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How Cost-Effective Are New Cancer Drugs in the U.S.?

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How Cost-Effective Are New Cancer Drugs in the U.S.?

Abstract

The number of drugs approved by the FDA for treating cancer has increased substantially during the last 40 years. Moreover, cancer drug innovation has been accelerating: more than 8 times as many new cancer drugs were approved during 2005-2015 as were approved during 1975-1985 (66 vs. 8). During the period 2010-2014, the average annual growth rate of cancer drug expenditure was 7.6%--more than 3.6 times the average annual growth rate of nominal U.S. GDP. This has contributed to a lively debate about the value and cost-effectiveness of new cancer drugs. In this study, we attempt to assess the average cost-effectiveness in the U.S. in 2014 of new cancer drugs approved by the FDA during 2000-2014. Cost-effectiveness is measured as the ratio of the impact of new cancer drugs on medical expenditure to their impact on potential years of life lost due to cancer. We use a difference-in-difference research design: we investigate whether there were larger declines in premature mortality from the cancers that had larger increases in the number of drugs ever approved, controlling for the change in cancer incidence and mean age at time of diagnosis. The vast majority of the data we rely on are publicly available.

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Our key findings can be summarized as follows:

- cancer sites with larger increases in the number of drugs ever approved tended to have larger declines in the number of potential years of life lost before ages 75 and 65.
- on average, one additional drug approved for a cancer site reduced the number of potential years of life lost before age 75 by 2.3%.
- new cancer drugs reduced the number of potential years of life lost before age 75 at an average annual rate of 0.93% during the period 1999-2014.
- cancer drugs approved during 2000-2014 are estimated to have reduced the number of potential years of life lost before age 75 in 2014 by 719,133.
- premature mortality in year t is strongly inversely related to the number of drugs approved in years $t-3$ to t (and earlier years), but unrelated to the number of drugs approved in years $t+1$ to $t+4$.
- one additional drug approval increases the odds of surviving at least 5 years after diagnosis by 2.4%.
- new cancer drugs reduced the number of cancer patient hospital days at an average annual rate of 0.83% during the period 1997-2013.
- cancer drugs approved between 1989 and 2005 are estimated to have reduced the number of hospital days in 2013 by 1.55 million, and hospital cost in 2013 by \$4.8 billion.
- our baseline estimate of the cost per life-year gained in 2014 from cancer drugs approved during 2000-2014 is \$7853. If we completely ignore the estimated reductions in old drug and hospital expenditure, the estimated cost per life-year gained is \$17,104. Even the higher estimate would imply that, overall, cancer drug innovation has been highly cost-effective, by the standards of the World Health Organization and other authorities.

I. Introduction

The number of drugs approved by the Food and Drug Administration (FDA) for treating cancer has increased substantially during the last 40 years. As shown in Figure 1, 27 drugs for treating cancer had been approved by the FDA by 1975; that number increased to 153 by 2015. Moreover, cancer drug innovation has been accelerating: more than 8 times as many new cancer drugs were approved during 2005-2015 as were approved during 1975-1985 (66 vs. 8). In contrast, as shown in Figure 2, the number of “non-cancer” drugs launched worldwide has tended to decline.

The rapid growth in the number of drugs for treating cancer has been accompanied by a substantial increase in expenditure on cancer drugs. Data on U.S. sales during 2010-2014 of all cancer drugs and of the 10 largest selling (in 2014) drugs are shown in Table 1. The average annual growth rate of total expenditure was 7.6%—more than 3.6 times the average annual growth rate of nominal U.S. GDP. This has contributed to a lively debate about the value and cost-effectiveness of new cancer drugs.

While the overall number of drugs for treating cancer has increased, data from the National Cancer Institute (NCI) and the FDA indicate that the size of the increase varied considerably across cancer sites (breast, colon, lung, etc.). The NCI publishes lists of drugs approved for 39 different types of cancer (National Cancer Institute (2016b)). The first year in which each drug was first approved by the FDA can be determined from the Drugs@FDA database (Food and Drug Administration (2016c)). By combining data from these two sources, we can measure the history of pharmaceutical innovation for each type of cancer. This is illustrated by Figure 3, which shows data on drugs that have been approved by the FDA for the treatment of one type of cancer, acute lymphoblastic leukemia. During the period 1994-2014, the number of drugs ever approved for acute lymphoblastic leukemia increased from 10 to 16. Figure 4 shows the number of drugs ever approved during the same period for four types of cancer. A similar number of (between 9 and 13) drugs had ever been approved for each of the four types in 1994. During the next 20 years, 16 new drugs for non-Hodgkin lymphoma and 17 new drugs for breast cancer were approved, but only 6 new drugs for acute lymphoblastic leukemia and one new drug for Hodgkin lymphoma were approved.

In this study, we will attempt to assess the average cost-effectiveness in the U.S. in 2014 of the drugs that the FDA approved for treating cancer during the period 2000-2014. Cost-

effectiveness will be measured as the ratio of the impact of new cancer drugs on medical expenditure to their impact on potential years of life lost (PYLL) due to cancer.¹ To estimate the impact of the drugs approved during the period 2000-2014 on PYLL (“premature mortality”) due to cancer in 2014, we will estimate difference-in-differences models using longitudinal data on the cancer sites defined by the National Cancer Institute (2016b). In essence, we will investigate whether there were larger declines in mortality from the cancers that had larger increases in the number of drugs ever approved, controlling for the change in cancer incidence and mean age at time of diagnosis.² We will analyze two alternative measures of premature mortality: potential years of life lost before ages 75 and 65. In addition, we will analyze the impact of the number of drugs approved on the 5-year observed survival rate, also controlling for the expected survival rate of non-cancer patients. Some of the estimated models will distinguish between the effects of “priority-review” drugs—drugs that the FDA believes demonstrate “the potential to provide a significant improvement in the safety or effectiveness of the treatment, diagnosis, or prevention of a serious or life-threatening condition” (FDA (2013))—and “standard-review” drugs—drugs that the FDA believes do not demonstrate such potential.

The effect of drug approvals on cancer mortality may be subject to a lag, so the lag structure of the relationship will be investigated. As a robustness check, we will also test whether mortality depends on *future* drug approvals.

To determine the impact of new cancer drugs on medical expenditure, we will also estimate difference-in-differences models of hospital utilization. All of the data used to estimate the models of cancer mortality and hospitalization are produced by U.S. government agencies and are publicly available.

In Section II, we describe econometric models of cancer patient outcomes. The data sources used to construct the data to estimate these models are described in Section III. Empirical results are presented in Section IV. In Section V, we use the estimates along with other data to produce an estimate of the average cost-effectiveness of new cancer drugs. Section VI provides a summary and conclusions.

¹ Burnet et al (2005) argued that “years of life lost (YLL) from cancer is an important measure of population burden – and should be considered when allocating research funds.”

² New drug approvals can improve outcomes for 2 reasons. First, the quality of newer products may be higher than the quality of older products, as in “quality ladder” models (see Grossman and Helpman (1991)). Second, “one of the principal means, if not the principal means, through which countries benefit from international trade is by the expansion of varieties” (Broda and Weinstein (2004)).

II. Models of premature cancer mortality, survival, and hospitalization

Longevity increase (or declining mortality rates) is a very important part of economic growth, broadly defined. Nordhaus (2005) argued that “improvements in health status have been a major contributor to economic welfare over the twentieth century. To a first approximation, the economic value of increases in longevity in the last hundred years is about as large as the value of measured growth in non-health goods and services.” The United Nations’ Human Development Index (HDI) is a composite statistic of life expectancy, education, and income per capita indicators, which are used to rank countries into four tiers of human development (United Nations (2016)).

Building on a large collection of previous research by Romer (1990), Grossman and Helpman (1991), Aghion and Howitt (1992), and others, Jones (2002, p. 221) presented a model in which “long-run growth is driven by the discovery of new ideas throughout the world.” He postulated an aggregate production function in which total output depends on the total stock of ideas available to this economy as well as on physical and human capital.

In general, measuring the number of ideas is challenging. One potential measure is the number of patents, but Patterson (2012, p. 8) noted that only 1% of patent applications made by Bell Labs “generated [commercial] value.” Fortunately, due to FDA regulation, measuring pharmaceutical “ideas” is considerably easier than measuring ideas in general.³ The measure of pharmaceutical ideas we will use is the number of new molecular entities approved by the FDA. Since we have precise information about when those ideas reached the market and the diseases to which they apply, we can assess the impact of those ideas on longevity and hospitalization in a difference-in-differences framework. We therefore believe that Nordhaus (2005) may have been unduly skeptical when he wrote that “we cannot at this stage attribute the growth in health income to particular investments or expenditures” and that “apply[ing] the techniques of growth accounting to health improvements...is especially challenging.”

³ Moreover, the medical substances and devices sector was the most R&D-intensive major industrial sector: almost twice as R&D-intensive as the next-highest sector (information and electronics), and three times as R&D-intensive as the average for all major sectors. R&D intensity is the ratio of R&D to sales. (National Science Foundation (2016)).

We will estimate models with (functions of) three types of dependent variables: PYLL (before two different age thresholds, 75 and 65), 5-year observed survival rates, and number of hospital days.

a. Premature cancer mortality model

The basic model of potential years of life lost before age 75⁴ is:

$$\ln(\text{PYLL75}_{s,t}) = \beta \text{N_APP_1948}_{t,s,t} + \gamma \ln(\text{CASES}_{s,t}) + \pi \text{AGE_DIAG}_{s,t} + \alpha_s + \delta_t + \varepsilon_{s,t} \quad (1)$$

where

$\text{PYLL75}_{s,t}$ = the number of years of potential life lost before age 75 due to cancer at site s in year t ($t = 1999, 2014$)

$\text{N_APP_1948}_{t,s,t}$ = the number of drugs for cancer at site s approved by the FDA between the end of 1948 and the end of year t ⁵

$\text{CASES}_{s,t}$ = the average annual number of people below age 75 diagnosed with cancer at site s in years $t-9$ to t

$\text{AGE_DIAG}_{s,t}$ = the mean age at which people below age 75 were diagnosed with cancer at site s in years $t-9$ to t

α_s = a fixed effect for cancer at site s

δ_t = a fixed effect for year t

The standard errors of eq. (1) will be clustered within cancer sites. The data exhibit heteroscedasticity. For example, cancer sites with larger mean premature mortality during 1999-2014 had smaller (positive and negative) annual percentage fluctuations in PYLL75_{st} . Eq. (1) will therefore be estimated by weighted least-squares, weighting by $\Sigma_t \text{PYLL75}_{st}$. This specification imposes the property of diminishing marginal productivity of drug approvals.

⁴ A similar model of potential years of life lost before age 65 will also be estimated.

⁵ 1949 was the first year in which a cancer drug included in the National Cancer Institute's lists of cancer drugs (National Cancer Institute (2016b)) was approved by the FDA.

The parameter of primary interest is β , the coefficient on the number of drugs that had been approved by the end of year t . Inclusion of year and cancer-site fixed effects controls for the overall change in premature mortality and for stable between-cancer-site differences in premature mortality. A negative and significant estimate of β in eq. (1) would signify that cancer sites for which there was more pharmaceutical innovation had larger declines in premature mortality.

We also control for the average annual number of people below age 75 diagnosed with cancer at site s in years $t-9$ to t , and their mean age; an increase in mean age at diagnosis is expected to reduce premature mortality. Due to data limitations, eq. (1) does not include other disease-specific, time-varying, explanatory variables. But both a patient-level U.S. study and a longitudinal country-level study have shown that controlling for numerous other potential determinants of longevity does not reduce, and may even increase, the estimated effect of pharmaceutical innovation. The study based on patient-level data (Lichtenberg (2013)) found that controlling for race, education, family income, insurance coverage, Census region, BMI, smoking, the mean year the person started taking his or her medications, and over 100 medical conditions had virtually no effect on the estimate of the effect of pharmaceutical innovation (the change in drug vintage) on life expectancy. The study based on longitudinal country-level data (Lichtenberg (2014a)) found that controlling for ten other potential determinants of longevity change (real per capita income, the unemployment rate, mean years of schooling, the urbanization rate, real per capita health expenditure (public and private), the DPT immunization rate among children ages 12-23 months, HIV prevalence and tuberculosis incidence) *increased* the coefficient on pharmaceutical innovation by about 32%.

Failure to control for non-pharmaceutical medical innovation (e.g. innovation in diagnostic imaging, surgical procedures, and medical devices) is also unlikely to bias estimates of the effect of pharmaceutical innovation on premature mortality, for two reasons. First, more than half of U.S. funding for biomedical research came from pharmaceutical and biotechnology firms (Dorsey et al (2010)).⁶ Much of the rest came from the federal government (i.e. the NIH), and new drugs often build on upstream government research (Sampat and Lichtenberg (2011)).

⁶ The National Cancer Institute (2016b) publishes lists of drugs used to treat different types of cancer, but it doesn't publish lists of medical devices, radiology procedures, or surgical procedures used to treat different types of cancer. Perhaps this is because National Cancer Institute staff believe that drugs are the most important type of cancer treatment innovation.

The National Cancer Institute (2015b) says that it “has played an active role in the development of drugs for cancer treatment for 50 years... [and] that approximately one half of the chemotherapeutic drugs currently used by oncologists for cancer treatment were discovered and/or developed” at the National Cancer Institute. Second, previous research based on U.S. data (Lichtenberg (2014b)) indicates that non-pharmaceutical medical innovation is not positively correlated across diseases with pharmaceutical innovation.

