The expanding pharmaceutical arsenal in the war on cancer

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Abstract

The five-year relative survival rate from all malignant cancers increased from 50.0% in 1975-1979 to 62.7% in 1995. This increase is not due to a favorable shift in the distribution of cancers. A variety of factors, including technological advances in diagnostic procedures that led to earlier detection and diagnosis, have contributed to this increase. This paper's main objective is to assess the contribution of pharmaceutical innovation to the increase in cancer survival rates. Only about one third of the approximately 80 drugs currently used to treat cancer had been approved when the war on cancer was declared in 1971.

The percentage increase in the survival rate varied considerably across cancer sites. We hypothesize that these differential rates of progress were partly attributable to different rates of pharmaceutical innovation for different types of cancer, and test this hypothesis within a "differences in differences" framework, by estimating models of cancer mortality rates using longitudinal, annual, cancer-site-level data based on records of 2.1 million people diagnosed with cancer during the period 1975-1995. We control for fixed cancer site effects, fixed year effects, incidence, stage distribution of diagnosed patients, mean age at diagnosis, percent of patients having surgery, and percent of patients having radiation.

Overall, the estimates indicate that cancers for which the stock of drugs increased more rapidly tended to have greater increases in survival rates. The estimates imply that, ceteris paribus, the 1975-1995 increase in the stock of drugs increased the 1-year crude cancer survival rate from 69.4% to 76.1%, the 5-year rate from 45.5% to 51.3%, and the 10-year rate from 34.2% to 38.1%. The increase in the stock of drugs accounted for about 50-60% of the increase in age-adjusted survival rates in the first 6 years after diagnosis.

We also estimate that the 1975-1995 increase in the lagged stock of drugs made the life expectancy of people diagnosed with cancer in 1995 just over a year greater than the life expectancy of people diagnosed with cancer in 1975. This figure increased from about 9.6 to 10.6 years. This is very similar to the estimate of the contribution of pharmaceutical innovation to longevity increase I obtained in an earlier study, although that study was based on a very different sample and methodology.

Since the lifetime risk of being diagnosed with cancer is about 40%, the estimates imply that the 1975-1995 increase in the lagged stock of cancer drugs increased the life expectancy of the *entire U.S. population* by 0.4 years, and that new cancer drugs accounted for 10.7% of the overall increase in U.S. life expectancy at birth.

The estimated cost to achieve the additional year of life per person diagnosed with cancer—below $3000—is well below recent estimates of the value of a statistical life-year. We are unable to measure quality-adjusted life-years (QALYS), but if new cancer drugs increased the quality of life as well as delayed death, the increase in QALYS is not necessarily less than the increase in life expectancy.

In 1971, President Nixon declared “war on cancer”, and the National Cancer Act was enacted.[1] Since that time, both government and industry have devoted enormous resources to fighting this war. Today, it behooves us to ask, "Are we winning the war?"

At first blush, the answer appears to be, “definitely not!”. As Figure 1 reveals, the age-adjusted U.S. mortality rate from all malignant cancers was essentially the same in 2000 as it was in 1969. (It was 8% *higher* in 1991 than it was in 1969.) During the same period, the age-adjusted mortality rate from all other causes of death declined by 38%. Today, cancer is the leading cause of years of potential life lost before age 75.[2]

But the stagnancy of the cancer mortality rate is potentially misleading. This mortality rate depends on two distinct factors: the probability of being diagnosed with cancer, and cancer survival rates—the probability of not dying t years after being diagnosed with cancer (t = 1, 2, …). As Figure 2 reveals, the cancer incidence rate—the number of new cancer cases per 100,000 people—increased sharply from 1975-1979 to 1992. Although it declined after 1992, it was still 16% higher in 2000 than it was in 1975-1979. The long-run increase in cancer incidence is presumably primarily attributable to the decline in mortality from other causes, particularly cardiovascular disease. Medical advances for diseases other than cancer have reduced the risk of dying from those diseases, and have thereby increased the risk of developing cancer. According to the National Cancer Institute, in the year 2000 the lifetime risk of developing cancer was about 40%.

Although cancer incidence has increased, so has cancer survival.[3] Figure 3 shows the five-year relative survival rate from all malignant cancers from 1975-1979 to 1995. The probability that a person diagnosed with cancer in 1975-1979 would not die

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[1] Cancer Facts and the War on Cancer.

[2] http://www.cdc.gov/nchs/data/hus/tables/2003/03hus030.pdf In 1980, cancer caused less premature mortality than heart disease. In 2001, cancer caused 35% more premature mortality than heart disease.

[3] Epidemiologists calculate two kinds of survival rates: *observed* and *relative* survival rates. The observed survival rate represents the proportion of cancer patients surviving for a specified time interval after diagnosis. Some of those not surviving died of the given cancer and some died of other causes. The relative survival rate is calculated using a procedure (Ederer et al., 1961) whereby the observed survival rate is adjusted for expected mortality. The relative survival rate approximates the likelihood that a patient will not die from causes associated specifically with the given cancer before some specified time after diagnosis. It is always larger than the observed survival rate for the same group of patients.

from causes associated specifically with the given cancer within 5 years was 50.0%. For a person diagnosed with cancer in 1995, that probability was 25% higher: 62.7%.

Figure 4 summarizes the trends in cancer mortality, incidence, and survival. The relative stability of the cancer mortality rate is the result of two offsetting trends: an increase in the cancer incidence rate, and an increase in the relative survival rate (or a decrease in the relative non-survival rate).

This paper's main objective is to assess the contribution of pharmaceutical innovation to the increase in cancer survival rates. I estimate that only about one third of the approximately 80 drugs currently used to treat cancer had been approved when the war on cancer was declared. In other words, there has been a threefold increase in the size of the cancer drug armamentarium[4] in the last three decades.[5]

I recognize, of course, that pharmaceutical innovation is just one of a number of factors that may have contributed to the increase in cancer survival. Other potential factors include: a changing mix of cancers over time; technological advances in diagnostic procedures that led to earlier detection and diagnosis; and changes in non-pharmaceutical cancer treatment (surgery and radiation). The available data will enable me to control for these factors to a very great extent.

The survival rate data shown in Figure 3 are for all cancers combined. The mix of cancers changes over time as the incidence of some cancers increases and the incidence of others decreases. Annual growth rates during the period 1950-2000 of the incidence of various cancers are shown in Figure 5. Incidence of two cancers—lung and bronchus (among females) and melanoma—increased more than 4% per year, while incidence of stomach and cervix uteri cancer declined more than 2% per year. Moreover, there is considerable variation in survival rates across cancers. As shown in Figure 6, in 1950, seven cancers had 5-year relative survival rates above 50%, while seven had rates at or below 10%.[6] In principle, the increase in the survival rate for all cancers combined could be partly due to an increase in the relative incidence of cancers with high (initial) survival

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[4] The word armamentarium has two definitions: "(1) the equipment and methods used, especially in medicine; and (2) matter available or utilized for an undertaking or field of activity." http://www.m-w.com/cgi-bin/dictionary?book=Dictionary&va=armamentarium

[5] The growth rate of the cumulative stock of approved cancer drugs has been greater than the growth rate of the cumulative stock of drugs approved for other diseases.

[6] The 5-year relative survival rate for all cancers combined in 1950 was 35.0%.

rates. In practice, this is not the case. As shown in Figure 7, there is essentially no relationship across cancers between the survival rate in 1950-54 and the 1950-2000 growth rate of incidence.[7]

Survival data, by cancer site, of the type shown in Figure 6 can be calculated for different periods. Cancer site-specific survival data (for whites only) for 1950-54 and 1992-99 are shown in Table 1 and Figure 8. In the figure, note that every point lies above the 45^{o} line: for every cancer site, the 1992-99 survival rate was greater than the 1950-54 survival rate. However the percentage increase in the survival rate varied considerably across cancer sites. For example, the 1950-54 survival rate for both brain and other nervous system cancers and childhood cancers was about 20%, but the 1992-99 survival rate was 32.1% for the former and 78.7% for the latter. Similarly, the survival rate for colon cancer increased from 41% to 63%, while the survival rate from prostate cancer increased from 43% to 98%. I hypothesize that these differential rates of progress are partly attributable to different rates of pharmaceutical innovation for different types of cancer.

To test this hypothesis within a "differences in differences" framework, I will estimate models of cancer mortality rates using longitudinal, annual, cancer-site-level data based on large samples of people diagnosed with cancer during the period 1975-1995. The explanatory variable of primary interest is the (lagged value of the) cumulative number of cancer drugs approved to treat that cancer type. The following covariates will be included in the model: fixed cancer site effects, fixed year effects, incidence, stage distribution of diagnosed patients, mean age at diagnosis, percent of patients having surgery, and percent of patients having radiation. Including these variables is likely to control for the effect of technological advances in diagnostic procedures. As noted in the SEER Cancer Statistics Review, "improved earlier detection and diagnosis of cancers may produce an *increase* in both incidence rates and survival rates." To the extent that these improvements apply to all forms of cancer, their effects are captured by the fixed year effects. Cancer-site-specific improvements in detection

[7] This confirms the observation that "while it is possible to adjust the survival rate for all cancers combined on the basis of the relative frequency of each specific cancer in some specified reference period, rates adjusted in this manner differ by only a small amount from unadjusted rates." (SEER Cancer Statistics Review, p. 13.)

and diagnosis are likely to lead to reductions in age at date of diagnosis and to increased measured incidence.

Figure 9 depicts the general model that we will estimate. Section I of the paper describes the data that will be used to estimate the model. Section II describes the econometric specification and procedure. Estimates of the model are presented in Section III. Interpretation and implications of the estimates are considered in Section IV. Section V contains a summary.

