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THE IMPACT OF NEW DRUG LAUNCHES ON LIFE-YEARS LOST IN 2015 FROM 19 TYPES OF CANCER IN 36 COUNTRIES

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Abstract: This study employs a two-way fixed effects research design to measure the mortality impact and cost-effectiveness of cancer drugs: It analyzes the correlation across 36 countries between the *relative* mortality from 19 types of cancer in 2015 and the *relative* number of drugs previously launched in that country to treat that type of cancer, controlling for relative incidence. The sample size (both in terms of number of observations and population covered) of this study is considerably larger than the sample sizes of previous studies; a new and improved method of analyzing the lag structure of the relationship between drug launches and life-years lost is used; and a larger set of measures of the burden of cancer is analyzed. The number of DALYs and life-years lost are unrelated to drug launches 0–4 years earlier. This is not surprising, since utilization of a drug tends to be quite low during the first few post-launch years. Moreover, there is likely to be a lag of several years between utilization of a drug and its impact on mortality. However, mortality is significantly inversely related to the number of drug launches at least 5 years earlier, especially to drug launches 5–9 years earlier. One additional drug for a cancer site launched during 2006–2010 is estimated to have reduced the number of 2015 DALYs due to cancer at that site by 5.8%;; one additional drug launched during 1982–2005 is estimated to have reduced the number of 2015 DALYs by about 2.6%. Lower quality (or effectiveness) of earlier vintage drugs may account for their smaller estimated effect. We estimate that drugs launched during the entire 1982–2010 period reduced the number of cancer DALYs in 2015 by about 23.0%, and that, in the absence of new drug launches during 1982–2010, there would have been 26.3 million additional DALYs in 2015. Also, the nine countries with the largest number of drug launches during 1982–2010 are estimated to have had 14% fewer cancer DALYs (controlling for incidence) in 2015 than the nine countries with the smallest number of drug launches during 1982–2010. Estimates of the cost per life-year gained in 2015 from drugs launched during 2006–2010 range between $1,635 (life-years gained at all ages) and $2,820 (life-years gained before age 65). These estimates are similar to those

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obtained in previous country-specific studies of Belgium, Canada, and Mexico, and are well below the estimate obtained in one study of Switzerland. Mortality in 2015 is strongly inversely related to the number of drug launches in 2006–2010. If the relationship between mortality in 2020 and the number of drug launches in 2011–2015 is similar, drug launches 5–9 years earlier will reduce mortality even more (by 9.9%) between 2015 and 2020 than they did (by 8.4%) between 2010 and 2015.

Keywords: cancer, mortality, pharmaceuticals, innovation, cost-effectiveness

1. INTRODUCTION

During the period 1982–2014, 186 new chemical entities (NCEs) for treating cancer were launched worldwide: about 5.6 new cancer drugs per year.[1] Moreover, the annual number of new cancer drug launches has been increasing: as shown in Figure 1, the number of new cancer drugs launched during 2005–2014 (76) was 77% larger than the number launched during 1985–1994 (43). In contrast, the number of new drugs for other diseases (e.g. cardiovascular and infectious diseases) launched during 2005–2014 (242) was 42% *lower* than the number launched during 1985–1994 (417). The acceleration in cancer drug innovation has contributed to sharply increasing cancer drug expenditure: costs of oncology therapeutics and supportive care drugs were $107 billion globally in 2015, an increase of 11.5% over 2014 (on a constant dollar basis) and up from $84 billion in 2010, as measured at invoice price levels. These costs are expected to reach $150 billion globally by 2020 [IMS Institute for Healthcare Informatics (2016, p. 4)].

The number of cancer drug launches has varied across cancer sites (breast, lung, colon, etc.). Figure 2 shows the average (across 36 countries) number of drug launches during 1982–2015 for 19 cancer sites.[2] The average number of launches was greater than 10 for 4 cancer sites (e.g. breast cancer and non-Hodgkin lymphoma), and lower than two for four cancer sites (e.g. thyroid cancer and Hodgkin lymphoma). The number of cancer drug launches has also varied across countries. Figure 3 shows the average (across the 19 cancer sites) number of drug launches during 1982–2015 for 36 countries. The mean number of cancer drugs launched in Canada (5.9) was 24% lower than the mean number of cancer drugs launched in the USA (7.8).

This study seeks to determine the extent to which the number of years of life lost (YLL) due to cancer[3] in 36 countries in 2015 was reduced by previous launches of new cancer drugs, and to measure the average cost-effectiveness of (cost per life-year gained from) those drugs. Several previous studies [Lichtenberg (2015, 2016a, 2016b, 2017)] have provided evidence about the mortality impact and cost-effectiveness of new cancer drugs in single (mostly small) countries (Canada, Belgium, Switzerland, and Mexico). These studies employed a difference-in-differences research design: They analyzed, within each country, the correlation across cancer sites between long-run increases in the number of

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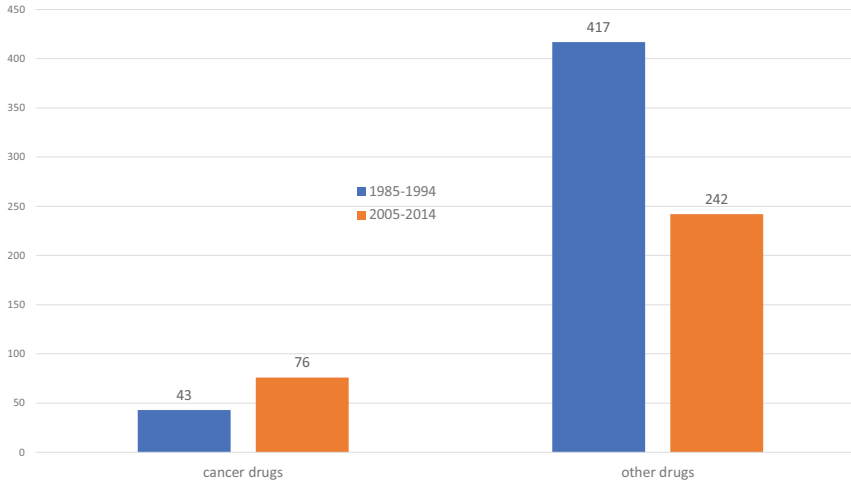

FIGURE 1. (Colour online) Number of new cancer drugs and other new drugs launched worldwide, 1985–1994 and 2005–2014. Source: Author's calculations based on IMS Health New Product Focus database "Cancer NMEs" are NMEs in EphMRA/PBIRG Anatomical Classification L (ANTINEOPLASTIC AND IMMUNOMODULATING AGENTS).

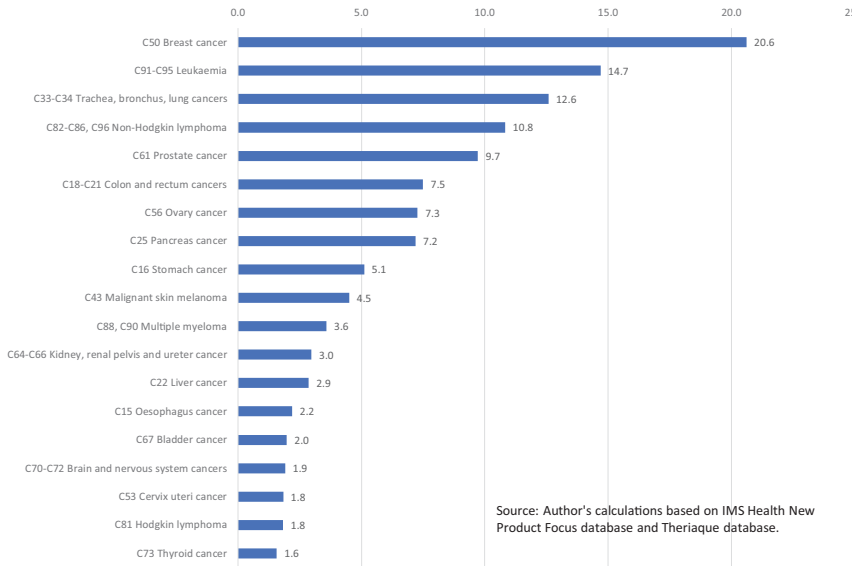

FIGURE 2. (Colour online) Mean (across 36 countries) number of drug launches, 1982–2015, by cancer site. Source: Author's calculations based on IMS Health New Product Focus database and Theriaque database.

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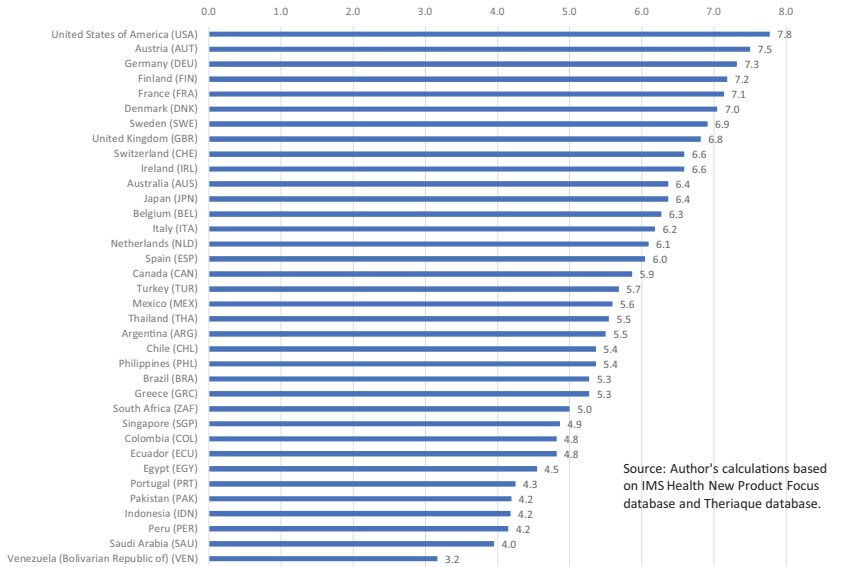

FIGURE 3. (Colour online) Mean (across 19 cancer sites) number of drug launches, 1982–2015, by country. Source: Author's calculations based on IMS Health New Product Focus database and Theriaque database.

drugs ever launched and mortality changes. All four studies found that new cancer drug launches had a significant negative impact on cancer mortality, and that new cancer drugs were highly cost-effective, according to a standard (based on per capita GDP) endorsed by the World Health Organization (WHO).

The present study will employ a two-way fixed effects research design [Somaini and Wolak (2016)]: In effect, I will analyze the correlation across countries between *relative* mortality from each type of cancer in 2015 and the *relative* number of drugs previously launched in that country to treat that type of cancer, controlling for relative incidence.[4] The mortality models I will estimate will include both country fixed effects, which control for the average (across cancer sites) level of cancer mortality in each country, and cancer-site fixed effects, which control for the average (across countries) level of mortality from each cancer site. This approach is feasible because the *relative* number of drugs launched for different types of cancer has varied considerably across the countries. This is illustrated by Figure 4, which shows the number of drugs launched during 2006–2015 in Japan and Portugal for 19 types of cancer.[5] The mean (across cancer sites) number of drugs launched during 2006–2015 was almost identical in Japan and Portugal (3.3 and 3.2, respectively), but Japan launched four more drugs for leukemia and four fewer drugs for ovary cancer. I will test the hypothesis that a relatively large number of drugs tend to be launched for a cancer site in a country when the relative incidence of cancer at that site in that country is high.

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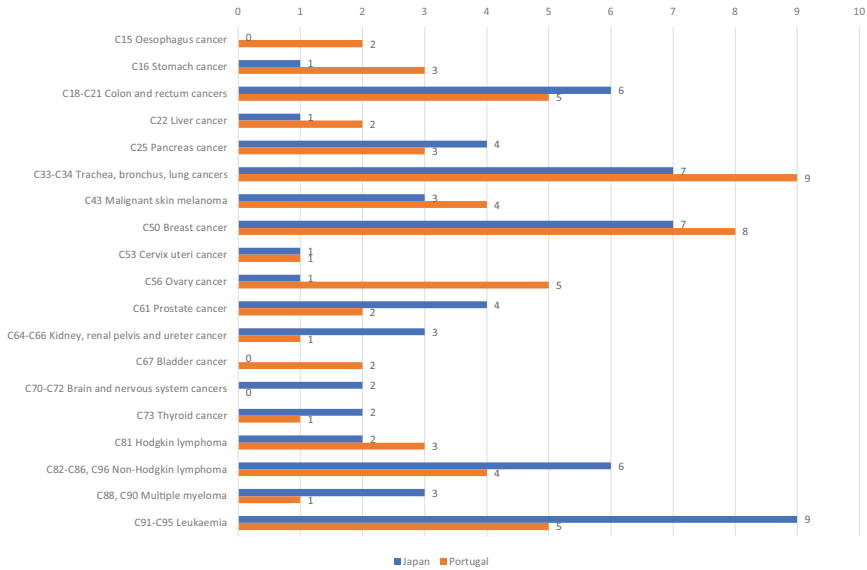

FIGURE 4. (Colour online) Number of drugs launched during 2006–2015 in Japan and Portugal for 19 types of cancer.

In addition to providing a means of triangulating[6] the results of earlier studies, the approach pursued in this study has a number of advantages. First, the sample size (both in terms of number of observations and population covered) of this study is considerably larger. Some of the previous studies were based on about 38 observations (19 cancer sites * 2 years [e.g. 2000 and 2011)]; this study is based on 684 observations (19 cancer sites * 36 countries). The size of the population covered in this study (2,322 million) is almost 13 times as large as the *sum* of the populations covered by the four previous studies (181 million). Second, a new and improved method of analyzing the lag structure of the relationship between drug launches and life-years lost will be used.[7] Third, a larger set of measures of the burden of cancer will be analyzed: The number of disability-adjusted life-years (DALYs), the number of years of healthy life lost due to disability, and the number of life-years lost based on the three different age thresholds.

In the next section, I provide background and motivation for the econometric model of life-years lost from cancer, which is developed in Section III. Data sources are discussed in Section IV. Section V provides evidence about the effect of incidence on the number of new drug launches. Cancer mortality model estimates are presented in Section VI. Implications of the results are discussed in Section VII. Section VIII concludes.

