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ORIGINAL RESEARCH ARTICLE

The Impact of Pharmaceutical Innovation on Premature Mortality, Cancer Mortality, and Hospitalization in Slovenia, 1997–2010

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Abstract

Background In Slovenia during the period 2000–2010, the number of years of potential life lost before the age of 70 years per 100,000 population under 70 years of age declined 25 %.

Objective The aim of this study was to test the hypothesis that pharmaceutical innovation played a key role in reducing premature mortality from all diseases in Slovenia, and to examine the effects of pharmaceutical innovation on the age-standardized number of cancer deaths and on hospitalization from all diseases. Estimates and other data were used to calculate the incremental cost effectiveness of pharmaceutical innovation in Slovenia.

Method Longitudinal disease-level data was analyzed to determine whether diseases for which there was greater pharmaceutical innovation—a larger increase in the number of new chemical entities (NCEs) previously launched—had larger declines in premature mortality, the age-standardized number of cancer deaths, and the number of hospital discharges. My methodology controls for the effects of macroeconomic trends and overall changes in the healthcare system.

Results Premature mortality from a disease is inversely related to the number of NCEs launched more than 5 years earlier. On average, the introduction of an additional NCE for a disease reduced premature mortality from the disease by 2.4 % 7 years later. The age-standardized number of cancer deaths is inversely related to the number of NCEs launched 1–6 years earlier, conditional on the age-standardized number of new cancer cases diagnosed 0–2 years earlier. On average, the launch of an NCE reduced the number of hospital discharges 1 year later by approximately 1.5 %.

Conclusions The estimates imply that approximately two-thirds of the 2000–2010 decline in premature mortality was due to pharmaceutical innovation. If no NCEs had been launched in Slovenia during 1992–2003, the age-standardized number of cancer deaths in 2008 would have been 12.2 % higher. The NCEs launched in Slovenia during 2003–2009 are estimated to have reduced the number of hospital discharges in 2010 by 7 %. If we assume that pharmaceutical expenditure was the only type of expenditure affected by pharmaceutical innovation, the cost per life-year saved was €3,953, which is well below even the lowest estimates of the value of a life-year saved. Moreover, 85 % of the increase in drug expenditure may have been offset by a reduction in hospital expenditure; therefore. the cost per life-year saved may have been only €611.

Key Points for Decision Makers

The estimates imply that approximately two-thirds of the 2000–2010 decline in premature mortality in Slovenia before the age of 70 years was due to pharmaceutical innovation.

The new chemical entities (NCEs) launched in Slovenia during 1992–2003 are estimated to have reduced the age-adjusted number of cancer deaths by 12.2 % in 2008.

The NCEs launched in Slovenia during 2003–2009 are estimated to have reduced the number of hospital discharges in 2010 by 7 %.

The cost per life-year saved was less than €4,000, which is well below even the lowest estimates of the value of a life-year saved.

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1 Introduction

A significant decline in premature mortality was seen in Slovenia during the period 2000–2010. As shown in Fig. 1, data from the World Health Organization (WHO) indicate that the number of years of potential life lost (YPLL) before the age of 70 years per 100,000 population under 70 years of age declined 25 %, from 7,533 in 2000 to 5,636 in 2010.[1]

In principle, the decline in premature mortality could have been due to a number of factors, such as changes in behavioral risk factors. Rehm et al. [2] argued that alcohol consumption accounts for a high proportion of premature mortality in Central and Eastern Europe. However, preliminary data provided by Kolšek [3] indicate that per capita consumption of pure alcohol in Slovenia *increased* from 16. L in the year 2000 to 17.0 l in 2007. Real per capita income increased by approximately 27 % between 2000 and 2010 but Lichtenberg [4–6] found that there was no correlation between longevity growth and income growth (and other socioeconomic variables such as educational attainment) across (1) US states, (2) German states, and (3) 30 developing and high-income countries.

In this study, the hypothesis that an important type of medical innovation—pharmaceutical innovation—played a key role in reducing premature mortality in Slovenia was tested.[2] The Organisation for Economic Co-operation and Development (OECD) [9] stated that "premature mortality can be influenced by advances in medical technology". More generally, economists have shown that longevity increase is an important part of economic growth and development [10], and that "growth … is driven by technological change that arises from intentional [R&D] investment decisions made by profit-maximizing agents" [11] and by government agencies such as the National Institutes of Health (NIH). Jones [12] argued that "technological progress [is] the ultimate driving force behind sustained economic growth" and that "technological progress is driven by research and development (R&D) in the advanced world". According to the National Science Foundation [13], medical devices and substances industries are the most research-intensive industries in the economy.

To test this hypothesis, longitudinal disease-level data was analyzed to determine whether diseases for which there was greater pharmaceutical innovation—a larger increase in the number of new chemical entities (NCEs) previously launched—had larger declines in premature mortality. The difference-in-differences research design controls for the effects of macroeconomic trends and overall changes in the healthcare system.

In addition to examining the effect of pharmaceutical innovation on premature mortality from all diseases (measured in several different ways), its effects on (1) age-standardized cancer mortality, and (2) hospitalization from all diseases were examined. Eurostat data [36] indicate that cancer accounted for almost one-third of Slovenian deaths in 2010. Cancer is the only type of disease for which there are data on incidence as well as mortality; therefore it is possible to control for incidence in an analysis of the effect of pharmaceutical innovation on age-standardized cancer mortality.

2 Methods

2.1 Premature Mortality Model

In his model of endogenous technological change, Romer [11] hypothesized an aggregate production function such that an economy's output depends on the 'stock of ideas' that have previously been developed, as well as on the economy's endowments of labor and capital. The premature mortality model that was estimated may be considered a health production function, in which premature mortality is an inverse indicator of health output or outcomes, and the cumulative number of drugs approved is analogous to the stock of ideas. The first model will be of the following form:

$$\ln(\text{YPLL70}_{it}) = \beta_k \text{CUM\_NCE}_{i,t-k} + \alpha_i + \delta_t + \varepsilon_{it} \qquad (1)$$

where

YPLL70_{it} = years of potential life lost before the age of 70 years from disease i in year t ($t = 2000, \ldots, 2010$);

$\text{CUM\_NCE}_{i,t-k} = \sum_d \text{IND}_{di}\text{LAUNCH}_{d,t-k}$ = the number of NCEs (drugs) to treat disease i that had been launched in Slovenia by the end of year $t-k$;

IND_{di} = 1 if drug d is used to treat (indicated for) disease i; = 0 if drug d is not used to treat (indicated for) disease i;

$\text{LAUNCH}_{d,t-k}$ = 1 if drug d was launched in Slovenia by the end of year $t-k$; = 0 if drug d was not launched in Slovenia by the end of year $t-k$.

α_i = a fixed effect for disease i

δ_t = a fixed effect for year t

[1] See Gardner and Sanborn [1] for a discussion of the measurement and significance of YPLL.

[2] Semerl and Sesok [7] and Artnik et al. [8] analyzed premature mortality in Slovenia in the 1990s but they did not investigate the role of medical innovation in reducing premature mortality.

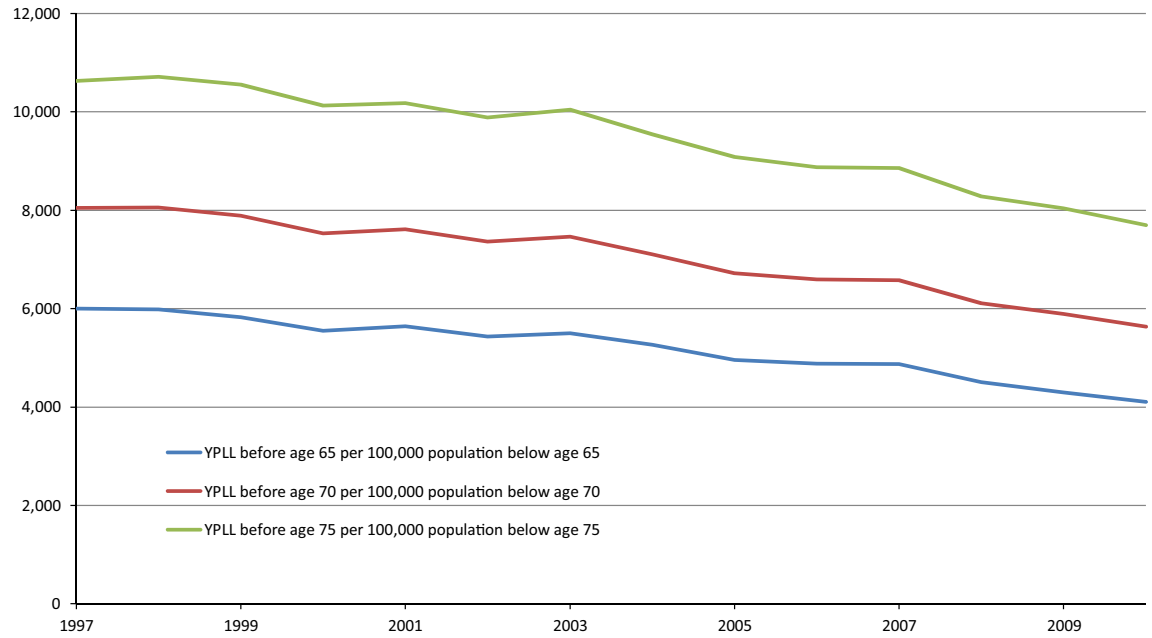

Fig. 1 Years of potential life lost before ages 65, 70, and 75 years per 100,000 population, Slovenia, 1997–2010. *YPLL* years of potential life lost

Inclusion of year and disease fixed effects controls for the overall decline in Slovenian premature mortality and for stable between-disease differences in premature mortality. A negative and significant estimate of β_k in Eq. 1 would signify that diseases for which there was more pharmaceutical innovation had larger declines in premature mortality. Since the data exhibit heteroskedasticity—diseases with smaller average values of YPLL70 had larger (positive and negative) annual percentage fluctuations in YPLL70—Eq. 1 was estimated by weighted least-squares, weighting by (Σ_t YPLL70$_{it}$). Standard errors were clustered within diseases.

