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The Impact of Pharmaceutical Innovation on Cancer Mortality in Belgium, 2004–2012

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Abstract: Cancer mortality declined in Belgium during the period 2004–2012, but there was considerable variation in the rate of decline across cancer sites (breast, lung, etc.). I analyze the effect that pharmaceutical innovation had on cancer mortality in Belgium, by investigating whether the cancer sites that experienced more pharmaceutical innovation had larger subsequent declines in mortality, controlling for changes in cancer incidence. The measures of mortality analyzed – premature (before ages 75 and 65) mortality rates and mean age at death – are not subject to lead-time bias. Premature cancer mortality rates are significantly inversely related to the cumulative number of drugs registered 15–23 years earlier. Since mean utilization of drugs that have been marketed for less than 10 years is less than one fourth as great as mean utilization of drugs that have been marketed for at least a decade, it is not surprising that premature mortality is strongly inversely related only to the cumulative number of drugs that had been registered at least 10 years earlier. Drugs registered during the period 1987–1995 are estimated to have reduced the premature cancer mortality rate in 2012 by 20%. Mean age at death from cancer increased by 1.17 years between 2004 and 2012. The estimates indicate that drugs registered during the period 1987–1995 increased mean age at death from cancer in 2012 by 1.52 years. The estimates also suggest that drugs (chemical substances) within the same class (chemical subgroup) are not "therapeutically equivalent," i.e. they do not have essentially the same effect in the treatment of a disease or condition. The estimates imply that the drugs registered during 1987–1995 reduced the number of life-years lost to cancer at all ages in 2012 by 41,207. The estimated cost per-life-year gained in 2012 from cancer drugs registered in Belgium during the period 1987–1995 was €1311. This estimate is well below even the lowest estimates from other studies of the value of a life-year saved. The largest reductions in premature mortality occur 15–23 years after drugs are registered, when their utilization increases significantly. This suggests that, if Belgium is to obtain substantial additional reductions in premature cancer mortality in the future (15 or

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more years from now) at a modest cost, pharmaceutical innovation (registration of new drugs) is needed today.

Keywords: Belgium; cancer; innovation; mortality; pharmaceutical.

1 Introduction

Previous authors have argued that "reducing premature mortality is a crucial public health objective" (Renard et al. 2014). A widely used measure of premature mortality is years of potential life lost (YPLL) before a given age (e.g. age 70), i.e. the number of years not lived by an individual who died before that age (Association of Public Health Epidemiologists in Ontario 2015; National Cancer Institute 2015a). Statistics of YPLL are published by the World Health Organization, the OECD, and government agencies of the US, Belgium, and other countries. Burnet et al. (2005) argue that YPLL "should be considered when allocating research funds."

As shown in Figure 1, in Belgium in 2012, cancer (malignant neoplasms) was the largest cause of premature mortality: the number of years of potential life lost before age 70 (YPLL70) due to cancer was 11% larger than YPLL70 due to external causes and 133% larger than YPLL70 due to diseases of the circulatory system. But as shown in Table 1, the premature cancer mortality rate has been declining: the pre-age-70 and pre-age-75 cancer mortality rates both declined by 17% between 1998 and 2012, and the overall age-adjusted cancer mortality rate declined by 20%.[1] During that period, the age-adjusted cancer incidence rate increased by 16%.

While the premature mortality rate from all cancers combined has declined in Belgium, Figure 2A indicates that there has been considerable variation in the rate of decline across cancer sites. During the period 2004–2012,[2] the premature (before age 75) mortality rate from four types of cancer (melanomas of skin, breast cancer, leukemias, and non-Hodgkin's lymphoma) declined by at least 10%, but the premature mortality rate from two types of cancer (pancreatic and liver cancer) increased by at least 5%. We will show that this variation in the rate of decline of premature mortality cannot be explained by variation in the rate of increase of incidence.

1 Mean age at death from cancer increased by 1.57 years, from 71.68 to 73.25 years, during that period.

2 I will analyze changes in cancer mortality during the period 2004–2012, in order to control for lagged cancer incidence. The first year in which detailed cancer incidence data are available (for a major region of Belgium, Flanders) is 1999.

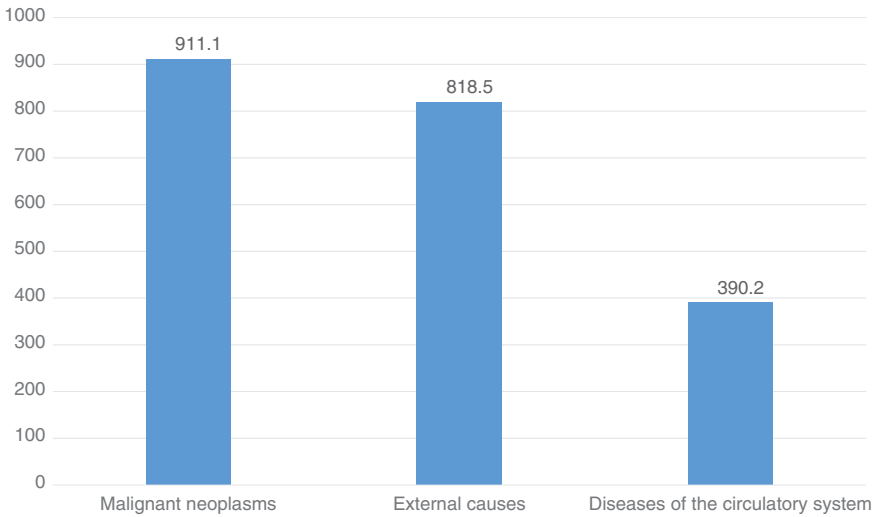

Figure 1: Three Largest Causes of Premature (before age 70) Mortality, Belgium, 2012. Years of potential life lost before age 70 per 100,000 population below age 70. Source: OECD.Stat, http://stats.oecd.org/index.aspx?DataSetCode=HEALTH_STAT#.

Table 1: Trends in Cancer Mortality and Incidence, Belgium, 1998–2012.

Year	YPLL70[a]	YPLL75[b]	Age-adjusted cancer mortality rate (per 100,000 population)[c]	Age-adjusted cancer incidence rate (per 100,000 population)[c]	Number of total cases[c]
1998	1315	1950	259	277	47,855
2000	1272	1866	243	282	47,948
2002	1267	1847	238	296	51,874
2008	1222	1776	222	309	59,945
2012	1095	1623	207	321	65,345
% change, 1998–2012	–17%	–17%	–20%	16%	37%

[a]YPLL70: years of potential life lost due to malignant neoplasms before age 70 per 100,000 population age 0–69. Source: author's calculations based on WHO Mortality Database.

[b]YPLL75: years of potential life lost due to malignant neoplasms before age 75 per 100,000 population age 0–74. Source: author's calculations based on WHO Mortality Database.

[c]Source: OECD Health Database. Data on the incidence rate and the number of total cases for the years 1998 and 2000 were obtained from the EUCAN data base, and for the years 2002, 2008, and 2012 were obtained from the GLOBOCAN database.

