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The impact of pharmaceutical innovation on cancer mortality in Mexico, 2003–2013

Frank R. Lichtenberg[1,2]

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Abstract I assess the impact that pharmaceutical innovation had on cancer mortality in Mexico during the period 2003–2013, by investigating whether there were larger declines in the age-standardized mortality rate of cancer sites (breast, lung, colon, etc.) that were subject to more pharmaceutical innovation, controlling for changes in the age-standardized cancer incidence rate. The estimates indicate that new drugs launched during 1991–2001 reduced the age-standardized cancer mortality rate by 16%, i.e., at an average annual rate of about 1.6%. I estimate that 105,661 life-years before age 70 were gained in 2013 due to cancer drugs launched during 1991–2001, and that the cost per life-year gained was in the neighborhood of $2146. By the standards of the World Health Organization, new cancer drugs have been very cost-effective in Mexico. The contribution of cancer drug innovation to Mexican longevity growth has been valuable, but, perhaps, it could have been even larger. Only half as many new cancer drugs were launched in Mexico during 2010–2014 as were launched in the US. In addition, when new drugs are launched in Mexico, their diffusion tends to be quite slow.

Keywords Pharmaceutical · Innovation · Mortality · Longevity · Cancer · Mexico · Cost-effectiveness

JEL classification I1 · J11 · L65 · O33

✉ Frank R. Lichtenberg
frl1@columbia.edu

[1] Columbia University, New York, NY, USA

[2] NBER, Cambridge, MA, USA

1 Introduction

Cancer mortality has declined in Mexico during the last 2 decades. As shown in Fig. 1, the age-standardized cancer mortality rate[1] of males declined by 13%, and that of females declined by 11%, between 1995 and 2014.[2] The mortality rate, or (unconditional) probability of death from cancer, depends to an important extent on two variables: the probability of getting (being diagnosed with) cancer, and the probability of dying from cancer, conditional on having been diagnosed with cancer: prob(death) $\approx$ prob(diagnosis) * prob(death|diagnosis).[3] Therefore, the decline in the mortality rate could be due to either a decline in cancer incidence[4], a decline in the probability of dying from cancer, conditional on having been diagnosed with cancer (e.g., due to improved treatment), or both.

The Mexican cancer incidence rate declined by 13% (from 147.3 to 128.4) between 2002 and 2008, although it increased 2% (from 128.4 to 131.5) between 2008 and 2012.[5] Since the cancer incidence rate declined at least as rapidly as the cancer mortality rate in recent years, the decline in cancer mortality could be entirely due to declining cancer incidence. However, the measurement of cancer incidence is subject to significant potential errors. For example, a decline in cancer surveillance or screening could lead to a decline in measured cancer incidence, even when true incidence is not declining.

The previous studies (Lichtenberg 2014a, 2015, 2016a, b) have shown that pharmaceutical innovation—the introduction and use of new cancer drugs—has significantly reduced cancer mortality in countries at a "very high" level of human development (as defined by the United Nations Development Programme[6]). In this study, I will assess the impact that pharmaceutical innovation and cancer incidence had on cancer mortality in Mexico, a country at a lower (but still "high") level of

[1] An age-standardized rate (ASR) is a summary measure of the rate that a population would have if it had a standard age structure. Standardization is necessary when comparing several populations that differ with respect to age, because age has a powerful influence on the risk of cancer. The ASR is a weighted mean of the age-specific rates; the weights are taken from population distribution of the *standard population*. The most frequently used standard population is the *World Standard Population*. The calculated incidence or mortality rate is then called age-standardized incidence or mortality rate (world). It is also expressed per 100,000. See http://globocan.iarc.fr/Pages/glossary.aspx#MORTALITY.

[2] In addition, between 1998 and 2013, mean age at death from cancer also increased by 1.8 years, from 62.3 to 64.1. Source: author's calculations based on WHO Mortality Database (World Health Organization (2016b)).

[3] This approximation assumes that the probability that someone who has never been diagnosed with cancer dies from cancer is quite small. This is plausible, because the cancer mortality rate (the unconditional probability of dying from cancer) is about half as great as the cancer incidence rate (the probability of being diagnosed with cancer).

[4] Incidence is the number of new cases arising in a given period in a specified population. This information is collected routinely by cancer registries. It can be expressed as an absolute number of cases per year or as a rate per 100,000 persons per year.

[5] Source: OECD Health Statistics 2016 database. Data on incidence prior to 2002 are not available. The decline in incidence may be due, in part, to a decline in cigarette smoking, a major risk factor for lung cancer. Between 2002 and 2015, the fraction of the population aged 15 + who are daily smokers declined from 12.4 to 7.6%.

[6] http://hdr.undp.org/en/countries.

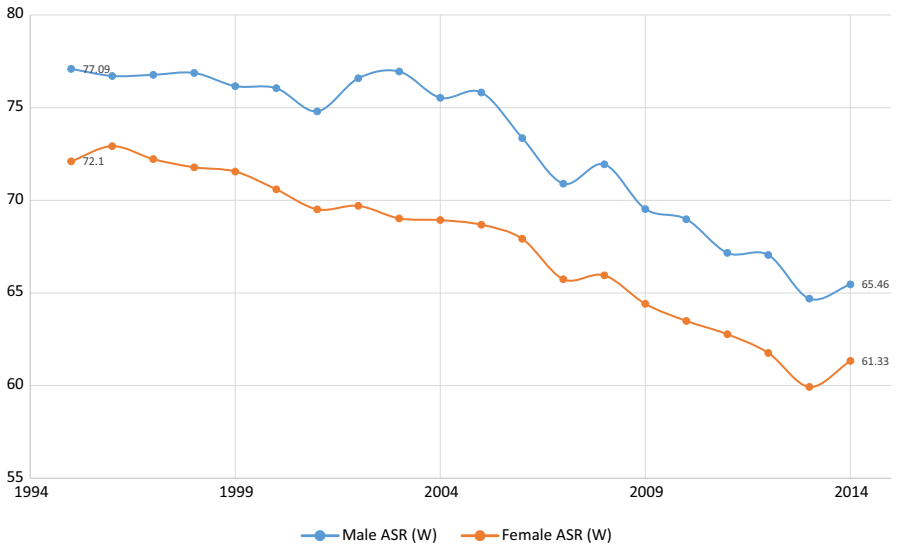

Fig. 1 Age-standardized cancer mortality rates, by sex, Mexico, 1995–2014 (Source: WHO Cancer Mortality database, http://www-dep.iarc.fr/WHOdb/WHOdb.htm)

human development. As in the previous studies, a difference-in-difference research design will be used: I will investigate whether the decline in mortality was greater for cancer sites (breast, lung, colon, etc.) subject to more pharmaceutical innovation and greater declines in incidence. As shown in Fig. 2, the rate of decline in the mortality rate varied considerably across cancer sites. The mortality rate declined by at least 34% for 3 cancer sites (cervix, stomach, and lung), but *increased* for 3 other cancer sites (colon, ovary, and breast).

In Sect. 2, I will formulate an econometric model of cancer mortality. The data sources used to estimate these models are described in Sect. 3. Empirical results are presented in Sect. 4. Rough estimates of the number of life-years gained in 2013 from the reduction in cancer mortality attributable to pharmaceutical innovation, and of the average cost-effectiveness (cost per life-year gained) of new cancer drugs, are developed in Sect. 5. Sect. 6 provides a summary and conclusions.

