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THE BENEFITS OF PHARMACEUTICAL INNOVATION: HEALTH, LONGEVITY, AND SAVINGS
(Incluant un sommaire en français)
By Frank R. Lichtenberg
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The Benefits of Pharmaceutical Innovation: Health, Longevity, and Savings

Montreal Economic Institute

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EXECUTIVE SUMMARY

Although the costs of new pharmaceuticals are often the subject of critical media coverage, they are rarely juxtaposed with the benefits that these new drugs bring. Between 1995 and 2012, life expectancy at birth in Canada increased by more than three years and curative care hospital discharges per 100,000 population (a measure of hospital utilization) decreased by 25%. While these improvements naturally have multiple sources, a substantial and growing number of studies have demonstrated that pharmaceutical innovation is responsible for a large part of such long-term improvements in health and longevity.

Furthermore, although new drugs can appear expensive when considered in isolation, pharmaceutical innovation leads to cost savings elsewhere in the system through the reduced use of health services like hospitals and nursing homes. Studies have also shown that pricing drugs appropriately is important in sustaining a robust rate of pharmaceutical innovation.

Longevity and Health

The positive impact of pharmaceutical innovation on longevity has been demonstrated repeatedly using different methodologies. One study using patient-level data for 22,000 elderly residents of Switzerland found that people who used newer cardiovascular drugs lived longer than those who used older cardiovascular drugs, with the most conservative estimates finding an increase in longevity between 2002 and 2012 of almost 3 months, at a cost per life-year gained of under US$10,000. Another study using region-level data for 30 developing and high-income countries found that life expectancy increased faster in countries with larger increases in drug vintage (world launch year), with the increase in the fraction of newer drugs consumed accounting for 73% of the increase in life expectancy at birth. A third study, this one using disease-level data for Canada found that the cancer sites (breast, lung, colon, etc.) that experienced more pharmaceutical innovation had larger declines in the premature mortality rate, at an estimated cost per life-year gained of US$2,730.

Health status and productivity are also positively affected by pharmaceutical innovation. Work days lost and school days missed per year because of illness or injury in the U.S. declined more rapidly from 1997 to 2010 for medical conditions with larger increases in the mean number of newer prescription drugs consumed. The use of newer prescription drugs also reduced the ratio of the number of workers receiving Social Security

SOMMAIRE

Bien que les coûts des nouveaux produits pharmaceutiques fassent souvent l’objet de critiques dans les médias, il est rare qu’on signale en même temps les bienfaits qu’apportent ces nouveaux médicaments. De 1995 jusqu’en 2012, l’espérance de vie à la naissance au Canada a été prolongée de plus de trois ans et les congés accordés par les hôpitaux de soins curatifs par tranche de 100 000 habitants (une mesure de l’utilisation des hôpitaux) ont diminué de 25 %. Même si, de toute évidence, ces améliorations résultent de facteurs multiples, un nombre important et croissant d’études ont démontré que l’innovation pharmaceutique explique en grande partie de telles améliorations à long terme au chapitre de la santé et de la longévité.

De plus, même si les nouveaux médicaments peuvent sembler dispendieux quand on les considère isolément, l’innovation pharmaceutique ouvre la voie à des économies de coûts ailleurs dans le système en réduisant l’utilisation de services de santé tels les hôpitaux et les résidences pour personnes âgées avec soins de longue durée. Des études ont aussi établi qu’il est important de fixer des prix appropriés pour les médicaments afin de maintenir un rythme vigoureux d’innovation pharmaceutique.

Longévité et santé

L’impact positif de l’innovation pharmaceutique sur la longévité a été démontré à maintes reprises au moyen de différentes méthodologies. Une étude utilisant des données sur les patients recueillies auprès de 22 000 résidents âgés de la Suisse a conclu que les patients consommant des médicaments cardiovasculaires plus récents vivaient plus longtemps que ceux en consommant de moins récents, les estimations les plus prudentes faisant état d’une longévité accrue de presque 3 mois de 2002 jusqu’en 2012 à un coût inférieur à 10 000 $US par année de vie gagnée. Une autre étude fondée sur des données régionales visant 30 pays en développement ou à revenu élevé a signalé que l’espérance de vie croissait plus rapidement dans ceux où on notait de plus fortes hausses du millésime des médicaments (l’année de lancement à l’échelle mondiale), la consommation accrue de médicaments plus récents représentant 73 % de l’augmentation de l’espérance de vie à la naissance. Selon une troisième étude utilisant cette fois des données sur les maladies au Canada, les sièges du cancer (sein, poumon, côlon, etc.) ayant fait l’objet d’une plus grande innovation pharmaceutique ont connu de plus fortes baisses du taux de mortalité
Disability Insurance benefits to the working-age population, and has had a positive effect on nursing home residents' ability to perform activities of daily living.

**Cost Savings Elsewhere in the Health Care System**

The costs of new pharmaceuticals are counterbalanced by cost savings elsewhere in the system through the reduced use of health services. One study on the utilization of cardiovascular drugs in 20 OECD countries estimated that if the proportion of newer drugs had not increased from 1995 to 2004, per capita expenditures on cardiovascular hospital stays would have been $89 higher in 2004. In comparison, per capita expenditure on cardiovascular drugs would have been just $24 lower with no new cardiovascular drugs. Another study using U.S. data for all diseases found an estimated reduction in hospital expenditure that was more than twice as large as the increase in pharmaceutical expenditure attributable to pharmaceutical innovation. Yet another study found that pharmaceutical innovation also leads to savings in terms of nursing home use.