I. Data

The National Cancer Act of 1971 mandated the collection, analysis, and dissemination of data useful in the prevention, diagnosis, and treatment of cancer. This mandate led to the establishment of the Surveillance, Epidemiology, and End Results (SEER) Program of the National Cancer Institute (NCI). A continuing project of the NCI, the population-based cancer registries participating in the SEER Program routinely collect data on all cancers occurring in residents of the participating areas. Trends in cancer incidence and patient survival in the U.S. are derived from this database. The SEER Program is a sequel to two earlier NCI programs — the End Results Program and the Third National Cancer Survey.

The SEER Program is considered as the standard for quality among cancer registries around the world. Quality control has been an integral part of SEER since its inception. Every year, studies are conducted in the SEER areas to evaluate the quality and completeness of the data being reported (SEER's standard for case ascertainment is 98 percent). In some studies, a sample of cases is reabstracted to evaluate the accuracy of each of the data elements collected from the medical records. In other studies, targeted information gathering is performed to address specific data quality needs. Computer edits also are used by registries to ensure accurate and consistent data.

The initial SEER reporting areas were the States of Connecticut, Iowa, New Mexico, Utah, and Hawaii; the metropolitan areas of Detroit, Michigan, and San Francisco-Oakland, California; and the Commonwealth of Puerto Rico. Case ascertainment began with January 1, 1973, diagnoses. In 1974-1975, the program was

expanded to include the metropolitan area of New Orleans, Louisiana, the thirteen-county Seattle-Puget Sound area in the State of Washington, and the metropolitan area of Atlanta, Georgia. New Orleans participated in the program only through the 1977 data collection year. In 1978, ten predominantly black rural counties in Georgia were added. American Indian residents of Arizona were added in 1980. In 1983, four counties in New Jersey were added with coverage retrospective to 1979. New Jersey and Puerto Rico participated in the program until the end of the 1989 reporting year. The National Cancer Institute also began funding a cancer registry that, with technical assistance from SEER, collects information on cancer cases among Alaska Native populations residing in Alaska. In 1992, the SEER Program was expanded to increase coverage of minority populations, especially Hispanics, by adding Los Angeles County and four counties in the San Jose-Monterey area south of San Francisco. In 2002, the SEER Program expanded coverage to include Kentucky and Greater California (the counties of California that were not already covered by SEER). Also in 2002, New Jersey and Louisiana became SEER participants again. Figure 10 is a map of SEER cancer registries.

Data from the 9 SEER geographic areas used in this study represent, respectively, approximately 10 percent of the U.S. population. By the end of the 1999 diagnosis year, the database contained information on over 3,200,000 cases diagnosed since 1973. Over 170,000 new cases are added annually.

Data contained in the SEER Public Use File (PUF) enable us to characterize a group of people diagnosed with a given type of cancer in a given year. They may be characterized in terms of:

- Their future survival prospects
- The size of the group (incidence)
- Their age distribution
- Their distribution by extent/severity of illness (cancer stage distribution)
- Whether their initial treatment included surgery and/or radiation

Future survival prospects. Each record in the SEER Public-Use File indicates whether the person had died by the cutoff date for this file (December 31, 2000), and if so, the date of death. This allows us to compute, for each cancer site and year of diagnosis, the survival distribution function (SDF) and several closely related functions.

The SDF evaluated at t is the probability that a member of the population will have a lifetime exceeding t, that is S(t) = Prob(T > t), where S(t) denotes the survival function and T is the lifetime of a randomly selected experimental unit. Some functions closely related to the SDF are the cumulative distribution function (CDF), the probability density function (PDF), and the hazard function. The CDF F(t) is defined as 1 – S(t) and is the probability that a lifetime is smaller than t. The PDF denoted f(t) is defined as the derivative of F(t), and the hazard function denoted h(t) is defined as f(t)/S(t). Hence h(t) = -S'(t)/S(t), where S'(t) is the derivative of S(t). The hazard rate is the percentage reduction in the survival rate.) Discrete time: $h(t) = (S(t) - S(t+1))/S(t) \rightarrow S(t) = \prod_{j=0}^{t-1} (1 - h(j))$

To illustrate, Figure 11 shows estimates of the survival and hazard functions of people diagnosed with all types of cancer in 1975.[8] The 5-year survival rate was 45%, and the 10-year survival rate was 34%. The hazard rate declines very sharply during the first several years. The probability of dying, conditional on being alive at the beginning of the year, is 31% in the first year, 15% in the second year, and 10% in the third year. It declines much more slowly during the next five years, when it levels off at about 5%.

We compute hazard functions of this type for each cancer site and year of diagnosis.[9] That is, we compute estimates of $HAZARD_{i,t-k,t}$: the hazard rate from year t to year t+1 of people diagnosed with cancer type i in year t-k (i = 1,…,30; t = 1975,…,2000; k=1,…,24). For example, suppose i = breast cancer, t = 1990, and k = 5. Then $HAZARD_{i,t-k,t}$ = the probability that a woman diagnosed with breast cancer in 1985 died in 1990, conditional on surviving until the beginning of 1990. We also compute standard errors of these estimates.

Incidence. Incidence of cancer type i in year t can be estimated by simply counting the number of cases in the SEER PUF. The incidence rate is the number of new cases per year per 100,000 persons:

$$INCIDENCE_{it} = CASES_{it} / POP_t$$

Hence $\ln(INCIDENCE_{it}) = \ln(CASES_{it}) - \ln(POP_t)$

[8] These survival and hazard rates, like all others we will compute and analyze, are observed rather than relative rates. However, the models we will estimate will include covariates (e.g. fixed diagnosis-year effects and mean age at diagnosis) that presumably effectively adjust for changes in "expected mortality".
[9] These are computed using the LIFETEST procedure (LIFETABLE method) in SAS.

$$= \ln(CASES_{it}) + \delta_t$$

where $\delta_t = -\ln(POP_t)$. Including $\ln(CASES_{it})$ and a set of diagnosis-year dummies (δ_t's) therefore controls for site-specific changes in cancer incidence. As observed in the National Cancer Institute's *SEER Cancer Statistics Review, 1975-2000*, "the improved earlier detection and diagnosis of cancers may produce an *increase* in both incidence rates and survival rates."[10] Hence including $\ln(CASES_{it})$ and a set of diagnosis-year dummies (δ_t's) in cancer survival or hazard models may control, to an important extent, for the effects of changes (improvements) in cancer detection and diagnosis.

Cancer stage. In addition to cancer site, each SEER record indicates cancer stage at the time of diagnosis. There are four main cancer stage categories:[11]

- In situ (Stage 0)—A noninvasive neoplasm; a tumor which has not penetrated the basement membrane nor extended beyond the epithelial tissue. Some synonyms are intraepithelial (confined to epithelial tissue), noninvasive and noninfiltrating.
- Localized (Stage 1)—An invasive neoplasm confined entirely to the organ of origin. It may include intraluminal extension where specified. For example for colon, intraluminal extension limited to immediately contiguous segments of the large bowel is localized, if no lymph nodes are involved. Localized may exclude invasion of the serosa because of the poor survival of the patient once the serosa is invaded.
- Regional (Stage 2)—A neoplasm that has extended 1) beyond the limits of the organ of origin directly into surrounding organs or tissues; 2) into regional lymph nodes by way of the lymphatic system; or 3) by a combination of extension and regional lymph nodes.
- Distant (Stage 4)—A neoplasm that has spread to parts of the body remote from the primary tumor either by direct extension or by discontinuous metastasis (e.g., implantation or seeding) to distant organs, issues, or via the lymphatic system to distant lymph nodes.

Survival rates of patients diagnosed in a given year are strongly inversely related to cancer stage, e.g. patients with Stage 4 cancer have much lower survival rates than patients with Stage 0 cancer. In principle, therefore, it might seem desirable to calculate survival rates by site, diagnosis year, *and stage*, rather than merely by site and diagnosis year. However due to a phenomenon known as *stage migration*, analysis of survival rates

[10] http://seer.cancer.gov/csr/1975_2000/results_merged/sect_01_overview.pdf

[11] There are two additional categories: Localized/Regional (Stage 8)—Only used for Prostate cases, and Unstaged (Stage 9)—Information is not sufficient to assign a stage. All lymphomas and leukemias are considered unstaged (code `9').

and other variables by site, diagnosis year, and stage is likely to lead to erroneous inferences.

The assignment of a given stage to a particular cancer may change over time due to advances in diagnostic technology. Stage migration occurs when diagnostic procedures change over time, resulting in an increase in the probability that a given cancer will be diagnosed in a *more advanced* stage. For example, certain distant metastases that would have been undetectable a few years ago can now be diagnosed by a computer tomography (CT) scan or by magnetic resonance imaging (MRI). Therefore, some patients who would have been diagnosed previously as having cancer in a *localized* or *regional* stage are now diagnosed as having cancer in a *distant* stage. The likely result would be to remove the worst survivors — those with previously undetected distant metastases — from the localized and regional categories and put them into the distant category. As a result, the stage-at-diagnosis distribution for a cancer may become less favorable over time, but the survival rates for each stage may improve: the early stage will *lose* cases that will survive *shorter* than those remaining in that category, while the advanced stage will *gain* cases that will survive *longer* than those already in that category. However, *overall survival would not change* (Feinstein et al., 1985). Stage migration is an important concept to understand when examining temporal trends in survival by stage at diagnosis as well as temporal trends in stage distributions; it could affect the analysis of virtually all solid tumors.[12]

Among people diagnosed with the same kind of cancer in the same year, those with later stage cancer always have lower survival rates. But, as we will show below, *increases* in the share of patients with later-stage cancer are not always associated with a reduction in the survival rate of that group.

