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The Impact of Public and Private Research on Premature Cancer Mortality and Hospitalization in the United States, 1999-2013

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Abstract
This article provides evidence about the impact that public and private research had on premature mortality and hospitalization due to cancer in the United States during the period 1999-2013. We estimate difference-in-differences models based on longitudinal, cancer-site-level data to determine whether the cancer sites about which more research-supported articles were published had larger subsequent reductions in premature mortality and hospitalization during the period 1999 to 2013, controlling for the change in the number of people diagnosed. Premature (before age 75 years) mortality is inversely related to the number of research-supported articles that had been published 9 to 15 years earlier, controlling for incidence and non-research publications. The number of hospital discharges attributed to cancer is also significantly inversely related to the number of research-supported articles previously published. Public and private research reduced the number of years of potential life lost before age 75 years due to cancer in 2013 by 566,000.

***JEL Classifications*:** I1, I18

Keywords
mortality, hospitalization, public research, private research, health care

Introduction

In a previous study, Lichtenberg (2013) used PubMed[1] data on the number of publications about different types of cancer (breast, colon, lung, etc.) to provide evidence about the impact of biomedical research on U.S. cancer mortality rates.[2] Estimates from that study indicated that mortality rates (a) are unrelated to the (current or lagged) stock of publications that had not received research funding, (b) are only weakly inversely related to the contemporaneous stock of published articles that received research funding, and (c) are strongly inversely related to the stock of articles that had received research funding and been published 5 to 10 years earlier.

In this article, we will extend and update the analysis performed in Lichtenberg (2013) in a number of important respects:

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- The sole outcome measure analyzed in the previous study was the age-adjusted mortality rate. In this article, we will analyze a different type of mortality measure: years of potential life lost (YPLL) before three ages (75, 65, and 55 years). Brustugun, Møller, and Helland (2014, p. 1014) argued that "number of years of life lost (YLL) may be a more appropriate indicator of [the] impact [of cancer] on society" than the number of deaths, and Burnet, Jefferies, Benson, Hunt, and Treasure (2005) argue that "years of life lost (YLL) from cancer is an important measure of population burden—and should be considered when allocating research funds" (p. 241). Estimates of YPLL models (but not of age-adjusted mortality rate models) enable us to calculate the number of life-years gained from biomedical research.
- In addition to analyzing the impact of biomedical research on premature cancer mortality, we will analyze its effect on hospitalization (the number of inpatient hospital discharges and days of care) due to cancer. Hospital care was the largest single component of U.S. medical expenditure in 2014, accounting for 32% of total expenditure (Centers for Medicare & Medicaid Services, Office of the Actuary, National Health Statistics Group, 2017).
- The previous study controlled for changes in incidence by including just the contemporaneous age-adjusted incidence rate (in year t) in the age-adjusted mortality model. In this article, we will control for the average annual number of patients diagnosed in years $t - 9$ to t in the premature mortality and hospitalization models.
- In the previous study, all publications in which a specific type of cancer was a topic were included. In this article, only publications in which a specific type of cancer was one of the *main topics* are included.[3]
- In the previous study, the maximum allowed lag from publication to mortality was 10 years. In this article, we allow for lags of up to 24 years.
- The functional form specified in the previous study was log-log. In this article, we will estimate semilogarithmic models. Comparison of the marginal effects of research-based and non-research-based publications is more straightforward in the semi-logarithmic model.
- In the previous study, the sample period was 1995-2009. This article will analyze a more recent period: 1999-2013.

In the next "Biomedical Research Expenditure, Scientific Knowledge, and Disease Burden" section of this article, we sketch a framework for conceptualizing the relationships between biomedical research expenditure, scientific knowledge, and disease burden (e.g., mortality). In the "Econometric Model of Premature Mortality and Hospitalization" section, we describe the econometric model of premature mortality and hospitalization that we will estimate. In the "Data Sources and Descriptive Statistics" section, we describe the data sources we rely upon to construct the dataset used to estimate the model and present descriptive statistics; all of the data are publicly available. Estimates of the models are presented in the "Empirical Results" section. Implications of the estimates are discussed in the "Discussion" section. "Summary and Conclusion" section contains a summary and conclusions.

Biomedical Research Expenditure, Scientific Knowledge, and Disease Burden

We will perform an empirical analysis of the relationship across cancer sites between changes in the number of publications and changes in disease burden (mortality and hospitalization). As shown in Figure 1, we hypothesize that the number of publications (and other indicators of the "stock of knowledge") depends on the amount of research expenditure, which in turn is influenced by both the supply of and demand for innovations.

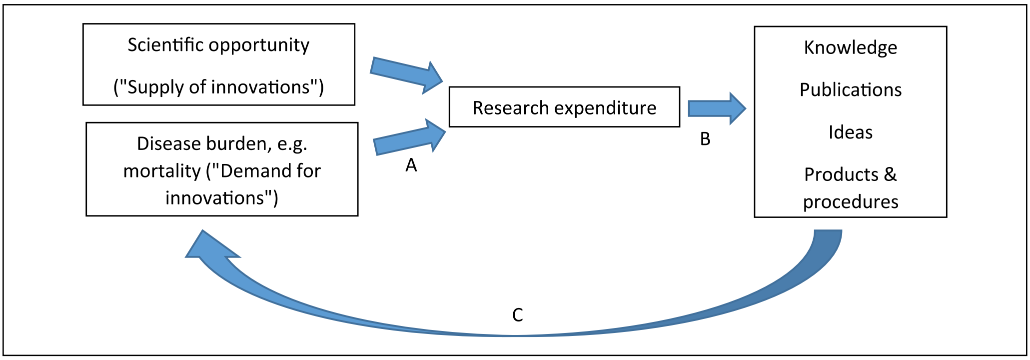

Figure 1. Determinants and consequences of biomedical research expenditure.

Regarding the left side of Figure 1, Lichtenberg (2001) developed a simple theoretical model of the allocation of the applied component of public biomedical research expenditure, which indicated that the amount of expenditure should depend upon research productivity (or "scientific opportunity") as well as on public health need, that is, the societal and economic burden of the disease/condition. Some of these concepts can be measured better than others—or not at all. Data on disease burden are readily available. We lack, at this point, useful disease-specific indicators of scientific opportunity (i.e., of the *cost* of achieving research advances). The National Institutes of Health (NIH) publishes annual estimates for the period 2013-2018 of NIH funding for a limited number of various research, condition, and disease categories (NIH, 2017).[4] As shown in Panel A of Figure 2, there is a significant (*p* value = .029) positive correlation across 11 cancer sites between (the log of) the number of deaths in 2015 and (the log of) NIH research expenditure in 2015. A 10% increase in the number of deaths is associated with a 5.2% increase in NIH research expenditure.

Regarding the right side of Figure 1, Griliches (1979) augmented the standard production function (which included just labor and physical capital as factors of production) to include "knowledge capital," which is accumulated by investment in research and development. This knowledge capital model has remained a cornerstone of the productivity literature, and has been applied in hundreds of empirical studies on firm-level productivity and also extended to macroeconomic growth models (see Griliches (1995) for a comprehensive survey).[5] There are a number of potential indicators of the size of the knowledge capital stock, including the number of patents and the number of publications. Panel B of Figure 2 shows that there is a significant (*p* value = .007) positive correlation across 11 cancer sites between (the log of) NIH research expenditure in 2015 and (the log of) the number of government-supported publications in 2016. A 10% increase in NIH research expenditure is associated with a 7.8% increase in the number of government-supported publications. Panel C of Figure 2 shows that there is also a significant (*p* value = .025) positive correlation across 11 cancer sites between (the log of) the number of deaths in 2015 and (the log of) the number of government-supported publications in 2016. A 10% increase in the number of deaths is associated with a 4.7% increase in the number of government-supported publications.

At least some of the relationships depicted in Figure 1 are characterized by substantial lags. Lichtenberg (2013) showed that the median lag from NIH project start date to publication is at least 6 years. Evidence from numerous case studies indicates that it takes a long time for research evidence to reach clinical practice. As noted by Morris, Wooding, and Grant (2011), Balas and Boren (2000), Grant, Green, and Mason (2003) and Wratschko (2009) all estimated a time lag of 17 years measuring different points of the process.