New research presented in this Research Paper investigates the impact that pharmaceutical innovation had on utilization of hospital care by cancer patients in Canada from 1995 to 2012. During this period, the number of cancer patient hospital days declined by 23%, even though the number of new cancer cases diagnosed increased by 46%. The model developed shows that the cancer sites (breast, prostate, lung, etc.) that experienced more pharmaceutical innovation had larger declines in utilization of hospital care. If no new drugs had been registered during the 1980-1997 period, there would have been 1.72 million additional cancer patient hospital days in 2012, at a cost of C$4.7 billion in hospital expenditure, whereas total spending on cancer drugs (old and new) in 2012 was an estimated C$3.8 billion. These pharmaceutical innovations therefore certainly led to substantial cost savings.

**The Impact of Financial Incentives on the Rate of Pharmaceutical Innovation**

A number of studies have provided evidence for the hypothesis that, in order to sustain a robust rate of pharmaceutical innovation, financial incentives are required. For instance, the amount of pharmaceutical innovation is positively related to the burden of disease in developed countries but not in developing countries. The most plausible explanation is that incentives to develop medicines for diseases primarily afflicting people in pre-matured, moyennant un coût estimé de 2730 $US par année de vie gagnée.

L’état de santé et la productivité de la population profitent aussi de l’innovation pharmaceutique. Les jours de travail et d’école manqués annuellement pour cause de maladie ou de blessure aux États-Unis ont diminué plus rapidement de 1997 jusqu’en 2010 en ce qui concerne les troubles médicaux pour lesquels on a noté une plus forte hausse du nombre moyen de médicaments d’ordonnance plus récents consommés. L’usage de médicaments d’ordonnance plus nouveaux a aussi fait diminuer le ratio du nombre de travailleurs touchant des prestations d’assurance invalidité de la Sécurité sociale sur la population en âge de travailler, en plus d’améliorer la capacité des résidents des centres de soins de longue durée à se livrer aux activités de la vie quotidienne.

**Des économies ailleurs dans le système de santé**

Les coûts des nouveaux produits pharmaceutiques sont contrebalancés par des économies ailleurs dans le système du fait que les services de santé sont moins utilisés. Une étude sur l’usage des médicaments cardiovasculaires dans 20 pays de l’OCDE a estimé que, si la proportion des médicaments plus récents n’avait pas augmenté de 1995 jusqu’en 2004, les dépenses par habitant liées aux hospitalisations pour troubles cardiovasculaires auraient été majorées de 89 $ en 2004. En comparaison, les dépenses par habitant pour des médicaments cardiovasculaires auraient été réduites d’à peine 24 $ sans les nouveaux médicaments. Une autre étude citant des données des États-Unis sur toutes les maladies a fait état d’une réduction estimée des dépenses d’hôpital plus de deux fois supérieure à l’augmentation des dépenses en médicaments attribuable à l’innovation pharmaceutique. Une autre étude encore a établi que l’innovation pharmaceutique génère aussi des économies pour ce qui est de l’utilisation des centres de soins de longue durée.

De nouvelles recherches présentées dans ce Cahier de recherche examinent l’impact de l’innovation pharmaceutique sur l’hospitalisation des patients atteints du cancer au Canada de 1995 à 2012. Durant cette période, le nombre de journées d’hospitalisation pour cause de cancer a diminué de 23 % même si le nombre de nouveaux diagnostics de cancer a cru de 46 %. Le modèle qu’on a élaboré fait état de plus fortes baisses des hospitalisations en ce qui concerne les sièges du cancer (sein, prostate, poumon, etc.) ayant fait l’objet d’une plus grande innovation pharmaceutique. Si aucun nouveau médicament n’avait été enregistré de 1980 à
developing countries have been weak or nonexistent. Similarly, the 1983 Orphan Drug Act in the United States, which gave firms incentives to develop drugs for diseases afflicting fewer than 200,000 people, led to increased development of such drugs.

A simple theoretical model of drug development suggests that in the long run, a 10% decline in drug prices from the re-importation of cheaper drugs into the U.S. would likely cause at least a 5-6% decline in pharmaceutical innovation. Other estimates indicate that there is a sizable, robust, negative relationship between the penetration of generics and early-stage pharmaceutical innovation.

1997, on aurait dénombré 1,72 million de journées d’hospitalisation additionnelles pour cas de cancer en 2012, ce qui aurait coûté 4,7 milliards de dollars canadiens en dépenses d’hôpital alors que les dépenses totales en médicaments anticancéreux (vieux et nouveaux) cette année-là ont été estimées à 3,8 milliards de dollars. Ainsi, ces innovations pharmaceutiques ont certainement généré des économies de coûts substantielles.

L’impact des incitations financières sur le rythme de l’innovation pharmaceutique

Plusieurs études ont apporté des preuves qui confirment l’hypothèse suivant laquelle des incitations financières sont nécessaires pour maintenir un rythme d’innovation pharmaceutique vigoureux. Par exemple, il existe un lien positif entre la quantité d’innovation pharmaceutique et le fardeau des maladies dans le monde développé mais non dans les pays en développement. Selon l’explication la plus plausible, les incitations pour développer des médicaments contre des maladies qui frappent surtout les habitants des pays en développement étaient négligeables ou inexistantes. Dans le même ordre d’idées, la Loi de 1983 sur les produits pharmaceutiques orphelins aux États-Unis, laquelle fournissait des incitations aux entreprises afin qu’elles développent des médicaments contre des maladies touchant moins de 200 000 personnes, a stimulé la mise au point de tels médicaments.