A (simpler) “long-difference” model can be derived from the fixed-effects model (eq. (1)). Setting t equal to 1999 and 2014 (the first and last years of the sample period) yields eqs. (2) and (3), respectively:

$$\begin{aligned} \ln(\text{PYLL75}_{s,1999}) = & \beta \text{N_APP_1948}_{t_s,1999} + \gamma \ln(\text{CASES}_{s,1999}) \\ & + \pi \text{AGE_DIAG}_{s,1999} + \alpha_s + \delta_{1999} + \varepsilon_{s,1999} \end{aligned} \quad (2)$$

$$\begin{aligned} \ln(\text{PYLL75}_{s,2014}) = & \beta \text{N_APP_1948}_{t_s,2014} + \gamma \ln(\text{CASES}_{s,2014}) \\ & + \pi \text{AGE_DIAG}_{s,2014} + \alpha_s + \delta_{2014} + \varepsilon_{s,2014} \end{aligned} \quad (3)$$

Subtracting (3) from (2) yields:

$$\begin{aligned} \Delta \ln(\text{PYLL75}_s) = & \beta \Delta \text{N_APP_1948}_{t_s} + \gamma \Delta \ln(\text{CASES}_s) \\ & + \pi \Delta \text{AGE_DIAG}_s + \delta' + \varepsilon'_s \end{aligned} \quad (4)$$

where

$\Delta \ln(\text{PYLL75}_{s,t}) = \ln(\text{PYLL75}_{s,2014}) - \ln(\text{PYLL75}_{s,1999})$ = the log change from 1999 to 2014 in the number of years of potential life lost before age 75 due to cancer at site s

$\Delta \text{N_APP_1948}_{t_s} = \text{N_APP_1948}_{t_s,2014} - \text{N_APP_1948}_{t_s,1999}$ = the change from 1999 to 2014 in the number of drugs for cancer at site s ever approved = the number of drugs for cancer at site s approved between 1999 and 2014

$\Delta \ln(\text{CASES}_s) = \ln(\text{CASES}_{s,2014}) - \ln(\text{CASES}_{s,1999})$ = the log change from 1999 to 2014 in the average annual number of people below age 75 diagnosed with cancer at site s in the previous 10 years

$\Delta \text{AGE_DIAG}_s = \text{AGE_DIAG}_{s,2014} - \text{AGE_DIAG}_{s,1999}$ = the change from 1999 to 2014 in the mean age at which people below age 75 were diagnosed with cancer at site s in the previous 10 years

$$\delta' = \delta_{2014} - \delta_{1999} = \text{the difference between the 2014 and 1999 year fixed effects}$$

In addition to estimating the basic model of years of potential life lost before age 75 (eq. (1)), we will modify and generalize the model in several different ways. These modifications of the model will allow us to (1) determine whether drugs approved at different times in the past have different effects on mortality; (2) perform a falsification test of whether drug approvals *after* year t affect mortality in year t ; and (3) test whether the approval of priority-review and standard-review drugs (defined below) have different effects on mortality. Now we will discuss these modifications in turn.

Heterogeneous effects of drugs approved at different times in the past. The number of drugs ever approved by the end of year t is the sum of the numbers of drugs approved during sub-periods prior to year t . For example, $N_APP_1948_t_{s,t}$ is the sum of the number of drugs approved more than 4 years before and 0-4 years before year t :

$$N_APP_1948_t_{s,t} = N_APP_1948_t-4_{s,t} + N_APP_t-4_t_{s,t} \quad (5)$$

where

$N_APP_1948_t-4_{s,t}$ = the number of drugs for cancer at site s approved by the FDA between the end of 1948 and the end of year $t-4$

$N_APP_t-4_t_{s,t}$ = the number of drugs for cancer at site s approved by the FDA between the end of year $t-4$ and the end of year t

Substituting (5) into (1) yields:

$$\begin{aligned} \ln(PYLL75_{s,t}) = & \beta [N_APP_1948_t-4_{s,t} + N_APP_t-4_{s,t}] \\ & + \gamma \ln(CASES_{s,t}) + \pi AGE_DIAG_{s,t} + \alpha_s + \delta_t + \varepsilon_{s,t} \end{aligned} \quad (6)$$

In eq. (6), the marginal effects on mortality of approvals in both periods are constrained to be identical. In the following more general model, the marginal effects on mortality of approvals in the two periods are allowed to differ:

$$\ln(\text{PYLL75}_{s,t}) = \beta_{5+} \text{N_APP_1948_t-4}_{s,t} + \beta_{0_4} \text{N_APP_t-4}_{s,t} + \gamma \ln(\text{CASES}_{s,t}) + \pi \text{AGE_DIAG}_{s,t} + \alpha_s + \delta_t + \varepsilon_{s,t} \quad (7)$$

The marginal effects of approvals in the two periods are likely to differ, for several reasons. There are two reasons to expect the magnitude of β_{0_4} to be smaller than the magnitude of β_{5+} . First, as shown in Appendix 1, mean utilization of a drug is lower 0-4 years after approval than it is more than 4 years after approval. Second, there is undoubtedly a lag between utilization of a drug and its impact on mortality. But another factor would tend to make the magnitude of β_{0_4} *larger* than the magnitude of β_{5+} : quality improvement. If newer drugs tend to be of higher quality than older drugs, a drug approved 0-4 years ago would reduce mortality more than a drug approved more than 4 years ago, if utilization of the two drugs were equal and if there were no lag from utilization to mortality reduction.

Effect of future drug approvals. Approvals in different years prior to year t may have different effects on mortality in year t . Approvals in years *after* year t should have *no* effect on mortality in year t . We will test this by including one additional regressor ($\text{N_APP_t_t+4}_{s,t}$) in the model:

$$\ln(\text{PYLL75}_{s,t}) = \beta_{5+} \text{N_APP_1948_t-4}_{s,t} + \beta_{0_4} \text{N_APP_t-4}_{s,t} + \beta_{\text{POST}} \text{N_APP_t_t+4}_{s,t} + \gamma \ln(\text{CASES}_{s,t}) + \pi \text{AGE_DIAG}_{s,t} + \alpha_s + \delta_t + \varepsilon_{s,t} \quad (8)$$

where

$\text{N_APP_t_t+4}_{s,t}$ = the number of drugs for cancer at site s approved by the FDA between the end of year t and the end of year $t+4$

Heterogeneous effects of priority-review and standard-review drugs. When the FDA begins its review of a new drug application, it designates the drug as either a priority-review drug or a standard-review drug.⁷ Priority review designation is assigned to applications for drugs that are expected to provide significant improvements in the safety or effectiveness of the treatment, diagnosis, or prevention of serious conditions compared to available therapies. Significant improvement may be demonstrated by the following examples: (1) evidence of increased

⁷ 63% of the cancer drugs approved during 1949-2015 were given priority review designation. Since the FDA's classification of a drug (priority vs. standard review) occurs at the beginning of the review process, it may be subject to considerable uncertainty; the fact that some drugs are withdrawn after marketing indicates that even the safety of a drug may not be well understood at the time of approval.

effectiveness in treatment, prevention, or diagnosis of condition; (2) elimination or substantial reduction of a treatment-limiting drug reaction; (3) documented enhancement of patient compliance that is expected to lead to an improvement in serious outcomes; or (4) evidence of safety and effectiveness in a new subpopulation. Standard review designation is assigned to applications for drugs that do not meet the priority-review designation criteria.⁸

We will estimate the following version of eq. (1) that distinguishes between priority-review and standard-review drugs:

$$\ln(\text{PYLL}_{75,s,t}) = \beta_{\text{PRI}} N_{\text{PRI_1948_t},s,t} + \beta_{\text{STD}} N_{\text{STD_1948_t},s,t} + \gamma \ln(\text{CASES}_{s,t}) + \pi \text{AGE_DIAG}_{s,t} + \alpha_s + \delta_t + \varepsilon_{s,t} \quad (9)$$

where

$N_{\text{PRI_1948_t},s,t}$ = the number of priority-review drugs for cancer at site s approved by the FDA between the end of 1948 and the end of year t

$N_{\text{STD_1948_t},s,t}$ = the number of standard-review drugs for cancer at site s approved by the FDA between the end of 1948 and the end of year t

b. 5-year observed survival rate model

In addition to estimating the premature mortality models described above, we will estimate models of the 5-year survival rate. The observed survival rate is the probability of surviving from all causes of death for a group of cancer patients under study. For example, it is the probability that a person diagnosed with cancer at the end of 2008 was still alive at the end of 2013.

Between 2000 and 2008, the 5-year observed survival rate for all cancer sites combined increased from 55.1% to 59.0%. However, the National Cancer Institute (2015a) points out that “certain factors may cause survival times to look like they are getting better when they are not. These factors include lead-time bias and overdiagnosis.”

Lead-time bias. Survival time for cancer patients is usually measured from the day the cancer is diagnosed until the day they die. Patients are often diagnosed after they have signs and symptoms of cancer. If a screening test leads to a diagnosis before a patient has any symptoms, the patient’s survival time is increased because the date of diagnosis is

⁸ First-in-class drugs are much more likely to receive priority-review status than follow-on drugs, so distinguishing between priority-review and standard-review drugs is similar to distinguishing between first-in-class and follow-on drugs.

earlier. This increase in survival time makes it seem as though screened patients are living longer when that may not be happening.⁹ This is called lead-time bias. It could be that the only reason the survival time appears to be longer is that the date of diagnosis is earlier for the screened patients. But the screened patients may die at the same time they would have without the screening test.

Over-diagnosis. Sometimes, screening tests find cancers that don't matter because they would have gone away on their own or never caused any symptoms. These cancers would never have been found if not for the screening test. Finding these cancers is called over-diagnosis. Over-diagnosis can make it seem like more people are surviving cancer longer, but in reality, these are people who would not have died from cancer anyway.

To guard against the risk that lead-time bias and over-diagnosis could bias our estimates of the effect of pharmaceutical innovation on observed cancer survival, we will control for (changes in) the number of people diagnosed (incidence) and for the *expected* survival rate—the survival probability of a population similar to the patient group with respect to age, sex, race, and calendar year but free of the specific disease under study (Ederer et al (1961)). We will estimate the following model:

$$\begin{aligned} \ln(\text{SURV_OBS}_{s,t}/(1 - \text{SURV_OBS}_{s,t})) = & \beta \text{N_APP_1948}_{t,s,t} + \gamma \ln(\text{CASES}_{s,t}) \\ & + \pi \ln(\text{SURV_EXP}_{s,t}/(1 - \text{SURV_EXP}_{s,t})) + \alpha_s + \delta_t + \varepsilon_{s,t} \end{aligned} \quad (10)$$

where

$\text{SURV_OBS}_{s,t}$ = the observed 5-year survival rate of patients diagnosed with cancer at site s in year t ($t = 2000, 2008$)

$\text{SURV_EXP}_{s,t}$ = the expected 5-year survival rate of patients diagnosed with cancer at site s in year t

Eq. (10) will be estimated by weighted least-squares, weighting by $\text{CASES}_{s,t}$. The standard errors of eq. (10) will be clustered within cancer sites.

⁹ Some studies have found no mortality benefit from more intensive screening. For example, data from the Prostate, Lung, Colorectal and Ovarian randomized screening trial showed that, after 13 years of follow up, men who underwent annual prostate cancer screening with prostate-specific antigen testing and digital rectal examination had a 12 percent higher incidence of prostate cancer than men in the control group but the same rate of death from the disease. No evidence of a mortality benefit was seen in subgroups defined by age, the presence of other illnesses, or pre-trial PSA testing (National Cancer Institute (2012)).

c. Hospital days model

To investigate the impact of cancer drug innovation on hospitalization, we will estimate the following model:

$$\begin{aligned} \ln(\text{HOSP_DAYS}_{s,t}) = & \beta \text{N_APP_1948}_{t,s,t} + \gamma \ln(\text{CASES}_{s,t}) \\ & + \pi \text{AGE_DIAG}_{s,t} + \alpha_s + \delta_t + \varepsilon_{s,t} \end{aligned} \quad (11)$$

where

$\text{HOSP_DAYS}_{s,t}$ = the number of hospital days in year t ($t = 1998, 2013$) for patients whose principal diagnosis was cancer at site s

Eq. (11) will be estimated by weighted least-squares, weighting by $\Sigma_t \text{HOSP_DAYS}_{s,t}$. The standard errors of eq. (11) will be clustered within cancer sites.

III. Data sources

Premature mortality. Data on years of potential life lost before ages 75 and 65, by cancer site and year (1999-2014), were constructed from data obtained from the Compressed Mortality database (Centers for Disease Control and Prevention (2016a)). In that database, most deaths are reported in 10-year age groups. We assumed that deaths in an age group occur at the midpoint of the age group, e.g. deaths in age group 55-64 occur at age 60.

Drug approvals by cancer site. Lists of drugs approved by the FDA for each type of cancer were obtained from the National Cancer Institute (2016b). The drugs@FDA database (Food and Drug Administration (2016c)) was used to determine the year in which each of these drugs was first approved by the FDA, and whether the drug was designated as priority-review or standard-review.

Cancer incidence and mean age at diagnosis. Annual data on the number of people diagnosed in SEER 9 registries with each type of cancer were obtained from SEER Research Data (National Cancer Institute (2016c)).

Observed and expected survival rates. Data on observed and expected survival rates, by cancer site and year, were obtained from SEER*Stat software Version 8.2.1 (National Cancer Institute (2016d)).