2 Econometric model of cancer mortality

The basic model which I will use to assess the impact of pharmaceutical innovation and cancer incidence on age-standardized cancer mortality rates in Mexico is:

$$\text{MORT}_{st} = \beta_k \text{CUM\_NCE}_{s,t-k} + \gamma\, \text{INCIDENCE}_{s,t-1} + \alpha_s + \delta_t + \varepsilon_{st}, \qquad (1)$$

where MORT_{st} = the age-standardized mortality rate from cancer at site s in year t ($t = 2003, 2013$); $\text{CUM\_NCE}_{s,t-k} = \sum_d \text{IND}_{ds}\ \text{LAUNCHED}_{d,t-k}$ = the number of

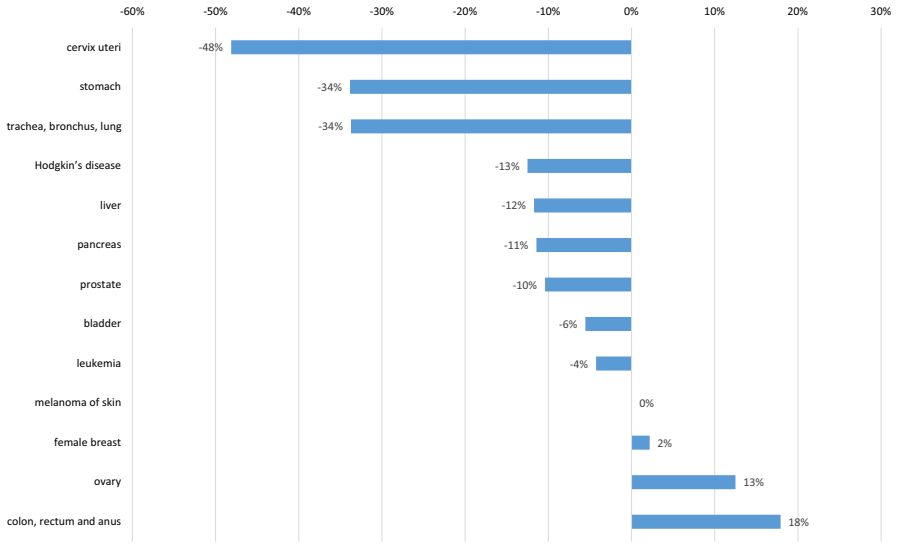

Fig. 2 % change in age-adjusted mortality rate, by cancer site, 2000–2013 (Source: OECD Health Statistics 2016 database)

new chemical entities (drugs) to treat cancer at site s that had been launched in Mexico by the end of year $t-k$ ($k = 0, 3, 6, \ldots, 18$); $\text{IND}_{ds} = 1$ if drug d is used to treat (indicated for) cancer at site $s = 0$ if drug d is not used to treat (indicated for) cancer at site s; $\text{LAUNCHED}_{d,t-k} = 1$ if drug d had been launched in Mexico by the end of year $t - k = 0$ if drug d had not been launched in Mexico by the end of year $t - k$; $\text{INCIDENCE}_{s,t-1}$ = the age-standardized incidence rate of cancer at site s in year $t - 1$; α_s = a fixed effect for cancer at site s; δ_t = a fixed effect for year t.

Inclusion of year and cancer-site fixed effects controls for the overall decline in cancer mortality and for stable between-cancer-site differences in mortality. Negative and significant estimates of β_k in Eq. (1) would signify that cancer sites for which there was more pharmaceutical innovation had larger declines in mortality, controlling for changes in incidence.

Due to data limitations, the number of new chemical entities is the only cancer-site-specific, time-varying, measure of medical innovation in Eq. (1). Both a patient-level US study and a longitudinal country-level study have shown that controlling for numerous other potential determinants of mortality does not reduce, and may even increase, the estimated effect of pharmaceutical innovation. The study based on patient-level data (Lichtenberg 2013) found that controlling for race, education, family income, insurance coverage, Census region, BMI, smoking, the mean year the person started taking his or her medications, and over 100 medical conditions had virtually no effect on the estimate of the effect of pharmaceutical innovation (the change in drug vintage) on life expectancy. The study based on longitudinal country-level data (Lichtenberg 2014b) found that controlling for ten other potential determinants of longevity change [real per capita income, the

unemployment rate, mean years of schooling, the urbanization rate, real per capita health expenditure (public and private), the DPT immunization rate among children ages 12–23 months, HIV prevalence, and tuberculosis incidence] *increased* the coefficient on pharmaceutical innovation by about 32%.

Failure to control for non-pharmaceutical medical innovation (e.g., innovation in diagnostic imaging, surgical procedures, and medical devices) is also unlikely to bias estimates of the effect of pharmaceutical innovation on premature mortality, for two reasons. First, more than half of US funding for biomedical research came from pharmaceutical and biotechnology firms (Dorsey et al. 2010). Much of the rest came from the federal government (i.e., the NIH), and new drugs often build on upstream government research (Sampat and Lichtenberg 2011). The National Cancer Institute (2016a, b) says that it "has played an active role in the development of drugs for cancer treatment for 50 years… [and] that approximately one half of the chemotherapeutic drugs currently used by oncologists for cancer treatment were discovered and/or developed" at the National Cancer Institute. Second, the previous research based on US data (Lichtenberg 2014a, c) indicates that non-pharmaceutical medical innovation is not positively correlated across diseases with pharmaceutical innovation. However, while non-pharmaceutical medical innovation may not be correlated with pharmaceutical innovation across diseases in the US, this need not hold for Mexico.

The measure of pharmaceutical innovation in Eq. (1)—the number of chemical substances previously registered to treat cancer at site *s*—is not the theoretically ideal measure. Mortality is presumably more strongly related to the drugs *actually* used to treat cancer than it is to the drugs that *could be* used to treat cancer. A preferable measure is the mean *vintage* of drugs used to treat cancer at site *s* in year *t*, defined as $\text{VINTAGE}_{st} = \sum_d Q_{dst}\,\text{LAUNCH\_YEAR}_d / \sum_d Q_{dst}$, where Q_{dst} = the quantity of drug *d* used to treat cancer at site *s* in year *t*, and LAUNCH_YEAR_d = the world launch year of drug *d*.[7] Unfortunately, measurement of VINTAGE_{st} is infeasible: even though data on the total quantity of each drug in each year ($Q_{d.t} = \Sigma_s Q_{dst}$) are available, many drugs are used to treat multiple diseases. There is no way to determine the quantity of drug *d used to treat cancer at site s* in year *t*.[8] However, Lichtenberg (2014c) showed that in France, there is a highly significant positive correlation across *drug classes* between changes in the (quantity-weighted) vintage of drugs and changes in the number of chemical substances previously registered within the drug class.

[7] According to the Merriam Webster dictionary, one definition of vintage is "a period of origin or manufacture (e.g., a piano of 1845 vintage)". http://www.merriam-webster.com/dictionary/vintage. Solow (1960) introduced the concept of vintage into economic analysis. Solow's basic idea was that technical progress is "built into" machines and other goods and that this must be taken into account when making empirical measurements of their roles in production. This was one of the contributions to the theory of economic growth that the Royal Swedish Academy of Sciences cited when it awarded Solow the 1987 Alfred Nobel Memorial Prize in Economic Sciences (Nobelprize.org 2016).

[8] Outpatient prescription drug claims usually do not show the indication of the drug prescribed. Claims for drugs administered by doctors and nurses (e.g., chemotherapy) often show the indication of the drug, but these data are not available for Mexico.

In principle, it could be desirable to control for the length of time between the 'world launch' of cancer drugs and their 'Mexico launch'.[9] According to Solow's vintage hypothesis, later, vintage goods (e.g., drugs whose world launch years were later) are likely to be of higher quality than earlier vintage goods. Holding constant the Mexican launch year of a drug, the shorter the lag from world launch year to Mexican launch year, the later the world launch year of the drug, and (according to the vintage hypothesis), the higher the drug's quality. However, controlling for the length of time between the 'world launch' of cancer drugs and their 'Mexico launch' is problematic. I can compute the mean lag between the world launch year and the Mexican launch year for cancer sites and years in which at least one drug had been launched in Mexico. However, I cannot compute the mean lag for cancer sites and years in which no drugs had been launched in Mexico. As shown in Table 2, 8 cancer sites had 0 drug launches by 1995; 4 cancer sites had 0 drugs launches by 2004. Controlling for the length of time between the 'world launch' of cancer drugs and their 'Mexico launch' would require excluding those observations.

In Eq. (1), mortality from cancer at site s in year t depends on the number of new chemical entities (drugs) to treat cancer at site s that had been launched in Mexico by the end of year $t - k$, i.e., there is a lag of k years. Equation (1) will be estimated for different values of k: $k = 0, 3, 6,\ldots,18$. A separate model is estimated for each value of k, rather than including multiple values ($\text{CUM\_NCE}_{s,t}$, $\text{CUM\_NCE}_{s,t-3}$, $\text{CUM\_NCE}_{s,t-6},\ldots$) in a single model, because CUM_NCE is highly serially correlated (by construction), which would result in extremely high multicollinearity if multiple values were included. One would expect there to be a substantial lag, because new drugs diffuse gradually—they will not be used widely until years after registration. Data from the IMS Health MIDAS database can be used to provide evidence about the process of diffusion of new medicines. I used data from that source linked to data on Mexican drug launch dates (described below) to estimate the following model:

$$\ln\left(\text{N\_RX}_{dy}\right) = \rho_d + \pi_y + \varepsilon_{dy}, \tag{2}$$

where N_RX_{dy}= the number of standard units of cancer drug d sold in Mexico per thousand population y years after it was launched (y = 0–3, 4–7, 8–11, 12–15, 16–19 years); ρ_d = a fixed effect for drug d; π_y = a fixed effect for age y.