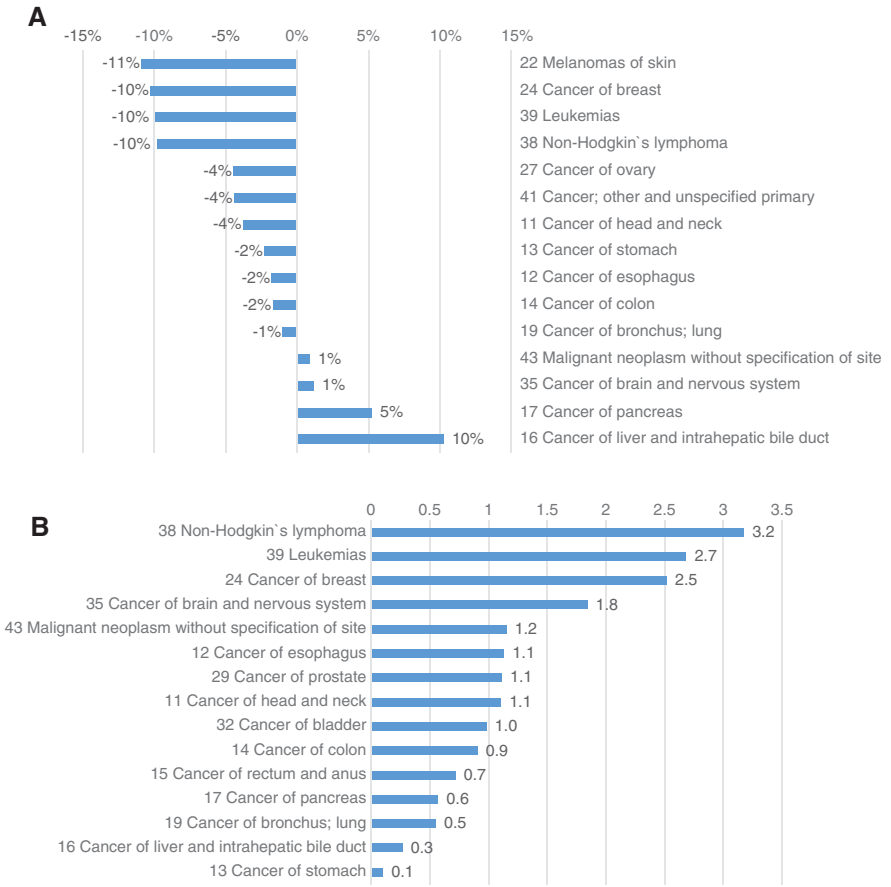

Figure 2: (A)% change in premature (before age 75) mortality rate, 2004–2012: 15 cancers with highest premature mortality rates in 2004. (B) Increase in mean age at death, 2004–2012: 15 cancers with largest number of deaths in 2012.

Figure 2B shows that the 2004–2012 change in mean age at death also varied considerably across cancer sites. Mean age at death caused by three types of cancer (non-Hodgkin's lymphoma, leukemias, and breast cancer) increased by at least 2.5 years, while mean age at death caused by liver and stomach cancer cancer increased by at most 0.3 years

In this paper, I will analyze the effect that pharmaceutical innovation had on several measures of cancer mortality – premature (before ages 75 and 65) mortality rates, and mean age at death – in Belgium during the period 2004–2012. As shown in Figure 3, the number of drugs used to treat cancer that had ever been registered in Belgium increased more than three-fold between 1980 and 2010; the

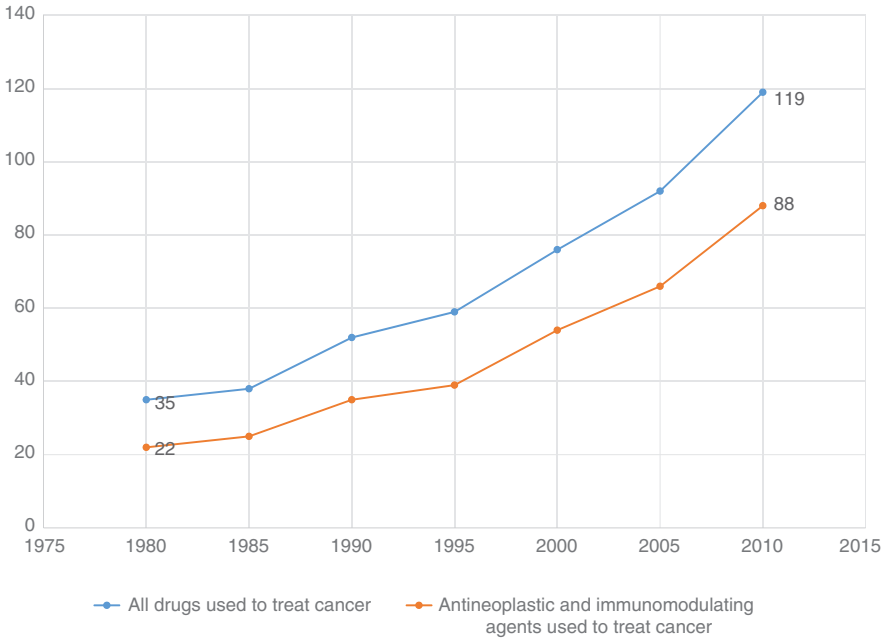

Figure 3: Number of Drugs Ever Launched in Belgium to Treat Cancer, 5-Year Intervals, 1980–2010.

number of "cancer drugs" (antineoplastic and immunomodulating agents) used to treat cancer increased four-fold.

The analysis will be performed using a difference-in-differences research design based on aggregate data – longitudinal data on 32 cancer sites.[3] In essence, I will investigate whether the cancer sites that experienced more pharmaceutical innovation had larger subsequent declines in premature mortality rates and larger subsequent increases in mean age at death; since these outcome measures are not conditional on diagnosis – they are based entirely on data contained in death certificates – they are not subject to lead-time bias.[4] Figure 4 illustrates that

3 The 32 cancer sites are all cancer sites defined in the Clinical Classifications Software developed by the US Agency for Healthcare Research and Quality.

4 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. See National Cancer Institute (2015b).

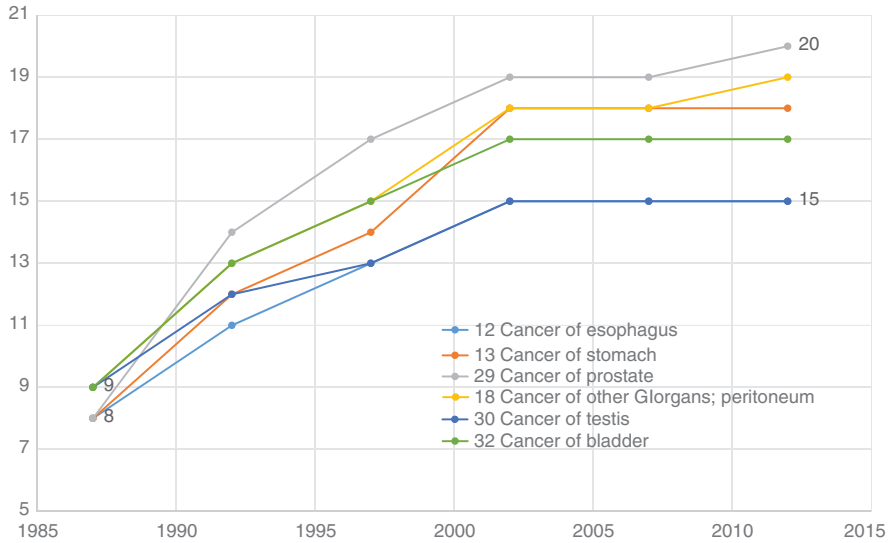

Figure 4: Number of Drugs for Treating Six Types of Cancer Ever Registered in Belgium, 1987–2012.

the rate of pharmaceutical innovation, as measured by the 1987–2012 increase in the number of drugs ever registered, varied considerably across cancer sites. During that quarter century, 12 drugs were registered for prostate cancer, while only six drugs were registered for cancer of testis.