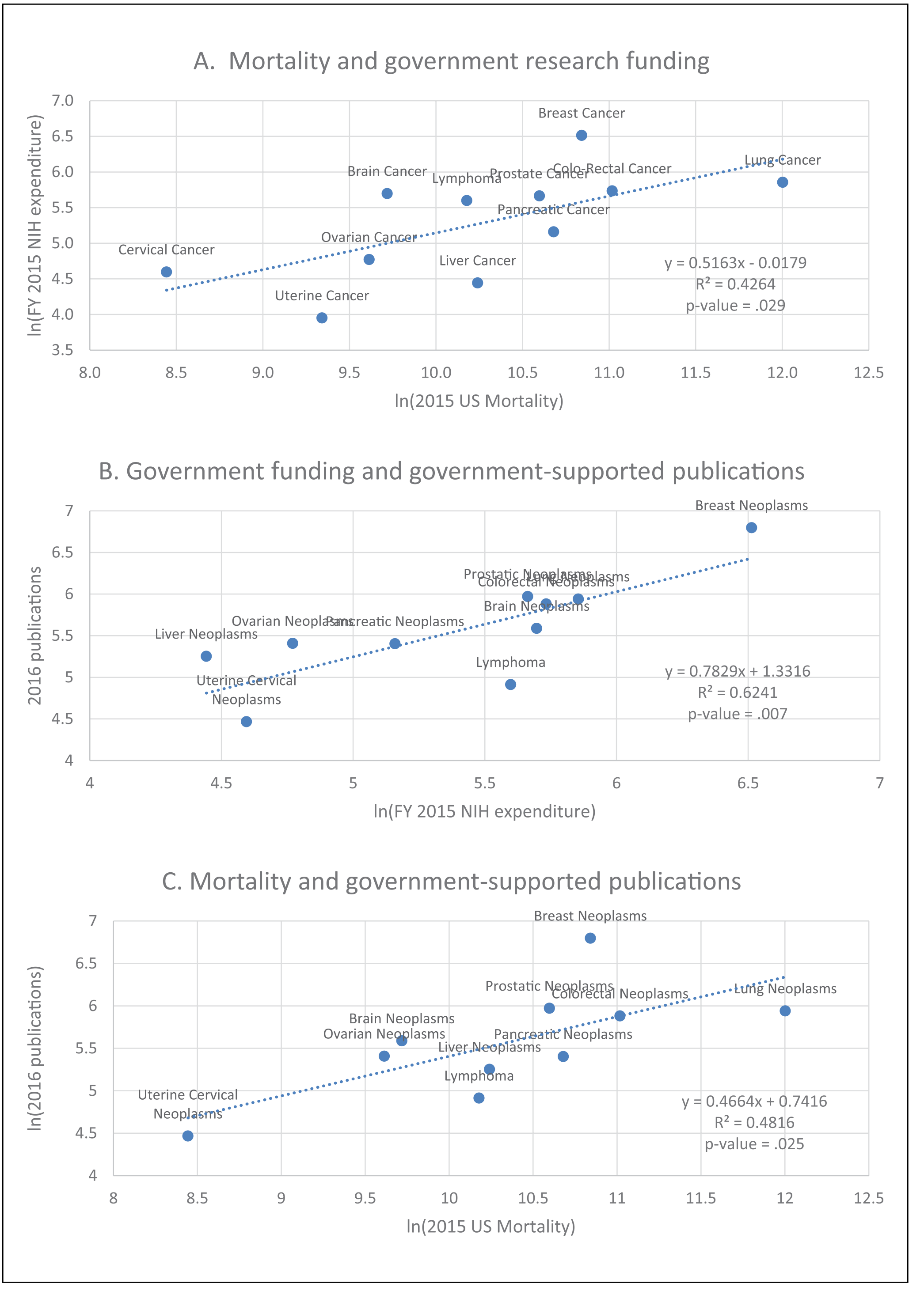

Figure 2. Correlations across cancer sites between mortality, government research funding, and publications.
Source. Author's calculations based on data from National Institutes of Health (2017).

Econometric Model of Premature Mortality and Hospitalization

To assess the impact of biomedical research on premature cancer mortality and hospitalization, I will estimate the following difference-in-differences model based on longitudinal, cancer-site-level data on about 30 cancer sites:

$$\begin{aligned}\ln\left(Y_{st}\right) &= \beta_{research} CUM\_RESEARCH\_PUBS_{s,t\text{-}k} + \beta_{other} CUM\_OTHER\_PUBS_{s,t\text{-}k} \\ &+ \gamma \ln\left(CASES\_10\_YEARS_{st}\right) + \alpha_s + \delta_t + \varepsilon_{st}\end{aligned} \quad (1)$$

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

$YPLL75_{st}$ = the number of YPLL before age 75 years from cancer at site *s* (*s* = 1, . . . , 30) in year *t* (*t* = 1999, . . . , 2013),

$YPLL65_{st}$ = the number of YPLL before age 65 years from cancer at site *s* in year *t*,

$YPLL55_{st}$ = the number of YPLL before age 55 years from cancer at site *s* in year *t*,

$DISCHARGES_{st}$ = the number of inpatient hospital discharges in year *t* for which the principal diagnosis was cancer at site *s*,

$HOSP\_DAYS_{st}$ = the number of days of inpatient hospital care in year *t* for which the principal diagnosis was cancer at site *s*,

and

$CUM\_RESEARCH\_PUBS_{s,\ t\text{-}k}$ = the number of PubMed articles published by the end of year t–k (*k* = 0, 3, 6, . . . , 24) that had cancer at site s as a "main topic" and that mentioned U.S. Government and/or non-U.S. Government research support,[6]

$CUM\_OTHER\_PUBS_{s,t\text{-}k}$ = the number of PubMed articles published by the end of year t–k that had cancer at site s as a "main topic" and that did *not* mention either U.S. Government or non-U.S. Government research support,

$CASES\_10\_YEARS_{st}$ = the average annual number of patients diagnosed with cancer at site *s* in Surveillance, Epidemiology, and End Results (SEER) 9 registries in years *t* – 9 to *t*,

α_s = a fixed effect for cancer at site *s*

δ_t = a fixed effect for year *t*

ε_{st} = a disturbance

The fixed year effects control for time-varying factors that influence cancer mortality and hospitalization in general. The models will be estimated by weighted least squares, weighting by $(1 / 15)\ \Sigma_t Y_{st}$. Disturbances will be clustered within cancer sites.

Data Sources and Descriptive Statistics

Premature Mortality Data

Data on the number of YPLL before ages 75, 65, and 55 years, by cancer site and year, were constructed from data contained in the World Health Organization (WHO) Mortality Database. Data for 1999 and 2013 are shown in Table 1. Figure 3 shows data on the number of YPLL before age 75 years in 1999 and 2013 for four cancer sites that had roughly similar numbers (between 141,000 and 196,000) of YPLL75 in 1999. The 1999-2013 change in YPLL75 varied considerably across these four cancer sites.

Hospitalization Data

Data on the number of inpatient hospital discharges and days of care, by cancer site and year, were constructed from data contained in the Healthcare Cost and Utilization Project Agency for Healthcare Research and Quality (2017). The number of days of care was computed as the number of discharges times average length of stay. Data for 1999 and 2013 are shown in Table 2.

Table 1. Number of Years of Potential Life Lost Before Ages 75, 65, and 55, by Cancer Site, 1999 and 2013.

