The impact of pharmaceutical innovation on premature mortality, hospital separations, and cancer survival in Australia

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Abstract

Premature (before age 75 and 80) mortality has been declining in Australia, but there has been considerable variation in the rate of decline across diseases. I first analyze the effect that pharmaceutical innovation had on premature mortality from all diseases in Australia during the period 1998-2011 by investigating whether the diseases that experienced more pharmaceutical innovation had larger declines in premature mortality. My estimates indicate that 60% of the 1998-2011 decline in premature (before age 75) mortality was due to previous pharmaceutical innovation. The estimates generally support the hypothesis that premature mortality depends on the number of drugs ever listed on the Pharmaceutical Benefits Scheme (PBS), not on the number of drug classes. This would be the case if drugs within the same class are not "therapeutically equivalent."

Next, I analyze the effect that pharmaceutical innovation had on hospital separations from all diseases during the period 1998-2011. The estimates indicate that if no new drugs had been listed on the PBS during 1986-1999, the number of hospital separations in 2011 would have been about 13% higher.

Lastly, I analyze the effect that pharmaceutical innovation had on survival from all types of cancer during the period 1986-2007, controlling for mean age at diagnosis, the number of patients diagnosed, and changes in the distribution of patients diagnosed, by cancer site. I estimate that previous pharmaceutical innovation accounted for 40% of the 1986-2007 increase (from 49.0% to 61.6%) in the 5-year relative cancer survival rate.

My estimates indicate that new drugs listed on the PBS during 1989-2002 reduced the number of life-years lost from all diseases before ages 75 and 80 in 2011 by 143,639 and 257,602, respectively, and that the innovation was *cost-saving*: the reduction in hospital expenditure attributable to it exceeded expenditure on the drugs. Even if one discounts or completely ignores the apparent reduction in hospital expenditure, the evidence indicates that pharmaceutical innovation was highly cost effective. If the true reduction in hospital expenditure was only 50% as large as I have estimated, the cost per life-year gained before age 75 and 80 was $AUS 15,280 and $AUS 8682, respectively. If there was *no* reduction in hospital expenditure, the cost per life-year gained before age 75 and 80 was $AUS 34,640 and $AUS 20,560, respectively. According to the World Health Organization, an intervention whose cost per quality-adjusted life-year gained is less than $AUS 66,608 should be considered highly cost-effective.

Because new drugs diffuse gradually, premature mortality is most strongly inversely related to the number of drugs that had ever been listed 9 years earlier. Therefore, if we assume that the relationship between pharmaceutical innovation and premature mortality remains the same until the year 2020, we can estimate the number of life-years that will be gained in that year from previous (until 2011) pharmaceutical innovation. I estimate that new drugs listed on the PBS during the period 1989-2011 will reduce the number of life-years lost before age 80 in the year 2020 by 308,245.

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I. Introduction

Previous authors have argued that "reducing premature mortality is a crucial public health objective" (Renard, Tafforeau, and Deboosere (2014)). A widely used measure of premature mortality is years of potential life lost (YPLL) before a given age (e.g. age 75), i.e. the number of years *not* lived by an individual who died before that age (Association of Public Health Epidemiologists in Ontario (2015)). Statistics of YPLL are published by the World Health Organization, the OECD, and government agencies of the U.S., Switzerland, and other countries. Burnet et al (2005) argue that YPLL "should be considered when allocating research funds."

The premature (before age 75) mortality rate has been declining in Australia; it declined 24% between 1998 and 2011.[1] But as shown in Figure 1, there has been considerable variation in the rate of decline across diseases. The figure displays data for the 10 diseases (ICD-10 blocks) with the largest average premature mortality rates. The premature mortality rates of three of these diseases declined by more than 40%, while the premature mortality rates of three other diseases declined by less than 10%.

In this paper, I will analyze the effect that pharmaceutical innovation had on premature mortality from all diseases in Australia during the period 1998-2011.[2] In essence, I will investigate whether the diseases that experienced more pharmaceutical innovation had larger declines in premature mortality. Figure 2 illustrates that the rate of pharmaceutical innovation, as measured by the 1986-2011 increase in the number of drugs ever listed in the Pharmaceutical Benefits Scheme (PBS),[3] varied considerably across diseases. Almost the same number of drugs (between 29 and 31) had been listed by 1986 for each of the 6 diseases shown. During the next 25 years, 41 additional drugs for hypertensive diseases were listed, while only 11 additional drugs were listed for acute upper respiratory infections.[4]

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[1] Source: Australian Institute of Health and Welfare, Supplementary data for Age at death, Table S3, http://www.aihw.gov.au/WorkArea/DownloadAsset.aspx?id=60129550392

[2] This period was chosen because a consistent cause-of-death classification (ICD-10) was used in these years.

[3] The PBS is a program of the Australian Government that provides subsidized prescription drugs to residents of Australia, as well as certain foreign visitors covered by a Reciprocal Health Care Agreement. The PBS seeks to ensure that Australian residents have affordable and reliable access to a wide range of necessary medicines. The scheme assumes responsibility for the cost of drugs to patients in the community setting rather than while in hospital, which is the responsibility of each state and territory. Together with Medicare, the PBS is a key component of health care in Australia.

[4] To illustrate the data on drugs for specific diseases, a list of drugs for acute upper respiratory infections (ICD-10 codes J00-J06), by PBS listing year, is shown in Appendix Table 1.

I will analyze the effect that pharmaceutical innovation had on hospital separations as well as on premature mortality from all diseases. Figure 3 shows that there was considerable variation across diseases in the 1998-2012 growth in the number of hospital separations. For example, the number of separations due to episodic and paroxysmal disorders (G40-G47) increased by 89%, while the number of separations due to diseases of veins, lymphatic vessels and lymph nodes, not elsewhere classified (I80-I89) increased by 23%.

I will also analyze the effect that pharmaceutical innovation had on survival from all types of cancer during the period 1986-2007. Cancer is the leading cause of burden of disease in Australia, accounting for about one fifth of the total burden (AIHW (2010)). With 1 in 2 Australians developing cancer and 1 in 5 dying from it before the age of 85, cancer has a major impact on individuals, their families and the health-care system (AIHW (2012a)). In the cancer survival analysis, I will control for the number of people diagnosed (incidence) and the mean age at which they were diagnosed.

Figure 4 presents a summary of trends in 5-year survival rates, by cancer site, between the periods 1982–1987 and 2006–2010.[5] In general, survival from most cancers improved over time. However, the change in survival was not uniform over time and across cancer types. For example, survival from cervical cancer increased until the early 1990s but did not change significantly thereafter. By way of contrast, survival from cancer of unknown primary site remained virtually unchanged until the 2000s when it more than doubled. The cancers that showed the greatest percentage-point increase in survival were: prostate cancer, kidney cancer, and non-Hodgkin lymphoma. Five-year survival from these cancers increased by 24 percentage points or more in absolute terms. Other cancers that showed a greater proportional increase in survival included liver cancer, cancer of unknown primary site, and acute myeloid leukemia. Five-year survival from these cancers more than doubled between the periods 1982–1987 and 2006–2010, despite remaining lower than the average.

The analysis will be based on aggregate (longitudinal disease-level) data[6] rather than patient-level data. 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

[5] Source: AIHW Australian Cancer Database (2007). Cancer survival and prevalence in Australia: period estimates from 1982 to 2010, Figure 3.5

[6] The premature mortality and hospital separations analyses will be based on data on about 170 diseases. The cancer survival analysis will be based on data on about 30 cancer sites.

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.[7]

In Section II, I describe econometric models of premature mortality, hospital separations, and cancer survival. The data sources used to construct the data to estimate these models are described in Section III. Empirical results are presented in Section IV. Key implications of the estimates are discussed in Section V. Section VI provides a summary and conclusions.

II. Econometric models of premature mortality, hospital separations, and cancer survival

A. Premature mortality models

In his model of endogenous technological change, Romer (1990) hypothesized an aggregate production function such that an economy's output depends on the "stock of ideas" that have previously been developed, as well as on the economy's endowments of labor and capital. The premature mortality model that I will estimate may be considered a health production function, in which premature mortality is an inverse indicator of health output or outcomes, and the cumulative number of drugs approved is analogous to the stock of ideas. The first model will be of the following form:

$$\ln(YPLL75_{it}) = \beta_k \, CUM\_NCE_{i,t-k} + \alpha_i + \delta_t + \varepsilon_{i,t} \qquad (1)$$

$$\ln(YPLL80_{it}) = \beta_k \, CUM\_NCE_{i,t-k} + \alpha_i + \delta_t + \varepsilon_{i,t} \qquad (2)$$

where

$YPLL75_{it}$ = years of potential life lost before age 75 from disease i in year t (t = 1998,…,2004, 2006,…,2011)[8] per 100,000 population below age 75

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

[8] Data on mortality by age and cause were not available for the year 2005.

$YPLL80_{it}$ = years of potential life lost before age 80 from disease i in year t per 100,000 population below age 80

$CUM\_NCE_{i,t-k}$ = $\sum_d IND_{di}\ LISTED\_PBS_{d,t-k}$ = the number of new chemical entities (drugs) to treat disease i that had been listed on the PBS by the end of year t-k

IND_{di} = 1 if drug d is used to treat (indicated for) disease i

= 0 if drug d is not used to treat (indicated for) disease i

$LISTED\_PBS_{d,t-k}$ = 1 if drug d was listed on the PBS by the end of year t-k

= 0 if drug d was not listed on the PBS by the end of year t-k

α_i = a fixed effect for disease i

δ_t = a fixed effect for year t

Inclusion of year and disease fixed effects controls for the overall decline in premature mortality and for stable between-disease differences in premature mortality.[9] Negative and significant estimates of β_k in eqs. (1) and (2) would signify that diseases for which there was more pharmaceutical innovation had larger declines in premature mortality. The functional form of eqs. (1) and (2) has the property of diminishing marginal productivity: the absolute reduction in premature mortality declines with each successive increase in the number of drugs.

From estimates of eq. (1) and (2), there are two alternative, nearly equivalent, ways to determine how much of the decline in premature mortality during the sample period (1998-2011) can be attributed to the registration of new drugs. The first way is to compute β_k * [mean($CUM\_NCE_{i,2011-k}$) - mean($CUM\_NCE_{i,1998-k}$)]. The second way is based on the year fixed effects. The expression ($\delta_{2011} - \delta_{1998}$) indicates the 1998-2011 decline in premature mortality, controlling for (holding constant) the number of drugs, i.e., in the absence of pharmaceutical innovation. Suppose eq. (1) is estimated, excluding $CUM\_NCE_{i,t-k}$, and that the year fixed effects from that equation are denoted by δ'_t. Then ($\delta'_{2011} - \delta'_{1998}$) indicates the 1998-2011 decline in premature mortality, not holding constant the number of drugs, i.e., in the presence of pharmaceutical innovation, and ($\delta'_{2011} - \delta'_{1998}$) - ($\delta_{2011} - \delta_{1998}$) is an estimate of the 1998-2011 decline in premature mortality attributable to pharmaceutical innovation.

[9] The year fixed effects also control for population growth.

The data exhibit heteroskedasticity: diseases with larger total premature mortality during 1998-2011 had smaller (positive and negative) annual percentage fluctuations in YPLL75 and YPLL80. Eqs. (1) and (2) will therefore be estimated by weighted least-squares, weighting by the mean premature mortality rate during 1998-2011 (e.g. $(\Sigma_t \text{ YPLL75}_{it}) / 13$). The standard errors of eq. (1) and (2) will be clustered within diseases.

The measure of pharmaceutical innovation in eqs. (1) and (2)—the number of chemical substances previously registered to treat a disease—is not the theoretically ideal measure. Premature mortality is presumably more strongly related to the drugs *actually* used to treat a disease than it is to the drugs that *could be* used to treat the disease. A preferable measure is the mean *vintage* of drugs used to treat disease i in year t, defined as $\text{VINTAGE}_{it} = \sum_d Q_{dit} \text{ LAUNCH\_YEAR}_d / \sum_d Q_{dit}$, where Q_{dit} = the quantity of drug d used to treat disease i in year t, and LAUNCH_YEAR_d = the world launch year of drug d.[10] Unfortunately, measurement of VINTAGE_{it} is infeasible: even though data on the total quantity of each drug in each year ($Q_{d.t} = \Sigma_i Q_{dit}$) are available, many drugs are used to treat multiple diseases,[11] and there is no way to determine the quantity of drug d *used to treat disease i* in year t.[12] However, Lichtenberg (2014a) showed that in France, there is a highly significant positive correlation across *drug classes* between changes in the (quantity-weighted) vintage of drugs and changes in the number of chemical substances previously registered within the drug class.

