The impact of pharmaceutical innovation on the longevity and hospitalization of New Zealand cancer patients, 1998-2012

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Working paper

28 July 2016

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This research was supported by Medicines New Zealand.

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We analyze the effect that pharmaceutical innovation—the introduction and use of new drugs used to treat cancer—had on the longevity and hospitalization of New Zealand cancer patients during the period 1998-2012, by investigating whether the cancer sites (e.g. breast, prostate, colon) that experienced more pharmaceutical innovation had larger subsequent declines in premature (before age 70 or 65) mortality and hospitalization rates and larger subsequent increases in 5-year survival rates, controlling for changes in incidence.

Premature (before age 70) mortality is inversely related to the number of drugs ever approved 5 to 16 years earlier. The finding of a lag is not surprising, since utilization of a drug tends to be quite low in the years immediately following its approval. Premature mortality is most strongly inversely related to the number of drugs ever approved 14 years earlier. The approval of one additional drug for a cancer site reduces premature mortality from cancer at that site by about 5% 14 years later.

The 5-year survival rate is significantly positively related to the number of drugs ever approved 7 to 25 years earlier, and is most strongly positively related to the number of drugs ever approved 13 years earlier. Between 1998 and 2010, the 5-year survival rate for all adult cancers increased from 57.7% to 63.3%. The estimates indicate that if no new drugs had been approved during 1985-1997, the 5-year survival rate would not have increased between 1998 and 2010.

The number of publicly-funded hospital days is significantly inversely related to the number of drugs ever approved 5 to 11 years earlier; it is most strongly inversely related to the number of drugs ever approved 9 years earlier. The approval of one additional drug for a cancer site is estimated to reduce the number of publicly-funded inpatient hospital days for cancer at that site by about 5.6% 9 years later.

Overall, the estimates 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.

Drugs for treating cancer that were approved in New Zealand during the period 1986-1997 are estimated to have reduced the number of life-years lost to cancer before age 70 in 2011 by 10,556. Even if we don't account for the apparent reduction in hospital utilization, 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. When the reduction in hospital utilization is taken into account, the evidence indicates that pharmaceutical innovation was cost-saving.

During the period 1986-2015, the number of cancer drugs launched in New Zealand was only half the number launched in the U.S. (68 vs. 139). Evidence from U.S. data indicates that the drugs that were not launched in New Zealand were no less valuable than the drugs that were launched in New Zealand.

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I. Introduction

A variety of statistics indicate that the longevity of New Zealand cancer patients has increased since the year 2000 or thereabouts. Between 1998 and 2010, the 5-year survival rate for all adult cancers increased from 57.7% to 63.3%, and the 5-year survival rate for all childhood (ages 0-14) cancers increased from 71.6% to 84.5% (Ministry of Health (2015a)). In principle, these increases could overstate true survival gains due to earlier diagnosis and increasing lead-time bias.[1] But other indicators that are not affected by changing patterns of diagnosis also point to longevity gains. Between 2000 and 2011, the age-standardized cancer mortality rate declined by 13.8%, from 146.1 to 125.9 per 100,000 people (Ministry of Health (2015b)), and the premature (before age 70) cancer mortality rate (the number of potential years of life lost due to malignant neoplasms before age 70 per 100,000 people below age 70) declined 19.4% (from 1127.5 to 908.6).[2] In principle, this could be attributable to declining cancer incidence. The age-standardized cancer incidence rate declined between 2000 and 2011, but by less than half as much (9.3%) as the premature mortality rate.[3]

Although the longevity of New Zealand cancer patients has increased overall, there has been considerable variation across cancer sites (e.g. breast, prostate, colon) in the size of the increase. For example, the increase in the 5-year survival rate for prostate cancer (from 81.9% to 91.1%) was much greater than the increase for Hodgkin lymphoma (from 83.0% to 84.5%). Figure 1 shows the percentage change between 2000 and 2011 in the premature (before age 70) mortality rate for the 12 cancers with the largest average premature mortality rates during that period. Five of the 12 cancer sites had declines in the premature mortality rate of at least 16%, but four sites had increases of at least 12%.