Estimation of this model enables determination of how much of the decline in Slovenian premature mortality during the sample period (2000–2010) can be attributed to the introduction of new drugs. The expression ($\delta_{2010}-\delta_{2000}$) indicates the 2000–2010 increase in longevity, controlling for (holding constant) the number of drugs, i.e. in the absence of pharmaceutical innovation. Suppose Eq. 1 is estimated, excluding CUM_NCE$_{i,t-k}$, and that the year fixed effects from that equation are denoted by δ'_t, then ($\delta'_{2010}-\delta'_{2000}$) indicates the 2000–2010 increase in longevity, not holding constant the number of drugs, i.e. in the presence of pharmaceutical innovation, and ($\delta'_{2010}-\delta'_{2000}$)−($\delta_{2010}-\delta_{2000}$) is an estimate of the 2000–2010 increase in longevity attributable to pharmaceutical innovation.

In Eq. 1, premature mortality from disease i in year t depends on the number of NCEs (drugs) to treat disease i launched in Slovenia by the end of year $t - k$, i.e. there is a lag of k years. One would expect there to be a substantial lag because (1) new drugs diffuse gradually—they will not be used widely until years after commercialization, and (2) drugs for chronic conditions (which account for most drug use) may have to be consumed for several years for their full health benefits to be realized. Equation 1 was estimated for different values of k: $k = 0,1,\ldots,10$.[3] The mean lag between the stock of drugs commercialized for a disease and premature mortality from the disease can be computed as follows, including only the values of k for which β_k is statistically significant: LAG_MEAN $= \sum_k \beta_k\, k / \sum_k \beta_k$.

In Eq. 1, the measure of premature mortality is the number of YPLL before the age of 70 years. Seventy is the age threshold used by the OECD. Other authorities use different age thresholds; the Centers for Disease Control and Prevention (CDC) [14] provides estimates of YPLL before the ages of 65, 70, 75, 80, and 85 years. To assess the robustness of results, models similar to Eq. 1 were estimated, using age thresholds of 65 and 75 years, as well as 70 years.

2.2 Age-Standardized Cancer Mortality Model

As noted above, cancer is the only type of disease for which there are data on incidence as well as mortality.

[3] A separate model is estimated for each value of k, rather than including multiple values (CUM_NCE$_{i,t-1}$, CUM_NCE$_{i,t-2}$, CUM_NCE$_{i,t-3}$, …) in a single model because CUM_NCE is highly serially correlated (by construction), which would result in extremely high multicollinearity if multiple values were included).

Difference-in-difference models of the age-standardized number of cancer deaths[4] were estimated using longitudinal data on 38 cancer sites (breast, prostate, lung, etc.) that include a distributed lag of the age-standardized number of new cancer cases diagnosed, as well as the cumulative number of NCEs that had previously been launched in Slovenia:

$$\begin{aligned} \text{N\_DEATHS\_STD}_{st} = {} & \beta_{\text{k}}\text{CUM\_NCE}_{s,t-k} \\ & + \Sigma_j \gamma_j \text{N\_DIAG\_STD}_{s,t-j} + \alpha_s \\ & + \delta_t + \varepsilon_{st} \end{aligned} \tag{2}$$

where

$$\begin{aligned} \text{N\_DEATHS\_STD}_{st} = {} & \text{the age - standardized number of deaths} \\ & \text{from cancer at site } s \text{ in year} \\ & t\,(t = 1997, \ldots, 2007);\ 38 \text{ cancer sites;} \\ \text{N\_DIAG\_STD}_{st-j} = {} & \text{the age - standardized number of} \\ & \text{new cancer cases diagnosed at site} \\ & s \text{ in year } t - j. \end{aligned}$$

Equation 2 was estimated by ordinary least-squares. Standard errors were clustered within cancer sites.

2.3 Hospital Discharges Model

To investigate the effect of pharmaceutical innovation on hospitalization from all diseases, models of the following form were estimated:

$$\ln(\text{DISCHARGES}_{it}) = \beta_k \text{CUM\_NCE}_{i,t-k} + \alpha_i + \delta_t + \varepsilon_{it} \tag{3}$$

where

$$\begin{aligned} \text{DISCHARGES}_{it} = {} & \text{number of hospital discharges for disease} \\ & i \text{ in year } t\,(t = 2004, \ldots, 2010);\ 90 \text{ diseases.} \end{aligned}$$

Since the hospital discharge data exhibit heteroskedasticity, Eq. 3 was estimated by weighted least-squares, weighting by (Σ_t DISCHARGES$_{it}$). Standard errors were clustered within diseases.

2.4 Data Sources and Descriptive Statistics

Premature mortality data (YPLL65, YPLL70, YPLL75) Data on YPLL before the ages of 65, 70, and 75 years, by disease and year, were constructed from the WHO Mortality Database [39], a compilation of mortality data by age, sex, and cause of death, as reported annually by Member States from their civil registration systems.[5] Figure 1 shows YPLL before the ages of 65, 70, and 75 years per 100,000 population in Slovenia during the period 1997–2010. The average annual rates of decline were 2.9, 2.7, and 2.5 %, respectively. Figure 2 shows the number of YPLL before the age of 70 years from selected major diseases; it indicates that the rate of decline varied substantially across diseases.

NCE launches in Slovenia (LAUNCH) Data on NCEs launched in Slovenia were constructed from the IMS LifeCycle New Product Focus database [40]. These data are left-censored, in two respects—the database only covers products launched worldwide since 1982, and coverage of Slovenia effectively began in 1993. Hence CUM_NCE$_{i,t-k}$ is the number of post-1981 (based on world launch date) NCEs (drugs) to treat disease i that had been launched in Slovenia after 1992 and by the end of year $t - k$. Left-censoring is likely to result in some measurement error in CUM_NCE$_{i,t\ -\ k}$, which may bias estimates of β_k towards zero. Figure 3 shows the number of post-1981 NCEs, by year first observed in Slovenia in the IMS LifeCycle New Product Focus database. The average annual number of NCEs launched in Slovenia during this period was 23.

Drug indications (IND). Data on drug indications were obtained from Thériaque [41], a database of official, regulatory, and bibliographic information on all drugs available in France, intended for health professionals. This database is produced by the Centre National Hospitalier d'Information sur le Médicament [16]. Figure 4 shows the number of post-1981 NCEs that had previously been launched in Slovenia for six selected diseases (cancer sites). The increase in the number of NCEs varied considerably across cancer sites. For example, the number of NCEs for breast cancer increased much more than the number of NCEs for male genital organs.

Age-standardized cancer mortality and incidence (N_DEATHS_STD, N_DIAG_STD). Data on age-standardized cancer mortality and incidence rates, by cancer site and year, were obtained from the European Cancer Observatory [17]. Age-standardized cancer incidence and mortality rates for all cancer sites combined are shown in Fig. 5. Between 1995 and 2007, the age- standardized cancer incidence rate

[4] The age-standardized number of cancer deaths is the age-standardized mortality rate × the population. Similarly, the age-adjusted number of new cancer cases diagnosed is the age-standardized incidence rate × the population. An age-standardized rate (ASR) is a summary measure of the rate that a population would have if it had a standard age structure. As indicated by the International Agency for Research on Cancer [15], 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.

[5] Mortality data are reported in 5-year age groups in the WHO Mortality Database. The author has assumed that deaths in a 5-year age group occur at the midpoint of the age group. For example, the author has assumed that deaths at age 35–39 years occurred at age 37.5 years.

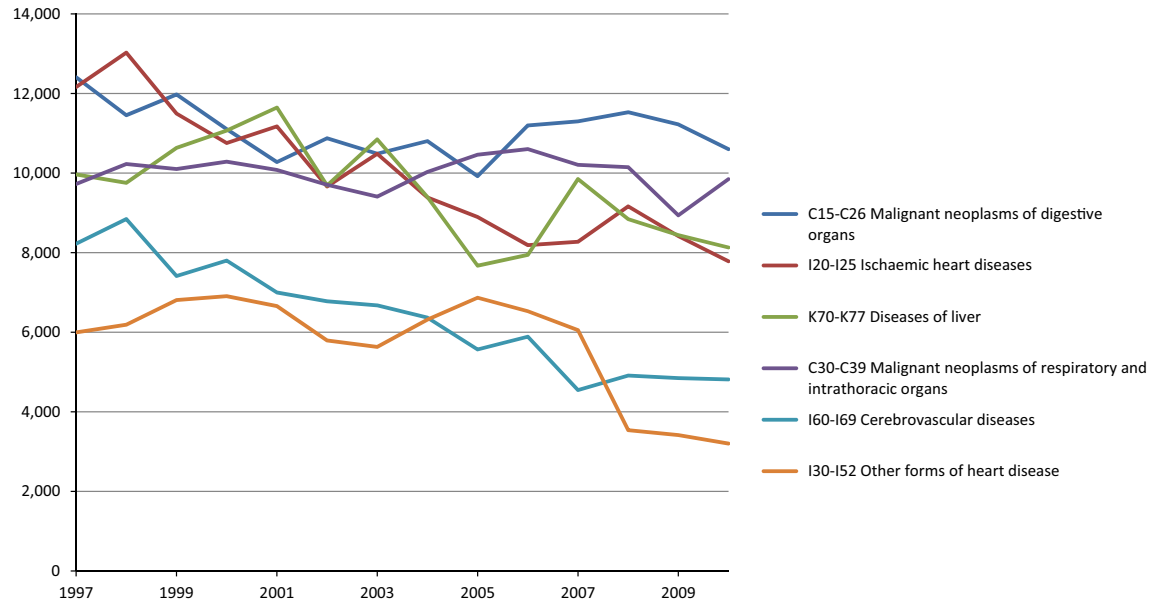

Fig. 2 Number of years of potential life lost before the age of 70 years from selected major diseases, Slovenia, 1997–2010