The expression $\exp\left(\pi_y - \pi_{16-19}\right)$ is a "relative utilization index": it is the mean ratio of the annual number of standard units of a cancer drug sold per thousand population y years after it was first launched in Mexico to the annual number of standard units of the same drug sold per thousand population 16–19 years after it was first launched in Mexico.

Using annual data on the number of standard units of cancer drugs sold in Mexico during the period 1999–2010, I estimated Eq. (2). Estimates of the "relative utilization index" are shown in Fig. 3. These estimates indicate that utilization of a drug is strongly positively related to how long the drug has been on the market. On average, a drug is used 50 times as often per year 16–19 years post-launch as it is

[9] The mean lag between the world launch date and the Mexican launch date is 3.0 years.

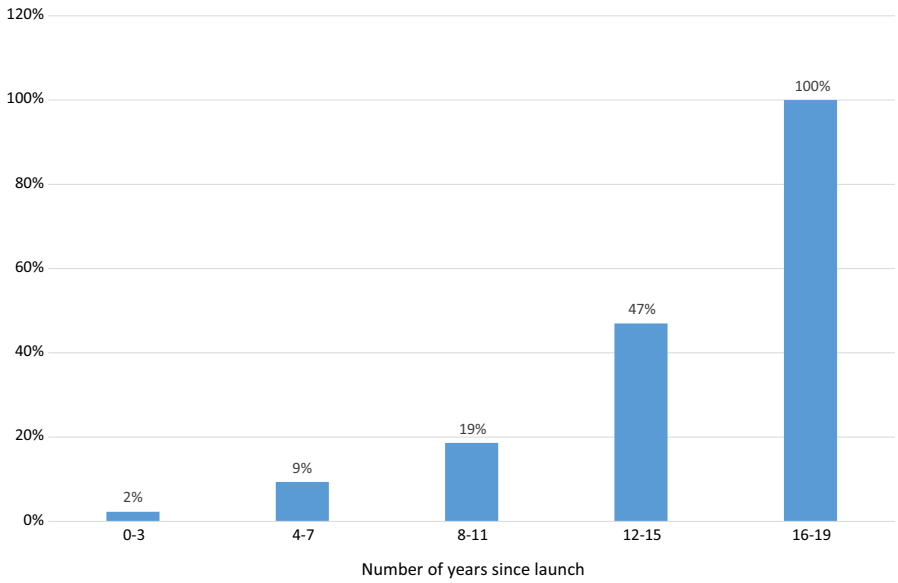

Fig. 3 Relative utilization of cancer drugs in Mexico, by number of years since launch (index: ratio of utilization y years since launch to utilization 16–19 years since launch)

0–3 year post-launch. Utilization appears to rise especially rapidly after year 11, when drug patents tend to expire and generics enter the market.

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

In principle, mortality in year t should depend on a distributed lag of incidence, i.e., on $\text{INCIDENCE}_{s,t}$, $\text{INCIDENCE}_{s,t-1}$, $\text{INCIDENCE}_{s,t-2}$, $\text{INCIDENCE}_{s,t-3}\ldots$ Unfortunately, data on incidence by cancer site are available for only 2 years (2002 and 2012); this is why $\text{INCIDENCE}_{s,t-2}$ is the only incidence variable included in Eq. (1). The limited availability of incidence data also means that we can only use mortality data for 2 years (2004 and 2014). Writing the model for each of these years:

$$\text{MORT}_{s,2003} = \beta_k \text{CUM\_NCE}_{s,2003-k} + \gamma \text{INCIDENCE}_{s,2002} + \alpha_s + \delta_{2003} + \varepsilon_{s,2003}, \tag{3}$$

$$\text{MORT}_{s,2013} = \beta_k \text{CUM\_NCE}_{s,2013-k} + \gamma \text{INCIDENCE}_{s,2012} + \alpha_s + \delta_{2013} + \varepsilon_{s,2013}. \tag{4}$$

Subtracting (3) from (4),

$$\begin{aligned}\left(\mathrm{MORT}_{s,2013} - \mathrm{MORT}_{s,2003}\right) &= \beta_k\left(\mathrm{CUM\_NCE}_{s,2013-k} - \mathrm{CUM\_NCE}_{s,2003-k}\right) \\ &+ \gamma\left(\mathrm{INCIDENCE}_{s,2012} - \mathrm{INCIDENCE}_{s,2002}\right) \\ &+ \left(\delta_{2013} - \delta_{2003}\right) + \left(\varepsilon_{s,2013} - \varepsilon_{s,2003}\right).\end{aligned} \tag{5}$$

Equation (5) may be rewritten as follows:

$$\begin{aligned}\Delta\mathrm{MORT}_s &= \beta_k \Delta\mathrm{CUM\_NCE\_}k_s \\ &+ \gamma\,\Delta\mathrm{INCIDENCE\_}1_s + \delta' + \varepsilon'_s,\end{aligned} \tag{6}$$

where $\Delta\mathrm{MORT}_s = \mathrm{MORT}_{s,2013} - \mathrm{MORT}_{s,2003}$ = the 2003–2013 change in the age-standardized mortality rate from cancer at site s; $\Delta\mathrm{CUM\_NCE\_}k_s = \mathrm{CUM\_NCE}_{s,2013k} - \mathrm{CUM\_NCE}_{s,2003-k}$ = the number of drugs for cancer at site s launched between year $2003 - k$ and $2013 - k$; $\Delta\mathrm{INCIDENCE\_}1_s = \mathrm{INCIDENCE}_{s,2012} - \mathrm{INCIDENCE}_{s,2002}$ = the 2002–2012 change in the age-standardized incidence rate of cancer at site s; $\delta' = \delta_{2013} - \delta_{2003}$.

Equation (6) indicates that the 2003–2013 change in the age-standardized mortality rate depends on two variables: the number of drugs launched between year 2003 − k and 2013 − k, and the 2002–2012 change in the age-standardized incidence rate.

For estimates of β_k from Eqs. (1) and (6) to be consistent estimates of the effect of drug launches on mortality, the "parallel trends" assumption needs to be satisfied. A simple way to test the validity of this assumption is to estimate a version of Eq. (6) that includes a control for the trend in mortality in the 'pre-period', e.g., the period 1993–2003. Therefore, I will estimate the following model:

$$\begin{aligned}\Delta\mathrm{MORT}_s &= \beta_k \Delta\mathrm{CUM\_NCE\_}k_s + \gamma\,\Delta\mathrm{INCIDENCE\_}1_s \\ &+ \pi\,\Delta\mathrm{MORT\_PRE}_s + \delta' + \varepsilon'_s,\end{aligned} \tag{7}$$

where $\Delta\mathrm{MORT\_PRE}_s = \mathrm{MORT}_{s,2003} - \mathrm{MORT}_{s,1993}$ = the 1993–2003 change in the age-standardized mortality rate from cancer at site s.

3 Data sources

Age-standardized cancer mortality rate data were obtained from the WHO Cancer Mortality database (World Health Organization (2016a)).

Age-standardized cancer incidence rate data were obtained from GLOBOCAN International Agency for Research on Cancer (2016). Mortality and incidence data are reported separately by sex. For cancers affecting both sexes, we computed the simple mean of the sex-specific rates. For cancers affecting only one sex (breast, cervical, ovarian, and prostate), we computed 50% of the single-sex rate.

Data on *drugs approved for different types of cancer* were obtained from the US National Cancer Institute.

Data on *Mexican launch dates of drugs* were obtained from the IMS Health New Product Focus database. This database contains data on drug launches (in Mexico and

many other countries) from 1982 to the present. The Mexican launch year (as indicated in the IMS New Product Focus database) is usually the year in which the drug was first sold in Mexico (as indicated in the IMS MIDAS database). In a few cases, the drug was first sold in Mexico in the year after the Mexican launch year. I define CUM_NCE_{st} as the number of *post-1981* new chemical entities (i.e., NCEs first launched anywhere in the world after 1981) used to treat cancer at site s that had been launched in Mexico by the end of year t. Since the New Product Focus data are left-censored (no pre-1982 data), this measure is subject to error, because CUM_NCE_{st} will not (but should) include pre-1982 NCEs that were first launched in Mexico after 1981. If this measurement error is random, it is likely to bias estimates of β_k towards zero.