In this paper, we will analyze the effect that pharmaceutical innovation—the introduction and use of new drugs used to treat cancer—had on the longevity and hospitalization of New

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[1] 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).

[2] Source: OECD (2016). *OECD Health Statistics 2015 online database,* http://stats.oecd.org/index.aspx?DataSetCode=HEALTH_STAT

[3] Moreover, mortality is likely to depend on *lagged* incidence, and the age-standardized cancer incidence rate declined more slowly (by 6.4%) between 1994 and 2005 than it did between 2000 and 2011.

Zealand cancer patients during the period 1998-2012. Between 1980 and 2000, the number of drugs used to treat cancer ever approved in New Zealand almost doubled, from 34 to 67; by 2015, 97 drugs used to treat cancer had been approved in New Zealand.

The analysis will be performed using a difference-in-differences research design based on aggregate data—longitudinal data on 23 cancer sites[4]. In essence, we will investigate whether the cancer sites that experienced more pharmaceutical innovation had larger subsequent declines in premature mortality and hospitalization rates and larger subsequent increases in 5-year survival rates, controlling for changes in incidence. As shown in Figure 2, there has been considerable variation across cancer sites in the number of new drugs. During the period 1990-2015, only 3 new drugs for treating Hodgkin lymphoma were approved, while 19 new drugs for treating breast cancer were approved.[5]

In Section II, we describe an econometric model of cancer patient outcomes. The data sources used to construct the data to estimate this model 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. Cancer patient outcomes 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 models that we will estimate may be considered health production functions, in which the outcome is an indicator of health output, and the cumulative number of drugs approved is analogous to the stock of ideas.[6] The model will be of the following form:

$$OUTCOME_{s,t} = \beta_k \, CUM\_NCE_{s,t-k} + \gamma \ln(INCIDENCE_{s,t}) + \alpha_s + \delta_t + \varepsilon_{s,t} \qquad (1)$$

[4] The 23 cancer sites are all cancer sites defined in the New Zealand Ministry of Health historical summary.
[5] Drugs for treating 3 different types of cancer approved in New Zealand are shown in Appendix Table 1.
[6] New drug approvals can improve outcomes for 2 reasons. First, the quality of newer products may be higher than the quality of older products, as in "quality ladder" models (see Grossman and Helpman (1991)). Second, "one of the principal means, if not the principal means, through which countries benefit from international trade is by the expansion of varieties" (Broda and Weinstein (2004)).

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

$\ln(YPLL70_{s,t})$ = the log of the number of years of potential life lost before age 70[7] due to cancer at site s in year t (t = 2000, 2011)

$\ln(YPLL65_{s,t})$ = the log of the number of years of potential life lost before age 65 due to cancer at site s in year t (t = 2000, 2011)

$\ln(SURV5\%_{s,t}/(1 - SURV5\%_{s,t}))$ = the log-odds of surviving at least 5 years after diagnosis with cancer at site s in year t[8] (t = 1998, 2010)

$\ln(HOSP\_DAYS_{s,t})$ = the log of the number of publicly-funded[9] inpatient hospital days for cancer at site s in year t (t = 2004, 2012)

and

$CUM\_NCE_{s,t-k}$ = $\sum_d IND_{ds}\ APPROVED_{d,t-k}$ = the number of new chemical entities (drugs) to treat cancer at site s that had been approved in New Zealand 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

$APPROVED_{d,t-k}$ = 1 if drug d was approved in New Zealand by the end of year t-k

= 0 if drug d was not approved in New Zealand by the end of year t-k

$INCIDENCE_{s,t}$ = the average annual number of patients diagnosed with cancer at site s in years t-10 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 outcomes[10] and for stable between-disease differences in outcomes. When $OUTCOME_{s,t} = \ln(YPLL70_{s,t})$, a

