Has medical innovation reduced cancer mortality?

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Two questions

• Are we making progress in the war on cancer?
• If so, how much of this progress is attributable to medical innovation—the development and use of new medical goods and services?
• Bailar and Gornik (1997): “The effect of new treatments for cancer on mortality has been largely disappointing.”

• Black and Welch (1993): “The increasing use of sophisticated diagnostic imaging promotes a cycle of increasing intervention that often confers little or no benefit.”
Age-adjusted mortality rates, 1950-2006

Source: Health, United States, 2009, Table 26
Survival rates vs. mortality rates

- Two types of statistics are often used to assess progress in the war on cancer: survival rates and mortality rates.
- Survival rates are typically expressed as the proportion of patients alive at some point subsequent to the diagnosis of their cancer. For example, the observed 5-year survival rate is defined as follows:

  \[
  \text{5-year Survival Rate} = \frac{\text{Number of people diagnosed with cancer at time } t \text{ alive at time } t+5}{\text{Number of people diagnosed with cancer at time } t}
  \]

  \[
  = 1 - \frac{\text{Number of people diagnosed with cancer at time } t \text{ dead at time } t+5}{\text{Number of people diagnosed with cancer at time } t}
  \]

- Hence, the survival rate is based on a conditional (upon previous diagnosis) mortality rate. The second type of statistic is the unconditional cancer mortality rate: the number of deaths, with cancer as the underlying cause of death, occurring during a year per 100,000 population.
Lead-time bias

Disease onset → occult disease

Screen-detected (age 45) → Clinically-detected (age 50) → overt disease → Death (age 60)
• Welch et al (2000) argued that “while 5-year survival is a perfectly valid measure to compare cancer therapies in a randomized trial, comparisons of 5-year survival rates across time (or place) may be extremely misleading. If cancer patients in the past always had palpable tumors at the time of diagnosis while current cancer patients include those diagnosed with microscopic abnormalities, then 5-year survival would be expected to increase over time even if new screening and treatment strategies are ineffective.”

• Welch et al (2000) found no correlation across cancer sites between the long-run (40-year) change in the (conditional) survival rate and the unconditional mortality rate.


http://jama.ama-assn.org/cgi/content/abstract/283/22/2975?ck=nck
• Welch et al concluded from this that “improving 5-year survival over time...should not be taken as evidence of improved prevention, screening, or therapy,” and “to avoid the problems introduced by changing patterns of diagnosis...progress against cancer [should] be assessed using population-based mortality rates.”
• Welch et al did not control for changes in cancer incidence.
• Lichtenberg (2009) showed that, when incidence growth is controlled for, there is a highly significant correlation across cancer sites, in both the U.S. and Australia, between the change in 5-year survival for a specific tumor and the change in tumor-related mortality.
Correlation across cancer sites between growth in unconditional mortality and growth in conditional mortality, controlling for growth in incidence

U.S.
Correlation across cancer sites between growth in unconditional mortality and growth in conditional mortality, controlling for growth in incidence

Australia

• They concluded that “observed changes in mortality due to cancer primarily reflect changing incidence or early detection. The effect of new treatments for cancer on mortality has been largely disappointing.”

Cancer mortality rate

1b. Age-adjusted mortality rate (per 100,000 population)
Cancer incidence rate

1c. Age-adjusted incidence rate (per 100,000 population)
• In this paper, I analyze the effects of two important types of medical innovation—diagnostic imaging innovation and pharmaceutical innovation—and cancer incidence rates on unconditional cancer mortality rates since the early to mid 1990s.
The unconditional cancer mortality rate is essentially the unconditional probability of death from cancer \((P(\text{death from cancer}))\). The law of total probability implies the following:

\[
P(\text{death from cancer}) = P(\text{death from cancer} | \text{cancer diagnosis}) \times P(\text{cancer diagnosis}) + P(\text{death from cancer} | \text{no cancer diagnosis}) \times (1 - P(\text{cancer diagnosis}))
\]

If the probability that a person who has never been diagnosed with cancer dies from cancer is quite small \((P(\text{death from cancer} | \text{no cancer diagnosis}) \approx 0)\), which seems plausible, this reduces to

\[
P(\text{death from cancer}) \approx P(\text{death from cancer} | \text{cancer diagnosis}) \times P(\text{cancer diagnosis})
\]
Hence

\[
\ln P(\text{death from cancer}) \approx \ln P(\text{death from cancer} \mid \text{cancer diagnosis}) + \ln P(\text{cancer diagnosis}) \quad (3)
\]