Un simple modèle théorique du développement des médicaments laisse entrevoir qu’à long terme, une baisse de 10 % des prix des médicaments résultant de la réimportation de médicaments moins dispendieux aux États-Unis entraînerait probablement une réduction d’au moins 5 ou 6 % de l’innovation pharmaceutique. Selon d’autres estimations, il existe une relation négative appréciable et solide entre la pénétration des médicaments génériques et l’innovation pharmaceutique au stade précoce.
INTRODUCTION

The health of the Canadian population improved remarkably over the course of the 20th century. Better hygiene conditions and great leaps in biomedical knowledge certainly helped a lot, as did the research and development of new drugs. Just between 1995 and 2013, the number of patents registered each year surged 79.1% in the United States, and 70.1% in Canada.

The results are that Canadians live healthier and longer lives than ever before. As shown in Figure I-1, between 1995 and 2012, life expectancy at birth increased by 3.6 years (from 78.0 to 81.6), and the number of curative care hospital discharges per 100,000 population decreased by 25% (from 11,046 to 8,319). A substantial and growing number of studies based on data from numerous countries and several methodologies have demonstrated that pharmaceutical innovation is responsible for a large part of long-term improvements in population health.

This Research Paper will review some of the existing evidence about the impact of pharmaceutical innovation on longevity, health, and use of health services (hospitals and nursing homes). Some new evidence will also be presented regarding the impact of cancer drug innovation on hospitalization of cancer patients in Canada. Finally, some of the existing evidence regarding the impact of financial incentives on the rate of pharmaceutical innovation will be reviewed.

“A substantial and growing number of studies based on data from numerous countries and several methodologies have demonstrated that pharmaceutical innovation is responsible for a large part of long-term improvements in population health.”

2. OECD, Patents by technology (Pharmaceuticals).
3. The World Bank, Life expectancy at birth, total (years), May 2016.
4. “Hospital discharge rates measure the number of patients who leave a hospital after receiving care. Hospital discharge is defined as the release of a patient who has stayed at least one night in hospital. It includes deaths in hospital following inpatient care. Same-day discharges are usually excluded.” OECD, Health care use, Hospital discharge rates.
5. People who are hospitalized tend to be in the worst health. In the U.S. in 2007, more than 1 in 3 deaths occurred in hospitals. See National Center for Health Statistics, Health, United States, 2010: With Special Feature on Death and Dying, DHHS publication No. 2011-1232, February 2011, p. 85; OECD, Database, Curative care discharges per 100 000 population, 1995-2012.
Figure I-1

Life expectancy in Canada, 1995-2012

Source: The World Bank, Life expectancy at birth, total (years), May 2016.
CHAPTER 1

The Impact of Pharmaceutical Innovation on Longevity and Health

The impacts of pharmaceutical innovation—the introduction and use of new drugs—on three main types of outcomes have been studied. This chapter deals with two of these: longevity (life expectancy) or its inverse, mortality; and health status, as reflected in the ability of people to work or to perform activities of daily living. The third type of outcome, namely the use of non-pharmaceutical health services, such as hospitals and nursing homes, will be discussed in the next chapter.

Longevity

The impact of pharmaceutical innovation on longevity has been studied using three different approaches, or research designs. The first approach is based on cross-sectional patient-level data; it investigates whether patients using newer drugs live longer than patients using older drugs, controlling for other factors. The second approach is based on longitudinal, region-level data; it investigates whether regions (e.g., countries) undergoing more rapid medical innovation have larger increases in longevity. The third approach is based on longitudinal, disease-level data; it investigates whether the medical conditions undergoing more rapid innovation have larger declines in mortality.

A number of investigators have argued that one of the two most important contributors to improved human survival is the treatment of cardiovascular disease. Weisfeldt and Zieman argued that “pharmaceutical agents play a major role in prevention of atherosclerosis and its consequences: heart attack, stroke, and heart failure.” Specifically, “protein enzymes, receptors, or channels identified by the pharmaceutical industry as ‘drugable targets’ have led to striking, remarkable, and repeated achievement,” and the “marked reduction in cardiovascular disease and its consequences was largely driven by the development and implementation of drugs for long-term use and by complicated and costly procedures and operations for acute disease management.”7 Ford et al. estimated that 47% of the decline between 1980 and 2000 in the age-adjusted U.S. death rate for coronary heart disease was due to “treatments,” 24% was due to reductions in total cholesterol, and 20% was due to reductions in systolic blood pressure.8 Many of these treatments identified were pharmaceutical treatments, and pharmaceuticals (e.g., statins) probably also played an important role in reducing cholesterol and blood pressure. Also, Ford and Capewell argued that “aggressive recommendations regarding targets for cholesterol, glucose, and blood pressure evolved, and the medications available to health care providers to treat these risk factors proliferated for secondary prevention, then increasingly for primary prevention.”9

“The most conservative estimates implied that cardiovascular drug innovation accounted for almost a quarter of the increase in longevity among elderly residents of Switzerland during 2003-2012, and that it increased their longevity by almost 3 months.”

