	3.47 (0.0627)	1.37 (0.2421)	3.25 (0.0713)	1.04 (0.3075)	0.6 (0.4389)
% white	-0.0249	-0.0033	0.2121	-0.1414	0.3692	0.3784
Chi-Square (p-value)	0 (0.9599)	0 (0.9952)	0.15 (0.7025)	0.05 (0.8209)	0.57 (0.4509)	0.47 (0.4945)
% male	0.6559	0.3514	0.4858	0.4739	0.5715	0.5613
Chi-Square (p-value)	3.62 (0.0572)	1.08 (0.2992)	1.47 (0.2258)	1.72 (0.1903)	2.73 (0.0987)	1.66 (0.1977)

Statistically significant estimates (p-value < 0.05) are **bold**. All models were estimated via weighted least-squares, weighting by the mean mortality rate of cancer site s during the period 1985-2009. Disturbances are clustered within cancer sites. All models include cancer-site fixed effects and year fixed effects (not reported to conserve space), and all models were estimated using annual data during the period 2000-2009. Also to conserve space, only estimates of the *sums* of coefficients of current and lagged values of variables (e.g. $\Sigma_{k=0}{}^{4}\,\beta_{1k}$) are reported. Sums of coefficients are estimates of long-run effects.

Table 7

Estimated contribution of different factors to the 2000-2009 decline in the age-adjusted cancer mortality rate

Column	1	2	3	4	5	6	7	
Factor	change in variable, 1996-2000 to 2005-2009	estimated long-run effect (Table 3, model 5)			contribution to 2000-2009 mortality rate decline			formula for calculating contribution
		Lower	Mean	Upper	Lower	Mean	Upper	
ln(inc_rate)	-3%	0.2174	0.3645	0.5116	-0.7%	**-1.2%**	-1.7%	$(\Sigma_{k=0}^{4} \gamma_k)$ ln(inc_rate$_{2005\text{-}2009}$ /inc_rate$_{1996\text{-}2000}$)
drug innovation	19%	-0.2126	-0.4124	-0.6121	-4.1%	**-8.0%**	-11.9%	$(\Sigma_{k=0}^{4} \beta_{1k})$ (drug_vintage$_{2005\text{-}2009}$ - drug_vintage$_{1996\text{-}2000}$)
imaging innovation	14%	-0.0354	-0.2807	-0.5261	-0.5%	**-4.0%**	-7.4%	$(\Sigma_{k=0}^{4} \beta_{2k})$ (imaging_vintage$_{2005\text{-}2009}$ - imaging_vintage$_{1996\text{-}2000}$)
Total					-5.3%	-13.2%	-21.0%	

During the period 2000-2009, the age-adjusted cancer mortality rate declined by 13.8%. If the distribution of cancer deaths by cancer site had not changed, the mortality rate would have declined slightly more, by 14.3%.

inc_rate$_{2005\text{-}2009}$ is the mean value of the age-adjusted incidence rate during 2005-2009

Appendix Table 1

Data on mortality, incidence, and treatment in 1996 and 2009, for 50 cancer sites not shown in Table 5 (ranked by average mortality rate during 1985-2009)