	YPLL75		YPLL65		YPLL55	
Cancer site	1999	2013	1999	2013	1999	2013
Respiratory Tract Neoplasms	1,094,462	1,039,040	386,680	339,215	96,512	64,067
Breast Neoplasms	420,346	399,430	209,158	182,937	78,561	60,710
Colonic Neoplasms	275,970	289,895	110,322	120,808	35,542	37,203
Genital Neoplasms, Female	235,153	270,230	112,295	117,903	43,355	39,580
Nervous System Neoplasms	196,118	210,359	115,921	115,574	63,378	59,851
Pancreatic Neoplasms	188,112	250,760	72,090	86,768	20,067	19,098
Lymphoma, Non-Hodgkin	167,540	117,849	78,995	49,712	33,860	19,272
Urologic Neoplasms	141,558	167,829	56,698	60,934	18,363	16,404
Liver Neoplasms	108,497	218,426	50,019	82,649	19,102	18,739
Skin Neoplasms	101,720	104,905	52,747	48,173	22,495	17,940
Leukemia, Myeloid	100,328	92,716	57,083	46,844	31,693	24,131
Esophageal Neoplasms	97,523	117,188	38,363	42,120	10,420	9,260
Stomach Neoplasms	93,130	93,463	42,295	41,833	16,045	14,738
Genital Neoplasms, Male	83,820	90,340	23,922	26,948	8,025	7,533
Soft Tissue Neoplasms	69,921	76,536	39,751	42,221	21,601	22,571
Leukemia, Lymphoid	58,720	52,851	36,000	30,199	23,160	18,294
Rectal Neoplasms	47,173	61,888	20,528	27,445	7,123	8,755
Endocrine Gland Neoplasms	30,117	29,386	19,665	17,254	12,892	10,409
Bone Neoplasms	29,268	30,206	21,418	21,316	15,010	14,663
Hodgkin Disease	26,302	15,765	17,394	9,643	10,694	5,493
Tongue Neoplasms	18,308	22,568	8,690	9,505	3,113	2,830
Gallbladder Neoplasms	11,625	13,463	4,260	4,800	1,113	1,135
Nasopharyngeal Neoplasms	9,349	8,660	5,159	4,335	2,364	1,680
Intestinal Neoplasms	8,918	9,275	4,175	3,780	1,508	1,243
Oropharyngeal Neoplasms	5,488	8,918	2,303	3,488	593	755
Peritoneal Neoplasms	5,183	5,855	2,188	2,070	723	533
Salivary Gland Neoplasms	4,758	6,305	2,190	2,700	818	935
Eye Neoplasms	2,581	2,955	1,513	1,440	843	652
Hypopharyngeal Neoplasms	2,525	2,558	1,070	965	298	190
Lip Neoplasms	235	428	68	180	13	33
Total	3,634,748	3,810,047	1,592,960	1,543,759	599,284	498,697

Source. Author's calculations based on data contained in the WHO Mortality Database.
Note. YPLL = Years of Potential Life Lost; WHO = World Health Organization.

Research-Based and Other Publications

Data on CUM_RESEARCH_PUBS and CUM_OTHER_PUBS, by cancer site and year, were constructed by performing searches on the PubMed Advanced Search Builder. As shown in Appendix Table 1, this tool allows the user to download data on the number of results (publications) by year after performing a search. We used the diseases branch (D) of the MeSH Tree to determine appropriate search terms (cancer site definitions). A publication was included in CUM_RESEARCH_PUBS if it had any one of the following "Publication Types": Research Support, American Recovery and Reinvestment Act; Research Support, N.I.H., Extramural; Research Support, N.I.H., Intramural; Research Support, Non-U.S. Government; Research Support, U.S. Government; Research Support, U.S. Government, Non-Public Health Service;

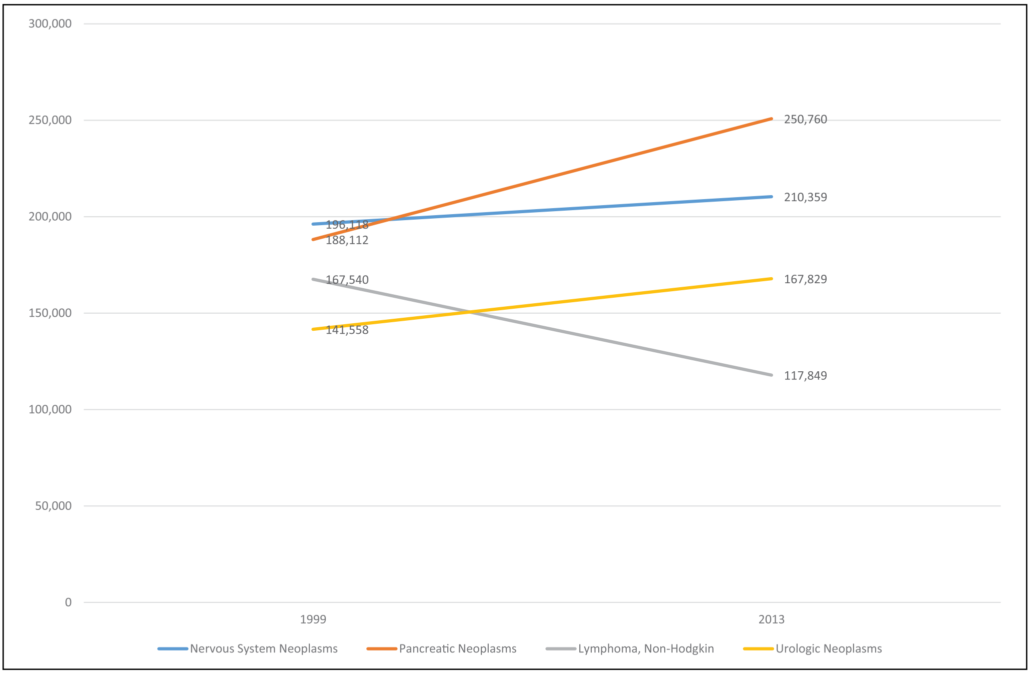

Figure 3. Number of years of potential life lost before age 75, four cancer sites, 1999 and 2013.

Research Support, U.S. Government, P.H.S. Data for 1999 and 2013 are shown in Table 3. Figure 4 shows data on the cumulative number of research-supported publications in 1989, 2001, and 2013 for four cancer sites that had similar numbers (between 4,261 and 4,678) of research-supported publications in 1989. The number of research-supported articles published during 1990-2013 varied considerably across these four cancer sites.

Incidence Data

Data on the number of people diagnosed in SEER 9 registries, by cancer site and year, were obtained from the National Cancer Institute's SEER*Stat Software. Data for 1999 and 2013 are shown in Table 4.

Empirical Results

Estimates of parameters of premature mortality models, Equation 1, where Y = YPLL75, YPLL65, or YPLL55, are shown in Table 5. Each row of the table represents a separate model, corresponding to a different dependent variable and assumed lag length (k) from publications to premature mortality. CUM_RESEARCH_PUBS and CUM_OTHER_PUBS are both measured in thousands.

In lines 1 to 9, the dependent variable is ln(YPLL75), and $k = 0, 3, 6, \ldots, 24$, respectively. As shown in lines 1 to 3, β_{research} is negative but not statistically significant when $k \le 6$. However, as shown in lines 4 to 6, β_{research} is negative and statistically significant (p value < .05) when $9 \le k \le 15$. This indicates that premature (before age 75 years) mortality is inversely related to the number of research-supported articles that had been published 9 to 15 years earlier, controlling for the number of other articles that had been published 9 to 15 years earlier, and for the average annual number of patients diagnosed in SEER 9 registries in the previous 10 years. The estimate in line

Table 2. Number of Inpatient Hospital Discharges and Days of Care, by Cancer Site, 1999 and 2013.

	Discharges		Hospital_days	
Cancer site	1999	2013	1999	2013
Respiratory Tract Neoplasms	148,391	130,900	1,200,377	860,233
Breast Neoplasms	116,916	67,425	340,917	176,961
Colonic Neoplasms	115,339	90,545	1,080,513	699,540
Genital Neoplasms, Male	101,978	71,485	389,868	170,760
Genital Neoplasms, Female	98,478	72,100	502,011	340,069
Urologic Neoplasms	78,107	78,630	475,148	424,923
Lymphoma, Non-Hodgkin	48,304	37,225	458,159	381,926
Rectal Neoplasms	46,428	38,890	416,847	295,085
Nervous System Neoplasms	35,464	35,295	257,927	236,890
Pancreatic Neoplasms	30,799	34,925	288,040	266,005
Stomach Neoplasms	25,018	22,355	270,778	202,975
Endocrine Gland Neoplasms	20,995	19,375	50,085	46,350
Liver Neoplasms	14,538	21,920	108,524	141,860
Bone Neoplasms	14,259	14,355	97,068	101,705
Esophageal Neoplasms	12,753	11,900	128,366	103,693
Skin Neoplasms	10,627	8,715	50,413	40,947
Hodgkin Disease	5,534	3,920	51,733	44,140
Total	925,923	761,973	6,168,774	4,536,074

Source. Author's calculations based on data extracted from the Healthcare Cost and Utilization Project (Agency for Healthcare Research and Quality, 2017).