In Section 2, I describe an econometric model of cancer mortality. The data sources used to construct the data to estimate this model are described in Section 3. Empirical results are presented in Section 4. Key implications of the estimates are discussed in Section 5. Section 6 provides a summary and conclusions.

2 Cancer Mortality Model

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 mortality model that I will estimate may be considered a health production function, in which mortality is an indicator of health output or outcomes, and the cumulative number of drugs registered is analogous to the stock of ideas. The model will be of the following form:

$$MORT_{s,t} = \beta_k CUM\_NCE_{s,t-k} + \gamma \ln(CASES\_FLANDERS\_6YEAR_{s,t}) + \pi AGE\_DX\_FLANDERS\_6YEAR_{s,t} + \alpha_s + \delta_t + \varepsilon_{s,t} \quad (1)$$

where $MORT_{s,t}$ is one of the following variables:

$\ln(YPLL75_{s,t})$ = the log of the number of years of potential life lost before age 75 due to cancer at site s per 100,000 people below age 75 in Belgium in year t (t=2004, …, 2012)

$\ln(YPLL65_{s,t})$ = the log of the number of years of potential life lost before age 65 due to cancer at site s per 100,000 people below age 65 in Belgium in year t

$AGE\_DEATH_{s,t}$ = mean age at death from cancer at site s in Belgium in year t

and

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

IND_{ds} = 1 if drug d is used to treat (indicated for) cancer at site s

= 0 if drug d is not used to treat (indicated for) cancer at site s

$REGISTERED_{d,t-k}$ = 1 if drug d was registered in Belgium by the end of year t-k

= 0 if drug d was not registered in Belgium by the end of year t-k

$CASES\_FLANDERS\_6YEAR_{s,t}$ = the average annual number of patients diagnosed in Flanders with cancer at site s in years t-5 to year t

$AGE\_DX\_FLANDERS\_6YEAR_{s,t}$ = the mean age at which patients were diagnosed in Flanders with cancer at site s in years t-5 to year t

α_s = a fixed effect for cancer at site s

δ_t = a fixed effect for year t

Inclusion of year and cancer-site fixed effects controls for the overall change in cancer mortality[5] and for stable between-disease differences in mortality. When

5 Some trends may have increased premature mortality. Between 1997 and 2008, the fraction of the Belgian population that was overweight or obese increased from 41.3% to 46.9%, and the fraction of the Belgian population that was obese increased from 10.8% to 13.8%. (These are self-reported figures as reported in OECD Health Statistics 2015.)

$MORT_{s,t}$=ln($YPLL75_{s,t}$), a negative and significant estimate of β_k in eq. (1) would signify that diseases for which there was more pharmaceutical innovation had larger declines in the premature mortality rate. When $MORT_{s,t}$=$AGE\_DEATH_{s,t}$, a positive and significant estimate of β_k in eq. (1) would signify that diseases for which there was more pharmaceutical innovation had larger increases in mean age at death.

The data exhibit heteroskedasticity: cancer sites with larger mean premature mortality rates during 2004–2012 had smaller (positive and negative) annual percentage fluctuations in $MORT_{s,t}$. Eq. (1) will therefore be estimated by weighted least-squares. When $MORT_{s,t}$=ln($YPLL75_{s,t}$), the weight will be the mean premature mortality rate during 2004–2012 (($\sum_t$ $YPLL75_{s,t}$)/9). When $MORT_{s,t}$=$AGE\_DEATH_{s,t}$, the weight will be the number of deaths from cancer at site s in year t ($N\_DEATHS_{s,t}$). The standard errors of eq. (1) will be clustered within cancer sites.

Eq. (1) controls for measures of incidence (the number of patients diagnosed and mean age at time of diagnosis) 0–5 years preceding the year in which mortality is measured.[6, 7] These measures of incidence are based on the Flanders region of Belgium, which began collecting incidence data in 1999; the other two regions of Belgium (Wallonia and Brussels) began collecting incidence data in 2004 (Belgian Cancer Registry 2016). Flanders accounted for 59% and 60% of Belgian cancer patients diagnosed in 2004 and 2012, respectively. As shown in Appendix A, during the period 2004–2012, there were very close relationships across cancer sites between both (1) growth in the number of patients diagnosed in Flanders and growth in the number of patients diagnosed in Belgium as a whole, and (2) the change in the mean age at which patients were diagnosed in Flanders and the change in the mean age at which patients were diagnosed in Belgium as a whole.

Although one would expect an increase in true cancer incidence to increase premature cancer mortality, cancer incidence rates are subject to measurement error, so one should not necessarily expect the coefficient on measured cancer incidence (γ) to be positive. Let I and I* represent measured and true cancer incidence, respectively. Then I=(I/I*)×I*, and ln(I)=ln(I/I*)+ln(I*). Measured cancer

6 When the dependent variable is ln($YPLL75_{s,t}$), the measures of incidence included are the log of the number of patients below age 75 diagnosed and their mean age at time of diagnosis. When the dependent variable is $AGE\_DEATH_{s,t}$, the measures of incidence included are the log of the number of patients of all ages diagnosed and their mean age at time of diagnosis.

7 Since median observed survival of patients diagnosed in Belgium during 2004–2008 was 58 months for males and >60 months for females (Belgian Cancer Registry 2012), I would prefer to also have data on the number of patients diagnosed in years t-6, t-7,… Those data are not available. However, cancer incidence is highly serially correlated: the correlation across 32 cancer sites between the log of the number of patients diagnosed in Belgium in 2004 and the log of the number of patients diagnosed in Belgium in 2012 is 0.98.

incidence can increase for two reasons: an increase in true cancer incidence, or an increase in the ratio of measured incidence to true incidence. The latter could occur as a result of increasing quantity or quality of cancer screening. More and better cancer screening could lead to earlier diagnosis, which might reduce premature mortality.[8] Therefore the effect on premature mortality of increases in I* and increases in (I/I*) may offset one another: the former is likely to increase premature mortality, but the latter may reduce it. For this reason, although controlling (in an unrestrictive manner) for measured incidence in the premature mortality model seems appropriate, we should not be surprised if we do not find a significant effect of measured incidence on premature mortality. Moreover, there is little reason to expect either measured evidence or true incidence to affect mean age at death.

Estimation of eq. (1) enables determination of how much of the decline in Belgian premature cancer mortality during the sample period (2004–2012) can be attributed to the introduction of new drugs. The expression (δ_{2012}–δ_{2004}) indicates the 2004–2012 decline in log premature cancer mortality, controlling for (holding constant) the number of drugs and cancer incidence, i.e. in the absence of pharmaceutical innovation. Suppose eq. (1) is estimated, excluding $CUM\_NCE_{s,t\text{-}k}$, and that the year fixed effects from that equation are denoted by δ'_t. Then (δ'_{2012}–δ'_{2004}) indicates the 2004–2012 decline in log premature mortality, not holding constant the number of drugs, i.e. in the presence of pharmaceutical innovation, and (δ'_{2012}–δ'_{2004})–(δ_{2012}–δ_{2004}) is an estimate of the 2004–2012 decline in log premature mortality attributable to pharmaceutical innovation. In the estimation procedure that we use (SAS GENMOD), δ'_{2012} and δ_{2012} are normalized to zero, so (δ_{2004}–δ'_{2004}) is an estimate of the 2004–2012 decline in log premature mortality attributable to pharmaceutical innovation. (δ_{2004}–δ'_{2012}) is equivalent to β_k*(CUM_NCE.,$_{2012\text{-}k}$–CUM_NCE.,$_{2004\text{-}k}$), where CUM_NCE.,$_{t\text{-}k}$ is the mean of $CUM\_NCE_{s,t\text{-}k}$.

