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The impact of pharmaceutical innovation on cancer mortality in Russia, 2001–2011

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Abstract

Objectives Assessment of the impact that pharmaceutical innovation (the Russian launch of new cancer drugs) and cancer incidence had on cancer mortality in Russia during the period 2001–2011.

Methods Investigation of whether the decline in mortality was greater for cancer sites (breast, lung, colon, etc.) subject to more pharmaceutical innovation and greater declines in incidence.

Key findings All of the measures of cancer mortality analyzed – the age-standardized mortality rate and the number of years of potential life lost before ages 75 and 65 are significantly inversely related to the number of new drugs that had been launched 6 or 7 years earlier. (As utilization of drugs is quite low during the first few years after launch, it is not surprising that mortality is not significantly related to the most recent drug launches.) New drugs launched during 1995–2004 are estimated to have reduced the age-standardized cancer mortality rate by 9.5% between 2001 and 2011, that is at an average annual rate of about 1.0%. New drugs launched during 1995–2004 accounted for almost all (94%) of the 2001–2011 reduction in the age-standardized mortality rate. On average, the launch of one additional drug for a cancer site is estimated to have reduced the number of years of potential life lost before age 75 due to cancer at that site 7 years later by 8406, and the number of years of potential life lost before age 65 due to cancer at that site 7 years later by 4152.

Conclusions The 14 new drugs launched during 1995–2004 are estimated to have reduced the number of years of potential life lost before age 75 in 2011 by 243 774. The estimated cost per life-year gained in 2011 was 2170 USD. This was about 15% of Russia's per capita GDP, and the World Health Organization considers interventions whose cost per quality-adjusted life-year gained is less than per capita GDP to be 'very cost-effective'.

Keywords health economics; modelling; outcomes research; pharmaco-economics

Introduction

Cancer mortality has been declining in Russia since the year 2000. Between 2001 and 2011,[1] the age-standardized cancer mortality rate declined by 10%. And as shown in Figure 1, during that period, the premature (before age 70) cancer mortality rate declined by 16%, that is at an average annual rate of 1.6%. The decline in cancer mortality does not appear to be due to a decline in cancer incidence: between 2002 and 2012, the age-standardized cancer incidence rate increased from 243.2 to 245.8 for males and from 160.6 to 187.1 for females.[2]

Although the overall premature cancer mortality rate declined, as shown in Figure 2, the rate of decline varied considerably across cancer sites. The mortality rate declined by at least 23% for four cancer sites (stomach, bladder, lung and leukaemia), but *increased* for two other cancer sites (prostate and cervix uteri).

There was also substantial variation across cancer sites with respect to the number of launches in Russia after 1994 of new drugs with relevant indications. Figure 3 shows data for the period 2000–2008 on the number of drugs for treating four types of cancer that had been launched in Russia after 1994. In 2000, there was the same number (2) of post-1994 drugs for treating all four cancer sites. In the next 8 years, there were five new drugs for treating lung cancer and three new drugs for colorectal cancer, but no new drugs for treating prostate cancer.

In this study, I will assess the impact that pharmaceutical innovation (the Russian launch of new cancer drugs) and cancer incidence had on cancer mortality in Russia during the period

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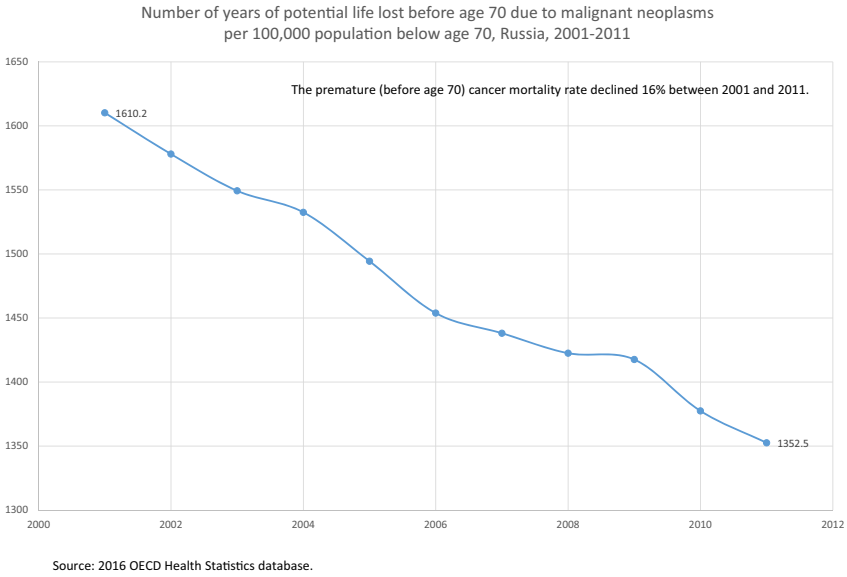

Figure 1 Number of years of potential life lost before age 70 due to malignant neoplasms per 100 000 population below age 70, Russia, 2001–2011. Source: 2016 OECD Health Statistics database.

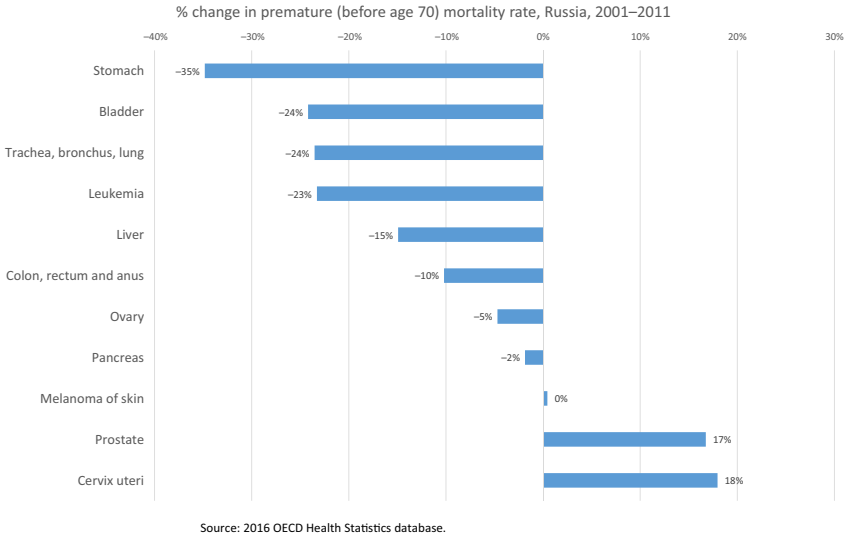

Figure 2 % change in premature (before age 70) mortality rate, Russia, 2001–2011. Source: 2016 OECD Health Statistics database.