Hospitalization. Annual data on the number of hospital days for patients with a principal diagnosis of each type of cancer were obtained from HCUPnet, an on-line query system based on data from the Healthcare Cost and Utilization Project (Agency for Healthcare Research and Quality (2016)).

Drug utilization and expenditure. Unpublished data on the quantity (measured in “standard units”) of and expenditure (before rebates) on cancer drugs, by molecule and year (2010-2014), were obtained from IMS Health.

Data on premature mortality, incidence, and hospitalization, by cancer site, are shown in Table 2. Data on observed and expected 5-year survival rates and number of patients diagnosed, by cancer site in 2000 and 2008, are shown in Table 3. Data on the number of drugs ever approved by the FDA, by cancer site and year (1990-2014), are shown in Table 4.

IV. Empirical results

a. Premature mortality model estimates

Estimates of models of potential years of life lost before age 75 (eqs. (1), (7), (8), and (9)) are presented in Table 5a. All models include $\ln(\text{CASES})$, AGE_DIAG, and cancer-site fixed effects; estimates of these parameters are not shown to conserve space. As expected, in all models, the coefficient on $\ln(\text{CASES})$ is positive and significant, and the coefficient on AGE_DIAG is negative and significant. The estimation procedure we use (PROC GENMOD in SAS) normalizes the final year fixed effect to be equal to zero, so $\Delta\delta$ denotes the difference between the initial and final year fixed effects, e.g. $\delta_{1999} - \delta_{2014}$.

In models 1-4, the initial and final years are 1999 and 2014, respectively. These models are based on the full time span of the mortality data, but they don’t allow us to perform the falsification test based on future drug approvals. In models 5-10, the initial and final years are 1999 and 2010, respectively; the falsification tests are performed in models 9 and 10.

Model 1 in Table 5a provides an estimate of $\Delta\delta (= \delta_{1999} - \delta_{2014})$ from eq. (1) when $N_APP_1948_t$ is excluded from the equation. This is an estimate of the weighted mean change of $\ln(PYLL75)$, controlling for the changes in $\ln(CASES)$ and AGE_DIAG , but *not* controlling for (or holding constant) $N_APP_1948_t$, i.e. in the *presence* of pharmaceutical innovation. It indicates that, controlling for the changes in $\ln(CASES)$ and AGE_DIAG , PYLL75 declined by 8.0% between 1999 and 2014.

Model 2 provides estimates of eq. (1) when $N_APP_1948_t$ is included in the equation. As expected, the coefficient on $N_APP_1948_t$ is negative and highly significant (p-value = 0.0005), indicating that cancer sites with larger increases in the number of drugs ever approved tended to have larger declines in PYLL75. The point estimate of this coefficient implies that, on average, one additional drug approved for a condition reduced PYLL75 by 2.3%. Figure 5 shows the correlation across cancer sites between the 1999-2014 change in the number of drugs ever approved (= the number of drugs approved during 2000-2014) and the 1999-2014 change in the log of PYLL75, controlling for the changes in incidence and mean age at diagnosis.¹⁰ During the period 1999-2014, PYLL75 due to all types of cancer increased by 4.3%, from 4.23 million to 4.42 million (Centers for Disease Control and Prevention (2016b)). The population below age 75 increased by 15.4% (from 256.4 million to 299.0 million) during that period, so the premature cancer mortality rate declined by 11.0% (from 1650 to 1477 per 100,000 population). The weighted mean number of drugs approved during 2000-2014 was 6.07, so the estimates of model 2 imply that in the absence of pharmaceutical innovation, PYLL75 due to all types of cancer would have increased by 18.3% ($= 4.3\% + (.023 * 6.07)$), and that the premature cancer mortality rate would have increased by 2.9% ($= 18.3\% - 15.4\%$), although the latter increase is probably not statistically significantly different from zero. Also, new cancer drugs reduced PYLL75 at an average annual rate of 0.93% ($= (.023 * 6.07) / 15$) during the period 1999-2014.

Model 3 in Table 5a corresponds to eq. (9), which distinguishes between priority-review and standard-review drugs. The difference between the coefficients on priority-review and standard-review drugs is not statistically significant, so we are unable to reject the null hypothesis that the two types of drugs had equal effects on PYLL75. Model 4 corresponds to eq.

¹⁰ This figure shows the correlation between the residual from the regression of $\Delta\ln(PYLL75_s)$ on $\Delta\ln(CASES_s)$ and ΔAGE_DIAG_s and the residual from the regression of $\Delta N_APP_1948_t$ on $\Delta\ln(CASES_s)$ and ΔAGE_DIAG_s (see eq. (4)).

(7), which distinguishes between drugs approved more than 4 years before year t and drugs approved 0-4 years before year t . The difference between the coefficients on drugs approved in the two periods is not statistically significant.

In models 5-10 of Table 5a, the initial and final years are 1999 and 2010. The estimate of the $N_APP_1948_t$ coefficient in model 6 is larger and more significant than the estimate in model 2 (based on a longer sample period). Models 7 and 8 show that the differences between the coefficients on priority-review and standard-review drugs and between the coefficients on drugs approved more than 4 years before and drugs approved 0-4 years before are again not statistically significant.

Models 9 and 10 include the number of drugs approved 0-4 years *after* year t . Model 9 does not distinguish between drugs approved more than 4 years before and drugs approved 0-4 years before year t ; model 10 does. As expected, the coefficient on the number of drugs approved 0-4 years *after* year t is not significant in either model. In contrast, in model 10 the coefficient on the number of drugs approved 0-4 years *before* year t is negative and highly significant.

Table 5b presents estimates of models similar to those presented in Table 5a, but in Table 5b the estimates are of models of potential years of life lost before age 65 (PYLL65), rather than age 75. The estimates in Table 5b are qualitatively similar to the estimates in Table 5a: the change in $\log(PYLL65)$ is strongly inversely related across cancer sites to the number of new drugs approved; the differences between the coefficients on priority-review and standard-review drugs and between the coefficients on drugs approved more than 4 years before and drugs approved 0-4 years before are not statistically significant; and in model 10 the coefficient on the number of drugs approved 0-4 years *after* year t is not significant, whereas the coefficient on the number of drugs approved 0-4 years *before* year t is negative and highly significant.

b. 5-year observed survival rate model estimates

Estimates of models of the observed 5-year survival rate (eq. (10)) are presented in Table 6. These estimates are based on data for the years 2000 and 2008 from all 18 SEER registries, 5 of which began providing data in 2000. Since the survival rate is “forward-looking,” the 2008 data are the most recent available data. The number of patients diagnosed in all registries

increased from 263,848 in 2000 to 287,954 in 2008. Between 2000 and 2008, the observed survival rate for all cancers combined increased from 56.1% to 60.3%, the expected survival rate increased from 86.5% to 88.6%, and the relative survival rate increased from 64.9% to 68.0%. Observations are weighted by number of patients diagnosed. All models in Table 6 include $\ln(\text{CASES})$, $\ln(\text{SURV_EXP}/(1 - \text{SURV_EXP}))$, and cancer-site fixed effects. As expected, the coefficients on $\ln(\text{CASES})$ and $\ln(\text{SURV_EXP}/(1 - \text{SURV_EXP}))$ are both positive and highly significant in all models: observed survival increased more for cancers that had larger increases in the number of people diagnosed and larger increases in expected survival (e.g. due to earlier diagnosis).

Model 1 of Table 6 indicates that, holding constant the number of people diagnosed and the expected survival rate, between 2000 and 2008 the odds of surviving for at least 5 years after diagnosis increased 10.2% ($= \exp(\delta_{2008} - \delta_{2000}) - 1$), although the increase is only marginally significant (p-value = .0810). Model 2 includes the number of drugs approved until year t (N_APP_{1948_t}). The coefficient on this variable is positive and highly significant (p-value = .0056). The point estimate indicates that one additional drug approval increases the odds of surviving 5 years by 2.4%. Figure 6 shows the correlation across cancer sites between the number of drugs approved during 2001-2008 and the 2000-2008 change in the log-odds of surviving at least 5 years after diagnosis, controlling for changes in incidence and the expected survival rate.

Model 3 distinguishes between priority-review and standard-review drugs. The coefficient on the former is positive and highly significant, whereas the coefficient on the latter is negative and marginally significant; the difference between the coefficients is highly significant. Model 4 distinguishes between drugs approved more than 4 years before and drugs approved 0-4 years before. The coefficients on both variables are positive and significant, but the coefficient on more recent drug approvals is significantly larger. Model 5 distinguishes between drugs approved more than 8 years before and drugs approved 0-8 years before. Once again, the coefficients on both variables are positive and significant, but in this case the difference between the coefficients is not statistically significant.

c. Hospital days model estimates

Now we will present estimates of several versions of the model of cancer patient hospital days (eq. (11)). The initial and final years of this analysis are 1997 and 2013, respectively. During that period, the number of cancer patient hospital days declined 22.1%, from 11.7 million to 9.1 million, despite the fact that the average annual number of patients diagnosed with cancer in SEER 9 registries increased by 29%. Model 1 of Table 7 indicates that, holding constant the number of patients diagnosed and their mean age, the number of cancer patient hospital days declined 32% ($= 1 - \exp(\delta_{2013} - \delta_{1997})$). Model 2 includes the number of drugs approved until year t . The coefficient on this variable is negative, as expected, but only marginally significant (p -value = 0.077). Model 3 distinguishes between priority-review and standard-review drugs; the difference between these coefficients is not significant. Model 4 distinguishes between drugs approved more than 4 years before and drugs approved 0-4 years before. Only the coefficient on the number of drugs approved more than 4 years before is statistically significant. Model 5 distinguishes between drugs approved more than 8 years before and drugs approved 0-8 years before. Only the coefficient on the number of drugs approved more than 8 years before is statistically significant. The estimate of $(\delta_{1997} - \delta_{2013})$ in model 5 implies that, in the absence of (lagged) pharmaceutical innovation (i.e. holding constant the number of drugs approved 8 years before, as well as the number of patients diagnosed and their mean age), the number of hospital days would have declined by 19.1%. Thus we estimate that lagged pharmaceutical innovation resulted in a 13.3% decline in the number of cancer patient hospital days during the period 1997-2013. Also, new cancer drugs reduced the number of cancer patient hospital days at an average annual rate of 0.83% ($= 13.3\% / 16$) during the period 1997-2013.

V. Cost-effectiveness estimation

Now we will use some of the estimates described in the previous section along with some other data to produce a baseline estimate of the average cost-effectiveness in 2014 of cancer drugs approved by the FDA during the period 2000-2014. The cost-effectiveness measure we will use is *cost per life-year gained*: the ratio of the cost in 2014 of drugs approved during the

period 2000-2014 (net of rebates and two types of “cost offsets”) to the number of life-years gained in 2014 attributable to those drugs.¹¹

Calculation of cost-effectiveness is described in Table 8. As shown in line 1, according to the IMS Institute for Healthcare Informatics (2015), total U.S. expenditure (before rebates) on cancer drugs in 2014 was \$32.3 billion.¹² Unpublished IMS MIDAS data indicate that 67.7% of 2014 cancer drug expenditure was on drugs approved after 1999 (line 2), so we estimate that 2014 expenditure (before rebates) on cancer drugs approved after 1999 was \$21.9 billion (line 3). However, the net social cost of these drugs is considerably lower than that, for three reasons: rebates, reduced expenditure on old drugs, and reduced hospital expenditure. We address these in turn.

Rebates. Drug rebates are believed to be pervasive, but are notoriously difficult to measure. Herper (2012) provided estimates of the effective rebates on 10 top-selling drugs (but not specifically cancer drugs) by comparing gross (pre-rebate) sales figures (reported to IMS Health) to net (post-rebate) sales figures (in company financial statements). Based on that methodology, he estimated that the weighted average rebate rate was 25%.¹³ We therefore assume that rebates on post-1999 cancer drugs amounted to \$5.5 billion (line 4 of Table 8). Therefore, net sales of these drugs was \$16.4 billion.

Reduced expenditure on old drugs. Lichtenberg (2014c, p. 465) showed that, in general, “about one-fourth of the...increase in new drug cost [is] offset by a reduction in old drug cost.” Once again, this estimate was based on data on (outpatient) drugs in general, not specifically on cancer drugs. But if it also applies to cancer drugs, then the \$16.4 billion net expenditure on new cancer drugs would reduce old cancer drug expenditure by \$4.1 billion (line 5).

Reduced hospital expenditure. The estimate of $\Delta\delta$ in model 1 of Table 7 implies that, holding constant the number of patients diagnosed and their mean age, HOSP_DAYS declined by 32.4% ($= \exp(-\Delta\delta) - 1$) between 1997 and 2013. In 1997, HOSP_DAYS was 11.7 million, so this

¹¹ We would prefer to measure cost per *quality-adjusted* life-year (QALY) gained, but systematic data on the average quality of life of cancer patients, by cancer site and year, are not available. The cost per QALY could be either greater than or less than the cost per life-year, because the number of QALYs gained could be either less than or greater than the number of life-years gained. Although patients’ quality of life in the marginal years (the additional life-years gained) is undoubtedly less than perfect, pharmaceutical innovation may also increase quality of life in the infra-marginal years.

¹² This figure is 11% higher than the estimate given in Table 1. To be conservative, we will use the higher figure.