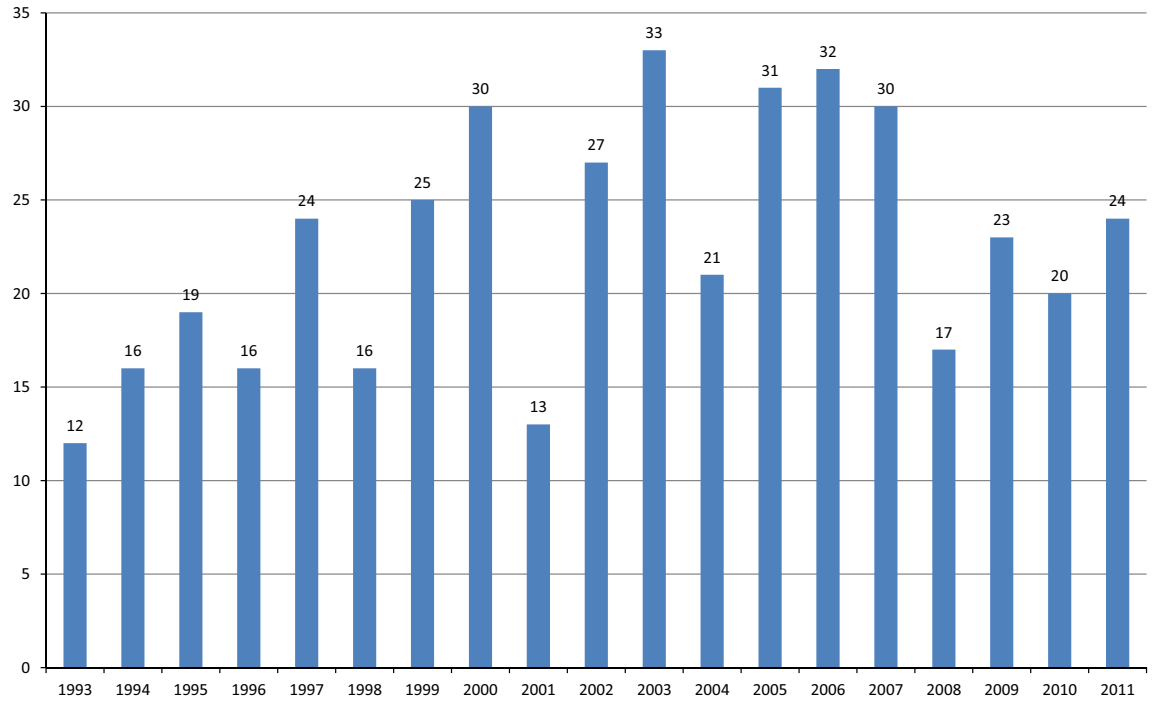

Fig. 3 Number of post-1981 new chemical entities, by year first observed in Slovenia in the IMS LifeCycle New Product Focus database

increased 14 %, but the age-standardized cancer mortality rate declined 8 %. Figure 6 shows the age-standardized mortality rates for five major cancer sites. The mortality rate for stomach cancer declined by 38 % but the mortality rate for prostate cancer increased 15 %. Data on population were obtained from Eurostat data [37].

Hospital discharges (DISCHARGES). Data on the number of hospital discharges, by disease and year, were obtained from Eurostat data [38]. Between 2004 and 2010, the number of hospital discharges from all causes of diseases, excluding external causes of injuries [International Classification of Diseases, 10th Edition (ICD-10)

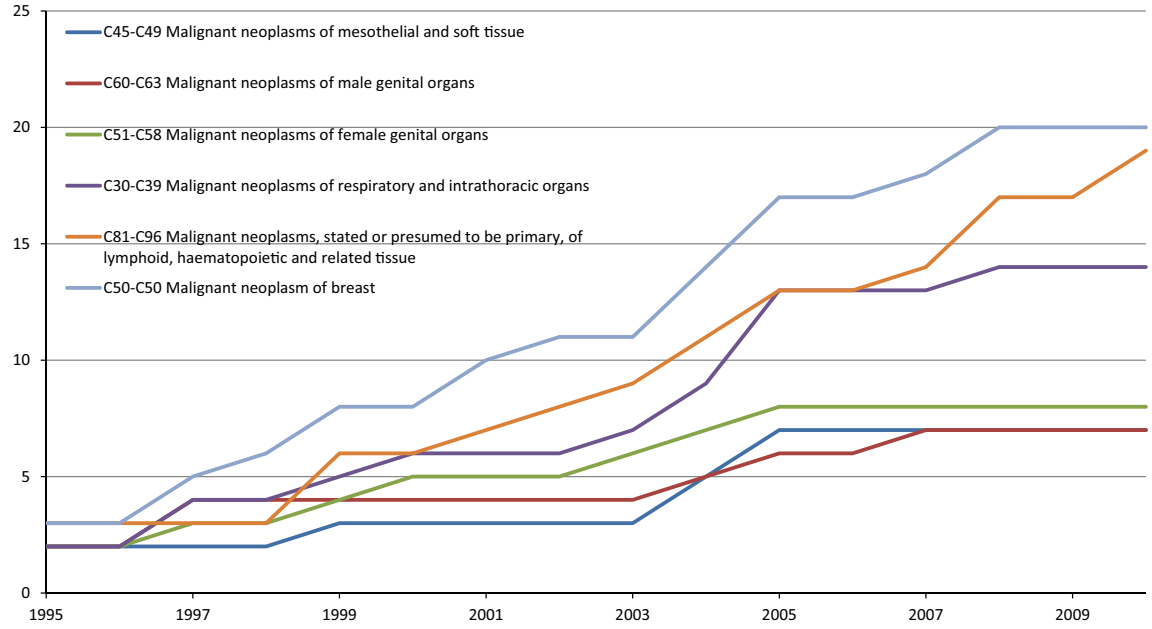

Fig. 4 Number of post-1981 new chemical entities that had previously been launched in Slovenia, six selected cancer sites

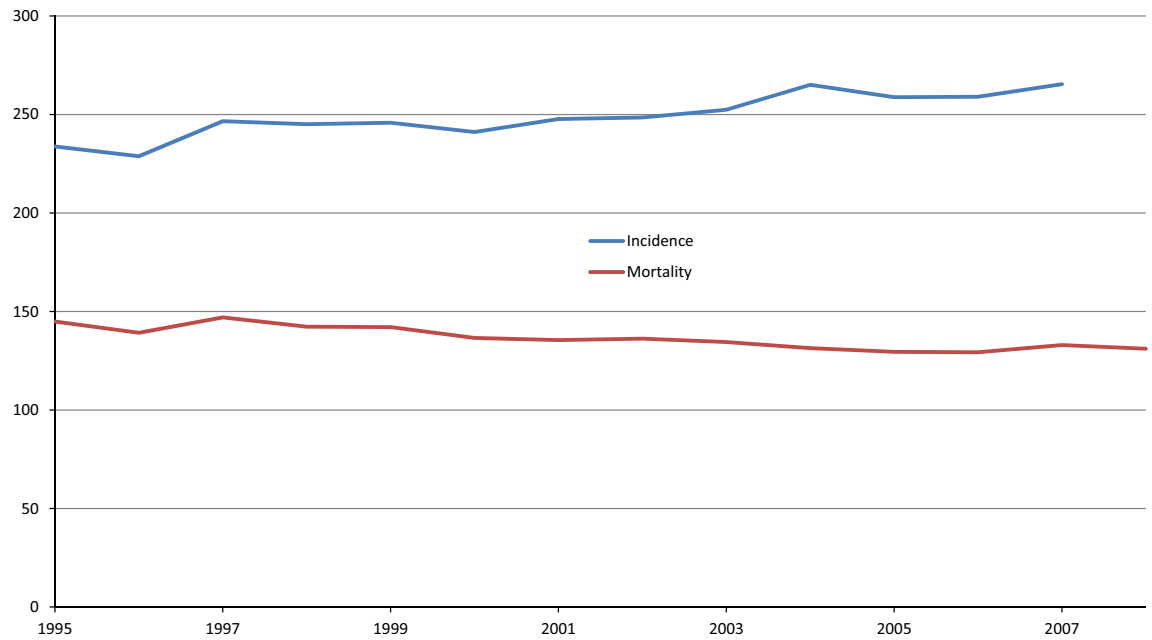

Fig. 5 Age-standardized cancer incidence and mortality rates per 100,000 population, Slovenia, 1995–2008

V00–Y98] and liveborn infants (Z38), per 100,000 population increased 5.5 %, from 15,476 to 16,324. As shown in Fig. 7, the number of discharges for respiratory system diseases increased 22 %, while the number of discharges for genitourinary system diseases declined 12 %.