The measure of pharmaceutical innovation in eq. (1) – the number of chemical substances previously commercialized to treat a disease – is not the theoretically ideal measure. Premature mortality is presumably more strongly

8 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).

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 cancer at site s in year t, defined as $VINTAGE_{st}=\sum_d Q_{dst}$ $LAUNCH\_YEAR_d/\sum_d Q_{dst}$, where Q_{dst}=the quantity of drug d used to treat cancer at site s in year t, and $LAUNCH\_YEAR_d$=the world launch year of drug d.[9] Unfortunately, measurement of $VINTAGE_{st}$ is infeasible: even though data on the total quantity of each drug in each year ($Q_{d.t}=\sum_s Q_{dst}$) are available, many drugs are used to treat multiple diseases,[10] and from the data available to me it was not possible to determine the quantity of drug d used to treat cancer at site s in year t.[11] However, Lichtenberg (2014a) showed that, in France during the period 2000–2009, there was 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 commercialized within the drug class.

Pharmaceutical innovation is not the only type of medical innovation that is likely to contribute to premature mortality. Other medical innovation, such as innovation in diagnostic imaging, surgical procedures, and medical devices, is also likely to affect premature mortality.[12] Therefore, measures of these other types of medical innovation should be included in the eq. (1). Unfortunately, longitudinal disease-level measures of non-pharmaceutical medical innovation are not available for Belgium. 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, about half of US funding for

9 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. 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).

10 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.

11 Outpatient prescription drug claims usually do not 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 Belgium.

12 A brief review of the history of several types of medical innovation (chemotherapy, diagnostic imaging, and radiation) for cancer treatment is provided in Lichtenberg (2014b).

biomedical research came from pharmaceutical and biotechnology firms (Moses et al. 2015).[13] 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 (2015c) 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 US data indicates that non-pharmaceutical medical innovation is not positively correlated across diseases with pharmaceutical innovation. In Lichtenberg (2014a), it is shown that, in the US 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 US cancer mortality rates were insensitive to the inclusion or exclusion of measures of non-pharmaceutical medical innovation. While evidence from the US suggests that failure to control for other medical innovation is unlikely to result in overestimation of the effect of pharmaceutical innovation on longevity growth, other factors specific to the Belgian health system could also affect mortality. For instance, improvements in care coordination or adherence in Belgium may not be correlated with changes in the US health care system or pharmaceutical innovation in Belgium, but could affect the mortality rates of Belgian cancer patients.

In eq. (1), premature mortality from cancer at site s in year t depends on the number of new chemical entities (drugs) to treat cancer at site s registered in Belgium by the end of year t-k, i.e. there is a lag of k years. Eq. (1) will be estimated for different values of k: k=0, 1, 2,…, 25.[14] One would expect there to

13 Data on the fraction of non-US funding for biomedical research that came from pharmaceutical and biotechnology firms are not available. But in 2011, industry (pharmaceutical, biotechnology, and medical device firms) accounted for a larger fraction of non-US biomedical R&D than it did of US biomedical R&D: 65% vs. 57%. In the US in 2012, pharmaceutical and biotechnology funded 83% of industry-funded biomedical R&D (Moses et al. 2015, figures 3 and 8).

14 A separate model is estimated for each value of k, rather than including multiple values ($CUM\_NCE_{i,t-1}$, $CUM\_NCE_{i,t-2}$, $CUM\_NCE_{i,t-3}$,…) 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.)

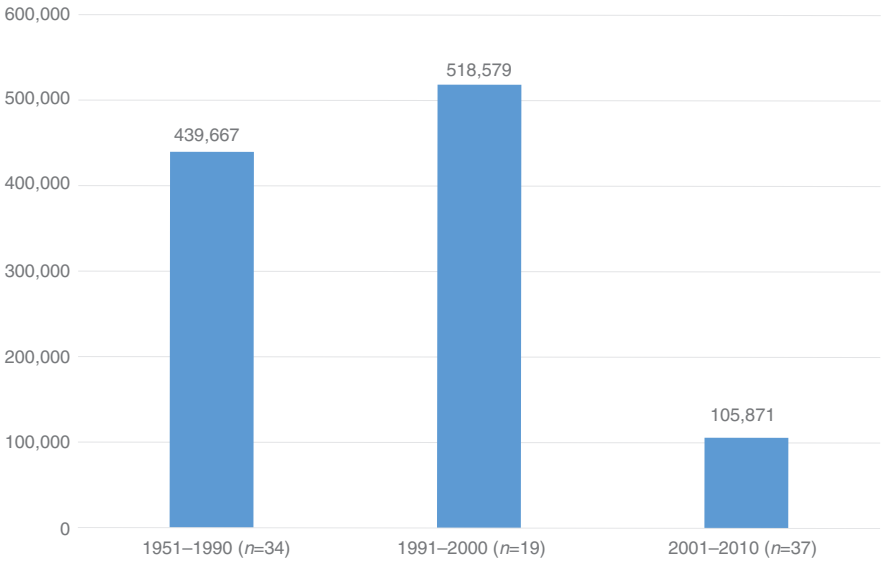

Figure 5: Mean Number of Standard Units of Antineoplastic and Immunomodulating Agents Sold in Belgium in 2010, by Period of Launch in Belgium.

be a substantial lag, for two reasons. The first reason is that new drugs diffuse gradually – they would not be used widely until years after commercialization. Figure 5 shows data on the mean number of standard units[15] of cancer drugs sold (in thousands) in Belgium in 2010, by period of launch in Belgium. Mean utilization in 2010 of drugs registered after 2000 is only 24% as high as mean utilization of drugs registered during 1951–1990, and 20% as high as mean utilization of drugs registered during 1991–2000. The relatively low utilization of new drugs may be due to several factors. One is that the prices of old drugs (most of which are no longer patent-protected) are considerably lower than the prices of new, patent-protected drugs. A second factor may be that it takes time

15 The number of standard "dose" units sold is determined by taking the number of counting units sold divided by the standard unit factor which is the smallest common dose of a product form as defined by IMS HEALTH. For example, for oral solid forms the standard unit factor is one tablet or capsule whereas for syrup forms the standard unit factor is one teaspoon (5 ml) and injectable forms it is one ampoule or vial. Other measures of quantity, such as the number of patients using the drug, prescriptions for the drug, or defined daily doses of the drug, are not available.

for physicians to become knowledgeable about new treatment options. A third potential factor is that new drugs may be targeted at smaller patient populations. Data from the U.S. Food and Drug Administration (2015) indicate that drugs approved by the FDA since 2000 were twice as likely to include pharmacogenomic information in their labeling as drugs approved before 2000. A fourth potential factor is that older drugs are more likely to have supplemental indications, i.e. indications approved after the drug was initially registered, than new drugs.[16]

The second reason for a long lag from drug registration to mortality is that there is usually a substantial lag from diagnosis (when drug treatment is likely to begin and be most intensive) to death. During the period 1999–2008, the 5-year observed survival rate of males for all tumors was 49.5%, indicating that the median lag from diagnosis until death was 5 years. The survival rate of females for all tumors was 60.7%, indicating that the median lag from diagnosis until death was more than 5 years (Belgian Cancer Registry 2012, Table 4).