¹³ Herper (2012) quotes a principal at a pharmaceutical marketing consultancy, who said that “the size of the rebate average[s] about 30% of a medicine’s sales.”

represents a HOSP_DAYS reduction of 3.78 million ($= 32.4\% * 11.7$ million). The estimate of $\Delta\delta$ in model 5 of Table 7 implies that, in the absence of pharmaceutical innovation, HOSP_DAYS would have declined by 19.1%, or 2.22 million ($= 19.1\% * 11.7$ million). Hence cancer drugs approved between 1989 and 2005 are estimated to have reduced HOSP_DAYS in 2013 by 1.55 million. In 2013, average cost per cancer patient hospital day was \$3076.¹⁴ Assuming that hospital costs are proportional to hospital days, this implies that cancer drugs approved between 1989 and 2005 reduced hospital costs in 2013 by \$4.77 billion ($= \$3076 * 1.55$ million). This is shown in line 6 of Table 8.

As shown in line 7, the estimated net social cost of post-1999 cancer drugs in 2014, after accounting for rebates and reduced expenditure on old drugs and hospital care, is \$7.5 billion. This represents expenditure on all patients. We want to estimate expenditure on patients below the age of 75, because the denominator of the cost-effectiveness ratio we will use is life-years gained before age 75. SEER data indicate that about 75% of cancer patients are diagnosed before the age of 75. As shown in line 8, we will assume that 75% of the net cost of post-1999 cancer drugs in 2014 was on patients below the age of 75,¹⁵ so net expenditure on these patients was \$5.6 billion.

The estimates in Table 5 can be used to calculate the number of life-years gained before age 75 in 2014 from cancer drugs approved during 2000-2014, controlling for changes in incidence and mean age at diagnosis. The estimate of $\Delta\delta$ in model 1 of Table 5a implies that, holding constant the number of patients diagnosed and their mean age, PYLL75 declined by 7.6% ($= \exp(-\Delta\delta) - 1$) between 1999 and 2014. In 1999, PYLL75 was 4.229 million, so this represents a PYLL75 reduction of 323,186 ($= 7.6\% * 4.229$ million). The estimate of $\Delta\delta$ in model 2 of Table 5a implies that, in the absence of pharmaceutical innovation, PYLL75 would have increased by 9.4%, or 395,947 ($= 9.4\% * 4.229$ million). Hence, as shown in line 9 of

¹⁴ The aggregate cost of cancer patient hospitalization was \$27.9 billion, and the aggregate number of hospital days was 9.1 million (Agency for Healthcare Research and Quality (2016)). Costs tend to reflect the actual costs of production, while charges represent what the hospital billed for the case. Total charges were converted to costs using cost-to-charge ratios based on hospital accounting reports from the Centers for Medicare and Medicaid Services (CMS). Hospital charges is the amount the hospital charged for the entire hospital stay. It does not include professional (MD) fees. Charges are not necessarily how much was reimbursed.

¹⁵ The true fraction of expenditure could be higher or lower. Treatments given to younger patients could be more expensive; on the other hand, people diagnosed before age 75 may continue to receive treatments after age 75.

Table 8, cancer drugs approved during 2000-2014 are estimated to have reduced PYLL75 in 2014 by 719,133 (= 323,186 + 395,947).

Our baseline estimate of the cost per life-year gained in 2014 from cancer drugs approved during 2000-2014 is \$7853 (line 10). Performing sensitivity analyses by modifying the estimates or assumptions described in Table 8 is straightforward. For example, if we completely ignore the estimated reductions in old drug and hospital expenditure, the estimated cost per life-year gained is \$17,104.

Even the higher estimate would imply that, overall, cancer drug innovation has been highly cost-effective, by the standards of the World Health Organization and other authorities (Hirth et al (2000)). The World Health Organization considers interventions whose cost per quality-adjusted life-year (QALY) gained is less than 3 times per capita GDP to be cost-effective, and those whose cost per QALY gained is less than per capita GDP to be highly cost-effective (World Health Organization (2016)); US per capita GDP in 2013 was \$53,041.

The cost per life-year gained may be considerably lower outside of the U.S. An analysis of unpublished data from IMS Health indicates that the average price of cancer drugs outside the U.S. is about 55% of the U.S. price.¹⁶

VI. Summary and conclusions

The number of drugs approved by the FDA for treating cancer has increased substantially during the last 40 years. Moreover, cancer drug innovation has been accelerating: more than 8 times as many new cancer drugs were approved during 2005-2015 as were approved during 1975-1985 (66 vs. 8). During the period 2010-2014, the average annual growth rate of cancer drug expenditure was 7.6%--more than 3.6 times the average annual growth rate of nominal U.S.

¹⁶ This relative price was calculated by estimating the following model by weighted least squares, weighting by the number of standard units, using 2014 data on 107 molecules: $\ln(P_{mr}) = \delta_r + \alpha_m + \varepsilon_{mr}$, where P_{mr} = manufacturer revenue per standard unit of molecule m in region r (r = USA, ROW (rest of the world)).

| Parameter | Estimate | Std. Err. | t Value | Pr > t |
|-------------------------------|----------|-----------|---------|---------|
| $\delta_{ROW} - \delta_{USA}$ | -0.591 | 0.093 | 6.37 | <.0001 |

GDP. This has contributed to a lively debate about the value and cost-effectiveness of new cancer drugs.

In this study, we attempted to assess the average cost-effectiveness in the U.S. in 2014 of new cancer drugs approved by the FDA during 2000-2014. Cost-effectiveness was measured as the ratio of the impact of new cancer drugs on medical expenditure to their impact on potential years of life lost due to cancer. We used a difference-in-difference research design: we investigated whether there were larger declines in premature mortality from the cancers that had larger increases in the number of drugs ever approved, controlling for the change in cancer incidence and mean age at time of diagnosis. The vast majority of the data we relied on are publicly available.

Our key findings can be summarized as follows:

- cancer sites with larger increases in the number of drugs ever approved tended to have larger declines in the number of potential years of life lost before ages 75 and 65.
- on average, one additional drug approved for a cancer site reduced the number of potential years of life lost before age 75 by 2.3%.
- new cancer drugs reduced the number of potential years of life lost before age 75 at an average annual rate of 0.93% during the period 1999-2014.
- cancer drugs approved during 2000-2014 are estimated to have reduced the number of potential years of life lost before age 75 in 2014 by 719,133
- premature mortality in year t is strongly inversely related to the number of drugs approved in years $t-3$ to t (and earlier years), but unrelated to the number of drugs approved in years $t+1$ to $t+4$.
- one additional drug approval increases the odds of surviving at least 5 years after diagnosis by 2.4%.
- new cancer drugs reduced the number of cancer patient hospital days at an average annual rate of 0.83% during the period 1997-2013.
- cancer drugs approved between 1989 and 2005 are estimated to have reduced the number of hospital days in 2013 by 1.55 million, and hospital cost in 2013 by \$4.8 billion.
- our baseline estimate of the cost per life-year gained in 2014 from cancer drugs approved during 2000-2014 is \$7853. If we completely ignore the estimated reductions in old drug and hospital expenditure, the estimated cost per life-year gained is \$17,104. Even the higher estimate would imply that, overall, cancer drug innovation has been highly cost-effective, by the standards of the World Health Organization and other authorities.

This study is subject to a number of limitations. The measure of pharmaceutical innovation we used is based on FDA-approved indications of cancer drugs; off-label uses of drugs were not accounted for. The primary outcome measure analyzed was life-years gained, rather than quality-adjusted life-years gained. We could not control for cancer-site-specific non-

pharmaceutical medical innovations. Although these are likely to be less important sources of longevity increase than new cancer drugs and may not be correlated with them, measuring and controlling for other medical innovations would be desirable.

Appendix 1

The cancer drug age-utilization profile

We used annual data for the period 2010-2014 on 86 cancer drugs (molecules) to provide evidence about the drug age-utilization profile, by estimating the following model:

$$\ln(N_SU_{mn}) = \rho_m + \pi_n + \varepsilon_{mn} \quad (A1)$$

where

N_SU_{mn} = the number of standard units of molecule m sold in the U.S. n years after it was approved by the FDA ($n = 0, 1, \dots, 25$)

ρ_m = a fixed effect for molecule m

π_n = a fixed effect for age n

The expression $\exp(\pi_n - \pi_9)$ is a “relative utilization index”: it is the mean ratio of the quantity of a cancer drug sold n years after it was approved to the quantity of the same drug sold 9 years after it was approved.

Estimates of the “relative utilization index” are shown in Appendix Figure 1. These estimates indicate that it takes about 9 years for a cancer drug to attain its peak level of utilization. The number of standard units 9 years after FDA approval is about twice as great as the number of standard units one year after FDA approval. Moreover, Appendix Figure 1 provides a conservative estimate of the slope of the age-utilization profile, because there was zero utilization of some molecules in the first few years after they were first listed.¹⁷

¹⁷ Since the dependent variable of eq. (A1) is logarithmic, observations for which $N_SU_{mn} = 0$ had to be excluded.

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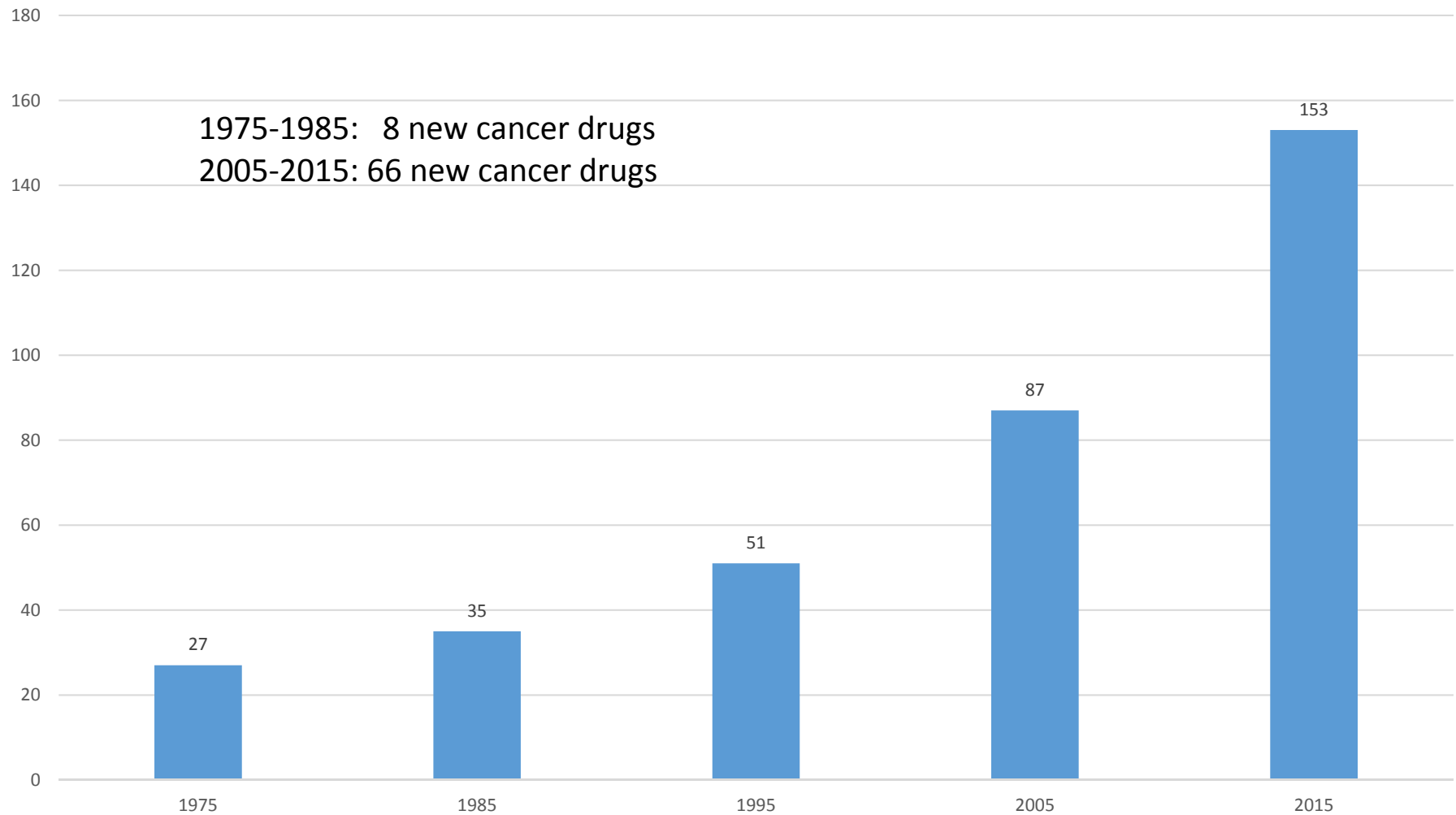
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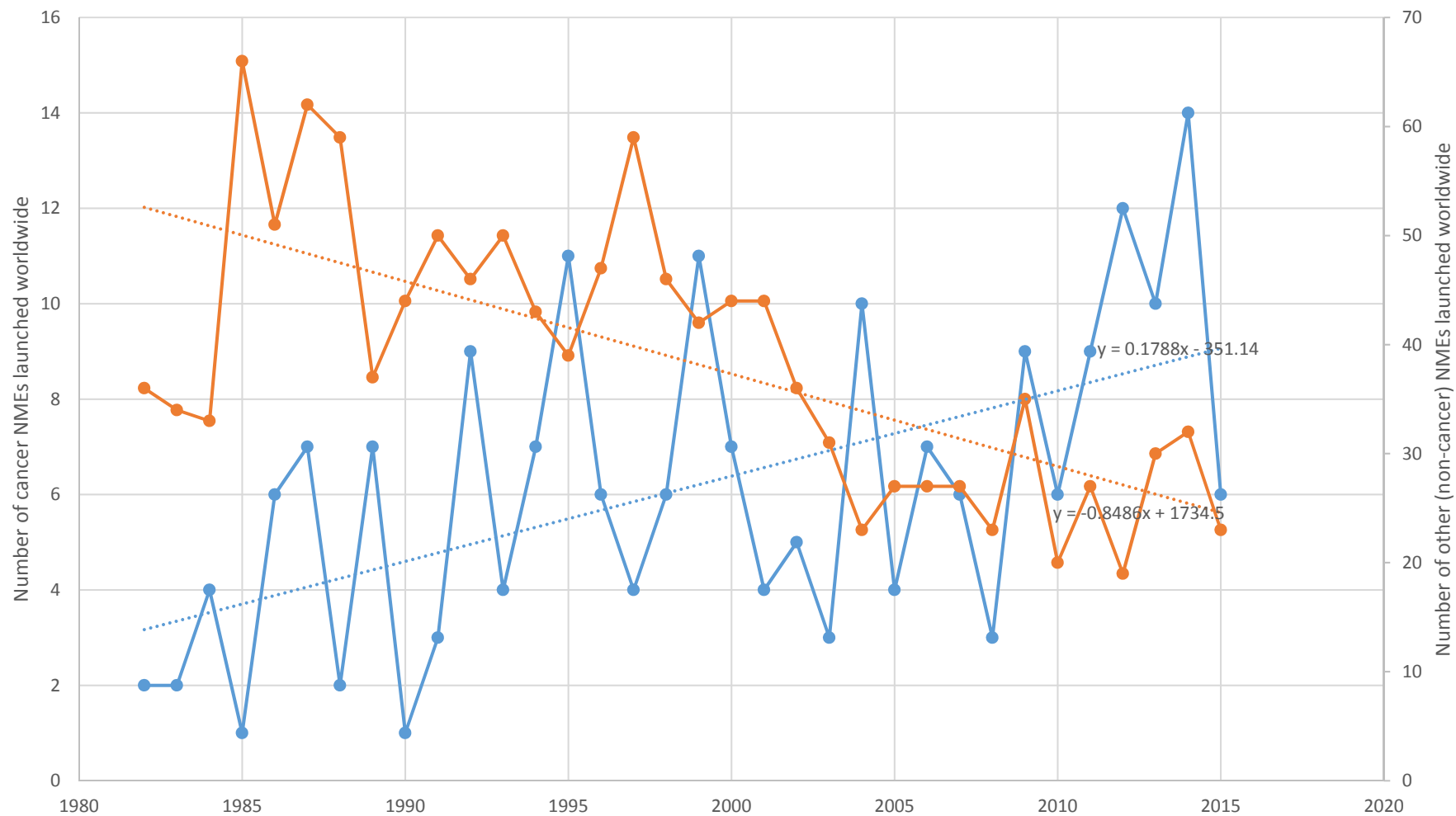
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Figure 1
Number of drugs used to treat cancer ever approved by the FDA