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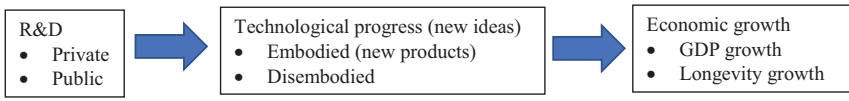
2. BACKGROUND AND MOTIVATION

Before describing the econometric model I will use to estimate the effect of new drug launches on life-years lost from cancer, I will provide some theoretical and empirical background and motivation for the model, which can be summarized by the following figure:



Starting on the right of this figure, longevity increase is a very important part of economic growth, broadly defined. Nordhaus (2005) argued that "improvements in health status have been a major contributor to economic welfare over the twentieth century. To a first approximation, the economic value of increases in longevity in the last hundred years is about as large as the value of measured growth in non-health goods and services." Murphy and Topel (2006) estimated that cumulative gains in life expectancy after 1900 were worth over $1.2 million to the representative American in 2000, whereas post-1970 gains added about $3.2 trillion per year to national wealth, equal to about half of GDP. The United Nations' Human Development Index, which is used to rank countries into four tiers of human development, is a composite statistic of life expectancy, income per capita, and education [United Nations (2017)].

There is a consensus among macroeconomists that technological progress is the principal source of GDP growth. Romer (1990) argued that "growth…is driven by technological change that arises from intentional investment decisions made by profit-maximizing agents" (S71). Jones argued that "long-run growth is driven by the discovery of new ideas throughout the world."[8] And Chien (2015) said that "it has been shown, both theoretically and empirically, that technological progress is the main driver of long-run growth."

Since technological progress, or the discovery of new ideas, is the fundamental source of one of the major components—GDP growth—of "human development," or economic growth, broadly defined, it is quite plausible that the discovery of new ideas has also played a major role in longevity growth. Some previous authors have suggested that this is the case. Fuchs (2010) said that "since World War II…biomedical innovations (new drugs, devices, and procedures) have been the primary source of increases in longevity," although he did not provide evidence to support this claim. Cutler et al. (2006) performed a survey of a large and diverse literature on the determinants of mortality, and "tentatively identif[ied] the application of scientific advance and technical progress (some of which is induced by income and facilitated by education) as the ultimate determinant of health." They concluded that "knowledge, science, and technology are the keys to any coherent explanation" of mortality.

In general, measuring the number of ideas is challenging. One potential measure is the number of patents, but Patterson (2012, p. 8) noted that only 1% of

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patent applications made by Bell Labs "generated [commercial] value." Fortunately, measuring pharmaceutical "ideas" is considerably easier than measuring ideas in general. The measure of pharmaceutical ideas I will use is the number of new molecular entities used to treat a disease launched in a country. Since we have precise information about when those ideas reached the market and the diseases to which they apply, we can assess the impact of those ideas on longevity in a two-way fixed effects framework.

Technological change may be either disembodied or embodied. Suppose firm X invests in R&D, and that this investment results in a valuable discovery. If the technological advance is disembodied, consumers and other firms could benefit from the discovery without purchasing firm X's goods or services; they could benefit just by reading or hearing about the discovery. However, if the technological advance is embodied, consumers and other firms must purchase firm X's goods or services to benefit from its discovery. Solow (1960) argued that "many if not most innovations need to be embodied in new kinds of durable equipment before they can be made effective. Improvements in technology affect output only to the extent that they are carried into practice either by net capital formation or by the replacement of old-fashioned equipment by the latest models…"[9] Romer (1990) also assumed that technological progress is embodied in new goods: "new knowledge is translated into goods with practical value," and "a firm incurs fixed design or research and development (R&D) costs when it creates a new good. It recovers those costs by selling the new good for a price that is higher than its constant cost of production." Hercowitz (1998, p. 223) concluded that "'embodiment' is the main transmission mechanism of technological progress to economic growth."

Most scholars agree with Jones' (1998, pp. 89–90) statement that "technological progress is driven by R&D in the advanced world." In 1997, the medical substances and devices sector was the most R&D-intensive[10] major industrial sector: almost twice as R&D-intensive as the next-highest sector (information and electronics), and three times as R&D-intensive as the average for all major sectors. [National Science Foundation (2017)]. In 2007, 89% of private biomedical research expenditure was funded by pharmaceutical and biotechnology firms, the remaining 11% was funded by medical device firms [Dorsey et al (2010)].

A U.S. government institute (the National Cancer Institute (NCI)) has also played an important role in cancer drug discovery and development.[11] Frequently, NCI's drug development efforts focus on the unmet needs that are not being adequately addressed by the private sector. NCI's cancer drug discovery and development activities originated from a congressionally mandated initiative known as the Cancer Chemotherapy National Service Center (CCNSC), which, in 1955, established a national resource to facilitate the evaluation of potential anticancer agents. In 1976, the CCNSC's functions were incorporated into the Developmental Therapeutics Program (DTP) in NCI's Division of Cancer Treatment and Diagnosis [National Cancer Institute (2017)].

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3. ECONOMETRIC MODEL OF LIFE-YEARS LOST FROM CANCER

To investigate the impact that new drugs launched during 1982–2015 had on the number of YLL from cancer in 2015, conditional on incidence in 2012, I will estimate the following two-way fixed effects model:

$$\begin{aligned}\ln(Y_{sc}) = {} & \beta_{0-4}\text{LAUNCHES\_2011\_2015}_{sc} + \beta_{5-9}\text{LAUNCHES\_2006\_2010}_{sc} \\ & + \beta_{10-14}\text{LAUNCHES\_2001\_2005}_{sc} \\ & + \beta_{15-33}\text{LAUNCHES\_1982\_2000}_{sc} \\ & + \gamma\ \ln(\text{CASES\_2012}_{sc}) + \alpha_s + \pi_c + \varepsilon_{sc}\end{aligned} \tag{1}$$

where Y_{sc} is one of the following variables:

DALYS_2015sc = the number of DALYs[12] lost due to cancer at site s in country c in 2015.
YLL_2015sc = the number of years of life lost (as measured in the WHO Global Burden of Disease Estimates) due to cancer at site s in country c in 2015.
YLD_2015sc = the number of years lost to disability due to cancer at site s in country c in 2015.
YLL75_2015sc = the number of years of life lost before age 75 due to cancer at site s in country c in 2015.
YLL65_2015sc = the number of years of life lost before age 65 due to cancer at site s in country c in 2015

and

LAUNCHES_2011_2015sc = the number of post-1981[13] new chemical entities used to treat cancer at site s launched in country c during 2011–2015.
LAUNCHES_2006_2010sc = the number of post-1981 new chemical entities used to treat cancer at site s launched in country c during 2006–2010.
LAUNCHES_2001_2005sc = the number of post-1981 new chemical entities used to treat cancer at site s launched in country c during 2001–2005.
LAUNCHES_1982_2000sc = the number of post-1981 new chemical entities used to treat cancer at site s launched in country c during 1982–2000.
CASES_2012sc = the number of people diagnosed with cancer at site s in country c in 2012.
α_s = a fixed effect for cancer at site s.
π_c = a fixed effect for country c.

Equation (1) will be estimated by weighted least squares, weighting by Y_{sc}.[14] The disturbances of equation (1) will be clustered within countries or within cancer sites.

In equation (1), drugs launched in four different periods (0–4 years, 5–9 years, 10–14 years, and 15–33 years before 2015) are permitted to have different effects on mortality or disability in 2015. The model is specified in this way because the effect of a drug's launch on mortality is hypothesized to depend on both the *quantity* and the *quality* (or effectiveness) of the drug. Indeed, it is likely to depend on the *interaction* between quantity and quality: A quality improvement will have a greater impact on mortality if drug utilization (quantity) is high. Drugs launched

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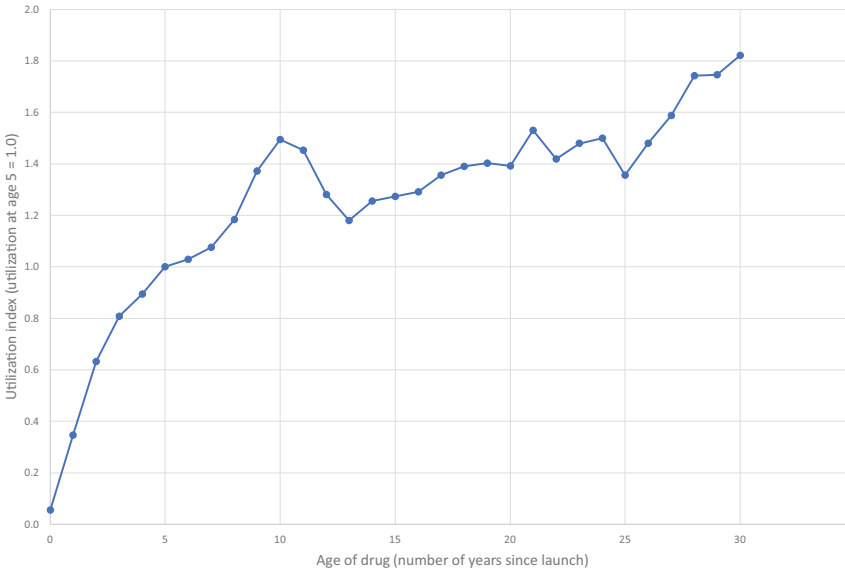

FIGURE 5. (Colour online) Cancer drug age-utilization profile.

in the four different periods are likely to vary (in opposite ways) with respect to both quantity (in 2015) and quality. Newer drugs are likely to be of higher quality than older drugs.[15] On the other hand, utilization of new drugs tends to be much lower than utilization of old drugs.

To provide evidence about the process of diffusion of new medicines, I estimated the following model, using annual data for the period 2010–2014 on global utilization of 80 cancer drugs (molecules):

$$\ln(\text{N\_SU}_{mn}) = \rho_m + \pi_n + \varepsilon_{mn} \quad \textbf{(2)}$$

where

N_SU_{mn} = the number of standard units of molecule m sold worldwide n years after it was first launched ($n = 0, 1, \ldots, 17$).
ρ_{m} = a fixed effect for molecule m.
π_{n} = a fixed effect for age n.

Data on the world launch year of molecule m were obtained from the IMS Health *New Product Focus* database. Data on the annual number of standard units of molecule m sold worldwide during 2010–2014 were obtained from the IMS Health MIDAS database. The expression $\exp(\pi_n - \pi_5)$ is a "relative utilization index": It is the mean ratio of the quantity of a cancer drug sold n years after it was launched to the quantity of the same drug sold 5 years after it was launched.

Estimates of the "relative utilization index" are shown in Figure 5. These estimates indicate that utilization of a cancer drug is generally increasing, at a de-

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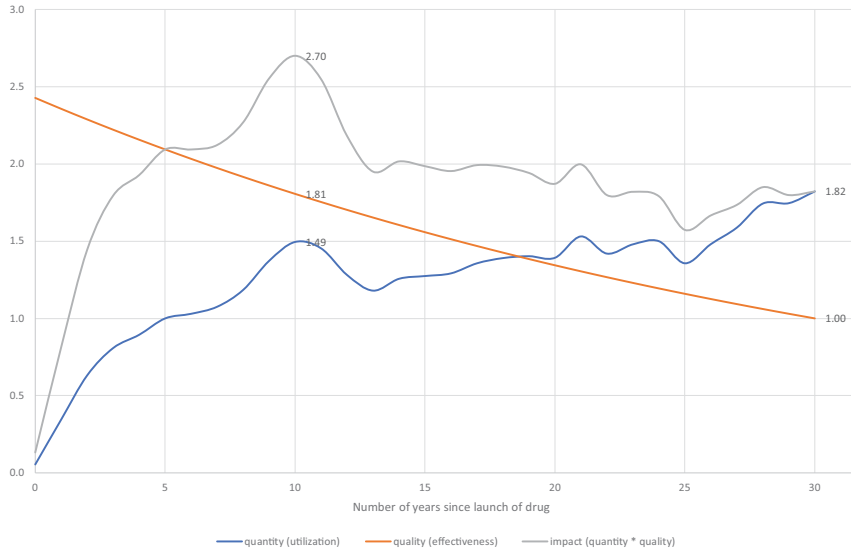

FIGURE 6. (Colour online) Hypothetical quantity, quality, and impact (= quantity * quality) of a drug when quality increases at a 3% annual rate with respect to launch year.

creasing rate, with respect to time since launch. As shown in the following table, mean utilization of a drug is about twice as high 5–9 years after launch as it was 0–4 years after launch:

Years since launch	Mean utilization (relative to utilization 5 years after launch)
0–4	0.55
5–9	1.13
10–14	1.33
15–31	1.49

If the quality of later vintage drugs is greater than the quality of earlier vintage drugs, the relationship between the age of a drug (number of years since launch) and its impact on mortality (which depends on quality * quantity) may have an inverted-U shape.[16] This is illustrated by Figure 6, which is based on the assumption that drug quality increases at a constant 3% annual rate with respect to vintage (e.g. a drug launched in 2018 is 3% better than a drug launched in 2017). Under this assumption, the drugs that have the largest impact on mortality are those that were launched 10 years before. Their impact would be 48% larger than that of drugs that were launched 30 years before, despite the fact that their utilization is 18% lower, because their quality is 81% higher.[17]

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TABLE 1. Summary Statistics, 19 Major Cancer Sites in 36 Countries

	2005	2015	% change
Disability-adjusted life-years (DALYs)	68,179,003	76,596,299	12%
Years of life lost, as measured in the WHO Global Burden of Disease Estimates (YLL)	65,246,858	72,439,899	11%
Years lost due to disability (YLD)	2,932,144	4,156,401	42%
Years of life lost before age 75 (YLL75)	23,398,525	25,137,974	7%
Years of life lost before age 65 (YLL65)	11,163,603	11,545,184	3%
Number diagnosed 3 years earlier (CASES)	4,474,445	5,716,879	28%

Source: Author's calculations based on *WHO Global Health Estimates 2015: Disease burden by Cause* database [World Health Organization (2016a)]; *WHO Global Health Estimates 2015: Deaths by Cause* database [World Health Organization (2016b)]; GLOBOCAN 2002 [Ferlay et al (2004)]; and GLOBOCAN 2012 [International Agency for Research on Cancer (2017b)].