[7] 70 is the age threshold used to measure premature mortality in the OECD Health Database.
[8] $SURV5\%_{s,t}$ = the fraction of people diagnosed with cancer at site s in year t who were alive 5 years after diagnosis.
[9] The vast majority (94%) of hospital discharges are publicly funded. In 2012-2013, there were 1.1 million publicly-funded discharges, and only 70 thousand privately-funded discharges.
[10] Some trends may have *increased* premature mortality. Between 1997 and 2014, the fraction of the New Zealand population that was obese increased from 18.8% to 29.9%. (These are self-reported figures as reported in OECD Health Statistics 2015**.)**

negative and significant estimate of β_k in eq. (1) would signify that cancer sites for which there was more pharmaceutical innovation had larger declines in premature (before age 70) mortality. When $OUTCOME_{s,t} = \ln(SURV5\%_{s,t}/(1 - SURV5\%_{s,t}))$, a positive and significant estimate of β_k in eq. (1) would signify that cancer sites for which there was more pharmaceutical innovation had larger increases in the 5-year survival rate.

The standard errors of eq. (1) will be clustered within cancer sites. The data exhibit heteroscedasticity. For example, cancer sites with larger mean premature mortality during 2000-2011 had smaller (positive and negative) annual percentage fluctuations in $YPLL70_{s,t}$. Eq. (1) will therefore be estimated by weighted least-squares. The weights used for each of the outcome measures are as follows:[11]

Outcome measure	Weight
$\ln(YPLL70_{s,t})$	$\Sigma_t\ YPLL70_{s,t}$
$\ln(YPLL65_{s,t})$	$\Sigma_t\ YPLL65_{s,t}$
$\ln(SURV5\%_{s,t}/(1 - SURV5\%_{s,t}))$	$N\_CASES_{s,t}$
$\ln(HOSP\_DAYS_{s,t})$	$\Sigma_t\ HOSP\_DAYS_{s,t}$

Due to data limitations, the number of new chemical entities and incidence are the only disease-specific, time-varying, explanatory variables in eq. (1). But both a patient-level U.S. study and a longitudinal country-level study have shown that controlling for numerous other potential determinants of longevity does not reduce, and may even increase, the estimated effect of pharmaceutical innovation. The study based on patient-level data (Lichtenberg (2013)) found that controlling for race, education, family income, insurance coverage, Census region, BMI, smoking, the mean year the person started taking his or her medications, and over 100 medical conditions had virtually no effect on the estimate of the effect of pharmaceutical innovation (the change in drug vintage) on life expectancy. The study based on longitudinal country-level data (Lichtenberg (2014d)) found that controlling for ten other potential determinants of longevity change (real per capita income, the unemployment rate, mean years of schooling, the urbanization rate, real per capita health expenditure (public and private), the DPT immunization

[11] $N\_CASES_{s,t}$ = the number of patients diagnosed with cancer at site s in year t.

rate among children ages 12-23 months, HIV prevalence and tuberculosis incidence) *increased* the coefficient on pharmaceutical innovation by about 32%.

Failure to control for non-pharmaceutical medical innovation (e.g. innovation in diagnostic imaging, surgical procedures, and medical devices) is also unlikely to bias estimates of the effect of pharmaceutical innovation on premature mortality, for two reasons. First, more than half of U.S. funding for biomedical research came from pharmaceutical and biotechnology firms (Dorsey et al (2010)). 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 (2015) says that it "has played a vital role in cancer drug discovery and development, and, today, that role continues." Second, previous research based on U.S. data (Lichtenberg (2014a, 2014b)) indicates that non-pharmaceutical medical innovation is not positively correlated across diseases with pharmaceutical innovation.

Eq. (1) controls for a measure of incidence: the number of patients diagnosed 0-10 years preceding the year in which the outcome is measured. 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 $I = (I / I^*) \times I^*$, and $\ln(I) = \ln(I / I^*) + \ln(I^*)$. Measured cancer 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.[12] 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 don't find a significant effect of measured incidence on premature mortality.

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12 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)).