Since stage migration is very likely to result in misleading statistics for cancer survival by stage, we will measure survival by cancer site and diagnosis year, rather than by cancer site, diagnosis year, and stage. However, we will control for the effect of changes in the measured stage distribution by including stage distribution variables (e.g., the % of cases that are Stage 0 cases) as covariates.

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[12] *SEER Cancer Statistics Review 1973-1999 Overview*, p. 12.

Cancer treatment. The medical community recognizes three types of conventional cancer treatment: surgery, radiation therapy, and drugs.

Surgery. Surgery is often the first step in cancer treatment because it is used both to diagnose and to treat cancer. Surgery alone sometimes cures cancer. Sometimes it is used in conjunction with other treatments such as chemotherapy (cancer drugs) or radiation therapy. More than half of the people diagnosed with cancer will have some type of surgery or operation at some point. Surgery is used to remove tumors confined to a small space. Surgery is also used to reduce the size of large tumors so that follow-up treatment by radiation therapy or chemotherapy will be even more effective.

From the SEER PUF, we can determine whether the patient's "first course of treatment" included surgery. The "first course of treatment" is either the planned course of treatment stated in the medical record, or the standard treatment for that site and extent of disease when there is no treatment plan in the chart. In general terms, first course of treatment extends through the end of the planned treatment, or until there is evidence of treatment failure (progression of disease), and the patient is switched to another type of treatment.

Radiation. Radiation therapy uses radiation (high-energy rays) to kill or shrink tumor cells. It is used to treat some, but not all cancers. Radiation therapy destroys cells either directly or by interfering with cell reproduction. Normal cells are able to recover from radiation damage better than cancer cells. Used alone, radiation therapy can be curative in many cases. It is also used in combination with other treatments/therapies such as surgery. It might be used both to reduce the size of tumors before surgery and to destroy any remaining cancer cells after surgery. Radiation therapy is also used with many other conventional cancer treatments such as chemotherapy and hormone therapy. When cure is not possible, radiation therapy can also help alleviate symptoms such as pain, and improve quality of life for patients. From the SEER PUF, we can also determine whether the patient's "first course of treatment" included radiation.

Chemotherapy. According to the SEER Program Code Manual, data on chemotherapy, hormone therapy, and immunotherapy are collected in SEER. With respect to chemotherapy, cancer registries are asked to "code any chemical [that] is

administered to treat cancer tissue and which is not considered to achieve its effect through change of the hormone balance."

Unfortunately, the SEER Public Use File does not contain any information about chemotherapy. According to NCI staff, this is because chemotherapy is generally not performed in an inpatient hospital setting—it is usually performed in an outpatient hospital setting, in a physician's office, or at home. Chemotherapy data collected by SEER are rather incomplete, so SEER does not include the information on the public use file.[13] I therefore constructed a cancer-site-specific and year-specific chemotherapy variable--the cumulative number of drugs approved to treat each type of cancer in each year--by combining data from two sources.

The first source is the Cancer Drug Manual produced by the British Columbia Cancer Agency, Division of Pharmacy (de Lemos (2004)). The Professional Drug Index contains monographs on 83 cancer drugs. The monographs were written, reviewed and edited by pharmacists practicing in oncology settings, and have been reviewed by oncologists and an oncology nurse clinician. Each monograph contains a section on the *uses* of the drug. For example, according to the monographs, there are seven uses for asparaginase (acute lymphocytic leukemia, acute myeloblastic leukemia, acute myelomonocytic leukemia, chronic lymphocytic leukemia, Hodgkin's disease, melanosarcoma, and non-Hodgkin's lymphoma), and four for dacarbazine (Hodgkin's disease, malignant melanoma, neuroblastoma, and soft tissue sarcomas). Using the information contained in all 83 monographs, I constructed a list of drugs used to treat each kind of cancer. I determined, for example that the following 12 drugs are used today to treat bladder cancer: bcg, carboplatin, cisplatin, doxorubicin, fluorouracil, gemcitabine, interferon alfa, methotrexate, mitomycin, porfimer, thiotepa, and vinblastine.

I used a second data source—Mosby's Drug Consult—to determine the year in which the FDA approved each of these drugs.[14] This enabled me to track the cumulative number of drugs approved by the FDA for each cancer type for each year.

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[13] E-mail communication from April Fritz, Manager, Data Quality, SEER Program, 8 January 2004.
[14] The list of cancer drugs, in order of year of FDA approval, is shown in Appendix Table 1.

As Figure 12 indicates, the rate of increase of the stock of drugs varies considerably across cancer sites in a given period, and also across periods for a given cancer site. For example, between 1969 and 2002, there was a 4.4-fold increase in the stock of drugs for breast cancer, and an 8-fold increase in the stock of drugs for prostate cancer. Also, the stock of drugs for colon and rectum cancer remained constant from 1974 to 1980, but then doubled from 1980 to 1982.

II. Econometric Model

For each cancer site and year of diagnosis (1975-1995), I computed a hazard function. For people diagnosed in 1975, the hazard function had 25 points—one for each of the years 1-25 (the cutoff date for the SEER PUF is Dec. 31, 2000). For people diagnosed in 1976, the hazard function had 24 points, and so forth. For people diagnosed in 1995, the hazard function had just 5 points.

I estimated a separate model of the hazard rate for each of the k years after diagnosis (k = 1, 2,…, 25): a model of the first-year hazard rate, the second-year hazard rate, etc. Each model was of the following form:

$$\ln(HAZARD_{i,t-k,t}) = \alpha_{ik} + \delta_{tk} + \beta_{1k} \ln(DRUG\_STOCK_{i,t-3}) + \beta_{2k} \ln(N_{i,t-k}) + \beta_{3k} AGE\_MEAN_{i,t-k} + \beta_{4k} SURGERY\%_{i,t-k} + \beta_{5k} RADIATION\%_{i,t-k} + \theta_{0k} STAGE0\%_{i,t-k} + \theta_{1k} STAGE1\%_{i,t-k} + \theta_{2k} STAGE2\%_{i,t-k} + \theta_{4k} STAGE4\%_{i,t-k} + \theta_{8k} STAGE8\%_{i,t-k} + \varepsilon_{i,t-k,t} \quad (1)$$

where:

$HAZARD_{i,t-k,t}$ = the hazard rate from year t to year t+1 of people diagnosed with cancer type i in year t-k.[15]

$DRUG\_STOCK_{i,t-3}$ = the cumulative number of drugs approved by the end of year t-3 that are (currently) used to treat cancer type i.

$N_{i,t-k}$ = the number of people diagnosed with cancer type i in year t-k.

$AGE\_MEAN_{i,t-k}$ = the mean age of people diagnosed with cancer type i in year t-k.

$SURGERY\%_{i,t-k}$ = the fraction of people diagnosed with cancer type i in year t-k whose initial treatment included surgery

$RADIATION\%_{i,t-k}$ = the fraction of people diagnosed with cancer type i in year t-k whose initial treatment included radiation

[15] For example, suppose i = breast cancer, t = 1990, and k = 5. Then $HAZARD_{i,t-k,t}$= the probability that a woman diagnosed with breast cancer in 1985 died in 1990, conditional on surviving until the beginning of 1990.

$STAGE0\%_{i,t-k}$ = the fraction of people diagnosed with cancer type i in year t-k whose cancer was classified as stage 0 (in situ).

$STAGE1\%_{i,t-k}$ = the fraction of people diagnosed with cancer type i in year t-k whose cancer was classified as stage 1 (localized)

$STAGE2\%_{i,t-k}$ = the fraction of people diagnosed with cancer type i in year t-k whose cancer was classified as stage 2 (regional)

$STAGE4\%_{i,t-k}$ = the fraction of people diagnosed with cancer type i in year t-k whose cancer was classified as stage 4 (distant)

$STAGE8\%_{i,t-k}$ = the fraction of people diagnosed with cancer type i in year t-k whose cancer was classified as stage 8 (localized/regional-prostate only)

Table 2 presents some summary statistics, by year of diagnosis, from the SEER Public Use File (PUF). There appear to be sharp breaks in several of the series between 1974 and 1975 and again between 1995 and 1996. We therefore restricted the sample to include only the 2.1 million people diagnosed with cancer during the years 1975-1995.

In eq. (1), the hazard rate in year t for patients diagnosed with cancer type i in year t-k is a function of: fixed cancer-site effects, fixed diagnosis-year effects, the stock of drugs approved to treat that type of cancer by the end of year t-3, cancer incidence, mean age at diagnosis, extent of surgery and radiation,[16] and cancer stage distribution. Since the dependent variable is the *logarithm* of the hazard rate, we are, in effect, estimating a *proportional hazards* model. Such a model assumes that changing an explanatory variable has the effect of multiplying the hazard rate by a constant. Introduced by D. R. Cox (1972),[17] the proportional hazards model was developed in order to estimate the effects of different covariates influencing the times-to-failure of a system, and has been widely used in the biomedical field.

We assume that the log of the hazard rate depends on the log of the lagged stock of drugs. Eq. (1) may be considered a health production function, and production functions are often assumed to be log-linear, consistent with the hypothesis of

[16] Ideally, we would like to measure the number (and importance) of surgical and radiological innovations, analogous to the number of pharmaceutical innovations. Since the FDA does not regulate surgery and radiology in the same way that it regulates drugs, this is not feasible. However changes in the frequency of surgery, for example, may be highly correlated with surgical innovation. If there are more surgical innovations for one cancer site than there are for another, one would expect a greater increase (or smaller decline) in surgical treatment of the former site.