Source: Author's calculations based on National Cancer Institute and FDA data:
<http://www.cancer.gov/about-cancer/treatment/drugs/cancer-type>
<http://www.fda.gov/Drugs/InformationOnDrugs/ucm135821.htm>

Figure 2
Number of cancer and other new molecular entities launched worldwide, 1982-2015



Source: author's calculations based on IMS Health New Product Focus database

"Cancer NMEs" are NMEs in EphMRA/PBIRG Anatomical Classification L (ANTINEOPLASTIC AND IMMUNOMODULATING AGENTS)

—●— cancer —●— other Linear (cancer) Linear (other)

Figure 3

Drugs approved for Acute Lymphoblastic Leukemia

| | |
|----------------------------|------|
| MERCAPTOPURINE | 1953 |
| METHOTREXATE SODIUM | 1953 |
| PREDNISONE | 1955 |
| CYCLOPHOSPHAMIDE | 1959 |
| VINCRIStINE SULFATE | 1963 |
| CYTARABINE | 1969 |
| DOXORUBICIN HYDROCHLORIDE | 1974 |
| DAUNORUBICIN HYDROCHLORIDE | 1979 |
| ASPARAGINASE | 1994 |
| PEGASPARGASE | 1994 |
| IMATINIB MESYLATE | 2001 |
| CLOFARABINE | 2004 |
| NELARABINE | 2005 |
| DASATINIB | 2006 |
| PONATINIB HYDROCHLORIDE | 2012 |
| BLINATUMOMAB | 2014 |

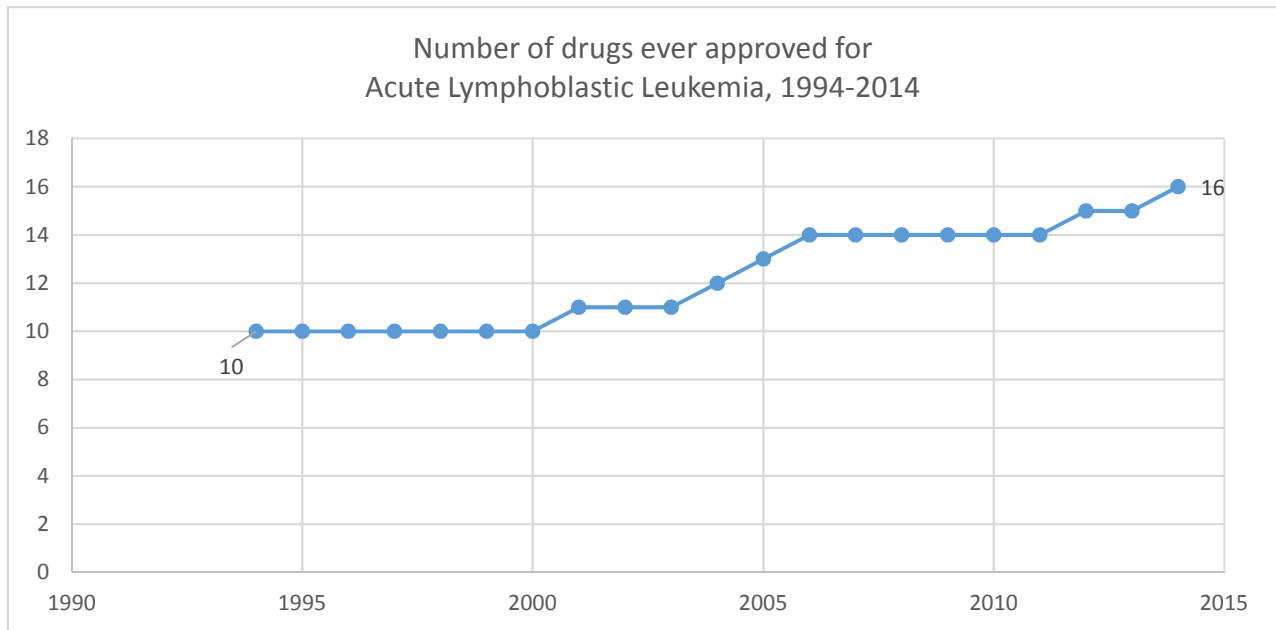


Figure 4
Number of drugs ever approved for 4 types of cancer, 1994-2014

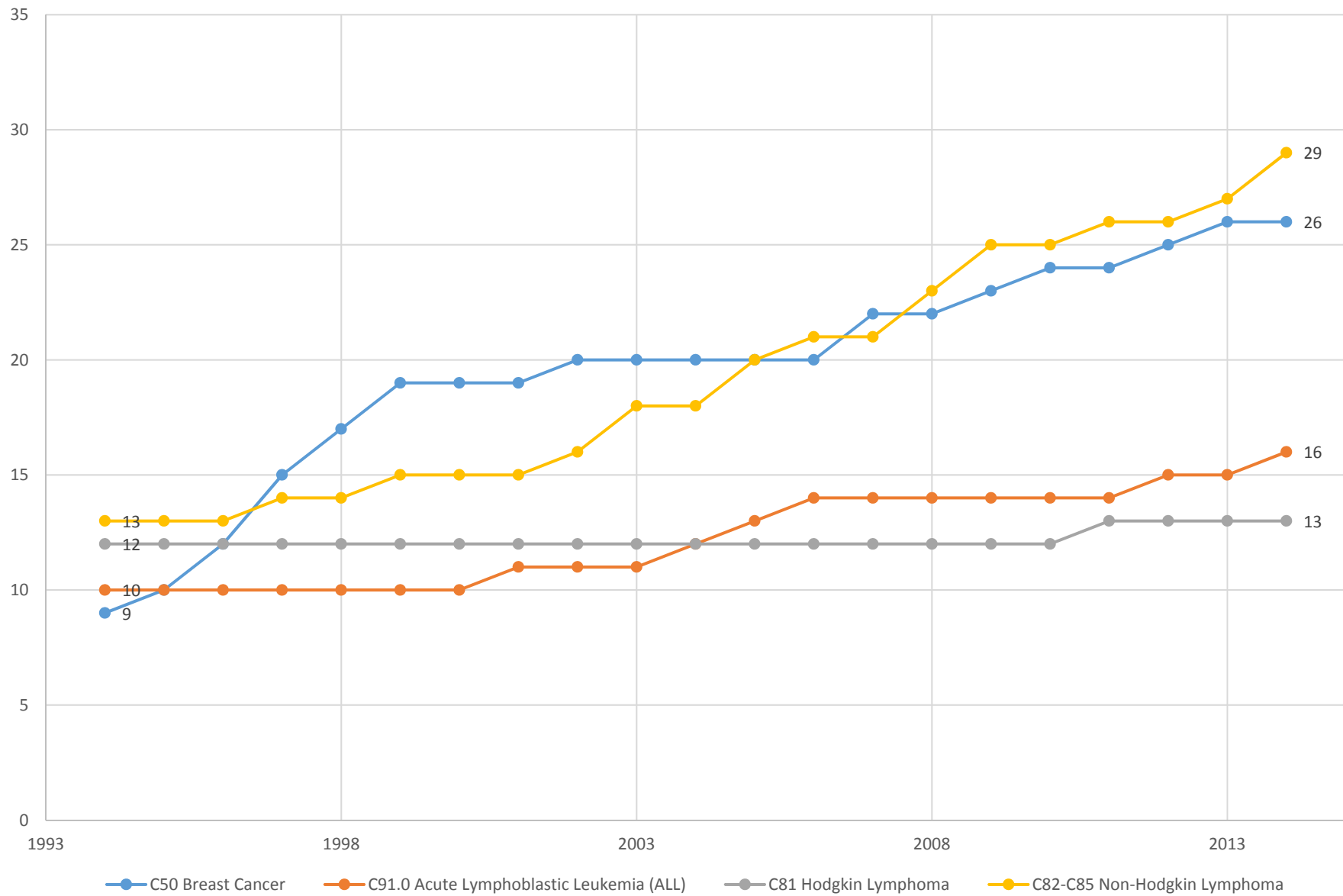
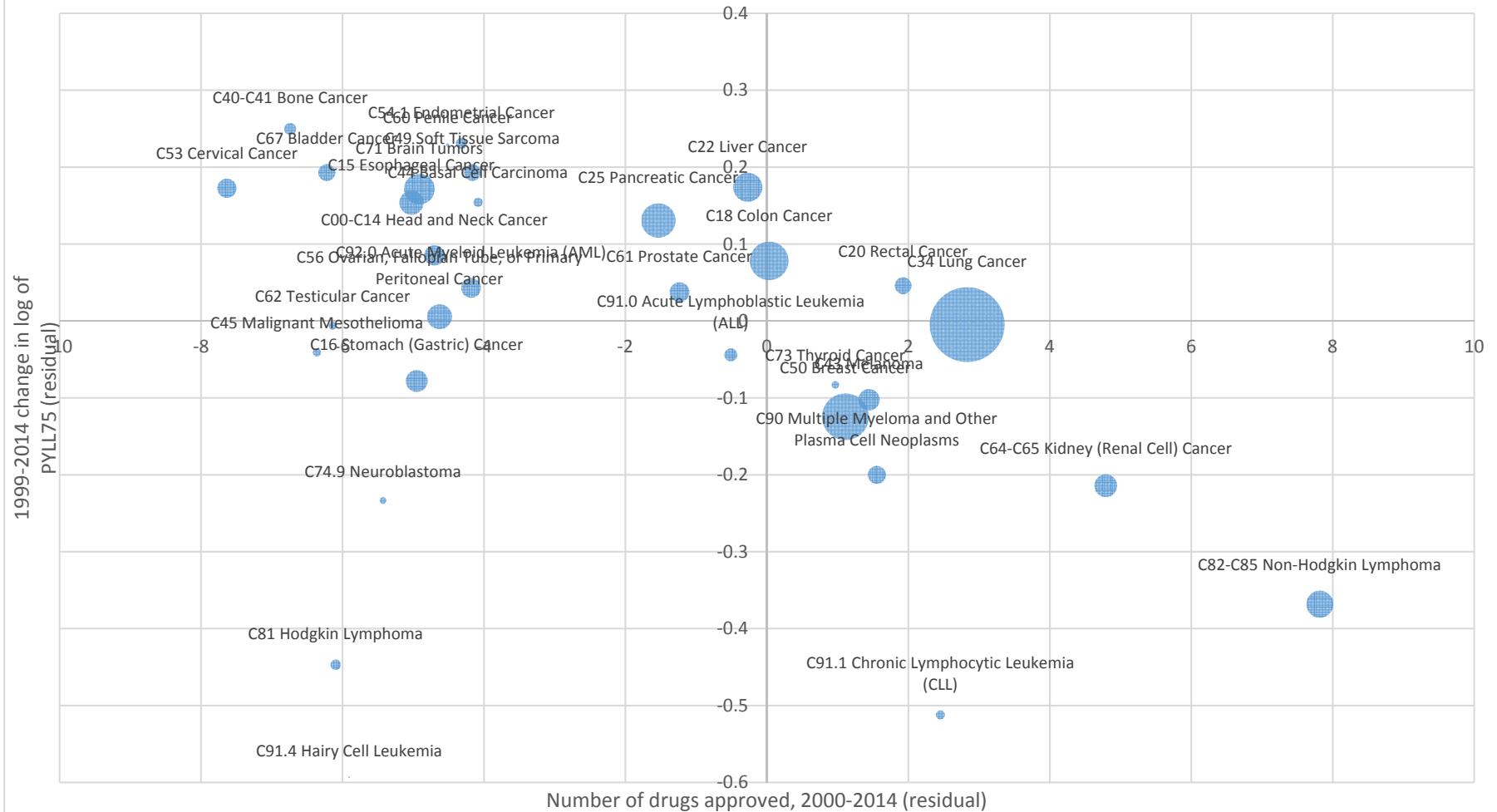