4. DATA AND DESCRIPTIVE STATISTICS

Data on DALYs, YLL, and years lost due to disability (YLD) were obtained from the *WHO Global Health Estimates 2015: Disease burden by Cause* database [World Health Organization (2016a)].[18] Data on years of potential life lost before ages 75 and 65 were constructed using the data obtained from the *WHO Global Health Estimates 2015: Deaths by Cause* database [World Health Organization (2016b)].

That source provides data on the number of deaths by 5-year age group, cancer site, country, and year. I assume that all the 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. Data on the number of patients diagnosed, by cancer site, country, and year, were obtained from GLOBOCAN 2002 [Ferlay et al. (2004), a computer software package] and GLOBOCAN 2012 [International Agency for Research on Cancer (2017b)].

Summary statistics for the 19 major cancer sites in the 36 countries we analyze[19] are shown in Table 1. In 2015, 76.6 million DALYs were lost. Ninety-five percent of this loss was due to premature mortality, rather than to disability. The number of DALYs increased by 12% between 2005 and 2015. However, the number of patients diagnosed 3 years earlier increased by 28%.[20] Therefore, the number of DALYs per patient diagnosed declined by 16% (= 28%–12%). The number of years of potential life lost before age 65 per patient diagnosed declined by even more: 25% (= 28%–3%).

Data on drugs with indications for different types of cancer were obtained from the *Thériaque* database [Centre National Hospitalier d'Information sur le Médicament (2017)]. These data are shown in Appendix Table A.2.

Data on drug launch years, by molecule and country, were obtained from the IMS Health *New Product Focus database*. These data are shown in Appendix Table A.3. A blank cell indicates that the drug had not been launched in that country by the end of 2015.

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Data on the annual number of standard units of cancer drugs sold worldwide during the period 2010–1014, by molecule, were obtained from the IMS Health *MIDAS database*.

5. THE EFFECT OF INCIDENCE ON THE NUMBER OF NEW DRUG LAUNCHES

As discussed in the introduction, estimation of the two-way fixed effects model of life-years lost [equation (1)] is feasible because the relative number of drugs launched for different types of cancer varies across countries, as illustrated by Figure 4. Why did Japan have more leukemia drug launches, but fewer ovary cancer drug launches, than Portugal? Previous studies have shown that both innovation (the number of drugs developed) and diffusion (the number of drugs launched in a country) depend on *market size*. Acemoglu and Linn (2004) found "economically significant and relatively robust effects of market size on innovation." Danzon et al (2005) found that "countries with lower expected prices or *smaller expected market size experience longer delays in new drug access*, controlling for per capita income and other country and firm characteristics" (emphasis added).

The hypothesis that the number of drug launches is influenced by market size can be investigated in a two-way fixed effects framework by estimating the following equation:

$$\text{N\_LAUNCHES\_2003\_2012}_{sc} = \sigma \ln(\text{CASES\_2002}_{sc}) + \alpha_s + \delta_c + \varepsilon_{sc} \qquad \textbf{(3)}$$

where

$\text{N\_LAUNCHES\_2003\_2012}_{sc}$ = the number of drugs to treat cancer at site s launched in country c during 2003–2012.

CASES_2002_{sc} = the number of patients diagnosed with cancer at site s in country c in 2002.

The estimate of σ is positive and significant: estimate = 0.1872; standard error = 0.0662; $Z = 2.83$; p-value = 0.0047. This signifies that larger relative market size (number of patients diagnosed) increases the relative number of drugs launched.

These findings are broadly consistent with the notion that "misery loves company" [Lichtenberg and Waldfogel (2009)]: The relative number of drugs launched for a cancer site in a country is higher when the relative incidence of that cancer is greater. As illustrated by Figure 7, the direct positive effect of incidence on mortality may be partially offset by an indirect negative effect, via increased drug launches.

6. CANCER MORTALITY MODEL ESTIMATES

Estimates of parameters of equation (1) are presented in Table 2; to conserve space, estimates of 19 cancer-site fixed-effects (α_s) and 36 country fixed effects (π_c) are not shown. Rows 1–5 show estimates of equation (1) when the dependent variable is

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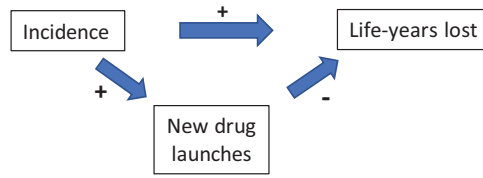

FIGURE 7. (Colour online) Direct and indirect effects of incidence on life-years lost.

TABLE 2. Estimates of two-way fixed effects Model of life-years lost [equation (1)]

Row	Parameter	Regressor	Estimate	Std. err.	Z	Pr > |Z|
		Dependent variable = ln(DALYS_2015)				
1	β_{0-4}	LAUNCHES_2011_2015	0.000	0.013	−0.03	0.977
2	β_{5-9}	LAUNCHES_2006_2010	**−0.058**	**0.012**	**−4.81**	**<0.0001**
3	β_{10-14}	LAUNCHES_2001_2005	**−0.026**	**0.011**	**−2.35**	**0.019**
4	β_{15-33}	LAUNCHES_1982_2000	**−0.027**	**0.009**	**−2.96**	**0.003**
5	γ	ln(CASES_2012)	**0.849**	**0.032**	**26.27**	**<0.0001**
		Dependent variable = ln(YLL_2015)				
6	β_{0-4}	LAUNCHES_2011_2015	0.003	0.014	0.23	0.818
7	β_{5-9}	LAUNCHES_2006_2010	**−0.064**	**0.013**	**−5.00**	**<0.0001**
8	β_{10-14}	LAUNCHES_2001_2005	**−0.026**	**0.011**	**−2.30**	**0.022**
9	β_{15-33}	LAUNCHES_1982_2000	**−0.029**	**0.010**	**−2.78**	**0.005**
10	γ	ln(CASES_2012)	**0.844**	**0.037**	**22.85**	**<0.0001**
		Dependent variable = ln(YLD_2015)				
11	β_{0-4}	LAUNCHES_2011_2015	−0.004	0.013	−0.32	0.746
12	β_{5-9}	LAUNCHES_2006_2010	−0.017	0.015	−1.11	0.267
13	β_{10-14}	LAUNCHES_2001_2005	−0.016	0.024	−0.68	0.496
14	β_{15-33}	LAUNCHES_1982_2000	**−0.024**	**0.011**	**−2.24**	**0.025**
15	γ	ln(CASES_2012)	**0.866**	**0.030**	**29.39**	**<0.0001**
		Dependent variable = ln(YLL75_2015)				
16	β_{0-4}	LAUNCHES_2011_2015	−0.013	0.021	−0.62	0.538
17	β_{5-9}	LAUNCHES_2006_2010	**−0.091**	**0.018**	**−5.05**	**<0.0001**
18	β_{10-14}	LAUNCHES_2001_2005	**−0.046**	**0.019**	**−2.43**	**0.015**
19	β_{15-33}	LAUNCHES_1982_2000	**−0.055**	**0.014**	**−4.06**	**<0.0001**
20	γ	ln(CASES_2012)	**0.856**	**0.049**	**17.43**	**<0.0001**
		Dependent variable = ln(YLL65_2015)				
21	β_{0-4}	LAUNCHES_2011_2015	−0.021	0.021	−1.03	0.303
22	β_{5-9}	LAUNCHES_2006_2010	**−0.100**	**0.018**	**−5.69**	**<0.0001**
23	β_{10-14}	LAUNCHES_2001_2005	**−0.057**	**0.023**	**−2.48**	**0.013**
24	β_{15-33}	LAUNCHES_1982_2000	**−0.064**	**0.017**	**−3.81**	**1E-04**
25	γ	ln(CASES_2012)	**0.833**	**0.063**	**13.16**	**<0.0001**

$N \approx 684$ (36 countries * 19 cancer sites).
Estimates in bold are statistically significant (p-value < 0.05).
Disturbances are clustered within cancer sites.

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$\ln(\text{DALYS\_2015}_{sc})$.[21] The estimate (in row 1) of $\beta_{0\text{–}4}$ is not statistically significant. This indicates that new drugs launched during 2011–2015 did not have a significant impact on the number of DALYs in 2015. This is not surprising since, as shown in Figure 5, utilization of a drug tends to be quite low during the first few years after it was launched. Moreover, there is likely to be a lag of several years between the utilization of a drug and its impact on mortality. The estimate (in row 2) of $\beta_{5\text{–}9}$ is negative and highly significant (p-value < 0.0001). This indicates that new drugs launched during 2006–2010 had a highly significant negative impact on the number of DALYs in 2015. One additional drug for a cancer site launched during 2006–2010 is estimated to have reduced the number of 2015 DALYs due to cancer at that site by 5.8%. The estimates (in rows 3 and 4) of $\beta_{10\text{–}14}$ and β_{15+} are also negative and highly significant (p-value ≤ 0.0187), but their magnitudes are about 45% of the magnitude of $\beta_{5\text{–}9}$.[22] One additional drug for a cancer site launched during 1982–2005 is estimated to have reduced the number of 2015 DALYs due to cancer at that site by about 2.6%. The smaller magnitudes of $\beta_{10\text{–}14}$ and β_{15+} may be due to lower quality (or effectiveness) of earlier-vintage drugs, and to left-censoring of the drug launch data. Panel A of Figure 8 is a graph of the point estimates and 95% confidence intervals of the estimates in rows 1–4. Row 5 of Table 2 shows the estimate of the coefficient γ on the incidence variable, $\ln(\text{CASES\_2012}_{sc})$. As expected, this coefficient is positive and highly significant (p-value < 0.0001); the fact that it is significantly less than 1 may be partly attributable to errors in the measurement of incidence.[23,24]

When we include the log of the number of cases in 2002 ($\ln(\text{CASES\_2002}_{sc})$) as well as the log of the number of cases in 2012 in the model, the coefficient on $\ln(\text{CASES\_2002}_{sc})$ is not statistically significant (estimate $= 0.064$; $Z = 1.35$; p-value $= 0.177$); the sum of the incidence coefficients is almost identical to the coefficient in row 5 of Table 2; and the estimates of the drug launch coefficients are virtually unchanged. Incidence is highly serially correlated: the estimate of κ from the weighted (by CASES_2012_{sc}) regression $\ln(\text{CASES\_2012}_{sc}) = \kappa \ln(\text{CASES\_2002}_{sc}) + \alpha_s + \pi_c + \varepsilon_{sc}$ is 0.778 ($Z = 15.58$; p-value < 0.0001). When we include both $\ln(\text{CASES\_2002}_{sc})$ and $\ln(\text{CASES\_2012}_{sc})$ in the model, and exclude both $\text{LAUNCHES\_2001\_2005}_{sc}$ and $\text{LAUNCHES\_1982\_2000}_{sc}$, the estimate of $\beta_{0\text{–}4}$ is far from significant, and the estimate of $\beta_{5\text{–}9}$ remains highly significant (p-value $= 0.0013$) and is slightly smaller than the estimate in row 2 of Table 2 (estimate $= -0.051$; $Z = 3.22$).

Rows 6–10 of Table 2 show estimates of equation (1) when the dependent variable is $\ln(\text{YLL\_2015}_{sc})$. The estimates of this equation are very similar to the estimates of the $\ln(\text{DALYS\_2015}_{sc})$ equation in rows 1–5. This is not surprising since, as noted above, 95% of DALYs were due to premature mortality, rather than to disability. Rows 11–15 of Table 2 show estimates of equation (1) when the dependent variable is $\ln(\text{YLD\_2015}_{sc})$. The only drug launch coefficient that is statistically significant (p-value $= 0.0254$) is β_{15+}, it implies that one additional drug for a cancer site launched during 1982–2000 reduced the number of years lost to disability due to cancer at that site in 2015 by 2.4%.

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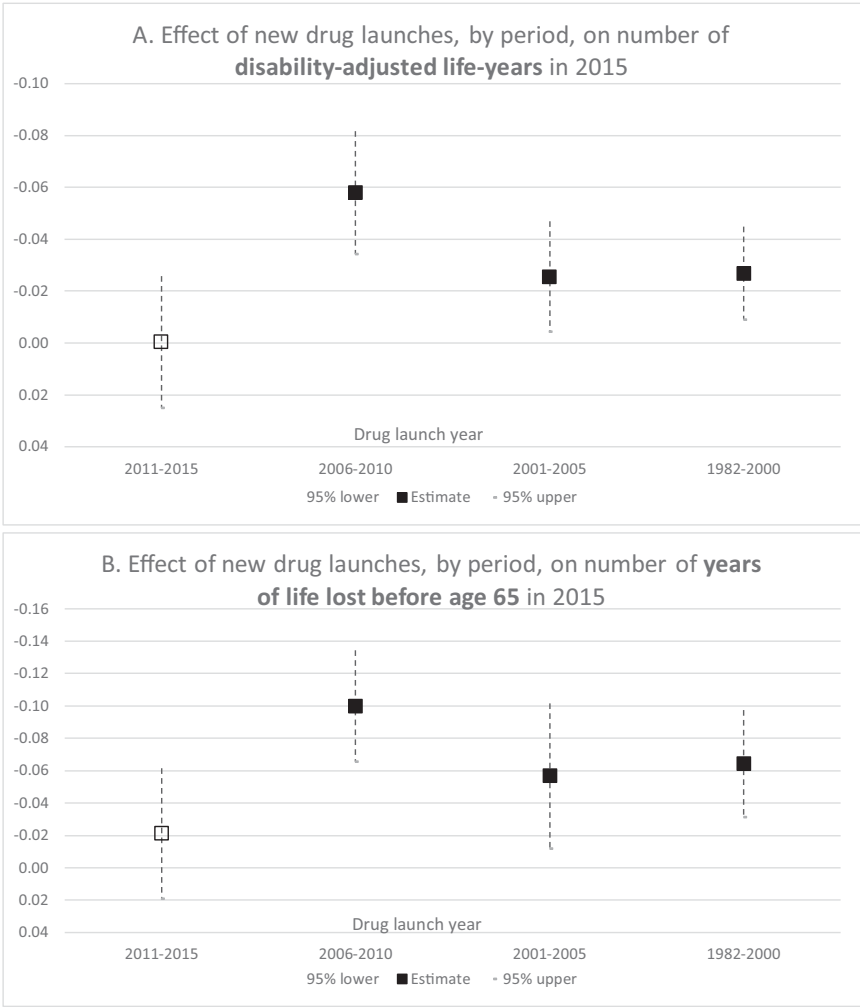

FIGURE 8. Estimated effects of new drug launches on DALYs and YLL65 in 2015. Vertical scale is inverted. Solid markers indicate significant (p-value < 0.05) estimates, hollow markers indicate insignificant estimates.