5 implies that 1000 additional research-supported publications is associated with a 1.3% YPLL75 reduction 12 years later.

Due to high multicollinearity between long-run increases in U.S. Government- and non-U.S. Government-supported publications, it is not feasible to obtain reliable estimates of the effects of each type of publication. The correlation across cancer sites between long-run (1999-2013) increases in the cumulative number of U.S. Government-supported and non-U.S. Government-supported publications is extremely high: .975.[7] When Equation 1 is estimated including separate measures of U.S. Government-supported and non-U.S. Government-supported publications with a 12-year lag ($CUM\_GOV\_RESEARCH\_PUBS_{s,\ t-12}$ and $CUM\_NON\text{-}GOV\_RESEARCH\_PUBS_{s,t-12}$, respectively), the estimates are as follows:

Regressor	Estimate	*SE*	*Z*	Pr >|*Z*|
$CUM\_GOV\_RESEARCH\_PUBS_{s,t-12}$	0.0273	0.0621	0.44	0.6595
$CUM\_NON\text{-}GOV\_RESEARCH\_PUBS_{s,t-12}$	−0.032	0.0371	−0.86	0.3876
$CUM\_OTHER\_PUBS_{s,t-12}$	0.0021	0.0046	0.45	0.6545
$\ln(CASES\_10\_YEARS_{st})$	0.5751	0.2574	2.23	0.0254

Neither the government nor the nongovernment publications coefficient is significant. The standard errors on these coefficients are 6 to 10 times as high as the standard error in line 5 of Table 5. Moreover, the difference between the two coefficients is far from statistically significant (p value = .548). These are typical consequences of multicollinearity; see https://en.wikipedia.org/wiki/Multicollinearity#Consequences_of_multicollinearity

Table 3. Cumulative Number of Research-Supported and Other Publications, by Cancer Site, 1999 and 2013.

	Cum_research_pubs			Cum_other_pubs		
	1989	2001	2013	1989	2001	2013
Endocrine Gland Neoplasms	7,238	19,698	45,683	54,197	89,459	141,778
Breast Neoplasms	5,795	22,455	67,139	33,553	63,902	112,570
Respiratory Tract Neoplasms	5,387	15,455	41,012	55,341	85,914	132,881
Liver Neoplasms	5,122	12,176	29,037	21,229	37,338	63,401
Leukemia, Myeloid	4,678	12,588	23,522	14,165	23,965	36,041
Genital Neoplasms, Female	4,507	14,290	36,426	52,815	80,413	118,927
Nervous System Neoplasms	4,353	12,740	29,135	41,802	68,471	107,005
Intestinal Neoplasms	4,261	15,293	42,889	30,939	54,612	95,987
Leukemia, Lymphoid	3,731	9,393	18,250	12,040	19,668	28,795
Colonic Neoplasms	3,262	7,928	16,254	13,909	20,536	29,189
Urologic Neoplasms	3,074	8,436	18,381	27,805	45,286	70,826
Skin Neoplasms	2,878	7,988	17,223	24,499	40,822	67,263
Genital Neoplasms, Male	2,728	10,454	33,937	19,156	36,880	68,072
Lymphoma, Non-Hodgkin	2,060	8,609	18,266	14,368	28,159	47,439
Bone Neoplasms	1,531	4,040	9,561	33,497	50,164	74,643
Pancreatic Neoplasms	1,522	4,490	12,568	9,507	16,851	30,963
Rectal Neoplasms	1,519	2,651	4,935	12,391	17,943	26,781
Eye Neoplasms	1,425	3,173	5,807	11,160	15,685	22,926
Hodgkin Disease	1,290	2,814	4,373	12,427	15,957	19,267
Stomach Neoplasms	1,173	4,324	13,624	21,951	32,729	48,321
Esophageal Neoplasms	421	1,966	6,755	8,855	15,226	24,896
Soft Tissue Neoplasms	418	1,310	2,377	3,182	7,977	15,123
Nasopharyngeal Neoplasms	339	1,056	3,273	3,171	4,736	7,166
Salivary Gland Neoplasms	279	741	1,499	4,703	7,286	10,711
Peritoneal Neoplasms	136	444	1,360	2,435	4,504	8,277
Tongue Neoplasms	111	302	963	2,415	3,477	5,052
Gallbladder Neoplasms	64	239	647	2,024	3,380	5,080
Oropharyngeal Neoplasms	55	271	851	1,121	1,975	3,667
Total	71,346	207,325	507,760	546,646	895,316	1,425,060

Source. Author's calculations based on data extracted from PubMed Advanced Search Builder.

The point estimates of $\beta_{research}$ when $18 \leq k \leq 24$ are similar to the point estimates when $9 \leq k \leq 15$, but the standard errors are much larger when $18 \leq k \leq 24$, so those estimates are not statistically significant.[8] The estimates of $\beta_{research}$ for $0 \leq k \leq 24$ from ln(YPLL75) models are shown (on an inverted scale) in Figure 5.

None of the estimates of β_{other} in lines 1 to 9 are statistically significant: Premature (before age 75 years) mortality is unrelated to the number of publications that did *not* mention either U.S. Government or non-U.S. Government research support. All of the estimates of γ in lines 1 to 9 are statistically significant: YPLL75 is significantly positively related to the number of people diagnosed in the previous 10 years.

In lines 10 to 18 of Table 5, the dependent variable is ln(YPLL65). These estimates are quite similar to the estimates in lines 1 to 9. PYLL65 is inversely related to the number of research-supported articles that had been published 12 to 15 years earlier, and is unrelated to the number of other articles. It is also unrelated to the number of people diagnosed in the previous 10 years, presumably because about half of cancer patients are diagnosed after the age of 65 years.[9]

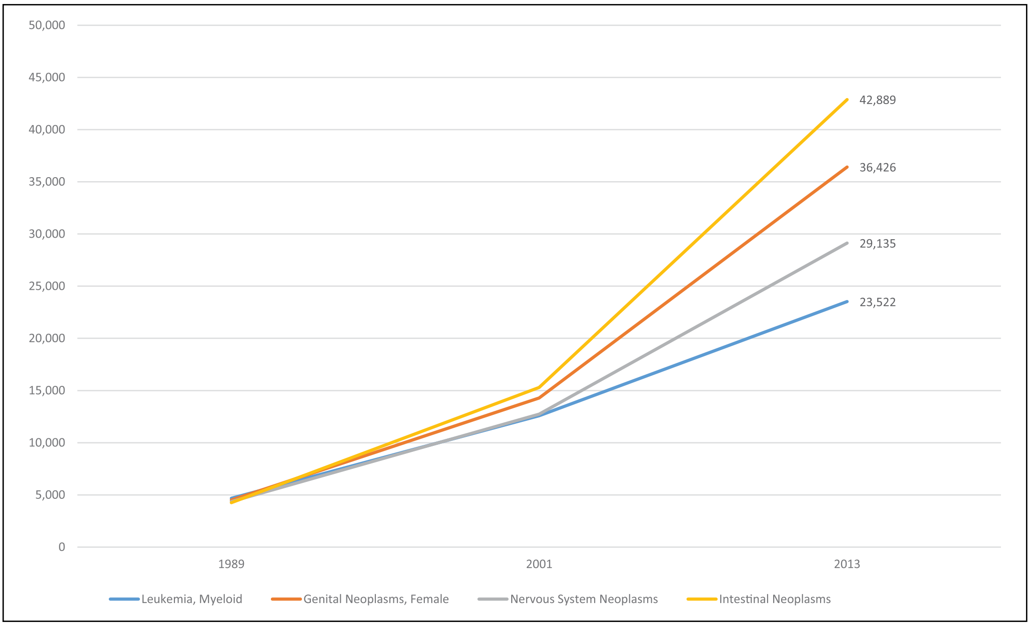

Figure 4. Cumulative number of research-supported publications, four cancer sites, 1989-2013.
Source. Author's calculations based on data extracted from PubMed Advanced Search Builder.