Figure 5

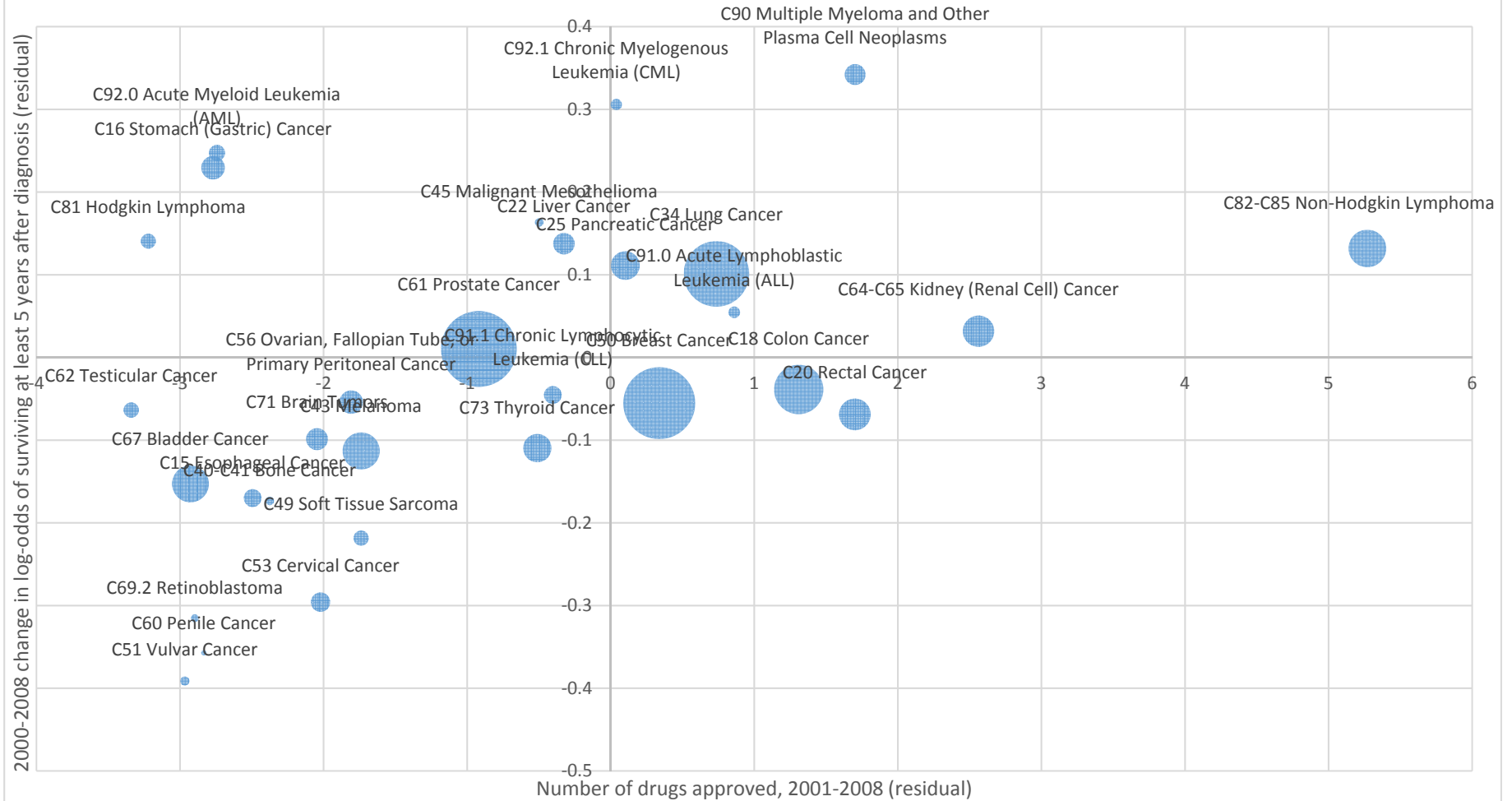
Correlation across cancer sites between number of drugs approved during 2000-2014 and 1999-2014 change in log of potential years of life lost before age 75 (PYLL75), controlling for changes in incidence and mean age at diagnosis



This figure shows the correlation between the residual from the regression of $\Delta \ln(\text{PYLL75}_s)$ on $\Delta \ln(\text{CASES}_s)$ and $\Delta \text{AGE_DIAG}_s$ and the residual from the regression of $\Delta \ln(\text{APP_1948_t}_s)$ on $\Delta \ln(\text{CASES}_s)$ and $\Delta \text{AGE_DIAG}_s$ (see eq. (4)). Bubble size is proportional to mean PYLL75.

Figure 6

Correlation across cancer sites between number of drugs approved during 2001-2008 and 2000-2008 change in log-odds of surviving at least 5 years after diagnosis, controlling for changes in incidence and expected survival rate



This figure shows the correlation between the residual from the regression of $\Delta \ln(\text{SURV_OBS}_s / (1 - \text{SURV_OBS}_s))$ on $\Delta \ln(\text{CASES}_s)$ and $\Delta \ln(\text{SURV_EXP}_s / (1 - \text{SURV_EXP}_s))$ and the residual from the regression of $\Delta \ln(\text{APP}_{1948_t_s})$ on $\Delta \ln(\text{CASES}_s)$ and $\Delta \ln(\text{SURV_EXP}_s / (1 - \text{SURV_EXP}_s))$. Bubble size is proportional to mean number of patients diagnosed.

Table 1

U.S. sales of top cancer drugs (\$ millions)

| Molecule | 2010 | 2011 | 2012 | 2013 | 2014 | Change |
|-------------------------|-----------------|-----------------|-----------------|-----------------|-----------------|----------------|
| All cancer drugs | \$21,385 | \$22,413 | \$23,299 | \$24,942 | \$28,971 | \$7,586 |
| RITUXIMAB | \$2,673 | \$2,879 | \$3,037 | \$3,199 | \$3,351 | \$679 |
| BEVACIZUMAB | \$2,993 | \$2,581 | \$2,543 | \$2,618 | \$2,790 | -\$203 |
| IMATINIB | \$1,363 | \$1,560 | \$1,674 | \$1,872 | \$2,333 | \$970 |
| DENOSUMAB | \$27 | \$478 | \$932 | \$1,229 | \$1,552 | \$1,525 |
| ABIRATERONE ACETATE | \$0 | \$174 | \$454 | \$767 | \$1,010 | \$1,010 |
| LENALIDOMIDE | \$311 | \$431 | \$537 | \$528 | \$974 | \$663 |
| EVEROLIMUS | \$108 | \$182 | \$426 | \$714 | \$841 | \$733 |
| DASATINIB | \$185 | \$291 | \$380 | \$549 | \$725 | \$540 |
| LEUPRORELIN | \$631 | \$650 | \$639 | \$651 | \$692 | \$62 |
| IPILIMUMAB | \$0 | \$339 | \$507 | \$541 | \$687 | \$687 |

Source: IMS Health.

Note: these figures represent the value of drugs sold at "list prices"; rebates are not accounted for.

Table 2

Data on premature mortality, incidence, and hospitalization, by cancer site

| | Potential years of life lost before age 75 | | Potential years of life lost before age 65 | | Average annual number diagnosed before age 75 (SEER 9) | | Mean age at diagnosis of patients diagnosed before age 75 (SEER 9) | | Number of hospital days | |
|---|--|-----------|--|---------|--|-----------|--|-----------|-------------------------|---------|
| | 1999 | 2014 | 1999 | 2014 | 1988-1997 | 2003-2012 | 1988-1997 | 2003-2012 | 1997 | 2013 |
| C00-C14 Head and Neck Cancer | 74,052 | 87,161 | 34,112 | 36,161 | 2,166 | 2,849 | 58.0 | 57.2 | 159,120 | 139,442 |
| C15 Esophageal Cancer | 99,905 | 121,933 | 40,205 | 45,788 | 821 | 959 | 62.1 | 61.6 | 132,260 | 103,241 |
| C16 Stomach (Gastric) Cancer | 95,716 | 94,763 | 43,796 | 43,253 | 1,199 | 1,449 | 61.4 | 59.7 | 262,018 | 199,976 |
| C18 Colon Cancer | 286,278 | 301,178 | 116,093 | 129,363 | 5,376 | 5,265 | 62.7 | 60.1 | 1,044,400 | 689,071 |
| C20 Rectal Cancer | 48,443 | 60,020 | 21,343 | 26,350 | 1,710 | 2,110 | 61.1 | 57.5 | 364,882 | 268,129 |
| C22 Liver Cancer | 109,239 | 220,317 | 49,824 | 83,537 | 869 | 2,245 | 59.3 | 58.6 | 81,381 | 141,369 |
| C25 Pancreatic Cancer | 194,392 | 269,310 | 75,797 | 96,095 | 1,627 | 2,508 | 62.8 | 61.7 | 276,671 | 265,989 |
| C34 Lung Cancer | 1,089,130 | 1,010,583 | 393,295 | 336,483 | 10,884 | 10,652 | 63.0 | 62.9 | 1,183,100 | 829,940 |
| C40-C41 Bone Cancer | 26,401 | 29,409 | 18,501 | 19,729 | 250 | 292 | 35.3 | 37.8 | 36,229 | 42,784 |
| C43 Melanoma | 88,005 | 85,268 | 47,315 | 40,233 | 3,634 | 5,515 | 50.5 | 53.7 | 15,321 | 11,540 |
| C44 Basal Cell Carcinoma | 15,193 | 19,996 | 6,528 | 7,616 | 291 | 439 | 50.0 | 53.4 | 28,348 | 27,511 |
| C45 Malignant Mesothelioma | 14,113 | 12,243 | 4,843 | 4,103 | 153 | 138 | 62.8 | 63.2 | 18,289 | 14,035 |
| C46 Kaposi Sarcoma | 590 | 570 | 435 | 345 | 262 | 170 | 39.1 | 43.0 | 1,439 | 0 |
| C49 Soft Tissue Sarcoma | 49,563 | 61,264 | 29,373 | 34,339 | 521 | 719 | 46.5 | 48.9 | 51,342 | 58,920 |
| C50 Breast Cancer | 427,324 | 401,888 | 214,099 | 186,728 | 14,100 | 17,705 | 56.6 | 56.4 | 326,240 | 157,356 |
| C51 Vulvar Cancer | 3,385 | 6,000 | 1,435 | 2,530 | 205 | 266 | 57.0 | 57.2 | 18,898 | 10,365 |
| C53 Cervical Cancer | 72,735 | 70,125 | 43,145 | 39,890 | 1,108 | 930 | 46.4 | 47.6 | 91,193 | 39,409 |
| C54.1 Endometrial Cancer | 19,773 | 31,253 | 7,393 | 11,158 | 2,429 | 3,837 | 58.6 | 58.5 | 159,234 | 100,397 |
| C56 Ovarian, Fallopian Tube, or Primary Peritoneal Cancer | 115,547 | 115,525 | 51,707 | 48,060 | 1,454 | 1,548 | 56.3 | 55.9 | 188,761 | 156,756 |
| C60 Penile Cancer | 1,565 | 2,388 | 690 | 1,038 | 56 | 87 | 60.2 | 60.4 | 3,157 | 4,730 |
| C61 Prostate Cancer | 76,492 | 83,051 | 16,342 | 20,171 | 12,716 | 14,350 | 65.7 | 62.9 | 389,198 | 153,372 |
| C62 Testicular Cancer | 12,311 | 12,710 | 8,836 | 9,110 | 731 | 852 | 34.2 | 34.9 | 9,287 | 12,436 |