[17] See also Cox and Oakes (1984).

diminishing marginal productivity of inputs. For example, in his model of endogenous technological change, Romer (1990) hypothesized the production function

$$\ln Y = (1-\alpha) \ln A + (1-\alpha) \ln L + \alpha \ln K,$$

where Y = output, A = the "stock of ideas", L = labor used to produce output, K = capital, and $0 < \alpha < 1$. The cumulative number of drugs approved (DRUG_STOCK) is analogous to the stock of ideas.

In principle, the hazard rate could depend on the number of drug *classes*, as well as (or instead of), the number of drugs. For example, introducing a drug that is the first in its class might have a greater impact on the hazard rate than introducing a drug that is the fifth in its class. We will test for this by estimating versions of the model that include the number of drug classes as well as the number of drugs.[18]

Inclusion of fixed cancer-site and year effects means that we are comparing the (percentage) *changes* in hazard rates of different cancer sites during the same period. Estimates of β_{1k} that are negative and significantly different from zero would signify that there were above-average declines in the hazard rates of cancer sites with above-average increases in the stock of drugs, *ceteris paribus*.

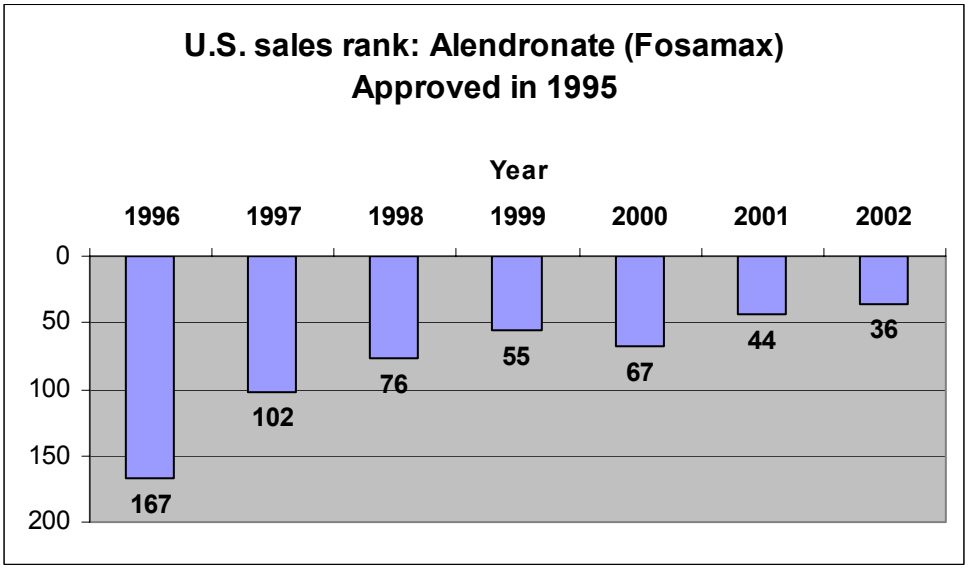
Instead of modeling hazard rates, one could model survival rates. Since, by definition, $H_t = (S_t - S_{t+1})/ S_t$, where H_t denotes the hazard rate during period t and S_t denotes the percent surviving until the beginning of period t,

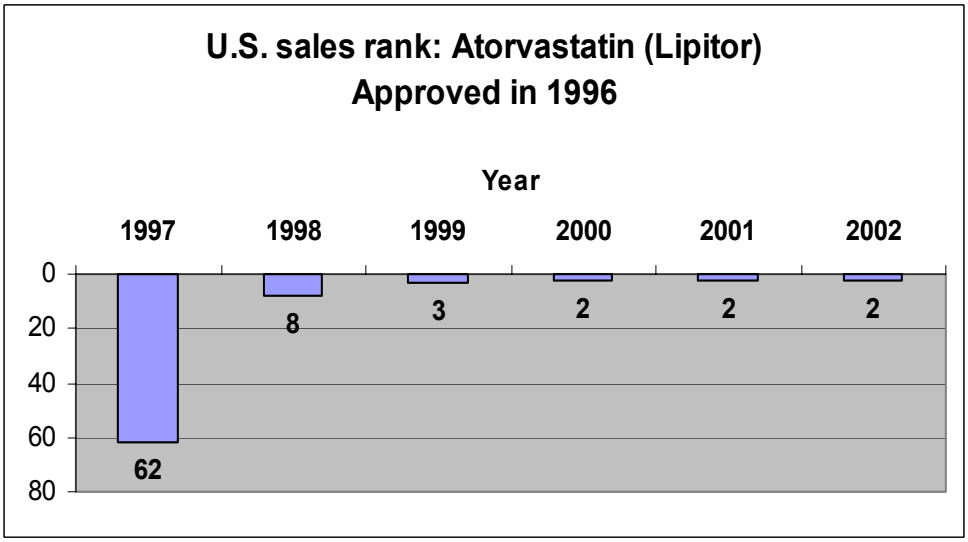
$$S_n = (1 - H_1) * (1 - H_2) * \ldots * (1 - H_{n-1})$$

The probability of surviving until the beginning of year n is the product of one minus the hazard rate of years 1 through n-1.[19] For example, the 10-year survival rate of patients diagnosed in 1975 depends on their hazard rates during 1975-1984. Suppose a new drug was approved in 1980. This would be expected to reduce hazard rates after 1980 (or even later, due to diffusion lags, discussed below), but not before that date. For this reason, to pinpoint the effect of new drug approvals, modeling annual hazard rates is more appropriate than modeling multi-year survival rates.

[18] The distribution of drugs, by drug class, is shown in Appendix Table 2.
[19] This also implies that $\ln S_n = \Sigma_i^{n-1} \ln (1 - H_i) \approx - \Sigma_i^{n-1} H_i$

There is ample evidence that, after a new drug is approved, it takes a few years for that drug to be widely utilized. This may be illustrated using the following data on the U.S. sales ranks of two major (non-cancer) drugs approved during the 1990s.[20]





It took at least 3 years for each of these drugs to attain its peak sales rank. It therefore seems sensible to hypothesize a lag of about three years in the impact of the stock of approved drugs on the hazard rate. I estimated the model with alternative assumed lags (1 to 4 years). Assuming a 3-year lag yielded the best fit. These are the estimates I will report in the next section.

[20] Source: NDC Health, as reported on http://www.rxlist.com/top200.htm.

III. Estimates

Estimates of eq. (1), by number of years after diagnosis (1,2,…,8) , are reported in Table 3. All equations included 30 cancer-site fixed effects and year fixed effects. The hazard models for the first six years (after diagnosis) were estimated using data on people diagnosed during 1975-1995, and included fixed effects for each of those years. Starting seven years after diagnosis, the sample period was reduced by one year for each year after diagnosis. For example, the year-7 hazard model was estimated using data on people diagnosed during 1975-1994 (due to censoring of the data after 12/31/2000). All equations were estimated by weighted least squares, weighting by the reciprocal of the estimated variance of the hazard rate.

The estimates shown in lines 1-10 are of the first-year hazard model, i.e. the hazard rate in the first year after diagnosis. The estimate of the coefficient on the lagged drug-stock is negative and highly statistically significant (line 1). This indicates that cancers for which the stock of drugs increased more rapidly tended to have larger declines in the first-year hazard rate (and larger increases in the one-year survival rate). During the period 1975-1995, the incidence-weighted mean increase in $\ln(DRUG\_STOCK_{i,t-3})$ was 1.31. (The stock of drugs increased 3.7-fold.) This implies that the 1975-1995 increase in the stock of drugs reduced the first-year hazard rate by about 22% (= .167 * 1.31). As shown in Figure 11, in 1975, the first-year hazard rate was 30.6%. Hence, we estimate that the 1975-1995 increase in the stock of drugs reduced the first-year hazard rate from 30.6% to 23.9%.

We consider next the coefficients on the other regressors in the first-year hazard model. The coefficient on $\ln(N_{i,t-k})$ is negative and highly significant (line 2), indicating that cancers with the highest growth of SEER incidence had the greatest declines in the first-year hazard rate. This may reflect the fact that cancers with the highest growth of SEER incidence had the greatest improvements in early detection and diagnosis. As the NCI observes, "The improved earlier detection and diagnosis of cancers may produce an *increase* in both incidence rates and survival rates. These increases can occur as a result of the introduction of a new procedure to screen subgroups of the population for a specific cancer; they need not be related to whether use of the screening test results in a

decrease in mortality from that cancer. As the proportion of cancers detected at screening increases, presumably as a result of increased screening of the population, patient survival rates will *increase*, because they are based on survival time *after diagnosis*."

Not surprisingly, the coefficient on $AGE\_MEAN_{i,t-k}$ is positive and highly significant (line 3): cancers with larger increases in mean age at diagnosis had smaller reductions in first-year hazard rates.[21]

The coefficient on $SURGERY\%_{i,t-k}$ is negative and highly significant (line 4). This indicates that cancers with greater increases in the probability of surgical treatment had greater reductions in the first-year hazard rate. However, the coefficient on $RADIATION\%_{i,t-k}$ is not significantly different from zero (line 5).

The last estimates to consider in the first-year hazard model are the coefficients on the stage-distribution variables (lines 6-10). As one might expect, the stage 4 coefficient is larger than the stage 2 coefficient, which is larger than the stage 1 coefficient. This indicates that a shift to later stages increases the first-year hazard rate. However the stage 1 coefficient is *smaller* than the stage 0 coefficient. This indicates that a shift from stage 0 (in situ) cancers to stage 1 (localized) cancers is associated with a *reduction* in the hazard rate. This is presumably due to differential rates of stage migration for different types of cancers.