The effect of a drug's registration 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.

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 (1st) level is the "anatomical main group" level; there are 14 anatomical main groups. The 2nd, 3rd, 4th, and 5th levels are "therapeutic subgroup," "pharmacological subgroup," "chemical subgroup," and "chemical substance,"

16 The measure of pharmaceutical innovation, $CUM\_NCE_{s,t-k}=\sum_d IND_{ds} REGISTERED_{d,t-k}$, is based on whether drug d had an indication for cancer at site s at the end of 2011. One would prefer to base the measure on whether drug d had an indication for cancer at site s at the end of year t-k. Data in the US FDA's Drugs@FDA data files indicate that about one in four new molecular entities has supplemental indications, i.e. indications approved after the drug was initially approved.

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 $CUM\_SUBGROUP_{s,t-k}$ is included in addition to or instead of $CUM\_NCE_{s,t-k}$, where

$CUM\_SUBGROUP_{s,t-k}$ = $\sum_g IND\_SUBGROUP_{gs} REGISTERED\_SUBGROUP_{g,t-k}$

$IND\_SUBGROUP_{gs}$ = 1 if any drugs in chemical subgroup g are used to treat (indicated for) cancer at site s

= 0 if no drugs in chemical subgroup g are used to treat (indicated for) cancer at site s

$REGISTERED\_SUBGROUP_{g,t-k}$ = 1 if any drugs in chemical subgroup g had been registered in Belgium by the end of year t-k

= 0 if no drugs in chemical subgroup g had been registered in Belgium by the end of year t-k

3 Data

3.1 NCE Registrations in Belgium (REGISTERED)

Data on the dates when new chemical entities were registered in Belgium were obtained from the National Association of the Innovative Pharmaceutical Indus-

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.

try, which obtained the data from two sources. Ten days before the end of each month, a list of all new reimbursed products is published in the Belgian Official Journal. Also each month, the National Pharmacist Association (APB) publishes a list of new products on the market (reimbursed and non-reimbursed).

3.2 Drug Indications (IND)

Data on drug indications were obtained from Thériaque, a database of official, regulatory, and bibliographic information on all drugs available in France, intended for health professionals. This database is produced by the Centre National Hospitalier 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.[18]

3.3 Mortality Data (YPLL75, AGE_DEATH, N_DEATHS)

Data on the number of deaths, mean age at death, and years of potential life lost before ages 75, 70, and 65, by cancer site and year (1998, 1999, 2002–2010), were constructed from data contained in the WHO Mortality Database.[19] This database provides data on deaths registered in national vital registration systems, with underlying cause of death as coded by the relevant national authority. Underlying cause of death is defined as "the disease or injury which initiated the train of morbid events leading directly to death, or the circumstances of the accident or violence which produced the fatal injury" in accordance with the rules of the International Classification of Diseases (World Health Organization 2016a). Deaths are reported in 5-year age groups. I assume that deaths in an age group occur at the midpoint of the age group (e.g. deaths in age group 65–69 occur at age 67.5), and that deaths in the highest age group (age 85+) occur at age 90. These approximations result in some imprecision in the mortality estimates, but should not cause any bias in the parameter estimates.

18 Many drug databases contain information about drug indications, but this information is usually in text form only.

19 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.

3.4 Cancer Incidence Data

Data on the number of new cancer cases, by cancer site and year (1999–2012), were obtained from the Belgian Cancer Registry.

4 Empirical Results

Now I will present estimates of eq. (1). All estimated models included measures of incidence (the log of the number of patients in the relevant age group diagnosed 0–5 years earlier and their mean age), cancer site fixed effects, and year fixed effects. The coefficients on the incidence measures were not significant in any of the ln(PYLL75) or ln(PYLL65) models. As discussed earlier, this may be because the effects on mortality of increases in true incidence and increases in the ratio of measured incidence to true incidence may offset one another. The coefficient on $\ln(\text{CASES\_FLANDERS\_6YEAR}_{s,t})$ was negative and significant in the AGE_DEATH model. However, controlling for this variable had virtually no effect on estimates of β_k. To conserve space, I will report only estimates of β_k.[20]

Estimates of β_k for k=0, 1,…, 25 for all three dependent variables are plotted in Figure 6. The circles in the figures are the point estimates of β_k, and the vertical lines indicate 95% confidence intervals. In Figure 6A, the dependent variable is ln(PYLL75). With one exception (when k=6), the estimates are not statistically significant when $k \leq 13$: the confidence interval includes 0. The estimates are negative and highly significant (p-value <0.02) when $15 \leq k \leq 23$. This signifies that premature (before age 75) cancer mortality is significantly inversely related to the number of drugs ever registered 15–23 years earlier. The estimate of β_{17} is the largest and most significant. It indicates that the registration of one additional drug reduces the premature (before age 75) mortality rate by 4.0% 17 years later. Estimates of β_k for $15 \leq k \leq 23$ are reported in Table 2. The relationship across cancer sites between the number of drugs registered during 1987–1995 and the log change from 2004 to 2012 in the premature (before age 75) mortality rate is shown in Figure 7.

In Figure 6B, the dependent variable is ln(PYLL65). Figure 6B looks very similar to Figure 6A. Once again, the estimates are not statistically significant when $k \leq 13$, but they are negative and highly significant (p-value<0.02) when