Pharmaceutical innovation is not the only type of medical innovation that is likely to reduce premature mortality. Other medical innovation, such as innovation in diagnostic imaging, surgical procedures, and medical devices, is also likely to affect premature mortality. Therefore, measures of these other types of medical innovation should be included in eqs. (1) and (2). Unfortunately, longitudinal disease-level measures of non-pharmaceutical medical innovation

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[10] 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. Robert Solow (1960) introduced the concept of vintage into economic analysis. Solow's basic idea was that technical progress is "built into" machines and other goods and that this must be taken into account when making empirical measurements of their roles in production. 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 (Nobelprize.org (2015)).

[11] For example, dactinomycin is used to treat C45-C49 connective and soft tissue neoplasms, C51-C58 female genital organ neoplasms, C60-C63 male genital organ neoplasms, and C64-C68 urinary organ neoplasms.

[12] Outpatient prescription drug claims usually don't show the indication of the drug prescribed. Claims for drugs administered by doctors and nurses (e.g. chemotherapy) often show the indication of the drug, but these account for just 15% of drug expenditure. These data are not available for Australia.

are not available for Australia. But failure to control for non-pharmaceutical medical innovation is 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)). 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)). 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 indicates that non-pharmaceutical medical innovation is not positively correlated across diseases with pharmaceutical innovation. Lichtenberg (2014a) showed that, in the U.S. during the period 1997-2007, the rate of pharmaceutical innovation was not positively correlated across diseases with the rate of medical procedure innovation and may have been *negatively* correlated with the rate of diagnostic imaging innovation. Also, Lichtenberg (2014b) found that estimates of the effect of pharmaceutical innovation on U.S. cancer mortality rates were insensitive to the inclusion or exclusion of measures of non-pharmaceutical medical innovation. This suggests that failure to control for other medical innovation is unlikely to result in overestimation of the effect of pharmaceutical innovation on longevity growth.

In eqs. (1) and (2), premature mortality from disease i in year t depends on the number of new chemical entities (drugs) to treat disease i that had been registered in Australia by the end of year t-k, i.e. there is a lag of k years. Eqs. (1) and (2) will be estimated for different values of k: k = 0, 3, 6, 9, 12, 15.[13] One would expect there to be a substantial lag because new drugs diffuse gradually—they won't be used widely until years after registration. Data from the *Australian Statistics on Medicines* (Pharmaceutical Benefits Scheme (2015)) can be used to provide evidence about the process of diffusion of new medicines.[14] I used data from that source linked to data on PBS drug initial listing dates (described below) to estimate the following model:

[13] A separate model is estimated for each value of k, rather than including multiple values ($CUM\_NCE_{i,t}$, $CUM\_NCE_{i,t-3}$, $CUM\_NCE_{i,t-5}$,…) in a single model because CUM_NCE is highly serially correlated (by construction), which would result in extremely high multicollinearity if multiple values were included.)

[14] The *Australian Statistics on Medicines* (ASM) is an annual publication produced by the Drug Utilisation Sub-Committee of the Pharmaceutical Benefits Advisory Committee. The data available in the ASM represent estimates of the aggregate community use of prescription medicines in Australia.

$$\ln(N\_RX_{my}) = \rho_m + \pi_y + \varepsilon_{my} \quad (3)$$

where

N_RX_{my} = the number of prescriptions for molecule m sold in Australia y years after it was listed on the PBS (y = 0, 1,…, 20)

ρ_m = a fixed effect for molecule m

π_y = a fixed effect for age y

The expression $\exp(\pi_y - \pi_0)$ is a "relative utilization index": it is the mean ratio of the number of prescriptions for a molecule y years after it was first listed on the PBS to the number of prescriptions for the same molecule in the year that it was first listed on the PBS. Using annual data on the number of prescriptions for molecules in Australia during the period 2007-2011, I estimated eq. (3). Estimates of the "relative utilization index," based on data on molecules that were first listed on the PBS after 1991, are shown in Figure 5. These estimates indicate that it takes about 9 years for a molecule to attain its peak level of utilization. The number of prescriptions 9 years after first PBS listing is about 2.6 times as great as the number of prescriptions one year after first PBS listing. Moreover, Figure 5 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.[15]

The effect of a drug's PBS listing on premature mortality is likely to depend on both the *quality* and the *quantity* of the drug. Indeed, it is likely to depend on the *interaction* between quality and quantity: a quality improvement will have a greater impact on mortality if drug utilization (quantity) is high. Although newer drugs tend to be of higher quality than older drugs (see Lichtenberg (2014c)), the relative quantity of very new drugs is quite low, so the impact on mortality of very new drugs is lower than the impact of older drugs.

The measure of pharmaceutical innovation, $CUM\_NCE_{i,t-k} = \sum_d IND_{di}\ LISTED\_PBS_{d,t-k}$, is based on whether drug d had an indication for disease i *at the end of 2011*. One would prefer to base the measure on whether drug d had an indication for disease i *at the end of year t-k*. FDA data indicate that about one in four new molecular entities has supplemental indications, i.e. indications approved after the drug was initially launched.[16]

[15] Since the dependent variable of eq. (2) is logarithmic, observations for which $N\_RX_{my} = 0$ had to be excluded.
[16] Source: author's calculations based on data contained in U.S. Food and Drug Administration (2015).

Chemical substances are divided into different groups according to the organ or system on which they act and their therapeutic, pharmacological and chemical properties. In the Anatomical Therapeutic Chemical (ATC) classification system developed by the World Health Organization Collaborating Centre for Drug Statistics Methodology, drugs are classified in groups at five different levels. The highest (1^{st}) level is the "anatomical main group" level; there are 14 anatomical main groups. The 2^{nd}, 3^{rd}, 4^{th}, and 5^{th} levels are "therapeutic subgroup," "pharmacological subgroup," "chemical subgroup," and "chemical substance," respectively.[17] Premature mortality from a disease may depend on the number of chemical (or pharmacological) *subgroups* that have previously been developed to treat the disease rather than, or in addition to, the number of chemical *substances* (drugs) that have previously been developed to treat the disease. This will be investigated by estimating versions of eq. (1) in which $CUM\_SUBGROUP_{i,t-k}$ is included in addition to or instead of $CUM\_NCE_{i,t-k}$, where

$CUM\_SUBGROUP_{i,t-k} = \sum_g IND\_SUBGROUP_{gi} \; LISTED\_PBS\_SUBGROUP_{g,t-k}$

$IND\_SUBGROUP_{gi}$ = 1 if any drugs in chemical subgroup g are used to treat (indicated for) disease i

= 0 if no drugs in chemical subgroup g are used to treat (indicated for) disease i

$LISTED\_PBS\_SUBGROUP_{g,t-k}$ = 1 if any drugs in chemical subgroup g had been listed on the PBS by the end of year t-k

[17] For example, the five levels associated with the chemical subgroup "nitrogen mustard analogues" are:

L	ANTINEOPLASTIC AND IMMUNOMODULATING AGENTS
L01	ANTINEOPLASTIC AGENTS
L01A	ALKYLATING AGENTS
L01AA	Nitrogen mustard analogues
L01AA01	cyclophosphamide
L01AA02	chlorambucil
L01AA03	melphalan
L01AA05	chlormethine
L01AA06	ifosfamide
L01AA07	trofosfamide
L01AA08	prednimustine
L01AA09	bendamustine

= 0 if no drugs in chemical subgroup g had been listed on the PBS by the end of year t-k

B. Hospital separations model

The hospital separations model I will estimate is:

$$\ln(N\_HOSP_{it}) = \beta_k \, CUM\_NCE_{i,t-k} + \alpha_i + \delta_t + \varepsilon_{i,t} \qquad (4)$$

where

N_HOSP_{it} = the number of hospital separations due to disease i in year t (t = 1998,…,2011)

The hospital separations data also exhibit heteroskedasticity: diseases with larger mean hospital separations during 1998-2011 had smaller (positive and negative) annual percentage fluctuations in N_HOSP. Eq. (4) will therefore be estimated by weighted least-squares, weighting by the mean number of hospital separations during 1998-2011 ($(\Sigma_t \, N\_HOSP_{it}) / 14$). The standard errors of eq. (4) will be clustered within diseases.

C. Cancer survival model

Now I will describe how I will analyze the effect that pharmaceutical innovation had on survival from all types of cancer during the period 1986-2007. The survival measure I will use is the 5-year relative survival rate. Five-year survival reflects the probability of being alive for at least five years after cancer diagnosis. It is a standard indicator used in reporting to reflect the prognosis of cancer and to compare survival across different cancers, time periods and groups of people.

Relative survival is the standard approach for measuring population-based cancer survival (Coleman et al. (2011)). It is calculated from two measures of crude survival: observed and expected survival. Observed survival refers to the proportion of people alive for a given amount of time after a diagnosis of cancer and is calculated from population-based cancer data. Expected survival refers to the proportion of people in the general population alive for a given amount of time and is calculated from life tables of the entire Australian population, assumed to be cancer-free. Relative survival is calculated from observed survival divided by expected

survival, where the numerator and denominator have been matched for sex, age, calendar year, and where applicable, remoteness and socioeconomic status.

One of the advantages of relative survival is that it does not require information on the cause of death. By adjusting the survival of individuals with cancer for the underlying mortality that they would have experienced in the general population, relative survival reflects the net survival associated with cancer. In other words, relative survival is an inverse measure of the excess mortality attributed, either directly or indirectly, to a diagnosis of cancer.

The relative survival data I will analyze were calculated using the period method (Brenner & Gefeller (1996)). The period method calculates survival from a given follow-up or at-risk time period. Survival estimates are based on the survival experience of people who were diagnosed before or during this period, and who were at risk of dying during this period. Because the period method allows recent years of follow-up to be selected, it produces up-to-date survival estimates that reflect recent changes in cancer survival trends (Brenner (2002); Brenner & Hakulinen (2002a, 2002b)). The period method is an alternative to the traditional cohort method, which focuses on a group of people diagnosed with cancer in a past time period, and follows these people over time.

The U.S. National Cancer Institute (2015a) says 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 earlier. This increase in survival time makes it seem as though screened patients are living longer when that may not be happening. 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 my estimates of the effect of pharmaceutical innovation on cancer survival, I will control for (changes in) the number of people diagnosed (incidence) and the mean age at which they were diagnosed.

The cancer survival model I will estimate is:

$$\ln(ODDS_{st}) = \beta_k \, CUM\_NCE_{s,t-k} + \pi \, AGE\_DIAG_{st} + \gamma \ln(N\_CASES_{st}) + \alpha_s + \delta_t + \varepsilon_{st} \qquad (5)$$

where

$ODDS_{st}$ = $RELSURV5_{st} / (1 - RELSURV5_{st})$

$RELSURV5_{st}$ = the 5-year relative survival rate from cancer at site s in year t (t = 1986,…,2007)

$CUM\_NCE_{s,t-k}$ = $\sum_d IND_{ds} \, LISTED\_PBS_{d,t-k}$ = the number of new chemical entities (drugs) to treat cancer at site s that had been listed on the PBS by the end of year t-k

AGE_DIAG_{st} = the mean age at which patients were diagnosed with cancer at site s in year t

N_CASES_{st} = the number of patients diagnosed with cancer at site s in year t

Eq. (5) will be estimated by weighted least-squares, weighting by N_CASES_{st}. The standard errors will be clustered within cancer sites.

III. Data sources

Initial PBS listing dates of drugs. Dates of first listing of PBS items (from which LISTED_PBS was computed) and their WHO ATC codes were provided by the PBS Information Management Section of the Pharmaceutical Policy Branch of the Pharmaceutical Benefits Division of the Department of Health.[18]

Drug indications (IND). Data on drug indications were obtained from Thériaque (2015), a database of official, regulatory, and bibliographic information on all drugs available in France,[19] intended for health professionals. This database is produced by the Centre National Hospitalier

[18] I am extremely grateful to Assistant Director Andrew Kopras for providing these data.

[19] A similar database is not available for Australia, but the indications of drugs are unlikely to differ substantially across countries.

d'Information sur le Médicament. In this database, drugs are coded according to WHO ATC codes, and diseases are coded according to WHO ICD-10 codes.[20]

Premature mortality data (YPLL75, YPLL80). Data on years of potential life lost before ages 75 and 80, by disease and year (1998-2004 and 2006-2011), and population by age and year were constructed from the *WHO Mortality Database* (World Health Organization (2015b)).[21]

Hospital separations data (N_HOSP). Data on inpatient hospital separations, by principal diagnosis and year (2005-2010), were obtained from the *AIHW Principal Diagnosis Data Cubes* (AIHW (2015a)). The principal diagnosis is defined as the diagnosis established after study to be chiefly responsible for occasioning the patient's episode of care in hospital.

Cancer survival data (RELSURV5). Data on 5-year relative survival rates, by cancer site and year (1986-2007), were obtained from *Cancer survival and prevalence in Australia: period estimates from 1982 to 2010* (AIHW (2012b)).

Cancer incidence and age at diagnosis data (N_CASES and AGE_DIAG) were constructed from data contained in *Australian Cancer Incidence and Mortality (ACIM) books* (AIHW (2015b)).