3 Results

3.1 Premature Mortality Model Estimates

Weighted least-squares estimates of β_k from Eq. 1 [$\ln(\text{YPLL70}_{it}) = \beta_k \ \text{CUM\_NCE}_{i,t-k} + \alpha_i + \delta_t + \varepsilon_{it}$] are

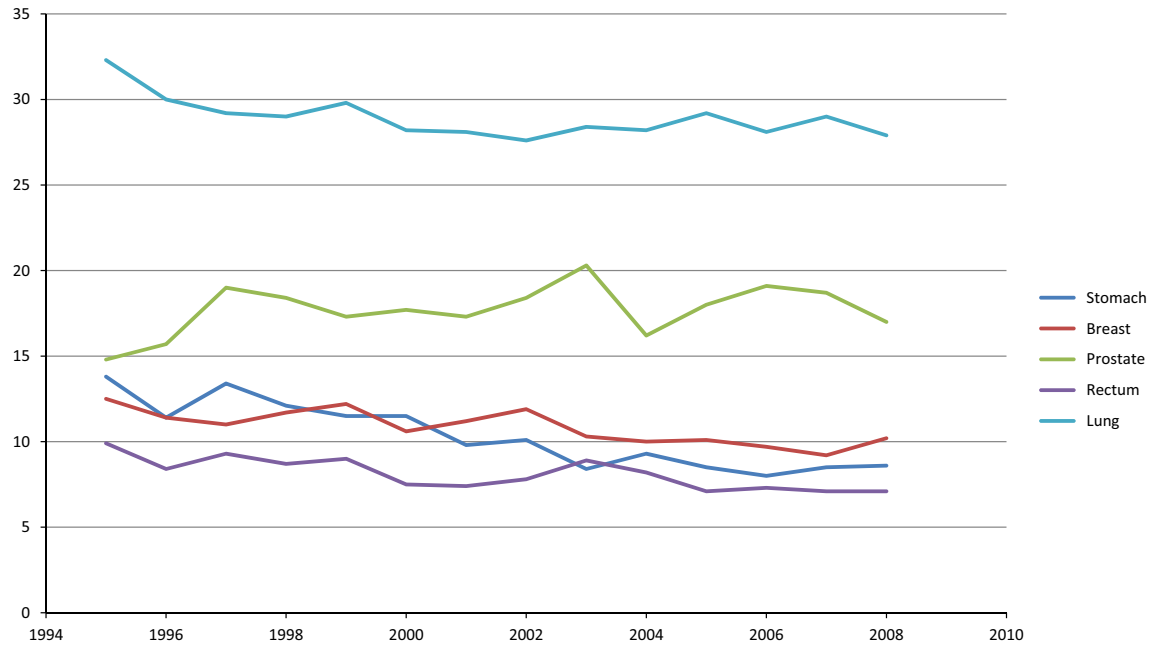

Fig. 6 Age-standardized mortality rates per 100,000 population, five major cancer sites, Slovenia, 1995–2008

shown in Table 1.[6] Each estimate is from a separate model. The estimates for $k = 0,\ldots,5$ are not statistically significant, indicating that premature mortality from a disease is unrelated to the number of NCEs launched less than 6 years earlier. However, the estimates for $k = 6,\ldots,10$ are negative and statistically significant ($p < 0.05$), indicating that premature mortality from a disease is inversely related to the number of NCEs launched more than 5 years earlier. Premature mortality is most strongly related to the number of NCEs that had been launched up until 7 years before. Complete estimates of the model based on a 7-year lag [$\ln(\text{YPLL70}_{it}) = \beta_7 \ \text{CUM\_NCE}_{i,t\text{-}7} + \alpha_i + \delta_t + \varepsilon_{it}$] are shown in electronic supplementary material Table 1. The estimates of this model indicate that, on average, the introduction of an additional NCE for a disease reduced premature mortality from the disease by 2.4 % 7 years later.

The estimates reported in Table 1 are based on an 11-year sample period ($t = 2000,\ldots,2010$). We also estimated the model for two shorter sample periods. The first of these excluded the last 3 years, i.e. $t = 2000,\ldots, 2007$. None of the estimates of β_k were significant for this sample period. The second shorter sample period excluded the first 3 years, i.e. $t = 2003,\ldots, 2010$. The estimates for $k = 0,\ldots,5$ were not statistically significant, and the estimates for $k = 6,\ldots,10$ were negative and statistically significant ($p < 0.05$). The finding that the relationship between premature mortality and the cumulative number of NCEs is significant only when we examine more recent data is, we believe, primarily attributable to declining errors of measurement of the explanatory variable. As noted earlier, the NCE launch data are left-censored, in two respects—the database only covers products launched worldwide since 1982, and coverage of Slovenia effectively began in 1993. As a result, errors in measuring $\text{CUM\_NCE}_{i,t-k}$ should decline as t increases.

Table 2 shows estimates of Eq. 1 based on two alternative age thresholds for calculating YPLL: 65 and 75 years. When the age threshold is 65 years, the coefficients are negative and significant for $k = 6$ and $k = 7$; they are only marginally significant ($0.05 < p < 0.10$) for $k = 8, 9, 10$. When the age threshold is 75 years, the estimates for $k = 6,\ldots,10$ are all negative and statistically significant. This suggests that pharmaceutical innovation had a larger impact on premature mortality at higher ages than it did on premature mortality at lower ages (e.g. infant and childhood mortality).

Between the year 2000 and 2010, the number of YPLL before the age of 70 years declined 25 %; the population below the age of 70 years was almost unchanged. As discussed above, we can estimate how much of this decline was attributable to pharmaceutical innovation by

[6] All of the models described in this article were estimated using the SAS GENMOD procedure [18]. Responses from different subjects were assumed to be statistically independent, and responses within subjects were assumed to be correlated. In the models whose estimates are reported in Table 1, the response variable was $\ln(\text{YPLL70}_{it})$, the link function was the identity function, and the correlation structure was independent. Estimates of models in which the response variable was $\ln(\text{YPLL70}_{it})$, the link function was the identity function, and the correlation structure was either exchangeable or first-order autoregressive were virtually identical to the estimates reported in Table 1.

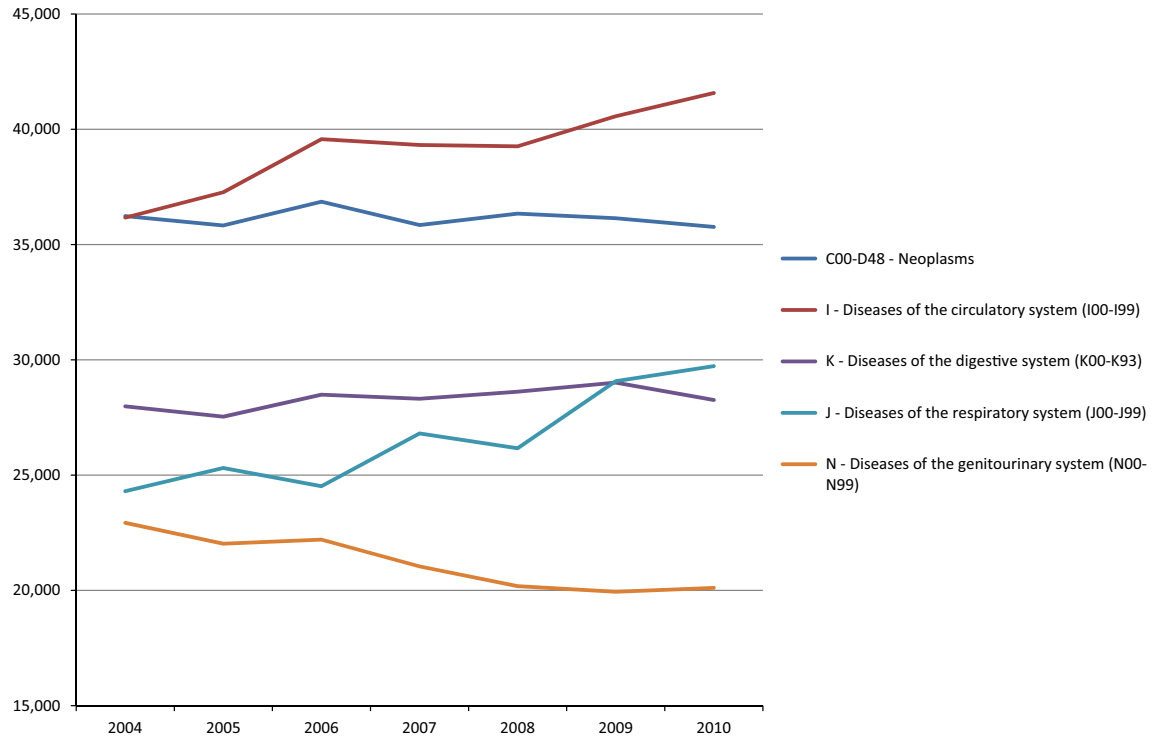

Fig. 7 Number of hospital discharges, six major diseases, Slovenia, 2004–2010

Table 1 Weighted least-squares estimates of β_k from Eq. (1) $\ln(\text{YPLL70}_{it}) = p_k\ \text{CUM\_NCE}_{i,t-k} + a_i + \delta_t + \varepsilon_{it}$ each estimate is from a separate model weight $= Z_t$ YPLL70_{it} disturbances are clustered within diseases