2001–2011. A difference-in-differences 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.

In Section Econometric models of cancer mortality will formulate econometric models of cancer mortality. The data sources used to estimate these models are described in Section Data sources. Empirical results are presented in Section Empirical results. Rough estimates of the number of life-years gained in 2011 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 Section Discussion. Section Summary and conclusions provides a summary and conclusions.

Econometric models of cancer mortality

One model I will use to assess the impact of pharmaceutical innovation and cancer incidence on cancer mortality in Russia is:

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

where MORT_ASR_{st} = the age-standardized mortality rate from cancer at site s in year t (t = 2001, 2011); $\text{CUM\_NCE}_{s,t-k} = \sum_d \text{IND}_{ds} \text{LAUNCHED}_{d,t-k}$ = the number of new

chemical entities (drugs) to treat cancer at site s that had been launched in Russia by the end of year $t - k$ ($k = 0, 1, 2,\ldots,7$)[3] ; $IND_{ds} = 1$ 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; $LAUNCHED_{d,t-k} = 1$ if drug d had been launched in Russia by the end of year $t - k = 0$ if drug d had not been launched in Russia by the end of year $t - k$; $INC\_ASR_{s,t+1}$ = 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;

Another model I will use to assess the impact of pharmaceutical innovation and cancer incidence on cancer mortality in Russia is:

$$Y_{st} = \beta_k \text{CUM\_NCE}_{s,t-k} + \gamma \text{CASES}_{s,t+1} + \alpha_s + \delta_t + \varepsilon_{st} \quad (2)$$

where Y_{st} is one of the following variables: $YPLL75_{st}$ = the number of years of potential life lost before age 75 due to cancer at site s in year t; $YPLL65_{st}$ = the number of years of potential life lost before age 65 due to cancer at site s in year t and $CASES_{s,t+1}$ = the number of patients diagnosed with cancer at site s in year $t + 1$

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 eqs. (1) and (2) would signify that cancer sites for which there was more pharmaceutical innovation had larger declines in mortality, controlling for changes in incidence.

An alternative to eq. (1) is the model ($MORT\_ASR_{st}/INC\_ASR_{s,t+1}$) = β_k $CUM\_NCE_{s,t-k} + \alpha_s + \delta_t + \varepsilon_{st}$, and an alternative to eq. (2) is the model ($Y_{st}/CASES_{s,t+1}$) = β_k $CUM\_NCE_{s,t-k} + \alpha_s + \delta_t + \varepsilon_{st}$. I estimate eqs. (1) and (2) rather than these alternative models for several reasons. First, previous studies,[1,2] have shown that the number of drugs developed or launched is positively related to market size (e.g. the incidence of a disease). My data are consistent with that: the change in CUM_NCE is significantly positively correlated across cancer sites with the change in CASES. Therefore, failure to control (in an unrestrictive manner) for changes in incidence would result in biased (towards zero) estimates of β_k. Second, the models I estimate are more general – they include one more parameter – than the alternative models. The alternative to eq. (1) is based on the implicit assumption that the elasticity of mortality with respect to incidence is 1, but the data indicate that the elasticity is much lower than 1 – about 0.5; this may be due, in part, to errors in the measurement of incidence. Third, the marginal effect of new drug launches on mortality is more likely to be equalised across cancer sites than their marginal effect on the mortality-incidence ratio. Fourth, it is more straightforward to estimate the number of life-years gained from new drug launches from eq. (2) than it would be from the alternative specification.

Due to data limitations, the number of new chemical entities is the only cancer-site-specific, time-varying, measure of medical innovation in eqs. (1) and (2). Both a patient-level U.S. 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[3] 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[4] found that controlling for ten other potential determinants of longevity change (real per capita income, the unemployment rate, mean years of schooling, the urbanisation rate, real per capita health expenditure (public and private), the DPT: diphtheria, pertussis (whooping cough), and tetanus (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 U.S. funding for biomedical research came from pharmaceutical and biotechnology firms.[4] [5] Much of the rest came from the federal government (i.e. the NIH), and new drugs often build on upstream government research[6]. The National Cancer Institute[7,8] says that it 'has played an active role in the development of drugs for cancer treatment for 50 years... [and] that approximately one half of the chemotherapeutic drugs currently used by oncologists for cancer treatment were discovered and/or developed' at the National Cancer Institute. Second, previous research based on U.S. data[9,10] 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 Russia.

Launching of new drugs in Russia may not be strictly exogenous with respect to Russian cancer mortality. To address the potential endogeneity of drug launches in Russia, I will estimate versions of eqs. (1) and (2) via instrumental variables (IV).[5] The instrument that I will use for $CUM\_NCE_{s,t-k}$ (the number of drugs to treat cancer at site s that had been launched in Russia by the end of year $t - k$) is $CUM\_NCE\_FOREIGN_{s,t-k}$ (the number of drugs to treat cancer at site s that had been launched *outside of* Russia by the end of year $t - k$),[6] defined as follows:

$CUM\_NCE\_FOREIGN_{s,t-k}$	$= \sum_d IND_{ds}$ $LAUNCHED\_FOREIGN_{d,t-k}$ = the number of post-1994 new chemical entities (drugs) to treat cancer at site s that had been launched *outside of* Russia by the end of year $t - k$
$LAUNCHED\_FOREIGN_{d,t-k}$	=1 if drug d had been launched *outside of* Russia by the end of year $t - k$ =0 if drug d had not been launched *outside of* Russia by the end of year $t - k$