Estimation of eq. (1) enables determination of how much of the change in outcomes during the sample period can be attributed to the introduction of new drugs. The expression ($\delta_{2011} - \delta_{2000}$) indicates the 2000-2011 change 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 $CUM\_NCE_{s,t-k}$, and that the year fixed effects from that equation are denoted by δ'_t. Then ($\delta'_{2011} - \delta'_{2000}$) indicates the 2000-2011 change in log premature mortality, not holding constant the number of drugs, i.e., in the presence of pharmaceutical innovation, and ($\delta'_{2011} - \delta'_{2000}$) - ($\delta_{2011} - \delta_{2000}$) is an estimate of the 2000-2011 change in log premature mortality attributable to pharmaceutical innovation. In the estimation procedure that we use (SAS GENMOD), δ'_{2011} and δ_{2011} are normalized to zero, so (δ_{2000} - δ'_{2000}) is an estimate of the 2000-2011 change in log premature mortality attributable to pharmaceutical innovation. (δ_{2000} - δ'_{2000}) is equivalent to β_k * ($CUM\_NCE._{,2011-k}$ - $CUM\_NCE._{,2000-k}$), where $CUM\_NCE._{,t-k}$ is the mean of $CUM\_NCE_{s,t-k}$.

The measure of pharmaceutical innovation in eq. (1)—the number of chemical substances previously approved 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 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.[13] Unfortunately, measurement of $VINTAGE_{st}$ is infeasible: even though data on the total quantity of each drug sold in each year ($Q_{d.t} = \Sigma_s Q_{dst}$) are available, many drugs are used to treat multiple diseases, and from the data available to us it was not possible to determine the quantity of drug d *used to treat cancer at site s* in year t.[14] However, Lichtenberg (2014a) showed that, in France during the period 2000-2009,

[13] 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)).

[14] 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 New Zealand.

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.

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 approved in New Zealand 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.[15] One would expect there to be a substantial lag, for two reasons.

The first reason is that new drugs diffuse gradually—they won't be used widely until years after approval. Figure 3 shows data on the mean annual number of standard units[16] of cancer drugs sold in New Zealand during 2004-2015, by age of drug, i.e. by the number of years since the drug was approved in New Zealand. Mean utilization of drugs that are 5-9 years old is almost 11 times as great as mean utilization of drugs that are 0-4 years old; mean utilization of drugs that are 10-14 years old is 21 times as great as mean utilization of drugs that are 0-4 years old. 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. Moreover, the entire cost of very new drugs is borne entirely by patients: Barber and Sheehy (2015) noted that the mean lag between regulatory approval of a drug in New Zealand and its inclusion in the New Zealand Pharmaceutical Schedule (a list of the prescription medicines and therapeutic products subsidized by the Government) is 23.7 months. A second factor may be that it takes time 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

[15] 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.)

[16] 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.

potential factor is that older drugs are more likely to have supplemental indications, i.e. indications approved after the drug was initially approved, than new drugs.[17]

The second reason for a long lag from drug approval to mortality reduction is that there is usually a substantial lag from diagnosis (when drug treatment is likely to begin and be most intensive) to death. The 5-year observed survival rate of all adult patients diagnosed with cancer in 1998 was 57.7%.

The effect of a drug's approval 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," respectively.[18]

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[17] The measure of pharmaceutical innovation, $CUM\_NCE_{s,t-k} = \sum_d IND_{ds} APPROVED_{d,t-k}$, 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 U.S. 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.

[18] 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

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

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

$IND\_SUBGROUP_{gs}$ = 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

$APPROVED\_SUBGROUP_{g,t-k}$ = 1 if any drugs in chemical subgroup g had been approved in New Zealand by the end of year t-k

= 0 if no drugs in chemical subgroup g had been approved in New Zealand by the end of year t-k

III. Data

Mortality data (YPLL70, YPLL65). Data on the number of years of potential life lost before ages 70 and 65, by cancer site and year (2000-2011), were constructed from data contained in the WHO (World Health Organization) Mortality Database.[19] This database provides data on deaths approved 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)).

Cancer survival data (SURV5). Data on 5-year survival rates, by cancer site and year (1994-2011), were obtained from Ministry of Health (2015a).

L01AA09 bendamustine

[19] Mortality data are reported in 5-year age groups. We assume that deaths in a 5-year age group occur at the midpoint of the age group. For example, we 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. These approximations result in some imprecision in the mortality estimates, but should not cause any bias in the parameter estimates.