Annual data on the number of standard units of cancer drugs sold in Mexico during the period 1999–2010 were obtained from the IMS Health MIDAS database.

Data on age-standardized mortality and incidence rates, by cancer site and year, are shown in Table 1.

Data on the number of post-1981 drugs ever launched in Mexico, by cancer site and year, are shown in Table 2.

Mexican launch dates of drugs used to treat different types of cancer are shown in Appendix Table 5.

4 Empirical results

Estimates of the pharmaceutical innovation (β_k) parameters of the cancer mortality rate model (Eq. (1) for different values of k are shown in Table 3. Each estimate is from a separate model. For simplicity, estimates of the incidence coefficient (γ) are not shown here. Estimates of the incidence coefficient were positive and significant (and virtually identical) in all models, indicating that mortality declined more for cancer sites that had larger declines in incidence.

The first seven rows of Table 3 show estimates based on mortality and incidence data for both sexes combined. Row 1 shows the estimate of β_0, i.e., of the pharmaceutical innovation coefficient when there is no lag between the number of drugs ever launched and the mortality rate. The estimate of β_0 is negative but only marginally statistically significant ($p = 0.07$). This is not surprising, since, as shown in Fig. 3, utilization of recently launched drugs tends to be quite low.

Row 2 shows the estimate of β_3, i.e., of the pharmaceutical innovation coefficient when there is a 3-year lag between the number of drugs ever launched and the mortality rate. The estimate of β_3 is negative and statistically significant ($p = 0.03$). Rows 3–7 of Table 3 show estimates of β_k for $k = 6$, 9, 12, 15, and 18, respectively. All five β_k estimates are negative and statistically significant ($p \leq 0.031$). These estimates signify that the mortality rate is inversely related to the number of drugs that had ever been launched 3–18 years earlier, controlling for the incidence rate.[10] The estimates of β_k based on data for both sexes combined are plotted in Panel A of Fig. 4.

[10] Controlling for incidence is important. If $\Delta INCIDENCE\_2_s$ is excluded from the model, none of the β_k parameter estimates are statistically significant. ΔCUM_NCE_k and $\Delta INCIDENCE\_2$ are positively correlated across cancer sites—there were more drug launches for cancer sites that had larger increases in incidence rates—although the correlation is statistically significant ($p < 0.05$) only when $k = 12$.

Table 1 Age-standardized mortality and incidence rates, by cancer site, 1993–2013

Cancer site	Both sexes					Female					Male				
	Mortality			Incidence		Mortality			Incidence		Mortality			Incidence	
	1993	2003	2013	2002	2012	1993	2003	2013	2002	2012	1993	2003	2013	2002	2012
C00–97, B21 all cancers	73.7	73.0	62.3	147.3	131.9	72.4	69.0	59.9	150.0	139.9	75.0	77.0	64.7	144.5	123.9
C00–14 lip, oral cavity and pharynx	1.2	1.1	1.0	3.4	3.2	0.7	0.7	0.6	2.2	2.2	1.6	1.5	1.3	4.5	4.1
C15 oesophagus	1.2	1.2	0.9	1.5	1.1	0.6	0.5	0.4	0.8	0.5	1.8	1.8	1.4	2.2	1.6
C16 stomach	7.7	6.4	4.7	11.3	7.0	6.4	5.3	4.0	9.4	6.0	9.0	7.4	5.3	13.1	7.9
C18–21 colon, rectum and anus	3.0	3.6	4.4	7.5	7.8	2.9	3.4	3.8	7.0	6.7	3.0	3.8	4.9	7.9	8.9
C25 pancreas		3.7	3.3	4.7	3.9		3.6	3.3	4.7	3.8		3.8	3.3	4.6	3.9
C33–34 lung (incl. trachea and bronchus)	10.3	8.8	5.7	11.9	7.7	5.2	4.9	3.8	6.7	4.9	15.4	12.7	7.6	17.0	10.5
C43 melanoma of skin	0.4	0.5	0.5	1.6	1.8	0.3	0.3	0.4	1.7	1.5	0.4	0.6	0.5	1.4	2.1
C50 breast	4.3	4.5	4.5	13.2	17.7	8.6	9.0	9.0	26.4	35.4					
C53 cervix uteri	6.9	5.0	3.1	14.8	11.7	13.7	9.9	6.1	29.5	23.3					
C56 ovary		1.7	1.7	3.7	2.8		3.3	3.4	7.4	5.6					
C61 prostate	4.9	6.1	5.0	15.0	13.7						9.8	12.1	10.0	29.9	27.3
C64 kidney		1.9	1.8	4.7	3.6		1.3	1.3	4.0	2.5		2.5	2.3	5.4	4.6
C70–72 brain, central nervous system		2.0	1.8	3.0	4.0		1.6	1.5	2.4	3.3		2.3	2.1	3.5	4.6
C73 thyroid		0.6	0.6	3.4	2.6		0.7	0.7	5.7	3.9		0.4	0.4	1.0	1.3
C81 hodgkin lymphoma		0.5	0.4	1.7	1.3		0.4	0.3	1.2	1.1		0.6	0.5	2.1	1.5
C82–85, C96 non-Hodgkin lymphoma		2.1	2.0	4.8	4.1		1.8	1.6	3.9	3.6		2.3	2.3	5.7	4.6
C88 + C90 multiple myeloma		1.0	1.0	1.4	1.3		0.8	0.9	1.2	1.1		1.1	1.1	1.6	1.4
C91–95 leukemia	3.2	3.7	3.3	5.0	5.6	2.9	3.3	3.0	4.3	5.1	3.4	4.1	3.6	5.6	6.0

Table 2 Number of post-1981 drugs ever launched in Mexico, by cancer site, 1986–2013

ICD_WHO	1986	1989	1992	1995	1998	2001	2004	2007	2010	2013
C00–14 lip, oral cavity and pharynx	0	0	0	1	1	1	2	2	2	2
C15 oesophagus	0	0	0	1	1	2	2	2	2	2
C16 stomach	0	0	0	1	1	2	2	2	2	2
C18–21 colon, rectum and anus	0	0	0	0	1	2	4	5	5	6
C25 pancreas	0	0	0	1	3	3	3	6	6	6
C33–34 lung (incl. trachea and bronchus)	0	0	1	3	5	5	6	9	10	11
C43 melanoma of skin	0	1	1	1	2	3	3	3	3	5
C45 mesothelioma	0	0	0	0	0	0	0	1	1	1
C50 breast	0	1	2	4	7	11	12	13	16	16
C53 cervix uteri	0	0	0	0	0	0	0	1	2	2
C56 ovary	0	0	1	2	3	3	3	4	5	5
C61 prostate	0	3	4	5	6	6	6	6	7	8
C64 kidney	0	0	0	0	1	1	1	4	4	6
C70–72 brain, central nervous system	0	0	0	0	0	1	1	3	3	3
C73 thyroid	0	0	0	0	0	0	0	0	0	0
C81 hodgkin lymphoma	0	0	0	0	0	0	0	0	0	0
C82–85, C96 non-hodgkin lymphoma	0	1	1	1	1	2	2	3	5	5
C88 + C90 multiple myeloma	0	0	0	0	0	1	1	2	4	4
C91–95 leukemia	0	2	3	3	3	5	5	7	8	8
Mean	0.0	0.4	0.7	1.2	1.8	2.5	2.8	3.8	4.5	4.8

To calculate the change in the mean mortality rate attributable to pharmaceutical innovation, we can multiply the estimate of β_k (column 1 of Table 3) by the mean value of ΔCUM_NCE_k (column 5); the result is shown in column 6. These calculations imply that new drugs launched during the period 1991–2001 had the largest (most negative) effect on the 2003–2011 change in mortality. Henceforth, I will focus on the estimates of the model when $k = 12$.