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

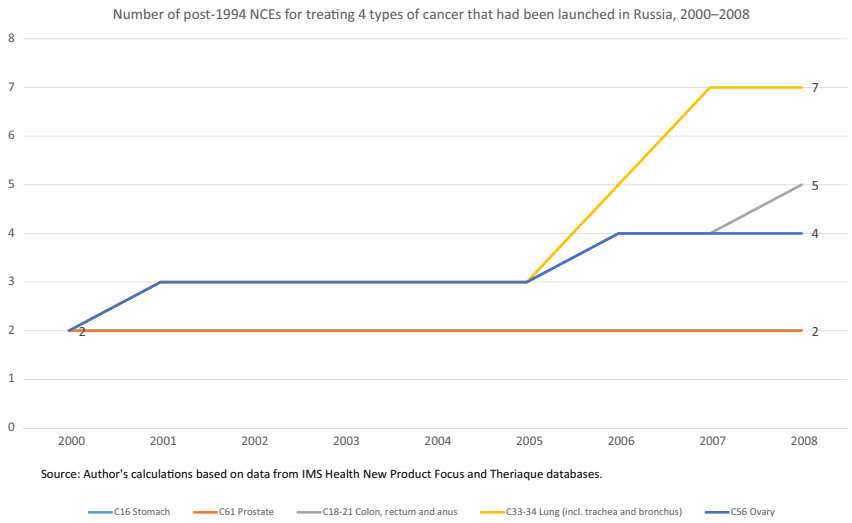

Figure 3 Number of post-1994 NCEs for treating four types of cancer that had been launched in Russia, 2000–2008. Source: Author's calculations based on data from IMS Health New Product Focus and Theriaque databases.

$$\text{CUM\_NCE}_{s,t-k} = \Omega \text{CUM\_NCE\_FOREIGN}_{s,t-k} + \alpha_s + \delta_t + \varepsilon_{st} \quad (3)$$

$\text{CUM\_NCE\_FOREIGN}_{s,t-k}$ appears to be a good instrument for $\text{CUM\_NCE}_{s,t-k}$: when $k = 7$, the estimate of Ω is 0.395 ($Z = 4.17$; P-value < 0.0001).

The measure of pharmaceutical innovation in eqs. (1) and (2)—the number of chemical substances previously launched 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 (e.g., the number of 'standard units', as defined by IMS Health) 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, a previous study[10] 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.

In eqs. (1) and (2), 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 Russia by the end of year $t - k$, i.e. there is a lag of k years. Eqs. (1) and (2) will be estimated for different values of k: $k = 0, 1, 2, \ldots, 9$. A separate model will be estimated for each value of k, rather than including multiple values ($\text{CUM\_NCE}_{s,t}$, $\text{CUM\_NCE}_{s,t-1}$, $\text{CUM\_NCE}_{s,t-2}, \ldots$) 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 Russian drug launch dates (described below) to calculate the mean quantity (number of 'standard units') of cancer drugs sold in Russia, by number of years since launch. The results are shown in Figure 4. The mean quantity of cancer drugs sold is 13 times higher 6 years after launch than it is 1 year after launch, and 48 times higher 10 years after launch than it is 1 year after launch.

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,[11] 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 $\text{INCIDENCE}_{s,t+1}$ is the only incidence variable included in eqs. (1) and (2). The limited availability of incidence data also means that we can only use mortality data for 2 years (2001 and 2011). Writing eq. (1) for each of these years:

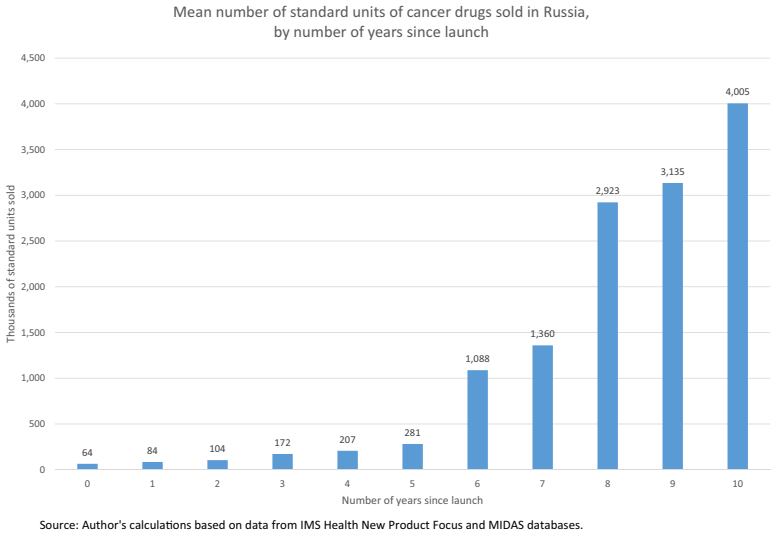

Figure 4 Mean number of standard units of cancer drugs sold in Russia, by number of years since launch. Source: Author's calculations based on data from IMS Health New Product Focus and MIDAS databases.

$$\text{MORT\_ASR}_{s,2001} = \beta_k \text{CUM\_NCE}_{s,2001-k} + \gamma \text{INC\_ASR}_{s,2002} + \alpha_s + \delta_{2001} + \varepsilon_{s,2001} \quad (4)$$

$$\text{MORT\_ASR}_{s,2011} = \beta_k \text{CUM\_NCE}_{s,2011-k} + \gamma \text{INC\_ASR}_{s,2012} + \alpha_s + \delta_{2011} + \varepsilon_{s,2011} \quad (5)$$

Subtracting (4) from (5),

$$\begin{aligned}&(\text{MORT\_ASR}_{s,2011} - \text{MORT\_ASR}_{s,2001}) \\ &= \beta_k(\text{CUM\_NCE}_{s,2011-k} - \text{CUM\_NCE}_{s,2001-k}) \\ &+ \gamma(\text{INC\_ASR}_{s,2012} - \text{INC\_ASR}_{s,2002}) + (\delta_{2011} - \delta_{2001}) \\ &+ (\varepsilon_{s,2011} - \varepsilon_{s,2001})\end{aligned} \quad (6)$$

Eq. (6) may be rewritten as follows:

$$\Delta\text{MORT\_ASR}_s = \beta_k \Delta\text{CUM\_NCE\_k}_s + \gamma \Delta\text{INC\_ASR}_s + \delta' + \varepsilon'_s \quad (7)$$

where $\Delta\text{MORT\_ASR}_s = \text{MORT\_ASR}_{s,2011} - \text{MORT\_ASR}_{s,2001}$ = the 2001–2011 change in the age-standardized mortality rate from cancer at site s; $\Delta\text{CUM\_NCE\_k}_s = \text{CUM\_NCE}_{s,2011k} - \text{CUM\_NCE}_{s,2001-k}$ = the number of drugs for cancer at site s launched between 2001 – k and 2011 – k; $\Delta\text{INC\_ASR}_s = \text{INC\_ASR}_{s,2012} - \text{INC\_ASR}_{s,2002}$ = the 2002–2012 change in the age-standardized incidence rate of cancer at site s; $\delta' = \delta_{2011} - \delta_{2001}$