Publicly-funded inpatient hospital days (HOSP_DAYS). Data on the number of publicly-funded inpatient hospital days in 2004-2005 and 2012-2013 were obtained from Ministry of Health (2015c, 2015d). The number of hospital days equals the number of hospital discharges times mean length of stay.

Cancer incidence data (INCIDENCE). Data on the number of new cancer cases, by cancer site and year (1948-2012), were obtained from Ministry of Health (2015b).

NCE approvals in New Zealand (APPROVED). We obtained data on the earliest dates at which molecules were approved by the New Zealand Medicines and Medical Devices Safety Authority, Medsafe, from that Authority's website. We collected these data for all molecules contained in medicines categorized as antineoplastic and immunomodulating agents under the European Pharmaceutical Market Research Association (EphMRA) Anatomical Therapeutic Chemical (ATC) classification system. The earliest approval date in New Zealand for any medicine containing the molecules of interest was obtained by performing a wildcard search for the molecule name using the online Medsafe Product/Application search tool. Results where the molecule was not listed as an active ingredient were omitted, and the earliest approval date in the remaining results recorded.

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.[20]

Pharmac (the New Zealand government agency that decides which pharmaceuticals to publicly fund in New Zealand) may not subsidize a drug for all of the indications listed in Thériaque. For instance, a medicine might be indicated for use against both breast and lung cancer in the Thériaque database, but is only subsidized for use against breast cancer in New Zealand. Some patients may pay out of pocket to use it for a clinical indication different from the one funded by Pharmac, but its overall utilization, and impact on health outcomes, would be lower than if it were available at a subsidized price for both sites.

Unit sales of cancer drugs. Data on total market unit sales of cancer drugs in New Zealand, by molecule and year (2004 – 2015), were obtained from IMS Health. Each molecule identified in

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

the data provided by IMS Health was matched to the corresponding five level WHO ATC code using the searchable WHO ATC/DDD index 2016. A small number of molecules including abatacept, alefacept, anakinra, apremilast, leflunomide, tocilizumab and vedolizumab, are included as antineoplastic and immunomodulating agents under the WHO ATC classification system but not the EphMRA system; therefore, were not included in the analysis.

IV. Empirical results

Now we will present estimates of eq. (1). All estimated models included $\ln(INCIDENCE_{s,t})$ (the log of the average annual number of patients diagnosed with cancer at site s in years t-10 to year t), cancer site fixed effects, and year fixed effects. The coefficients on the incidence measures were not significant in any of the premature mortality or survival rate 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. To conserve space, we will report only estimates of β_k.

Estimates of β_k from the premature mortality and survival rate models are shown in Table 1 and plotted in Figure 4. The left side of Table 1 and the top chart in Figure 4 show estimates from models of the first premature mortality measure, i.e. potential years of life lost before age 70 in 2000 and 2011. When $k < 5$, estimates of β_k are not statistically significant, which indicates that premature (before age 70) mortality in year t is unrelated to the number of drugs ever registered by years t-4 to t. However, estimates of β_k are negative and statistically significant for $5 \leq k \leq 16$: premature (before age 70) mortality is inversely related to the number of drugs ever approved 5 to 16 years earlier. The finding of a lag is not surprising, since as discussed earlier utilization of a drug tends to be quite low in the years immediately following its approval. Premature (before age 70) mortality is most strongly inversely related to the number of drugs ever approved 14 years earlier. The estimate of β_{14} implies that the approval of one additional drug for a cancer site reduces premature mortality from cancer at that site by about 5% 14 years later.

The middle of Table 1 and the middle chart in Figure 4 show estimates from models of the second premature mortality measure, i.e. potential years of life lost before age 65 in 2000 and 2011. Cancer mortality before age 65 in year t is unrelated to the number of drugs ever approved

in year t-4 to year t, but is significantly inversely related to the number of drugs ever approved in every year from year t-22 to year t-5. Premature (before age 65) mortality is most strongly inversely related to the number of drugs ever approved 12 years earlier.