Parameter	Estimate	Empirical standard error estimates	95% Lower confidence limit	95% Upper confidence limit	z	Pr > |Z|
cum nce0	0.003	0.012	−0.021	0.026	0.22	0.8276
cum nce1	0.000	0.013	−0.024	0.025	0.03	0.9747
cum nce2	−0.003	0.012	−0.026	0.020	−0.26	0.7919
cum nce3	−0.007	0.010	−0.026	0.013	−0.66	0.5094
cum_nce4	−0.009	0.009	−0.026	0.008	−1.04	0.2992
cum nce5	−0.012	0.008	−0.029	0.004	−1.45	0.1471
cum nce6	**−0.021**	**0.008**	**−0.036**	**−0.006**	**−2.75**	**0.0059**
cum nce7	**−0.024**	**0.008**	**−0.040**	**−0.009**	**−3.06**	**0.0022**
cum nce8	**−0.023**	**0.009**	**−0.041**	**−0.004**	**−2.40**	**0.0165**
cum nce9	**−0.025**	**0.011**	**−0.047**	**−0.004**	**−2.30**	**0.0216**
cum_nce10	**−0.031**	**0.016**	**−0.062**	**0.000**	**−1.98**	**0.0483**

Bold values are statistically significant at $p < 0.05$

$YPLL70_{it}$ years of potential life lost before age 70 from disease i in year t, $CUM\_NCE_{i,t-k}$ the number of new chemical entities (drugs) to treat disease i that had been launched in Slovenia by the end of year $t-k$

comparing estimates of the year fixed effects (δ_t's) when $\text{CUM\_NCE}_{i,t-k}$ is included in Eq. 1 (the number of NCEs is held constant) with estimates of the year fixed effects when $\text{CUM\_NCE}_{i,t-k}$ is excluded from Eq. 1 (the number of NCEs is not held constant). These calculations (based on a 7-year lag) are shown in Fig. 8. The estimates indicate that approximately two-thirds of the 2000–2010 decline in YPLL before the age of 70 years was due to pharmaceutical innovation.

3.2 Age-Standardized Number of Cancer Deaths Model Estimates

Ordinary least-squares estimates of β_k from Eq. 2 ($\text{N\_DEATHS\_STD}_{st} = \beta_k \quad \text{CUM\_NCE}_{s,t-k} + \Sigma_j\ \gamma_j\ \text{N\_DIAG\_STD}_{s,t-j} + \alpha_s + \delta_t + \varepsilon_{st}$) are shown in Table 3.[7]

[7] In the models estimated, the response variable was N_DEATHS_STD_{st}, the link function was the identity function, and the correlation structure was independent.

Table 2 Estimates of Eq. (1) based on two alternative age thresholds: 65 and 75

Parameter	Estimate	Empirical standard error estimates	95% Lower confidence limit	95% Upper confidence limit	z	Pr > |Z|
Dependent variable: ln(YPLL65)						
cum nce1	0.0023	0.0127	−0.0227	0.0272	0.18	0.8594
cum_nce2	−0.0017	0.0117	−0.0246	0.0212	−0.15	0.8833
cum nce3	−0.0047	0.01	−0.0244	0.015	−0.47	0.6395
cum_nce4	−0.0061	0.0088	−0.0233	0.011	−0.70	0.4841
cum_nce5	−0.0089	0.0085	−0.0255	0.0078	−1.04	0.2974
cum_nce6	**−0.0177**	**0.0081**	**−0.0335**	**−0.002**	**−2.20**	**0.0276**
cum_nce7	**−0.0213**	**0.0086**	**−0.0383**	**−0.0044**	**−2.46**	**0.0137**
cum nce8	−0.0196	0.0103	−0.0398	0.0006	−1.90	0.0569
cum nce9	−0.0219	0.0122	−0.0458	0.0019	−1.80	0.0714
cum_ncel0	−0.0279	0.0168	−0.0608	0.005	−1.66	0.0965
Dependent variable: ln(YPLL75)						
cum ncel	−0.0014	0.0123	−0.0255	0.0226	−0.12	0.9078
cum nce2	−0.0048	0.0112	−0.0268	0.0172	−0.43	0.6696
cum nce3	−0.0085	0.0099	−0.0279	0.0109	−0.86	0.3886
cum nce4	−0.0113	0.0087	−0.0284	0.0057	−1.30	0.1925
cum_nce5	−0.014	0.0083	−0.0304	0.0023	−1.68	0.0925
cum_nce6	**−0.0219**	**0.0072**	**−0.0361**	**−0.0077**	**−3.03**	**0.0024**
cum nce7	**−0.0249**	**0.0071**	**−0.0388**	**−0.0109**	**−3.50**	**0.0005**
cum nce8	**−0.0231**	**0.0081**	**−0.0389**	**−0.0072**	**−2.85**	**0.0043**
cum nce9	**−0.0259**	**0.0093**	**−0.0441**	**−0.0077**	**−2.79**	**0.0053**
cum_nce10	**−0.032**	**0.0135**	**−0.0586**	**−0.0055**	**−2.36**	**0.018**

Weighted least-squares estimates of β_k from Eq. (1) $\ln(\text{YPLL65}_{it}) = \beta_k\ \text{CUM\_NCE}_{i,t-k} + a_i + \delta_t + \varepsilon_{it}$ each estimate is from a separate model weight $= \Sigma_t\ \text{YPLL65}_{it}$ disturbances are clustered within diseases

Bold values are statistically significant at $p < 0.05$

YPLL65$_{it}$ years of potential life lost before age 65 from disease *i* in year *t*, *YPLL75*$_{it}$ years of potential life lost before age 75 from disease *i* in year *t*, *CUM_NCE*$_{i,t-k}$ the number of new chemical entities (drugs) to treat disease *i* that had been launched in Slovenia by the end of year *t*−*k*

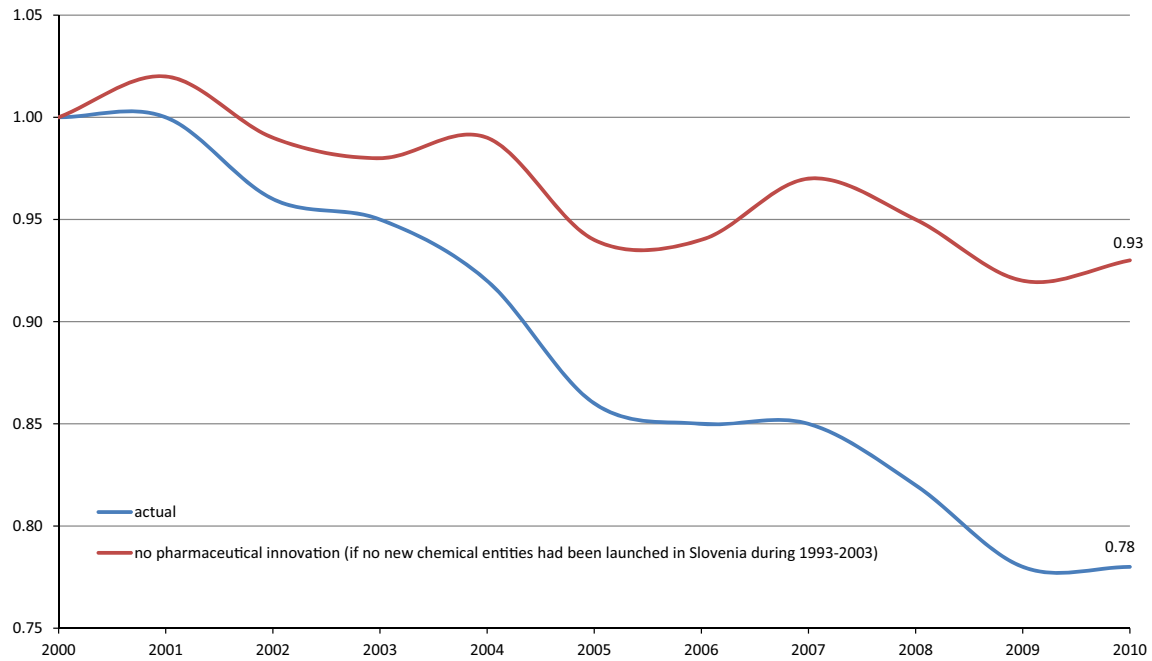

Fig. 8 Years of potential life lost before the age of 70 years, Slovenia, 2000–2010 (index 2000 = 1.00): actual vs. without pharmaceutical innovation

Table 3 Ordinary least-squares estimates of β_k from Eq. (2) N_DEATHS_STD$_{st}$ = (β_k CUM_NCE$_{s,t-k}$ + Σ_j γ_j y N_DIAG_STD$_{S,t-j}$+ α_s each estimate is from a separate model disturbances are clustered within cancer sites

Parameter	Estimate	Empirical standard error estimates	95% Lower confidence limit	95% Upper confidence limit	*Z*	*Pr* > |Z|
cum nce0	−2.4286	1.3352	−5.0456	0.1885	−1.82	0.0689
cum nce1	**−2.7463**	**1.245**	**−5.1864**	**−0.3061**	**−2.21**	**0.0274**
cum nce2	**−2.9892**	**1.3648**	**−5.6641**	**−0.3143**	**−2.19**	**0.0285**
cum nce3	**−3.1828**	**1.3019**	**−5.7344**	**−0.6312**	**−2.44**	**0.0145**
cum nce4	**−3.208**	**1.3669**	**−5.887**	**−0.529**	**−2.35**	**0.0189**
cum nce5	**−3.2666**	**1.268**	**−5.7519**	**−0.7813**	**−2.58**	**0.01**
cum nce6	**−3.1818**	**1.4045**	**−5.9346**	**−0.429**	**−2.27**	**0.0235**
cum nce7	−3.0295	1.5748	−6.1161	0.057	−1.92	0.0544
cum nce8	−2.1433	1.999	−6.0613	1.7746	−1.07	0.2836
cum nce9	−2.9139	2.7526	−8.3089	2.4811	−1.06	0.2898
cum nce10	−2.731	4.0008	−10.5725	5.1105	−0.68	0.4949