Drug utilization and expenditure data. Data on the number of prescriptions for and expenditure on drugs, by molecule and year (2007-2011), were obtained from the *Australian Statistics on Medicines* (Pharmaceutical Benefits Scheme (2015)).

IV. Empirical results

A. Premature mortality model estimates

Estimates of CUM_NCE coefficients from models of premature mortality caused by all diseases (eqs. (1) and (2)) are presented in Panels A and B of Table 1. Panel A shows estimates of eq. (1), where the dependent variable is the log of years of potential life lost before age 75 per 100,000 people below age 75. Models are estimated for 6 alternative assumed values of the lag (in years) from the number of drugs ever listed on the PBS to premature mortality: k = 0, 3, 6, 9, 12, 15. As shown in lines 1 and 2, the estimates of β_0 and β_3 are not statistically significant.

[20] Many drug databases contain information about drug indications, but this information is usually in text form only.
[21] Mortality data are reported in 5-year age groups. I assume that deaths in a 5-year age group occur at the midpoint of the age group. For example, I assume that deaths at age 35-39 years occurred at age 37.5. The Association of Public Health Epidemiologists in Ontario (2015) uses this method.

However, as shown in lines 3 and 4, the estimates of β_6 and β_9 are negative and statistically significant (p-value < .04). This signifies that the number of life-years lost before age 75 is inversely related to the number of drugs that had been listed on the PBS up until 6-9 years earlier. Since, as shown in Figure 5, drugs are used much less frequently during the first few years after they are first listed on the PBS than they are later on, it is not surprising that it takes 6-9 years for the addition of new drugs to the PBS formulary to have a significant negative effect on premature mortality. The insignificance of β_{12} and β_{15} may be due to the fact that newer drugs (e.g. drugs listed 9 years earlier) are of higher quality than older drugs (e.g. drugs listed 15 years earlier).

Panel B shows estimates of eq. (2), where the dependent variable is the log of years of potential life lost before age 80 per 100,000 people below age 80. Once again, the estimates of β_0 and β_3 are not statistically significant (p-value > .05), although the estimate of β_3 is nearly significant (p-value = .056). As shown in lines 9-11 of Table 1, the estimates of β_6, β_9, and β_{12} are all negative and statistically significant: the number of life-years lost before age 80 is inversely related to the number of drugs that had been listed on the PBS up until 6-12 years earlier.

As discussed above, the reduction in premature mortality attributable to previous pharmaceutical innovation can be estimated by comparing the year fixed effects from a model including a CUM_NCE measure to the year fixed effects from a similar model that excludes the CUM_NCE measure. I have done this for the model shown in line 4 of Table 1: $\ln(YPLL75_{it}) = \beta_9 CUM\_NCE_{i,t-9} + \alpha_i + \delta_t + \varepsilon_{i,t}$.[22] (Mortality before ages 75 and 80 are both most strongly inversely related to the number of drugs ever listed 9 years earlier.) The calculations are depicted in Figure 6. In 1998, the number of potential years of life lost before age 75 per 1,000 population under age 75 years was 54.7 (Source: AIHW (2015c), Table S3). Between 1998 and 2011, the premature (before age 75) mortality rate declined by 11.7, to 43.0.[23] The estimates indicate that if no new drugs had been listed on the PBS during 1989-2002, the premature

[22] Estimates of parameters of models of $\ln(YPLL75_{it})$ and $\ln(YPLL80_{it})$ including and excluding $CUM\_NCE_{i,t-9}$ are shown in Appendix Table 2.

[23] Since eq. (1) includes fixed disease effects, this decline controls for changes in the distribution of deaths, by cause. When changes in the distribution of deaths, by cause, are not controlled for, the decline is slightly greater, from 54.7 to 41.6.

mortality rate would have declined by only 4.7, from 54.7 to 50.0. Hence 60% (= 1 - (4.7 / 11.7)) of the decline in premature mortality was due to previous pharmaceutical innovation.

The effects on premature mortality of both the number of drugs and the number of chemical subgroups (drug classes) for the disease ever listed 9 years earlier are investigated in Table 2. Six models are presented in the table. The dependent variable in the first 3 models (lines 4, 4a, and 4b) is the log of the premature (before age 75) mortality rate. The model in line 4 of Table 2 is identical to the model in line 4 of Table 1: the only regressor (aside from disease and year fixed effects) is $CUM\_NCE_{i,t-9}$. In line 4a, the only regressor is $CUM\_SUBGROUP_{i,t-9}$. The coefficient on this variable is insignificant. The model in line 4b includes both $CUM\_NCE_{i,t-9}$ and $CUM\_SUBGROUP_{i,t-9}$. Only the coefficient on $CUM\_NCE_{i,t-9}$ is significant.

The dependent variable in the last 3 models (lines 10, 10a, and 10b) is the log of the premature (before age 80) mortality rate. The model in line 10 of Table 2 is identical to the model in line 10 of Table 1. In line 10a, the only regressor is $CUM\_SUBGROUP_{i,t-9}$. The coefficient on this variable is insignificant. The estimates of the first 5 models in Table 2 support the hypothesis that premature mortality depends only on the number of drugs ever listed on the PBS, not on the number of drug classes. This would be the case if drugs within the same class are not "therapeutically equivalent."[24] In the model in line 10b, the coefficient on $CUM\_NCE_{i,t-9}$ is negative and significant, and the coefficient on $CUM\_SUBGROUP_{i,t-9}$ is positive and significant. High collinearity between these two variables may account for this. Moreover, the net effect of growth of the number of drugs and the number of drug classes is to reduce premature mortality.

B. Hospital separations model estimates

Estimates of CUM_NCE coefficients from models of hospital separations caused by all diseases (eq. (4)) are presented in Table 3. As shown in line 13, the number of hospital separations in year t is not significantly related to the number of drugs ever listed on the PBS in year t. However, as shown in lines 14-18, the number of hospital separations is significantly inversely related to the number of drugs ever listed on the PBS 3-15 years earlier. The number

[24] Drugs are considered to be therapeutically equivalent if they have essentially the same effect in the treatment of a disease or condition. http://medical-dictionary.thefreedictionary.com/therapeutic+equivalent

of hospital separations is most strongly inversely related to the number of drugs ever listed on the PBS 12 years earlier. The reduction in hospital separations attributable to previous pharmaceutical innovation can be estimated by comparing the year fixed effects from a model including a CUM_NCE measure to the year fixed effects from a similar model that excludes the CUM_NCE measure. I have done this for the model shown in line 17 of Table 3: $\ln(N\_HOSP_{it}) = \beta_{12} CUM\_NCE_{i,t-12} + \alpha_i + \delta_t + \varepsilon_{i,t}$.[25] The results are displayed in Figure 7. Between 1998 and 2011, the number of hospital separations increased by 47%, from 5.7 million to 8.4 million.[26] (The population of Australia increased by 21% during this period.) The estimates indicate that if no new drugs had been listed on the PBS during 1986-1999, the number of hospital separations would have increased by 66%, from 5.7 million to 9.5 million. The number of hospital separations in 2011 would have been 12.6% higher: 1.06 million additional separations.

C. Cancer survival model estimates

Estimates of CUM_NCE coefficients from models of cancer survival (eq. (5)) are presented in Table 4. AGE_DIAG_{st} and $\ln(N\_CASES_{st})$ were included as covariates in all models. For simplicity, the coefficients on these variables are not shown in Table 4; both of them were highly significant and had the expected signs, and were very similar for different values of k. For example, when k=9, the coefficient on AGE_DIAG_{st} is -0.0954 (std. err. = .0199; Z = 4.80), and the coefficient on $\ln(N\_CASES_{st})$ is 0.6123 (std. err. = .1488; Z = 4.11). Thus reductions in mean age at diagnosis and increases in the number of patients diagnosed are associated with increases in survival rates.

As shown in lines 19-23, the cancer survival rate is significantly positively related to the number of drugs that had ever been listed on the PBS 0-12 years earlier, controlling for mean age at diagnosis and the number of patients diagnosed. The cancer survival rate is most strongly positively related to the number of drugs that had ever been listed on the PBS 9 years earlier.

[25] Estimates of parameters of models of $\ln(N\_HOSP_{it})$ including and excluding $CUM\_NCE_{i,t-12}$ are shown in Appendix Table 3.

[26] Since eq. (4) includes fixed disease effects, this increase controls for changes in the distribution of separations, by principal diagnosis. When changes in the distribution of separations, by principal diagnosis, are not controlled for, the increase is greater, from 5.7 million to 9.3 million.

The increase in the cancer survival rate attributable to previous pharmaceutical innovation can be estimated by comparing the year fixed effects from a model including a CUM_NCE measure to the year fixed effects from a similar model that excludes the CUM_NCE measure. I have done this for the model shown in line 22 of Table 4: $\ln(ODDS_{st}) = \beta_9 CUM\_NCE_{s,t-9} + \pi AGE\_DIAG_{st} + \gamma \ln(N\_CASES_{st}) + \alpha_s + \delta_t + \varepsilon_{st}$.[27] The results are displayed in Figure 8.[28] Between 1986 and 2007, the 5-year relative survival rate increased from 49.0% to 61.6%, controlling for mean age at diagnosis, the number of patients diagnosed, and changes in the distribution of patients diagnosed, by cancer site.[29] The estimates indicate that if no new drugs had been listed on the PBS during 1977-1998, the 5-year relative survival rate would have increased from 49.0% to 56.5%, *ceteris paribus*. Hence previous pharmaceutical innovation is estimated to have accounted for 40% (= 1 - (56.5% - 49.0%)/(61.6% - 49.0%)) of the 1986-2007 increase in the 5-year relative survival rate.

V. Discussion

Now I will use the estimates of eqs. (1), (2), and (4) to calculate the number of life-years gained in 2011 from previous pharmaceutical innovation and medical expenditure per life-year gained. The calculations are summarized in Table 5. According to AIHW (2015c, Table S3), 870,672 years of potential life were lost before age 75 in 2011.[30] The difference between the two estimates of the 1998 year fixed effect in line 2 of Appendix Table 2 imply that if no new drugs had been listed on the PBS during 1989-2002, the number of years of potential life lost before age 75 in 2011 would have been 143,639 (16.5% = exp(.2417-.0890)-1) higher. I also estimate that 1,170,597 years of potential life were lost before age 80 in 2011.[31] The difference between the two estimates of the 1998 year fixed effect in line 16 of Appendix Table 2 imply that if no new drugs had been listed on the PBS during 1989-2002, the number of years of

[27] Estimates of parameters of models of $\ln(ODDS_{st})$ including and excluding $CUM\_NCE_{s,t-9}$ are shown in Appendix Table 4.
[28] Since the dependent variable in eq. (5) is $\ln(ODDS_{st})$, where $ODDS_{st} = RELSURV5_{st} / (1 - RELSURV5_{st})$, Figure 8 shows the following function of the year fixed effects: $1 / (1 + (1 / \exp(\delta_t)))$.
[29] When these factors are not controlled for, the increase in the cancer survival rate was larger, from 49.0% in 1986 to 64.2% in 2007.
[30] This figure is 2.3% higher than my estimate (851,295) based on data in the WHO Mortality Database.
[31] This figure is 2.3% higher than my estimate (1,144,545) based on data in the WHO Mortality Database.

potential life lost before age 80 in 2011 would have been 257,602 (22.0% = exp(.2482-.0493)-1) higher.

Data from *Australian Statistics on Medicines* (ASM) linked with information on the dates of first listing of PBS items indicate that expenditure in 2011 on drugs that were first listed on the PBS during 1989-2002 was $AUS 5769 million.[32] I need to estimate how much of the expenditure on these drugs was made by, or on behalf of, patients below the ages of 75 and 80. I do not have any data on the distribution of drug expenditure by age group for Australia, but I do have this kind of data for the U.S., from the Medical Expenditure Panel Survey (Agency for Healthcare Research and Quality (2015)). In 2011, 86% of U.S. outpatient drug expenditure was for patients below age 75; 92% was for patients below age 80. Assuming that the same fractions apply to expenditure on PBS drugs, expenditure in 2011 for patients below age 75 and 80 on drugs that were first listed on the PBS during 1989-2002 was $AUS 4976 million and $AUS 5296, respectively.

The difference between the two estimates of the 1998 year fixed effect in line 2 of Appendix Table 3 imply that if no new drugs had been listed on the PBS during 1986-1999, the number of hospital separations in 2011 would have been 13.1% (= exp(-.3812 - (-.5044)) - 1) higher. I will assume that hospital expenditure in 2011 would also have been 13.1% higher. Total expenditure on public hospital services and private hospitals in 2011 was $AUS 52,220 million (AIHW (2014), Table A1).[33] Hence I estimate that if no new drugs had been listed on the PBS during 1986-1999, hospital expenditure in 2011 would have been $AUS 6847 million (= 13.1% * $AUS 52,220 million) higher. People below age 75 and 80 account for 81% and 89%, respectively, of Australian hospital separations.[34] This implies that if no new drugs had been listed on the PBS during 1986-1999, hospital expenditure in 2011 on people below ages 75 and 80 would have been $AUS 5562 million (= 81% * $AUS 6847 million) and $AUS 6119 million (= 89% * $AUS 6847 million) higher, respectively.