The right of Table 1 and the bottom chart in Figure 4 show estimates from models of the log-odds of surviving 5 years after diagnosis in 1998 and 2010. The 5-year survival rate in year t is unrelated to the number of drugs ever approved in year t-6 to year t, but is significantly positively related to the number of drugs ever approved in every year from year t-25 to year t-7. The 5-year survival rate is most strongly positively related to the number of drugs ever approved 13 years earlier. The relationship across cancer sites between the number of new drugs approved during 1985-1997 and the 1998-2010 change in the log-odds of 5-year survival is shown in Figure 5.[21] This relationship implies that if no new drugs had been approved during 1985-1997, the 5-year survival rate would not have increased between 1998 and 2010; it might have even decreased slightly, although the predicted (counterfactual) decline is not statistically significantly different from zero.

Estimates of β_k from the publicly-funded hospital days models are shown and plotted in Table 2. The number of publicly-funded hospital days in year t is unrelated to the number of drugs ever approved in year t-4 to year t, but is significantly inversely related to the number of drugs ever approved in every year from year t-11 to year t-5. The number of publicly-funded hospital days is most strongly inversely related to the number of drugs ever approved 9 years earlier. The estimate of β_9 implies that the approval of one additional drug for a cancer site reduces the number of publicly-funded inpatient hospital days for cancer at that site by about 5.6% 9 years later. The relationship across cancer sites between the number of new drugs approved during 1995-2003 and the 2004-2012 log change in the number of publicly-funded inpatient hospital days is shown in Figure 6.

As discussed above, in principle the outcomes of patients with a disease might depend on the number of chemical *subgroups* that have previously been approved to treat the disease rather than, or in addition to, the number of chemical *substances* (drugs) that have previously been approved to treat the disease. Estimates of the effects of the number of drugs, the number of chemical subgroups, or both, on outcomes are shown in Table 3. In models 1-3 of Table 3, the

[21] Controlling for the change in incidence had essentially no effect on this estimated relationship.

dependent variable is $\ln(YPLL70_{s,t})$, and the assumed lag from cumulative drugs and/or chemical subgroups to premature mortality is 14 years. Model 1 includes the lagged number of drugs ($CUM\_NCE_{s,t-14}$) but not the lagged number of chemical subgroups ($CUM\_SUBGROUP_{s,t-14}$); this estimate is the same as the one shown in Table 1. Model 2 includes $CUM\_SUBGROUP_{s,t-14}$ but not $CUM\_NCE_{s,t-14}$. The coefficient on $CUM\_SUBGROUP_{s,t-14}$ is negative and significant, but the relationship between $CUM\_SUBGROUP_{s,t-14}$ and $\ln(YPLL70_{s,t})$ is weaker than the relationship between $CUM\_NCE_{s,t-14}$ and $\ln(YPLL70_{s,t})$. Model 3 includes both $CUM\_SUBGROUP_{s,t-14}$ and $CUM\_NCE_{s,t-14}$. The coefficient on $CUM\_SUBGROUP_{s,t-14}$ is far from significant, and the estimate of the coefficient on $CUM\_NCE_{s,t-14}$ is almost identical to the estimate in model 1.

In models 4-6 of Table 3, the dependent variable is $\ln(YPLL65_{s,t})$, and the assumed lag from cumulative drugs and/or chemical subgroups to premature mortality is again 14 years. The findings are similar to those from models 1-3: premature mortality is inversely related to $CUM\_NCE_{s,t-14}$ but not to $CUM\_SUBGROUP_{s,t-14}$, conditional on $CUM\_NCE_{s,t-14}$. As shown in models 7-9, the log-odds of surviving 5 years after diagnosis is positively related to $CUM\_NCE_{s,t-13}$ but not to $CUM\_SUBGROUP_{s,t-13}$, conditional on $CUM\_NCE_{s,t-13}$.