Cancer site	year	average mort. rate, 1985-2009	mort-ality rate	incid-ence rate	total drug procs.	post-1995 drug procs./total drug procs.	total imaging procs.	advanced imaging procs./total imaging procs.	total radiation procs.	post-1995 radiation procs./total radiation procs.	total surgical procs.	post-1995 surgical procs./total surgical procs.
25010 Melanoma of the Skin	1996	2.7	2.8	17.3	20,724	0%	20,724	31%	268	0%	2,526	3%
25010 Melanoma of the Skin	2009	2.7	2.8	22.6	20,548	6%	20,548	57%	308	23%	3,118	10%
35021 Acute myeloid	1996	2.5	2.4	3.5	12,772	1%	12,772	15%	29	0%	618	13%
35021 Acute myeloid	2009	2.5	2.9	3.6	51,695	24%	51,695	39%	213	4%	1,836	56%
35012 Chronic Lymphocytic Leukemia	1996	1.5	1.7	4.6	9,796	0%	9,796	31%	4	0%	564	5%
35012 Chronic Lymphocytic Leukemia	2009	1.5	1.4	4.5	18,841	24%	18,841	78%	15	0%	1,222	17%
27010 Cervix Uteri	1996	1.5	1.6	4.8	13,848	3%	13,848	43%	1,175	0%	495	2%
27010 Cervix Uteri	2009	1.5	1.2	3.4	9,204	18%	9,204	73%	1,362	28%	951	30%
22020 Larynx	1996	1.4	1.5	4.3	6,499	0%	6,499	29%	1,489	0%	689	11%
22020 Larynx	2009	1.4	1.1	3.1	5,404	16%	5,404	74%	795	40%	752	5%
24000 Soft Tissue including Heart$	1996	1.4	1.5	2.8	8,680	1%	8,680	52%	604	0%	658	5%
24000 Soft Tissue including Heart$	2009	1.4	1.3	3.3	15,896	19%	15,896	65%	960	23%	1,278	21%
27030 Uterus, NOS	1996	1.1	1.0	0.2	2,055	1%	2,055	58%	349	1%	112	4%
27030 Uterus, NOS	2009	1.1	1.2	0.3	2,882	3%	2,882	79%	150	10%	265	34%
27020 Corpus Uteri	1996	1.0	1.0	12.2	10,026	0%	10,026	47%	1,141	0%	982	8%
27020 Corpus Uteri	2009	1.0	0.9	13.3	22,193	14%	22,193	70%	1,102	18%	2,966	34%
35043 Aleukemic, subleukemic and NOS	1996	1.0	1.0	0.4	5,478	0%	5,478	24%	87	0%	266	19%
35043 Aleukemic, subleukemic and NOS	2009	1.0	1.0	0.4	5,044	2%	5,044	50%	49	16%	307	48%
35041 Other Acute Leukemia	1996	1.0	1.0	0.5	1,843	0%	1,843	26%	24	0%	102	4%
35041 Other Acute Leukemia	2009	1.0	0.6	0.2	3,285	8%	3,285	38%	2	0%	150	64%
25020 Other Non-Epithelial Skin	1996	0.9	0.8	1.9	49,504	7%	49,504	20%	660	0%	23,392	4%
25020 Other Non-Epithelial Skin	2009	0.9	0.9	2.0	37,340	6%	37,340	55%	672	15%	18,324	25%
21072 Intrahepatic Bile Duct	1996	0.9	0.9	0.9	281	.	281	50%	27	0%	42	5%
21072 Intrahepatic Bile Duct	2009	0.9	1.3	0.8	2,474	29%	2,474	52%	52	10%	279	12%
21080 Gallbladder	1996	0.8	0.8	1.1	821	0%	821	50%	37	0%	35	6%
21080 Gallbladder	2009	0.8	0.6	1.2	1,300	42%	1,300	67%	.	.	103	22%
35022 Chronic Myeloid Leukemia	1996	0.7	0.9	1.8	7,458	0%	7,458	14%	61	0%	466	12%
35022 Chronic Myeloid Leukemia	2009	0.7	0.3	1.7	7,140	7%	7,140	58%	24	13%	518	33%
20020 Tongue	1996	0.7	0.7	2.6	3,509	0%	3,509	29%	589	0%	372	5%
20020 Tongue	2009	0.7	0.6	3.3	8,341	17%	8,341	73%	885	54%	958	9%
21090 Other Biliary	1996	0.6	0.6	1.3	1,293	11%	1,293	18%	155	1%	68	1%
21090 Other Biliary	2009	0.6	0.4	1.7	3,130	43%	3,130	70%	149	44%	320	8%
20100 Other Oral Cavity and Pharynx	1996	0.6	0.6	0.4	1,415	2%	1,415	33%	167	0%	135	4%

Appendix Table 1

Data on mortality, incidence, and treatment in 1996 and 2009, for 50 cancer sites not shown in Table 5 (ranked by average mortality rate during 1985-2009)