Rows 16–20 and 21–25 of Table 2 show estimates of equation (1) when the dependent variable is $\ln(\text{YLL75\_2015}_{sc})$ and $\ln(\text{YLL65\_2015}_{sc})$, respectively. The estimates are qualitatively similar to those in rows 1–5 and 6–10: The estimate of $\beta_{0–4}$ is insignificant, the estimates of the other launch coefficients are all negative and significant, and the magnitudes of $\beta_{10–14}$ and β_{15+} are significantly smaller than the magnitude of $\beta_{5–9}$. But the magnitudes of $\beta_{5–9}$, $\beta_{10–14}$, and β_{15+} are larger in rows 16–20 and 21–25 than they are in rows 1–5 and 6–10. For example, as

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shown in row 22, one additional drug for a cancer site launched during 2006–2010 is estimated to have reduced the number of years of potential life lost before age 65 due to cancer at that site in 2015 by 10.0%. Panel B of Figure 8 is a graph of the point estimates and 95% confidence intervals of the estimates in rows 21–24.

The estimates in Table 2 are based on data for 36 countries, including the United States. I estimated similar models using data for 35 countries, i.e. excluding the United States. These estimates are shown in Table A.5. The magnitude of the point estimates based on the U.S.-excluded sample are generally about 15% smaller than the magnitude of the point estimates based on the full sample (although some are larger), and the U.S.-excluded estimates are somewhat less significant. However, most of the estimates continue to be highly significant (p-value < 0.04), and the basic pattern of the estimates remains: DALYs and life-years lost are unrelated to drug launches 0–4 years earlier, and inversely related to drug launches at least 5 years earlier, especially to drug launches 5–9 years earlier.

7. DISCUSSION

By combining the estimates in Table 2 with other data, we can estimate the number of life-years gained (i.e. the reduction in life-years lost) in 2015 attributable to previous new drug launches. We can also estimate expenditure in 2015 on these drugs, so we can obtain estimates of an important indicator of cost-effectiveness: pharmaceutical expenditure per life-year gained.

Due to limitations of the available data, we can estimate (under reasonable assumptions) expenditure in 2015 on drugs launched during 2006–2010, but we cannot estimate expenditure in 2015 on drugs launched during earlier periods. Therefore, although the estimates in Table 2 indicate that drugs launched before 2006 as well as those launched during 2006–2010 reduced the number of life-years lost in 2015, I will only provide estimates of the cost-effectiveness in 2015 of drugs launched during 2006–2010.[25]

Calculations of the number of life-years gained in 2015 from, and of the cost-effectiveness of, drugs launched during 2006–2010 are shown in Table 3. The first column shows the calculations for the first disease burden measure: DALYs. Row 1 shows the point estimates of the $\beta_{5\text{–}9}$ coefficients from Table 2. Row 2 of Table 3 shows the weighted mean value of LAUNCHES_2006_2010, weighted by the corresponding disease burden measure. The average number of drugs launched during 2006–2010 for a cancer site was about 1.5. Row 3 shows the log-change in 2015 life-years lost due to LAUNCHES_2006_2010 [$=\beta_{5\text{–}9}$ * mean(LAUNCHES_2006_2010)]. The estimates imply that drugs launched during 2006–2010 reduced the number of cancer DALYs by about 8.4% [$=-(\exp(-0.087) - 1)$]. As shown in row 4, there were 88.1 million DALYs from all types of cancer in the 36 countries in 2015. The estimates imply that, in the absence of new drug launches during 2006–2010, there would have been 8.04 million additional DALYs. Similar calculations in columns 2–4 imply that, in the absence of new drug launches during 2006–2010, there would have been 8.28

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TABLE 3. Calculation of pharmaceutical expenditure per life-year gained

Column		1	2	3	4	
		Disease burden measure				
Row		DALY	YLL	YLL75	YLL65	Basis
		Life-years gained calculation				
1	β_{5-9}	−0.058	−0.064	−0.091	−0.100	Table 2
2	weighted mean(LAUNCHES_2006_2010)	1.505	1.487	1.532	1.607	Author's calculations based on IMS *New Product Focus* and *Theriaque* databases
3	Log-change in 2015 life-years lost due to LAUNCHES_2006_2010	−0.087	−0.095	−0.139	−0.161	(1) * (2)
4	Life-years lost due to all types of cancer in 36 countries in 2015	88,108,225	83,467,085	30,255,229	14,451,091	World Health Organization (2016a, 2016b).
5	Reduction in 2015 life-years lost due to LAUNCHES_2006_2010	8,035,792	8,280,097	4,509,546	2,520,071	(exp(−(3))−1) * (4)
		Pharmaceutical expenditure calculation				
6	Global cost (in millions) of oncology therapeutics and supportive care drugs in 2015, measured at invoice price levels	$107,000				IMS Institute for Healthcare Informatics (2016, p. 20)
7	36-country share of total pharmaceutical expenditure in 2014	78%				International Federation of Pharmaceutical Manufacturers & Associations (2017, Annex 2)

TABLE 3. Continued

Column		1	2	3	4	
8	36-country cost (in millions) of oncology therapeutics and supportive care drugs in 2015			$83,076		(6) * (7)
9	Fraction of 2010 pharma expend. on drugs launched in country during 2001–2005, 31 countries			16%		Author's calculations based on IMS MIDAS data
10	Estimated 36-country expenditure (in millions) in 2015 on cancer drugs launched during 2006–2010			$13,539		(8) * (9)
	Age group	All ages	All ages	Below 75	Below 65	
11	Estimated age group share of cancer drug expenditure	100%	100%	76%	52%	International Agency for Research on Cancer (2017b)
12	Estimated 2015 36-country expenditure (in millions) by age group on cancer drugs launched during 2006–2010	$13,539	$13,539	$10,264	$7,106	(10) * (11)
	Pharmaceutical expenditure per life-year gained calculation					
13	Pharmaceutical expenditure per life-year gained	$1,685	$1,635	$2,276	$2,820	(12)/(5)

million additional YLL (YLL at all ages), 4.51 million additional YLL75 (YLL before age 75), and 2.52 million additional YLL65 (YLL before age 65).

Additional calculations indicate that drugs launched during the entire 1982–2010 period reduced the number of cancer DALYs in 2015 by about 23.0%, and that, in the absence of new drug launches during 1982–2010, there would have been 26.3 million additional DALYs in 2015. Also, the nine countries with the largest number of drug launches during 1982–2010 (weighted by the coefficients in rows 2–4 of Table 2) are estimated to have had 14% fewer cancer DALYs (controlling for incidence) in 2015 than the nine countries with the smallest number of drug launches during 1982–2010.

Calculations of 2015 expenditure on drugs launched during 2006–2010 are shown in rows 6–13. As shown in row 6, according to the IMS Institute for Healthcare Informatics (2016, p. 4), "the total [global] cost of oncology therapeutics and supportive care drugs rose from $90 billion in 2011 to $107 billion in 2015, measured at invoice price levels."[26] The 36 countries in our sample accounted for 78% of world pharmaceutical expenditure in 2014 (row 7); I assume that they also accounted for 78% of world oncology drug expenditure in 2015, so I estimate the 36-country cost of oncology therapeutics and supportive care drugs in 2015 to be $83.1 billion (= 78% * $107 billion; row 8). This is an estimate of expenditure in the 36 countries in 2015 on *all* cancer drugs, i.e. drugs launched in all previous years. To estimate expenditure on cancer drugs launched during 2006–2010, we should multiply this estimate by the fraction of 2015 expenditure that was on drugs launched 5–9 years earlier. Data on expenditure in 2015, by molecule and country, are not available, but data on expenditure in 2010, by molecule and country, are available for 31 of the 36 countries from the IMS MIDAS database. As shown in row 9, those data indicate that about one-sixth (16%) of 2010 pharmaceutical expenditure was on drugs launched in the respective country 5–9 years earlier (i.e. during 2001–2005).[27] Assuming that the same fraction applies to 2015 cancer drug expenditure, 2015 expenditure in the 36 countries on cancer drugs launched during 2006–2010 was $13.5 billion (=16% * $83.1 billion; row 10). This is an estimate of expenditure by, or on behalf of, *all* cancer patients, i.e. patients of all ages. To calculate cost per-life year gained before ages 75 and 65, we require estimates of the fractions of cancer drug expenditure by, or on behalf of, cancer patients below ages 75 and 65. According to GLOBOCAN 2012, globally 76% of cancer patients are diagnosed before age 75, and 52% are diagnosed before age 65 [International Agency for Research on Cancer (2017b); row 11]. I therefore assume that 76% of cancer drug expenditure was on patients below age 75, and 52% of cancer drug expenditure was on patients below age 65 (row 12). These estimates may be conservative (i.e. overestimates), because some drug expenditure on a patient diagnosed before age x may occur after the patient is older than age x.

Estimates of the cost-effectiveness measure—the ratio of estimated 2015 expenditure on drugs launched during 2006–2010 (row 12) to the reduction in 2015 life-years lost due to those drugs (row 5)—are shown in row 13. The estimated cost per life-year gained ranges between $1,635 (life-years gained at all ages) and $2,820

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(life-years gained before age 65). These estimates are similar to those obtained in three previous country-specific studies (Belgium: €1,311 [Lichtenberg (2016a)]; Mexico $2,146 [Lichtenberg (2017)]; Canada: $2,730 [Lichtenberg (2015)]), it is well below the estimate obtained in one country-specific study (Switzerland: $21,228–$28,673 [Lichtenberg (2016b)]).

As noted by Bertram et al (2016), authors writing on behalf of the WHO's *Choosing Interventions that are cost-effective* project (WHO-CHOICE) suggested in 2005 that "interventions that avert one DALY for less than average per capita income for a given country or region are considered very cost–effective; interventions that cost less than three times average per capita income per DALY averted are still considered cost–effective." Population-weighted average per capita income (GDP) in the 36 countries in 2015 was $US 21,359, so these estimates indicate that the new drugs launched during 2006–2010 were very cost-effective, overall.

Two considerations suggest that the figures in row 13 of Table 3 may overestimate the true net cost per life-year gained. First, those estimates are based on drug cost measured at invoice price levels, but "cancer medicines are subject to different types of off-invoice discounts, rebates and price concessions based on how the medicines are reimbursed or administered to patients" [IMS Institute for Healthcare Informatics (2016, p. 26)].[28] Second, a previous study based on U.S. data [Lichtenberg (2014)] showed that about 25% of the cost of new drugs (for all diseases) is offset by reduced expenditure on old drugs.[29]

8. SUMMARY

Several previous studies have provided evidence about the mortality impact and cost-effectiveness of new cancer drugs in single (mostly small) countries, by employing one kind of two-way fixed effects research design: they analyzed, within each country, the correlation across cancer sites between long-run increases in the number of drugs ever launched and mortality changes. This study has employed a different kind of two-way fixed effects research design to measure the mortality impact and cost-effectiveness of cancer drugs: it analyzed the correlation across 36 countries between *relative* mortality from 19 types of cancer in 2015 and the *relative* number of drugs previously launched in that country to treat that type of cancer, controlling for relative incidence. The sample size (both in terms of the number of observations and the population covered) of this study was considerably larger than the sample sizes of previous studies; a new and improved method of analyzing the lag structure of the relationship between drug launches and life-years lost was used; and a larger set of measures of the burden of cancer was analyzed. We showed that the relative number of drugs launched for a cancer site in a country is positively related to relative market size (number of patients diagnosed).

DALYs and life-years lost are unrelated to drug launches 0–4 years earlier. This is not surprising, since utilization of a drug tends to be quite low during the first few post-launch years. Moreover, there is likely to be a lag of several years between utilization of a drug and its impact on mortality. However, mortality is significantly

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inversely related to the number of drug launches at least 5 years earlier, especially to drug launches 5–9 years earlier. One additional drug for a cancer site launched during 2006–2010 is estimated to have reduced the number of 2015 DALYs due to cancer at that site by 5.8%; one additional drug launched during 1982–2005 is estimated to have reduced the number of 2015 DALYs by about 2.6%. Lower quality (or effectiveness) of earlier vintage drugs may account for their smaller estimated effect.

When the United States is excluded from the sample, the magnitude of the point estimates is generally about 15% smaller than the magnitude of the point estimates based on the full sample (although some are larger), and the U.S.-excluded estimates are somewhat less significant. However, most of the estimates continue to be highly significant (p-value < 0.04), and the basic pattern of the estimates remains.

The estimates implied that drugs launched during 2006–2010 reduced the number of cancer DALYs in 2015 by about 8.7% and that, in the absence of new drug launches during 2006–2010, there would have been 8.04 million additional DALYs lost due to cancer in the 36 countries. The estimates also implied that, in the absence of new drug launches during 2006–2010, there would have been 4.51 million additional YLL before age 75, and 2.52 million additional YLL before age 65.

We also estimated that drugs launched during the entire 1982–2010 period reduced the number of cancer DALYs in 2015 by about 23.0%, and that, in the absence of new drug launches during 1982–2010, there would have been 26.3 million additional DALYs lost in 2015. Also, the nine countries with the largest number of drug launches during 1982–2010 are estimated to have had 14% fewer cancer DALYs (controlling for incidence) in 2015 than the nine countries with the smallest number of drug launches during 1982–2010.