Estimates of the second-year hazard model are shown in lines 12-21. In most respects, this set is qualitatively similar to the first-year set. Once again, the estimate of the coefficient on the lagged drug-stock is negative and highly statistically significant (line 12). The only notable difference from the first-year estimates is that the coefficient on $RADIATION\%_{i,t-k}$ is now *positive* and significant (line 16). This indicates that cancers with greater increases in the probability of radiation treatment had smaller reductions in the second-year hazard rate.

In the third-year hazard model estimates (lines 23-32), the coefficient on the lagged drug-stock is negative and similar in magnitude to the coefficients in the first two years, but is only marginally significant (p-value = 0.08). As in the estimates for the previous two years, the hazard rate increases with respect to age at diagnosis, and declines with respect to incidence and surgical intervention. The radiation variable is

[21] What is surprising, however, is that mean age at diagnosis increased from 61.4 in 1975 to 62.7 in 1995.

insignificant, and the stage-distribution coefficients (for stages 0-4) have their expected, monotonic profile.

In the fourth-year hazard model estimates (lines 34-43), the coefficient on the lagged drug-stock is *positive* and its magnitude is large (0.48), which is inconsistent with our hypothesis. However, the mean hazard rate in year 4 is substantially lower than it is in previous years, and we will show below that this large positive effect offsets only a small part of the negative effects of the drug stock on the hazard rates in years 1-3.

The remainder of Table 3 shows estimates of the hazard model in years 5-8. To summarize, in the first eight years, the coefficient on the drug stock is negative three times as often as it is positive, and it is negative and significant twice as often as it is positive and significant. Moreover, the coefficient on the drug stock is negative in the first three years (and significant in the first two), when the hazard rate is highest.

We estimated models that included the log of the number of drug classes in year t-3, as well as the log of the number of drugs in year t-3. In general, the coefficient on the drug-class variable was far from statistically significant, and inclusion of this variable had virtually no effect on the estimates of β_{1k}. This suggests that the introduction of a first-in-class drug does not increase cancer survival more than the introduction of subsequent drugs within the class (over and above the general effect of diminishing marginal productivity).

IV. Interpretation and Implications of Estimates

We can use the estimates of the drug-stock coefficients for all years (years 1-23) to assess the effect of new drug introductions on the entire cancer survival distribution function and on life expectancy at time of diagnosis. We begin with the vector of 1975 hazard rates shown in Figure 11. These reflect the prevailing conditions at that time: the distribution of cancers by site and stage, average age of patients diagnosed, percent of patients receiving surgery and radiation, etc. They also reflect the drugs that were available at that time.

We then use our estimates to "predict" hazard rates in 1995, given the drugs available in 1995, if all other conditions had remained the same as they had been in 1973. The predicted k-year hazard rate (HAZ_PRE_k) is computed as follows:

$$HAZ\_PRE_k = HAZ\_ACT_k * (1 + \beta_{1k}\, \Delta\ln(DRUG\_STOCK_{t-3}))$$

where HAZ_ACT_k is the actual 1975 k-year hazard rate and $\Delta\ln(DRUG\_STOCK_{t-3})$ is the 1975-1995 change in the incidence-weighted mean of $\ln(DRUG\_STOCK_{i,t-3})$. As noted above, this is equal to 1.31. Hence

$$HAZ\_PRE_k = HAZ\_ACT_k * (1 + (1.31* \beta_{1k})).$$

From the vectors of actual and predicted hazard rates, we can compute vectors of actual and predicted survival rates:

$$SURV\_ACT_n = (1 - HAZ\_ACT_1) * (1 - HAZ\_ACT_2) * \ldots * (1 - HAZ\_ACT_{n-1})$$

$$SURV\_PRE_n = (1 - HAZ\_PRE_1) * (1 - HAZ\_PRE_2) * \ldots * (1 - HAZ\_PRE_{n-1})$$

These calculations are shown in Table 4. Columns 1-4 show the estimates of β_{1k} for k =1,2,…,24. Actual 1975 hazard rates (HAZ_ACT_k) are shown in column 5. Predicted 1975 hazard rates (computed as $HAZ\_PRE_k = HAZ\_ACT_k * (1 + (1.31* \beta_{1k}))$) are shown in column 6. Actual and predicted 1975 survival rates are shown in columns 7 and 8. Actual 1995 survival rates for years 1-7 are shown in column 9. The three vectors of survival rates are plotted in Figure 13.

Our estimates imply that, ceteris paribus—holding constant the cancer site- and stage-distribution, cancer incidence, mean age at diagnosis, and the probability of surgery and radiation—the 1975-1995 increase in the stock of drugs increased the 1-year cancer survival rate from 69.4% to 76.1%, the 5-year cancer survival rate from 45.5% to 51.3%, and the 10-year cancer survival rate from 34.2% to 38.1%.

From these figures, it appears that the increase in the stock of drugs accounted for a very large percentage of the actual increase in survival rates between 1975 and 1995. For example, the difference between 1-year predicted and actual 1975 survival rates (76.1% - 69.4%) is 91% of the actual increase in 1-year survival rates (76.7% - 69.4%). But these are crude survival rates, not age-adjusted rates.[22] The mean age of people diagnosed with cancer increased during the sample period. As a result, the age-adjusted

[22] Since we include mean age as a covariate in eq. (1), β_{ik} is an estimate of the effect of the drug stock on the *age-adjusted* hazard rate.

survival rate increased more than the crude survival rate. Using methods similar to those described above, we can "predict" what the 1975 survival function would have been if mean age in 1975 had been the same as it was in 1995. These are the calculations for years 1-6:

Year	1975 survival rate	1975 survival rate if mean age same as in 1995	1995 survival rate
0	100.0%	100.0%	100.0%
1	69.4%	66.4%	76.7%
2	59.2%	55.9%	67.9%
3	53.2%	50.0%	62.6%
4	49.0%	45.8%	58.6%
5	45.5%	42.5%	55.2%
6	42.5%	39.8%	51.8%

Consequently, the increase in the stock of drugs accounted for a smaller percentage of the age-adjusted increase in survival rates than it did of the crude increase:

Year	% of increase in *crude* survival rate accounted for by increase in stock of drugs	% of increase in *age-adjusted* survival rate accounted for by increase in stock of drugs
1	91%	65%
2	92%	66%
3	88%	66%
4	47%	35%
5	60%	46%
6	74%	57%

Although the surgical treatment rate (SURGERY%) had a significant negative effect on hazard rates in a number of years, there was very little change in the overall surgical treatment rate during the sample period—it was actually slightly lower in 1995 (62.6%) than it was in 1975 (63.4%). Hence, our estimates imply that changes in the surgical treatment rate had a negligible impact on cancer survival rates during this period. The radiation treatment rate also remained almost constant (at about 27%); its impact on cancer survival rates also appears to have been negligible.

The vectors of actual and predicted survival rates allow us to compute actual and predicted values of life expectancy at time of diagnosis:

$$LE\_ACT = \Sigma_{k=0} (k + 0.5) * (SURV\_ACT_k - SURV\_ACT_{k+1})$$

$$LE\_PRE = \Sigma_{k=0} (k + 0.5) * (SURV\_PRE_k - SURV\_PRE_{k+1})$$

Since the cutoff date for the SEER PUF is 12/31/2000, for people diagnosed in 1975, the data are right-censored at 25 years. About 17.5% of people diagnosed in 1975 were alive at the cutoff date. For these people, we need to make an assumption about remaining life expectancy, and this assumption will affect the levels of LE_ACT and LE_PRE. However, because $SURV\_PRE_{25}$ is virtually equal to $SURV\_ACT_{25}$, this assumption will *not* affect the difference LE_PRE - LE_ACT. Estimated values of LE_PRE, LE_ACT, and their difference, under three alternative assumptions about the longevity (from time of diagnosis) of people surviving past the cutoff date (L') are as follows:

L'	LE_ACT	LE_PRE	difference
27.5	9.13	10.15	1.02
30.0	9.56	10.59	1.03
35.0	10.44	11.47	1.03

If we assume that people diagnosed in 1975 who are alive at the end of 2000 die in 2005 (30 years after diagnosis), then the actual life expectancy of all people diagnosed in 1975 was 9.56 years, and their predicted life expectancy (had they had access to the 1995 stock of drugs) was 10.59 years. In this sense, the 1975-1995 increase in the lagged stock of drugs made the life expectancy of people diagnosed with cancer in 1995 just over a year greater than the life expectancy of people diagnosed with cancer in 1975.

In a previous study (Lichtenberg (2003)), I estimated the effect of launches of new drugs for *all* diseases on the longevity of the entire populations of 52 countries (including the U.S.) during the period 1986-2000. The methodology used in that study differed from the one used here: the dependent variable was a measure of the age distribution of deaths, rather than the hazard rate of people previously diagnosed.[23] Although the sample and methodology were quite different, the estimated contribution of pharmaceutical innovation to longevity increase was very similar to the one calculated above. Before I estimated that the average annual increase in life expectancy of the entire population resulting from new chemical entity launches is .056 years, or 2.93 weeks. Now I estimate that the average annual increase in life expectancy of Americans

[23] 27% of the deaths occurring in that sample were caused by cancer.

diagnosed with cancer resulting from new chemical entity launches is .051 years, or 2.67 weeks.

According to the National Cancer Institute, the lifetime risk of being diagnosed with cancer is about 40%. This implies that the 1975-1995 increase in the lagged stock of cancer drugs increased the life expectancy of the *entire U.S. population* by 0.4 years (= 40% * 1.03 years). Between 1975 and 1995, U.S. life expectancy at birth increased by 3.8 years, from 72.3 years to 76.1 years.[24] Thus, new cancer drugs accounted for 10.7% of the overall increase in life expectancy at birth.