According to eq. (7), the 2001–2011 change in the age-standardized mortality rate depends on two variables: the number of drugs launched between year 2001 – k and 2011 – k, and the 2002–2012 change in the age-standardized incidence rate.[9] Similarly,

$$\Delta Y_s = \beta_k \Delta\text{CUM\_NCE\_k}_s + \gamma \Delta\text{CASES}_s + \delta' + \varepsilon'_s \quad (8)$$

where $\Delta Y_s = Y_{s,2011} - Y_{s,2001}$ = the 2001–2011 change in the number of deaths or years of potential life lost from cancer at site s; $\Delta\text{CASES}_s = \text{CASES}_{s,2012} - \text{CASES}_{s,2002}$ = the 2002–2012 change in the number of patients diagnosed with cancer at site s

Data sources

Mortality data

Data on MORT_ASR were obtained from the WHO Cancer Mortality Database.[15] Data on YPLL75 and YPLL65 were constructed from data contained in Global Health Estimates 2015.[16]

Incidence data

Data on INC_ASR and CASES were obtained from GLOBOCAN.

Mortality and incidence data are reported separately by sex. For cancers affecting both sexes, we computed the age-standardized rates as the simple mean of the sex-specific rates. For cancers affecting only one sex (breast, cervical, ovarian and prostate), we computed the age-standardized rates as 50% of the single-sex rate.

Data on drugs approved for different types of cancer were obtained from the Thériaque database.[17] Data on

Russian launch dates of drugs were obtained from the IMS Health New Product Focus database. This database contains data on drug launches in many countries from 1982 to the present, but coverage in Russia began in 1995. The Russian launch year (as indicated in the IMS New Product Focus database) is usually the year in which the drug was first sold in Russia (as indicated in the IMS MIDAS database).

I define CUM_NCE_{st} as the number of *post-1994* new chemical entities (i.e. NCEs first launched anywhere in the world after 1994) used to treat cancer at site s that had been launched in Russia by the end of year t. As the New Product Focus data are left-censored (no pre-1995 data for Russia), this measure is subject to error, because CUM_NCE_{st} will not (but should) include pre-1995 NCEs that were first launched in Russia after 1994. 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 Russia during the period 1999–2010 were obtained from the IMS Health MIDAS database.

Mortality and incidence data, by cancer site and year, are shown in Table 1.

Data on the number of post-1994 drugs ever launched in Russia, by cancer site and year, are shown in Table 2.

Russian launch dates of drugs used to treat different types of cancer are shown in Appendix Table A1.

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, and are plotted in Figure 5. Each estimate is from a separate model. For simplicity, estimates of the incidence rate 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 less for cancer sites that had larger increases in incidence.

All of the estimates of β_k are negative, but for $k < 4$, only one (β_0) is statistically significant (P-value < 0.05). This is not surprising since, as shown in Figure 4, utilization of cancer drugs is quite low 0–5 years after launch. However, estimates of β_k are negative and statistically significant (P-value < 0.05) for $k \geq 4$.[10] This signifies that the age-standardized mortality rate is inversely related to the number of cancer drugs that had been launched up until 4 years earlier, controlling for the age-standardized incidence rate. The IV estimate of β_7, where $CUM\_NCE\_FOREIGN_{s,t-7}$ is the instrument for $CUM\_NCE_{s,t-7}$, is also negative and highly significant; its magnitude is about 20% smaller than the OLS estimate (estimate = −0.320; $Z = 2.36$; P-value = 0.018).

As shown in Table 2, between 2001 and 2011, the mean value of $CUM\_NCE_{s,t-7}$ increased by 1.71, from 0 to 1.71. The estimate of β_7 in Table 3 implies that the 2001–2011 increase in $CUM\_NCE_{s,t-7}$ reduced $MORT\_ASR_{st}$ by 0.69 (=0.403 × 1.71). As shown in Table 1, between 2001 and 2011, the mean value of $MORT\_ASR_{st}$ declined by 0.73, from 7.08 to 6.35. Hence, the 2001–2011 increase in $CUM\_NCE_{s,t-7}$—in other words, new drugs launched during 1995–2004—accounted for 94% of the 2001–2011 reduction in the age-standardized mortality rate.[11] The relationship across cancer sites between the number of drugs launched during 1995–2004 and the 2001–2011 change in the age-standardized mortality rate, controlling for the 2002–2012 change in age-standardized incidence rate, is shown in Figure 6. It is evident from Figure 6, that breast cancer is an outlier with respect to the number of drug launches. If breast cancer is

Table 1 Mortality and incidence data, by cancer site and year

Cancer site	Deaths		mort_asr		Cases		inc_asr	
Year	2001	2011	2001	2011	2002	2012	2002	2012
C00-14 Lip, oral cavity and pharynx	8743	9171	4.90	4.75	11 863	14 800	6.85	7.65
C15 Oesophagus	7239	6795	3.85	3.35	7344	7263	4.05	3.65
C16 Stomach	42 614	33 205	20.70	14.65	50 844	38 417	26.25	17.65
C18-21 Colon, rectum and anus	34 968	37 948	15.70	15.25	47 776	59 928	23.25	25.90
C22 Liver (specified as primary)	8330	8546	4.10	3.80	6485	6812	3.35	3.15
C25 Pancreas	13 386	15 689	6.30	6.65	11 833	14 512	5.85	6.35
C33-34 Lung (incl. trachea and bronchus)	56 994	50 422	31.70	25.70	62 563	55 805	36.70	29.10
C43 Melanoma of skin	2720	3368	1.35	1.50	5744	8717	2.90	4.05
C50 Breast	21 590	23 317	8.50	8.20	43 432	57 502	19.40	22.80
C53 Cervix uteri	6281	6376	2.55	2.65	12 215	15 342	5.95	7.65
C56 Ovary	7298	7581	2.85	2.75	9918	13 373	4.55	5.65
C61 Prostate	6984	10 555	4.25	5.65	10 401	26 885	6.40	15.05
C67 Bladder	7251	6844	3.95	3.25	12 274	13 853	7.00	7.00
C70-72 Brain, central nervous system	5650	6985	3.25	3.65	5189	7377	3.35	4.35
C82-85,C96 Non-Hodgkin lymphoma	2987	3773	1.55	1.70	4085	7715	2.40	3.90
C88 + C90 Multiple myeloma	1563	2162	0.75	0.95	2304	2738	1.15	1.20
C91-95 Leukaemia	7694	7194	4.15	3.50	10 847	11 773	6.35	6.50
Mean	14 252	14 114	7.08	6.35	18 536	21 342	9.75	10.09