Impact of cardiovascular drug innovation in Switzerland. Lichtenberg showed that among Swiss inhabitants age 65 and over, 90% of the 1994-2010 decline in the overall death rate was due to the decline in the rate of deaths from diseases of the circulatory system, and that little if any of the decline in cardiovascular mortality is likely to have been due to changes in behavioral risk factors, especially tobacco use and obesity. That study examined the impact of cardiovascular drug innovation on the longevity of elderly residents of Switzerland using cross-sectional patient-level data on about 22,000 patients insured by a major health insurer (CSS) during the period 2003-2011. It investigated the effect of the vintage (world launch year) of the cardiovascular drugs used by an individual in 2003 on his or her longevity (time till death), controlling for several demographic characteristics and indicators of health status. It was possible to track a patient’s vital status until December 31, 2011, eight years after the end of the period in which cardiovascular drug use (and other variables) are measured.10


The estimates indicated that people who used newer cardiovascular drugs in 2003 lived longer than people who used older cardiovascular drugs, controlling for the number of 2003 prescriptions and their distribution by main anatomical group, the number of 2003 doctor visits and their distribution by specialty, whether the person was hospitalized in 2003, sex, and age. The most conservative estimates implied that cardiovascular drug innovation accounted for almost a quarter of the increase in longevity among elderly residents of Switzerland during 2003-2012, and that it increased their longevity by almost 3 months. Other estimates were about twice as large. All of the estimates were consistent with the hypothesis that newer classes of drugs tend to be therapeutically superior to older classes of drugs, and that within the same class, newer drugs tend to be superior to older drugs.

Even the more conservative estimates indicated that the use of new cardiovascular drugs by elderly residents of Switzerland was highly cost-effective. The conservative estimate of the cost per life-year gained from cardiovascular drug innovation was below US$10,000, and some economists have argued that the value of a statistical life-year is as high as US$300,000\(^{11}\).

Longevity growth in 30 developing and high-income countries. Lichtenberg examined the impact of pharmaceutical innovation, as measured by the vintage (world launch year) of prescription drugs used, on longevity using longitudinal, country-level data on 30 developing and high-income countries during the period 2000-2009. The study controlled for fixed country and year effects, real per capita income, the unemployment rate, mean years of schooling, the urbanization rate, real per capita health expenditure (public and private), the DPT immunization rate among children ages 12-23 months, HIV prevalence and tuberculosis incidence. The estimates indicated that life expectancy at all ages and survival rates above age 25 increased faster in countries with larger increases in drug vintage, ceteris paribus, and that the increase in life expectancy at birth due to the increase in the fraction of drugs consumed that were launched after 1990 was 1.27 years—73% of the actual increase in life expectancy at birth.\(^{12}\)

**Infant mortality and life expectancy at 65 in Canada.** Crémieux et al. provided a concurring analysis:

> “Pharmaceutical innovation during the period 1985-1996 reduced the number of years of potential life lost to cancer before age 75 in 2011 by 105,366.”

Premature cancer mortality in Canada. The premature cancer mortality rate has been declining in Canada, but there has been considerable variation in the rate of decline across cancer sites. Lichtenberg analyzed the effect that pharmaceutical innovation had on premature cancer mortality in Canada during the period 2000-2011, by investigating whether the cancer sites (breast, lung, colon, etc.) that experienced more pharmaceutical innovation had larger declines in the premature mortality rate, controlling for changes in the incidence rate.\(^{14}\)

Premature mortality before age 75 was significantly inversely related to the cumulative number of drugs registered at least 10 years earlier (see Figure 1-1). Since mean utilization of drugs that have been marketed for less than 10 years is only one-sixth as great as mean utilization of drugs that have been marketed for at least a decade, it is not surprising that premature mortality was strongly inversely related only to the cumulative number of drugs that had been registered at least ten years earlier. Premature mortality before age 65 and 55 was also strongly inversely related to the cumulative number of drugs that had been registered at least ten years earlier. Controlling for the cumulative number of drugs, the cumulative number of chemical subgroups does not

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11. Idem.
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have a statistically significant effect on premature mortality. This suggests that drugs (chemical substances) within the same class (chemical subgroup) are not therapeutically equivalent.15

During the period 2000-2011, the premature (before age 75) cancer mortality rate declined by about 8.4%. The estimates implied that, in the absence of pharmaceutical innovation during the period 1985-1996, the premature cancer mortality rate would have increased about 12.3% during the period 2000-201116 (see Figure 1-2). The estimates implied that pharmaceutical innovation during the period 1985-1996 reduced the number of years of potential life lost to cancer before age 75 in 2011 by 105,366.17

The cost per life-year before age 75 gained from previous pharmaceutical innovation was estimated to have been US$2,730. Most of the previously-registered drugs were off-patent by 2011, but evidence suggests that, even if these drugs had been sold at branded rather than generic prices, the cost per life-year gained would have been below US$11,000,18 a figure well below even the lowest estimates of the value of a life-year gained.

According to the World Health Organization, an intervention whose cost per life-year gained is below 3 times per capita GDP is considered to be cost-effective, while an intervention whose cost per life-year gained is below per capita GDP is highly cost-effective.19 Since Canadian


16. A substantial decline in the “competing risk” of death from cardiovascular disease could account for this. Pharmaceutical and other medical innovation has substantially reduced the risk of dying from a heart attack or stroke. Since people are less likely to die from heart attacks and strokes today than they were decades ago, their risk of developing, and dying from, cancer would have increased substantially in the absence of progress in the war on cancer. See Bo E. Honoré and Adriana Lleras-Muney, “ Bounds in Competing Risks Models and the War on Cancer,” Econometrica, Vol. 74, No. 6, November 2006, pp. 1675-1698.