The two explanatory variables (ΔCUM_NCE_12 and ΔINCIDENCE_1) in the mortality change (ΔMORT) model jointly explain 77% of the variance across cancer sites in the 2003–2013 change in the mortality rate. The mean mortality rate declined by 0.47 between 2003 and 2013. The estimates imply that new drugs launched during 1991–2001 reduced the mean mortality rate by 0.47. The mean mortality rate in 2003 was 2.99, so this indicates that new drugs launched during 1998–2008 reduced the mean mortality rate by 16% (= 0.47/2.99), i.e., at an average annual rate of about 1.6%. The decline in incidence also reduced the mean mortality rate, but by only 60% as much as pharmaceutical innovation (0.28). The estimates

Table 3 Estimates of β_k parameters of Eq. (1), $\text{MORT}_{st} = \beta_k \text{ CUM\_NCE}_{s,t-k} + \gamma \text{ INCIDENCE}_{s,t-1} + \alpha_s + \delta_t + \varepsilon_{st}$ for different values of k

Column		Parameter	1	2	3	4	5	6
Row	Lag		Estimate	Std. err.	Z	Pr > |Z|	Mean (ΔCUM_NCE_k)	β_k * mean (ΔCUM_NCE_k)
	Both sexes (mean ΔMORT = − 0.50)							
1	0	β_0	− 0.1628	0.0887	− 1.84	0.0664	2.3	− 0.380
2	3	β_3	**− 0.1788**	**0.0827**	**− 2.16**	**0.0306**	2.2	− 0.387
3	6	β_6	**− 0.1702**	**0.0787**	**− 2.16**	**0.0306**	2.3	− 0.397
4	9	β_9	**− 0.1909**	**0.0511**	**− 3.74**	**0.0002**	2.2	− 0.424
5	12	β_{12}	**− 0.223**	**0.046**	**− 4.85**	**< 0.0001**	2.1	− 0.471
6	15	β_{15}	**− 0.217**	**0.0646**	**− 3.36**	**0.0008**	1.6	− 0.338
7	18	β_{18}	**− 0.257**	**0.0973**	**− 2.64**	**0.0083**	1.3	− 0.328
							Average	− 0.389
	Female (mean ΔMORT = − 0.39)							
8	0	β_0	− 0.0949	0.0733	− 1.29	0.1953	2.4	− 0.223
9	3	β_3	− 0.1388	0.081	− 1.71	0.0866	2.2	− 0.310
10	6	β_6	− 0.1704	0.1013	− 1.68	0.0925	2.5	− 0.421
11	9	β_9	**− 0.2081**	**0.0939**	**− 2.22**	**0.0267**	2.2	− 0.465
12	12	β_{12}	**− 0.2218**	**0.0908**	**− 2.44**	**0.0145**	2.1	− 0.470
13	15	β_{15}	− 0.1552	0.0826	− 1.88	0.0601	1.4	− 0.219
14	18	β_{18}	**− 0.2841**	**0.1175**	**− 2.42**	**0.0156**	1.1	− 0.301
							Average	− 0.344
	Male (mean ΔMORT = − 0.69)							
15	0	β_0	− 0.1219	0.0913	− 1.33	0.1819	2.2	− 0.268
16	3	β_3	− 0.1153	0.0901	− 1.28	0.2008	2.0	− 0.231
17	6	β_6	− 0.0852	0.0955	− 0.89	0.3722	2.1	− 0.182
18	9	β_9	− 0.1512	0.1592	− 0.95	0.3423	1.9	− 0.282
19	12	β_{12}	**− 0.3191**	**0.1155**	**− 2.76**	**0.0058**	1.7	− 0.553
20	15	β_{15}	**− 0.3212**	**0.1014**	**− 3.17**	**0.0015**	1.3	− 0.407
21	18	β_{18}	**− 0.2563**	**0.0819**	**− 3.13**	**0.0018**	1.1	− 0.290
							Average	− 0.316

Estimates in bold are statistically significant (p-value < .05)

also indicate that if no new drugs had been launched during 1991–2001 and the incidence rate had not declined between 2002 and 2012, the mortality rate would have increased by 0.28 between 2003 and 2013, although the estimated increase (the intercept) is not statistically significant.

Rows 8–14 of Table 3 show estimates based on mortality and incidence data for females only. The estimates are not statistically significant when $k \leq 6$, but 3 of the 4 estimates for $k \geq 9$ are negative and statistically significant. These estimates are plotted in Panel B of Fig. 4.

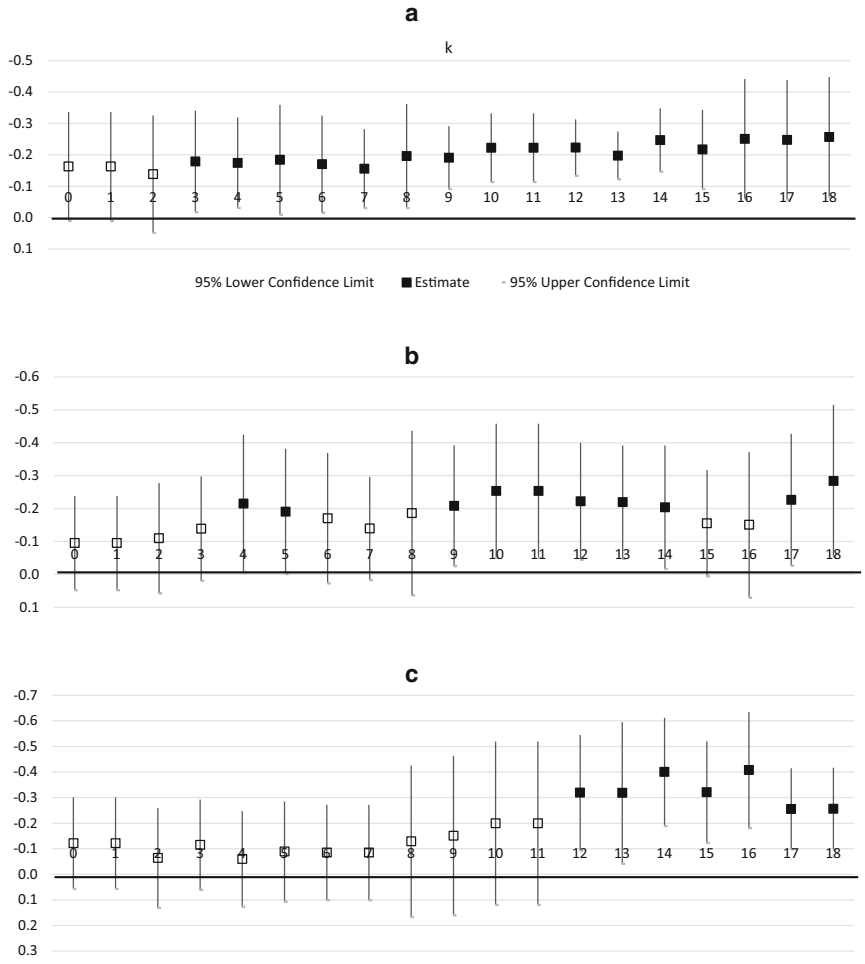

Fig. 4 Estimates of β_k parameters of Eq. (1), $\text{MORT}_{st} = \beta_k \text{ CUM\_NCE}_{s,\,t-k} + \gamma \text{ INCIDENCE}_{s,\,t-1} + \alpha_s + \delta_t + \varepsilon_{st}$ for different values of k. **a** Both sexes, **b** females, **c** males

Rows 15–21 of Table 3 show estimates based on mortality and incidence data for males only. The estimates are not statistically significant when $k \leq 9$, but all three estimates for $k \geq 12$ are negative and statistically significant. These estimates are plotted in Panel C of Fig. 4. The difference between the effects of pharmaceutical innovation on female and male cancer mortality rates is not statistically significant. For example, the p value on the difference between the female and male estimates of β_{12} in Table 3 ($0.0972 = -0.2218$ to (-0.3191)) is 0.51 (Chi-square = 0.44).

Launching of new drugs in Mexico may not be strictly exogenous with respect to Mexican cancer mortality. To address the potential endogeneity of drug launches in

Mexico, I estimated a version of Eq. (1) via instrumental variables (IV). The instrument that I used for $\text{CUM\_NCE}_{s,t-k}$ (the number of drugs to treat cancer at site s that had been launched in Mexico by the end of year $t-k$) is $\text{CUM\_NCE\_FOREIGN}_{s,t-k}$ (the number of drugs to treat cancer at site s that had been launched *outside of* Mexico by the end of year $t-k$), defined as follows: $\text{CUM\_NCE\_FOREIGN}_{s,t-k} = \sum_d \text{IND}_{ds}\ \text{LAUNCHED\_FOREIGN}_{d,t-k}$ = the number of new chemical entities (drugs) to treat cancer at site s that had been launched *outside of* Mexico by the end of year $t-k$ ($k = 0,\ 3,\ 6,\ldots,18$):$\text{LAUNCHED\_FOREIGN}_{d,t-k}$ = 1 if drug d had been launched *outside of* Mexico by the end of year $t-k$= 0 if drug d had not been launched *outside of* Mexico by the end of year $t-k$.