How much did it cost to achieve this additional year of life per person diagnosed with cancer? To determine this cost (c), I will estimate the average amount spent on cancer drugs by a cancer patient from time of diagnosis until death, using the following formula:

$$c = \text{total drug expenditure in 1995} \times \frac{\text{cancer drug expenditure}}{\text{total drug expenditure}} \div \text{1995 cancer prevalence} \times \text{mean life expectancy at time of diagnosis}$$

According to the Center for Medicare and Medicaid Services, Americans spent $60.8 billion on prescription drugs in 1995.[25] We have two different estimates of the share of cancer drug expenditure in total drug expenditure. According to the Census Bureau, "specific antineoplastic agents" accounted for 1.3% of the value of 1995 shipments of pharmaceutical preparations (except biologicals). According to IMS Health, cytostatic drugs accounted for 3.6% of total U.S. drug sales in 2002.[26] Hence total cancer drug expenditure during 1995 was presumably between $803 million (= 1.3% * $60.8 billion) and $2194 million (= 3.6% * $60.8 billion). According to the NCI, cancer prevalence was 8.0 million in 1995. Hence average 1995 expenditure on cancer drugs per cancer patient was in the range $100-$274. As discussed above, estimated life expectancy of people diagnosed with cancer in 1995 is about 10.6 years. Hence, average (undiscounted) cancer drug expenditure per cancer patient from diagnosis till death is in the range $1064-$2907. The cost per life-year gained is in the $1040-$2842 range.

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[24] Arias and Smith (2003), Table 11.
[25] http://cms.hhs.gov/statistics/nhe/historical/t2.asp
[26] http://open.imshealth.com/download/oct2002.pdf

This is far below recent estimates of the value of a statistical life-year. Murphy and Topel (2003) and Nordhaus (2003) estimate that this value is in the neighborhood of $150,000. Moreover, since drug expenditures calculated above include expenditures on old as well as new drugs, this range represents an upper bound on the cost per life-year gained. Data from the Medical Expenditure Panel Survey suggest that, in general, new drugs—drugs approved within the previous 15-20 years—account for about half of total drug expenditure. If this applied to cancer drugs, we should divide the cost per life-year estimates by two. However, given the rapid increase in the number of cancer drugs, new cancer drugs may account for more than half of total cancer drug expenditure.

We have examined the effect of new cancer drugs on the life expectancy, or number of remaining life-years, of cancer patients at time of diagnosis. Ideally, we would like to measure the effect on the number of *quality-adjusted* life-years. Health economists generally postulate a quality-of-life index (QOL) that ranges between 1 (corresponding to perfect health) and 0 (corresponding to death). The number of quality-adjusted life-years (QALYs) is the number of years multiplied by the average value of the quality-of-life index during those years. For example, 10 years lived at mean QOL=0.7 equals 7 QALYs. Unfortunately, SEER does not collect any data on the quality of life of cancer survivors, so calculating the impact of new cancer drugs on the number of QALYs is not feasible.

While new cancer drugs appear to have increased the longevity of cancer survivors by about a year, QOL in that additional year is likely to have been much less than 1. However, it is also plausible that, in addition to delaying death, new cancer drugs increased the quality of life of people at a given number of years after diagnosis. If this is the case, the increase in QALYS is not necessarily less than the increase in life expectancy.

This is illustrated by Figure 14. Suppose that new cancer drugs shifted the time-QOL profile from the curve labeled ‘1975’ to the curve labeled ‘1995’. This shift reflects the estimated increase in life expectancy, from 9.56 years to 10.59 years. The increase in life-years is equal to the sum of areas A and B. This is significantly larger than area A alone—the QOL-adjusted value of the additional 1.03 years. But we hypothesize that new drugs also increased average QOL from year 0 to year 9.56. The increase in QALYs

during that period is measured by area C. Clearly A < (A + B), but (A + C) is not necessarily smaller than (A + B). Whether it is depends on the relative magnitudes of B and C: average QOL in the marginal years versus QOL improvement in the inframarginal years.

One might suppose that increasing the longevity of cancer patients will inevitably result in an increase in medical expenditure on them. But Lubitz et al (2003) found that although elderly persons in better health had a longer life expectancy than those in poorer health, they had similar cumulative health care expenditures until death.

V. Summary

The age-adjusted U.S. mortality rate from all malignant cancers was essentially the same in 2000 as it was in 1969. During the same period, the age-adjusted mortality rate from all other causes of death declined by 38%. This suggests that the war on cancer has been a failure. However, the relative stability of the cancer mortality rate is the result of two offsetting trends: an increase in the cancer incidence rate, and an increase in the relative survival rate. The five-year relative survival rate from all malignant cancers increased from 50.0% in 1975-1979 to 62.7% in 1995. This increase is not due to a favorable shift in the distribution of cancers.

A variety of factors, including technological advances in diagnostic procedures that led to earlier detection and diagnosis, have probably contributed to this increase. This paper's main objective has been to assess the contribution of pharmaceutical innovation to the increase in cancer survival rates. Only about one third of the approximately 80 drugs currently used to treat cancer had been approved when the war on cancer was declared in 1971. In other words, there has been a threefold increase in the size of the cancer drug armamentarium in the last three decades.

The percentage increase in the survival rate varied considerably across cancer sites. For example, the survival rate for colon cancer increased from 41% to 63%, while the survival rate from prostate cancer increased from 43% to 98%. We hypothesized that these differential rates of progress were partly attributable to different rates of pharmaceutical innovation for different types of cancer. The rate of increase of the stock

of drugs also varied considerably across cancer sites in a given period, and also across periods for a given cancer site. For example, between 1969 and 2002, there was a 4.4-fold increase in the stock of drugs for breast cancer, and an 8-fold increase in the stock of drugs for prostate cancer. Also, the stock of drugs for colon and rectum cancer remained constant from 1974 to 1980, but then doubled from 1980 to 1982.

We tested this hypothesis within a "differences in differences" framework, by estimating models of cancer mortality rates using longitudinal, annual, cancer-site-level data based on records of 2.1 million people diagnosed with cancer during the period 1975-1995. The explanatory variable of primary interest was the (lagged value of the) cumulative number of cancer drugs approved to treat that cancer type. The following covariates were also included in the model: fixed cancer site effects, fixed year effects, incidence, stage distribution of diagnosed patients, mean age at diagnosis, percent of patients having surgery, and percent of patients having radiation. Including these variables is likely to control for the effect of technological advances in diagnostic procedures.

We argued that estimation of hazard-rate models was better suited to our purposes than estimation of survival-rate models, and we estimated separate hazard models for each of the years following diagnosis. Overall, the estimates indicated that cancers for which the stock of drugs increased more rapidly tended to have larger reductions in hazard rates. In hazard-rate models for the first eight years after diagnosis, the coefficient on the drug stock was negative three times as often as it was positive, and it was negative and significant twice as often as it was positive and significant. Moreover, the coefficient on the drug stock was negative in the first three years (and significant in the first two), when the hazard rate is highest. The estimates provided no support for the hypothesis that the introduction of a first-in-class drug increases cancer survival more than the introduction of subsequent drugs within the class.

We used the estimates of the drug-stock coefficients to assess the effect of new drug introductions on the cancer survival distribution function and on life expectancy at time of diagnosis. The estimates implied that, ceteris paribus—holding constant the cancer site- and stage-distribution, cancer incidence, mean age at diagnosis, and the probability of surgery and radiation—the 1975-1995 increase in the stock of drugs

increased the 1-year crude cancer survival rate from 69.4% to 76.1%, the 5-year rate from 45.5% to 51.3%, and the 10-year rate from 34.2% to 38.1%. The increase in the stock of drugs accounted for about 50-60% of the increase in age-adjusted survival rates in the first 6 years after diagnosis.

Although the surgical treatment rate had a significant negative effect on hazard rates in a number of years, there was very little change in the overall surgical treatment rate during the sample period. Hence, our estimates imply that changes in the surgical treatment rate (and in the radiation treatment rate) had a negligible impact on cancer survival rates during this period.

We also estimated that the 1975-1995 increase in the lagged stock of drugs made the life expectancy of people diagnosed with cancer in 1995 just over a year greater than the life expectancy of people diagnosed with cancer in 1975. This figure increased from about 9.6 to 10.6 years. This is very similar to the estimate of the contribution of pharmaceutical innovation to longevity increase I obtained in an earlier study, although that study was based on a very different sample (all diseases in 52 countries) and methodology.

Since the lifetime risk of being diagnosed with cancer is about 40%, the estimates imply that the 1975-1995 increase in the lagged stock of cancer drugs increased the life expectancy of the *entire U.S. population* by 0.4 years, and that new cancer drugs accounted for 10.7% of the overall increase in U.S. life expectancy at birth.

The estimated cost to achieve the additional year of life per person diagnosed with cancer is well below recent estimates of the value of a statistical life-year. The average amount spent on (new *and* old) cancer drugs by a cancer patient from time of diagnosis until death in 1995 was apparently below $3000. Previous authors estimate that the value of a statistical U.S. life-year is in the neighborhood of $150,000.

Ideally, we would have measured the effect of new cancer drugs on the number of *quality-adjusted* life-years (QALYs), but we were unable to do so due to lack of data. While new cancer drugs appear to have increased the longevity of cancer survivors by about a year, quality of life in that additional year is likely to have been much less than 1. However, if new cancer drugs increased the quality of life of people as well as delayed

their death, the increase in QALYS is not necessarily less than the increase in life expectancy.