17. Idem.


19. World Health Organization, Threshold values for intervention cost-effectiveness by Region.
GDP per capita is above US$40,000, pharmaceutical innovation is a highly efficient way to increase longevity. Moreover, this estimate did not account for potential reductions in hospital cost resulting from cancer drug innovation, which will be documented in the next chapter.

Health Status and Productivity

Work-loss and school-loss days. Lichtenberg investigated whether diseases subject to more rapid pharmaceutical innovation experienced greater declines in Americans’ disability days during the period 1997-2010, controlling for several other factors, using data from the Medical Expenditure Panel Survey. The mean number of work-loss days and school-loss days declined more rapidly among medical conditions with larger increases in the mean number of new (post-1990) prescription drugs consumed.

The mean number of work-loss days of employed Americans 18 years of age and older declined at an average annual rate of at least 1.8% during the period 1997-2010; some estimates imply that it declined more than twice as much. The mean number of “additional bed-days” (days other than work days in which the person spent at least half a day in bed, because of a physical illness, injury or a mental or emotional problem) declined at an average annual rate of 3.5% during the period 1997-2010. The mean number of school days missed per year because of illness or injury for children aged 5 to 17 also declined significantly.

Note: Premature (before age 75) cancer mortality rate: actual vs. estimated in the absence of previous pharmaceutical innovation. The premature (before age 75) cancer mortality rate is the number of years of potential life lost due to cancer before age 75 per 100,000 population age 0-74.


20. OECD, Level GDP per capita and productivity.

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Impact of pharmaceutical innovation on longevity, three different approaches

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Receipt of Social Security Disability payments. Lichtenberg analyzed longitudinal state-level data during the period 1995-2004 to investigate whether use of newer prescription drugs has reduced the ratio of the number of workers receiving Social Security Disability Insurance benefits to the working-age population (the “DI recipiency rate”). All of the estimates indicate that there is a significant inverse relationship between disability recipiency and a good indicator of pharmaceutical innovation use: the mean vintage (FDA approval year) of Medicaid prescriptions. From 1995 to 2004, the actual disability rate increased 30%, from 2.62% to 3.42%. The estimates imply that in the absence of any post-1995 increase in drug vintage, the disability rate would have increased from 2.62% to 3.65%. This means that in the absence of any post-1995 increase in drug vintage, about 418,000 more working-age Americans would have been DI recipients.22

Nursing home medication use. Lichtenberg examined the effect of pharmaceutical innovation on the functional status of nursing home residents, by estimation of econometric models of the ability of nursing home residents to perform activities of daily living (ADLs) using cross-sectional, patient-level data from the 2004 National Nursing Home Survey. The explanatory variables of primary interest were the characteristics (e.g., the mean vintage (FDA approval year)) of the medications used by the resident. The study controlled for age, sex, race, marital status, veteran status, where the resident lived prior to admission, primary diagnosis at the time of admission, up to 16 diagnoses at the time of the interview, sources of payment, and facility fixed effects.

“In the absence of any post-1995 increase in drug vintage, about 418,000 more working-age Americans would have been DI recipients.”

The ability of nursing home residents to perform ADLs was positively related to the number of “new” (post-1990) medications they consumed, but unrelated to the number of old medications they consumed. It was estimated that, if 2004 nursing home residents had used only old medications, the fraction of residents with all five ADL dependencies (number of activities for which the resident was not independent) would have been 58%, instead of 50%. During 1990-2004, pharmaceutical innovation reduced the functional limitations of nursing home residents by between 1.2% and 2.1% per year.23


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CHAPTER 2

Pharmaceutical Innovation and the Use of Non-Pharmaceutical Health Services

The impacts of the introduction and use of new drugs on two types of outcomes were examined in the first chapter: longevity and health status. This second chapter examines the impact on a third type of outcome, namely the use of non-pharmaceutical health services, such as hospitals and nursing homes, and provides some new evidence about the impact of cancer drug innovation on hospitalization of cancer patients in Canada.

Use of Health Services

Cardiovascular hospitalization in OECD countries. Lichtenberg examined the effect of changes in the vintage distribution of cardiovascular system drugs on hospitalization and mortality due to cardiovascular disease using longitudinal country-level data. The vintage of a drug is the first year in which it was marketed anywhere in the world. Annual data on the utilization of over 1,100 cardiovascular drugs (active ingredients) in 20 OECD countries during the period 1995-2004 were used. Countries with larger increases in the share of cardiovascular drug doses that contained post-1995 ingredients had smaller increases in the cardiovascular disease hospital discharge rate, controlling for the quantity of cardiovascular medications consumed per person, the use of other medical innovations (computed tomography scanners and magnetic resonance imaging units), potential risk factors (average consumption of calories, tobacco, and alcohol), and demographic variables (population size and age structure, income, and educational attainment).