Table 2

Data on premature mortality, incidence, and hospitalization, by cancer site

| | Potential years of life lost before age 75 | | Potential years of life lost before age 65 | | Average annual number diagnosed before age 75 (SEER 9) | | Mean age at diagnosis of patients diagnosed before age 75 (SEER 9) | | Number of hospital days | |
|--|--|---------|--|---------|--|-----------|--|-----------|-------------------------|---------|
| | 1999 | 2014 | 1999 | 2014 | 1988-1997 | 2003-2012 | 1988-1997 | 2003-2012 | 1997 | 2013 |
| C64-C65 Kidney (Renal Cell) Cancer | 92,658 | 103,563 | 40,028 | 40,348 | 1,990 | 3,796 | 58.0 | 57.7 | 210,836 | 229,344 |
| C67 Bladder Cancer | 49,151 | 60,795 | 16,286 | 19,515 | 3,059 | 3,602 | 62.7 | 62.7 | 244,471 | 191,431 |
| C69.2 Retinoblastoma | 422 | 205 | 257 | 110 | 21 | 26 | 4.9 | 3.7 | 381 | 895 |
| C71 Brain Tumors | 176,630 | 199,026 | 97,895 | 101,896 | 1,291 | 1,546 | 45.9 | 46.9 | 223,031 | 221,945 |
| C73 Thyroid Cancer | 9,078 | 12,773 | 3,968 | 5,113 | 1,605 | 4,281 | 44.5 | 47.7 | 45,057 | 46,112 |
| C74.9 Neuroblastoma | 9,095 | 8,178 | 5,645 | 4,918 | 35 | 37 | 21.4 | 17.8 | 14,985 | 13,315 |
| C81 Hodgkin Lymphoma | 26,015 | 15,628 | 17,000 | 9,463 | 683 | 744 | 36.1 | 38.0 | 41,761 | 44,139 |
| C82-C85 Non-Hodgkin Lymphoma | 170,143 | 121,130 | 79,183 | 50,615 | 3,439 | 4,171 | 54.6 | 56.4 | 456,126 | 386,511 |
| C90 Multiple Myeloma and Other Plasma Cell Neoplasms | 62,555 | 63,338 | 22,540 | 20,973 | 882 | 1,370 | 62.3 | 61.2 | 162,886 | 213,160 |
| C91.0 Acute Lymphoblastic Leukemia (ALL) | 33,325 | 31,268 | 23,035 | 20,743 | 326 | 446 | 19.7 | 22.0 | 113,448 | 156,189 |
| C91.1 Chronic Lymphocytic Leukemia (CLL) | 16,876 | 13,585 | 5,101 | 4,065 | 668 | 1,157 | 62.8 | 62.2 | 47,874 | 32,660 |
| C91.4 Hairy Cell Leukemia | 610 | 360 | 275 | 120 | 73 | 89 | 54.7 | 54.3 | 0 | 0 |
| C92.0 Acute Myeloid Leukemia (AML) | 66,432 | 77,876 | 35,282 | 36,561 | 495 | 710 | 53.0 | 54.3 | 248,775 | 390,516 |
| C92.1 Chronic Myelogenous Leukemia (CML) | 22,590 | 7,940 | 13,065 | 4,145 | 240 | 329 | 52.0 | 51.4 | 54,344 | 33,370 |

Table 3

Observed and expected 5-year survival rates and number of patients diagnosed, by cancer site, 2000 and 2008

| Cancer site | Observed 5-year survival rate | | Expected 5-year survival rate | | Number of patients diagnosed | |
|---|-------------------------------|-------|-------------------------------|-------|------------------------------|--------|
| | 2000 | 2008 | 2000 | 2008 | 2000 | 2008 |
| C15 Esophageal Cancer | 13.5% | 14.1% | 86.2% | 88.0% | 2,754 | 2,994 |
| C16 Stomach (Gastric) Cancer | 18.8% | 26.0% | 83.9% | 86.2% | 5,055 | 4,972 |
| C18 Colon Cancer | 50.6% | 54.6% | 80.7% | 83.9% | 22,409 | 21,575 |
| C20 Rectal Cancer | 54.7% | 59.4% | 85.6% | 89.1% | 9,208 | 8,998 |
| C22 Liver Cancer | 10.4% | 16.5% | 90.8% | 91.6% | 3,149 | 5,253 |
| C25 Pancreatic Cancer | 4.2% | 6.3% | 86.2% | 88.6% | 6,663 | 8,226 |
| C34 Lung Cancer | 12.6% | 15.2% | 86.2% | 86.6% | 38,808 | 38,678 |
| C40-C41 Bone Cancer | 66.4% | 68.0% | 96.1% | 96.7% | 619 | 691 |
| C43 Melanoma | 81.1% | 82.2% | 90.1% | 89.7% | 10,889 | 13,949 |
| C45 Malignant Mesothelioma | 5.0% | 8.3% | 80.7% | 87.4% | 647 | 653 |
| C49 Soft Tissue Sarcoma | 59.4% | 58.7% | 91.0% | 91.2% | 1,927 | 2,295 |
| C50 Breast Cancer | 79.5% | 81.8% | 90.0% | 91.4% | 45,901 | 47,537 |
| C51 Vulvar Cancer | 65.4% | 60.0% | 86.0% | 86.7% | 737 | 778 |
| C53 Cervical Cancer | 68.1% | 65.0% | 95.8% | 96.5% | 3,557 | 3,248 |
| C56 Ovarian, Fallopian Tube, or Primary Peritoneal Cancer | 40.3% | 43.4% | 92.1% | 93.0% | 4,869 | 5,014 |
| C60 Penile Cancer | 61.4% | 57.1% | 82.3% | 83.8% | 246 | 258 |
| C61 Prostate Cancer | 80.6% | 85.2% | 81.9% | 86.4% | 49,820 | 53,557 |
| C62 Testicular Cancer | 94.2% | 94.4% | 98.5% | 98.4% | 2,049 | 2,237 |
| C64-C65 Kidney (Renal Cell) Cancer | 56.9% | 66.6% | 88.3% | 90.0% | 7,148 | 10,573 |
| C67 Bladder Cancer | 62.6% | 62.8% | 80.3% | 81.4% | 11,874 | 12,633 |
| C69.2 Retinoblastoma | 78.7% | 76.2% | 89.4% | 90.5% | 557 | 562 |
| C71 Brain Tumors | 28.9% | 29.9% | 97.2% | 97.2% | 4,084 | 4,520 |
| C73 Thyroid Cancer | 92.2% | 93.9% | 96.1% | 96.1% | 5,170 | 9,228 |
| C81 Hodgkin Lymphoma | 81.2% | 84.9% | 97.1% | 96.9% | 1,931 | 2,170 |
| C82-C85 Non-Hodgkin Lymphoma | 54.6% | 62.4% | 88.0% | 88.6% | 11,964 | 13,585 |
| C90 Multiple Myeloma and Other Plasma Cell Neoplasms | 28.9% | 42.4% | 85.5% | 87.4% | 3,644 | 4,241 |
| C91.0 Acute Lymphoblastic Leukemia (ALL) | 62.3% | 66.5% | 99.1% | 99.1% | 1,145 | 1,311 |
| C91.1 Chronic Lymphocytic Leukemia (CLL) | 64.0% | 68.3% | 81.9% | 83.1% | 2,550 | 3,153 |
| C92.0 Acute Myeloid Leukemia (AML) | 16.6% | 23.6% | 94.8% | 95.3% | 2,303 | 2,454 |
| C92.1 Chronic Myelogenous Leukemia (CML) | 45.5% | 57.0% | 90.6% | 90.9% | 1,100 | 1,209 |

Table 4

Number of drugs ever approved by the FDA, by cancer site and year, 1990-2014

| | All drugs | | | | | | | | Priority-review drugs | | | | | | |
|---|-----------|------|------|------|------|------|------|--|-----------------------|------|------|------|------|------|------|
| | 1990 | 1994 | 1998 | 2002 | 2006 | 2010 | 2014 | | 1990 | 1994 | 1998 | 2002 | 2006 | 2010 | 2014 |
| C00-C14 Head and Neck Cancer | 3 | 3 | 4 | 4 | 5 | 5 | 5 | | 2 | 2 | 3 | 3 | 3 | 3 | 3 |
| C15 Esophageal Cancer | 0 | 0 | 2 | 2 | 2 | 2 | 3 | | 0 | 0 | 1 | 1 | 1 | 1 | 1 |
| C16 Stomach (Gastric) Cancer | 3 | 3 | 5 | 5 | 5 | 5 | 6 | | 3 | 3 | 4 | 4 | 4 | 4 | 4 |
| C18 Colon Cancer | 2 | 2 | 4 | 5 | 8 | 8 | 11 | | 2 | 2 | 4 | 5 | 5 | 5 | 6 |
| C20 Rectal Cancer | 2 | 2 | 4 | 5 | 8 | 8 | 11 | | 2 | 2 | 4 | 5 | 5 | 5 | 6 |
| C22 Liver Cancer | 0 | 0 | 0 | 0 | 1 | 1 | 1 | | 0 | 0 | 0 | 0 | 1 | 1 | 1 |
| C25 Pancreatic Cancer | 2 | 3 | 5 | 5 | 7 | 8 | 8 | | 2 | 3 | 5 | 5 | 7 | 8 | 8 |
| C34 Lung Cancer | 5 | 7 | 11 | 11 | 15 | 15 | 21 | | 5 | 7 | 10 | 10 | 13 | 13 | 16 |
| C40-C41 Bone Cancer | 3 | 3 | 3 | 3 | 3 | 4 | 4 | | 3 | 3 | 3 | 3 | 3 | 3 | 3 |
| C43 Melanoma | 2 | 3 | 3 | 4 | 4 | 4 | 10 | | 0 | 0 | 0 | 0 | 0 | 0 | 1 |
| C44 Basal Cell Carcinoma | 1 | 1 | 2 | 2 | 2 | 2 | 3 | | 1 | 1 | 1 | 1 | 1 | 1 | 2 |
| C45 Malignant Mesothelioma | 0 | 0 | 0 | 0 | 1 | 1 | 1 | | 0 | 0 | 0 | 0 | 1 | 1 | 1 |
| C46 Kaposi Sarcoma | 3 | 4 | 4 | 4 | 4 | 4 | 4 | | 2 | 3 | 3 | 3 | 3 | 3 | 3 |
| C49 Soft Tissue Sarcoma | 3 | 3 | 3 | 4 | 4 | 5 | 5 | | 3 | 3 | 3 | 4 | 4 | 4 | 4 |
| C50 Breast Cancer | 7 | 9 | 17 | 20 | 20 | 24 | 26 | | 4 | 6 | 11 | 12 | 12 | 16 | 16 |
| C51 Vulvar Cancer | 1 | 1 | 1 | 1 | 1 | 1 | 1 | | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| C53 Cervical Cancer | 1 | 1 | 2 | 2 | 3 | 3 | 3 | | 0 | 0 | 1 | 1 | 1 | 1 | 1 |
| C54.1 Endometrial Cancer | 1 | 1 | 1 | 1 | 1 | 1 | 1 | | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| C56 Ovarian, Fallopian Tube, or Primary Peritoneal Cancer | 5 | 6 | 8 | 8 | 9 | 9 | 10 | | 4 | 5 | 7 | 7 | 7 | 7 | 8 |
| C60 Penile Cancer | 1 | 1 | 1 | 1 | 1 | 1 | 1 | | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| C61 Prostate Cancer | 5 | 5 | 7 | 7 | 7 | 9 | 12 | | 4 | 4 | 6 | 6 | 6 | 7 | 10 |
| C62 Testicular Cancer | 6 | 6 | 7 | 7 | 7 | 7 | 7 | | 4 | 4 | 4 | 4 | 4 | 4 | 4 |
| C64-C65 Kidney (Renal Cell) Cancer | 3 | 4 | 4 | 4 | 7 | 10 | 12 | | 3 | 3 | 3 | 3 | 5 | 7 | 7 |
| C67 Bladder Cancer | 3 | 3 | 3 | 3 | 3 | 3 | 3 | | 2 | 2 | 2 | 2 | 2 | 2 | 2 |
| C69.2 Retinoblastoma | 1 | 1 | 1 | 1 | 1 | 1 | 1 | | 1 | 1 | 1 | 1 | 1 | 1 | 1 |

Table 4

Number of drugs ever approved by the FDA, by cancer site and year, 1990-2014

| | All drugs | | | | | | | | Priority-review drugs | | | | | | |
|--|-----------|------|------|------|------|------|------|--|-----------------------|------|------|------|------|------|------|
| | 1990 | 1994 | 1998 | 2002 | 2006 | 2010 | 2014 | | 1990 | 1994 | 1998 | 2002 | 2006 | 2010 | 2014 |
| C71 Brain Tumors | 2 | 2 | 2 | 3 | 4 | 5 | 5 | | 1 | 1 | 1 | 2 | 2 | 3 | 3 |
| C73 Thyroid Cancer | 1 | 1 | 1 | 1 | 2 | 2 | 4 | | 1 | 1 | 1 | 1 | 2 | 2 | 4 |
| C74.9 Neuroblastoma | 3 | 3 | 3 | 3 | 3 | 3 | 3 | | 3 | 3 | 3 | 3 | 3 | 3 | 3 |
| C81 Hodgkin Lymphoma | 12 | 12 | 12 | 12 | 12 | 12 | 13 | | 9 | 9 | 9 | 9 | 9 | 9 | 9 |
| C82-C85 Non-Hodgkin Lymphoma | 13 | 13 | 14 | 16 | 21 | 25 | 29 | | 11 | 11 | 11 | 11 | 15 | 18 | 21 |
| C90 Multiple Myeloma and Other Plasma Cell Neoplasms | 4 | 5 | 6 | 7 | 9 | 10 | 12 | | 4 | 5 | 6 | 7 | 9 | 10 | 10 |
| C91.0 Acute Lymphoblastic Leukemia (ALL) | 8 | 10 | 10 | 11 | 14 | 14 | 16 | | 8 | 8 | 8 | 9 | 12 | 12 | 13 |
| C91.1 Chronic Lymphocytic Leukemia (CLL) | 4 | 5 | 6 | 7 | 7 | 9 | 12 | | 4 | 5 | 5 | 5 | 5 | 6 | 8 |
| C91.4 Hairy Cell Leukemia | 1 | 1 | 1 | 1 | 1 | 1 | 1 | | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| C92.0 Acute Myeloid Leukemia (AML) | 8 | 8 | 8 | 9 | 9 | 9 | 9 | | 8 | 8 | 8 | 9 | 9 | 9 | 9 |
| C92.1 Chronic Myelogenous Leukemia (CML) | 4 | 4 | 4 | 5 | 6 | 7 | 10 | | 4 | 4 | 4 | 5 | 6 | 6 | 7 |