Estimates of the cost per life-year gained in 2015 from drugs launched during 2006–2010 ranged between $1,635 (life-years gained at all ages) and $2,820 (life-years gained before age 65). These estimates are similar to those obtained in previous country-specific studies of Belgium, Canada, and Mexico, and are well below the estimate obtained in one study of Switzerland.

Mortality in 2015 is strongly inversely related to the number of drug launches in 2006–2010. If the relationship between mortality in 2020 and the number of drug launches in 2011–2015 is similar, drug launches 5–9 years earlier will reduce mortality even more (by 9.9%) between 2015 and 2020 than they did (by 8.4%) between 2010 and 2015.

NOTES

1 A new molecular entity (NME) or new chemical entity (NCE) is a drug or chemical that is without precedent among regulated and approved drug products. The NME designation indicates that a drug in development is not a version or derivative of an existing and previously investigated, trialed, and approved substance. http://www.glossary.pharma-mkting.com/NME.htm

2 Some cancer drugs are used to treat several types of cancer. I consider the launch of a drug used to treat three types of cancer as three launches: one launch for each type of cancer.

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3 If 100 people die from lung cancer at age 60, they have collectively lost 500 (= 100 * (65–60)) years of life before age 65, and 1,500 (= 100 * (75–60)) years of life before age 75. Hence, YLL depends on the number of deaths, age at death, and the age cut-off that is used. Brustugun et al (2014, p. 1014) argue that "number of years of life lost (YLL) may be a more appropriate indicator of [the] impact [of cancer] on society" than the number of deaths, and Burnet et al (2005, p. 241) argue that "years of life lost (YLL) from cancer is an important measure of population burden—and should be considered when allocating research funds." Kirch (2008, p. 1365) also states that "the most widely used summary health indexes [which are used to analyze the benefits of health interventions] are disability-adjusted life years (DALY), quality-adjusted life years (QALY), healthy life expectancy (HALE), and years of potential life lost (YPLL)."

4 A two-way fixed effects model in effect analyzes the correlation between Y' and X', where $Y' = [(Y_{A2}-Y_{A1})-(Y_{B2}-Y_{B1})]$ and Y_{sc} ($s = A, B$; $c = 1, 2$) is the mean value of Y of observations where the first attribute equals s and the second attribute equals c; X' and X_{sc} are similarly defined. One of the most common types of two-way fixed effects models is a "difference-in-difference model," in which s refers to different sectors (e.g. industries or states), and c refers to different time periods. In the two-way fixed effects models that I will estimate, s will refer to 19 different cancer sites, and c will refer to 36 different countries. Although I will in effect be analyzing the correlation between Y' and X' (as defined above), to avoid confusion I will not refer to my model as a difference-in-differences model.

5 Appendix Table A.1 shows the number of drugs launched during 2006–2015, for all countries and cancer sites.

6 In the social sciences, *triangulation* is often used to indicate that two (or more) methods are used to check the results of one and the same subject. The idea is that one can be more confident with a result if different methods lead to the same result. https://en.wikipedia.org/wiki/Triangulation_(social_science)

7 The new method allows us to test the hypothesis that, due to offsetting trends in drug quantity (utilization) and quality (effectiveness), the relationship between the year in which a drug was launched and its effect on mortality in 2015 is nonmonotonic (inverted-U-shaped).

8 The discovery of new ideas could increase economic output for two different reasons. First, output could simply be positively related to the *quantity* (and variety) of ideas ever discovered. Second, output could be positively related to the (mean or maximum) *quality* of ideas ever discovered, and new ideas may be better (of higher quality), on average, than old ideas.

9 We hypothesize that innovations may be embodied in nondurable goods (e.g. drugs) and services as well as in durable equipment.

10 R&D intensity is the ratio of R&D to sales.

11 Sampat and Lichtenberg (2011) showed that government funding has played an indirect role—for example, by funding basic underlying research that is built on in the drug discovery process—in almost half of the drugs approved and in almost two-thirds of priority-review drugs.

12 The DALY is a summary measure that combines time lost through premature death and time lived in states of less than the optimal health, loosely referred to as "disability." The DALY is a generalization of the well-known Potential Years of Life Lost measure (PYLL) to include lost good health. One DALY can be thought of as one lost year of "healthy" life and the measured disease burden is the gap between a population's health status and that of a normative reference population. DALYs for a specific cause are calculated as the sum of the YLLs from that cause and the YLDs for people living in states of less than good health resulting from the specific cause [World Health Organization (2017a), p. 5].

13 My data on drug launches are left-censored: I only have data on drugs launched after 1981. A post-1981 new chemical entity is one that was first launched anywhere in the world after 1981.

14 When equation (1) is estimated without weighting, the residuals clearly exhibit heteroskedasticity: The variance of the residuals is strongly inversely related to $Y_{sc,2015}$.

15 Grossman and Helpman (1993) argued that "innovative goods are better than older products simply because they provide more 'product services' in relation to their cost of production." Bresnahan and Gordon (1996) stated simply that "new goods are at the heart of economic progress," and Bils (2004) said that "much of economic growth occurs through growth in quality as new models of consumer

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goods replace older, sometimes inferior, models." As noted by Jovanovic and Yatsenko (2012), in "the Spence–Dixit–Stiglitz tradition…new goods [are] of higher quality than old goods."

16 The mortality impact will increase with respect to drug age (time since launch) if the rate of increase of quantity with respect to age is greater than the rate of decline of quality with respect to age; otherwise the mortality impact will decline.

17 A smaller estimated impact on mortality of drugs launched in earlier periods could also be partly attributable to left-censoring of the data on drug launches: Unmeasured launches of pre-1983 drugs were more likely to occur in earlier years than in more recent years.

18 See World Health Organization (2017a) for a description of WHO methods and data sources for global burden of disease estimates.

19 The 19 cancer sites account for 87% of all cancer DALYs and about 80% of YLL65.

20 Improved cancer screening and detection may account for part of this increase.

21 Estimates of all parameters of this model are shown in Appendix Table A.4.

22 The difference ($\beta_{5–9}-\beta_{10–14}$) is highly significant (p-value = 0.0006); the difference ($\beta_{10–14}-\beta_{15+}$) is insignificant ($p$-value = 0.9149).

23 See http://globocan.iarc.fr/Pages/DataSource_and_methods.aspx for a discussion of GLOBOCAN 2012 incidence measurement.

24 I also estimated equation (1) where the dependent variable was the log of the *number of deaths* from cancer at site s in country c in 2015. The only launch coefficient that was statistically significant was the coefficient on LAUNCHES_2006_2010 (estimate = −0.031; $Z = 2.49$; p-value = 0.0127).

25 These drugs are probably more expensive than older drugs because they are more likely to retain patent protection, the estimates in Table 2 indicate that they are also more effective.

26 This amount is 9.74% of world pharmaceutical expenditure ($1,098 million) in 2014 [International Federation of Pharmaceutical Manufacturers & Associations (2017, Annex 2)]. According to the IMS Institute, "the United States derive 11.5% of its total drug costs from oncology, up from 10.5% in 2011. In developed countries, between 8.6% and 15.9% of the total drug bill is spent on oncology and supportive care medicines. Oncology accounts for a smaller portion of total medicines costs in pharmerging countries, where between 2.5% and 11.5% of total drug cost is for cancer treatments" [IMS Institute for Healthcare Informatics (2016), p. 22].

27 That estimate applies to all drugs, not just cancer drugs.

28 According to the IMS Institute, in the United States, net price growth on existing branded oncology drugs is estimated to have averaged 4.8% in 2015, versus 6.4% invoice price growth. In Europe, a range of discounts and other mechanisms also exist, resulting in lower realized prices by manufacturers [IMS Institute for Healthcare Informatics (2016), p. 5].

29 That study also demonstrated that pharmaceutical innovation has reduced work-loss days.

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Appendix

TABLE A.1. Number of drugs launched during 2006–2015, by country and cancer site

Country	Mean	C15 oesophagus cancer	C16 stomach cancer	C18–C21 Colon and rectum cancers	C22 liver cancer	C25 pancreas cancer	C33–C34 trachea, bronchus, lung cancers	C43 malignant skin melanoma	C50 breast cancer	C53 cervix uteri cancer	C56 ovary cancer	C61 prostate cancer	C64–C66 kidney, renal pelvis and ureter cancer	C67 bladder cancer	C70–C72 brain and nervous system cancers	C73 thyroid cancer	C81 hodgkin lymphoma	C82–C86, C96 Non-hodgkin lymphoma	C88, C90 multiple myeloma	C91–C95 leukaemia
Argentina	**1.6**	1	0	3	0	2	5	0	3	1	1	3	2	0	1	1	0	3	1	4
Australia	**2.9**	0	2	5	1	2	5	5	7	0	0	4	1	0	1	1	1	7	3	10
Austria	**3.8**	0	2	6	2	4	7	6	4	0	2	4	2	1	1	3	2	10	4	13
Belgium	**3.4**	0	0	7	2	3	8	1	6	2	4	4	2	1	1	2	1	8	3	9
Brazil	**2.2**	0	1	4	1	4	3	2	6	1	1	3	2	0	0	1	1	4	2	6
Canada	**1.8**	0	0	5	1	2	1	2	3	0	1	2	1	0	0	1	1	5	1	8
Chile	**2.9**	0	1	3	2	4	7	2	9	2	4	4	2	1	1	1	0	5	3	4
Colombia	**1.7**	0	0	2	1	2	5	1	5	2	2	1	2	0	0	1	0	3	2	4
Denmark	**3.1**	0	1	5	1	2	6	5	3	0	1	4	2	0	1	3	2	9	3	11
Ecuador	**1.2**	0	0	2	1	2	2	0	4	0	1	0	1	0	0	1	0	3	2	4
Egypt	**3.0**	1	3	5	2	3	7	0	11	2	4	5	1	1	1	1	0	2	1	7
Finland	**3.2**	0	1	4	1	2	7	6	3	0	1	4	2	0	1	3	2	9	3	11
France	**3.1**	1	2	4	1	2	6	4	5	0	1	5	1	0	1	2	1	8	3	11
Germany	**3.0**	0	0	3	1	2	5	5	3	0	1	4	2	0	1	3	2	10	3	12
Greece	**1.2**	0	0	2	1	2	2	0	1	0	0	2	1	0	0	1	0	3	2	6
Indonesia	**1.1**	0	0	2	1	3	2	0	4	0	0	1	1	0	0	1	0	1	1	4
Ireland	**3.3**	0	1	3	2	3	7	4	6	0	3	4	2	1	1	2	2	9	3	9

TABLE A.1. Continued

Country	Mean	C15 oesophagus cancer	C16 stomach cancer	C18–C21 Colon and rectum cancers	C22 liver cancer	C25 pancreas cancer	C33–C34 trachea, bronchus, lung cancers	C43 malignant skin melanoma	C50 breast cancer	C53 cervix uteri cancer	C56 ovary cancer	C61 prostate cancer	C64–C66 kidney, renal pelvis and ureter cancer	C67 bladder cancer	C70–C72 brain and nervous system cancers	C73 thyroid cancer	C81 hodgkin lymphoma	C82–C86, C96 Non-hodgkin lymphoma	C88, C90 multiple myeloma	C91–C95 leukaemia
Italy	**1.8**	0	0	2	1	2	2	2	3	0	1	2	0	0	0	1	1	7	2	9
Japan	**3.3**	0	1	6	1	4	7	3	7	1	1	4	3	0	2	2	2	6	3	9
Mexico	**2.2**	0	0	2	0	4	3	2	5	1	2	3	1	0	1	1	1	7	3	5
Netherlands	**1.8**	0	1	3	1	1	2	3	3	0	0	4	1	0	0	2	0	3	3	7
Pakistan	**0.9**	0	0	2	1	3	3	0	4	1	1	0	1	0	0	1	0	0	0	1
Peru	**2.1**	1	2	2	2	2	2	1	8	1	2	4	0	1	0	1	1	3	1	6
Philippines	**2.3**	0	1	4	1	4	6	0	6	2	3	2	2	0	1	1	0	4	2	4
Portugal	**3.2**	2	3	5	2	3	9	4	8	1	5	2	1	2	0	1	3	4	1	5
Saudi	**1.8**	0	2	1	1	2	3	0	7	1	1	3	0	0	1	1	0	5	1	5
Singapore	**2.1**	0	0	2	2	4	4	1	6	0	2	3	1	1	1	1	1	4	1	5
South	**2.8**	1	1	5	2	3	5	2	6	1	4	5	1	1	0	1	1	6	3	6
Spain	**2.8**	1	1	3	1	2	6	3	6	1	2	5	1	0	1	1	1	6	2	10
Sweden	**3.2**	1	2	4	1	2	6	5	5	0	1	4	2	0	1	3	2	9	2	11
Switzerland	**2.6**	0	0	3	1	3	4	4	5	0	1	4	1	0	1	3	1	7	2	10
Thailand	**1.8**	0	0	3	1	2	1	1	5	0	1	3	1	0	1	1	0	5	3	6
Turkey	**2.1**	0	0	5	1	3	3	2	5	1	2	2	2	0	1	1	0	4	1	7
UK	**2.7**	0	1	3	1	3	6	3	4	0	1	4	1	0	1	2	1	8	2	10
USA	**3.4**	0	1	4	0	3	6	7	5	0	1	4	2	0	2	2	2	10	5	11
Venezuela	**0.1**	0	0	0	0	0	0	0	2	0	0	0	0	0	0	0	0	0	0	0