The first stage of the two-stage IV estimation procedure is to estimate the following equation:

$$\text{CUM\_NCE}_{s,t-\text{k}} = \Omega\ \text{CUM\_NCE\_FOREIGN}_{s,t-k} + \alpha_s + \delta_t + \varepsilon_{st}. \qquad (8)$$

$\text{CUM\_NCE\_FOREIGN}_{s,t-k}$ is a good instrument for $\text{CUM\_NCE}_{s,t-k}$: when $k = 12$, the estimate of Ω is 0.8368 ($Z = 6.24$; $p < 0.0001$). The second stage is to estimate Eq. (1), replacing the actual value of $\text{CUM\_NCE}_{s,t-k}$ by its predicted value from Eq. (8). The IV estimate of β_{12} for both sexes (IV estimate = 0.2329; $Z = 4.06$; $p < 0.0001$) is very similar to the OLS estimate shown in row 5 of Table 3.

As discussed earlier, the "parallel trends" assumption needs to be satisfied for the estimates in Table 3 and Fig. 4 to be consistent estimates of the effect of drug launches on mortality. To provide evidence about the validity of this assumption, in Table 4, I present estimates of Eq. (7), which includes a control for the trend in mortality in the 'pre-period', e.g., the period 1993–2003. These estimates are based on a smaller set of cancer sites, because, as shown in Table 1, data on age-standardized mortality rates are less complete in 1993 than they are in 2003 and 2013. Rows 22–28 of Table 4 show estimates of Eq. (7) based on data for both sexes combined for this smaller set of cancer sites when the trend in mortality in the 'pre-period' (1993–2003) is excluded from the equation. Rows 29–35 show estimates of Eq. (7) based on the same sample when the trend in mortality in the 'pre-period' is included in the equation. The coefficient (π) on the pre-period mortality trend is significant (and positive) only when $k \geq 15$. Controlling for the pre-period mortality trend does not substantially change the estimates of β_k. The 2003–2013 change in the age-standardized mortality rate is inversely related to the change in the number of drugs ever launched 12–18 years earlier, controlling for the 2002–2012 change in incidence and the 'pre-period' (1993–2003) change in the mortality rate.

The relationship across cancer sites between the number of new drugs launched during 1985–1995 and the 2003–2013 change in the mortality rate, controlling for the "pre-period" (1993–2003) change in the mortality rate and the 2002–2012 change in the incidence rate, is shown in Fig. 5; this chart corresponds to the estimate of β_{18} shown in row 35 of Table 4. The figure indicates that the three cancer sites with the largest number of new drugs launched during 1985–1995 had

Table 4 Estimates of β_k parameters of Eq. (7), $\Delta\text{MORT}_s = \beta_k\,\Delta\text{CUM\_NCE\_}k_s + \gamma\,\Delta\text{INCIDENCE\_1}_s + \pi\,\Delta\text{MORT\_PRE}_s + \delta' + \varepsilon_s'$ excluding and including $\Delta\text{MORT\_PRE}_s$

Row	Lag	Parameter	Estimate	Std. err.	T	p value
			Without control for ΔMORT_PREV			
22	0	β_0	**− 0.26361**	**0.09837**	**− 2.67978**	**0.03155**
23	3	β_3	**− 0.26209**	**0.10704**	**− 2.44851**	**0.0442**
24	6	β_6	− 0.16993	0.10048	− 1.69117	0.13465
25	9	β_9	− 0.20238	0.09249	− 2.18828	0.06484
26	12	β_{12}	**− 0.26289**	**0.07605**	**− 3.45699**	**0.01059**
27	15	β_{15}	**− 0.27366**	**0.08422**	**− 3.24925**	**0.01407**
28	18	β_{18}	− 0.27399	0.12188	− 2.24806	0.05937
			With control for ΔMORT_PREV			
29	0	β_0	− 0.23336	0.09856	− 2.36765	0.0557
30	3	β_3	− 0.22552	0.11339	− 1.98885	0.09387
31	6	β_6	− 0.12894	0.11267	− 1.14446	0.29603
32	9	β_9	− 0.16884	0.10131	− 1.66657	0.14665
33	12	β_{12}	**− 0.23641**	**0.08384**	**− 2.81985**	**0.03036**
34	15	β_{15}	**− 0.26438**	**0.06602**	**− 4.00487**	**0.00708**
35	18	β_{18}	**− 0.3807**	**0.03866**	**− 9.84795**	**0.00006**

Estimates in bold are statistically significant (p-value $< .05$)

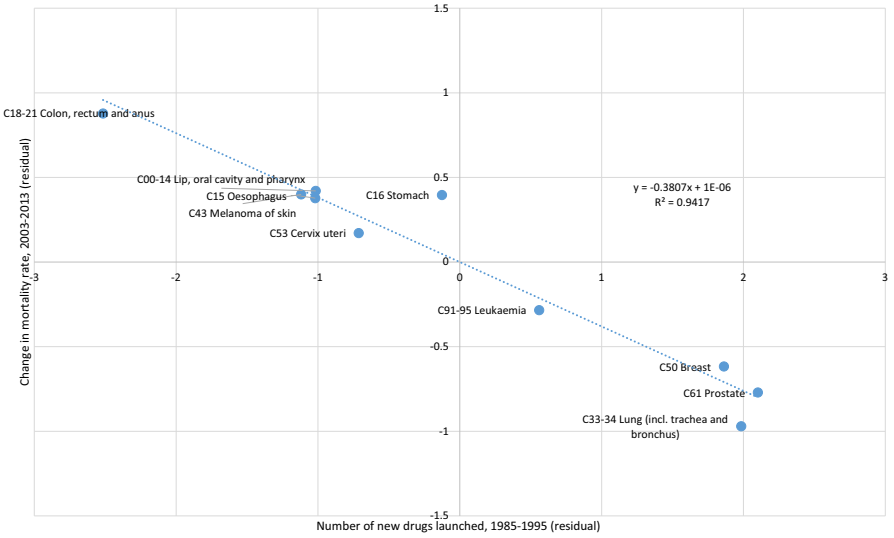

Fig. 5 Relationship across cancer sites between the number of new drugs launched during 1985–1995 and the 2003–2013 change in the mortality rate, controlling for the 1993–2003 change in the mortality rate and the 2002–2012 change in the incidence rate

the largest 2003–2013 reductions in the mortality rate, controlling for the 2002–2012 change in the incidence rate and the trend in mortality in the pre-period. Excluding these three cancer sites from the sample does not have much effect on the estimate of β_{18}; when they are excluded, the estimate of β_{18} is -0.357 ($t = 8.15$; $p = 0.0039$).

5 Discussion

The estimates indicate that the launch of new drugs subsequently reduced cancer mortality. New drugs launched during 1991–2001 are estimated to have reduced the age-standardized cancer mortality rate by 16%, i.e., at an average annual rate of about 1.6%.

Now, I will develop a rough estimate of the number of life-years gained in 2013 from the reduction in cancer mortality attributable to pharmaceutical innovation, and of the average cost-effectiveness (cost per life-year gained) of new cancer drugs.

To do this, I will estimate the decline in the *premature* mortality rate attributable to pharmaceutical innovation. The premature mortality rate is the number of potential years of life lost (PYLL) per 100,000 population (OECD 2017a, b). PYLL is a summary measure of premature mortality that provides an explicit way of weighting deaths occurring at younger ages. The calculation of PYLL involves summing up deaths occurring at each age and multiplying this with the number of remaining years to live up to a selected age limit.[11] The limit of 70 years was chosen for the calculations in *OECD Health Statistics*. To assure cross-country and trend comparison, the PYLL are standardized, for each country and each year. The total OECD population in 2010 is taken as the reference population for age standardization.