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[32] This is just over half (52%) of the total cost (government and patient contribution) of PBS drugs in 2011 ($AUS 11,145) reported in ASM. The latter figure is 8.6% higher than the figure for total pharmaceutical sales reported in the OECD Health database ($AUS 10,261), which is surprising since, as noted earlier, the PBS does not assume responsibility for the cost of drugs to patients while they are in the hospital.

[33] This figure is the average of the 2010-2011 and 2011-2012 figures, $AUS 50,931 and $AUS 53,509 million, respectively.

[34] These figures are based on hospital separations during the period 1998−99 to 2007−08. Source: AIHW (2015a).

These calculations imply that previous pharmaceutical innovation reduced the number of life-years lost before ages 75 and 80 in 2011 by 143,639 and 257,602, respectively, and that the innovation was *cost-saving*: the reduction in hospital expenditure attributable to it exceeded expenditure on the drugs.[35] Even if one discounts or completely ignores the apparent reduction in hospital expenditure, the evidence indicates that pharmaceutical innovation was highly cost effective. If the true reduction in hospital expenditure was only 50% as large as I have estimated, the cost per life-year gained before age 75 and 80 was $AUS 15,280 and $AUS 8682, respectively. If there was *no* reduction in hospital expenditure, the cost per life-year gained before age 75 and 80 was $AUS 34,640 and $AUS 20,560, respectively.

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 (2015c)); Australia's per capita GDP in 2011 was $AUS 66,608.[36] Also, Hirth et al (2000) performed a search of the value-of-life literature, and identified 41 estimates of the value of life from 37 articles based on data from a number of countries. From estimates of the value of life, they calculated estimates of the value of a QALY. Four types of methods were used to produce those estimates: revealed preference/job risk, contingent valuation, revealed preference/non-occupational safety, and human capital. Even if we completely ignore the apparent reduction in hospital expenditure, the cost per life-year gained from previous pharmaceutical innovation is well below the vast majority of estimates from the value-of-life literature of the value of a life-year.

VI. Summary and conclusions

Premature (before age 75 and 80) mortality has been declining in Australia, but there has been considerable variation in the rate of decline across diseases. I first analyzed the effect that

[35] A previous study (Lichtenberg (2014c)) found that pharmaceutical innovation was cost-saving in the U.S. In that study, the measure of pharmaceutical innovation was the mean vintage of drugs. An instrument for pharmaceutical innovation--the potential size of the market for drugs for a medical condition—was used. The value of the benefits of pharmaceutical innovation (primarily reduction in hospital expenditure and work-loss days) implied by the IV estimates was about 30 percent larger than the value implied by the OLS estimates.

[36] Lichtenberg (2009) demonstrated that the number of QALYs gained from pharmaceutical innovation could be either greater than or less than the number of life-years gained.

pharmaceutical innovation had on premature mortality from all diseases in Australia during the period 1998-2011 by investigating whether the diseases that experienced more pharmaceutical innovation had larger declines in premature mortality. My estimates indicated that 60% of the 1998-2011 decline in premature (before age 75) mortality was due to previous pharmaceutical innovation. The estimates generally supported the hypothesis that premature mortality depends on the number of drugs ever listed on the PBS, not on the number of drug classes. This would be the case if drugs within the same class are not "therapeutically equivalent."

Next, I analyzed the effect that pharmaceutical innovation had on hospital separations from all diseases during the period 1998-2011. The estimates indicated that if no new drugs had been listed on the PBS during 1986-1999, the number of hospital separations in 2011 would have been about 13% higher.

Lastly, I analyzed the effect that pharmaceutical innovation had on survival from all types of cancer during the period 1986-2007, controlling for mean age at diagnosis, the number of patients diagnosed, and changes in the distribution of patients diagnosed, by cancer site. I estimated that previous pharmaceutical innovation accounted for 40% of the 1986-2007 increase (from 49.0% to 61.6%) in the 5-year relative survival rate.

My estimates indicated that new drugs listed on the PBS during 1989-2002 reduced the number of life-years lost from all diseases before ages 75 and 80 in 2011 by 143,639 and 257,602, respectively, and that the innovation was *cost-saving*: the reduction in hospital expenditure attributable to it exceeded expenditure on the drugs. Even if one discounts or completely ignores the apparent reduction in hospital expenditure, the evidence indicates that pharmaceutical innovation was highly cost effective. If the true reduction in hospital expenditure was only 50% as large as I have estimated, the cost per life-year gained before age 75 and 80 was $AUS 15,280 and $AUS 8682, respectively. If there was *no* reduction in hospital expenditure, the cost per life-year gained before age 75 and 80 was $AUS 34,640 and $AUS 20,560, respectively. According to the World Health Organization, an intervention whose cost per quality-adjusted life-year gained is less than $AUS 66,608 should be considered highly cost-effective.

Because new drugs diffuse gradually, premature mortality is most strongly inversely related to the number of drugs that had ever been listed 9 years earlier. Therefore, if we assume that the relationship between pharmaceutical innovation and premature mortality remains the

same until the year 2020, we can estimate the number of life-years that will be gained in that year from previous (until 2011) pharmaceutical innovation. I estimate that new drugs listed on the PBS during the period 1989-2011 will reduce the number of life-years lost before age 80 in the year 2020 by 308,245.

References

Association of Public Health Epidemiologists in Ontario (2015). Calculating Potential Years of Life Lost (PYLL), http://www.apheo.ca/index.php?pid=190

AIHW (2010). Australia's health 2010. Australia's health series no. 12. Cat. no. AUS 122. Canberra: AIHW, http://www.aihw.gov.au/publication-detail/?id=6442468376
.
AIHW (2012a). Cancer incidence projections: Australia, 2011 to 2020. Cancer Series no. 66. Cat. no. CAN 62. Canberra: AIHW, http://www.aihw.gov.au/publication-detail/?id=10737421461

AIHW (2012b). Cancer survival and prevalence in Australia: period estimates from 1982 to 2010. Cancer series no. 69. Cat. no. CAN 65. Canberra: AIHW, http://www.aihw.gov.au/publication-detail/?id=10737422720&tab=3

AIHW (2014). Health expenditure Australia 2011-12: analysis by sector. Health and welfare expenditure series no. 51. Cat. no. HWE 60. Canberra: AIHW, http://www.aihw.gov.au/publication-detail/?id=60129550226

AIHW (2015a). Principal Diagnosis Data Cubes, http://www.aihw.gov.au/hospitals-data/principal-diagnosis-data-cubes/

AIHW (2015b). Australian Cancer Incidence and Mortality (ACIM) books, http://www.aihw.gov.au/acim-books

AIHW (2015c), Supplementary data for age at death, http://www.aihw.gov.au/WorkArea/DownloadAsset.aspx?id=60129553293

Agency for Healthcare Research and Quality (2015), Medical Expenditure Panel Survey, http://meps.ahrq.gov/mepsweb/

Australian Government Department of Health (2015), Australian Statistics on Medicines, http://www.pbs.gov.au/info/browse/statistics#ASM

Braithwaite RS, Meltzer DO, King JT Jr, Leslie D, Roberts MS (2008). What does the value of modern medicine say about the $50,000 per quality-adjusted life-year decision rule? *Med Care* 46(4): 349-56, April.

Brenner H (2002). Long-term survival rates of cancer patients achieved by the end of the 20th century: a period analysis. *Lancet* 360(9340): 1131–35.

Brenner H & Gefeller O (1996). An alternative approach to monitoring cancer patient survival. *Cancer* 78(9): 2004–10.

Brenner H & Hakulinen T (2002a). Up-to-date long-term survival curves of patients with cancer by period analysis. *Journal of Clinical Oncology* 20(3):826–32.

Brenner H & Hakulinen T (2002b). Advanced detection of time trends in long-term cancer patient survival: experience from 50 years of cancer registration in Finland. *American Journal of Epidemiology* 156(6): 566–77.

Brustugun OT, Møller B, Helland Å (2014). Years of life lost as a measure of cancer burden on a national level. *British Journal of Cancer* 111, 1014–1020, http://www.nature.com/bjc/journal/v111/n5/full/bjc2014364a.html

Burnet NG, Jefferies SJ, Benson RJ, Hunt DP, Treasure FP (2005). Years of life lost (YLL) from cancer is an important measure of population burden--and should be considered when allocating research funds. *British Journal of Cancer* 92 (2): 241–5, January, http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2361853/

Coleman MP, Forman D, Bryant H, Butler J, Rachet B, Maringe C, Nur U et al. (2011). Cancer survival in Australia, Canada, Denmark, Norway, Sweden, and the UK, 1995–2007 (the International Cancer Benchmarking Partnership): an analysis of population-based cancer registry data. *Lancet* 377: 127–38.

Commonwealth Fund (2011). The U.S. Health System in Perspective: A Comparison of Twelve Industrialized Nations.

Dorsey ER, et al (2010). Financial Anatomy of Biomedical Research, 2003-2008. *Journal of the American Medical Association* 303(2): 137–143.

Feinstein AR, Sosin DM, Wells CK (1985), "The Will Rogers Phenomenon. Stage Migration and New Diagnostic Techniques as a Source of Misleading Statistics for Survival in Cancer," *New England Journal of Medicine* 312: 1604–8.

Gardner JW, Sanborn JS (1990). Years of potential life lost (YPLL)--what does it measure? *Epidemiology* 1(4): 322-9, July.

Hirth RA, Chernew ME, Miller E, Fendrick AM, Weissert WG (2000), Willingness to Pay for a Quality-adjusted Life Year: In Search of a Standard, *Med Decis Making* 20(3): 332-342, Jul-Sep, http://users.phhp.ufl.edu/jharman/healthecon/Hirth%20WTP%20QALY.pdf

Jalan J, Ravallion M (2001) Does Piped Water Reduce Diarrhea for Children in Rural India?, World Bank Development Research Group, Policy Research Working Paper 2664, http://www1.worldbank.org/prem/poverty/ie/dime_papers/332.pdf

Lichtenberg FR (2009). The effect of new cancer drug approvals on the life expectancy of American cancer patients, 1978–2004. *Economics of Innovation and New Technology* 18 (5): 407–428, July.

Lichtenberg FR (2014a). The impact of pharmaceutical innovation on longevity and medical expenditure in France, 2000–2009, *Economics and Human Biology* 13: 107-127, March.

Lichtenberg FR (2014b). Has Medical Innovation Reduced Cancer Mortality? *CESifo Economic Studies* 60 (1): 135-177.

Lichtenberg FR (2014c). "The impact of pharmaceutical innovation on disability days and the use of medical services in the United States, 1997-2010," *Journal of Human Capital* 8(4): 432-480, Winter.

National Cancer Institute (2015a). Cancer Screening Overview, http://www.cancer.gov/cancertopics/pdq/screening/overview/patient/page5

National Cancer Institute (2015b). Drug Discovery at the National Cancer Institute, http://www.cancer.gov/cancertopics/factsheet/NCI/drugdiscovery

National Cancer Institute (2015c). Person-Years of Life Lost. *Cancer Trends Progress Report, 2009/2010 Update*, http://progressreport.cancer.gov/doc_detail.asp?pid=1&did=2007&chid=76&coid=730&mid=#estimate

Nobelprize.org (2015). The Prize in Economics 1987 - Press Release, http://www.nobelprize.org/nobel_prizes/economic-sciences/laureates/1987/press.html

Pharmaceutical Benefits Scheme (2015), PBS Statistics, http://www.pbs.gov.au/info/browse/statistics#ASM

Renard F, Tafforeau J, Deboosere P (2014). Premature mortality in Belgium in 1993-2009: leading causes, regional disparities and 15 years change. *Arch Public Health* 72(1): 34, Oct 1.

Romer P (1990). Endogenous Technological Change. *Journal of Political Economy* 98 (5, Part 2): S71-S102.

Sampat BN, Lichtenberg FR (2011). What are the Respective Roles of the Public and Private Sectors in Pharmaceutical Innovation? *Health Affairs* 30(2): 332-9.

Solow RM (1960). Investment and technological progress, in: Arrow, K., Karlin, S., Suppes, P. (eds.), *Mathematical Methods in Social Sciences 1959*, Stanford University Press, 89-104.