The estimates indicated that if drug vintage had not increased during 1995-2004, hospitalization would have been higher in 2004. It was estimated that per capita expenditure on cardiovascular hospital stays would have been 70% ($89) higher in 2004 had drug vintage not increased during 1995-2004. However, the estimate of the increase in expenditure on cardiovascular hospital stays was about 3.7 times as large as the estimate of the reduction in per capita expenditure for cardiovascular drugs that would have occurred ($24).24

Hospitalization for all diseases in the U.S. The study described in Chapter 1 that examined the impact of pharmaceutical innovation on disability days in the U.S. during 1997-2010 using longitudinal disease-level data also analyzed its impact on hospitalization. The mean number of inpatient hospital admissions declined more rapidly among medical conditions with larger increases in the mean number of new (post-1990) prescription drugs consumed. The estimated reduction in hospital expenditure was more than twice as large as the increase in pharmaceutical expenditure attributable to pharmaceutical innovation.25

Demand for long-term care. During the last few decades, the proportion of elderly Americans who live in nursing homes has declined. The age-adjusted rate of nursing home residence declined at a 1.7% annual rate during the period 1985-1999. Living in a nursing home is considerably more expensive than living in the community, so the decline in nursing home residence rates reduced the total costs incurred by Americans age 80 and over by about US$10 billion in 1999.

Lichtenberg showed that diseases with more rapid rates of pharmaceutical innovation had larger declines in the nursing home residence rate during the period 1985-1999. Pharmaceutical innovation is estimated to have accounted for almost three-quarters of the decline in the age-adjusted nursing home residence rate of people 65 and over, and 56% of the decline in the rate of people age 80 and over. It was estimated that 55% of expenditure on new drugs by people age 65 and over was offset by reduced expenditures on nursing home care, and that among people age 80 and over, the reduction in expenditure on nursing home care due to the

use of new drugs exceeded expenditure on new drugs by 26%.26

The Impact of Cancer Drug Innovation on Hospitalization in Canada

As discussed in Chapter 1, a previous study provided evidence that pharmaceutical innovation played a significant role in reducing premature (before ages 75, 65, and 55) cancer mortality in Canada during the period 2000-2011.27 A similar research design will be used in this section to investigate the impact that pharmaceutical innovation had on utilization of hospital care by cancer patients in Canada during the period 1995-2012.

As shown in Figure 2-1, during that period, the number of cancer patient hospital days declined by 23%, even though the number of new cancer cases diagnosed increased by 46%. The rate of decline of the number of hospital days was more than twice as large as the estimated increase in pharmaceutical expenditure attributable to pharmaceutical innovation.

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27. Frank R. Lichtenberg, op. cit., footnote 15.
cancer patient hospital days varied considerably across cancer sites (breast, prostate, lung, etc.), as shown in Figure 2-2. For example, the number of breast cancer patient hospital days declined by 59%, while the number of colorectal cancer patient hospital days declined by only 10%. As shown in Figure 2-3, the rate of increase of the number of new cancer cases diagnosed varied much less across cancer sites; for all four cancer sites shown there, the increase was between 33% and 43%.

In contrast, the increase in the number of drugs ever registered for treating cancer varied considerably across cancer sites. For example, as shown in Figure 2-4, by 1987 the number of drugs that had been registered for treating bladder cancer (11) was greater than the number of drugs that had been registered for treating prostate cancer (9). By 2012, the opposite was true: the number of drugs that had been registered for treating prostate cancer (22) was greater than the number of drugs that had been registered for treating bladder cancer (18). Also, the numbers of drugs for treating breast cancer and lung cancer were equal in 1987; during the next quarter-century, there were 25 new drugs for treating breast cancer and only 16 new drugs for treating lung cancer.

"Pharmaceutical innovation is estimated to have accounted for almost three-quarters of the decline in the age-adjusted nursing home residence rate of people 65 and over, and 56% of the decline in the rate of people age 80 and over."
This section will investigate whether the cancer sites that experienced more pharmaceutical innovation had larger declines in utilization of hospital care, controlling for growth in the number of new cancer cases. This will be done by obtaining weighted least-squares estimates of the model presented in Box 2-1.

One would expect there to be a substantial lag because new drugs diffuse gradually—they aren’t used widely until years after registration. Lichtenberg presented two kinds of evidence—“within molecule” and “between molecule”—that supported the gradual diffusion hypothesis. The “within molecule” estimates indicated that the number of drug doses sold 10 years after registration is about ten times as great as the number of units sold one year after registration. The “between-molecule” evidence was based on data on the mean number of cancer drug doses sold in Canada in 2010, by period of registration in Canada. Mean utilization in 2010 of drugs registered after 2000 was only 15% as high as mean utilization of drugs registered during 1991-2000, and 17% as high as mean utilization of drugs registered during 1981-1990.30

Estimates of the $\beta_k$ parameters from eq. (1) are shown in Table 2-1. Not surprisingly, estimates of $\beta_0$ and $\beta_5$ are far from statistically significant (p-value > 0.25). The estimate of $\beta_{10}$ is marginally significant (p-value = .096), and the

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29. Observations are weighted by mean hospital days during 1995-2012 ($\sum t \text{DAYS}_{s,t} / 18$).

30. Frank R. Lichtenberg, op. cit., footnote 15. The data sources used for this analysis are the same ones used in Lichtenberg (2015b), with one addition: annual data on the number of hospital days (number of hospital discharges x mean length of stay), by cancer site and year (1995-2012), were obtained from the OECD Health Statistics 2015 online database. This database provides information on the eight cancer sites shown in Figure 2-2, and on “other malignant neoplasms” combined. The OECD obtains these data from the Discharge Abstract Database and Hospital Morbidity Database maintained by the Canadian Institute for Health Information.
The Benifits of Pharmaceutical Innovation: Health, Longevity, and Savings

The estimate of $\beta_{15}$ is highly significant (p-value = .004). This signifies that cancer sites with larger growth in the number of drugs ever registered between 1980 and 1997 had larger declines in the number of hospital days between 1995 and 2012. As shown in Figure 2-5, the two cancer sites (breast and prostate) with the largest increases in the lagged number of drugs had the largest declines in hospital days, and the cancer site (colorectal) with the smallest increase in the lagged number of drugs had the smallest decline in hospital days, controlling for the % increase in the number of new cancer cases diagnosed.