Cancer site	year	average mort. rate, 1985-2009	mort-ality rate	incid-ence rate	total drug procs.	post-1995 drug procs./total drug procs.	total imaging procs.	advanced imaging procs./total imaging procs.	total radiation procs.	post-1995 radiation procs./total radiation procs.	total surgical procs.	post-1995 surgical procs./total surgical procs.
20100 Other Oral Cavity and Pharynx	2009	0.6	0.5	0.2	562	0%	562	26%	8	38%	70	10%
33010 Hodgkin Lymphoma	1996	0.5	0.5	2.8	17,161	0%	17,161	49%	776	0%	843	7%
33010 Hodgkin Lymphoma	2009	0.5	0.4	2.9	18,714	17%	18,714	79%	566	13%	950	29%
35011 Acute Lymphocytic Leukemia	1996	0.5	0.5	1.4	11,047	5%	11,047	17%	81	0%	635	10%
35011 Acute Lymphocytic Leukemia	2009	0.5	0.5	1.4	32,476	3%	32,476	36%	177	14%	1,321	59%
20050 Gum and Other Mouth	1996	0.5	0.5	1.8	1,766	0%	1,766	38%	217	0%	254	4%
20050 Gum and Other Mouth	2009	0.5	0.3	1.6	1,862	23%	1,862	71%	114	31%	411	11%
32010 Thyroid	1996	0.5	0.5	6.5	7,647	1%	7,647	13%	201	0%	738	8%
32010 Thyroid	2009	0.5	0.5	14.3	24,995	36%	24,995	27%	288	32%	3,364	5%
23000 Bones and Joints	1996	0.5	0.5	0.8	7,445	4%	7,445	41%	747	0%	497	4%
23000 Bones and Joints	2009	0.5	0.4	1.0	13,354	15%	13,354	49%	453	27%	1,445	24%
21030 Small Intestine	1996	0.4	0.4	1.7	2,186	0%	2,186	32%	5	0%	208	4%
21030 Small Intestine	2009	0.4	0.4	2.2	3,206	23%	3,206	78%	79	35%	302	15%
32020 Other Endocrine including Thymus$	1996	0.3	0.3	0.7	4,322	0%	4,322	59%	393	0%	203	5%
32020 Other Endocrine including Thymus$	2009	0.3	0.3	0.7	6,024	33%	6,024	64%	148	31%	700	38%
20030 Salivary Gland	1996	0.3	0.2	1.3	1,691	0%	1,691	70%	327	0%	137	5%
20030 Salivary Gland	2009	0.3	0.2	1.3	1,953	15%	1,953	83%	436	50%	214	19%
20060 Nasopharynx	1996	0.2	0.3	0.8	1,730	0%	1,730	47%	289	0%	104	2%
20060 Nasopharynx	2009	0.2	0.2	0.6	2,023	8%	2,023	71%	170	42%	226	31%
21130 Other Digestive Organs	1996	0.2	0.2	0.4	353	.	353	33%	.	.	59	0%
21130 Other Digestive Organs	2009	0.2	0.3	0.5	343	0%	343	78%	1	0%	27	11%
27060 Vulva	1996	0.2	0.2	1.2	820	0%	820	10%	53	0%	122	1%
27060 Vulva	2009	0.2	0.2	1.3	1,089	21%	1,089	67%	87	11%	167	10%
20070 Tonsil	1996	0.2	0.2	1.2	1,721	0%	1,721	29%	412	0%	107	3%
20070 Tonsil	2009	0.2	0.2	1.8	4,666	14%	4,666	84%	840	62%	404	6%
20080 Oropharynx	1996	0.2	0.2	0.3	432	33%	432	31%	122	0%	31	3%
20080 Oropharynx	2009	0.2	0.2	0.3	1,463	12%	1,463	92%	312	60%	130	3%
22010 Nose, Nasal Cavity and Middle Ear	1996	0.2	0.2	0.7	1,184	.	1,184	68%	267	0%	89	0%
22010 Nose, Nasal Cavity and Middle Ear	2009	0.2	0.2	0.7	1,863	11%	1,863	77%	224	47%	327	3%
35023 Other Myeloid/Monocytic Leukemia	1996	0.2	0.1	0.2	1,828	0%	1,828	4%	42	0%	108	10%
35023 Other Myeloid/Monocytic Leukemia	2009	0.2	0.2	0.1	1,798	7%	1,798	51%	.	.	70	60%
21060 Anus, Anal Canal and Anorectum	1996	0.2	0.2	1.3	2,207	0%	2,207	39%	373	0%	149	11%
21060 Anus, Anal Canal and Anorectum	2009	0.2	0.2	1.7	6,046	16%	6,046	79%	725	32%	630	54%