Stukel TA, Fisher ES, Wennberg DE, Alter DA, Gottlieb DJ, Vermeulen MJ. (2007) Analysis of Observational Studies in the Presence of Treatment Selection Bias: Effects of Invasive Cardiac Management on AMI Survival Using Propensity Score and Instrumental Variable Methods. *JAMA* 297(3):278-285, http://jama.jamanetwork.com/article.aspx?articleid=205172

Thériaque (2015), http://www.theriaque.org/apps/contenu/accueil.php

U.S. Food and Drug Administration (2015), Drugs@FDA Data Files, http://www.fda.gov/Drugs/InformationOnDrugs/ucm079750.htm

World Health Organization (2015a), ICD-10 Version 2015, Chapter II, Neoplasms, http://apps.who.int/classifications/icd10/browse/2015/en#/II

World Health Organization (2015b), WHO Mortality Database, http://www.who.int/healthinfo/statistics/mortality_rawdata/en/

World Health Organization (2015c), Cost-effectiveness thresholds, http://www.who.int/choice/costs/CER_thresholds/en/

Figure 1

Percentage change in premature (before age 75) mortality rate, 1998-2011:
10 diseases (ICD-10 blocks) with largest average premature mortality rates

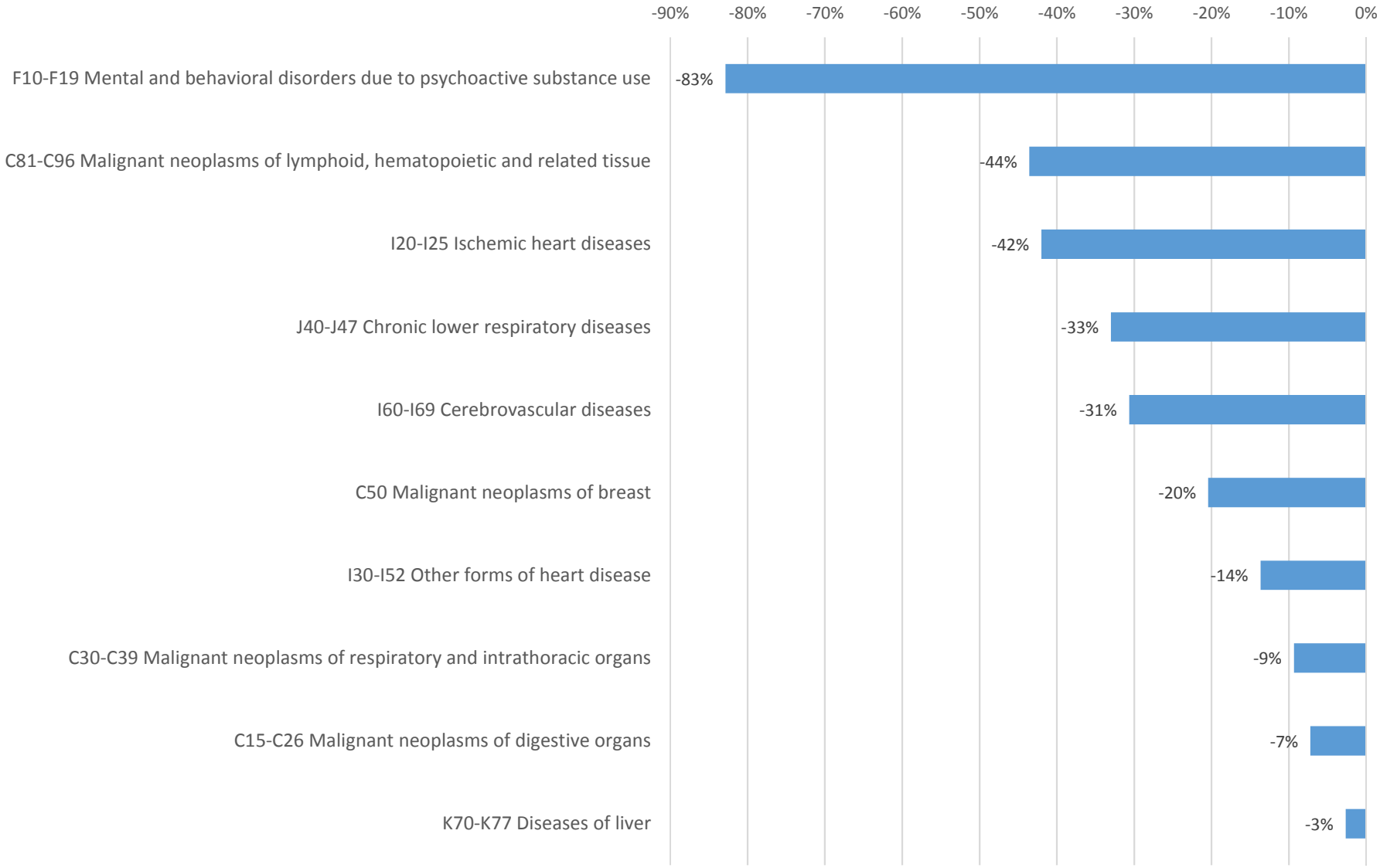


Figure 2
Number of drugs (chemical substances) ever listed in Pharmaceutical Benefits Scheme,
5-year intervals, 1986-2011: 6 diseases

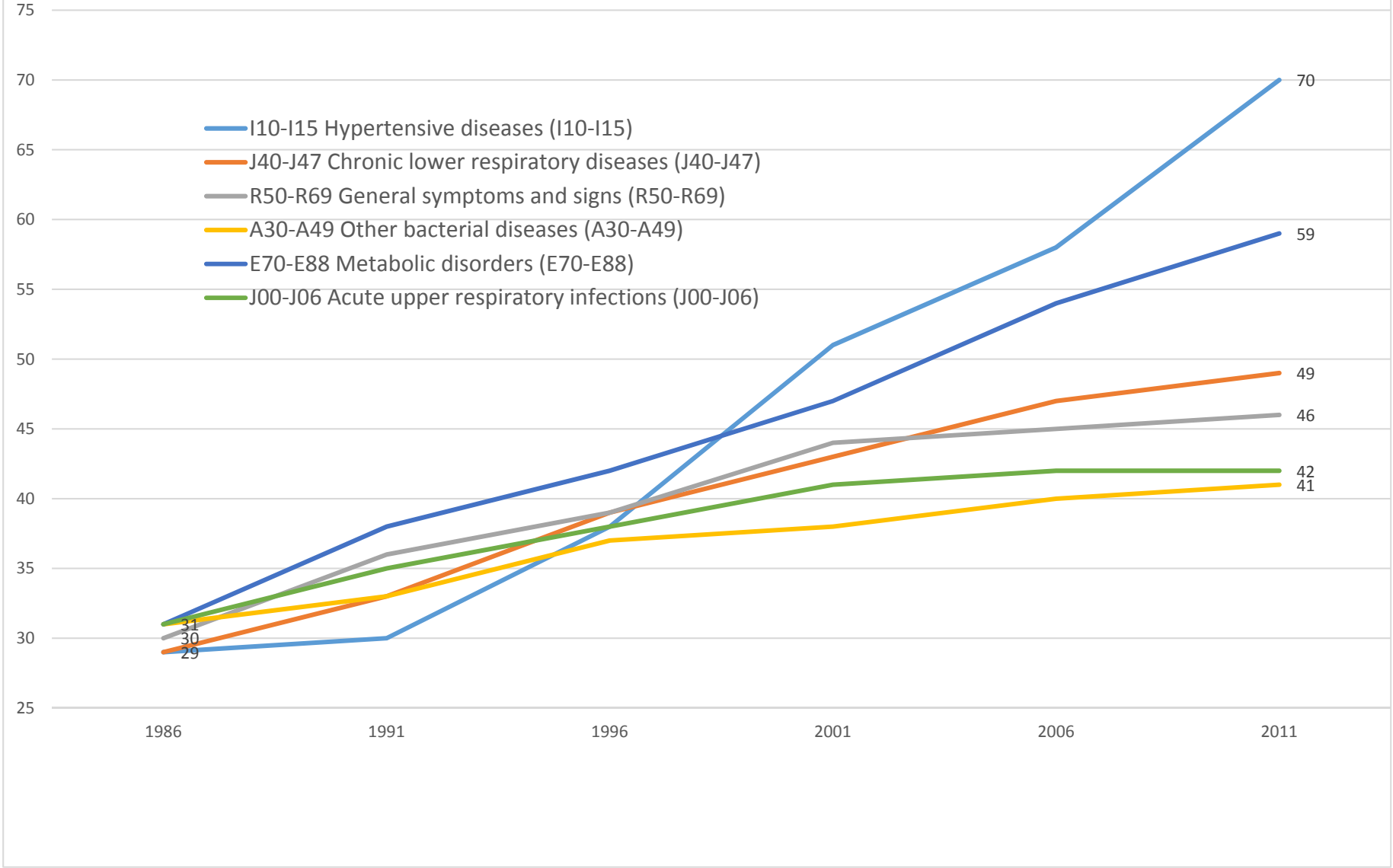


Figure 3
Number of hospital separations, 1998-2012: 6 diseases

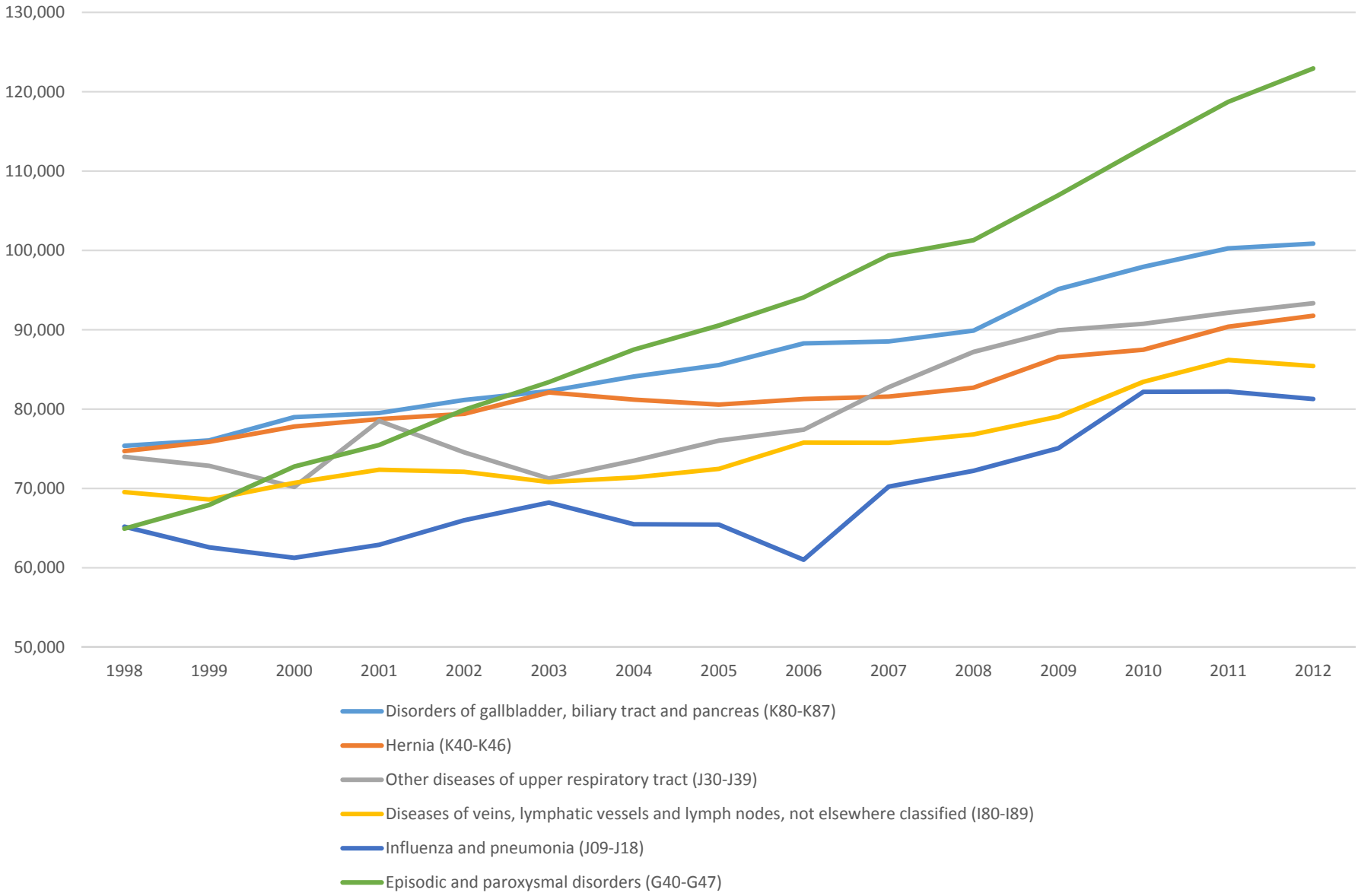
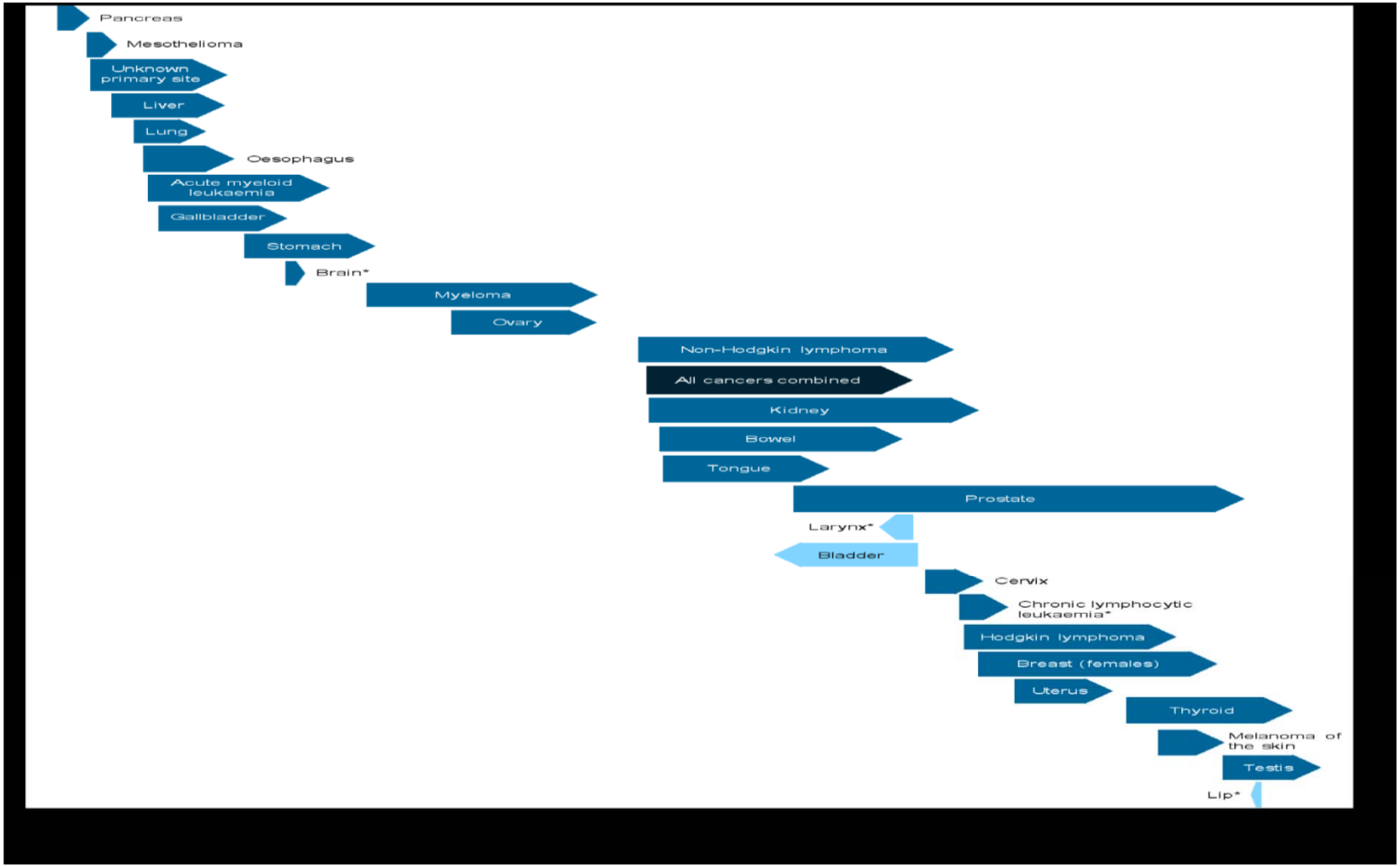