20 In Table 3, I will show estimates of the incidence coefficients (γ and π) for models with one specific lag (k = 17).

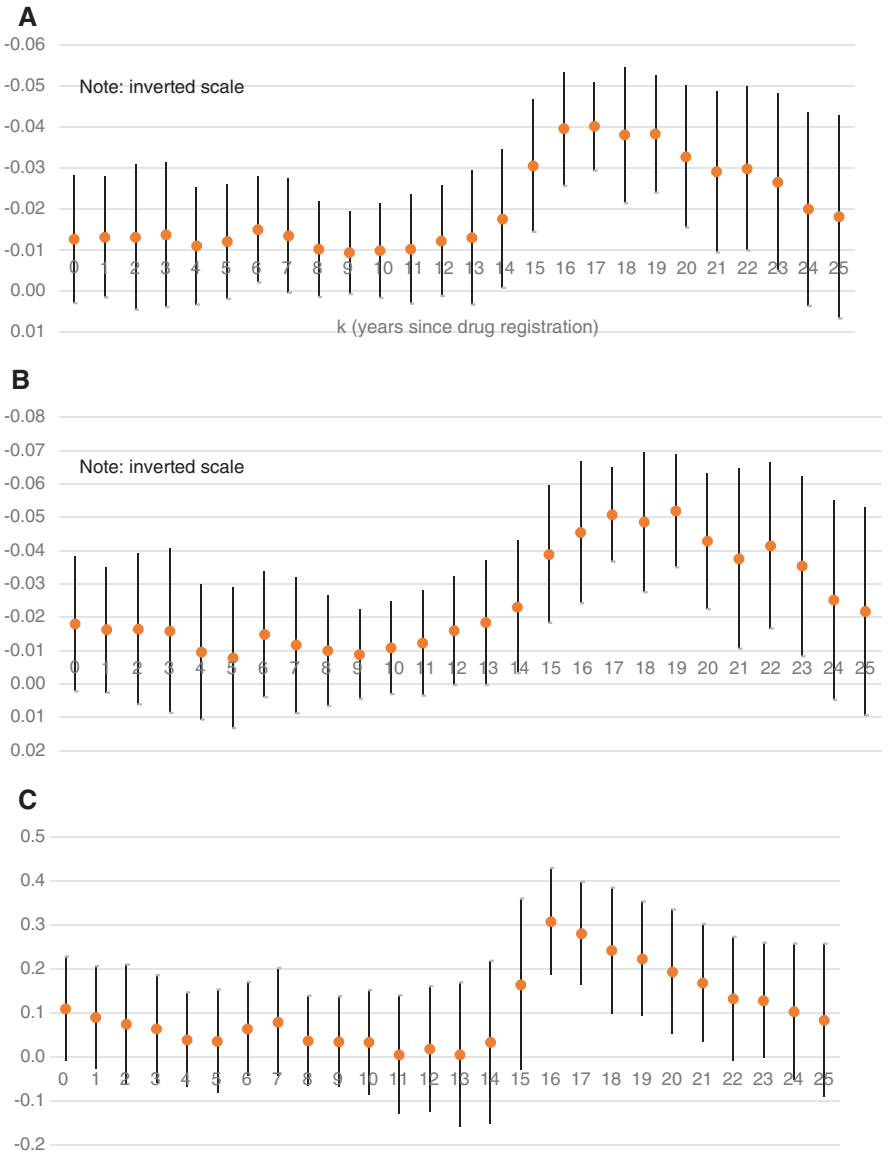

Figure 6: Estimates of β_k Parameters from eq. (1).
(A) Dependent variable: ln(YPLL75$_{s,t}$). (B) Dependent variable: ln(YPLL65$_{s,t}$). (C) Dependent variable: AGE_DEATH$_{s,t}$.

$15 \leq k \leq 23$. Also, the estimate of β_{17} is the largest and most significant. It indicates that the registration of one additional drug reduces the premature (before age 65) mortality rate by 5.1% 17 years later.

Table 2: Difference-in-differences Estimates of the Effect of the Number of Drugs to Treat Cancer that had been Registered in Belgium by the End of Year t-k on Mortality Measures in Year t.

Parameter	Estimate	Standard error	Z	Pr>|Z|
Dependent variable: $\ln(YPLL75_{s,t})$				
β_{15}	−0.031	0.008	−3.72	0.0002
β_{16}	−0.040	0.007	−5.58	<0.0001
β_{17}	**−0.040**	**0.006**	**−7.27**	**<0.0001**
β_{18}	−0.038	0.009	−4.51	<0.0001
β_{19}	−0.038	0.007	−5.26	<0.0001
β_{20}	−0.033	0.009	−3.72	0.0002
β_{21}	−0.029	0.010	−2.90	0.0037
β_{22}	−0.030	0.010	−2.93	0.0034
β_{23}	−0.027	0.011	−2.40	0.0162
Dependent variable: $\ln(YPLL65_{s,t})$				
β_{15}	−0.039	0.011	−3.68	0.0002
β_{16}	−0.045	0.011	−4.18	<0.0001
β_{17}	**−0.051**	**0.007**	**−7.05**	**<0.0001**
β_{18}	−0.049	0.011	−4.50	<0.0001
β_{19}	−0.052	0.009	−6.01	<0.0001
β_{20}	−0.043	0.010	−4.11	<0.0001
β_{21}	−0.038	0.014	−2.72	0.0066
β_{22}	−0.041	0.013	−3.26	0.0011
β_{23}	−0.035	0.014	−2.56	0.0106
Dependent variable: $\ln(AGE\_DEATH_{s,t})$				
β_{15}	0.164	0.100	1.64	0.1002
β_{16}	**0.307**	**0.062**	**4.94**	**<0.0001**
β_{17}	0.280	0.060	4.67	<0.0001
β_{18}	0.241	0.073	3.30	0.001
β_{19}	0.222	0.067	3.34	0.0009
β_{20}	0.192	0.073	2.65	0.008
β_{21}	0.168	0.069	2.44	0.0147
β_{22}	0.132	0.072	1.83	0.0675
β_{23}	0.128	0.067	1.91	0.0562

The estimates are of the β_k parameters from eq. (1). Each estimate is from a separate model. All models include measures of incidence (log of number of patients in relevant age group diagnosed 0–5 years earlier and their mean age), cancer site fixed effects, and year fixed effects. Estimates in bold are the most significant ones (they have the largest Z values).

In Figure 6C, the dependent variable is AGE_DEATH. Figure 6C looks very similar to Figures 6A and B. The estimates are positive and highly significant (p-value<0.02) when $16 \leq k \leq 21$. The estimate of β_{16} is the largest and most

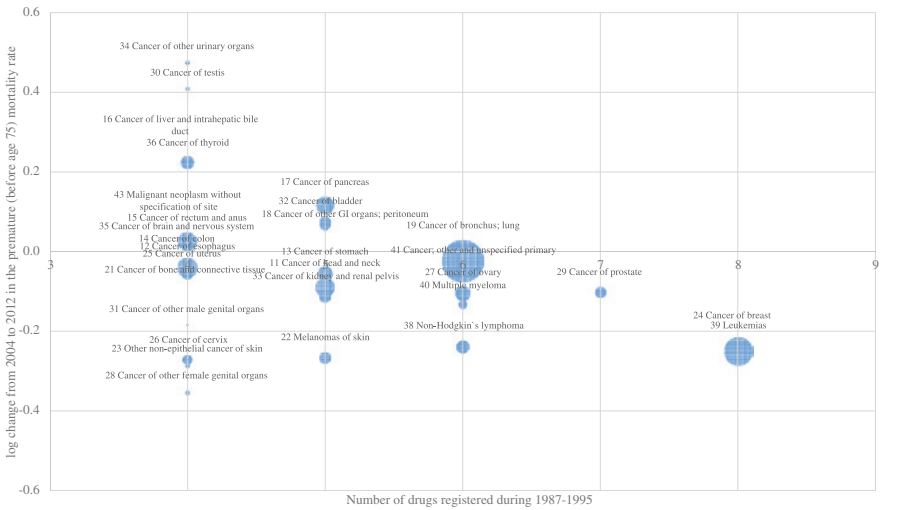

Figure 7: Relationship Across Cancer Sites between Number of Drugs Registered During 1987–1995 and Log Change From 2004 to 2012 of the Premature (before age 75) Mortality Rate. Note: Bubble size is proportional to mean premature (before age 75) mortality rate during 2004–2012.

significant. It indicates that the registration of one additional drug increases mean age at death by 0.74 months 16 years later.