Table 2 Number of post-1994 drugs ever launched in Russia, by cancer site, 1995–2012

Cause	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012
C00-14 Lip, oral cavity and pharynx	0	0	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
C15 Oesophagus	0	0	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
C16 Stomach	0	0	1	1	1	2	2	2	2	2	2	2	2	2	2	2	2	2
C18-21 Colon, rectum and anus	0	0	0	0	0	2	3	3	3	3	3	4	4	5	5	6	6	6
C22 Liver (specified as primary)	0	0	0	1	1	1	1	1	1	1	1	1	1	2	2	2	2	2
C25 Pancreas	0	0	0	1	1	1	1	1	1	1	1	1	2	4	4	4	4	4
C33-34 Lung (incl. trachea and bronchus)	0	0	1	2	2	2	3	3	3	3	3	5	7	7	7	7	7	7
C43 Melanoma of skin	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
C50 Breast	0	0	2	3	3	4	5	6	6	6	6	8	8	11	11	11	11	11
C53 Cervix uteri	0	0	0	0	0	0	1	1	1	1	1	2	2	2	2	2	2	2
C56 Ovary	0	0	0	1	2	2	3	3	3	3	3	4	4	4	5	5	5	5
C61 Prostate	0	0	2	2	2	2	2	2	2	2	2	2	2	2	2	2	3	6
C67 Bladder	0	0	0	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
C70-72 Brain, central nervous system	0	0	0	0	0	0	1	1	1	1	1	1	1	1	1	1	1	1
C82-85,C96 Non-Hodgkin lymphoma	0	0	0	0	0	0	1	1	1	1	1	2	2	2	3	4	5	5
C88 + C90 Multiple myeloma	0	0	0	0	0	0	0	0	0	0	0	1	1	1	1	2	2	2
C91-95 Leukaemia	0	0	0	0	0	0	1	2	2	2	2	2	2	4	7	7	8	8
Average	0.00	0.00	0.47	0.82	0.88	1.12	1.59	1.71	1.71	1.71	1.71	2.24	2.41	2.94	3.24	3.41	3.59	3.76

excluded from the sample, the magnitude of the estimate of β_7 *increases* by 67% (from −0.403 to −0.671).

Estimates of the pharmaceutical innovation (β_k) parameters of models of years of potential life lost (eq. 2) for different values of k are shown in Table 4. Once again, each estimate is from a separate model. All models included $CASES_{s,t+1}$, the number of patients diagnosed with cancer at site s in year $t + 1$. For simplicity, estimates of the coefficient of this variable (γ) are not shown here. Estimates of this coefficient were positive and significant in all models, indicating that the number of years of potential life lost declined less for cancer sites that had larger increases in the number of patients diagnosed.

Columns 1–3 of Table 4 show estimates of β_k parameters of eq. (2) when Y_{st} = the number of years of potential life lost before age 75 due to cancer at site s in year t. All of the estimates of β_k are negative, but for $k < 6$, only two (β_0 and β_4) are statistically significant (P-value < 0.05). The estimates of β_6 and β_7 have the largest magnitudes and are highly statistically significant (P-value < 0.001). The estimate of β_7 implies that, on average, one additional drug launch for a cancer site reduced the number of years of potential life lost before age 75 due to cancer at that site 7 years later by 8406.[12] The IV estimate of β_7 is also negative and highly significant; its magnitude is about 10% smaller than the OLS estimate (estimate = −7524; Z = 2.68; P-value = 0.007). Columns 4–6 of Table 4 show estimates of β_k parameters of eq. (2) when Y_{st} = the number of years of potential life lost before age 65 due to cancer at site s in year t. All of the estimates of β_k are negative, but for $k < 6$, only three (β_0, β_1 and β_3) are statistically significant (P-value < 0.05). The estimates of β_6 and β_7 have the largest magnitudes and are highly statistically significant (P-value < 0.004). On average, one additional drug launch for a cancer site reduced the number of years of potential life lost before age 65 due to cancer at that site 7 years later by 4152. The IV estimate of β_7 is also negative and highly

Table 3 Estimates of β_k from eq. (1), $MORT\_ASR_{st} = \beta_k CUM\_NCE_{s,t-k} + \gamma\ INC\_ASR_{s,t+1} + \alpha_s + \delta_t + \varepsilon_{st}$

lag (k)	Estimate	Z	Pr > |Z|
0	**−0.197**	**−2.20**	**0.028**
1	−0.093	−1.14	0.256
2	−0.079	−0.94	0.348
3	−0.113	−1.58	0.115
4	**−0.150**	**−2.16**	**0.031**
5	**−0.202**	**−2.49**	**0.013**
6	**−0.276**	**−4.13**	**<0.0001**
7	**−0.403**	**−3.93**	**<0.0001**

$MORT\_ASR_{st}$ = the age-standardized mortality rate from cancer at site s in year t (t = 2001, 2011). $CUM\_NCE_{s,t-k}$ = the number of post-1994 new chemical entities (drugs) to treat cancer at site s that had been launched in Russia by the end of year $t - k$ (k = 0, 1, 2,. . .,7). $INC\_ASR_{s,t+1}$ = the age-standardized incidence rate of cancer at site s in year $t + 1$.

Each estimate is from a separate model. All models control for $INC\_ASR_{s,t+1}$.