Appendix Table 1

Data on mortality, incidence, and treatment in 1996 and 2009, for 50 cancer sites not shown in Table 5 (ranked by average mortality rate during 1985-2009)

Cancer site	year	average mort. rate, 1985-2009	mort-ality rate	incid-ence rate	total drug procs.	post-1995 drug procs./total drug procs.	total imaging procs.	advanced imaging procs./total imaging procs.	total radiation procs.	post-1995 radiation procs./total radiation procs.	total surgical procs.	post-1995 surgical procs./total surgical procs.
21120 Peritoneum, Omentum and Mesentery	1996	0.2	0.2	0.5	1,261	0%	1,261	43%	4	0%	92	4%
21120 Peritoneum, Omentum and Mesentery	2009	0.2	0.2	0.6	2,939	23%	2,939	59%	.	.	476	31%
35013 Other Lymphocytic Leukemia	1996	0.2	0.2	0.5	2,366	7%	2,366	44%	.	.	177	3%
35013 Other Lymphocytic Leukemia	2009	0.2	0.1	0.4	1,938	13%	1,938	76%	1	100%	139	17%
20090 Hypopharynx	1996	0.2	0.2	0.9	597	.	597	38%	129	0%	79	1%
20090 Hypopharynx	2009	0.2	0.1	0.6	522	0%	522	55%	11	36%	120	13%
28020 Testis	1996	0.1	0.1	2.6	8,682	1%	8,682	51%	388	0%	365	2%
28020 Testis	2009	0.1	0.1	2.9	11,454	12%	11,454	71%	180	16%	752	7%
22050 Pleura	1996	0.1	0.2	0.0	881	0%	881	29%	44	0%	66	0%
22050 Pleura	2009	0.1	0.1	0.0	1,278	28%	1,278	47%	.	.	79	24%
27050 Vagina	1996	0.1	0.1	0.3	618	.	618	37%	81	1%	72	3%
27050 Vagina	2009	0.1	0.1	0.4	1,163	14%	1,163	85%	139	37%	111	18%
29030 Ureter	1996	0.1	0.1	0.6	328	.	328	42%	3	0%	30	3%
29030 Ureter	2009	0.1	0.1	0.6	359	0%	359	16%	10	20%	94	34%
22060 Trachea, Mediastinum and Other Respiratory Organs	1996	0.1	0.1	0.2	4,975	0%	4,975	32%	339	0%	483	1%
22060 Trachea, Mediastinum and Other Respiratory Organs	2009	0.1	0.1	0.2	1,086	0%	1,086	36%	64	33%	152	13%
27070 Other Female Genital Organs	1996	0.1	0.1	0.4	2,716	1%	2,716	54%	175	0%	172	12%
27070 Other Female Genital Organs	2009	0.1	0.1	0.6	2,049	29%	2,049	77%	.	.	191	21%
21110 Retroperitoneum	1996	0.1	0.1	0.4	833	0%	833	73%	2	0%	106	3%
21110 Retroperitoneum	2009	0.1	0.1	0.4	1,425	0%	1,425	55%	11	0%	296	41%
28030 Penis	1996	0.1	0.1	0.3	636	0%	636	50%	.	.	62	2%
28030 Penis	2009	0.1	0.1	0.4	157	.	157	68%	.	.	35	6%
30000 Eye and Orbit	1996	0.1	0.1	0.9	1,864	6%	1,864	75%	173	0%	151	11%
30000 Eye and Orbit	2009	0.1	0.1	0.8	1,971	24%	1,971	81%	121	26%	221	27%
29040 Other Urinary Organs	1996	0.1	0.1	0.3	1,130	15%	1,130	56%	21	0%	94	1%
29040 Other Urinary Organs	2009	0.1	0.1	0.3	819	4%	819	87%	80	9%	60	20%
20040 Floor of Mouth	1996	0.1	0.1	1.1	606	.	606	0%	53	0%	107	4%
20040 Floor of Mouth	2009	0.1	0.0	0.7	851	11%	851	68%	102	11%	212	6%
35031 Acute Monocytic Leukemia	1996	0.1	0.1	0.2	1,088	.	1,088	11%	.	.	36	17%
35031 Acute Monocytic Leukemia	2009	0.1	0.0	0.2	1,098	0%	1,098	87%	.	.	29	66%
20010 Lip	1996	0.0	0.0	1.4	440	.	440	14%	13	0%	91	22%
20010 Lip	2009	0.0	0.0	0.6	230	17%	230	31%	11	36%	40	8%