I hypothesize that the conditional mortality rate \( P(\text{death from cancer} \mid \text{cancer diagnosis}) \) depends (inversely) upon the average quality of imaging and pharmaceutical procedures:

\[
\ln P(\text{death from cancer} \mid \text{cancer diagnosis}) = \beta_1 \text{image}_\text{quality} + \beta_2 \text{drug}_\text{quality} \quad (4)
\]

Substituting (4) into (3),

\[
\ln P(\text{death from cancer}) \approx \beta_1 \text{image}_\text{quality} + \beta_2 \text{drug}_\text{quality} + \ln P(\text{cancer diagnosis}) \quad (5)
\]
I will estimate difference-in-difference (DD) versions of eq. (5) using longitudinal, cancer-site-level data on over 60 cancer sites. The equations will be of the following form:

\[
\ln(\text{mort\_rate}_{st}) = \beta_1 \text{adv\_imag\%}_{s,t-k} + \beta_2 \text{new\_drug\%}_{s,t-k} \\
+ \beta_3 \ln(\text{inc\_rate}_{s,t-k}) + \alpha_s + \delta_t + \varepsilon_{st}
\] (6)

where

\text{mort\_rate}_{st} = \text{the age-adjusted mortality rate from cancer at site } s \ (s = 1,\ldots, 60) \ \text{in year } t \ (t=1991,\ldots,2006)

\text{adv\_imag\%}_{s,t-k} = \text{advanced imaging procedures as } \% \ \text{of total imaging procedures associated with cancer at site } s \ \text{in year } t-k \ (k=0,1,\ldots)

\text{new\_drug\%}_{s,t-k} = \text{“new” (e.g. post-1990) drug procedures as } \% \ \text{of all drug procedures associated with cancer at site } s \ \text{in year } t-k \ (k=0,1,\ldots)

\text{inc\_rate}_{s,t-k} = \text{the age-adjusted incidence rate of cancer at site } s \ \text{in year } t-k

\alpha_s = \text{a fixed effect for cancer site } s

\delta_t = \text{a fixed effect for year } t

\varepsilon_{st} = \text{a disturbance}
• If cancer sites that have had above-average increases in adv_imag% had above-average reductions in the age-adjusted mortality rate, then $\beta_1 < 0$ in eq. (6).

• Eq. (6) includes lagged values of adv_imag% and the other explanatory variables, since it may take several years for advanced imaging procedure utilization to have its peak effect on mortality rates.
Imaging procedure innovation measure

$$\text{adv}_\text{imag}_{\text{st}} = \frac{\sum_{p} n_{\text{proc}_{\text{pst}}} \text{adv}_p}{\sum_{p} n_{\text{proc}_{\text{pst}}}}$$

where

$$n_{\text{proc}_{\text{pst}}} = \text{the number of times diagnostic imaging procedure } p \text{ was performed in connection with cancer diagnosed at site } s \text{ in year } t$$

$$\text{adv}_p = 1 \text{ if procedure } p \text{ is an advanced imaging procedure}$$

$$= 0 \text{ if procedure } p \text{ is a standard imaging procedure}$$
Drug procedure innovation measure

\[
\text{new\_drug}\%_{st} = \frac{\sum_{p} n_{\text{proc}_{pst}\text{post\_year}_{p}}}{\sum_{p} n_{\text{proc}_{pst}} }
\]

where

\( n_{\text{proc}_{pst}} = \) the number of times drug procedure \( p \) was performed in connection with cancer diagnosed at site \( s \) in year \( t \)

\( \text{post\_year}_{p} = 1 \) if the active ingredient of drug procedure \( p \) was approved by the FDA after year \( y \)

\( = 0 \) if the active ingredient of drug procedure \( p \) was approved by the FDA before year \( y+1 \)

I will define \( y \) in two different ways: \( y=1990 \) and \( y=1995 \).
Data and descriptive statistics

- **Cancer incidence and mortality rates.** Data on age-adjusted cancer incidence and mortality rates, by cancer site and year, were obtained from the National Cancer Institute’s Cancer Query Systems (http://seer.cancer.gov/canques/index.html).

- **Diagnostic imaging innovation.** Data on the number of diagnostic imaging procedures, by CPT code, principal diagnosis (ICD9) code, and year (n_proc_pst) were obtained from MEDSTAT MarketScan Commercial Claims and Encounters Database produced by Thomson Medstat (Ann Arbor, MI). Each claim in this database includes information about the procedure performed (CPT code), the patient’s diagnosis (ICD9 code), and the date of service.