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Figure 1
U.S. Mortality Age-Adjusted Rates, Total U.S., 1969-2000
(Index: 1969=1.00)

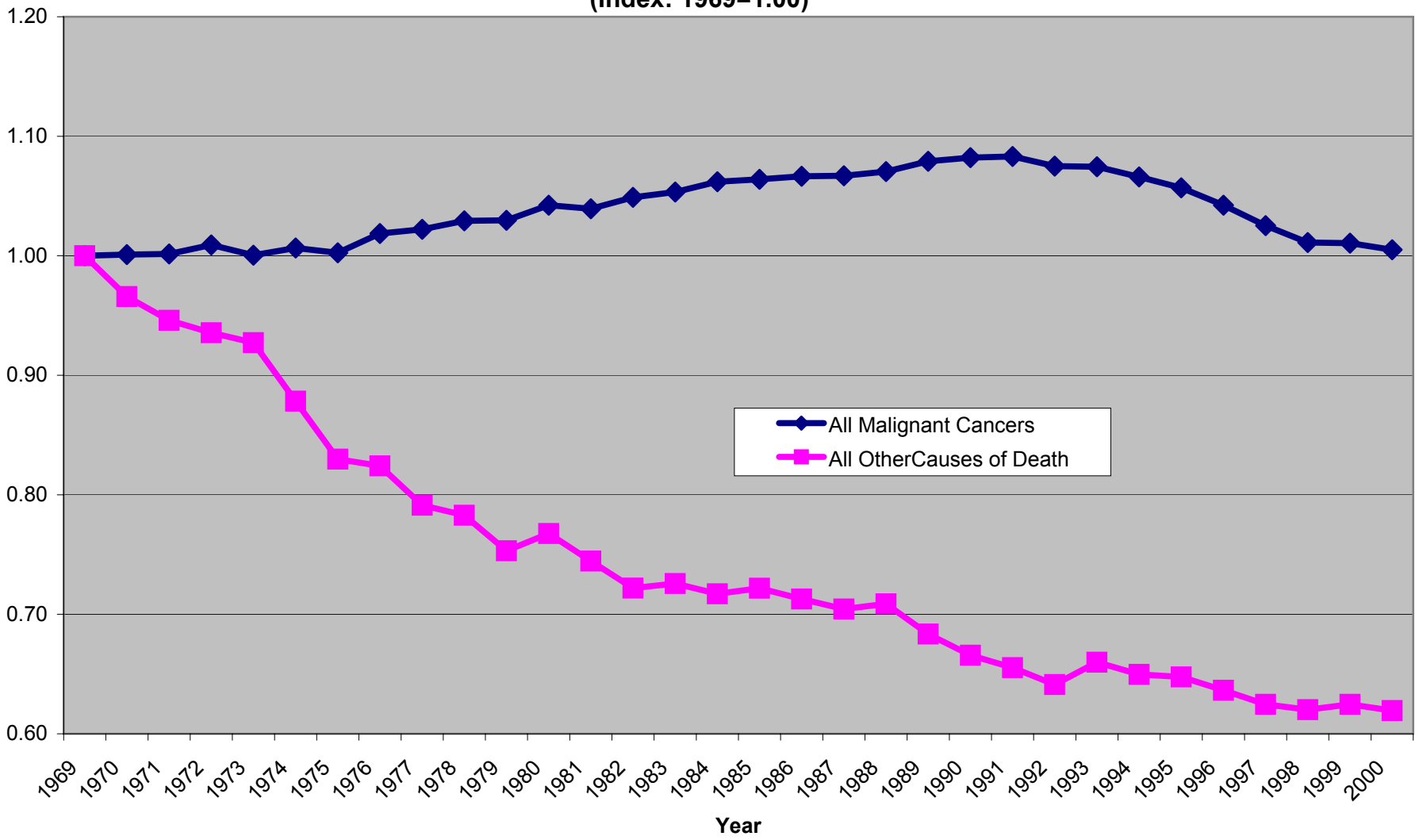


Figure 2
Cancer incidence rate:
Number of new cancer cases per year per 100,000 persons