Bold values are statistically significant at $p < 0.05$

N_DEATHS_STD$_{st}$ the age-standardized number of deaths from cancer at site *s* in year *t*, *CUM_NCE$_{s,t-k}$* the number of new chemical entities (drugs) to treat cancer at site s that had been launched in Slovenia by the end of year *t*−*k*, *N_DIAG_STD$_{s,t-j}$* the age-standardized number of new cancer cases diagnosed at site s in year *t*−*j*

The age-standardized number of deaths is assumed to depend on the age-standardized number of cases diagnosed in the current year and the two previous years, i.e. $j = 0, 1, 2$. The estimates for $k = 1,\ldots,6$ are negative and statistically significant ($p < 0.05$), indicating that the age-standardized number of deaths from cancer at site s is inversely related to the number of NCEs launched 1–6 years earlier, conditional on the age-standardized number of cases of the cancer diagnosed 0–2 years earlier. The estimated effect after 5 years is the largest and most significant. Complete estimates of the model based on a 5-year lag (N_DEATHS_STD$_{st}$ = β_2 CUM_NCE$_{s,t-5}$ + Σ_j γ_j N_-DIAG_STD$_{s,t-j}$ + α_s + δ_t + ε_{st}) are shown in electronic supplementary material Table 2. The sum of current and lagged incidence coefficients is positive and significant, but controlling for incidence has virtually no effect on estimates of β_k. As shown in Fig. 9, the age-standardized number of cancer deaths declined by 9.4 %, from 3,151 to 2,855, between 1997 and 2007, controlling for the age-standardized number of cases diagnosed 0–2 years earlier. The estimates indicate that in the absence of pharmaceutical innovation, the age-standardized number of cancer deaths would have increased by 1.7 %, from 3,151 to 3,204. Hence, we estimate that if no NCEs had been launched in Slovenia during 1992–2003, the age-standardized number of cancer deaths in 2008 would have been 12.2 % [=(3,204/2,855) − 1] higher. The actual number of cancer deaths in Slovenia in 2008 was 5,645, therefore if no NCEs had been launched in Slovenia during 1992–2003, there might have been 691 (=12.2 % × 5,645) more cancer deaths in Slovenia in 2008.

3.3 Hospital Discharges Model Estimates

Weighted least-squares estimates of β_k from Eq. 3 [ln(DISCHARGES$_{it}$) = β_k CUM_NCE$_{i,t-k}$ + α_i + δ_t + ε_{it}] are shown in Table 4.[8] The estimates for $k = 0, 1, 2$ are negative and at least marginally significant ($p < 0.07$); the estimate for $k = 1$ is significant at the 0.05 level.[9] Complete estimates of the model based on a 1-year lag [ln(DISCHARGES$_{it}$) = β_1 CUM_NCE$_{i,t-1}$ + α_i + δ_t + ε_{it}] are shown in electronic supplementary material Table 3. These estimates suggest that, on average, the launch of an NCE reduced the number of hospital discharges 1 year later by approximately 1.5 %. As shown in Fig. 10, the NCEs launched in Slovenia during 2003–2009 are estimated to have reduced the number of hospital discharges in 2010 by 7 %. In other words, pharmaceutical innovation reduced hospitalization in Slovenia at an average annual rate of approximately 1.2 %. This estimate is quite similar to estimates obtained from three other countries: Lichtenberg and Pettersson [19] estimated that pharmaceutical innovation reduced the number of hospital days in Sweden by approximately 1.2 % per year; Lichtenberg et al. [20] estimated that

[8] In the models estimated, the response variable was ln(DISCHARGES$_{it}$), the link function was the identity function, and the correlation structure was independent.

[9] When we estimated a model in which the response variable was DISCHARGES$_{it}$, the link function was the log function, and the correlation structure was independent; the magnitude of the point estimate of the coefficient on CUM_NCE$_{i,t-1}$ was about twice as large: −0.0281 ($Z = 2.07$, $p = 0.039$). However, the convergence of this model was questionable.

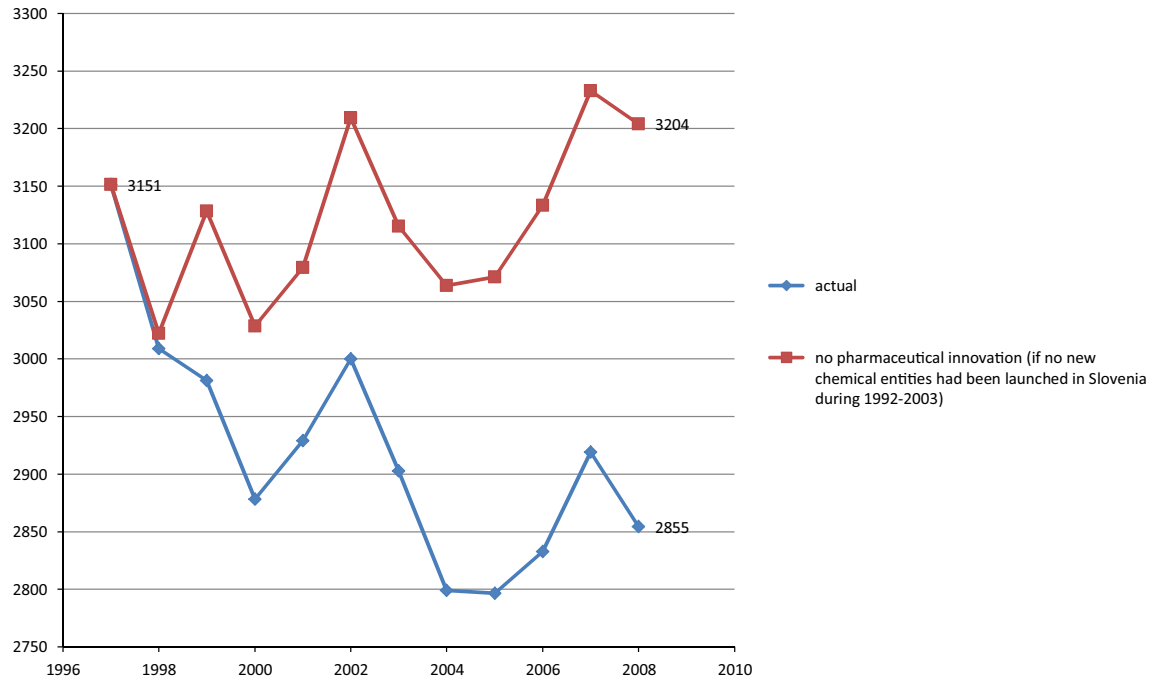

Fig. 9 Age-standardized number of cancer deaths, controlling for age-standardized number of cases diagnosed 0–2 years earlier, 1997–2008: actual vs. without pharmaceutical innovation

Table 4 Weighted least-squares estimates of β_k from Eq. (3) $\ln(\text{DISCHARGES}_{it}) = \beta_k\ \text{CUMNCE}_{i,t-k} + \alpha_i + \delta_t + \varepsilon_{it}$ each estimate is from a separate model weight $= \Sigma_t\ \text{DISCHARGES}_{it}$ disturbances are clustered within diseases

Parameter	Estimate	Empirical standard error estimates	95% Lower confidence limit	95% Upper confidence limit	Z	$\Pr > \lvert Z \rvert$
cum nee	−0.0156	0.008	−0.0312	0.0001	−1.95	0.0511
cum_ncel	**−0.0147**	**0.0073**	**−0.029**	**−0.0004**	**−2.01**	**0.0441**
cum nce2	−0.0158	0.0085	−0.0325	0.0009	−1.85	0.0644
cum nce3	−0.0149	0.0095	−0.0336	0.0038	−1.57	0.1175
cum_nce4	−0.0143	0.0102	−0.0342	0.0056	−1.41	0.1598
cum_nce5	−0.0145	0.0116	−0.0372	0.0083	−1.25	0.2122

Bold values are statistically significant at $p < 0.05$

$DISCHARGES_{it}$ number of hospital discharges for disease i in year t, $CUM\_NCE_{i,t-k}$ the number of new chemical entities (drugs) to treat disease i that had been launched in Slovenia by the end of year $t-k$

it reduced the number of hospital days in Turkey by approximately 1 % per year; and Lichtenberg [21] estimated that it reduced the number of hospital discharges in the US by approximately 1.6 % per year.

4 Discussion

The measure of pharmaceutical innovation in Eqs. 1 to 3—the number of chemical substances previously commercialized to treat a disease—is theoretically not the ideal measure. Longevity and hospitalization are presumably more strongly related to the drugs actually used to treat a disease than they are to the drugs that could be used to treat the disease. A preferable measure is the mean vintage of drugs used to treat a disease, defined as $\text{VINTAGE}_{it} = \sum_d Q_{dit}\ \text{LAUNCH\_YEAR}_d / \sum_d Q_{dit}$, where Q_{dit} = the quantity of drug d used to treat disease i in year t, and LAUNCH_YEAR_d = the world launch year of drug d.[10] Unfortunately, measurement of

[10] 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 [22] 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.