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

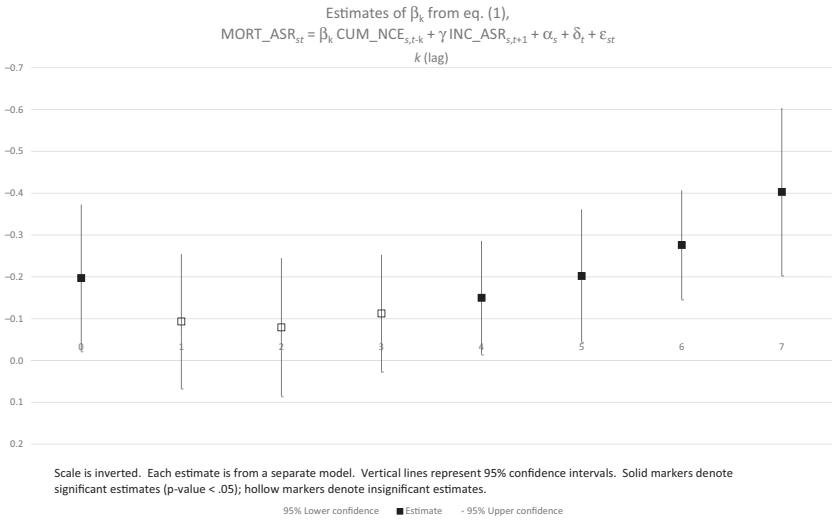

Figure 5 Estimates of β_k from eq. (1), $MORT\_ASR_{st} = \beta_k\ CUM\_NCE_{s,t-k} + \gamma\ INC\_ASR_{s,t+1} + \alpha_s + \delta_t + \varepsilon_{st}$. Scale is inverted. Each estimate is from a separate model. Vertical lines represent 95% confidence intervals. Solid markers denote significant estimates (P-value < 0.05); hollow markers denote insignificant estimates.

significant; its magnitude is slightly larger than the OLS estimate (estimate = −4228; $Z = 2.86$; P-value = 0.004).

Discussion

The estimates indicate that the launch of new drugs subsequently reduced cancer mortality. New drugs launched during 1995–2004 are estimated to have reduced the age-standardized cancer mortality rate by 9.5% between 2001 and 2011 that is at an average annual rate of about 1.0%.

Now I will develop a rough estimate of the number of life-years gained in 2011 from cancer drugs launched during the period 1995–2004, and of the average cost-effectiveness (cost per life-year gained) of new cancer drugs. IMS MIDAS data indicate that expenditure (in USD) in 2011 on cancer drugs launched during 1995–2004 was 673 million USD. GLOBOCAN data indicate that 79% of patients diagnosed with cancer in 2012 were below age 75. Therefore, I estimate that 529 million USD (=79% × 673 million USD) was spent in 2011 on cancer drugs launched during 1995–

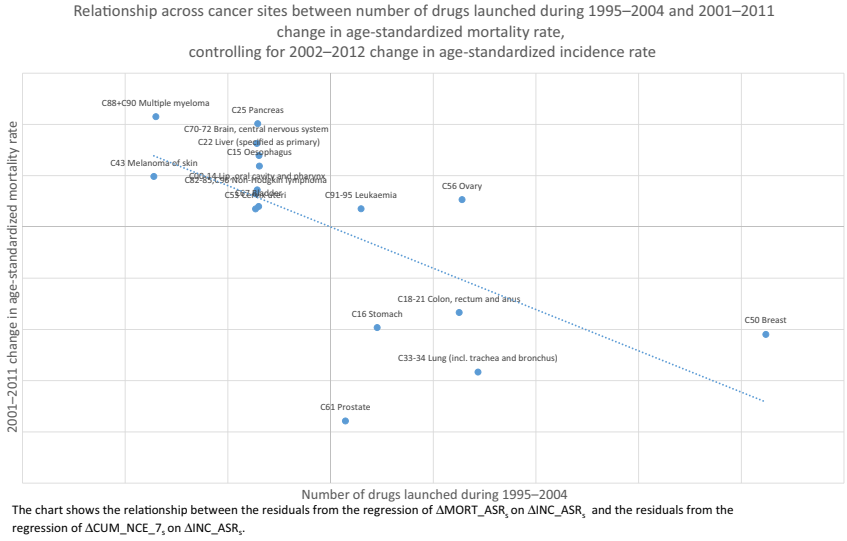

Figure 6 Relationship across cancer sites between number of drugs launched during 1995-2004 and 2001-2011 change in age-standardized mortality rate, controlling for 2002–2012 change in age-standardized incidence rate. The chart shows the relationship between the residuals from the regression of ΔMORT__ASR$_s$ on ΔINC_ASR$_s$ and the residuals from the regression of ΔCUM_NCE_7$_s$ on ΔINC_ASR$_s$.

Table 4 Estimates of β_k from eq. (2), $Y_{st} = \beta_k$ CUM_NCE$_{s,t-k}$ + γ CASES$_{s,t+1}$ + α_s + δ_t + ε_{st}

Column	1	2	3	4	5	6
	Y = YPLL75			Y = YPLL65		
lag	Estimate	Z	Pr > |Z|	Estimate	Z	Pr > |Z|
0	**−3735.83**	**−2.6**	**0.0103**	**−2258**	**−3.13**	**0.0018**
1	−2356.47	−1.4	0.154	**−1727**	**−2.14**	**0.0327**
2	−1871.64	−1.1	0.268	−1318	−1.53	0.1257
3	−2768.56	−1.9	0.0528	**−1667**	**−2.29**	**0.0217**
4	**−3342.61**	−2.0	**0.0486**	−1788	−1.93	0.053
5	−3182.31	−1.8	0.0688	−1436	−1.40	0.1607
6	**−5411.55**	**−3.6**	**0.0004**	**−2607**	**−2.92**	**0.0035**
7	**−8405.99**	**−3.9**	**0.0001**	**−4152**	**−3.73**	**0.0002**

Y_{st} = the number of years of potential life lost before age 75 or 65 due to cancer at site s in year t; CUM_NCE$_{s,t-k}$ = the number of post-1994 NCEs for cancer at site s that had been launched in Russia by the end of year $t - k$; CASES$_{s,t+1}$ = the number of patients diagnosed with cancer at site s in year $t + 1$.

Each estimate is from a separate model. All models control for CASES$_{s,t+1}$.

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

2004 for patients below age 75; this may be an overestimate, because patients diagnosed before age 75 may continue to be treated with drugs after reaching age 75.

The estimate of β_7 in Table 4 when Y = YPLL75 is −8406: one additional new drug for an indication reduces the number of years of potential life lost before age 75 by 8406. The 14 new drugs launched during 1995–2004 had 29 indications, so new drugs launched during 1995–2004 are estimated to have reduced the number of years of potential life lost before age 75 in 2011 by 243 774 (=29 × 8406). The estimated cost per life-year gained in 2011 is 2170 USD (=529 million USD/243 774 life-years).[13]

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'[18]; Russia's per capita GDP in 2011 was $14 212.[14] The estimated cost per life-year gained from 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.[20]

Summary and conclusions

I have assessed the impact that pharmaceutical innovation (the Russian launch of new cancer drugs) and cancer incidence had on cancer mortality in Russia during the period 2001–2011, by investigating whether the decline in mortality was greater for cancer sites (breast, lung, colon, etc.) subject to more pharmaceutical innovation and greater declines in incidence.