In lines 19 to 27 of Table 5, the dependent variable is ln(YPLL55). The estimates of $\beta_{research}$ for $0 \leq k \leq 24$ from ln(YPLL55) models are shown in Figure 6. The point estimates of $\beta_{research}$ are strictly increasing with respect to lag length. The estimates for $0 \leq k \leq 15$ are not statistically significant, but the estimates for $18 \leq k \leq 24$ are statistically significant. This indicates that the number of YPLL before age 55 years is inversely related to the number of research-supported articles that had been published 18 to 24 years earlier, and that 1,000 additional research-supported publications is associated with a 4.2% YPLL55 reduction 24 years later. Evidently, the lag from research-supported publications to premature mortality reduction is considerably longer for YPLL55 than it is for YPLL75.

Estimates of parameters of hospitalization models, Equation 1, where Y = DISCHARGES or HOSP_DAYS, are shown in Table 6. In lines 1 to 9, the dependent variable is ln(DISCHARGES). The estimates of $\beta_{research}$ for $0 \leq k \leq 24$ from ln(DISCHARGES) models are shown in Figure 7. For all values of k, the estimate is negative and statistically significant. Once again, the point estimates of $\beta_{research}$ are strictly increasing with respect to lag length. The estimate of $\beta_{research}$ in line 9 of Table 6 indicates that 1,000 additional research-supported publications is associated with a 10% DISCHARGES reduction 24 years later. The estimates in lines 1 to 9 indicate that the number of hospital discharges is significantly positively related to the number of people diagnosed in the previous 10 years, as expected. The estimates also indicate that the number of hospital discharges is also significantly positively related to the number of other (non-research-supported) publications, which is somewhat surprising. However, the magnitudes of the β_{other} coefficients are much smaller than the magnitudes of the $\beta_{research}$ coefficients: The estimate of β_{other} in line 9 indicates that 1,000 additional non-research-supported publications is associated with only a 1.6% DISCHARGES increase 24 years later.

In lines 10 to 18, the dependent variable is ln(HOSP_DAYS). Estimates of the parameters of HOSP_DAYS models are quite similar to estimates of the parameters of DISCHARGES models.

Table 4. Average Annual Number of Patients Diagnosed in SEER Nine Registries in Previous 10 Years, by Cancer Site, 1999 and 2013.

Cancer site	1999	2013
Genital Neoplasms, Male	19,166	21,336
Breast Neoplasms	17,183	20,725
Respiratory Tract Neoplasms	16,902	18,410
Colonic Neoplasms	9,462	9,122
Urologic Neoplasms	7,652	10,917
Genital Neoplasms, Female	6,817	8,053
Lymphoma, Non-Hodgkin	4,553	6,057
Skin Neoplasms	4,252	7,349
Rectal Neoplasms	3,566	3,684
Pancreatic Neoplasms	2,595	3,719
Stomach Neoplasms	2,039	2,145
Endocrine Gland Neoplasms	1,711	4,094
Nervous System Neoplasms	1,632	1,937
Leukemia, Lymphoid	1,496	2,115
Leukemia, Myeloid	1,349	1,774
Liver Neoplasms	1,116	2,399
Esophageal Neoplasms	1,077	1,376
Hodgkin Disease	733	830
Soft Tissue Neoplasms	658	974
Tongue Neoplasms	591	987
Intestinal Neoplasms	389	671
Lip Neoplasms	302	206
Gallbladder Neoplasms	286	332
Salivary Gland Neoplasms	284	389
Hypopharyngeal Neoplasms	238	192
Bone Neoplasms	226	272
Eye Neoplasms	202	250
Nasopharyngeal Neoplasms	172	198
Peritoneal Neoplasms	88	187
Oropharyngeal Neoplasms	72	119

Source. Author's calculations based on data extracted from the National Cancer Institute's SEER*Stat Software.
Note. SEER = Surveillance, Epidemiology, and End Results.

Discussion

The estimates of Equation 1 indicate that cancer sites about which more research-supported articles were published since the 1970s had larger reductions in premature mortality and hospitalization during the period 1999- 2013, controlling for the change in the number of people diagnosed. Cancer sites for which more non-research-supported articles were published did not have larger reductions in premature mortality or hospitalization.

We can use the estimates to calculate the reduction in premature mortality in 2013 attributable to previous publication of research-supported articles. Lines 1 to 9 of Table 5 indicate that $YPLL75_{st}$ is most strongly inversely correlated with $CUM\_RESEARCH\_PUBS_{s,\,t-12}$. The weighted, by (1 / 15) Σ_t $YPLL75_{st}$, mean 1999-2013 increase in $CUM\_RESEARCH\_PUBS_{s,\,t-12}$ was 9.01 (= 12.13 − 3.11). The estimate of $\beta_{research}$ in the YPLL75 model when $k = 12$ is −0.013, so we estimate that, if no research-supported articles had been published during the

Table 5. Estimates of Premature Mortality Model Parameters From Equation 1:

$$\ln(Y_{st}) = \beta_{research}\mathrm{CUM\_RESEARCH\_PUBS}_{s,t\text{-}k} + \beta_{other}\mathrm{CUM\_OTHER\_PUBS}_{s,t\text{-}k} + \gamma \ln(\mathrm{CASES\_10\_YEARS}_{st}) + \alpha_s + \delta_t + \varepsilon_{st}.$$

		$\beta_{research}$				β_{other}				γ			
Line	lag	Estimate	*SE*	*Z*	Pr >|*Z*|	Estimate	*SE*	*Z*	Pr >|*Z*|	Estimate	*SE*	*Z*	Pr >|*Z*|
Y = YPLL75													
1	0	−0.001	0.002	−0.73	0.4681	−0.002	0.002	−0.85	0.3938	**0.55**	0.26	2.10	**0.0357**
2	3	−0.002	0.002	−0.99	0.3225	−0.002	0.002	−0.86	0.3914	**0.54**	0.26	2.10	**0.0361**
3	6	−0.004	0.003	−1.51	0.1307	−0.002	0.002	−0.64	0.5199	**0.54**	0.26	2.08	**0.0374**
4	9	**−0.008**	**0.004**	**−2.04**	**0.0411**	−0.001	0.003	−0.20	0.8408	**0.54**	0.26	2.06	**0.0391**
5	12	**−0.013**	**0.006**	**−2.23**	**0.0258**	0.001	0.003	0.20	0.8442	**0.54**	0.27	2.04	**0.0412**
6	15	**−0.018**	**0.008**	**−2.17**	**0.0300**	0.001	0.004	0.32	0.7484	**0.55**	0.27	2.03	**0.0428**
7	18	−0.019	0.014	−1.40	0.1614	0.001	0.005	0.20	0.8399	**0.56**	0.28	2.03	**0.0423**
8	21	−0.015	0.022	−0.68	0.4990	0.000	0.006	−0.03	0.9732	**0.56**	0.27	2.09	**0.0371**
9	24	−0.014	0.031	−0.45	0.6559	−0.001	0.007	−0.13	0.8971	**0.57**	0.27	2.13	**0.0330**
Y = YPLL65													
10	0	−0.002	0.002	−0.84	0.4012	−0.002	0.002	−0.92	0.3580	0.32	0.26	1.20	0.2318
11	3	−0.003	0.003	−0.99	0.3229	−0.002	0.003	−0.91	0.3610	0.31	0.26	1.19	0.2329
12	6	−0.004	0.003	−1.34	0.1787	−0.002	0.003	−0.72	0.4734	0.31	0.26	1.18	0.2384
13	9	−0.009	0.005	−1.80	0.0726	−0.001	0.004	−0.34	0.7332	0.31	0.26	1.16	0.2449
14	12	**−0.015**	**0.007**	**−2.12**	**0.0340**	0.000	0.004	0.01	0.9909	0.31	0.27	1.15	0.2483
15	15	**−0.020**	**0.009**	**−2.24**	**0.0249**	0.001	0.005	0.14	0.8852	0.32	0.28	1.16	0.2452
16	18	−0.023	0.014	−1.63	0.1023	0.001	0.006	0.10	0.9166	0.33	0.28	1.18	0.2385
17	21	−0.020	0.022	−0.92	0.3593	0.000	0.007	−0.04	0.9643	0.34	0.28	1.21	0.2278
18	24	−0.020	0.031	−0.64	0.5208	−0.001	0.008	−0.14	0.8876	0.34	0.28	1.22	0.2209
Y = YPLL55													
19	0	−0.003	0.004	−0.81	0.4187	−0.002	0.004	−0.45	0.6493	0.03	0.16	0.19	0.8496
20	3	−0.004	0.006	−0.64	0.5253	−0.003	0.005	−0.52	0.6045	0.03	0.16	0.21	0.8371
21	6	−0.005	0.008	−0.67	0.5040	−0.003	0.006	−0.45	0.6496	0.03	0.16	0.20	0.8415
22	9	−0.009	0.010	−0.94	0.3498	−0.002	0.006	−0.29	0.7720	0.03	0.16	0.19	0.8467
23	12	−0.015	0.011	−1.41	0.1577	−0.001	0.006	−0.08	0.9329	0.04	0.16	0.22	0.8279
24	15	−0.022	0.011	−1.93	0.0531	0.000	0.006	0.00	0.9972	0.05	0.16	0.29	0.7701
25	18	**−0.028**	**0.012**	**−2.29**	**0.0223**	0.001	0.007	0.09	0.9297	0.07	0.17	0.38	0.7076
26	21	**−0.033**	**0.016**	**−2.13**	**0.0332**	0.001	0.007	0.16	0.8697	0.08	0.18	0.43	0.6656
27	24	**−0.042**	**0.021**	**−2.04**	**0.0413**	0.002	0.008	0.23	0.8164	0.09	0.19	0.46	0.6452