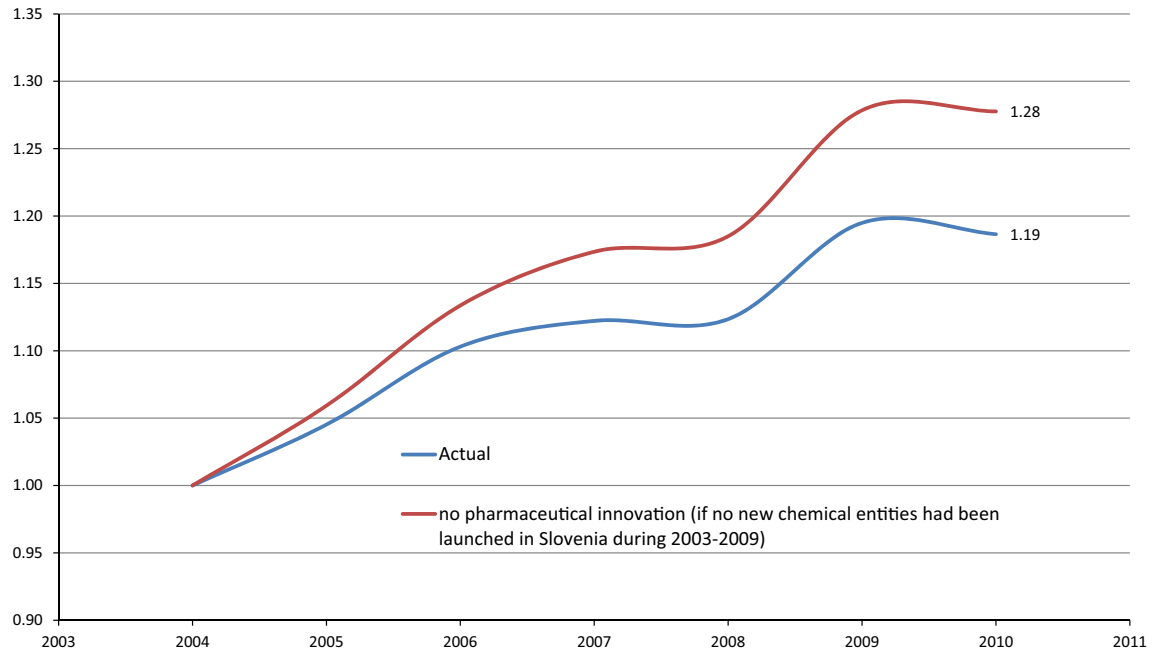

Fig. 10 Number of hospital discharges, Slovenia, 2004–2010: actual vs. without pharmaceutical innovation (index 2004 = 1.00)

$VINTAGE_{it}$ is infeasible: even if data on the total quantity of each drug in each year ($Q_{d.t} = \Sigma_i Q_{dit}$) were available, many drugs are used to treat multiple diseases, and there is no way to determine the quantity of drug *d* used to treat disease *i* in year *t*.[11] However, as shown in Appendix 1 of the paper by Lichtenberg [24], 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 commercialized within the drug class.

The measure of pharmaceutical innovation, $CUM\_NCE_{i,t-k} = \sum_d IND_{di}\, LAUNCH_{d,t-k}$, is based on whether drug d had an indication for disease *i* at the end of 2011. One would prefer to base the measure on whether drug *d* had an indication for disease *i* at the end of year *t*−*k*. FDA data [25] indicate that approximately one in four new molecular entities has supplemental indications, i.e. indications approved after the drug was initially launched.

Pharmaceutical innovation is not the only type of medical innovation that is likely to affect mortality and hospitalization. Other medical innovation, such as innovation in diagnostic imaging, surgical procedures, and medical devices, are also likely to affect them. Therefore, measures of these other types of medical innovation should be included in Eq. 1 to 3. Unfortunately, longitudinal disease-level measures of non-pharmaceutical medical innovation are not available for Slovenia. However, failure to control for non-pharmaceutical medical innovation is unlikely to bias estimates of the effect of pharmaceutical innovation on mortality and hospitalization, for several reasons.

First, the number of people exposed to pharmaceutical innovation tends to be much larger than the number of people exposed to other types of medical innovation: for example, in 2007, 62 % of Americans consumed prescription drugs, while only 8 % of Americans were admitted to hospitals.[12] Second, pharmaceuticals are more research-intensive than other types of medical care: in 2007, prescription drugs accounted for 10 % of US health expenditure [27] (Table 2), but more than half of US funding for biomedical research came from pharmaceutical and biotechnology firms [28]. Much of the rest came from the federal government (i.e. the NIH), and new drugs often build on upstream government research [29].

Third, previous research based on US data indicates that non-pharmaceutical medical innovation is not positively correlated across diseases with pharmaceutical innovation.

[11] Outpatient prescription drug claims usually do not show the indication of the drug prescribed. Claims for drugs administered by doctors and nurses (e.g. chemotherapy) often show the indication of the drug. For the US, data from MEDSTAT MarketScan and IMS Health's National Sales Perspectives indicate that approximately 70 % of cancer drug expenditure is on drugs administered by providers [23]. (Only 10 % of expenditure on other (non-cancer) drugs is on drugs administered by providers.) These data are not available for Slovenia.

[12] Source: US Medical Expenditure Panel Survey, 2007 Full-Year Consolidated Data File. Lichtenberg [26] found that therapeutic procedure innovation increased the life expectancy of Western Australia hospital patients (whose mean life expectancy was approximately 10 years) by 2–3 months between 2000 and 2007. Since the fraction of the population that is hospitalized is fairly low, the implied contribution of hospital procedure innovation to aggregate longevity growth is fairly modest—much smaller than estimates of the contribution of pharmaceutical innovation to aggregate longevity growth.

Table 5 Pharmaceutical and hospital expenditure in Slovenia, 2002–2012

Column Year	(1) Aggregate expenditure on prescribed medicines (millions)	(2) Population	(3) = (1)/(2) Per capita expenditure on prescribed medicines	(4) Index of consumer prices for pharmaceutical products (2002 = 1.00)	(5) = (3)/(4) Real per capita expenditure on prescribed medicines	(6) = 0.81 × (5) Estimated real per capita expenditure on prescribed medicines, 0–64 year-olds	(7) Per capita expenditure on inpatient curative and rehabilitative care
2002	€ 340	1,994,026	€ 170	1.00	€ 170	€ 138	
2003	€ 359	1,995,033	€ 180	1.08	€ 167	€ 135	€ 297
2004	€ 382	1,996,433	€ 191	1.04	€ 184	€ 149	€ 316
2005	€ 405	1,997,590	€ 203	1.04	€ 196	€ 158	€ 327
2006	€ 432	2,003,358	€ 215	1.03	€ 210	€ 170	€ 335
2007	€ 429	2,010,377	€ 213	1.03	€ 208	€ 168	€ 356
2008	€ 455	2,010,269	€ 226	1.03	€ 220	€ 178	€ 430
2009	€ 474	2,032,362	€ 233	1.04	€ 224	€ 181	€ 448
2010	€ 477	2,046,976	€ 233	1.07	€ 218	€ 176	€ 448
2011	€ 473	2,050,189	€ 231	1.07	€ 216	€ 175	€ 452
2012	€ 449	2,055,496	€ 219	1.09	€ 200	€ 162	€ 436

Sources: *(1)* OECD, *(2)* Eurostat, *(4)* European Central Bank, *(7)* OECD

In Appendix 2 of the paper by Lichtenberg [24], it is shown that, in the US during the period 1997–2007, the rate of pharmaceutical innovation was not positively correlated across diseases with the rate of medical procedure innovation and may have been negatively correlated with the rate of diagnostic imaging innovation. In addition, Lichtenberg [23] found that estimates of the effect of pharmaceutical innovation on US cancer mortality rates were insensitive to the inclusion or exclusion of measures of non-pharmaceutical medical innovation. This suggests that failure to control for other medical innovation is unlikely to result in overestimation of the effect of pharmaceutical innovation on longevity growth.

The estimates of Eq. 1 and 3, as well as other data, were used to calculate the incremental cost effectiveness of pharmaceutical innovation in Slovenia. As noted earlier, data from the WHO indicate that YPLL before the age of 70 years per 100,000 population under 70 years of age declined by 1,897 (or 25 %), from 7,533 in 2000 to 5,636 in 2010.[13] The estimates depicted in Fig. 8 indicated that approximately two-thirds of the 2000–2010 decline in YPLL before the age of 70 years was due to pharmaceutical innovation. Hence, pharmaceutical innovation is estimated to have reduced YPLL before the age of 70 years per 100,000 population under the age of 70 years by 1,265 [=(2/3) × 1897].

Pharmaceutical innovation undoubtedly caused per capita pharmaceutical expenditure to rise. Due to data limitations, the precise magnitude of the increase in Slovenian pharmaceutical expenditure attributable to pharmaceutical innovation cannot be calculated. However, we can estimate the 2000–2010 increase in real per capita pharmaceutical expenditure, and we think that this may be viewed as an upper bound on the increase in pharmaceutical expenditure attributable to pharmaceutical innovation.