Appendix Table 1

Data on mortality, incidence, and treatment in 1996 and 2009, for 50 cancer sites not shown in Table 5 (ranked by average mortality rate during 1985-2009)

Cancer site	year	average mort. rate, 1985-2009	mort-ality rate	incid-ence rate	total drug procs.	post-1995 drug procs./total drug procs.	total imaging procs.	advanced imaging procs./total imaging procs.	total radiation procs.	post-1995 radiation procs./total radiation procs.	total surgical procs.	post-1995 surgical procs./total surgical procs.
28040 Other Male Genital Organs	1996	0.0	0.0	0.2	342	.	342	69%	116	0%	14	0%
28040 Other Male Genital Organs	2009	0.0	0.0	0.2	243	.	243	68%	.	.	20	0%

Appendix Table 2

Estimates of all parameters of model 5 in Table 6

Parameter	Estimate	Empirical Standard Error Estimates	Z	Pr > |Z|
$drug\_vintage_{it}$	-0.1219	0.0376	-3.25	0.0012
$drug\_vintage_{it-1}$	-0.1138	0.037	-3.08	0.0021
$drug\_vintage_{it-2}$	-0.0768	0.0299	-2.57	0.0102
$drug\_vintage_{it-3}$	-0.0759	0.0323	-2.35	0.0188
$drug\_vintage_{it-4}$	-0.024	0.0419	-0.57	0.5671
$imaging\_vintage_{it}$	-0.0745	0.0495	-1.50	0.1324
$imaging\_vintage_{it-1}$	-0.0337	0.0368	-0.92	0.3601
$imaging\_vintage_{it-2}$	-0.0515	0.0376	-1.37	0.1706
$imaging\_vintage_{it-3}$	-0.051	0.0377	-1.35	0.1763
$imaging\_vintage_{it-4}$	-0.07	0.0502	-1.40	0.163
$radiation\_vintage_{it}$	-0.0198	0.0334	-0.59	0.5531
$radiation\_vintage_{it-1}$	-0.0118	0.0322	-0.37	0.7126
$radiation\_vintage_{it-2}$	-0.0317	0.0306	-1.04	0.3
$radiation\_vintage_{it-3}$	-0.0494	0.0409	-1.21	0.2273
$radiation\_vintage_{it-4}$	-0.0413	0.0471	-0.88	0.3805
$surgery\_vintage_{it}$	-0.1026	0.0572	-1.79	0.0729
$surgery\_vintage_{it-1}$	0.0889	0.0475	1.87	0.0614
$surgery\_vintage_{it-2}$	0.0588	0.0471	1.25	0.212
$surgery\_vintage_{it-3}$	0.0516	0.0404	1.28	0.2018
$surgery\_vintage_{it-4}$	0.0708	0.0687	1.03	0.3023
$\ln(inc\_rate_{it})$	0.1368	0.0598	2.29	0.0221
$\ln(inc\_rate_{it-1})$	0.1761	0.0419	4.20	<.0001
$\ln(inc\_rate_{it-2})$	0.0015	0.0406	0.04	0.9711
$\ln(inc\_rate_{it-3})$	-0.0154	0.0343	-0.45	0.6543
$\ln(inc\_rate_{it-4})$	0.0655	0.0524	1.25	0.2114
age_diag_{it}	0.011	0.0028	3.96	<.0001
age_diag_{it-1}	0.0048	0.0029	1.65	0.0994
age_diag_{it-2}	0.001	0.0034	0.30	0.7654
age_diag_{it-3}	0	0.003	-0.01	0.9942
age_diag_{it-4}	-0.0002	0.0023	-0.09	0.9321
$\%in\_situ_{it}$	0.0199	0.1652	0.12	0.9043