In models 10-12 of Table 3, the dependent variable is $\ln(HOSP\_DAYS_{s,t})$, and the assumed lag from cumulative drugs and/or chemical subgroups to hospital days is 9 years. The coefficient on $CUM\_SUBGROUP_{s,t-9}$ is negative and significant in model 11, but the relationship between $CUM\_SUBGROUP_{s,t-9}$ and $\ln(HOSP\_DAYS_{s,t})$ is weaker than the relationship between $CUM\_NCE_{s,t-9}$ and $\ln(HOSP\_DAYS_{s,t})$. When both $CUM\_SUBGROUP_{s,t-9}$ and $CUM\_NCE_{s,t-9}$ are included (in model 12), neither coefficient is significant; presumably due to high multicollinearity between these two measures of pharmaceutical innovation. Overall, the estimates in Table 3 suggest that drugs (chemical substances) within the same class (chemical subgroup) are not "therapeutically equivalent,"[22] i.e. they do not have essentially the same effect in the treatment of a disease or condition.

[22] 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

V. Discussion

Now we will use the estimates described above to calculate the number of life-years gained in 2011 by pharmaceutical innovation during the period 1986-1997. In other words, how many additional life-years would have been lost to cancer in 2011, if no drugs for treating cancer had been approved in New Zealand during the period 1986-1997?

According to the OECD, the premature (before age 70) cancer mortality rate in 2011 was 908.6 per 100,000 population below age 70. The population below age 70 in 2011 was 3,997,660, so 36,325 (= 908.6 * (3,997,660 / 100,000)) potential years of life were lost to cancer before age 70 in 2011. The estimates indicate if no drugs for treating cancer had been approved in New Zealand during the period 1986-1997, the number of potential years of life lost to cancer before age 70 in 2011 would have been 29% higher: 46,881.[23] Hence drugs for treating cancer that were approved in New Zealand during the period 1986-1997 are estimated to have reduced the number of life-years lost to cancer before age 70 in 2011 by 10,556.

As shown in Table 4, the cost of community and hospital pharmacy dispensing to cancer patients in 2008 was $51 million. (As shown in Table 5, this is considerably higher than PHARMAC expenditure on chemotherapeutic agents in 2008: $21.1 million.) As shown in Table 6, 57% of people diagnosed with cancer in 2012 were below the age of 70, so we estimate that the cost of community and hospital pharmacy dispensing to cancer patients below age 70 in 2008 was $29 million (= 57% * $51 million).

This is the cost of *all* cancer drugs, not just the cost of drugs for treating cancer that were approved in New Zealand during the period 1986-1997. Data from IMS Health indicate that in 2015, drugs approved during 1990-2001 accounted for 17% of total cancer drug expenditure. Hence the cost in 2008 of cancer drugs approved in New Zealand during the period 1983-1994 for patients below age 70 might have been $5 million (= 17% * $29 million). The ratio of this cost to the number of life-years gained from them is $467 (= $5 million / 10,556).

[23] The 2000-2011 change in log premature cancer mortality, controlling for (holding constant) the number of drugs and cancer incidence ($\delta_{2011} - \delta_{2000}$) is 0.280. The 2000-2011 change in log premature mortality, not holding constant the number of drugs ($\delta'_{2011} - \delta'_{2000}$) is 0.025. Hence the estimate of the 2000-2011 change in log premature mortality attributable to pharmaceutical innovation (($\delta'_{2011} - \delta'_{2000}$) - ($\delta_{2011} - \delta_{2000}$)) is -0.255. We estimate that in the absence of new drug approvals during 1986-1997, would have been (1 / exp(-0.255)) * 36,325 = 46,881.

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)); New Zealand's per capita GDP in 2013 was $US 41,555.[24] 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.

Therefore, even if we don't account for the apparent reduction in hospital utilization, 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. When the reduction in hospital utilization is taken into account, the evidence indicates that pharmaceutical innovation was *cost-saving*. The estimates in Table 2 imply that in the absence of 8 years of previous pharmaceutical innovation, the number of cancer patient inpatient days in 2011 would have been 17% higher. It seems reasonable to assume that in the absence of 11 years of innovation, the number of cancer patient inpatient days in 2011 would have been 23% (= (11/8) * 17%) higher.[25] As shown in Table 4, the cost of public hospital discharges of cancer patients in 2008 was $215 million. Since 57% of people diagnosed with cancer in 2012 were below the age of 70, we estimate that the cost of public hospital discharges of cancer patients below age 70 in 2008 was $123 million. The estimates indicate that in the absence of 11 years of innovation, the cost of public hospital discharges of cancer patients below age 70 in 2008 would have been $28 million (= 23% * $123 million) higher. This is almost the same as the cost of *all* cancer drugs dispensed to cancer patients below age 70 in 2008 ($29 million), and presumably much larger than the cost of drugs approved during a previous 11-year period.