Aggregate time-series data on Slovenian pharmaceutical expenditure are shown in Table 5. The OECD [30] publishes data (shown in column 1; http://stats.oecd.org/Index.aspx?DataSetCode=SHA) on nominal expenditure (in national currency units) on prescribed medicines during the period 2002–2012. This indicates that nominal per capita expenditure increased from €170 in 2002 to €233 in 2010 (column 3). The European Central Bank publishes a harmonised index of consumer prices for pharmaceutical products. This price increased 7 % (or approximately 0.9 % per year) during the period 2002–2010 (column 4). Real per capita pharmaceutical expenditure (in 2002 €) increased from €170 in 2002 to €218 in 2010 (column 5). US data indicate that in 2011, per capita expenditure on prescribed medicines by people below the age of 65 years was approximately 19 % below per capita expenditure of the entire population (source: MEPSnet/Household Component). Similarly, Danish data indicate that per capita expenditure on prescribed medicines by people below the age of 65 years is approximately 23 % below per capita expenditure of the entire population (source: medstat.dk). Hence, it seems reasonable to estimate that real

[13] The OECD also publishes estimates of YPLL before the age of 70 years per 100,000 population under 70 years of age. For unknown reasons, the OECD figures for Slovenia are quite a bit lower, but declined more rapidly, than the estimates based on WHO data. (The OECD figures for the US are also lower than estimates provided by the CDC [14] but the differences are not as great.) According to the OECD, YPLL before the age of 70 years per 100,000 population under 70 years of age declined by 1,684 (or 33 %), from 5,091 in 2000 to 3,407 in 2010. The OECD estimate of the absolute decline is only 11 % lower than the WHO-based estimate.

Table 6 Comparison of estimates of the cost per life-year gained from pharmaceutical innovation in five countries

Country	Study	GDP (PPP) per capita, 2013	Estimated cost per life-year gained from pharmaceutical innovation	
			Excluding hospital cost offset	Including hospital cost offset
Sweden	Lichtenberg and Pettersson [19]	$43,533	$19,192	$233
Germany	Lichtenberg [5]	$43,332	$16,173	
France	Lichtenberg [24]	$36,907	$37,000	$8,065
Slovenia	Present study	$28,298	$4,981	$770
Turkey	Lichtenberg et al. [20]	$18,975	$3,128	$2,776

per capita pharmaceutical expenditure by Slovenians below the age of 65 years increased from €138 in 2002 to €176 in 2010—approximately €5 per year (column 6). 'Backcasting' this rate of growth to the year 2000 implies that real per capita pharmaceutical expenditure by Slovenians below the age of 65 years increased by approximately €50 between 2000 and 2010.

It is assumed that the entire increase in real per capita pharmaceutical expenditure was due to the introduction of new drugs. Under that assumption, which is probably conservative, pharmaceutical innovation increased expenditure on prescribed medicines by €5.0 million (=100,000 × €50) per 100,000 people below the age of 70 years. Therefore, if we assume that pharmaceutical expenditure was the only type of expenditure affected by pharmaceutical innovation, the cost per life-year saved was €3,953 (=€5.0 million/1,265 life-years).

Previous studies have produced a range of estimates of the value of (or consumers' willingness to pay for) a (quality-adjusted) life-year (QALY). Some of the studies were based on surveys of individuals, while others relied on evidence about compensating wage differentials. The European value of a QALY study described by Pennington et al. [31] concluded that "a mean value ranging from $10,000 to $30,000 can be placed on one extra QALY estimated in scenarios involving certainty". The Health Council in Slovenia has adopted a cost-effectiveness threshold of €30,000 per QALY [32]. The base-case analyses performed by Braithwaite et al. [33] suggested that plausible lower and upper bounds for a cost-effectiveness decision rule for the US are $183,000 per life-year and $264,000 per life-year, respectively.[14] My estimate of the cost per life-year saved is well below even the lowest estimates of the value of a life-year saved.

Moreover, the estimates of Eq. 3 indicated that the 2003–2009 increase in cumulative NCEs reduced the number of hospital discharges in 2010 in Slovenia by 7 %. Assuming that hospital expenditure is proportional to the number of hospital discharges, this implies that 1 year of pharmaceutical innovation reduced hospital expenditure by approximately 1.2 % (=7 %/6). In Slovenia in 2010, per capita spending on inpatient curative and rehabilitative care was €448 (source: OECD). In the US in 2011, mean spending on inpatient care by people below 65 years of age was 25 % lower than mean spending on inpatient care by all people (source: MEPSnet/Household Component), therefore per capita spending on inpatient curative and rehabilitative care by Slovenians below 65 years of age may have been €334. Our estimates imply that, in the absence of 10 prior years of pharmaceutical innovation, this figure would have been €376 (=€334 × 1.012^{10})—€42 higher. Hence, 85 % (=€42/€ 50) of the increase in drug expenditure may have been offset by a reduction in hospital expenditure, and the cost per life-year saved may have been only €611 (=15 % × €3,953).

Recent studies have estimated the incremental cost effectiveness of pharmaceutical innovation in four other countries—France, Germany, Sweden and Turkey. Estimates from those studies are shown in Table 6. All four studies provided estimates of the cost per life-year gained from pharmaceutical innovation, excluding the hospital cost offset. The estimate for Slovenia ($4,980, equal to €3,953 evaluated at the current exchange rate of 1.26 $/€) is well below the estimates of the three countries with higher per capita GDP, and higher than the estimate for the country with lower per capita GDP (Turkey). Three of the studies provided estimates of the cost per life-year gained from pharmaceutical innovation, including the hospital cost offset. The estimate for Slovenia ($770) is higher than the estimate for Sweden but well below the estimates for Turkey and France.

Our findings are subject to several limitations. One limitation is that our estimates do not account for potential cross-disease spillovers, whereby the introduction of a drug

[14] Aldy and Viscusi [34] estimated that, in the US, the average value of (willingness to pay for) a life-year is $300,000. Per capita gross domestic product (GDP) in Slovenia is just over half (53 %) of US per capita GDP; if the value of a statistical life-year (VSLY) was proportional to per capita GDP, the value of a statistical life-year in Slovenia might be $159,000 (=53 % × $300,000). However, Viscusi [35] argues that "estimates of the income elasticity of the value of a statistical life range from 0.5 to 0.6": when income falls by 10 %, the value of a statistical life declines by only 5–6 %. This implies that the value of a statistical life-year in Slovenia might be $212,125 (=$0.53^{0.55}$ × $300,000).

for disease A may affect mortality and hospitalization due to disease B. These spillovers could be either negative (e.g. cardiovascular drug innovation could increase cancer mortality due to 'competing risks') or positive (e.g. new mental health drugs could result in fewer diabetes hospitalizations and deaths due to better disease management). A second limitation is that the precise magnitude of the increase in Slovenian pharmaceutical expenditure attributable to pharmaceutical innovation could not be calculated, therefore we used the increase in real per capita pharmaceutical expenditure as a proxy for this. A third limitation is that we were unable to control for non-pharmaceutical medical innovation, although we argued that it is unlikely that this would bias our estimates of the effect of pharmaceutical innovation on mortality and hospitalization.

5 Conclusions

In Slovenia during the period 2000–2010, the number of YPLL before the age of 70 years per 100,000 population under the age of 70 years declined 25 %. It is quite unlikely that the decline was due to changes in behavioral risk factors or rising income.

In this study, the hypothesis that an important type of medical innovation—pharmaceutical innovation—played a key role in reducing premature mortality in Slovenia was tested. To test this hypothesis, longitudinal disease-level data was analyzed to determine whether diseases for which there was greater pharmaceutical innovation—a larger increase in the number of NCEs previously launched—had larger declines in premature mortality. My methodology controlled for the effects of macroeconomic trends and overall changes in the healthcare system.

The estimates indicated that premature mortality from a disease is inversely related to the number of NCEs launched more than 5 years earlier. One would expect there to be a substantial lag because new drugs diffuse gradually, and drugs for chronic conditions (which account for most drug use) may have to be consumed for several years for their full health benefits to be realized. On average, the introduction of an additional NCE for a disease reduced premature mortality from the disease by 2.4 % 7 years later. Pharmaceutical innovation had a larger impact on premature mortality at higher ages than it did on premature mortality at lower ages (e.g. infant and childhood mortality). The estimates imply that approximately two-thirds of the 2000–2010 decline in premature mortality was due to pharmaceutical innovation.

In addition to examining the effect of pharmaceutical innovation on premature mortality from all diseases (measured in several different ways), its effects on the age-standardized number of cancer deaths was examined. It was found that cancer mortality is inversely related to the number of NCEs launched 1–6 years earlier, conditional on the incidence of the cancer 0–2 years earlier. Controlling for incidence had virtually no effect on estimates of the effect of pharmaceutical innovation on cancer mortality. Cancer drugs have a more immediate impact on mortality than other drugs. The NCEs launched in Slovenia during 1995–2005 are estimated to have reduced the age-adjusted cancer mortality rate by 12 % in 2007. If no NCEs had been launched in Slovenia during 1992–2003, there might have been 691 more cancer deaths in Slovenia in 2008.

The effect of pharmaceutical innovation on hospitalization from all diseases was also examined. It was found that, on average, the launch of an NCE reduced the number of hospital discharges 1 year later by approximately 1.5 %. The NCEs launched in Slovenia during 2003–2009 are estimated to have reduced the number of hospital discharges in 2010 by 7 %.

Finally, the estimates and other data were used to calculate the incremental cost effectiveness of pharmaceutical innovation in Slovenia. If we assume that pharmaceutical expenditure was the only type of expenditure affected by pharmaceutical innovation, the cost per life-year saved was €3,953, which is well below even the lowest estimates of the value of a life-year saved. Moreover, 83 % of the increase in drug expenditure may have been offset by a reduction in hospital expenditure; therefore, the cost per life-year saved may have only been €611.

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