The weighted (by mean hospital days during 1995-2012) mean value of the 15-year lagged growth of the number of drugs registered in Canada ($\ln(CUM_{NCE_{1997}}/CUM_{NCE_{1980}})$) was 0.79. This implies that new drugs registered during 1980-1997 reduced the growth of hospital days during 1995-2012 by 0.67 (= $-\beta_{15} \times$ mean $[\ln(CUM_{NCE_{1997}}/CUM_{NCE_{1980}})] = 0.848 \times 0.79$). If no new drugs had been registered during 1980-1997, the number of hospital days in 2012 would have been 96%.

"The two cancer sites (breast and prostate) with the largest increases in the lagged number of drugs had the largest declines in hospital days, and the cancer site (colorectal) with the smallest increase in the lagged number of drugs had the smallest decline in hospital days."

Sources: Author’s calculations based on data obtained from Health Canada Drug Product Database and from Thériaque.

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31. Figure 2-5 depicts the relationship across cancer sites between the % increase in the number of drugs ever registered, 1980-1997, and the % change in the number of hospital days, 1995-2012, controlling for the % increase in the number of new cancer cases diagnosed, 1995-2012. Appendix Figure A-1 depicts the relationship across cancer sites between the % increase in the number of drugs ever registered, 1980-1997, and the % change in the number of hospital days, 1995-2012, not controlling for the % increase in the number of new cancer cases diagnosed, 1995-2012. The two figures look very similar.
In eq. (1), the 1995-2012 growth in hospital use for cancer at site s depends on the growth in the number of new chemical entities (drugs) to treat cancer at site s registered in Canada k years earlier, i.e. there is a lag of k years. Eq. (1) will be estimated for different values of k: k = 0, 5, 10, 15, and 20.
In 2012, total hospital expenditure (for all diagnoses) was C$60.5 billion,32 and total hospital days (for all diagnoses) was 22 million,33 so mean expenditure per hospital day was C$2,751. Assuming that mean expenditure per hospital day of cancer patients in 2012 was also C$2,751, this implies that the new drugs for treating cancer that were registered during 1980-1997 reduced hospital expenditure in 2012 by C$4.7 billion.

In 2012, total prescribed drug expenditure was C$27.7 billion.34 Cancer drugs (antineoplastic and immunomodulating agents) accounted for 13.8% of total public drug expenditure.

Note: Relationship across cancer sites between the % increase in the number of drugs ever registered, 1980-1997, and the % change in the number of hospital days, 1995-2012, controlling for the % increase in the number of new cancer cases diagnosed, 1995-2012. Bubble size is proportional to mean number of hospital days during 1995-2012.

program expenditure. Assuming that cancer drugs also accounted for 13.8% of private drug expenditure, cancer drug expenditure in 2012 was C$3.8 billion. Expenditure in 2012 on cancer drugs registered during 1980-1997 was probably a small fraction of total cancer drug expenditure in 2012. Hence the reduction in 2012 hospital expenditure attributable to cancer drugs registered during 1980-1997 was likely to have been much larger than expenditure on those drugs in 2012. New cancer drugs were therefore economical for the health care system as a whole.

36. Using data from IMS Health, Lichtenberg estimated that expenditure in 2010 on 40 cancer drugs that were registered during the period 1985-1996 was US$409 million. Frank R. Lichtenberg, op. cit., footnote 15, p. 354.
CHAPTER 3

The Impact of Financial Incentives on the Rate of Pharmaceutical Innovation

A number of studies have provided evidence for the hypothesis that, in order to sustain a robust rate of pharmaceutical innovation, financial incentives are required. A few of those studies are summarized in this chapter.

Disease burden in developed vs. developing countries. Lichtenberg performed two analyses of the relationship across diseases between pharmaceutical innovation and the burden of disease in developed and developing countries. Both analyses indicated that the amount of pharmaceutical innovation is positively related to the burden of disease in developed countries but not to the burden of disease in developing countries. The most plausible explanation for the lack of a relationship between the burden of disease in developing countries and the amount of pharmaceutical innovation is that incentives for firms to develop medicines for diseases primarily afflicting people in developing countries have been weak or nonexistent.37

“...The most plausible explanation for the lack of a relationship between the burden of disease in developing countries and the amount of pharmaceutical innovation is that incentives for firms to develop medicines for diseases primarily afflicting people in developing countries have been weak or nonexistent.”

1983 Orphan Drug Act. In 1983, the U.S. Congress passed the Orphan Drug Act (ODA), which gave firms special incentives to develop drugs for diseases affecting fewer than 200,000 persons per year. The ODA contained provisions that reduced the cost, and raised the appropriability, of research on rare diseases. First, under the Act, drug makers receive seven years of exclusive marketing upon FDA approval of newly-developed drugs qualifying as “orphan drugs”—i.e., drugs for disorders affecting fewer than 200,000 persons. According to the FDA, this is the “most sought incentive.” For seven years following FDA approval, the FDA cannot approve another drug for the same indication without the sponsor’s consent. Second, drug makers qualify for a tax credit for clinical research expense of up to 50% of clinical testing expense. In addition, the FDA provides grant support for investigation of rare disease treatments. Together, these provisions (a) increase the effective market size; and (b) reduce fixed (sunk) costs. In doing so, the Act provided a natural experiment for measuring the impact of increased market size, relative to fixed costs, on product development, consumption, and welfare. Lichtenberg and Waldfogel found that the Orphan Drug Act “worked,” in the sense that it increased development of drugs targeted at small populations and that these populations are now more likely to take drugs38 (see Figure 3-1).