Table 5a

Weighted least-squares estimates of models of potential years of life lost **before age 75**

| | Estimate | Std. Err. | Z | Pr > Z | Difference p-value | | Estimate | Std. Err. | Z | Pr > Z | Difference p-value |
|----------------|-------------------------|-----------|-------|---------|-----------------------|--|-------------------------|-----------|-------|---------|-----------------------|
| | Years 1999, 2014 | | | | | | Years 1999, 2010 | | | | |
| | Model 1 | | | | | | Model 5 | | | | |
| $\Delta\delta$ | 0.0795 | 0.0292 | 2.72 | 0.0065 | | | 0.0799 | 0.0221 | 3.62 | 0.0003 | |
| | Model 2 | | | | | | Model 6 | | | | |
| N_APP_1948_t | -0.0230 | 0.0066 | -3.51 | 0.0005 | | | -0.0325 | 0.0060 | -5.41 | <.0001 | |
| $\Delta\delta$ | -0.0895 | 0.0399 | -2.25 | 0.0247 | | | -0.0699 | 0.0306 | -2.29 | 0.0222 | |
| | Model 3 | | | | | | Model 7 | | | | |
| N_PRI_1948_t | -0.0183 | 0.0108 | -1.70 | 0.0893 | 0.4251 | | -0.0266 | 0.0070 | -3.82 | 0.0001 | 0.1933 |
| N_STD_1948_t | -0.0308 | 0.0088 | -3.50 | 0.0005 | | | -0.0505 | 0.0154 | -3.28 | 0.0011 | |
| $\Delta\delta$ | -0.0950 | 0.0394 | -2.41 | 0.0159 | | | -0.0777 | 0.0317 | -2.45 | 0.0141 | |
| | Model 4 | | | | | | Model 8 | | | | |
| N_APP_1948_t-4 | -0.0252 | 0.0059 | -4.25 | <.0001 | 0.0912 | | -0.0333 | 0.0054 | -6.19 | <.0001 | 0.0939 |
| N_APP_t-4_t | -0.0152 | 0.0085 | -1.79 | 0.0728 | | | -0.0487 | 0.0077 | -6.35 | <.0001 | |
| $\Delta\delta$ | -0.1020 | 0.0411 | -2.48 | 0.0130 | | | -0.0283 | 0.0391 | -0.72 | 0.4695 | |
| | | | | | | | Model 9 | | | | |
| N_APP_1948_t | | | | | | | -0.0340 | 0.0057 | -5.98 | <.0001 | |
| N_APP_t_t+4 | | | | | | | 0.0076 | 0.0084 | 0.90 | 0.3677 | |
| $\Delta\delta$ | | | | | | | -0.0528 | 0.0285 | -1.85 | 0.0643 | |
| | | | | | | | Model 10 | | | | |
| N_APP_1948_t-4 | | | | | | | -0.0337 | 0.0059 | -5.71 | <.0001 | 0.1532 |
| N_APP_t-4_t | | | | | | | -0.0483 | 0.0079 | -6.14 | <.0001 | |
| N_APP_t_t+4 | | | | | | | 0.0026 | 0.0097 | 0.27 | 0.7890 | |
| $\Delta\delta$ | | | | | | | -0.0248 | 0.0355 | -0.70 | 0.4845 | |

Note: all models include ln(CASES), AGE_DIAG, and cancer-site fixed effects; estimates of these parameters are not shown to conserve space.

$\Delta\delta$ denotes the difference between initial and final year fixed effects, e.g. $\delta_{1999} - \delta_{2014}$. Standard errors are clustered within cancer sites.

Observations are weighted by mean potential years of life lost before age 75.

Table 5b

Weighted least-squares estimates of models of potential years of life lost **before age 65**

| | Estimate | Std. Err. | Z | Pr > Z | Difference p-value | | Estimate | Std. Err. | Z | Pr > Z | Difference p-value |
|----------------|-------------------------|-----------|-------|---------|-----------------------|--|-------------------------|-----------|-------|---------|-----------------------|
| | Years 1999, 2014 | | | | | | Years 1999, 2010 | | | | |
| | Model 1 | | | | | | Model 5 | | | | |
| $\Delta\delta$ | 0.1387 | 0.0281 | 4.93 | <.0001 | | | 0.1487 | 0.0374 | 3.97 | <.0001 | |
| | Model 2 | | | | | | Model 6 | | | | |
| N_APP_1948_t | -0.0264 | 0.0055 | -4.82 | <.0001 | | | -0.0322 | 0.0058 | -5.52 | <.0001 | |
| $\Delta\delta$ | -0.0631 | 0.0481 | -1.31 | 0.1894 | | | -0.0510 | 0.0377 | -1.35 | 0.1756 | |
| | Model 3 | | | | | | Model 7 | | | | |
| N_PRI_1948_t | -0.0250 | 0.0088 | -2.85 | 0.0044 | 0.8031 | | -0.0307 | 0.0073 | -4.19 | <.0001 | 0.7360 |
| N_STD_1948_t | -0.0288 | 0.0097 | -2.98 | 0.0029 | | | -0.0369 | 0.0150 | -2.46 | 0.0141 | |
| $\Delta\delta$ | -0.0659 | 0.0473 | -1.39 | 0.1634 | | | -0.0543 | 0.0425 | -1.28 | 0.2018 | |
| | Model 4 | | | | | | Model 8 | | | | |
| N_APP_1948_t-4 | -0.0281 | 0.0052 | -5.38 | <.0001 | 0.1280 | | -0.0327 | 0.0055 | -5.94 | <.0001 | 0.2695 |
| N_APP_t-4_t | -0.0202 | 0.0069 | -2.94 | 0.0033 | | | -0.0437 | 0.0080 | -5.43 | <.0001 | |
| $\Delta\delta$ | -0.0749 | 0.0499 | -1.50 | 0.1333 | | | -0.0120 | 0.0518 | -0.23 | 0.8170 | |
| | | | | | | | Model 9 | | | | |
| N_APP_1948_t | | | | | | | -0.0332 | 0.0059 | -5.66 | <.0001 | |
| N_APP_t_t+4 | | | | | | | 0.0056 | 0.0104 | 0.53 | 0.5941 | |
| $\Delta\delta$ | | | | | | | -0.0360 | 0.0402 | -0.90 | 0.3696 | |
| | | | | | | | Model 10 | | | | |
| N_APP_1948_t-4 | | | | | | | -0.0332 | 0.0060 | -5.49 | <.0001 | 0.3209 |
| N_APP_t-4_t | | | | | | | -0.0434 | 0.0079 | -5.51 | <.0001 | |
| N_APP_t_t+4 | | | | | | | 0.0028 | 0.0111 | 0.25 | 0.7989 | |
| $\Delta\delta$ | | | | | | | -0.0070 | 0.0487 | -0.14 | 0.8863 | |

Note: all models include ln(CASES), AGE_DIAG, and cancer-site fixed effects; estimates of these parameters are not shown to conserve space. Dd denotes the difference between initial and final year fixed effects, e.g. d1999 - d2014. Standard errors are clustered within cancer sites. Observations are weighted by mean potential years of life lost before age 65.

Table 6

Weighted least-squares estimates of models of the **observed 5-year survival rate** (eq. (10))

| Parameter | Estimate | Std. Err. | Z | Pr > Z | Difference p-value |
|---------------------------------|-------------------------|-----------|-------|---------|--------------------|
| | Years 2000, 2008 | | | | |
| | Model 1 | | | | |
| $\delta_{2000} - \delta_{2008}$ | -0.0971 | 0.0557 | -1.74 | 0.0810 | |
| | | | | | |
| | Model 2 | | | | |
| N_APP_1948_t | 0.0240 | 0.0087 | 2.77 | 0.0056 | |
| $\delta_{2000} - \delta_{2008}$ | -0.0158 | 0.0528 | -0.30 | 0.7654 | |
| | | | | | |
| | Model 3 | | | | |
| N_PRI_1948_t | 0.0471 | 0.0098 | 4.82 | <.0001 | 0.0005 |
| N_STD_1948_t | -0.0389 | 0.0200 | -1.94 | 0.0519 | |
| $\delta_{2000} - \delta_{2008}$ | -0.0294 | 0.0491 | -0.60 | 0.5501 | |
| | | | | | |
| | Model 4 | | | | |
| N_APP_1948_t-4 | 0.0353 | 0.0093 | 3.78 | 0.0002 | 0.0003 |
| N_APP_t-4_t | 0.0212 | 0.0091 | 2.33 | 0.0200 | |
| $\delta_{2000} - \delta_{2008}$ | -0.0443 | 0.0569 | -0.78 | 0.4362 | |
| | | | | | |
| | Model 5 | | | | |
| N_APP_1948_t-8 | 0.0257 | 0.0089 | 2.88 | 0.0040 | 0.4546 |
| N_APP_t-8_t | 0.0214 | 0.0100 | 2.14 | 0.0327 | |
| $\delta_{2000} - \delta_{2008}$ | -0.0301 | 0.0594 | -0.51 | 0.6121 | |

Note: all models include $\ln(\text{CASES})$, $\ln(\text{SURV_EXP}/(1 - \text{SURV_EXP}))$, and cancer-site fixed effects; estimates of these parameters are not shown to conserve space. Standard errors are clustered within cancer sites. Observations are weighted by number of patients diagnosed.

Table 7

Weighted least-squares estimates of models of the number of hospital days (eq. (11))

| Parameter | Estimate | Std. Err. | Z | Pr > Z | Difference p-value |
|---------------------------------|-------------------------|-----------|-------|---------|--------------------|
| | Years 1997, 2013 | | | | |
| | Model 1 | | | | |
| $\delta_{1997} - \delta_{2013}$ | 0.3913 | 0.0741 | 5.28 | <.0001 | |
| | | | | | |
| | Model 2 | | | | |
| N_APP_1948_t | -0.0195 | 0.0110 | -1.77 | 0.0769 | |
| $\delta_{1997} - \delta_{2013}$ | 0.2789 | 0.0801 | 3.48 | 0.0005 | |
| | | | | | |
| | Model 3 | | | | |
| N_PRI_1948_t | -0.0351 | 0.0301 | -1.17 | 0.2439 | 0.5592 |
| N_STD_1948_t | 0.0037 | 0.04 | 0.09 | 0.9268 | |
| $\delta_{1997} - \delta_{2013}$ | 0.2838 | 0.078 | 3.64 | 0.0003 | |
| | | | | | |
| | Model 4 | | | | |
| N_APP_1948_t-4 | -0.0224 | 0.0101 | -2.22 | 0.0265 | 0.0854 |
| N_APP_t-4_t | 0.0211 | 0.0243 | 0.87 | 0.3848 | |
| $\delta_{1997} - \delta_{2013}$ | 0.2293 | 0.0859 | 2.67 | 0.0076 | |
| | | | | | |
| | Model 5 | | | | |
| N_APP_1948_t-8 | -0.0291 | 0.0124 | -2.34 | 0.0192 | 0.0610 |
| N_APP_t-8_t | -0.0028 | 0.0125 | -0.23 | 0.8213 | |
| $\delta_{1997} - \delta_{2013}$ | 0.2115 | 0.0947 | 2.23 | 0.0256 | |

Note: all models include $\ln(\text{CASES})$, AGE_DIAG, and cancer-site fixed effects; estimates of these parameters are not shown to conserve space. Standard errors are clustered within cancer sites. Observations are weighted by mean number of hospital days.

Table 8

Calculation of the cost per life-year gained in 2014 from cancer drugs approved during 2000-2014

| Line | Description | Basis | Value |
|------|---|---|------------------|
| (1) | Total expenditure (before rebates) on cancer drugs in 2014 | IMS Institute for Healthcare Informatics (2015) | \$32,300,000,000 |
| (2) | Fraction of total expenditure on post-1999 drugs | Author's calculations based on IMS MIDAS data | 67.7% |
| (3) | Expenditure (before rebates) on post-1999 cancer drugs in 2014 | (1) * (2) | \$21,867,100,000 |
| (4) | Rebates on post-1999 drugs, assuming 25% rebate rate (Herper (2012)) | 25% * (3) | \$5,466,775,000 |
| (5) | Reduction in old drug cost (assumed to be 25% of new drug cost) (Lichtenberg (2014c)) | 25% * ((3) - (4)) | \$4,100,081,250 |
| (6) | Hospital cost reduction | Author's calculations based on estimates of models 1 and 5 in Table 6. | \$4,770,000,000 |
| (7) | Net expend--all ages | (3) - ((4) + (5) + (6)) | \$7,530,243,750 |
| (8) | Net expend--below age 75 (assumed to be 75% of net expenditure for all ages) | 75% * (7) | \$5,647,682,813 |
| (9) | Life-years before age 75 gained, controlling for incidence and mean age at diagnosis | Author's calculations based on estimates of models 1 and 2 in Table 5a. | 719,133 |
| (10) | Cost per life-year gained before age 75 | (9) / (8) | \$7,853 |

Appendix Figure 1
Mean ratio of the quantity of a cancer drug sold n years after approval
to the quantity of the same drug sold 9 years after approval