Figure 4

Survival trends, 1982-1987 to 2006-2010

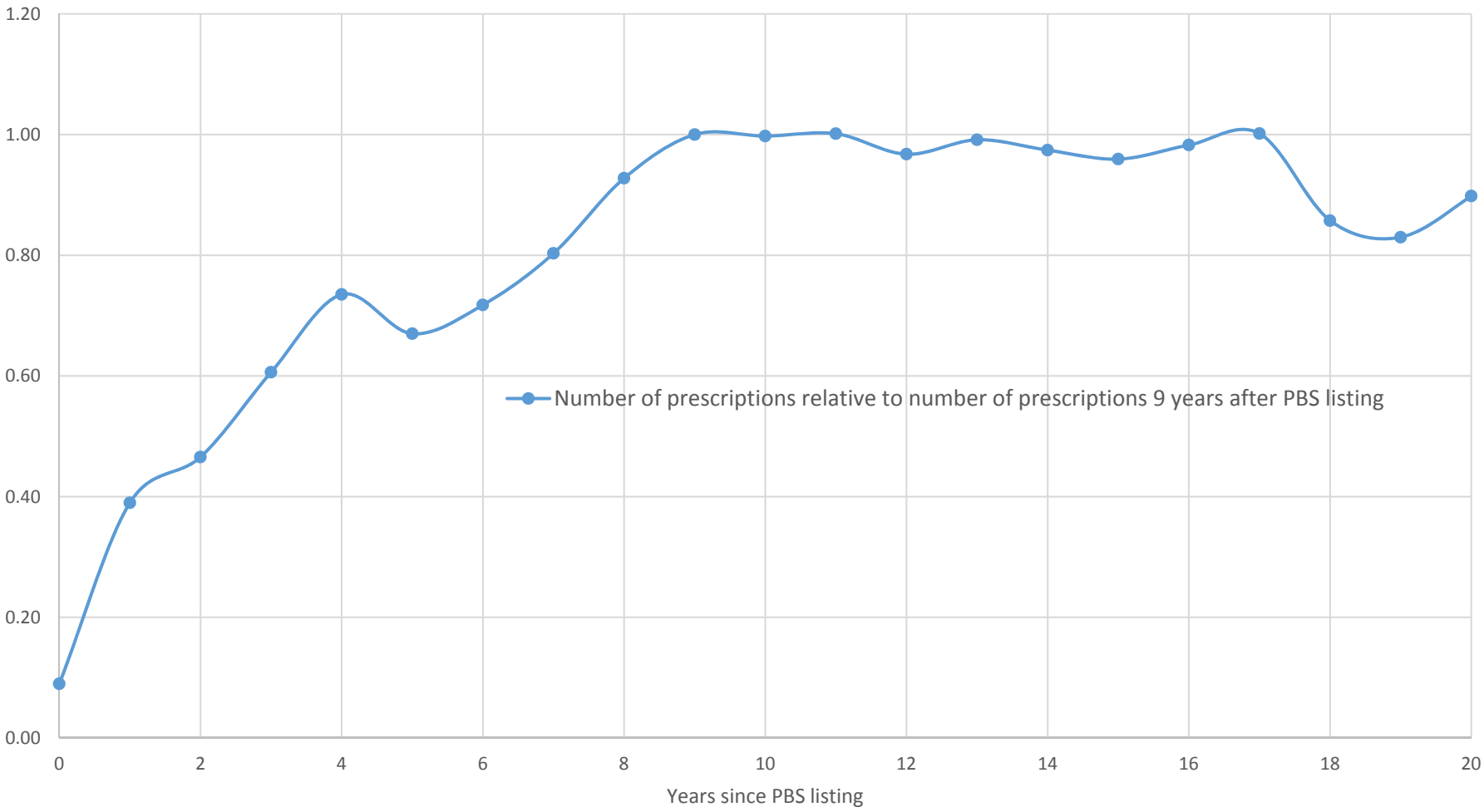


5-year relative survival

Arrow positions indicate survival estimates and arrow lengths indicate the change in survival between the period 1982-1987 and 2006-2010. Cancers labeled with an asterisk (*) indicate changes that were not statistically significant. Data for 1988-1993, instead of 1982-1987, are used for liver cancer due to the small number of cases from the earlier time period.

Source: AIHW Australian Cancer Database (2007). Cancer survival and prevalence in Australia: period estimates from 1982 to 2010, Figure 3.5

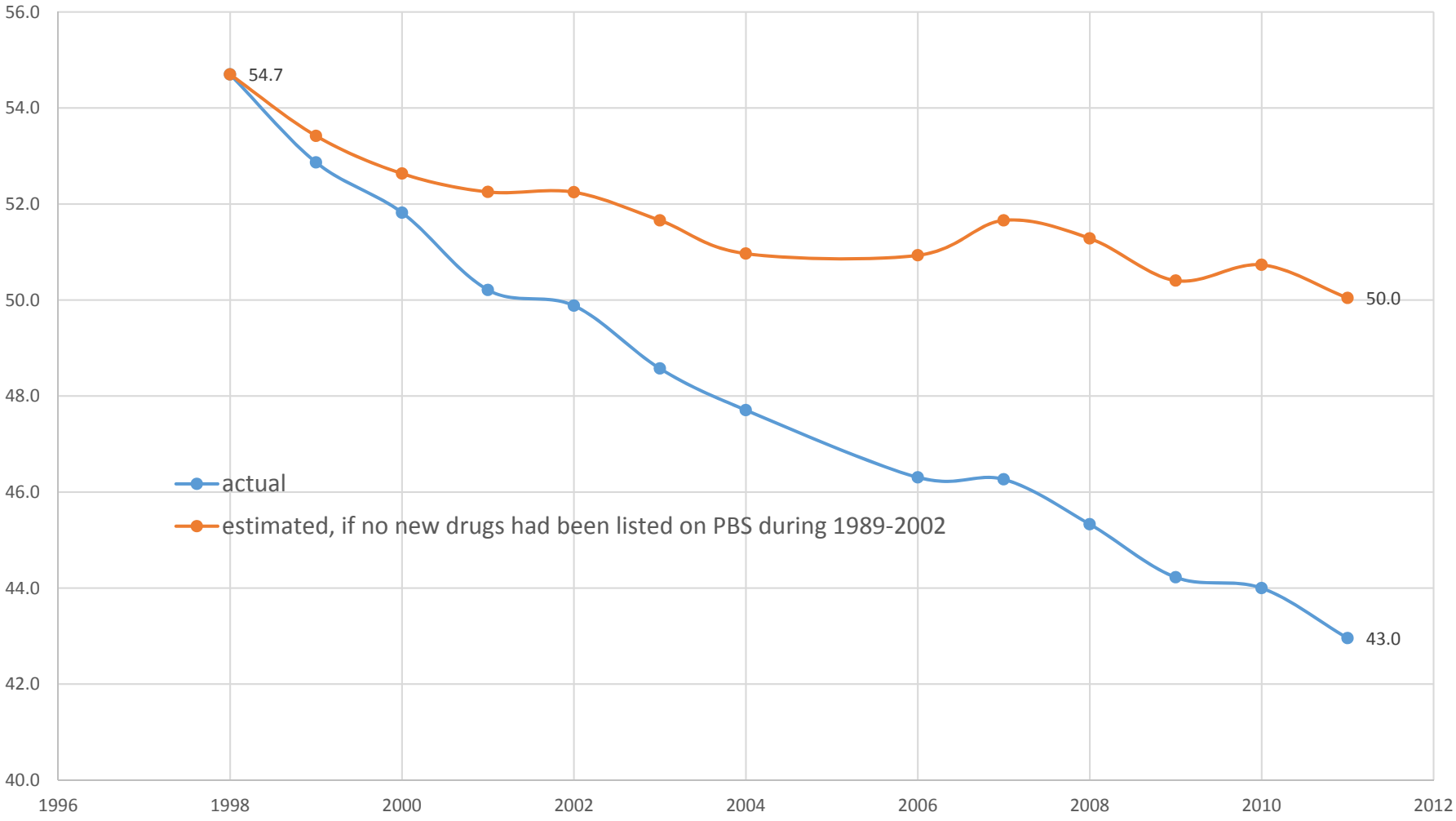
Figure 5
Drug age-utilization profile



The graph shows estimates of $\exp(\delta_y - \delta_9)$ for y = 0, 1,...,20 from the equation $\ln(N\_RX_{dy}) = \alpha_d + \delta_y + \varepsilon_{dy}$, where N_RX_{dy} = the number of prescriptions for drug d y years after PBS listing.

Figure 6

Premature (before age 75) mortality rate, Australia, 1998-2011:
actual vs. estimated, if no new drugs had been listed on PBS during 1989-2002



The premature mortality rate is the number of years of potential life lost before age 75 per 1,000 population under age 75 years.