As shown in Table 1, between 2003 and 2013, the age-standardized mortality rate for all cancers combined declined by 15%, from 73.0 to 62.3. The estimates in Table 4 imply that virtually, this entire decline was due to the previous launches of new cancer drugs. During the same period, according to the OECD, the premature cancer mortality rate (the number of PYLL before age 70/100,000 population below age 70) declined by 11.4%, from 782.4 to 693.4. It seems reasonable to assume that this entire decline was also due to the previous launches of new cancer drugs. Therefore, in the absence of the previous new drug launches, premature cancer mortality would have been 12.8% (= (1/(1 − 0.114)) − 1) higher in 2013 than it actually was. Actual PYLL before age 70 due to cancer in 2013 was 823,209 (= 693.4 * (118,720,632/100,000)). I estimate that in the absence of previous new drug launches, premature cancer mortality would have been 928,870 (= 112.8% * 823,209).

This calculation implies that 105,661 life-years before age 70 were gained in 2013 due to new cancer drugs. This is a rough estimate of the longevity benefit in 2013 to people under 70 of cancer drugs launched during the period 1991–2001. To calculate the average cost-effectiveness of these drugs, I would like to measure

[11] This measure incorporates both the reduction in the number of deaths and the increase in mean age at death.

expenditure in 2013 by (or on behalf of) people under 70 on cancer drugs launched during the period 1991–2001. Unfortunately, these data are not available. However, I do have unpublished data from the IMS Health MIDAS database on expenditure (by or on behalf of all patients) by drug in 2010. Expenditure in 2010 on cancer drugs launched during 1991–2001 was $315 million.[12] 72% of people diagnosed with cancer in 2012 were below age 70 (source: GLOBOCAN). Expenditure in 2010 by or on behalf of people below age 70 on cancer drugs launched during 1994–2004 may, therefore, have been $227 million (= 72% * $315 million).

These calculations imply that the cost per life-year gained by people below age 70 from new cancer drugs was in the neighborhood of $2146 (= $227 million/105,661 life-years). This figure may be somewhat underestimated, since it is based on 2010 expenditure data.[13] On the other hand, Lichtenberg (2014a) showed that in the US, about 25% of the cost of new drugs (for all diseases) tends to be offset by reduced expenditure on old drugs, so the cost per life-year gained may have been below $2000.

The World Health Organization considers interventions whose cost per quality-adjusted life-year (QALY) gained is less than per capita GDP to be "very cost-effective" (Bertram et al. 2016); Mexico's per capita GDP in 2011 was $10,307.[14] The estimated cost per life-year gained from the previous pharmaceutical innovation is also well below the vast majority of estimates from the value-of-life literature of the value of a life-year (see Hirth et al. 2000).

6 Summary and conclusions

I assessed the impact that pharmaceutical innovation had on cancer mortality in Mexico during the period 2003–2013, by investigating whether there were larger declines in mortality for cancer sites (breast, lung, colon, etc.) that were subject to more pharmaceutical innovation, controlling for changes in cancer incidence. New drugs launched during 1991–2001 are estimated to have reduced the age-standardized cancer mortality rate by 16%, i.e., at an average annual rate of about 1.6%. I estimated that 105,661 life-years before age 70 were gained in 2013 due to cancer drugs launched during 1997–2007, and that the cost per life-year gained was in the neighborhood of $2146. By the standards of the World Health Organization, new cancer drugs have been very cost-effective in Mexico.

The contribution of cancer drug innovation to Mexican longevity growth has been valuable, but, perhaps, it could have been even larger. According to the IMS Institute for Healthcare Informatics (2016), during the period 2010–2014, 49 new cancer medicines were launched worldwide. As shown in Fig. 6, about twice as

[12] Expenditure in 2010 on *all* post-1981 cancer drugs was $393 million. This represents 2.4% of total 2010 pharmaceutical expenditure ($16.6 billion of US dollars at exchange rate) reported in MIDAS. The OECD estimate of total pharmaceutical sales in 2010 is 24% higher: $20.6 billion.

[13] According to the OECD, between 2010 and 2013, total pharmaceutical sales (in US$ at exchange rate) increased 3.6% (from $20.6 billion to $21.3 billion).

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

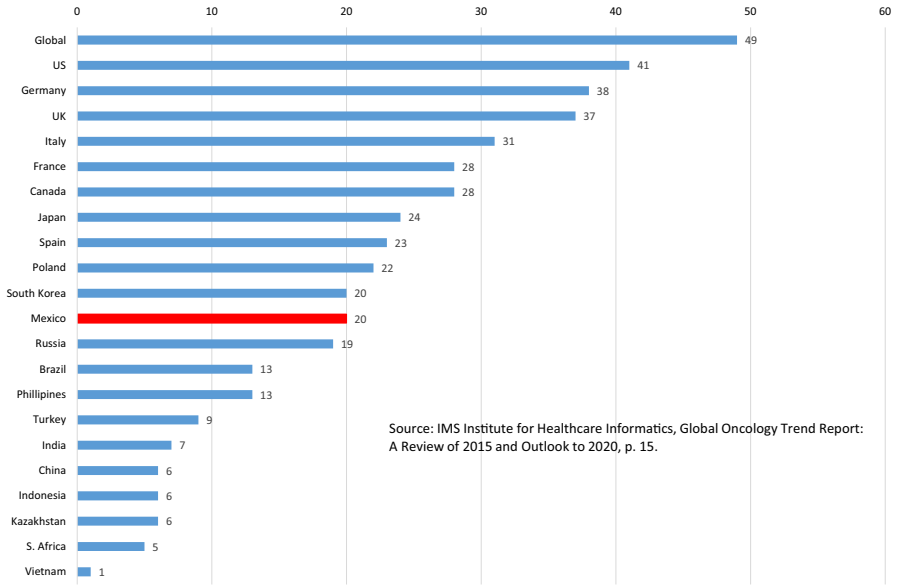

Fig. 6 Number of 2010–2014 cancer medicines that have been launched in various regions

many of these have been launched in the US as have been launched in Mexico.[15] In addition, as shown in Fig. 3, when new drugs are launched in Mexico, their diffusion is quite slow.

Due to unavailability of data, this study is subject to several limitations. The measure of pharmaceutical innovation—the number of chemical substances previously launched to treat cancer—is not the theoretically ideal measure. The number of chemical substances previously launched was the only cancer-site-specific, time-varying, measure of medical innovation. The previous research based on US data indicates that non-pharmaceutical medical innovation is not positively correlated across diseases with pharmaceutical innovation, but this may not apply to Mexico. Future research may be able to overcome these and other limitations.

Appendix

See Table 5.

[15] The IMS Institute for Healthcare Informatics (2016, p 22) also notes that "Mexico and South Africa are the only pharmerging countries in which oncology costs have fallen in proportion to total medicines costs in the last 5 years.".

Table 5 Mexican launch dates of drugs used to treat different types of cancer

Cancer site	Drug	Launch year
C00–C14 head and neck cancer	Docetaxel	1995
C00–C14 head and neck cancer	Cetuximab	2004
C15 esophageal cancer	Docetaxel	1995
C15 esophageal cancer	Trastuzumab	2000
C16 stomach (gastric) cancer	Docetaxel	1995
C16 stomach (gastric) cancer	Trastuzumab	2000
C18, C20 colon and rectal cancer	Irinotecan	1998
C18, C20 colon and rectal cancer	Capecitabine	2000
C18, C20 colon and rectal cancer	Oxaliplatin	2002
C18, C20 colon and rectal cancer	Cetuximab	2004
C18, C20 colon and rectal cancer	Bevacizumab	2005
C18, C20 colon and rectal cancer	Panitumumab	2011
C18, C20 colon and rectal cancer	Aflibercept	2014
C25 pancreatic cancer	Paclitaxel	1995
C25 pancreatic cancer	Gemcitabine	1997
C25 pancreatic cancer	Irinotecan	1998
C25 pancreatic cancer	Erlotinib	2006
C25 pancreatic cancer	Everolimus	2006
C25 pancreatic cancer	Sunitinib	2006
C34 lung cancer	Carboplatin	1992
C34 lung cancer	Docetaxel	1995
C34 lung cancer	Paclitaxel	1995
C34 lung cancer	Gemcitabine	1997
C34 lung cancer	Vinorelbine	1998
C34 lung cancer	Gefitinib	2004
C34 lung cancer	Bevacizumab	2005
C34 lung cancer	Pemetrexed	2005
C34 lung cancer	Erlotinib	2006
C34 lung cancer	Topotecan	2008
C34 lung cancer	Crizotinib	2012
C40–C41 bone cancer	Denosumab	2012
C43 melanoma	Interferon alfa-2b	1987
C43 melanoma	Aldesleukin	1996
C43 melanoma	Peginterferon alfa-2b	2001
C43 melanoma	Ipilimumab	2012
C43 melanoma	Vemurafenib	2012
C44 basal cell carcinoma	Imiquimod	1999
C45 malignant mesothelioma	Pemetrexed	2005
C46 kaposi sarcoma	Interferon alfa-2b	1987
C46 kaposi sarcoma	Paclitaxel	1995
C49 soft tissue sarcoma	Imatinib	2001
C49 soft tissue sarcoma	Trabectedin	2010