All of the measures of cancer mortality I analyzed—the age-standardized mortality rate and the number of years of potential life lost before ages 75 and 65—were significantly inversely related to the number of new drugs that had been launched 6 or 7 years earlier. (As utilization of drugs is quite low during the first few years after launch, it is not surprising that mortality was not significantly related to the most recent drug launches.)

New drugs launched during 1995–2004 are estimated to have reduced the age-standardized cancer mortality rate by 9.5% between 2001 and 2011 that is at an average annual rate of about 1.0%. New drugs launched during 1995–2004 accounted for almost all (94%) of the 2001–2011 reduction in the age-standardized mortality rate. On average, the launch of one additional drug for a cancer site is estimated to have reduced the number of years of potential life lost before age 75 due to cancer at that site seven years later by 8406, and the number of years of potential life lost before age 65 due to cancer at that site 7 years later by 4152.

The 14 new drugs launched during 1995–2004 are estimated to have reduced the number of years of potential life lost before age 75 in 2011 by 243 774. The estimated cost per life-year gained in 2011 is 2170 USD. This was about 15% of Russia's per capita GDP, and the World Health Organization considers interventions whose cost per QALY gained is less than per capita GDP to be 'very cost-effective'.

Declarations

Conflict of interests

The Author(s) declare(s) that they have no conflicts of interest to disclose.

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Authors' contributions

All Authors state that they had complete access to the study data that support the publication

Notes

1. Unfortunately, 2011 is the most recent year for which the WHO publishes statistics about the age-standardized cancer mortality rate in Russia.
2. The increase in measured incidence could be attributable, in part, to an increase in cancer screening for example mammography.
3. k represents the length (in years) of the lag between the launch of a drug and its effect on mortality.
4. In 2007, 89% of private biomedical research expenditure was funded by pharmaceutical and biotechnology firms; the remaining 11% was funded by medical device firms.[3]
5. In statistics, econometrics, epidemiology and related disciplines, the IV method is used to estimate causal relationships when controlled experiments are not feasible or when a treatment is not successfully delivered to every unit in a randomized experiment.[12] IV estimation may also address the issue of 'parallel trends' that affects difference-in-difference models such as eqs. (1) and (2).

6. During the period 1995–2015, 50 cancer drugs were launched in Russia, and 77 were launched in other countries. Drugs are launched later in Russia than they are in other countries (e.g. the US, the UK, Germany, and France), so the lagged value of CUM_NCE_FOREIGN would probably be a better instrument for CUM_NCE than the contemporaneous value of CUM_NCE_FOREIGN. However, due to left-censoring of the Russian drug launch data and the limited availability of incidence data (for 2002 and 2012 only), the instrument I will use is the contemporaneous value of CUM_NCE_FOREIGN.
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. Robert Solow[13] 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.[14]
8. Outpatient prescription drug claims usually don't show the indication of the drug prescribed. Claims for drugs administered by doctors and nurses (e.g. chemotherapy) often show the indication of the drug, but these data are not available for Russia.
9. Below I will provide a chart (Figure 6) based on eq. (6).
10. Because coverage of Russia in the IMS New Product Focus database began in 1995, we cannot estimate the model for $k > 7$.
11. The 0.34 increase in the mean age-standardized incidence rate (from 9.75 to 10.09) is estimated to have caused a 0.18 increase in the mean age-standardized mortality rate.
12. Many drugs have multiple indications. The average number of indications of the 22 cancer drugs launched in Russia during 1995–2004 was 1.86. Therefore, on average, one additional drug launch is estimated to have reduced the number of years of potential life lost from cancer before age 75 seven years later by 15 635 (=1.86 × 8406).
13. A previous study showed that in the USA, about 25% of the cost of new drugs (for all diseases) tends to be offset by reduced expenditure on old drugs, so the true cost per life-year gained may have been lower than 1346 USD.
14. A previous study demonstrated that the number of QALYs gained from pharmaceutical innovation could be either greater than or less than the number of life-years gained.[19]

References

1. Acemoglu D, Linn J. Market size in innovation: theory and evidence from the pharmaceutical industry. *Quart J Econ* 2004; 119: 1049–1090.
2. Danzon PM *et al.* The impact of price regulation on the launch delay of new drugs-evidence from twenty-five major markets in the 1990s. *Health Econ* 2005; 14: 269–292.
3. Lichtenberg FR. 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 Economic Policy* 2013; 16: 1–33.
4. Lichtenberg FR. Pharmaceutical innovation and longevity growth in 30 developing and high-income countries, 2000–2009. *Health Policy Technol* 2014b; 3: 36–58.
5. Dorsey ER *et al.* Financial Anatomy of Biomedical Research, 2003–2008. *J Am Med Assoc* 2010; 303: 137–143.
6. Sampat BN, Lichtenberg FR. What are the respective roles of the public and private sectors in pharmaceutical innovation? *Health Aff* 2011; 30: 332–339.
7. National Cancer Institute. *Enhancing Drug Discovery and Development*. 2016. https://www.cancer.gov/research/areas/treatment/enhancing-drug-discovery (accessed February 08 2018).
8. National Cancer Institute. *Drugs Approved for Different Types of Cancer*. 2016. https://www.cancer.gov/about-cancer/treatment/drugs/cancer-type (accessed February 08 2018).
9. Lichtenberg FR. Has medical innovation reduced cancer mortality? *CESifo Economic Studies* 2014a; 60: 135–177.
10. Lichtenberg FR. The impact of pharmaceutical innovation on longevity and medical expenditure in France, 2000–2009. *Economics Human Biol* 2014c; 13: 107–127.
11. Lichtenberg FR. The impact of pharmaceutical innovation on disability days and the use of medical services in the United States, 1997–2010. *J Hum Cap* 2014d; 8: 432–480.
12. Imbens G, Angrist J. Identification and estimation of local average treatment effects. *Econometrica* 1994; 62: 467–476.
13. Solow RM. Investment and technological progress. In: Arrow K, Karlin S, Suppes P, eds. *Mathematical Methods in Social Sciences 1959*. Palo Alto, California: Stanford University Press, 1960: 89–104.
14. Nobelprize.org. *The Prize in Economics 1987 – Press Release*. 2016. http://www.nobelprize.org/nobel_prizes/economic-sciences/laureates/1987/press.html (accessed February 08 2018).
15. World Health Organization. *WHO Cancer Mortality Database*. 2017. http://www-dep.iarc.fr/WHOdb/WHOdb.htm (accessed February 08 2018).
16. World Health Organization. *Global Health Estimates 2015: Deaths by Cause, Age, Sex, by Country and by Region, 2000–2015*. 2017. http://www.who.int/healthinfo/global_burden_disease/estimates/en/index1.html (accessed February 08 2018).
17. Centre National Hospitalier d'Information sur le Médicament. *Thériaque database*. 2017. http://www.theriaque.org/apps/contenu/accueil.php (accessed February 08 2018).
18. World Health Organization. *WHO Methods and Data Sources for Country-Level Causes of Death 2000–2015, Global Health Estimates Technical Paper WHO/HIS/IER/GHE/2016.3*, Department of Information, Evidence and Research. 2017. http://www.who.int/healthinfo/global_burden_disease/GlobalCOD_method_2000_2015.pdf (accessed February 08 2018).
19. Lichtenberg FR. The effect of new cancer drug approvals on the life expectancy of American cancer patients, 1978–2004. *Economic Innova New Technol* 2009; 18: 407–428.
20. Hirth RA *et al.* Willingness to pay for a quality-adjusted life year: in search of a standard. *Med Decis Making* 2000;20:332–342.