As discussed above, in principle mortality from a disease might depend on the number of chemical 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. Estimates of models excluding and including the number of chemical subgroups registered until year t-17 are shown in Table 3. In models 1 and 2, the dependent variable is $\ln(PYLL75_{s,t})$. Model 1 includes $CUM\_NCE_{s,t-17}$ but not $CUM\_SUBGROUP_{s,t-17}$; model 2 includes both regressors. When $CUM\_SUBGROUP_{s,t-17}$ is added to the equation, the coefficient on $CUM\_NCE_{s,t-17}$ remains significant (although its magnitude is reduced) but the coefficient on $CUM\_SUBGROUP_{s,t-17}$ is insignificant. In models 3 and 4, the dependent variable is $\ln(PYLL65_{s,t})$. When $CUM\_SUBGROUP_{s,t-17}$ is added to the equation, neither of the the coefficients is significant. In models 5 and 6, the dependent variable is $AGE\_DEATH_{s,t}$. When $CUM\_SUBGROUP_{s,t-17}$ is added to the equation, the coefficient on $CUM\_NCE_{s,t-17}$ remains significant but the coefficient on $CUM\_SUBGROUP_{s,t-17}$ is insignificant. These estimates suggest that drugs (chemical substances) within the same class (chemical subgroup) are not

Table 3: Estimates of Models Excluding and Including the Lagged Number of Chemical Subgroups.

Model	Dependent variable		$CUM\_NCE_{s,t-17}$	$CUM\_SUBGROUP_{s,t-17}$	$ln(CASES\_FLANDERS\_6YEAR_{s,t})$	$AGE\_DX\_FLANDERS\_6YEAR_{s,t}$
1	$ln(PYLL75_{s,t})$	Estimate	**−0.0402**		0.1006	0.0006
		Z	**−7.27**		1.08	0.04
		Pr>|Z|	**<0.0001**		0.2796	0.9659
2	$ln(PYLL75_{s,t})$	Estimate	**−0.0276**	−0.0282	0.0914	−0.004
		Z	**−2.15**	−1.55	0.97	−0.28
		Pr>|Z|	**0.0316**	0.1202	0.3313	0.7832
3	$ln(PYLL65_{s,t})$	Estimate	**−0.0507**		0.0448	−0.0077
		Z	**−7.05**		0.44	−0.41
		Pr>|Z|	**<0.0001**		0.6569	0.6823
4	$ln(PYLL65_{s,t})$	Estimate	−0.0323	−0.0419	0.0315	−0.0152
		Z	−1.84	−1.74	0.31	−0.77
		Pr>|Z|	0.0652	0.0816	0.7601	0.4406
5	$AGE\_DEATH_{s,t}$	Estimate	**0.2799**		**−0.7746**	0.1266
		Z	**4.67**		**−2.85**	0.95
		Pr>|Z|	**<0.0001**		**0.0043**	0.3441
6	$AGE\_DEATH_{s,t}$	Estimate	**0.2479**	0.0819	**−0.7411**	0.1381
		Z	**2.62**	0.59	**−2.81**	1.05
		Pr>|Z|	**0.0088**	0.5582	**0.005**	0.2923

Estimates in bold are statistically significant (Z-value <0.05).

"therapeutically equivalent,"[21] i.e. they do not have essentially the same effect in the treatment of a disease or condition.

5 Discussion

Now I will use the estimates described above to calculate the number of life-years saved in 2012 by pharmaceutical innovation during the period 1987–1995. In other words, how many additional life-years would have been lost to cancer in 2012, if no drugs for treating cancer had been registered in Belgium during the period 1987–1995?

First, let us calculate the number of life-years saved before age 75. In 2012, the premature (before age 75) cancer mortality rate was 1622.8 per 100,000 people below age 75. The estimates indicate that in the absence of pharmaceutical innovation during 1987–1995, the premature mortality rate would have been about 25% higher[22] (2030.1) in 2012.[23] The Belgian population below age 75 in 2012 was 10.1 million (=101 hundred thousand), so those estimates imply that the drugs registered during 1987–1995 reduced the number of life-years lost to cancer before age 75 in 2012 by 41,238 (=(2030.1–1622.8)*101).

Next, let us calculate the number of life-years saved at any age. As noted above, the estimates of the AGE_DEATH equation implied that pharmaceutical innovation during 1988–1996 increased mean age at death in 2012 by 1.52 years.[24] There were 27,033 deaths from cancer in Belgium in 2012. Therefore, if pharmaceutical innovation did not affect the number of deaths,[25] it reduced the number of life-years lost to cancer at all ages in 2012 by 41,207 (=27,033*1.52).

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21 According to one medical dictionary, drugs that have "essentially the same effect in the treatment of a disease or condition" are therapeutically equivalent. Drugs that are therapeutically equivalent may or may not be chemically equivalent, bioequivalent, or generically equivalent. http://medical-dictionary.thefreedictionary.com/therapeutic+equivalent

22 $25\%=(1/\exp(\beta_{17}*(\text{mean}(\text{CUM\_NCE}_{1995})-\text{mean}(\text{CUM\_NCE}_{1987}))-1$. $\text{mean}(\text{CUM\_NCE}_t)$ is the weighted mean value of CUM_NCE in year t, weighted by the mean premature mortality rate during 2004-2012. As discussed above, the difference-in-differences estimate of the year fixed effects $((\delta'_{2012}-\delta'_{2004})-(\delta_{2012}-\delta_{2004}))$ yields the same result.

23 Honoré and Lleras-Muney (2006) argued that the decline in mortality rates from cardiovascular disease may be somewhat responsible for the rise in cancer mortality.

24 $1.52=\beta_{16}*(\text{mean}(\text{CUM\_NCE}_{1996})-\text{mean}(\text{CUM\_NCE}_{1988}))$.

25 The data are consistent with the hypothesis that pharmaceutical innovation did not affect the number of deaths. When $\text{MORT}_{s,t}$ in eq. (1) is defined as $\ln(\text{N\_DEATHS}_{s,t})$, estimates of β_k are far from significant.

The reduction in premature mortality is an estimate of the benefit to Belgian residents in 2012 of pharmaceutical innovation during the period 1987–1995. Now I will calculate an estimate of the (social) cost of this innovation, i.e. the 2012 expenditure on drugs registered during 1987–1995 that are used to treat cancer. According to the OECD Health database, in 2012 total pharmaceutical expenditure in Belgium was €5.94 billion. Data from IMS Health indicate that in 2010 (when total pharmaceutical expenditure in Belgium was only 1% lower, €5.88 billion), expenditure on cancer drugs (drugs in EphMRA/PBIRG anatomical class L, antineoplastic and immuno-modulating agents) was €1.04 billion: about 17% of total pharmaceutical expenditure was on cancer drugs.[26] Data from IMS Health also indicate that in 2012, expenditure on cancer drugs registered in Belgium during the period 1987–1995 accounted for only 5% of total expenditure on cancer drugs; 89% of 2012 expenditure on cancer drugs was on drugs registered after 1995. I therefore estimate that in 2012, €54 million (=5%*€1.04 billion) was spent on cancer drugs registered in Belgium during the period 1987–1995. This implies that the cost per-life-year gained in 2012 from cancer drugs registered in Belgium during the period 1987–1995 was €1311 (=€54 million/41,207).

This estimate of the cost per-life-year gained is considerably lower than estimates reported in published cancer-related cost–utility analyses. Greenberg et al. (2010) identified and reviewed 242 cancer-related cost–utility analyses published through 2007 and included in the Tufts Medical Center Cost-Effectiveness Analysis (CEA) Registry. According to their review, median reported incremental cost-effectiveness ratios (in 2008 US $) were $27,000 for breast cancer, $22,000 for colorectal cancer, $34,500 for prostate cancer, $32,000 for lung cancer, and $48,000 for hematologic cancers.[27] The weighted (by incidence in Belgium in 2012) mean of these figures is $31,016. My estimate of the cost per life-year gained from cancer drugs in Belgium could be considerably lower than the estimates obtained by Greenberg et al. (2010) for a number of reasons. First, the cost-effectiveness ratios reported in the CEA Registry are primarily if not entirely based on the prices of treatments at the time of launch. I am estimating the cost per-life-year gained in 2012 from cancer drugs registered in Belgium during the period 1987–1995; most if not all of these drugs were off-patent in 2012, so their prices were considerably lower than their prices when they were first launched. Second, half of the studies reviewed by Greenberg et al. (2010) were based on US data;

26 This fraction is considerably higher than the fraction estimated by Jönsson and Wilking (2007), who estimated that during the period 1995–1999, cancer drugs accounted for only 3.5% of total drug costs.