Note. Estimates in bold are statistically significant (*p* value < .05). The models were estimated by weighted least squares, weighting by $(1 / 15)\ \Sigma_t Y_{st}$. Disturbances were clustered within cancer sites. YPLL = Years of Potential Life Lost.

period 1987-2001, the number of YPLL before age 75 years due to cancer in 2013 would have been 12.8%, = exp(0.013 × 9.01) – 1, higher. As previous research reduced YPLL75 by 12.8% over a 14-year period, it reduced premature mortality at an average annual rate of 0.9% (= 12.8% / 14). According to the Centers for Disease Control (2017), about 4,407,000 years of potential life were lost before age 75 years due to cancer in 2013, so we estimate that, if no research-supported articles had been published during the period 1987- 2001, the number of YPPL before age 75 years due to cancer in 2013 would have been 566,000 (= 12.8% × 4,407,000) higher.

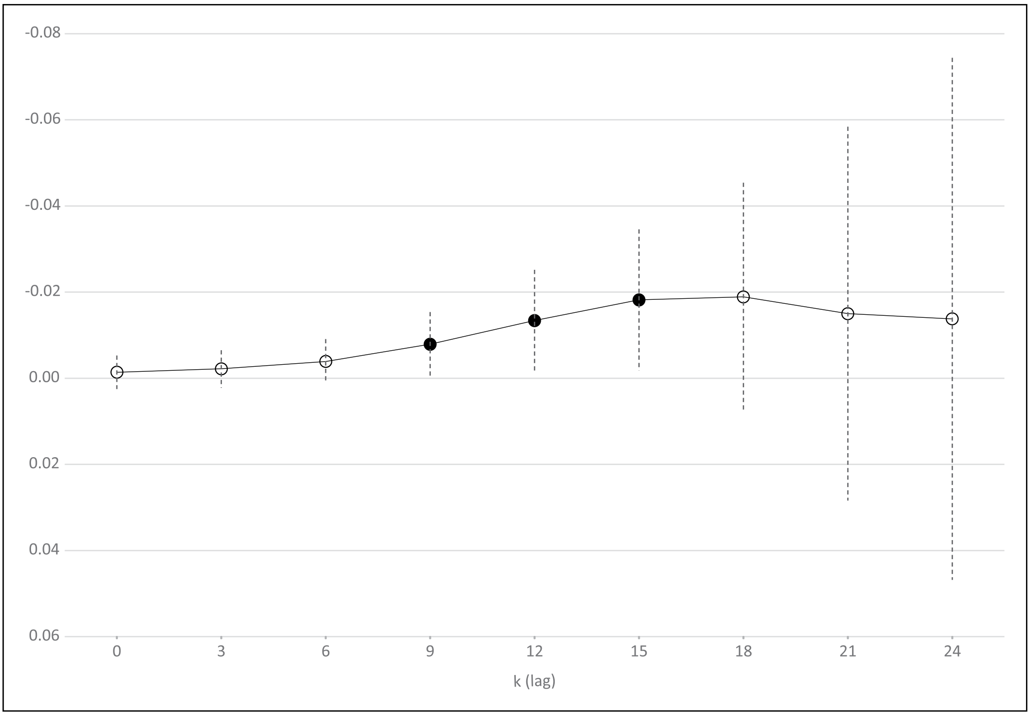

Figure 5. Estimates of $\beta_{research}$ from Equation 1 where dependent variable is ln(YPLL75).
Note. Scale is inverted. Vertical lines represent 95% confidence intervals. Estimates represented by solid circles are statistically significant (*p* value < .05). YPLL = Years of Potential Life Lost.

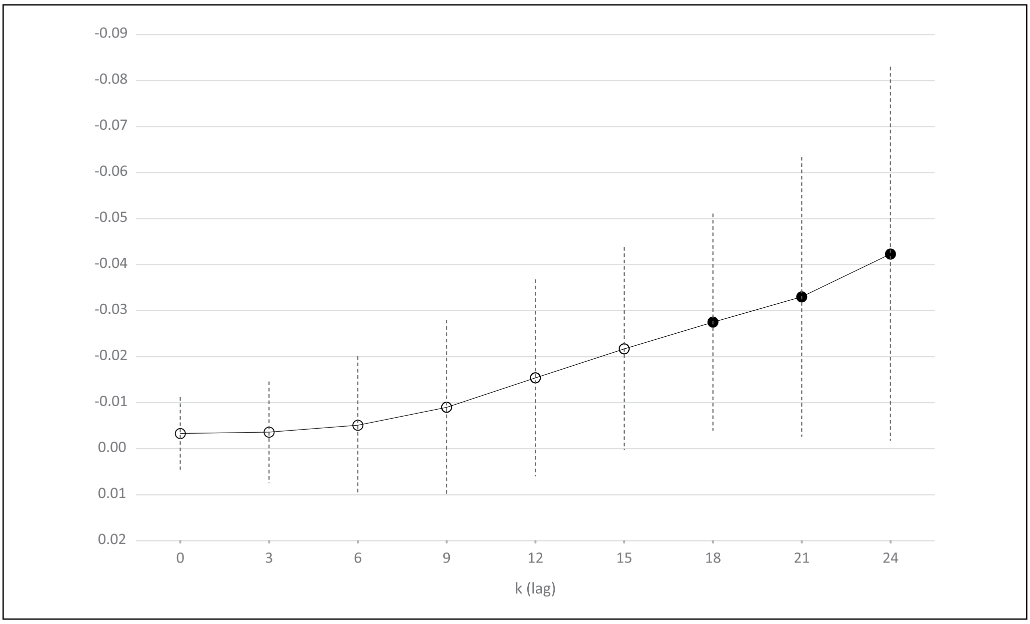

Figure 6. Estimates of $\beta_{research}$ from Equation 1 where dependent variable is ln(YPLL55).
Note. Scale is inverted. Vertical lines represent 95% confidence intervals. Estimates represented by solid circles are statistically significant (*p* value < .05). YPLL = Years of Potential Life Lost.