Impact of re-importation on innovation. Prices of drugs are lower in most other countries than they are in the U.S. Consequently, legalizing re-importation of drugs into the U.S. would result in a decline in U.S. drug prices. Lichtenberg assessed the consequences of importation for new drug development. First, a simple theoretical model of drug development was developed which suggests that the elasticity of innovation with respect to the expected price of drugs should be at least as great as the elasticity of innovation with respect to expected market size (disease incidence). Then, the cross-sectional relationship between pharmaceutical innovation and market size was examined among a set of diseases (different types of cancer) exhibiting substantial exogenous variation in expected market size. Two different measures of pharmaceutical innovation were analyzed: the number of distinct chemotherapy regimens for treating a cancer site, and the number of articles published in scientific journals and indexed in PubMed39 pertaining to drug therapy for that cancer site. Both analyses indicated that the amount of pharmaceutical innovation increases with disease incidence. The elasticity


39. PubMed comprises over 25 million citations for biomedical literature from MEDLINE, life science journals, and online books. PubMed citations and abstracts include the fields of biomedicine and health, covering portions of the life sciences, behavioral sciences, chemical sciences, and bioengineering. PubMed is a free resource that is developed and maintained by the National Center for Biotechnology Information (NCBI), at the U.S. National Library of Medicine (NLM), located at the National Institutes of Health (NIH). See National Center for Biotechnology Information, PubMed Help, February 14, 2016.
of the number of chemotherapy regimens with respect to the number of cases was 0.53. The elasticity of PubMed drug cites with respect to cancer incidence throughout the world was 0.60. This suggested that in the long run, a 10% decline in drug prices would be likely to cause at least a 5% to 6% decline in two measures of pharmaceutical innovation: the number of chemotherapy regimens, and the number of scientific articles about cancer. This estimate is very consistent with Giaccotto et al.’s estimate (0.583) of the elasticity of pharmaceutical industry R&D with respect to the real price of pharmaceuticals. That study employed time series econometric techniques to explain R&D growth rates using industry-level data from 1952 to 2001.


“Generic competition. Estimates obtained by Branstetter, Chatterjee, and Higgins indicated that there is a sizable, robust, negative relationship across therapeutic classes of drugs between generic penetration (the fraction of prescriptions in the class that were for generic products) and early-stage pharmaceutical innovation. A 10% increase in generic penetration is associated with an approximately 7.9% decline in early-stage innovations in the same therapeutic market. When they restricted their sample to novel innovations, they found that a 10%
The effect of generic drug penetration on innovation

<table>
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<th>GENERIC PENETRATION</th>
<th>EARLY-STAGE INNOVATIONS</th>
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<tr>
<td>▲ 10%</td>
<td>▼ 8%</td>
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Increase in generic penetration was associated with a roughly 4.6% decline in early-stage innovations in the same market. Their estimated effects appear to vary across therapeutic classes in sensible ways, reflecting the differing degrees of substitution between generic and branded drugs.42

“In the long run, a 10% decline in drug prices would be likely to cause at least a 5% to 6% decline in two measures of pharmaceutical innovation.”

Effective patent duration. Budish, Roin, and Williams found that R&D investments in cancer treatments are strongly negatively correlated with expected survival time. They observed lower levels of R&D investment in inventions that required longer commercialization lags, and therefore reduce effective patent duration.43

CONCLUSION

A substantial and growing number of studies based on data from numerous countries and several methodologies have demonstrated that pharmaceutical innovation is responsible for a large part of long-term improvements in three types of health outcomes: longevity, health status (as reflected in the ability of people to work or to perform activities of daily living), and use of non-pharmaceutical health services, such as hospitals and nursing homes. This Research Paper has reviewed some of these studies, and also presented some new evidence about the impact of cancer drug innovation on hospitalization of cancer patients in Canada.

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“If no new cancer drugs had been registered during 1980-1997, the number of cancer patient hospital days in 2012 would have been almost twice as high as it actually was.”

Cancer sites with larger growth in the number of drugs ever registered between 1980 and 1997 had larger declines in the number of hospital days between 1995 and 2012. The two cancer sites (breast and prostate) with the largest increases in the lagged number of drugs had the largest declines in hospital days, and the cancer site (colorectal) with the smallest increase in the lagged number of drugs had the smallest decline in hospital days. The estimates implied that if no new cancer drugs had been registered during 1980-1997, the number of cancer patient hospital days in 2012 would have been almost twice as high as it actually was: There would have been 1.72 million additional cancer patient hospital days in 2012. The reduction in 2012 hospital expenditure attributable to cancer drugs registered during 1980-1997 was likely to have been much larger than expenditure on those drugs in 2012.

Several studies were also reviewed that indicate that, in order to sustain a robust rate of pharmaceutical innovation, financial incentives are required.
APPENDIX

Figure A-1

Effects of new cancer drugs on the number of hospital days

Note: This figure is the same as Figure 2-5 except that it does not control for the % increase in the number of new cancer cases diagnosed. Bubble size is proportional to mean number of hospital days during 1995-2012.
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