TABLE A.2. Post-1981 drugs indicated for different types of cancer

	C15 oesophagus cancer	C16 stomach cancer	C18–C21 colon and rectum cancers	C22 liver cancer	C25 pancreas cancer	C33–C34 trachea, bronchus, lung cancers	C43 malignant skin melanoma	C50 breast cancer	C53 cervix uteri cancer	C56 ovary cancer	C61 prostate cancer	C64–C66 kidney, renal pelvis and ureter cancer	C67 Bladder cancer	C70–C72 brain and nervous system cancers	C73 thyroid cancer	C81 hodgkin lymphoma	C82–C86, C96 non-hodgkin lymphoma	C88, C90 multiple myeloma	C91–C95 leukaemia
No. of drugs	**3**	**6**	**10**	**3**	**9**	**18**	**10**	**26**	**2**	**8**	**12**	**4**	**2**	**4**	**3**	**3**	**19**	**7**	**27**
Afatinib						1													
Aflibercept			1																
Alemtuzumab																			1
Amifostine										1									
Amsacrine																			1
Anastrozole								1											
Arsenic trioxide																			1
Azacitidine																			1
Bevacizumab			1			1		1	1	1		1							
Bexarotene																	1		
Bicalutamide											1								
Blinatumomab																			1
Bortezomib																	1	1	
Bosutinib																			1
Brentuximab vedotin																1	1		
Buserelin											1								
Cabazitaxel											1								
Capecitabine		1	1					1											

TABLE A.2. Continued

	C15 oesophagus cancer	C16 stomach cancer	C18–C21 colon and rectum cancers	C22 liver cancer	C25 pancreas cancer	C33–C34 trachea, bronchus, lung cancers	C43 malignant skin melanoma	C50 breast cancer	C53 cervix uteri cancer	C56 ovary cancer	C61 prostate cancer	C64–C66 kidney, renal pelvis and ureter cancer	C67 Bladder cancer	C70–C72 brain and nervous system cancers	C73 thyroid cancer	C81 hodgkin lymphoma	C82–C86, C96 non-hodgkin lymphoma	C88, C90 multiple myeloma	C91–C95 leukaemia
Carboplatin						1				1									
Ceritinib						1													
Cetuximab			1																
Cladribine																			1
Clofarabine																			1
Cobimetinib							1												
Crizotinib						1								1			1		
Dabrafenib							1												
Daratumumab																		1	
Dasatinib																			1
Decitabine																			1
Degarelix											1								
Denileukin diftitox																	1		
Denosumab											1								
Dinutuximab														1					
Docetaxel	1	1				1		1			1								
Enzalutamide											1								
Epirubicin	1	1		1	1	1		1		1			1			1	1		
Eribulin								1											
Erlotinib					1	1													
Everolimus					1			1											

TABLE A.2. Continued

	C15 oesophagus cancer	C16 stomach cancer	C18–C21 colon and rectum cancers	C22 liver cancer	C25 pancreas cancer	C33–C34 trachea, bronchus, lung cancers	C43 malignant skin melanoma	C50 breast cancer	C53 cervix uteri cancer	C56 ovary cancer	C61 prostate cancer	C64–C66 kidney, renal pelvis and ureter cancer	C67 Bladder cancer	C70–C72 brain and nervous system cancers	C73 thyroid cancer	C81 hodgkin lymphoma	C82–C86, C96 non-hodgkin lymphoma	C88, C90 multiple myeloma	C91–C95 leukaemia
Exemestane								1											
Fludarabine																			1
Flutamide											1								
Formestane								1											
Fotemustine							1							1					
Fulvestrant								1											
Fadobenic acid								1											
Fefitinib						1													
Gemcitabine				1	1	1		1		1			1						
Goserelin								1			1								
Ibandronic acid								1											
Ibrutinib																	1	1	1
Idarubicin																			1
Idelalisib																	1		1
Imatinib																			1
Interferon alfa-2a							1					1					1		1
Interferon alfa-2b							1										1	1	1
Ipilimumab							1												
Irinotecan			1																

TABLE A.2. Continued

	C15 oesophagus cancer	C16 stomach cancer	C18–C21 colon and rectum cancers	C22 liver cancer	C25 pancreas cancer	C33–C34 trachea, bronchus, lung cancers	C43 malignant skin melanoma	C50 breast cancer	C53 cervix uteri cancer	C56 ovary cancer	C61 prostate cancer	C64–C66 kidney, renal pelvis and ureter cancer	C67 Bladder cancer	C70–C72 brain and nervous system cancers	C73 thyroid cancer	C81 hodgkin lymphoma	C82–C86, C96 non-hodgkin lymphoma	C88, C90 multiple myeloma	C91–C95 leukaemia
Iapatinib								1											
Lenalidomide																	1	1	
Lenvatinib															1				
Letrozole								1											
Leuprorelin								1			1								
Miltefosine								1											
Mitoxantrone								1			1						1		1
Nelarabine																	1		1
Nilotinib																			1
Nilutamide											1								
Nivolumab						1	1					1				1			
Obinutuzumab																	1		1
Octreotide		1			1														
Ofatumumab																			1
Oxaliplatin			1																
Paclitaxel					1	1		1		1									
Panitumumab			1																
Panobinostat																		1	
Pasireotide					1														

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TABLE A.2. Continued

	C15 oesophagus cancer	C16 stomach cancer	C18–C21 colon and rectum cancers	C22 liver cancer	C25 pancreas cancer	C33–C34 trachea, bronchus, lung cancers	C43 malignant skin melanoma	C50 breast cancer	C53 cervix uteri cancer	C56 ovary cancer	C61 prostate cancer	C64–C66 kidney, renal pelvis and ureter cancer	C67 Bladder cancer	C70–C72 brain and nervous system cancers	C73 thyroid cancer	C81 hodgkin lymphoma	C82–C86, C96 non-hodgkin lymphoma	C88, C90 multiple myeloma	C91–C95 leukaemia
Pazopanib												1							
Pegaspargase																			1
Pembrolizumab						1	1												
Pemetrexed						1													
Pentostatin																			1
Pertuzumab								1											
Pirarubicin								1											
Pixantrone																	1		
Plerixafor																	1	1	
Ponatinib																			1
Porfimer sodium	1					1													
Raltitrexed			1																
Ramucirumab		1	1			1													
Regorafenib			1																
Rituximab																	1		1
Romidepsin																	1		

TABLE A.2. Continued

	C15 oesophagus cancer	C16 stomach cancer	C18–C21 colon and rectum cancers	C22 liver cancer	C25 pancreas cancer	C33–C34 trachea, bronchus, lung cancers	C43 malignant skin melanoma	C50 breast cancer	C53 cervix uteri cancer	C56 ovary cancer	C61 prostate cancer	C64–C66 kidney, renal pelvis and ureter cancer	C67 Bladder cancer	C70–C72 brain and nervous system cancers	C73 thyroid cancer	C81 hodgkin lymphoma	C82–C86, C96 non-hodgkin lymphoma	C88, C90 multiple myeloma	C91–C95 leukaemia
Sorafenib				1											1				
Streptozocin					1														
Sunitinib					1														
Temozolomide														1					
Temsirolimus																	1		
Topotecan						1			1	1									
Toremifene								1											
Trabectedin										1									
Trametinib							1												
Trastuzumab		1						1											
Trastuzumab emtansine								1											
Vandetanib															1				
Vemurafenib							1												
Vinorelbine						1		1											
Zorubicin																			1

TABLE A.3. Drug launch years

	Argentina	Australia	Austria	Belgium	Brazil	Canada	Chile	Colombia	Denmark	Ecuador	Egypt	Finland	France	Germany	Greece	Indonesia	Ireland	Italy
AFATINIB		2014		2014			2014		2013			2013	2014				2014	
AFLIBERCEPT		2012	2013	2013	2013	2013	2013		2012	2014		2012	2013	2012	2014	2014	2013	2013
ALEMTUZUMAB	2005	2007	2001	2003		2006			2001			2002	2002	2001		2007	2001	2002
AMIFOSTINE	1995	1998	1995	1999	1997	1996		1998	1996	1998		1996	1995	1995	1997	1998		1998
AMSACRINE		1985		2014					1985			1986	2004	1985			1997	
ANASTROZOLE	1997	1997	1996	1997	1997	1996	2000	1998	1997	2001	2004	1996	1997	1996	1998	1998	1996	1996
ARSENIC TRIOXIDE			2002	2005									2003		2007			2004
AZACITIDINE	2009	2009	2009		2011	2013	2011	2011	2009	2012	2015	2009	2009	2009	2010		2009	2010
BEVACIZUMAB	2006	2005	2005	2007	2006	2005	2006	2006	2005	2005	2011	2005	2005	2005	2005	2005	2005	2005
BEXAROTENE			2002	2007					2005	2007		2005	2002	2002	2004		2002	2004
BICALUTAMIDE	1996	1996	1997	1997	1996	1996	1999	1998	1996	2001	2004	1995	1998	1996	1997		1995	1996
BLINATUMOMAB																		
BORTEZOMIB	2005	2007	2004	2005	2006	2005	2006	2006	2004	2007	2011	2004	2004	2004	2006	2006	2004	2005
BOSUTINIB			2013						2013					2013				
BRENTUXIMAB VEDOTIN		2011	2012	2014	2015	2013			2012			2012	2013	2012			2013	2014
BUSERELIN	1990		1987	1986	1993	1988		1992	1985			1985	1986	1984	1987		1986	1985
CABAZITAXEL	2011	2012	2011	2012	2011		2014		2011			2011	2011	2011		2013	2012	
CAPECITABINE	2003	1999	2000	2001	1999	1998	1999	2000	2001	2001	2011	2001	1998	2001	1999	2000	2001	2001
CARBOPLATIN	1989	1987	1988	1994	1990	1986	2001	1998	1990	1998	2004	1988	2003	1988	1987	1992	2012	1989
CERITINIB			2015			2015			2015			2015	2015	2015				
CETUXIMAB	2006	2005	2004	2006	2007	2008	2005	2009	2004	2005	2012	2004	2004	2004	2006	2007	2004	2005
CLADRIBINE	1998	1994	2004	2011		1993	2009	1999	1994			1995	2005	2004	1999		1996	1999
CLOFARABINE	2011	2006	2007	2008						2012		2008	2006	2006			2013	2008

TABLE A.3. Continued

	Argentina	Australia	Austria	Belgium	Brazil	Canada	Chile	Colombia	Denmark	Ecuador	Egypt	Finland	France	Germany	Greece	Indonesia	Ireland	Italy
COBIMETINIB																		
CRIZOTINIB	2013	2014	2012	2013			2014		2012			2012	2012	2012			2014	
DABRAFENIB			2013			2013			2013			2013	2013	2013			2014	2014
DARATUMUMAB																		
DASATINIB	2008	2007	2007	2007	2008	2007	2007	2007	2006	2013	2012	2006	2006	2006	2007	2007		2007
DECITABINE	2007		2012	2013	2009				2013			2013	2014	2012		2008	2013	2014
DEGARELIX	2010	2010	2009	2010	2012		2014		2009		2013	2009	2010	2009	2009		2009	
DENILEUKIN DIFTITOX																		
DENOSUMAB	2011	2010	2010	2010	2012	2010	2011		2010		2013	2010	2012	2010	2014		2010	2011
DINUTUXIMAB																		
DOCETAXEL	1996	1996	1996	1997	1995	1995	2004	2000	1996	1999	2011	1996	2010	1996	1996	1997	1996	1996
ENZALUTAMIDE		2014	2013	2014		2013	2014		2013			2013	2014	2013			2014	2014
EPIRUBICIN	1984	1986	1986	1986	1985	1985	1985	1998	1985	2001	1989	1986	1986	1984	1985	2003	1985	1984
ERIBULIN		2014	2011	2013	2014				2011			2011	2012	2011			2012	2012
ERLOTINIB	2007	2006	2005	2006	2006	2005	2007	2006	2005	2006		2005	2005	2005	2006	2007	2005	2006
EVEROLIMUS	2005	2005	2004	2005	2006		2006	2004	2004	2005	2011	2004	2005	2004	2004	2009	2009	2005
EXEMESTANE	2000	2001	2000	2000	2000	2000	2006	2003	2000	2001	2005	2000	2000	2000	2001	2004	2000	2000
FLUDARABINE	2003	1997	2015	2010	2013	2013		2004	1995	2012	2012	2009	2008	1997	1997		2015	1995
FLUTAMIDE	1986	1991	1987	1986	1986	1985	1983	1986	1985	1988	2006	1993	1987	1984	1987	1988	1986	1986
FORMESTANE	1998		1994		1996	1994	1998		1995		1997	1996	1995	1994	1995	1996	1993	1995
FOTEMUSTINE	1994	1993	1995	2005									1989		2000			2001
FULVESTRANT	2005	2008	2004	2006	2003	2006	2009	2006	2004		2014	2004	2004	2004	2004		2004	2005
GADOBENIC ACID		2006	1999	2001					2000			2000	2002	1998	2001	2011	2002	1999