Figure 7
Number of hospital discharges, 1998-2011:
actual vs. estimated, if no new drugs had been listed on the PBS during 1986-1999

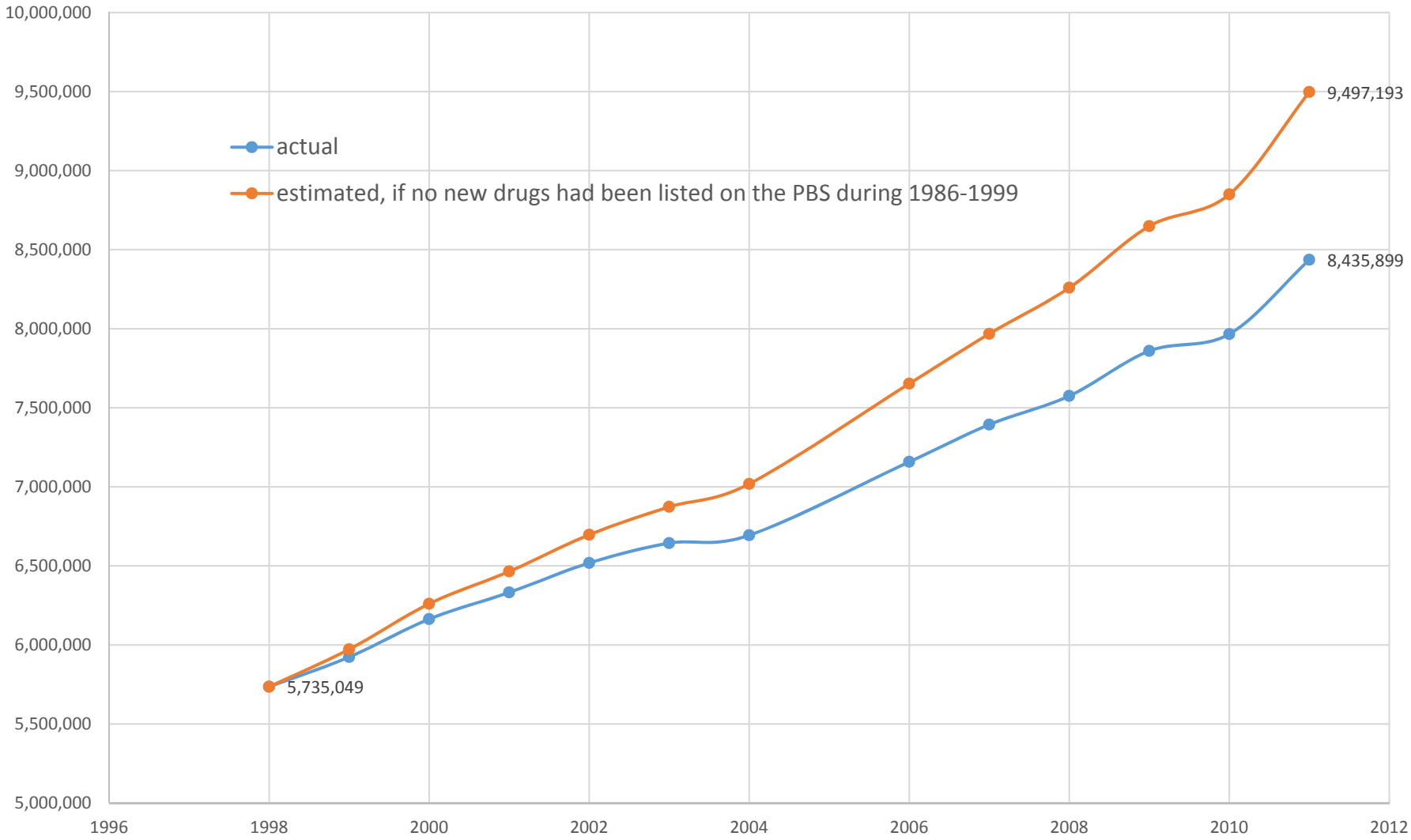


Figure 8
5-year relative cancer survival rate, 1986-2007:
actual vs. estimated, if no new drugs had been listed on the PBS during 1977-1998

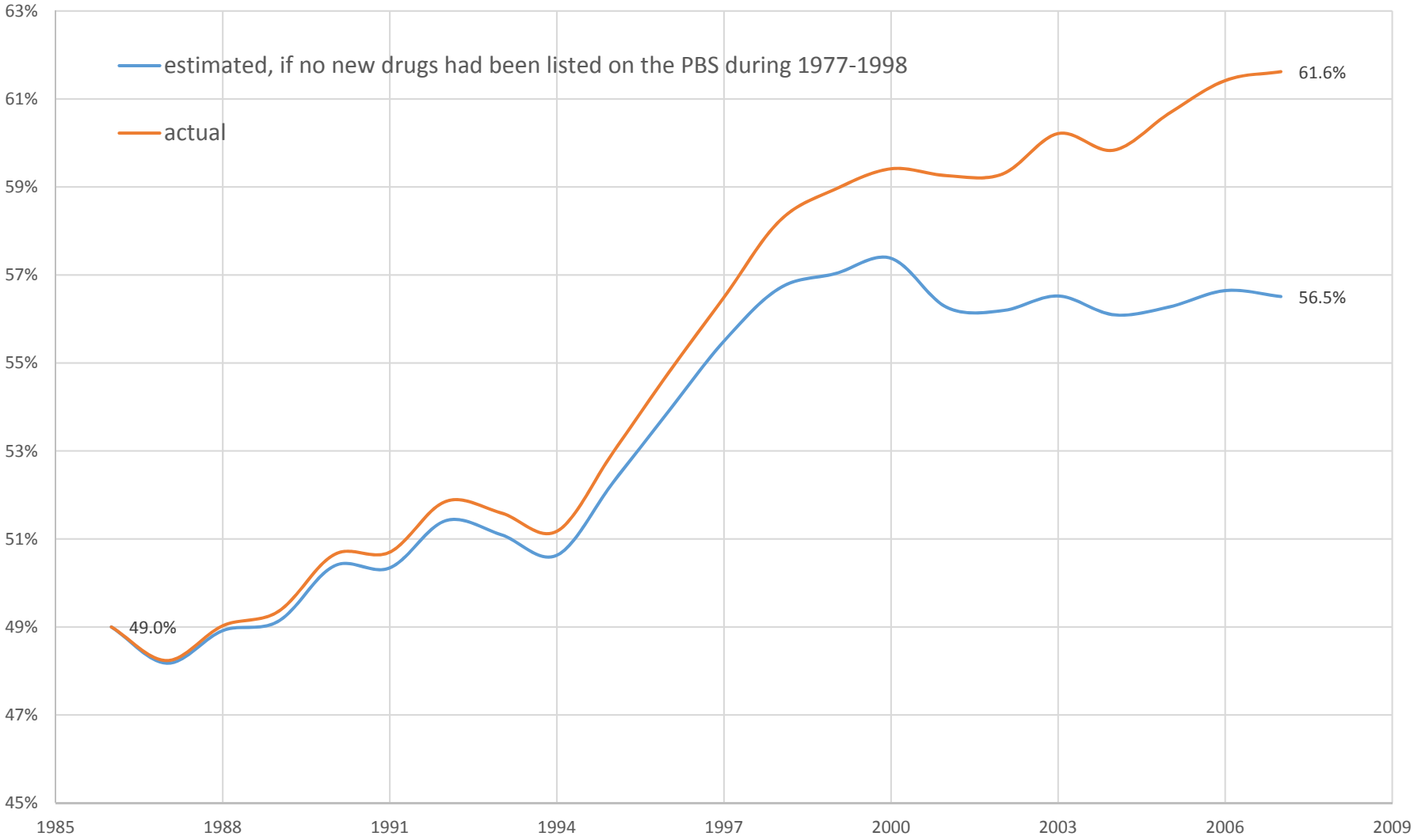


Table 1

Estimates of CUM_NCE coefficients from premature mortality equations (eqs. (1) and (2))

Line	Parameter	Estimate	Standard error	Z	Pr > |Z|
A. Eq. (1): $\ln(YPLL75_{it}) = \beta_k CUM\_NCE_{i,t-k} + \alpha_i + \delta_t + \varepsilon_{i,t}$					
1	β_0	-0.0147	0.0107	-1.37	0.1696
2	β_3	-0.0147	0.0090	-1.64	0.1013
3	**β_6**	**-0.0153**	**0.0072**	**-2.11**	**0.0352**
4	**β_9**	**-0.0136**	**0.0057**	**-2.38**	**0.0175**
5	β_{12}	-0.0121	0.0069	-1.75	0.0800
6	β_{15}	-0.012	0.0090	-1.34	0.1806
B. Eq. (2): $\ln(YPLL80_{it}) = \beta_k CUM\_NCE_{i,t-k} + \alpha_i + \delta_t + \varepsilon_{i,t}$					
7	β_0	-0.0177	0.0116	-1.53	0.1261
8	β_3	-0.0187	0.0098	-1.91	0.0556
9	**β_6**	**-0.0189**	**0.0081**	**-2.32**	**0.0203**
10	**β_9**	**-0.0171**	**0.0062**	**-2.75**	**0.0059**
11	**β_{12}**	**-0.0154**	**0.0074**	**-2.08**	**0.0373**
12	β_{15}	-0.0157	0.0092	-1.70	0.0889

Each estimate is from a different model. Estimates in bold are statistically significant (p-value < .05). N = 1788. All models include 170 fixed disease effects and 13 fixed year effects. Models were estimated via weighted least-squares. Weight used in lines 1-6 was (Σ_t $YPLL75_{it}$) / 13); weight used in lines 7-12 was (Σ_t $YPLL80_{it}$) / 13). Standard errors were clustered within diseases.

Table 2

Effects of the number of drugs and the number of chemical subgroups on premature mortality

			Regressor:	
Line	**Dependent variable**		**$CUM\_NCE_{i,t-9}$**	**$CUM\_SUBGROUP_{i,t-9}$**
4	log of premature (before age 75) mortality rate	Estimate	**-0.0136**	
		Std. Err.	**0.0057**	
		Z	**-2.38**	
		Pr > |Z|	**0.0175**	
4a	log of premature (before age 75) mortality rate	Estimate		-0.0016
		Std. Err.		0.0144
		Z		-0.11
		Pr > |Z|		0.9115
4b	log of premature (before age 75) mortality rate	Estimate	**-0.0172**	0.0193
		Std. Err.	**0.0052**	0.0138
		Z	**-3.34**	1.4
		Pr > |Z|	**0.0008**	0.1624
10	log of premature (before age 80) mortality rate	Estimate	**-0.0171**	
		Std. Err.	**0.0062**	
		Z	**-2.75**	
		Pr > |Z|	**0.0059**	
10a	log of premature (before age 80) mortality rate	Estimate		0.003
		Std. Err.		0.0133
		Z		0.23
		Pr > |Z|		0.8192
10b	log of premature (before age 80) mortality rate	Estimate	**-0.0217**	**0.0272**
		Std. Err.	**0.0048**	**0.011**
		Z	**-4.48**	**2.47**
		Pr > |Z|	**<.0001**	**0.0135**

Table 3

Estimates of CUM_NCE coefficients from hospital separations equation (eq. (4)):

$$\ln(N\_HOSP_{it}) = \beta_k \, CUM\_NCE_{i,t-k} + \alpha_i + \delta_t + \varepsilon_{i,t}$$

Line	Parameter	Estimate	Standard error	Z	Pr > |Z|
13	β_0	-0.0138	0.0088	-1.57	0.1161
14	**β_3**	**-0.0154**	**0.0074**	**-2.09**	**0.0370**
15	**β_6**	**-0.0161**	**0.0063**	**-2.57**	**0.0103**
16	**β_9**	**-0.0144**	**0.0052**	**-2.80**	**0.0051**
17	**β_{12}**	**-0.0164**	**0.0056**	**-2.94**	**0.0033**
18	**β_{15}**	**-0.0147**	**0.0065**	**-2.28**	**0.0227**

Each estimate is from a different model. Estimates in bold are statistically significant (p-value < .05). N = 1662. All models include 170 fixed disease effects and 13 fixed year effects. Models were estimated via weighted least-squares. Weight used was (Σ_t N_HOSP_{it}) / 13). Standard errors were clustered within diseases.

Table 4

Estimates of CUM_NCE coefficients from cancer survival equation (eq. (5)):

$$\ln(ODDS_{st}) = \beta_k \, CUM\_NCE_{s,t-k} + \pi \, AGE\_DIAG_{st} + \gamma \ln(N\_CASES_{st}) + \alpha_s + \delta_t + \varepsilon_{st}$$

Line	Parameter	Estimate	Standard error	Z	Pr > |Z|
19	β_0	**0.0131**	**0.0063**	**2.08**	**0.0379**
20	β_3	**0.0136**	**0.0054**	**2.52**	**0.0118**
21	β_6	**0.0135**	**0.0058**	**2.35**	**0.0190**
22	β_9	**0.0182**	**0.0067**	**2.72**	**0.0066**
23	β_{12}	**0.0230**	**0.0114**	**2.02**	**0.0435**
24	β_{15}	0.0187	0.0139	1.35	0.1769

Each estimate is from a different model. Estimates in bold are statistically significant (p-value < .05). N = 525. All models include 30 fixed cancer-site effects and 30 fixed year effects. Models were estimated via weighted least-squares. Weight used was N_CASES_{st}. Standard errors were clustered within cancer sites.