- Advanced imaging procedures involve either a computed tomography (CT) scan or magnetic resonance imaging (MRI).
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<thead>
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<tbody>
<tr>
<td>22030</td>
<td>Lung and Bronchus</td>
<td>57.9</td>
<td>51.7</td>
<td>66.4</td>
<td>60.0</td>
<td>10,425</td>
<td>39,897</td>
<td>39%</td>
<td>70%</td>
<td>2,301</td>
<td>26%</td>
<td>40%</td>
<td>9%</td>
<td>27%</td>
<td></td>
</tr>
<tr>
<td>21040</td>
<td>Colon excluding Rectum</td>
<td>18.7</td>
<td>14.3</td>
<td>39.3</td>
<td>32.9</td>
<td>3,296</td>
<td>22,609</td>
<td>51%</td>
<td>84%</td>
<td>1,635</td>
<td>2%</td>
<td>31%</td>
<td>0%</td>
<td>27%</td>
<td></td>
</tr>
<tr>
<td>28010</td>
<td>Prostate</td>
<td>18.0</td>
<td>11.8</td>
<td>84.5</td>
<td>81.6</td>
<td>3,132</td>
<td>17,389</td>
<td>46%</td>
<td>74%</td>
<td>636</td>
<td>3%</td>
<td>35%</td>
<td>1%</td>
<td>26%</td>
<td></td>
</tr>
<tr>
<td>26000</td>
<td>Breast</td>
<td>16.8</td>
<td>13.2</td>
<td>73.3</td>
<td>66.4</td>
<td>27,894</td>
<td>93,405</td>
<td>16%</td>
<td>48%</td>
<td>3,836</td>
<td>13%</td>
<td>43%</td>
<td>3%</td>
<td>32%</td>
<td></td>
</tr>
</tbody>
</table>
Figure 2
Cancer imaging procedures

- Advanced procedures as % of total procedures (left axis)
- Number of MEDSTAT imaging procedures associated with cancer diagnosis (right axis)
Figure 3
Percent of 1991 and 2007 imaging procedures accounted for by top 15 procedures in 2007

- 72193-CT Pelvis w Dye (10.1%)
- 71260-CT Thorax w Dye (10.1%)
- 76830-Transvaginal Us, Non-Ob (9.3%)
- 73020-Chest X-Ray (8.8%)
- 76856-Us Exam, Pelvic, Complete (7.2%)
- 70553-MRI Brain wo&w Dye (5.0%)
- 74170-CT Abdomen wo&w/Dye (4.2%)
- 71010-Chest X-Ray (4.0%)
- 76942-Echo Guide for Biopsy (1.9%)
- 70491-CT Soft Tissue Neck w Dye (1.8%)
- 76645-Us Exam, Breast(s) (1.5%)
- 76950-Echo Guidance Radiotherapy (1.5%)
- 71250-CT Thorax wo Dye (1.3%)
- 72194-CT Pelvis wo&w/Dye (1.1%)

Legend:
- Blue: percent of imaging procedures in 1991
- Red: percent of imaging procedures in 2007
Figure 4
Cancer drug procedures

- post-1990 drug procedures as % of total drug procedures (left axis)
- post-1995 drug procedures as % of total drug procedures (left axis)
- Number of MEDSTAT drug procedures associated with cancer diagnosis (right axis)
Figure 5
Percent of 1999 and 2007 drug procedures accounted for by top 15 procedures in 2007

<table>
<thead>
<tr>
<th>Procedure</th>
<th>1999</th>
<th>2007</th>
</tr>
</thead>
<tbody>
<tr>
<td>J1100-Dexamethasone Sodium Phos</td>
<td>7.9%</td>
<td>8.4%</td>
</tr>
<tr>
<td>J7050-Normal Saline Solution Infus</td>
<td>7.4%</td>
<td>10.6%</td>
</tr>
<tr>
<td>J1642-Inj Heparin Sodium Per 10 U</td>
<td>4.0%</td>
<td>3.0%</td>
</tr>
<tr>
<td>J1200-Diphenhydramine HCl Injectio</td>
<td>3.0%</td>
<td>0.0%</td>
</tr>
<tr>
<td>J2469-Palonosetron hcl</td>
<td>3.8%</td>
<td>0.0%</td>
</tr>
<tr>
<td>J7040-Normal Saline Solution Infus</td>
<td>3.5%</td>
<td>3.3%</td>
</tr>
<tr>
<td>J1644-Inj Heparin Sodium Per 1000u</td>
<td>3.1%</td>
<td>1.3%</td>
</tr>
<tr>
<td>J2405-Ondansetron HCl Injection</td>
<td>2.9%</td>
<td>0.0%</td>
</tr>
<tr>
<td>J9190-Fluorouracil Injection</td>
<td>2.8%</td>
<td>0.0%</td>
</tr>
<tr>
<td>J9355-Trastuzumab</td>
<td>2.4%</td>
<td>0.0%</td>
</tr>
<tr>
<td>J9265-Paclitaxel Injection</td>
<td>1.9%</td>
<td>2.7%</td>
</tr>
<tr>
<td>J2250-Inj Midazolam Hydrochloride</td>
<td>0.2%</td>
<td>1.9%</td>
</tr>
<tr>
<td>J0640-Leucovorin Calcium Injection</td>
<td>1.8%</td>
<td>0.0%</td>
</tr>
<tr>
<td>J7030-Normal Saline Solution Infus</td>
<td>1.7%</td>
<td>1.6%</td>
</tr>
<tr>
<td>J3010-Fentanyl Citrate Injection</td>
<td>1.7%</td>
<td>0.0%</td>
</tr>
</tbody>
</table>
Figure 6
Effect of incidence in year t-k on mortality in year t, k=0,1,…,8
Figure 7
Effect of adv_image% in year t-k on mortality in year t, k=0,1,…,5