Appendix Table 2

Estimates of all parameters of model 5 in Table 6

Parameter	Estimate	Empirical Standard Error Estimates	Z	Pr > |Z|
$\%in\_situ_{it-1}$	0.0742	0.1176	0.63	0.5279
$\%in\_situ_{it-2}$	-0.0804	0.1199	-0.67	0.5023
$\%in\_situ_{it-3}$	0.2073	0.1402	1.48	0.1394
$\%in\_situ_{it-4}$	-0.1316	0.1203	-1.09	0.2741
$\%loc\_reg_{it}$	0.0372	0.0313	1.19	0.2343
$\%loc\_reg_{it-1}$	-0.0003	0.0263	-0.01	0.9912
$\%loc\_reg_{it-2}$	-0.0339	0.0323	-1.05	0.2936
$\%loc\_reg_{it-3}$	0.0249	0.028	0.89	0.3737
$\%loc\_reg_{it-4}$	-0.0133	0.031	-0.43	0.6673
$\%distant_{it}$	0.1278	0.1243	1.03	0.3038
$\%distant_{it-1}$	0.0155	0.0846	0.18	0.8549
$\%distant_{it-2}$	0.0085	0.0901	0.09	0.9245
$\%distant_{it-3}$	-0.0415	0.0811	-0.51	0.609
$\%distant_{it-4}$	0.0767	0.1493	0.51	0.6076
$\%male_{it}$	0.3862	0.0921	4.19	<.0001
$\%male_{it-1}$	0.1145	0.1269	0.90	0.3668
$\%male_{it-2}$	-0.0738	0.1675	-0.44	0.6594
$\%male_{it-3}$	-0.004	0.1122	-0.04	0.9716
$\%male_{it-4}$	0.1485	0.1244	1.19	0.2324
$\%white_{it}$	-0.0394	0.1506	-0.26	0.7938
$\%white_{it-1}$	0.1751	0.1568	1.12	0.264
$\%white_{it-2}$	0.0917	0.1486	0.62	0.5372
$\%white_{it-3}$	0.1204	0.1543	0.78	0.4353
$\%white_{it-4}$	0.0214	0.138	0.15	0.8769
year 2000	-0.0078	0.0311	-0.25	0.8019
year 2001	-0.0049	0.0266	-0.19	0.8529
year 2002	0.007	0.0238	0.30	0.7679
year 2003	0.0146	0.0226	0.65	0.5179
year 2004	0.0229	0.0217	1.05	0.2914
year 2005	0.0268	0.0186	1.44	0.1512
year 2006	0.0153	0.0166	0.92	0.356
year 2007	0.0073	0.012	0.60	0.5452
year 2008	-0.0023	0.007	-0.33	0.7414