Table 6. Estimates of Hospitalization Model Parameters From Equation 1:

$$\ln(Y_{st}) = \beta_{research} CUM\_RESEARCH\_PUBS_{s,t-k} + \beta_{other} CUM\_OTHER\_PUBS_{s,t-k} + \gamma \ln(CASES\_10\_YEARS_{st}) + \alpha_s + \delta_t + \varepsilon_{st}.$$

		$\beta_{research}$				β_{other}				γ			
Line	lag	Estimate	*SE*	*Z*	Pr >|*Z*|	Estimate	*SE*	*Z*	Pr >|*Z*|	Estimate	*SE*	*Z*	Pr >|*Z*|
Y = DISCHARGES													
1	0	**−0.014**	0.003	−5.55	**<.0001**	0.006	0.003	2.22	**0.0265**	0.40	0.19	2.11	**0.0348**
2	3	**−0.019**	0.003	−5.80	**<.0001**	0.006	0.003	2.30	**0.0215**	0.42	0.18	2.31	**0.0208**
3	6	**−0.025**	0.004	−6.91	**<.0001**	0.008	0.003	2.67	**0.0075**	0.43	0.17	2.46	**0.0139**
4	9	**−0.035**	0.005	−7.76	**<.0001**	**0.010**	0.003	3.19	**0.0014**	0.44	0.17	2.58	**0.0098**
5	12	**−0.046**	0.006	−7.85	**<.0001**	**0.012**	0.004	3.43	0.0006	0.47	0.17	2.77	**0.0055**
6	15	**−0.062**	0.007	−8.40	**<.0001**	**0.014**	0.004	3.54	0.0004	0.51	0.17	3.02	**0.0025**
7	18	**−0.077**	**0.015**	−5.26	**<.0001**	**0.016**	0.006	2.77	**0.0056**	0.54	0.18	3.03	**0.0024**
8	21	**−0.089**	**0.027**	−3.28	**0.0010**	**0.017**	0.008	2.05	**0.0399**	0.55	0.19	2.89	**0.0039**
9	24	−0.100	**0.037**	−2.71	**0.0068**	0.016	0.009	1.72	0.0857	0.55	0.19	2.89	**0.0039**
Y = HOSP_DAYS													
10	0	**−0.019**	0.007	−2.81	**0.0049**	0.009	0.003	2.53	**0.0113**	0.71	0.12	5.67	**<.0001**
11	3	**−0.025**	0.009	−2.84	**0.0044**	**0.010**	0.004	2.62	**0.0087**	0.71	0.11	6.23	**<.0001**
12	6	**−0.032**	**0.011**	−2.92	**0.0035**	**0.011**	0.004	2.71	**0.0067**	0.73	0.11	6.79	**<.0001**
13	9	**−0.038**	**0.012**	−3.17	**0.0015**	**0.012**	0.004	2.90	**0.0038**	0.76	0.11	7.19	**<.0001**
14	12	**−0.043**	**0.011**	−4.07	**<.0001**	**0.012**	0.003	3.37	0.0007	0.78	0.11	7.28	**<.0001**
15	15	**−0.050**	**0.010**	−5.08	**<.0001**	**0.012**	0.003	3.69	0.0002	0.80	0.11	7.07	**<.0001**
16	18	**−0.057**	**0.015**	−3.90	**<.0001**	**0.012**	0.004	3.04	**0.0023**	0.80	0.12	6.44	**<.0001**
17	21	**−0.066**	**0.022**	−3.07	**0.0022**	**0.013**	0.005	2.48	**0.0132**	0.80	0.14	5.81	**<.0001**
18	24	**−0.080**	**0.026**	−3.05	**0.0023**	**0.014**	0.006	2.34	**0.0195**	0.81	0.14	5.62	**<.0001**

Note. Estimates in bold are statistically significant (*p*. value < .05). The models were estimated by weighted least squares, weighting by (1 / 15) $\Sigma_t Y_{st}$. Disturbances were clustered within cancer sites.

We can also use the estimates to calculate the reduction in hospital discharges in 2013 attributable to previous publication of research-supported articles. Lines 1 to 9 of Table 6 indicate that $DISCHARGES_{st}$ is most strongly inversely correlated with $CUM\_RESEARCH\_PUBS_{s,\,t-15}$. The weighted, by (1 / 15) Σ_t $DISCHARGES_{st}$, mean 1999 to 2013 increase in $CUM\_RESEARCH\_PUBS_{s,\,t-15}$ was 7.31 (= 9.17 − 1.86). The estimate of $\beta_{research}$ in the DISCHARGES model when $k = 15$ is −0.062, so we estimate that, if no research-supported articles had been published during the period 1984- 1998, the number of hospital discharges due to cancer in 2013 would have been 57.0%, = exp(0.062 × 7.31) – 1, higher. As previous research reduced DISCHARGES by 57.0% over a 14-year period, it reduced hospital discharges at an average annual rate of 4.1% (= 57.0% / 14). According to HCUPnet (2017), there were 1,082,000 hospitalizations due to cancer in 2013, so we estimate that, if no research-supported articles had been published during the period 1984- 1998, the number of hospital discharges due to cancer in 2013 would have been 566,000 (= 57.0% × 1,082,000) higher.

Summary and Conclusion

A previous study used PubMed data on the number of publications about different types of cancer (breast, colon, lung, etc.) to provide evidence about the impact of biomedical research on U.S.

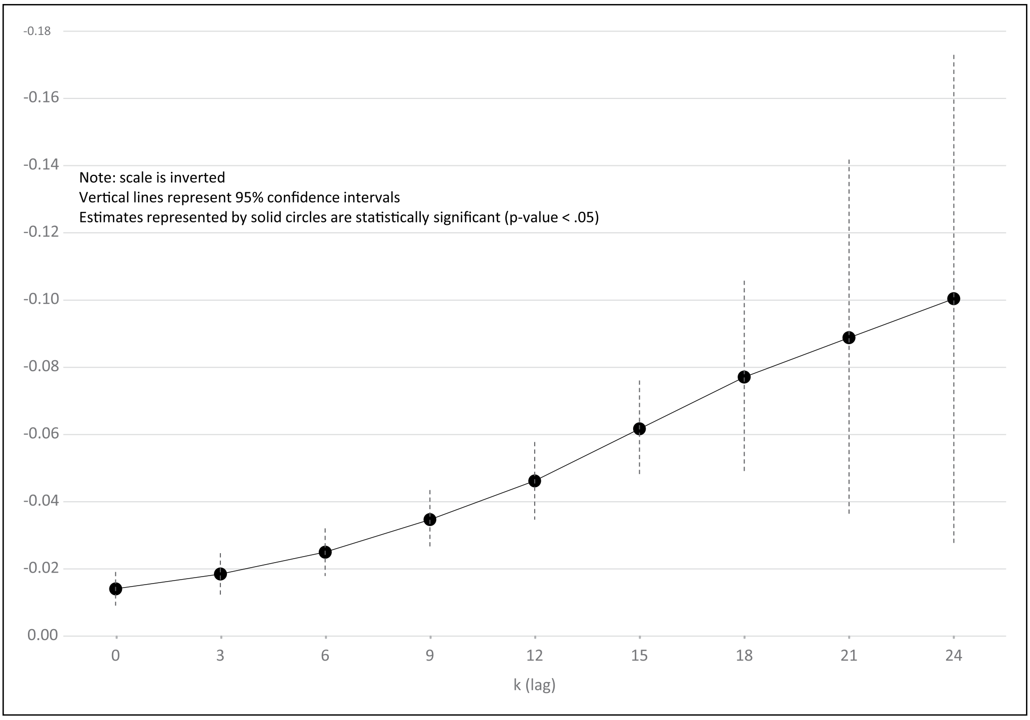

Figure 7. Estimates of $\beta_{research}$ from Equation 1 where dependent variable is ln(DISCHARGES).
Note. Scale is inverted. Vertical lines represent 95% confidence intervals. Estimates represented by solid circles are statistically significant (*p* value < .05).

cancer mortality rates. In this article, we extended and updated the analysis performed in the earlier study in several important respects: we analyzed a different type of mortality measure (YPLL before three ages [75, 65, and 55 years]), we analyzed the effect of research-supported publications on hospitalization as well as on mortality, we controlled for lagged as well as current cancer incidence, and we allowed for longer (24 years vs. 10 years) lags from publication to cancer outcomes.

To assess the impact of biomedical research on premature cancer mortality and hospitalization, we estimated difference-in-differences models based on longitudinal, cancer-site-level data on about 30 cancer sites. The estimates indicated that cancer sites about which more research-supported articles were published since the 1970s had larger reductions in premature mortality and hospitalization during the period 1999- 2013, controlling for the change in the number of people diagnosed. Cancer sites for which more non-research-supported articles were published did not have larger reductions in premature mortality or hospitalization.

Premature (before age 75 years) mortality is inversely related to the number of research-supported articles that had been published 9 to 15 years earlier, controlling for the number of other articles that had been published 9 to 15 years earlier and for the average annual number of patients diagnosed in SEER 9 registries in the previous 10 years. The estimates indicated that 1,000 additional research-supported publications is associated with a 1.3% YPLL75 reduction 12 years later. Estimates of models of YPLL65 were quite similar to estimates of models of YPLL75. YPLL65 is inversely related to the number of research-supported articles that had been published 12 to 15 years earlier, and is unrelated to the number of other articles.