Table 5

Estimates of the number of life-years gained in 2011 from previous pharmaceutical innovation and medical expenditure per life-year gained

	before age 75	before age 80
life years gained in 2011	143,639	257,602
total expenditure on drugs age 9-22 in 2011	$5,768,556,127	$5,768,556,127
% of 2011 US outpatient drug expend that is by patients below age 75/80	86%	92%
estimated expend on drugs age 9-22 in 2011 by people below age 75/80	$4,975,693,434	$5,296,292,926
estimated reduction in 2010-11 hospital expenditure (all ages) due to drugs age 9-22	$6,846,596,600	$6,846,596,600
% of 1998−99 to 2007−08 Australian hospital separations of patients below age 75 or 80	81%	89%
estimated reduction in 2010-11 hospital expenditure (patients below age 75 or 80) due to drugs age 9-22	$5,561,844,228	$6,119,478,688
Cost per life-year gained based on:		
100% of hospital cost offset	-$4,081	-$3,196
50% of hospital cost offset	$15,280	$8,682
0% of hospital cost offset	$34,640	$20,560

Appendix Table 1

Drugs for acute upper respiratory infections (ICD-10 codes J00-J06), by PBS listing year

Drug	PBS listing year		Drug	PBS listing year
H02AB01 betamethasone	1964		A01AD11 various	1983
H02AB02 dexamethasone	1964		B05CB01 sodium chloride	1983
H02AB04 methylprednisolone	1964		R01AA05 oxymetazoline	1983
H02AB06 prednisolone	1964		R01AD01 beclometasone	1983
H02AB07 prednisone	1964		R01BA02 pseudoephedrine	1983
H02AB09 hydrocortisone	1964		J01CR02 amoxicillin and enzyme inhibitor	1986
J01AA07 tetracycline	1964		N02BA51 acetylsalicylic acid, combinations excl. psycholeptics	1986
J01CA01 ampicillin	1964		N02BE51 paracetamol, combinations excl. psycholeptics	1986
J01CE01 benzylpenicillin	1964		R05CA10 combinations	1986
J01CE02 phenoxymethylpenicillin	1964		J01DD04 ceftriaxone	1987
J01CE30 combinations	1964		J01MA02 ciprofloxacin	1988
J01FA01 erythromycin	1964		J01CR03 ticarcillin and enzyme inhibitor	1989
J01AA02 doxycycline	1968		J01DC04 cefaclor	1989
J01AA05 metacycline	1969		J01FA06 roxithromycin	1992
J01GB03 gentamicin	1969		J01FA10 azithromycin	1995
H02AB08 triamcinolone	1970		J01FA09 clarithromycin	1996
J01EE01 sulfamethoxazole and trimethoprim	1970		J01CF01 dicloxacillin	1997
J01DB01 cefalexin	1971		J01DC02 cefuroxime	1999
J01XA01 vancomycin	1972		J01DE01 cefepime	1999
M01AE01 ibuprofen	1973		J01MA14 moxifloxacin	2002
J01CA04 amoxicillin	1974		R01AA03 ephedrine	.
J01GB01 tobramycin	1976			

Appendix Table 2

Estimates of parameters of premature mortality models including and excluding $CUM\_NCE_{i,t-9}$

			$CUM\_NCE_{i,t-9}$ included					$CUM\_NCE_{i,t-9}$ excluded			
			A. Eq. (1): $\ln(YPLL75_{it}) = \beta_9 CUM\_NCE_{i,t-9} + \alpha_i + \delta_t + \varepsilon_{i,t}$								
Line	**Parameter**		**Estimate**	**Standard Error**	**Z**	**Pr > |Z|**		**Estimate**	**Standard Error**	**Z**	**Pr > |Z|**
1	**$CUM\_NCE_{i,t-9}$**		-0.0136	0.0057	-2.38	0.0175					
2	**Year**	1998	0.089	0.0873	1.02	0.3078		0.2417	0.0621	3.89	<.0001
3	**Year**	1999	0.0653	0.0807	0.81	0.4183		0.2076	0.0581	3.57	0.0004
4	**Year**	2000	0.0505	0.081	0.62	0.5328		0.1876	0.0543	3.46	0.0005
5	**Year**	2001	0.0432	0.0568	0.76	0.4469		0.156	0.0442	3.53	0.0004
6	**Year**	2002	0.0431	0.0541	0.8	0.4255		0.1495	0.0377	3.96	<.0001
7	**Year**	2003	0.0318	0.0471	0.68	0.499		0.1229	0.0337	3.65	0.0003
8	**Year**	2004	0.0183	0.0399	0.46	0.6468		0.1049	0.0296	3.54	0.0004
9	**Year**	2006	0.0176	0.029	0.61	0.5431		0.0751	0.0213	3.52	0.0004
10	**Year**	2007	0.0318	0.0221	1.44	0.1495		0.0742	0.0145	5.1	<.0001
11	**Year**	2008	0.0245	0.0172	1.42	0.1556		0.0538	0.0162	3.32	0.0009
12	**Year**	2009	0.0072	0.0145	0.5	0.6188		0.0291	0.0133	2.19	0.0289
13	**Year**	2010	0.0137	0.0123	1.12	0.2628		0.024	0.0103	2.33	0.0198
14	**Year**	2011	0	0	.	.		0	0	.	.
			B. Eq. (2): $\ln(YPLL80_{it}) = \beta_9 CUM\_NCE_{i,t-9} + \alpha_i + \delta_t + \varepsilon_{i,t}$								
15	**$CUM\_NCE_{i,t-9}$**		-0.0171	0.0062	-2.75	0.0059					
16	Year	1998	0.0493	0.0811	0.61	0.5434		0.2482	0.0685	3.62	0.0003
17	Year	1999	0.0318	0.0755	0.42	0.6736		0.2174	0.0638	3.41	0.0007
18	Year	2000	0.0149	0.0753	0.2	0.8428		0.1934	0.0583	3.32	0.0009
19	Year	2001	0.0178	0.0527	0.34	0.7353		0.1648	0.0509	3.24	0.0012
20	Year	2002	0.0196	0.0518	0.38	0.705		0.1582	0.0429	3.69	0.0002
21	Year	2003	0.0086	0.0443	0.19	0.8458		0.1275	0.038	3.35	0.0008
22	Year	2004	-0.0057	0.0392	-0.14	0.8852		0.107	0.0341	3.14	0.0017
23	Year	2006	-0.0034	0.0296	-0.12	0.9076		0.0713	0.0225	3.16	0.0016
24	Year	2007	0.0133	0.0217	0.61	0.5391		0.0684	0.0157	4.35	<.0001
25	Year	2008	0.014	0.016	0.88	0.3789		0.0521	0.0171	3.04	0.0024
26	Year	2009	-0.0031	0.0129	-0.24	0.8111		0.0252	0.013	1.93	0.0531
27	Year	2010	0.0066	0.0107	0.61	0.5402		0.0198	0.0084	2.36	0.0185
28	Year	2011	0	0	.	.		0	0	.	.

Appendix Table 3

Estimates of parameters of hospital separations model including and excluding $CUM\_NCE_{i,t-12}$

$$\ln(N\_HOSP_{it}) = \beta_{12}\, CUM\_NCE_{i,t-12} + \alpha_i + \delta_t + \varepsilon_{i,t}$$

			$CUM\_NCE_{i,t-12}$ included					$CUM\_NCE_{i,t-12}$ excluded			
Line	**Parameter**		**Estimate**	**Standard Error**	**Z**	**Pr > |Z|**		**Estimate**	**Standard Error**	**Z**	**Pr > |Z|**
1	**$CUM\_NCE_{i,t-12}$**		-0.0164	0.0056	-2.94	0.0033					
2	**Year**	1998	-0.5044	0.0553	-9.12	<.0001		-0.3812	0.0485	-7.86	<.0001
3	**Year**	1999	-0.4639	0.053	-8.75	<.0001		-0.3454	0.0461	-7.49	<.0001
4	**Year**	2000	-0.4168	0.0496	-8.4	<.0001		-0.3008	0.0442	-6.81	<.0001
5	**Year**	2001	-0.3847	0.0446	-8.62	<.0001		-0.2677	0.0367	-7.29	<.0001
6	**Year**	2002	-0.3494	0.042	-8.32	<.0001		-0.239	0.0364	-6.56	<.0001
7	**Year**	2003	-0.3234	0.0387	-8.35	<.0001		-0.2174	0.034	-6.39	<.0001
8	**Year**	2004	-0.3025	0.0335	-9.02	<.0001		-0.2251	0.0318	-7.07	<.0001
9	**Year**	2006	-0.216	0.0257	-8.41	<.0001		-0.1641	0.0288	-5.69	<.0001
10	**Year**	2007	-0.1756	0.0231	-7.59	<.0001		-0.1232	0.0238	-5.18	<.0001
11	**Year**	2008	-0.1397	0.0149	-9.38	<.0001		-0.1173	0.0171	-6.87	<.0001
12	**Year**	2009	-0.0936	0.0121	-7.74	<.0001		-0.0717	0.0176	-4.06	<.0001
13	**Year**	2010	-0.0706	0.0233	-3.03	0.0024		-0.0443	0.015	-2.96	0.0031
14	**Year**	2011	0	0	.	.		0	0	.	.

Appendix Table 4

Estimates of parameters of cancer survival model including and excluding $CUM\_NCE_{s,t-9}$

$$\ln(ODDS_{st}) = \beta_9 CUM\_NCE_{s,t-9} + \pi AGE\_DIAG_{st} + \gamma \ln(N\_CASES_{st}) + \alpha_s + \delta_t + \varepsilon_{st}$$

			$CUM\_NCE_{s,t-12}$ included					$CUM\_NCE_{s,t-12}$ excluded			
Line	**Parameter**		**Estimate**	**Standard Error**	**Z**	**Pr > |Z|**		**Estimate**	**Standard Error**	**Z**	**Pr > |Z|**
1	**$CUM\_NCE_{s,t-9}$**		0.0182	0.0067	2.72	0.0066					
2	**AGE_DIAG_{st}**		-0.0954	0.0199	-4.8	<.0001		-0.1061	0.0193	-5.51	<.0001
3	**$\ln(N\_CASES_{st})$**		0.6123	0.1488	4.11	<.0001		0.5769	0.1497	3.85	0.0001
4	**year**	1986	-0.3019	0.152	-1.99	0.0471		-0.5135	0.1385	-3.71	0.0002
5	**year**	1987	-0.3349	0.1264	-2.65	0.008		-0.5441	0.1275	-4.27	<.0001
6	**year**	1988	-0.3052	0.1368	-2.23	0.0257		-0.5124	0.1355	-3.78	0.0002
7	**year**	1989	-0.2967	0.1394	-2.13	0.0334		-0.4994	0.1363	-3.66	0.0002
8	**year**	1990	-0.2464	0.1388	-1.78	0.0758		-0.4477	0.1363	-3.28	0.001
9	**year**	1991	-0.2482	0.1319	-1.88	0.0599		-0.4455	0.1281	-3.48	0.0005
10	**year**	1992	-0.2053	0.1308	-1.57	0.1165		-0.3994	0.1251	-3.19	0.0014
11	**year**	1993	-0.218	0.1431	-1.52	0.1278		-0.4098	0.1463	-2.8	0.0051
12	**year**	1994	-0.2367	0.1299	-1.82	0.0684		-0.4265	0.1305	-3.27	0.0011
13	**year**	1995	-0.1711	0.0967	-1.77	0.0768		-0.3553	0.0921	-3.86	0.0001
14	**year**	1996	-0.1059	0.0853	-1.24	0.2147		-0.2822	0.0652	-4.33	<.0001
15	**year**	1997	-0.0412	0.0798	-0.52	0.6057		-0.2124	0.0579	-3.67	0.0002
16	**year**	1998	0.0078	0.0714	0.11	0.9133		-0.1412	0.0589	-2.4	0.0165
17	**year**	1999	0.0212	0.0637	0.33	0.7392		-0.1116	0.0477	-2.34	0.0193
18	**year**	2000	0.0354	0.0632	0.56	0.576		-0.0924	0.044	-2.1	0.0356
19	**year**	2001	-0.01	0.0547	-0.18	0.8555		-0.0989	0.0475	-2.08	0.0373
20	**year**	2002	-0.0131	0.0475	-0.28	0.7821		-0.0974	0.043	-2.27	0.0235
21	**year**	2003	0.0005	0.0475	0.01	0.9919		-0.0591	0.0486	-1.22	0.2239
22	**year**	2004	-0.0169	0.0451	-0.38	0.7075		-0.0749	0.0359	-2.09	0.0368
23	**year**	2005	-0.0096	0.0273	-0.35	0.725		-0.0397	0.0252	-1.58	0.1149
24	**year**	2006	0.0055	0.0207	0.27	0.7907		-0.0085	0.0187	-0.45	0.6511
25	**year**	2007	0	0	.	.		0	0	.	.