Note: values are plotted on an inverted scale
### Table 3
Estimates of effects of imaging and drug innovation on cancer mortality rate, controlling and not controlling for other factors

<p>| Regressor                        | Covariates                  | Estimate | Standard Error | 95% Lower Confidence Limit | 95% Upper Confidence Limit | Z       | Pr &gt; |Z| |
|----------------------------------|------------------------------|----------|----------------|----------------------------|----------------------------|---------|-------|---|
| adv_imag%&lt;sub&gt;s,t-5&lt;/sub&gt;        | post1990%&lt;sub&gt;s,t&lt;/sub&gt;     | -0.252   | 0.079          | -0.407                     | -0.097                     | -3.18   | 0.0015|
|                                  | ln(inc_rate&lt;sub&gt;s,t-5&lt;/sub&gt;) |          |                |                            |                            |         |       |   |
| adv_imag%&lt;sub&gt;s,t-5&lt;/sub&gt;        | none                         | -0.286   | 0.098          | -0.478                     | -0.093                     | -2.90   | 0.0037|
| post1990%&lt;sub&gt;s,t&lt;/sub&gt;          | adv_imag%&lt;sub&gt;s,t&lt;/sub&gt;,    | -0.161   | 0.066          | -0.290                     | -0.032                     | -2.44   | 0.0145|
|                                  | ln(inc_rate&lt;sub&gt;s,t-5&lt;/sub&gt;) |          |                |                            |                            |         |       |   |
| post1990%&lt;sub&gt;s,t&lt;/sub&gt;          | none                         | -0.164   | 0.073          | -0.306                     | -0.022                     | -2.26   | 0.0239|
| post1995%&lt;sub&gt;s,t&lt;/sub&gt;          | adv_imag%&lt;sub&gt;s,t&lt;/sub&gt;,    | -0.161   | 0.074          | -0.305                     | -0.016                     | -2.18   | 0.0294|
|                                  | ln(inc_rate&lt;sub&gt;s,t-5&lt;/sub&gt;) |          |                |                            |                            |         |       |   |
| post1995%&lt;sub&gt;s,t&lt;/sub&gt;          | none                         | -0.205   | 0.089          | -0.380                     | -0.030                     | -2.30   | 0.0216|</p>
<table>
<thead>
<tr>
<th>Factor</th>
<th>Contribution to the 1996-2006 decline in the age-adjusted cancer mortality rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>imaging innovation</td>
<td>5.3%</td>
</tr>
<tr>
<td>drug innovation</td>
<td>3.7%</td>
</tr>
<tr>
<td>decline in age-adjusted incidence</td>
<td>1.0%</td>
</tr>
<tr>
<td>other factors</td>
<td>3.4%</td>
</tr>
<tr>
<td>TOTAL</td>
<td>13.4%</td>
</tr>
</tbody>
</table>
• A 1 percent reduction in cancer mortality is worth nearly $500 billion.

Impact on U.S. life expectancy

• The calculations above imply that cancer imaging innovation and drug innovation reduced the cancer mortality rate by 10.2 (= 40% * 25.9) and 7.1 (= 27% * 25.9) deaths per 100,000 population, respectively.

• During this period, the age-adjusted mortality rate from all causes of death declined by 119.4 deaths per 100,000 population, from 894.5 to 775.1, and life expectancy at birth increased by 1.6 years, from 76.1 to 77.7 years.

• If the decline in cancer mortality had no effect on mortality from other causes of death, about 9% (= 10.2 / 119.4) of the decline in the mortality rate from all causes of death is attributable to cancer imaging innovation, and about 6% is attributable to cancer drug innovation.

• Life expectancy at birth may have been increased by just under three months (= (9% + 6%) * 1.6 years) between 1996 and 2006 by the combined effects of cancer imaging and cancer drug innovation.