TABLE A.3. Continued

	Argentina	Australia	Austria	Belgium	Brazil	Canada	Chile	Colombia	Denmark	Ecuador	Egypt	Finland	France	Germany	Greece	Indonesia	Ireland	Italy
GEFITINIB	2004	2003	2009	2010	2011	2004	2005	2012	2009		2015	2009	2002	2009	2010	2004	2003	2010
GEMCITABINE	1996	1995	2009	2009	1996	1997	2006	1998	1997	2001	2014	1995	1996	1996	1997	1997	2012	1996
GOSERELIN	1992	1989	1988	1988	1992	1990	2001	1997	1988	1999	1997	1988	1988	1988	1991	1992		1988
IBANDRONIC ACID	2006	2008	1996	2005	2006	2004	2006	2006	1998	2004	2012	1997	2007	1996	2000	2007	2004	2005
IBRUTINIB			2014	2015		2014			2014				2014	2014			2015	
IDARUBICIN	1991	2011	1991	1992	2008	1991	1998	1998	1990	2001	2012	1993	1992	1991	1998	1992	1990	1990
IDELALISIB			2014						2014			2014	2014	2014				2015
IMATINIB	2001	2001	2001	2002	2001	2001	2004	2001	2001	2001	2011	2001	2001	2001	2002	2002	2002	2002
INTERFERON ALFA-2A	1990	1988	1990	1989	1989	1989	1995	1992	1993	1992	1993	1989	1996	1987	1990	1995	1987	1987
INTERFERON ALFA-2B	1987	2014	1987	1986	1989	1986	1994	1989	1986	1988	1990	1986	1996	1987	1988	2005	1985	1987
IPILIMUMAB		2014	2011	2012	2013		2014	2014	2011			2011	2011	2011			2012	2013
IRINOTECAN	1997	1997	2009	2009	2001	1997	2004	1998	1998	2001	2007	1997	1995	1998	1998	2000	1998	1997
LAPATINIB	2007	2007	2008	2009	2008	2009	2008		2008	2009	2011		2008	2008	2008	2008	2009	2009
LENALIDOMIDE	2011		2007	2008			2011	2009	2007	2009		2008	2007	2007	2011		2007	2008
LENVATINIB			2015						2015			2015	2015	2015				
LETROZOLE	1998	1997	1997	1999	1998	1997	2000	1999	1997	1999	1998	1997	1997	1997	1998	2002	2000	1997
LEUPRORELIN	1987	1986	1994	2005	1990	1985	1992	1989	1992	1994	2009	1992	1987	1984	1990	1993	1991	1989
MILTEFOSINE	1998						2000			2007		2007	1997	1993				2003
MITOXANTRONE	1987	1985	2004	1986	1987	1984	1989	2006	1987	2001	1990	1989	1986	1985	1987		1984	1987
NELARABINE			2009	2008		2008			2007			2007	2008	2007			2007	2008
NILOTINIB		2008	2008	2008	2009	2008	2012	2009	2008		2012	2008	2008	2008	2008	2007	2008	2008
NILUTAMIDE	1990	1997			1989	1992		1998	1998		1994	1993	1987		1999			
NIVOLUMAB			2015						2015			2015		2015			2015	
OBINUTUZUMAB		2015	2015			2014			2014			2014		2014			2015	
OCTREOTIDE	1999	2000	2010	1988	2008	1999	1993	1991	1988	1996	2005	1990	1991	1991	1990	1992	1988	1990

TABLE A.3. Continued

	Argentina	Australia	Austria	Belgium	Brazil	Canada	Chile	Colombia	Denmark	Ecuador	Egypt	Finland	France	Germany	Greece	Indonesia	Ireland	Italy
OFATUMUMAB		2015	2010						2010			2010	2010	2010	2011			2011
OXALIPLATIN	1997	2007	2006	2008	2001	2007	1998	1998	2006	1999	2004	2006	1996	1999	2005	2001	2003	2000
PACLITAXEL	1993	1996	1993	1994	1994	1993	1998	2004	1994	2003	1996	1994	1994	1994	1994	1994	2004	1995
PANITUMUMAB	2011	2006	2008	2008	2011	2008	2012		2008	2015	2009	2008	2008	2008			2008	2009
PANOBINOSTAT			2015									2015						
PASIREOTIDE			2012			2013			2012			2012	2012	2012				
PAZOPANIB	2015	2010	2010	2011	2011	2010	2011	2012	2010	2011		2010	2013	2010	2011	2011	2010	
PEGASPARGASE						1998							2003	1997				
PEMBROLIZUMAB		2015	2015									2015	2015	2015				
PEMETREXED	2006	2004	2005	2006	2005	2004	2007	2007	2005	2006	2007	2004	2004	2004	2004	2011	2005	2005
PENTOSTATIN						1993			2010					1994	2007			1996
PERTUZUMAB		2013	2013						2013	2014		2013		2013				
PIRARUBICIN	1996		1991										1990					
PIXANTRONE			2012									2012		2012			2015	2015
PLERIXAFOR		2011	2009	2010	2012		2015		2009			2009	2010	2009			2013	2012
PONATINIB		2015	2013									2013	2013	2013			2015	2015
PORFIMER SODIUM	2011					1993							1999	1999				
RALTITREXED	1998	1997	1998		2000	1996		1999				1997					1996	1997

TABLE A.3. Continued

	Argentina	Australia	Austria	Belgium	Brazil	Canada	Chile	Colombia	Denmark	Ecuador	Egypt	Finland	France	Germany	Greece	Indonesia	Ireland	Italy
RAMUCIRUMAB		2015	2015						2015			2015	2014				2015	
REGORAFENIB		2014	2013	2015		2013			2013				2015	2013				
RITUXIMAB	2005	1998	1998	2000		2000	2001	2000	1998	2002	2011	1998		1998	1999	2004	1998	1999
ROMIDEPSIN																		
SORAFENIB		2006	2006	2007	2006	2006	2006	2007	2006	2007	2011	2006	2006	2006	2006	2007	2006	2006
STREPTOZOCIN		2003	1987			1985												
SUNITINIB	2009	2006	2006	2007	2006	2006	2007	2007	2006	2007	2011	2006	2006	2006	2006	2008	2006	2006
TEMOZOLOMIDE	1999	2000	1999	2001	2000	1999	2000	2002	1999	2003	2011	1999	1998	1999	1999	2002	1999	2000
TEMSIROLIMUS	2011	2009	2008	2008	2010	2008	2008		2008			2008	2008	2007	2008		2008	2008
TOPOTECAN	1997	1997	1997	2011	1997	1997	2007	2007	1997	2000	2012	1997	1997	1997	1998		1997	1997
TOREMIFENE	1997	1997	1997	1999	1997			1998	1997			1989	2000	1996	1997		1996	1997
TRABECTEDIN			2007	2009		2010	2014		2007	2012	2013	2007	2008	2007			2008	2009
TRAMETINIB		2014	2015			2013			2015			2015						
TRASTUZUMAB	2005	2015	2000	2001	1999	1999	2007	2001		2002	2011	2000	1999	2000	2000	2003	2000	2001
TRASTUZUMAB EMTANSINE				2014	2014	2013	2014	2014		2014			2014				2015	2014
VANDETANIB	2014		2012	2013					2012			2012		2012			2014	
VEMURAFENIB		2012	2012		2012		2015		2012			2012	2013	2012			2013	
VINORELBINE	1991	2004	1994	1999	1995	1994	2002	2005	1998	2005	2011	1996	1989	1996	1997	2004	2007	1992
ZORUBICIN														1987				

TABLE A.3. Continued

	Japan	Mexico	Netherlands	Pakistan	Peru	Philippines	Portugal	Saudi Arabia	Singapore	South Africa	Spain	Sweden	Switzerland	Thailand	Turkey	UK	USA	Venezuela
AFATINIB	2014					2015			2013		2014		2014			2013	2013	
AFLIBERCEPT	2012	2014	2012			2014	2013		2013		2013	2012	2012	2014	2014	2012	2011	
ALEMTUZUMAB	2015		2001						2004	2006	2002	2001	2002	2007	2007	2001	2001	
AMIFOSTINE		1997	1996	2002	2002	1996			1998	1996	1999	1998	1997	1999	1998	1995	1996	2001
AMSACRINE			1982				2013		1992			1983	1993			1984		
ANASTROZOLE	2001	1998	1997	2000	2004	1999	1998	2001	1997	1996	1997	1996	1996	1998	1998	1995	1996	1999
ARSENIC TRIOXIDE	2004										2004					2006	2000	
AZACITIDINE	2011	2012	2008			2011			2010	2010	2009	2009	2006	2007	2007		2004	
BEVACIZUMAB	2007	2005	2005	2005		2006			2005	2006	2005	2005	2004	2005	2006	2005	2004	
BEXAROTENE			2003								2002	2001			2015	2002	2000	
BICALUTAMIDE	1999	1997	1995	2003	2006	2000	1999		1998	1996	1996	1996	1996	1998	1996	1995	1995	1997
BLINATUMOMAB																	2014	
BORTEZOMIB	2006	2006	2004		2013	2006		2008	2005	2006	2004	2004	2005	2006	2005	2004	2003	
BOSUTINIB	2014											2013	2014			2013	2012	
BRENTUXIMAB VEDOTIN	2014	2014					2012		2014		2014	2012	2013			2012	2011	
BUSERELIN	1988	2000	1985			1987	1988	1992	1986	1988	1986	1988	1995	1992	1988	1986		
CABAZITAXEL	2014	2012	2011		2012	2012			2012	2012	2011	2011	2011	2012	2013	2011	2010	
CAPECITABINE	2003	2000	2001	2002	2012	1999	2013	2006	1999	2000	2001	2001	1998	1998	2002	2001	1998	1999
CARBOPLATIN	1990	1992	1986	1991	1998	1988	2011	1996	1986	2010	1992	1987	1986	1999	1994	1986	1989	2002
CERITINIB			2015				2015					2015				2015	2014	
CETUXIMAB	2008	2004	2004	2009		2005			2005	2008	2005	2004	2003	2007	2014	2004	2004	
CLADRIBINE	2002		1996			2004	2012			2000	2008	1994	1999	1996	2014	1995	1993	

TABLE A.3. Continued

	Japan	Mexico	Netherlands	Pakistan	Peru	Philippines	Portugal	Saudi Arabia	Singapore	South Africa	Spain	Sweden	Switzerland	Thailand	Turkey	UK	USA	Venezuela
CLOFARABINE	2013	2009							2008		2007			2013	2013	2006	2005	
COBIMETINIB													2015				2015	
CRIZOTINIB	2012	2012				2015		2013	2012		2013	2012	2012	2013	2015	2012	2011	
DABRAFENIB			2013								2014	2013			2015		2013	
DARATUMUMAB																	2015	
DASATINIB	2009	2007	2006		2014	2007		2008	2007	2009	2007	2006	2007	2008	2008	2006	2006	
DECITABINE			2012			2009			2013		2014		2012	2009	2010	2013	2006	
DEGARELIX	2012	2010	2009					2012	2014	2014	2015	2010	2010	2014		2009	2009	
DENILEUKIN DIFTITOX																	1999	
DENOSUMAB	2012	2012	2011		2011	2012	2012	2013	2012	2014	2011	2010	2010	2013	2013	2010	2010	
DINUTUXIMAB																	2015	
DOCETAXEL	1997	1995	1996	2005	1997	1997	2011	1997	1997	1995	2010	2010	1997	1997	1997	1996	1996	1996
ENZALUTAMIDE	2014		2013								2014		2013			2013	2012	
EPIRUBICIN	1989	1987	1986	1988	2006	1986	2011	1989	1985	2009	1987	1987	1984	1986	2003	1985	1999	
ERIBULIN	2011		2011			2013			2011		2013	2011	2011	2013		2011	2010	
ERLOTINIB	2007	2006	2005	2006		2006			2006	2009	2006	2005	2005	2005	2009	2005	2004	
EVEROLIMUS	2007	2006	2004	2007	2014	2006		2008	2006	2005	2005	2003	2005	2005	2005	2009	2009	
EXEMESTANE	2002	2004	2000	2011	2002	2003	2000	2011	2001	2002	2000	1999	1999	2001	2005	2000	2000	2010
FLUDARABINE	2010		1994		2012			2012		2011	2008	2014	2008		1994	2010	1992	
FLUTAMIDE	1994	1987	1989	1995	1995	1986	1984	1990	2005	1985	1987	1993	1985	1989	1990	1990	1989	1992
FORMESTANE			1994	1999		1997					1995		1995	1996	1996	1993		
FOTEMUSTINE															1996			
FULVESTRANT	2011	2009	2004		2009	2007			2006	2007	2004	2004	2004	2009	2006	2004	2002	

TABLE A.3. Continued

	Japan	Mexico	Netherlands	Pakistan	Peru	Philippines	Portugal	Saudi Arabia	Singapore	South Africa	Spain	Sweden	Switzerland	Thailand	Turkey	UK	USA	Venezuela
GADOBENIC ACID			2000			2013					2007	1998		2009	2004	1999	2005	
GEFITINIB	2002	2004	2009			2003			2003		2010		2004	2004		2009	2003	
GEMCITABINE	1999	1997	1995	1999	1997	1997	2013	2001	2012	1995	1995	1995	1997	1997	1997	1995	1996	1995
GOSERELIN	1991	1991	1988		2006	1994	1988	1994	1992		1991	1988	1991	1994	1993	1987	1990	1998
IBANDRONIC ACID	2013	2006	2004	2006	2006	2004	2006	2007	2000	2002	2007	2008	1999	1998	2007	2002	2005	2006
IBRUTINIB			2014				2015					2015	2015				2013	
IDARUBICIN	1995	1992	1991	2001	2006	1993	2013	1991	1993		2014	1993	1992	1994	1995	1990	1990	
IDELALISIB							2015					2014	2015				2014	
IMATINIB	2001	2001	2001	2002	2006	2002		2004	2001	2002	2002	2001	2001	2001	2002	2001	2001	1990
INTERFERON ALFA-2A	1988	1993	1986	1992		1988	1988	1990		1988	1989	1989	1986	1988	1991	1986	1986	1993
INTERFERON ALFA-2B	1988	1987	1986	1995	1998	1987	1989	1988		1986	1988	1986	1986	1988	1991	1986	1986	2001
IPILIMUMAB	2015	2012			2014		2012			2015	2012	2011	2011			2011	2011	
IRINOTECAN	1994	1998	1998	2008	2002	1997	2012	2003	1996	2009	1997	1998	1998	1998	1998	1997	1996	2004
LAPATINIB	2009	2009		2010	2009	2007	2008	2008	2007	2010	2008	2008	2007	2008	2008	2008	2007	
LENALIDOMIDE	2010	2008	2007			2010				2014	2008	2008		2011	2010	2007	2006	
LENVATINIB	2015											2015	2015				2015	
LETROZOLE	2006	2000	1998	1999	2009	1998	2002	2002	2014	1997	1997	1996	1997	1998	1999	1996	1997	1997
LEUPRORELIN	1992	1989	1989	2002	1994	1992	1987	1997		2012	1986	1987	1993	1994	1995	1991	1985	1992
MILTEFOSINE						1999			2003		1999							
MITOXANTRONE	1987	1987	1986	1999	2001	1986		2011	1986	2007	1995	1988	1985	1998	1999	1984	1988	2004
NELARABINE	2007										2008	2007	2007			2007	2006	
NILOTINIB	2009	2007	2007	2009	2012	2008		2009	2008	2008	2008	2008	2007	2008	2009	2008	2007	
NILUTAMIDE		2000	1990		1994		1989					1990					1996	
NIVOLUMAB	2014						2015					2015					2014	