The number of YPLL before age 55 years is inversely related to the number of research-supported articles that had been published 18 to 24 years earlier; 1,000 additional research-supported publications is associated with a 4.2% YPLL55 reduction 24 years later. Evidently, the lag from research-supported publications to premature mortality reduction is considerably longer for YPLL55 than it is for YPLL75.

The number of hospital discharges attributed to cancer is significantly inversely related to the number of research-supported articles at every lag length investigated (from 0 to 24 years), but the magnitude of the effect is strictly increasing with respect to lag length. The estimates indicated that 1,000 additional research-supported publications is associated with a 10% reduction in hospital discharges 24 years later.

The research support that contributed to articles published during 1987- 2001 reduced premature (before age 75 years) mortality at an average annual rate of 0.9% during the period 1999-2013, and it reduced the number of YPLL before age 75 years due to cancer in 2013 by 566,000. The research support that contributed to articles published during 1984- 1998 reduced hospital discharges at an average annual rate of 4.1% during the period 1999- 2013, and it reduced the number of hospital discharges due to cancer in 2013 by 566,000.

According to the Federation of American Societies for Experimental Biology (2018), between fiscal year (FY) 2003 and FY 2015, the NIH lost 22% of its capacity to fund research due to budget cuts, sequestration, and inflationary losses. That funding reduction is likely to reduce current and future rates of decline in cancer mortality and hospitalization. Congress has begun restoring the NIH Budget: In both FY 2016 and FY 2017, Congress raised the NIH budget by US$2 billion.

Our analysis is subject to several limitations. Due to high multicollinearity between long-run increases in U.S. Government- and non-U.S. Government-supported publications, it was not feasible to obtain reliable estimates of the effects of each type of publication. Also, mortality and hospitalization may be more strongly related to the number of publications, weighted by publication quality or number of citations, than they are to the unweighted number of publications.[10] Perhaps future studies can overcome these and other limitations.

Appendix

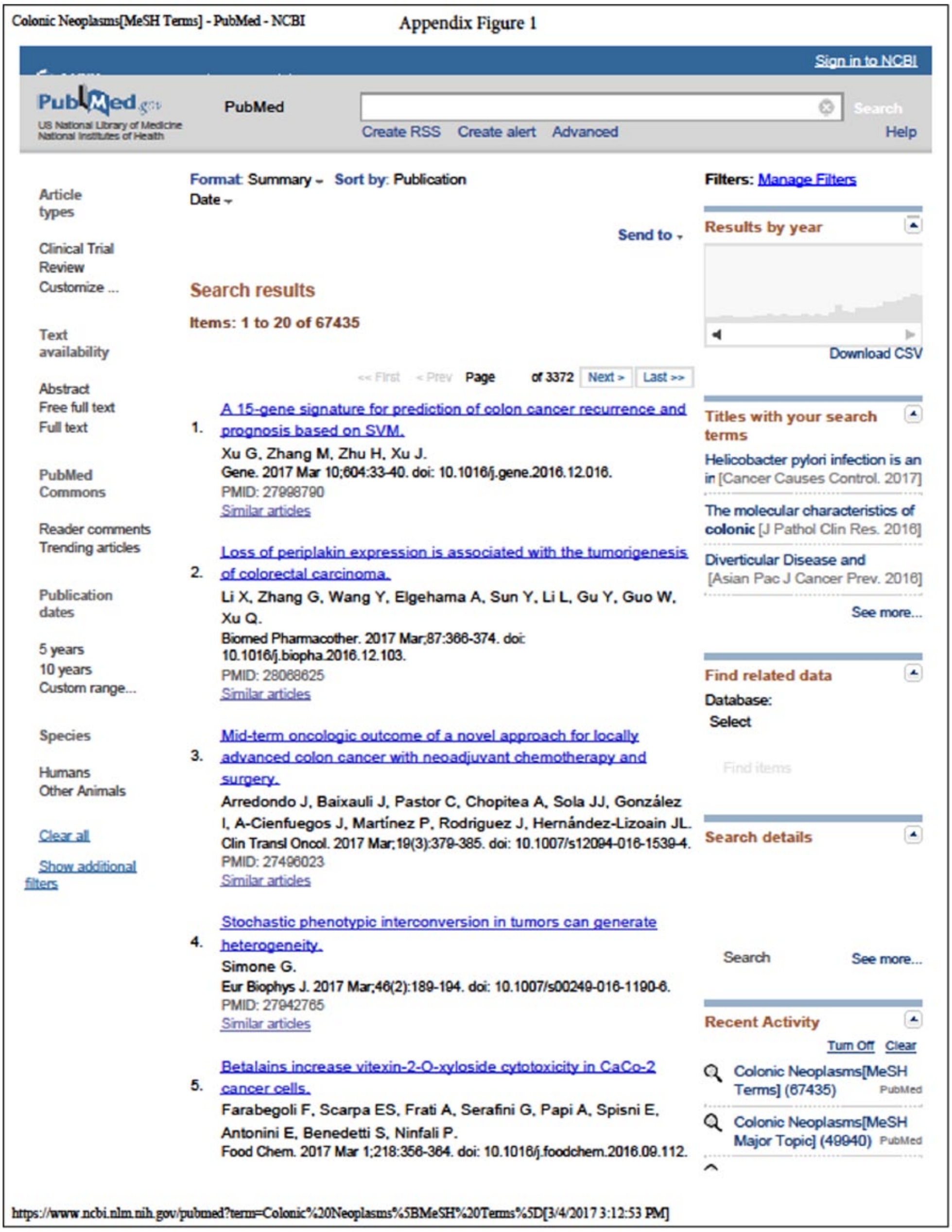

Figure A1. Colonic Neoplasms[MeSH Terms]—PubMed—NCBI.

Declaration of Conflicting Interests

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Notes

1. PubMed comprises more than 26 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 also provides access to additional relevant web sites and links to the other National Center for Biotechnology Information (NCBI) molecular biology resources. PubMed is a free resource that is developed and maintained by the NCBI, at the U.S. National Library of Medicine (NLM), located at the National Institutes of Health (NIH).
2. Previous research on the agricultural (Evenson & Kislev, 1973) and manufacturing (Adams, 1990) sectors of the economy had found that counts of publications are useful indicators of the stock of knowledge.
3. As of March 4, 2017, "breast neoplasms" was a topic in 247,546 publications, and was a "main topic" in 207,485 publications; "colonic neoplasms" was a topic in 67,435 publications, and was a "main topic" in 49,940 publications.
4. The NIH provides a number of caveats about these estimates, for example, "the NIH does not expressly budget by category." The availability of data on publications is much greater than the availability of data on research funding. Publications data are available for a much larger set of diseases (cancer sites) over a much longer period of time (40 years vs. 6 years). Also, data on both U.S. Government-funded and non-U.S. Government-funded publications are available, but data on nongovernment research funding by disease are not available.
5. Nordhaus (2005) argued that "to a first approximation, the economic value of increases in longevity in the last hundred years is about as large as the value of measured growth in non-health goods and services."
6. Non-U.S. Government financial support includes support by American societies, institutes, state governments, universities, and private organizations, and by foreign sources (national, departmental, provincial, academic, and private organizations). U.S. governmental funding support is likely to be more geared toward basic research, whereas non-U.S. governmental (especially if private, such as from drug companies) is more likely to affect development. However, disentangling the effects of U.S. Government and non-U.S. Government research support is difficult. As shown in Lichtenberg (2013), almost half of the publications that cite U.S. Government research support also cite non-U.S. Government research support.
7. The correlation between growth rates (percentage changes) of these two variables is also very high: .84.
8. The large standard errors may be attributable, to an important extent, to left censoring of the data on research-supported articles: PubMed did not record information about research support until 1975 (National Library of Medicine, 2017).
9. https://www.cancer.gov/about-cancer/causes-prevention/risk/age
10. However, publications in higher quality journals may not have a larger impact on premature cancer mortality and hospitalization than publications in lower quality journals. Two journals of undoubtedly high quality are the *Journal of the American Medical Association* and the *New England Journal of Medicine*. The fraction of cancer-related articles published in those two journals that were research-based was much lower than the fraction of cancer-related articles published in other journals that were research-based (17% vs. 29%). Our estimates indicate that premature cancer mortality and hospitalization are only related to the number of research-based publications.

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