Table 5 continued

Cancer site	Drug	Launch year
C49 soft tissue sarcoma	Pazopanib	2012
C50 breast cancer	Epirubicin	1987
C50 breast cancer	Goserelin	1991
C50 breast cancer	Docetaxel	1995
C50 breast cancer	Paclitaxel	1995
C50 breast cancer	Gemcitabine	1997
C50 breast cancer	Anastrozole	1998
C50 breast cancer	Raloxifene	1998
C50 breast cancer	Toremifene	1999
C50 breast cancer	Capecitabine	2000
C50 breast cancer	Letrozole	2000
C50 breast cancer	Trastuzumab	2000
C50 breast cancer	Exemestane	2004
C50 breast cancer	Everolimus	2006
C50 breast cancer	Fulvestrant	2009
C50 breast cancer	Ixabepilone	2009
C50 breast cancer	Lapatinib	2009
C50 breast cancer	Trastuzumab emtansine	2014
C53 cervical cancer	Bevacizumab	2005
C53 cervical cancer	Topotecan	2008
C56 ovarian, fallopian tube, or primary peritoneal cancer	Carboplatin	1992
C56 ovarian, fallopian tube, or primary peritoneal cancer	Paclitaxel	1995
C56 ovarian, fallopian tube, or primary peritoneal cancer	Gemcitabine	1997
C56 ovarian, fallopian tube, or primary peritoneal cancer	Bevacizumab	2005
C56 ovarian, fallopian tube, or primary peritoneal cancer	Topotecan	2008
C61 prostate cancer	Flutamide	1987
C61 prostate cancer	Mitoxantrone	1987
C61 prostate cancer	Leuprorelin	1989
C61 prostate cancer	Goserelin	1991
C61 prostate cancer	Docetaxel	1995
C61 prostate cancer	Bicalutamide	1997
C61 prostate cancer	Degarelix	2010
C61 prostate cancer	Cabazitaxel	2012
C64–C65 kidney (renal cell) cancer	Aldesleukin	1996
C64–C65 kidney (renal cell) cancer	Bevacizumab	2005
C64–C65 kidney (renal cell) cancer	Everolimus	2006
C64–C65 kidney (renal cell) cancer	Sunitinib	2006
C64–C65 kidney (renal cell) cancer	Temsirolimus	2011
C64–C65 kidney (renal cell) cancer	Pazopanib	2012
C71 brain tumors	Temozolomide	1999
C71 brain tumors	Bevacizumab	2005

Table 5 continued

Cancer site	Drug	Launch year
C71 brain tumors	Everolimus	2006
C73 thyroid cancer	Vandetanib	2014
C81 hodgkin lymphoma	Brentuximab vedotin	2014
C82–C85 non-hodgkin lymphoma	Interferon alfa-2b	1987
C82–C85 non-hodgkin lymphoma	Rituximab	1999
C82–C85 non-hodgkin lymphoma	Bortezomib	2006
C82–C85 non-hodgkin lymphoma	Lenalidomide	2008
C82–C85 non-hodgkin lymphoma	Plerixafor	2009
C82–C85 non-hodgkin lymphoma	Brentuximab vedotin	2014
C90 multiple myeloma and other plasma cell neoplasms	Zoledronic acid	2001
C90 multiple myeloma and other plasma cell neoplasms	Bortezomib	2006
C90 multiple myeloma and other plasma cell neoplasms	Lenalidomide	2008
C90 multiple myeloma and other plasma cell neoplasms	Plerixafor	2009
C91, C92 leukemia	Interferon alfa-2b	1987
C91, C92 leukemia	Mitoxantrone	1987
C91, C92 leukemia	Idarubicin	1992
C91, C92 leukemia	Rituximab	1999
C91, C92 leukemia	Imatinib	2001
C91, C92 leukemia	Dasatinib	2007
C91, C92 leukemia	Nilotinib	2007
C91, C92 leukemia	Clofarabine	2009
C91, C92 leukemia	Obinutuzumab	2014

References

Bertram MY, Lauer JA, De Joncheere K, Edejer T, Hutubessy R, Kieny MP, Hill SR (2016) Cost-effectiveness thresholds: pros and cons. Bull World Health Organ 94(12):925–930

Dorsey ER et al (2010) Financial anatomy of biomedical research, 2003–2008. J Am Med Assoc 303(2):137–143

Hirth RA, Chernew ME, Miller E, Fendrick AM, Weissert WG (2000) Willingness to pay for a quality-adjusted life year: in search of a standard. Med Decis Mak 20(3):332–342

IMS Institute for Healthcare Informatics (2016) Global oncology trend report: a review of 2015 and outlook to 2020, June. http://www.imshealth.com/en_US/thought-leadership/quintilesims-institute/reports/global-oncology-trend-report-a-review-of-2015-and-outlook-to-2020. Accessed 14 Oct 2017

International Agency for Research on Cancer (2016) GLOBOCAN database. http://globocan.iarc.fr/Default.aspx. Accessed 14 Oct 2017

Lichtenberg FR (2013) The effect of pharmaceutical innovation on longevity: patient level evidence from the 1996–2002 medical expenditure panel survey and linked mortality public-use files. Forum Health Econ Policy 16(1):1–33

Lichtenberg FR (2014a) Has medical innovation reduced cancer mortality? CESifo Econ Stud 60(1):135–177

Lichtenberg FR (2014b) Pharmaceutical innovation and longevity growth in 30 developing and high-income countries, 2000–2009. Health Policy Technol 3(1):36–58

Lichtenberg FR (2014c) The impact of pharmaceutical innovation on longevity and medical expenditure in France, 2000–2009. Econ Human Biol 13:107–127

Lichtenberg FR (2014d) The impact of pharmaceutical innovation on disability days and the use of medical services in the United States, 1997–2010. J Hum Cap 8(4):432–480
Lichtenberg FR (2015) The impact of pharmaceutical innovation on premature cancer mortality in Canada, 2000–2011. Int J Health Econ Manag 15(3):339–359
Lichtenberg FR (2016a) The impact of pharmaceutical innovation on premature cancer mortality in Switzerland, 1995–2012. Eur J Health Econ 17(7):833–854
Lichtenberg F (2016b) The impact of pharmaceutical innovation on cancer mortality in Belgium, 2004–2012. Forum Health Econ Policy. doi:10.1515/fhep-2015-0042
National Cancer Institute (2016a) Enhancing drug discovery and development. https://www.cancer.gov/research/areas/treatment/enhancing-drug-discovery. Accessed 14 Oct 2017
National Cancer Institute (2016b) Drugs approved for different types of cancer. https://www.cancer.gov/about-cancer/treatment/drugs/cancer-type. Accessed 14 Oct 2017
Nobelprize.org (2016) The Prize in Economics 1987—Press Release. http://www.nobelprize.org/nobel_prizes/economic-sciences/laureates/1987/press.html. Accessed 13 Oct 2017
OECD (2017a) OECD Health Statistics 2016 database
OECD (2017b) OECD Health Statistics 2016, Definitions, Sources and Methods, Potential years of life years lost by ICD categories
Sampat BN, Lichtenberg FR (2011) What are the respective roles of the public and private sectors in pharmaceutical innovation? Health Aff 30(2):332–339
Solow RM (1960) Investment and technological progress. In: Arrow K, Karlin S, Suppes P (eds) Mathematical methods in social sciences 1959. Stanford University Press, Palo Alto, pp 89–104
World Health Organization (2016a) WHO Cancer Mortality database. http://www-dep.iarc.fr/WHOdb/WHOdb.htm. Accessed 13 Oct 2017
World Health Organization (2016b) WHO Mortality database. http://www.who.int/healthinfo/statistics/mortality_rawdata/en/. Accessed 13 Oct 2017