TABLE A.3. Continued

	Japan	Mexico	Netherlands	Pakistan	Peru	Philippines	Portugal	Saudi Arabia	Singapore	South Africa	Spain	Sweden	Switzerland	Thailand	Turkey	UK	USA	Venezuela
OBINUTUZUMAB		2014	2014									2014				2014	2013	
OCTREOTIDE	1989	1990	1989	1994	1998	2010	1991	1990	1990	1990	1993	1989	1988	1992	1992	1989	1989	
OFATUMUMAB	2013		2010								2014	2010	2011			2010	2009	
OXALIPLATIN	2005	2002	2007	2005	2002	1999	2015	2004	1999	2006	2007	1999	1999	1999	2004	1999	2002	
PACLITAXEL	1997	1995	1993	2000	2002	1994	2015	1996	1994	1999	2004	1993	1994	1994	1996	1993	1992	1998
PANITUMUMAB	2010	2011				2014			2014		2008	2007	2008		2013	2008	2006	
PANOBINOSTAT	2015		2015														2015	
PASIREOTIDE		2013										2012	2013	2015	2015	2012	2013	
PAZOPANIB	2012	2012	2010	2011		2011			2011		2011	2010	2010	2012	2011	2010	2009	
PEGASPARGASE																	1994	
PEMBROLIZUMAB							2015					2015	2015			2015	2014	
PEMETREXED	2007	2005	2004	2007		2006		2008	2004	2006	2005	2004	2005	2004	2004	2004	2004	
PENTOSTATIN	1996		1993													1993	1992	
PERTUZUMAB			2013								2014	2013	2012	2014		2013	2012	
PIRARUBICIN	1988																	
PIXANTRONE												2012				2013		
PLERIXAFOR		2009							2011	2014	2010		2015	2013		2009	2009	
PONATINIB												2013					2013	
PORFIMER SODIUM	1996		1999													2001	1996	
RALTITREXED		2003	1997			2000			2000	2000			1999		2002	1996		1999
RAMUCIRUMAB	2015											2015				2015	2014	

TABLE A.3. Continued

	Japan	Mexico	Netherlands	Pakistan	Peru	Philippines	Portugal	Saudi Arabia	Singapore	South Africa	Spain	Sweden	Switzerland	Thailand	Turkey	UK	USA	Venezuela
REGORAFENIB	2013		2013		2014	2014	2013			2014		2013	2013	2014	2015		2012	
RITUXIMAB	2001	1999	1998	2004	2006	1998		2008	1998	1999	1999	1998	1997	1999	2002	1998	1997	1997
ROMIDEPSIN																	2010	
SORAFENIB	2008		2006	2009	2014	2007		2012	2007	2007	2007	2006	2006	2007	2008	2006	2005	
STREPTOZOCIN	2015		1998										2008				1982	
SUNITINIB	2008	2006	2006	2009		2006		2011	2007	2008	2007	2006	2006	2007	2008	2006	2006	
TEMOZOLOMIDE	2006	1999	1999		2002	2002			1999	1999	1999	1999	1999	2001	2003	1999	1999	
TEMSIROLIMUS	2010	2011				2010		2012	2011	2010	2008	2008	2009	2012	2009	2008	2007	
TOPOTECAN	2001	2008	1996	2008	2006	2007	2013	2011		2000	2008	1997	1997	1998	2000	1997	1996	2001
TOREMIFENE	1995	1999			1997					1998	1997	1994	1997		2006	1996	1997	2001
TRABECTEDIN		2010				2010			2009	2013	2007	2007	2011	2010	2013	2007	2015	
TRAMETINIB			2014														2013	
TRASTUZUMAB	2001	2000	2013	2004		2000		2008	1999	2002		2000	1999	2001	2003	2000	1998	1999
TRASTUZUMAB EMTANSINE		2014					2014						2013				2013	
VANDETANIB		2014	2012				2015					2012	2012			2012	2011	
VEMURAFENIB	2015	2012	2012				2013		2012	2013	2013	2012	2011	2014	2014	2012	2011	
VINORELBINE	1999	1998	2002	1995	1993	1998			1992	1999	1993	1996	2007	1998	1995	1997	1995	
ZORUBICIN																		

TABLE A.4. Complete estimates of ln(DALYS_2015) model

Parameter	Estimate	Standard error	95% confidence limits		Z	Pr > |Z|
$\beta_{0–4}$	0.000	0.013	−0.026	0.025	−0.03	0.9772
$\beta_{5–9}$	−0.058	0.012	−0.082	−0.034	−4.81	<0.0001
$\beta_{10–14}$	−0.026	0.011	−0.047	−0.004	−2.35	0.0187
$\beta_{15–33}$	−0.027	0.009	−0.045	−0.009	−2.96	0.0031
γ	0.849	0.032	0.786	0.912	26.27	<0.0001
Argentina (ARG)	−0.011	0.060	−0.129	0.107	−0.18	0.8588
Australia (AUS)	−0.478	0.075	−0.625	−0.331	−6.37	<0.0001
Austria (AUT)	−0.387	0.109	−0.600	−0.173	−3.54	0.0004
Belgium (BEL)	−0.372	0.139	−0.645	−0.099	−2.67	0.0076
Brazil (BRA)	0.207	0.067	0.076	0.338	3.10	0.0019
Canada (CAN)	−0.345	0.081	−0.504	−0.185	−4.23	<0.0001
Chile (CHL)	−0.126	0.077	−0.277	0.026	−1.63	0.104
Colombia (COL)	0.257	0.076	0.109	0.406	3.40	0.0007
Denmark (DNK)	−0.498	0.108	−0.710	−0.287	−4.61	<0.0001
Ecuador (ECU)	−0.107	0.119	−0.340	0.127	−0.89	0.3708
Egypt (EGY)	0.137	0.087	−0.035	0.308	1.57	0.1175
Finland (FIN)	−0.601	0.118	−0.832	−0.369	−5.08	<0.0001
France (FRA)	−0.079	0.074	−0.224	0.065	−1.08	0.2823
Germany (DEU)	−0.099	0.080	−0.255	0.057	−1.24	0.2145
Greece (GRC)	−0.275	0.074	−0.420	−0.130	−3.71	0.0002
Indonesia (IDN)	0.393	0.067	0.262	0.524	5.88	<0.0001
Ireland (IRL)	−0.664	0.109	−0.877	−0.450	−6.08	<0.0001
Italy (ITA)	−0.202	0.074	−0.346	−0.058	−2.74	0.0061
Japan (JPN)	−0.148	0.090	−0.325	0.028	−1.65	0.0993
Mexico (MEX)	0.085	0.063	−0.039	0.208	1.34	0.181
Netherlands (NLD)	−0.304	0.114	−0.528	−0.080	−2.66	0.0077
Pakistan (PAK)	0.608	0.062	0.486	0.730	9.77	<0.0001
Peru (PER)	−0.137	0.054	−0.243	−0.031	−2.54	0.0111
Philippines (PHL)	0.440	0.069	0.305	0.575	6.38	<0.0001
Portugal (PRT)	−0.467	0.064	−0.593	−0.342	−7.31	<0.0001
Saudi Arabia (SAU)	−0.024	0.090	−0.201	0.153	−0.26	0.7918
Singapore (SGP)	−0.506	0.124	−0.748	−0.263	−4.09	<0.0001
South Africa (ZAF)	0.381	0.091	0.202	0.559	4.17	<0.0001
Spain (ESP)	−0.165	0.084	−0.330	0.001	−1.95	0.0509
Sweden (SWE)	−0.443	0.112	−0.663	−0.223	−3.95	<0.0001
Switzerland (CHE)	−0.594	0.113	−0.815	−0.373	−5.27	<0.0001
Thailand (THA)	0.292	0.069	0.157	0.427	4.24	<0.0001
Turkey (TUR)	0.344	0.055	0.236	0.451	6.26	<0.0001
United Kingdom (GBR)	−0.140	0.076	−0.289	0.009	−1.84	0.0657
United States of America (USA)	0.015	0.093	−0.167	0.196	0.16	0.8745
Venezuela (Bolivarian Republic of) (VEN)	0.000	0.000	0.000	0.000	–	–
C15 Oesophagus cancer	−0.547	0.099	−0.741	−0.354	−5.56	<0.0001

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TABLE A.4. Continued

Parameter	Estimate	Standard error	95% confidence limits		Z	Pr > |Z|
C16 Stomach cancer	−0.594	0.084	−0.759	−0.430	−7.08	<0.0001
C18−C21 Colon and rectum cancers	−0.729	0.088	−0.902	−0.556	−8.27	<0.0001
C22 Liver cancer	−0.380	0.097	−0.569	−0.191	−3.93	<0.0001
C25 Pancreas cancer	−0.212	0.066	−0.341	−0.083	−3.22	0.0013
C33−C34 Trachea, bronchus, lung cancers	−0.062	0.073	−0.205	0.081	−0.85	0.3949
C43 Malignant skin melanoma	−1.682	0.098	−1.873	−1.490	−17.22	<0.0001
C50 Breast cancer	−0.604	0.061	−0.723	−0.485	−9.96	<0.0001
C53 Cervix uteri cancer	−0.998	0.098	−1.190	−0.805	−10.16	<0.0001
C56 Ovary cancer	−0.590	0.066	−0.720	−0.460	−8.90	<0.0001
C61 Prostate cancer	−1.499	0.088	−1.672	−1.326	−16.98	<0.0001
C64−C66 Kidney, renal pelvis and ureter cancer	−1.087	0.092	−1.268	−0.906	−11.78	<0.0001
C67 Bladder cancer	−1.485	0.108	−1.697	−1.273	−13.75	<0.0001
C70−C72 Brain and nervous system cancers	−0.407	0.100	−0.603	−0.210	−4.06	<0.0001
C73 Thyroid cancer	−2.158	0.097	−2.349	−1.968	−22.23	<0.0001
C81 Hodgkin lymphoma	−1.385	0.093	−1.568	−1.202	−14.85	<0.0001
C82−C86, C96 Non−Hodgkin lymphoma	−0.691	0.037	−0.764	−0.619	−18.69	<0.0001
C88, C90 Multiple myeloma	−0.762	0.080	−0.918	−0.607	−9.59	<0.0001
C91-C95 Leukaemia	0.000	0.000	0.000	0.000	–	–
Intercept	5.021	0.267	4.498	5.543	18.83	<0.0001
GEE model information						
Correlation structure	Independent					
Subject effect	cause (19 levels)					
Number of clusters	19.000					
Correlation matrix dimension	36.000					
Maximum cluster size	36.000					
Minimum cluster size	33.000					
GEE fit criteria						
QIC	749.493					
QICu	737.000					

$N = 684$ (=19 cancer sites*36 countries). Disturbances are clustered within cancer sites.

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TABLE A.5. Estimates of two-way fixed effects model of life-years lost [equation (1)] based on sample excluding the USA

Row	Parameter	Regressor	Estimate	Std. err.	Z	Pr>|Z|
		Dependent variable = DALYS_2015				
1	β_{0-4}	LAUNCHES_2011_2015	−0.008	0.018	−0.44	0.6608
2	β_{5-9}	LAUNCHES_2006_2010	**−0.047**	**0.016**	**−3.02**	**0.0025**
3	β_{10-14}	LAUNCHES_2001_2005	**−0.027**	**0.012**	**−2.16**	**0.0309**
4	β_{15-33}	LAUNCHES_1982_2000	**−0.028**	**0.011**	**−2.59**	**0.0095**
5	γ	ln(CASES_2012)	**0.870**	**0.033**	**26.36**	**<0.0001**
		Dependent variable = YLL_2015				
6	β_{0-4}	LAUNCHES_2011_2015	−0.006	0.019	−0.32	0.7486
7	β_{5-9}	LAUNCHES_2006_2010	**−0.050**	**0.016**	**−3.17**	**0.0015**
8	β_{10-14}	LAUNCHES_2001_2005	**−0.027**	**0.013**	**−2.15**	**0.0318**
9	β_{15-33}	LAUNCHES_1982_2000	**−0.030**	**0.012**	**−2.55**	**0.0109**
10	γ	ln(CASES_2012)	**0.869**	**0.037**	**23.38**	**<0.0001**
		Dependent variable = YLD_2015				
11	β_{0-4}	LAUNCHES_2011_2015	−0.015	0.017	−0.92	0.3593
12	β_{5-9}	LAUNCHES_2006_2010	−0.004	0.017	−0.25	0.8006
13	β_{10-14}	LAUNCHES_2001_2005	−0.022	0.025	−0.87	0.3843
14	β_{15-33}	LAUNCHES_1982_2000	−0.019	0.011	−1.80	0.0713
15	γ	ln(CASES_2012)	0.860	0.033	26.27	<0.0001
		Dependent variable = YLL75_2015				
16	$\beta_{0\text{-}4}$	LAUNCHES_2011_2015	−0.012	0.028	−0.42	0.6768
17	β_{5-9}	LAUNCHES_2006_2010	**−0.077**	**0.026**	**−2.97**	**0.003**
18	β_{10-14}	LAUNCHES_2001_2005	−0.042	0.024	−1.77	0.0761
19	β_{15-33}	LAUNCHES_1982_2000	**−0.050**	**0.018**	**−2.79**	**0.0053**
20	γ	ln(CASES_2012)	**0.887**	**0.051**	**17.56**	**<0.0001**
		Dependent variable = YLL65_2015				
21	β_{0-4}	LAUNCHES_2011_2015	−0.019	0.027	−0.70	0.4838
22	β_{5-9}	LAUNCHES_2006_2010	**−0.086**	**0.027**	**−3.21**	**0.0013**
23	β_{10-14}	LAUNCHES_2001_2005	−0.051	0.029	−1.73	0.0836
24	β_{15-33}	LAUNCHES_1982_2000	**−0.058**	**0.022**	**−2.70**	**0.007**
25	γ	ln(CASES_2012)	**0.863**	**0.065**	**13.31**	**<0.0001**

Estimates in bold are statistically significant (p-value < 0.05).
$N = 665$ (=19 cancer sites*35 countries). Disturbances are clustered within cancer sites.

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