Appendix

Table A1 Russian launch dates of drugs used to treat different types of cancer

Cancer site	Drug	Year
C00-14 Lip, oral cavity and pharynx	DOCETAXEL	1997
C15 Oesophagus	DOCETAXEL	1997
C16 Stomach	DOCETAXEL	1997
C16 Stomach	CAPECITABINE	2000
C18-21 Colon, rectum and anus	CAPECITABINE	2000
C18-21 Colon, rectum and anus	OXALIPLATIN	2000
C18-21 Colon, rectum and anus	RALTITREXED	2001
C18-21 Colon, rectum and anus	BEVACIZUMAB	2006
C18-21 Colon, rectum and anus	CETUXIMAB	2008
C18-21 Colon, rectum and anus	PANITUMUMAB	2010
C18-21 Colon, rectum and anus	AFLIBERCEPT	2014
C22 Liver (specified as primary)	GEMCITABINE	1998

Appendix. (continued)

Cancer site	Drug	Year
C22 Liver (specified as primary)	SORAFENIB	2008
C25 Pancreas	GEMCITABINE	1998
C25 Pancreas	ERLOTINIB	2007
C25 Pancreas	EVEROLIMUS	2008
C25 Pancreas	SUNITINIB	2008
C33-34 Lung (incl. trachea and bronchus)	DOCETAXEL	1997
C33-34 Lung (incl. trachea and bronchus)	GEMCITABINE	1998
C33-34 Lung (incl. trachea and bronchus)	TOPOTECAN	2001
C33-34 Lung (incl. trachea and bronchus)	BEVACIZUMAB	2006
C33-34 Lung (incl. trachea and bronchus)	GEFITINIB	2006
C33-34 Lung (incl. trachea and bronchus)	ERLOTINIB	2007
C33-34 Lung (incl. trachea and bronchus)	PEMETREXED	2007
C33-34 Lung (incl. trachea and bronchus)	AFATINIB	2014
C43 Melanoma of skin	DABRAFENIB	2015
C50 Breast	ANASTROZOLE	1997
C50 Breast	DOCETAXEL	1997
C50 Breast	GEMCITABINE	1998
C50 Breast	CAPECITABINE	2000
C50 Breast	IBANDRONIC ACID	2001
C50 Breast	EXEMESTANE	2002
C50 Breast	BEVACIZUMAB	2006
C50 Breast	FULVESTRANT	2006
C50 Breast	EVEROLIMUS	2008
C50 Breast	LAPATINIB	2008
C50 Breast	LETROZOLE	2008
C50 Breast	ERIBULIN	2013
C50 Breast	GADOBENIC ACID	2014
C50 Breast	PERTUZUMAB	2015
C53 Cervix uteri	TOPOTECAN	2001
C53 Cervix uteri	BEVACIZUMAB	2006
C56 Ovary	GEMCITABINE	1998
C56 Ovary	AMIFOSTINE	1999
C56 Ovary	TOPOTECAN	2001
C56 Ovary	BEVACIZUMAB	2006
C56 Ovary	TRABECTEDIN	2009
C61 Prostate	BICALUTAMIDE	1997
C61 Prostate	DOCETAXEL	1997
C61 Prostate	DEGARELIX	2011
C61 Prostate	ABIRATERONE ACETATE	2012
C61 Prostate	CABAZITAXEL	2012
C61 Prostate	DENOSUMAB	2012
C67 Bladder	GEMCITABINE	1998
C70-72 Brain, central nervous system	TEMOZOLOMIDE	2001
C82-85,C96 Non-Hodgkin lymphoma	RITUXIMAB	2001
C82-85,C96 Non-Hodgkin lymphoma	BORTEZOMIB	2006
C82-85,C96 Non-Hodgkin lymphoma	NELARABINE	2009
C82-85,C96 Non-Hodgkin lymphoma	LENALIDOMIDE	2010
C82-85,C96 Non-Hodgkin lymphoma	TEMSIROLIMUS	2011
C82-85,C96 Non-Hodgkin lymphoma	PLERIXAFOR	2014
C82-85,C96 Non-Hodgkin lymphoma	IBRUTINIB	2015
C88 + C90 Multiple myeloma	BORTEZOMIB	2006
C88 + C90 Multiple myeloma	LENALIDOMIDE	2010
C88 + C90 Multiple myeloma	PLERIXAFOR	2014
C88 + C90 Multiple myeloma	IBRUTINIB	2015
C91-95 Leukaemia	RITUXIMAB	2001
C91-95 Leukaemia	IMATINIB	2002
C91-95 Leukaemia	ALEMTUZUMAB	2008
C91-95 Leukaemia	DECITABINE	2008
C91-95 Leukaemia	DASATINIB	2009
C91-95 Leukaemia	NELARABINE	2009
C91-95 Leukaemia	NILOTINIB	2009
C91-95 Leukaemia	AZACITIDINE	2011
C91-95 Leukaemia	BOSUTINIB	2015
C91-95 Leukaemia	IBRUTINIB	2015
C91-95 Leukaemia	PONATINIB	2015