Appendix Table 2

Estimates of all parameters of model 5 in Table 6

Parameter	Estimate	Empirical Standard Error Estimates	Z	Pr > |Z|
year 2009	0	0	.	.
site 20010 Lip	-5.9498	0.2247	-26.48	<.0001
site 20020 Tongue	-2.7438	0.1287	-21.33	<.0001
site 20030 Salivary Gland	-3.2657	0.1647	-19.83	<.0001
site 20040 Floor of Mouth	-5.2176	0.23	-22.69	<.0001
site 20050 Gum and Other Mouth	-2.9853	0.1501	-19.89	<.0001
site 20060 Nasopharynx	-2.9887	0.303	-9.86	<.0001
site 20070 Tonsil	-3.5872	0.1854	-19.35	<.0001
site 20080 Oropharynx	-3.0913	0.273	-11.32	<.0001
site 20090 Hypopharynx	-4.179	0.2239	-18.66	<.0001
site 20100 Other Oral Cavity and Pharynx	-2.0194	0.2858	-7.07	<.0001
site 21010 Esophagus	-1.1834	0.1189	-9.95	<.0001
site 21020 Stomach	-1.3349	0.121	-11.03	<.0001
site 21030 Small Intestine	-3.0813	0.1245	-24.75	<.0001
site 21060 Anus, Anal Canal and Anorectum	-3.4776	0.1804	-19.27	<.0001
site 21071 Liver	-1.0747	0.1587	-6.77	<.0001
site 21072 Intrahepatic Bile Duct	-1.5006	0.2068	-7.26	<.0001
site 21080 Gallbladder	-2.2607	0.1588	-14.24	<.0001
site 21090 Other Biliary	-2.817	0.1352	-20.84	<.0001
site 21100 Pancreas	-0.4293	0.101	-4.25	<.0001
site 21110 Retroperitoneum	-3.964	0.2557	-15.50	<.0001
site 22010 Nose, Nasal Cavity and Middle Ear	-3.4404	0.2091	-16.46	<.0001
site 22020 Larynx	-2.2216	0.1272	-17.46	<.0001
site 22030 Lung and Bronchus	0.4585	0.1912	2.40	0.0165
site 22060 Trachea, Mediastinum and Other Respiratory Organs	-3.5571	0.3365	-10.57	<.0001
site 23000 Bones and Joints	-2.3116	0.3	-7.71	<.0001
site 24000 Soft Tissue including Heart$	-1.8317	0.1611	-11.37	<.0001
site 25010 Melanoma of the Skin	-1.9887	0.1486	-13.38	<.0001
site 25020 Other Non-Epithelial Skin	-2.2481	0.1609	-13.97	<.0001
site 26000 Breast	-0.4356	0.2505	-1.74	0.0821
site 27010 Cervix Uteri	-1.5047	0.2913	-5.17	<.0001
site 27020 Corpus Uteri	-2.4597	0.1971	-12.48	<.0001
site 27030 Uterus, NOS	-0.9538	0.32	-2.98	0.0029
site 27040 Ovary	-0.7829	0.2152	-3.64	0.0003
site 27050 Vagina	-3.2256	0.3498	-9.22	<.0001
site 27060 Vulva	-2.9244	0.3359	-8.71	<.0001
site 27070 Other Female Genital Organs	-3.3376	0.3176	-10.51	<.0001
site 28010 Prostate	-1.2188	0.255	-4.78	<.0001

Appendix Table 2

Estimates of all parameters of model 5 in Table 6

Parameter	Estimate	Empirical Standard Error Estimates	Z	Pr > |Z|
site 28020 Testis	-4.098	0.3064	-13.38	<.0001
site 29010 Urinary Bladder	-1.7334	0.1193	-14.53	<.0001
site 29020 Kidney and Renal Pelvis	-1.3938	0.0874	-15.95	<.0001
site 29040 Other Urinary Organs	-3.837	0.2772	-13.84	<.0001
site 30000 Eye and Orbit	-4.2201	0.2183	-19.33	<.0001
site 31010 Brain and Other Nervous System	-0.7299	0.1629	-4.48	<.0001
site 32010 Thyroid	-2.899	0.2435	-11.91	<.0001
site 32020 Other Endocrine including Thymus	-2.5717	0.2759	-9.32	<.0001
site 34000 Myeloma	-1.4358	0.2013	-7.13	<.0001
site 35011 Acute Lymphocytic Leukemia	-2.3424	0.4727	-4.96	<.0001
site 35012 Chronic Lymphocytic Leukemia	-2.3112	0.172	-13.43	<.0001
site 35013 Other Lymphocytic Leukemia	-3.7868	0.2478	-15.28	<.0001
site 35021 Acute myeloid	-1.5428	0.2144	-7.20	<.0001
site 35022 Chronic Myeloid Leukemia	-3.1786	0.2173	-14.63	<.0001
site 35041 Other Acute Leukemia	-2.0083	0.2609	-7.70	<.0001
site 35043 Aleukemic, subleukemic and NOS	-1.811	0.246	-7.36	<.0001
site 37000 Miscellaneous Malignant Cancer	0	0	.	.
Intercept	0.3112	0.8416	0.37	0.7116