27 The median cost-effectiveness ratios and the distributions of cost-effectiveness ratios in their study were similar to those found in other fields of health care (p. 86).

data from IMS Health indicate that in 2014, the mean price of cancer drugs outside the US was about 55% of the mean US price. Third, the cost-effectiveness ratios reported in the CEA Registry are probably based on "list prices," i.e. they do not account for manufacturer rebates; Herper (2012) estimated that in the US, "the size of the rebate average[s] about 30% of a medicine's sales." Fourth, it is plausible that treatments that are more cost-effective are used more frequently; if so, the utilization-weighted mean cost-effectiveness ratio is lower than the unweighted mean or median cost-effectiveness ratio.

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 2016b); Belgium's per capita GDP in 2012 was $US 44,828.[28] 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. 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.

6 Summary and Conclusions

Cancer mortality declined in Belgium during the period 2004–2012, but there was considerable variation in the rate of decline across cancer sites (breast, lung, etc.). I analyzed the effect that pharmaceutical innovation had on cancer mortality in Belgium, by investigating whether the cancer sites that experienced more pharmaceutical innovation had larger subsequent declines in mortality, controlling for changes in cancer incidence. The measures of mortality analyzed – premature (before ages 75 and 65) mortality rates and mean age at death – are not subject to lead-time bias.

Premature cancer mortality rates are significantly inversely related to the cumulative number of drugs registered 15–23 years earlier. As mean utilization of drugs that have been marketed for less than 10 years is less than one fourth as great as mean utilization of drugs that have been marketed for at least a decade,

28 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.

it is not surprising that premature mortality is strongly inversely related only to the cumulative number of drugs that had been registered at least 10 years earlier. Drugs registered during the period 1987–1995 are estimated to have reduced the premature cancer mortality rate in 2012 by 20%.

Mean age at death from cancer increased by 1.17 years between 2004 and 2012. The estimates indicate that drugs registered during the period 1987–1995 increased mean age at death from cancer in 2012 by 1.52 years. The estimates also suggest that drugs (chemical substances) within the same class (chemical subgroup) are not "therapeutically equivalent," i.e. they do not have essentially the same effect in the treatment of a disease or condition.

The estimates imply that the drugs registered during 1987–1995 reduced the number of life-years lost to cancer at all ages in 2012 by 41,207. The estimated cost per-life-year gained in 2012 from cancer drugs registered in Belgium during the period 1987–1995 was €1311. This estimate is well below even the lowest estimates from other studies of the value of a life-year saved.

The analysis was based on aggregate data rather than patient-level data. Aggregated data have several strengths. 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.[29] Aggregate data are also more accessible and less expensive than patient-level data. But aggregate data may also have important weaknesses, the main of these being the potential for ecological fallacy.

This study was subject to several limitations. Data on the quality of life of cancer patients were not available, so the outcome measure analyzed was life-years, not quality-adjusted life-years. We were unable to control for the impact of non-pharmaceutical medical innovations. And the cost-effectiveness calculation was based on the implicit assumption that pharmaceutical innovation had no effect on non-pharmaceutical medical expenditure; previous research (e.g. Lichtenberg 2014c) indicates that pharmaceutical innovation tends to reduce hospital expenditure.

The largest reductions in premature mortality occur 15–23 years after drugs are registered, when their utilization increases significantly. This suggests that, if Belgium is to obtain substantial additional reductions in premature cancer

29 Stukel et al. (2007) argue that comparisons of outcomes between patients treated and untreated in observational studies may be biased due to differences in patient prognosis between groups, often because of unobserved treatment selection biases. Jalan and Ravallion (2001) argued that "aggregation to village level may well reduce measurement error or household-specific selection bias" (p. 10).

mortality in the future (15 or more years from now) at a modest cost, pharmaceutical innovation (registration of new drugs) is needed today.

During the period 1982–2015, the number of new cancer drugs launched in Belgium was more than 10% lower than the number launched in a dozen other countries: 97 were launched in Belgium, while more than 120 were launched in the USA, Germany, Finland, and Austria.[30] This may be partly attributable to international differences in price regulation. Danzon et al. (2005) analyzed the effect of price regulation on delays in launch of new drugs, and found that countries with lower expected prices have fewer launches and longer launch delays, controlling for per capita income and other country and firm characteristics.

Funding: Association générale de l'industrie du medicament (pharma.be).

Appendix A

The relationship between cancer incidence in Flanders and cancer incidence in Belgium as a whole, 2004–2012

To determine whether there was a close relationship across cancer sites between growth in the number of patients diagnosed in Flanders and growth in the number of patients diagnosed in Belgium as a whole, I estimated the following model:

$$\ln(\text{CASES\_FLANDERS}_{s,t}) = \beta_1 \ln(\text{CASES\_BELGIUM}_{s,t}) + \alpha_s + \delta_t + \varepsilon_{s,t} \quad \text{(A1)}$$

where

$\text{CASES\_FLANDERS}_{s,t}$ = the number of patients diagnosed with cancer at site s in year t in Flanders

$\text{CASES\_BELGIUM}_{s,t}$ = the number of patients diagnosed with cancer at site s in year t in Belgium.

I estimated eq. (A1) using annual data during the period 2004–2012 by weighted least squares, weighting by $(1/9)\sum_t \text{CASES\_FLANDERS}_{s,t}$. The estimate of β_1 was:

Parameter	Estimate	Standard error	Z	Pr>|Z|
β_1	0.9737	0.0582	16.72	<0.0001

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

To determine whether there was a close relationship across cancer sites between the change in the mean age at which patients were diagnosed in Flanders and the change in the mean age at which patients were diagnosed in Belgium as a whole, I estimated the following model:

$$AGE\_DX\_FLANDERS_{s,t} = \beta_2 AGE\_DX\_BELGIUM_{s,t} + \alpha_s + \delta_t + \varepsilon_{s,t} \quad (A2)$$

where

$AGE\_DX\_FLANDERS_{s,t}$ = the mean age at which patients were diagnosed with cancer at site s in year t in Flanders

$AGE\_DX\_BELGIUM_{s,t}$ = the mean age at which patients were diagnosed with cancer at site s in year t in Belgium.

I estimated eq. (A2) using annual data during the period 2004–2012 by weighted least squares, weighting by $CASES\_FLANDERS_{s,t}$. The estimate of β_2 was:

Parameter	Estimate	Standard Error	Z	Pr>|Z|
β_2	0.8974	0.06	14.95	<0.0001

These estimates indicate that during the period 2004–2012 there were very close relationships across cancer sites between both (1) growth in the number of patients diagnosed in Flanders and growth in the number of patients diagnosed in Belgium as a whole, and (2) the change in the mean age at which patients were diagnosed in Flanders and the change in the mean age at which patients were diagnosed in Belgium as a whole.

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