Data from the IMS Health New Product Focus database indicate that during the period 1986-2015, the number of cancer drugs launched in New Zealand was only half the number launched in the U.S. (68 vs. 139). In principle, it is possible that the drugs that were launched in

[24] 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.

[25] The length of the sample period for the premature mortality estimate was 11 years; the length of the sample period for the hospital days estimate was 8 years.

the U.S. but not launched in New Zealand provide little or no benefit to patients, and therefore that New Zealand patients were not harmed by more limited access to new cancer drugs. We tested this hypothesis by estimating a model similar to eq. (1) using U.S. data on outcomes and drug approvals, and by distinguishing between the effects on U.S. premature cancer mortality of (1) drugs launched in both the U.S. and New Zealand, and (2) drugs launched in the U.S. and not launched in New Zealand. We found that the two sets of drugs had almost identical (negative) effects on U.S. cancer mortality.[26] This indicates that, in general, the drugs that were not launched in New Zealand were no less valuable than the drugs that were launched in New Zealand.

VI. Summary and conclusions

We have analyzed the effect that pharmaceutical innovation—the introduction and use of new drugs used to treat cancer—had on the longevity and hospitalization of New Zealand cancer patients during the period 1998-2012, by investigating whether the cancer sites that experienced more pharmaceutical innovation had larger subsequent declines in premature (before age 70 or 65) mortality and hospitalization rates and larger subsequent increases in 5-year survival rates, controlling for changes in incidence.

Premature (before age 70) mortality is inversely related to the number of drugs ever approved 5 to 16 years earlier. The finding of a lag is not surprising, since utilization of a drug tends to be quite low in the years immediately following its approval. Premature (before age 70) mortality is most strongly inversely related to the number of drugs ever approved 14 years

[26] The table below shows estimates of the effects of drug approvals on U.S. premature (before age 75) cancer mortality:

Model	Parameter	Estimate	Standard Error	Z	Pr > |Z|
1	cum_drug (all drugs)	-0.0239	0.0061	-3.93	<.0001
2	cum_nz (drugs launched in both the U.S. and NZ)	-0.0246	0.0122	-2.03	0.0428
2	cum_not_nz (drugs launched in the U.S. and not launched in NZ)	-0.0236	0.0068	-3.48	0.0005

earlier. The approval of one additional drug for a cancer site reduces premature mortality from cancer at that site by about 5% 14 years later.

The 5-year survival rate is significantly positively related to the number of drugs ever approved 7 to 25 years earlier, and is most strongly positively related to the number of drugs ever approved 13 years earlier. Between 1998 and 2010, the 5-year survival rate for all adult cancers increased from 57.7% to 63.3%. The estimates indicate that if no new drugs had been approved during 1985-1997, the 5-year survival rate would not have increased between 1998 and 2010; it might have even decreased slightly, although the predicted (counterfactual) decline is not statistically significantly different from zero.

The number of publicly-funded hospital days is significantly inversely related to the number of drugs ever approved 5 to 11 years earlier; it is most strongly inversely related to the number of drugs ever approved 9 years earlier. The approval of one additional drug for a cancer site is estimated to reduce the number of publicly-funded inpatient hospital days for cancer at that site by about 5.6% 9 years later.

Overall, the estimates 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.

Drugs for treating cancer that were approved in New Zealand during the period 1986-1997 are estimated to have reduced the number of life-years lost to cancer before age 70 in 2011 by 10,556. Even if we don't account for the apparent reduction in hospital utilization, 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. When the reduction in hospital utilization is taken into account, the evidence indicates that pharmaceutical innovation was cost-saving.

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