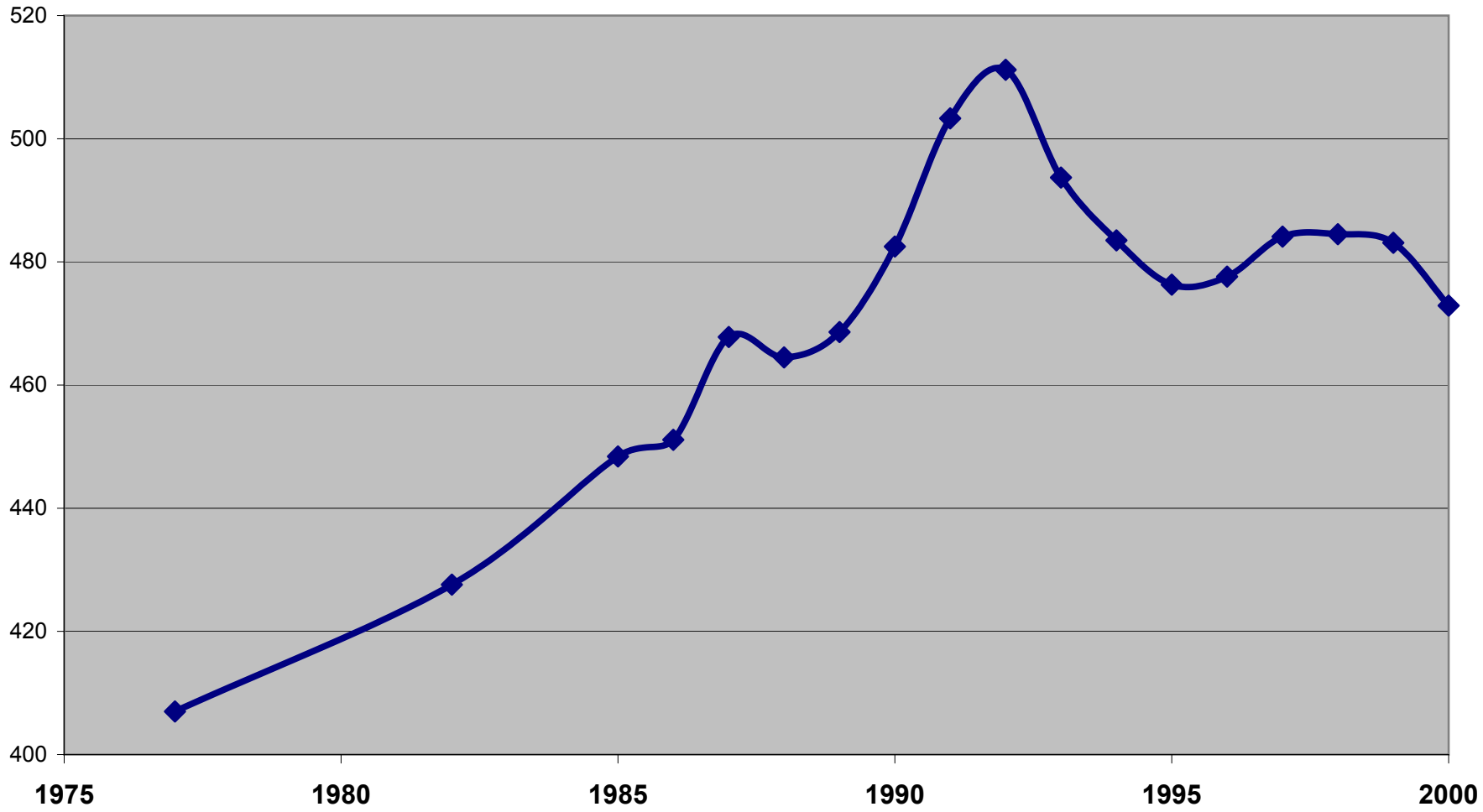


Figure 3
5-year relative survival rate

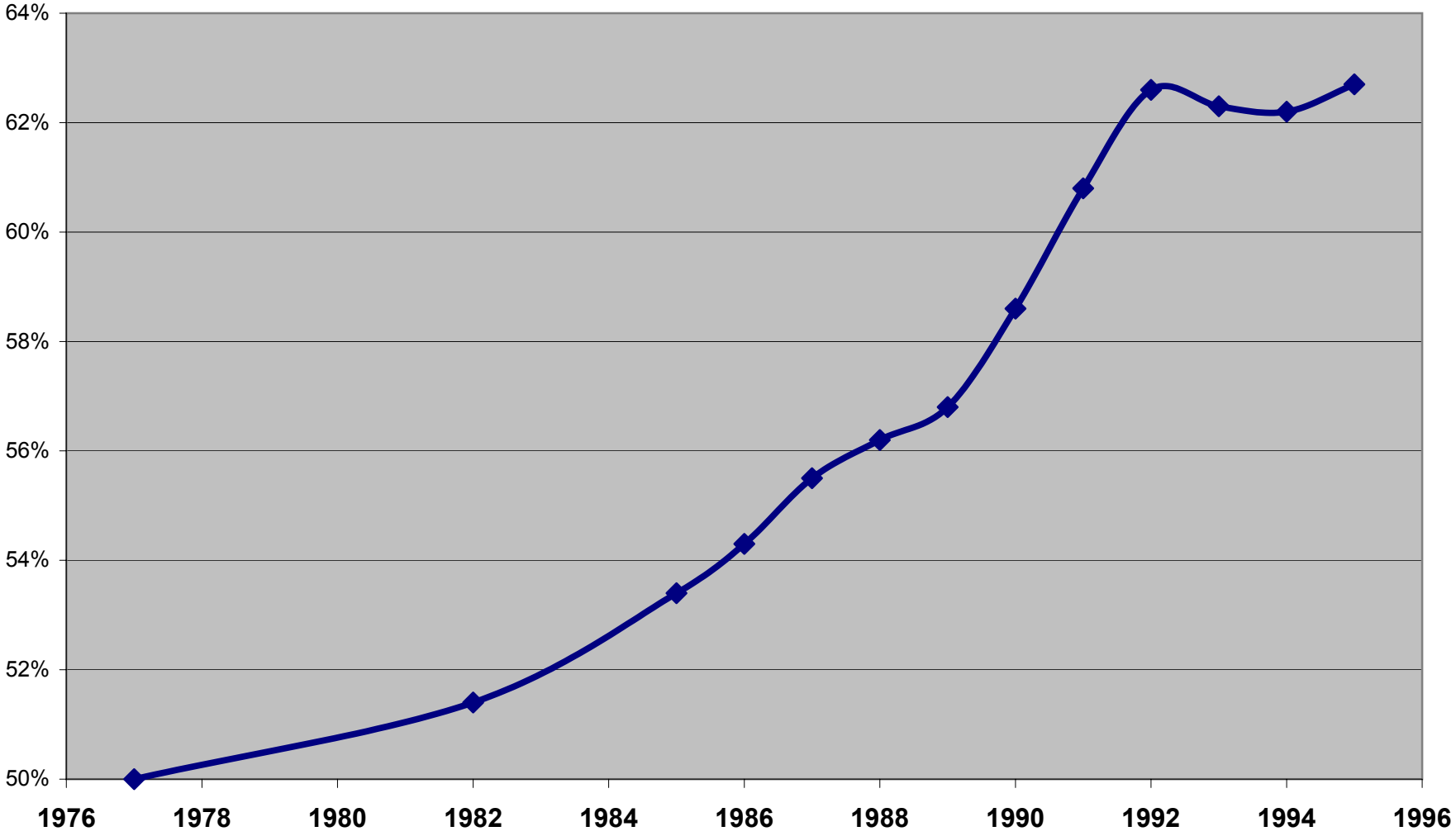
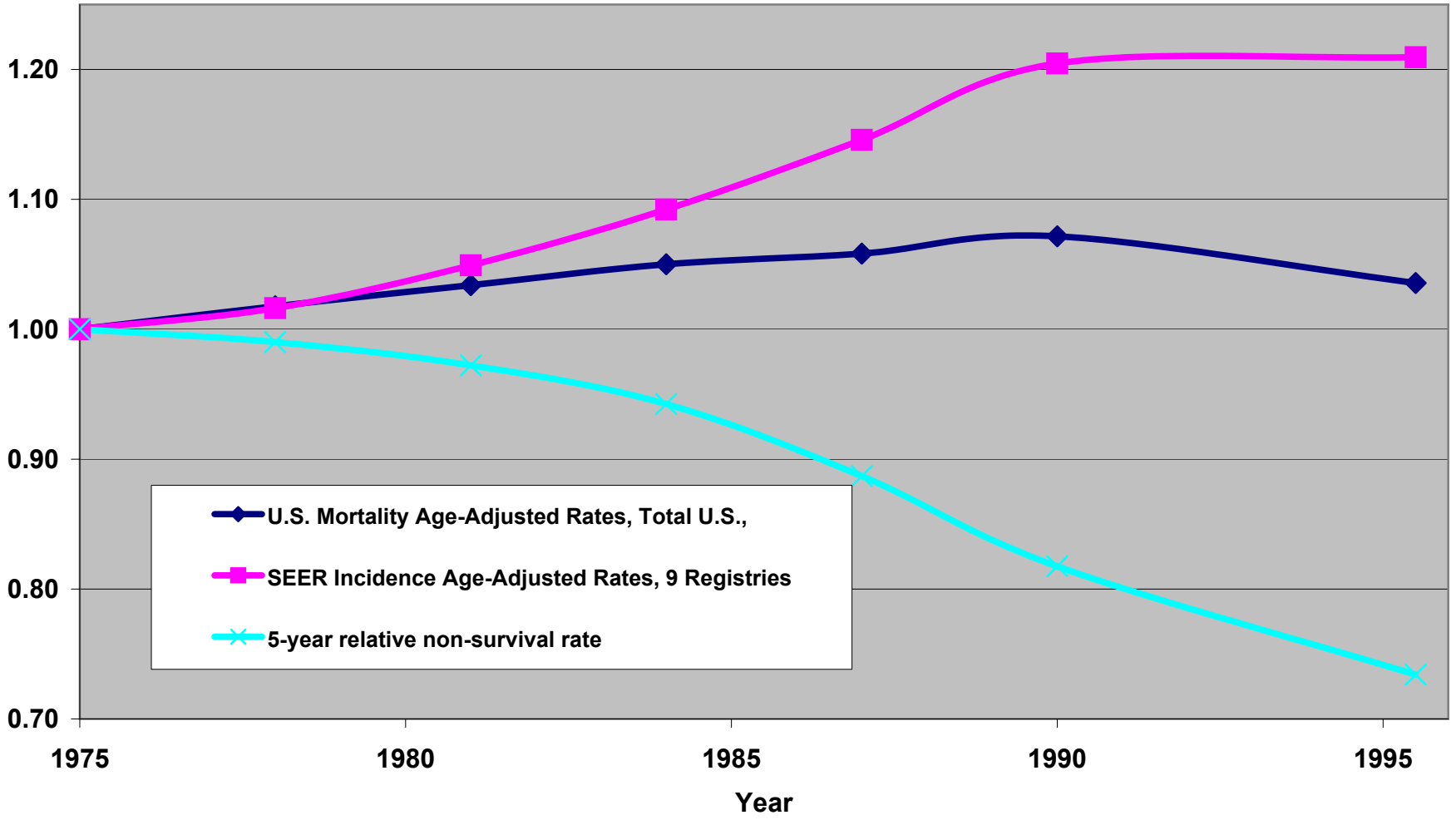


Figure 4
Trends in cancer mortality, incidence, and survival
(Indices: 1975=1.00)



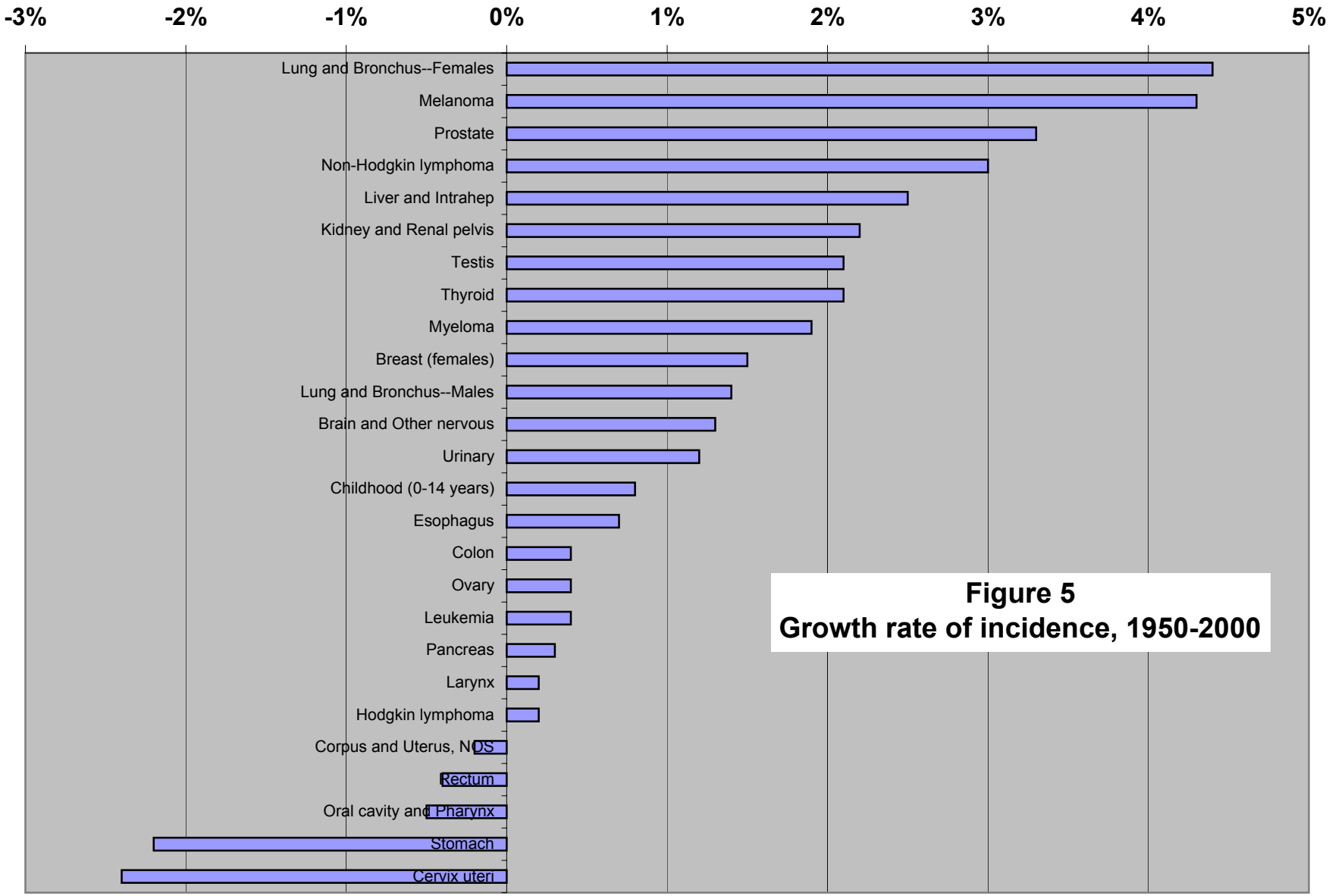


Figure 5
Growth rate of incidence, 1950-2000

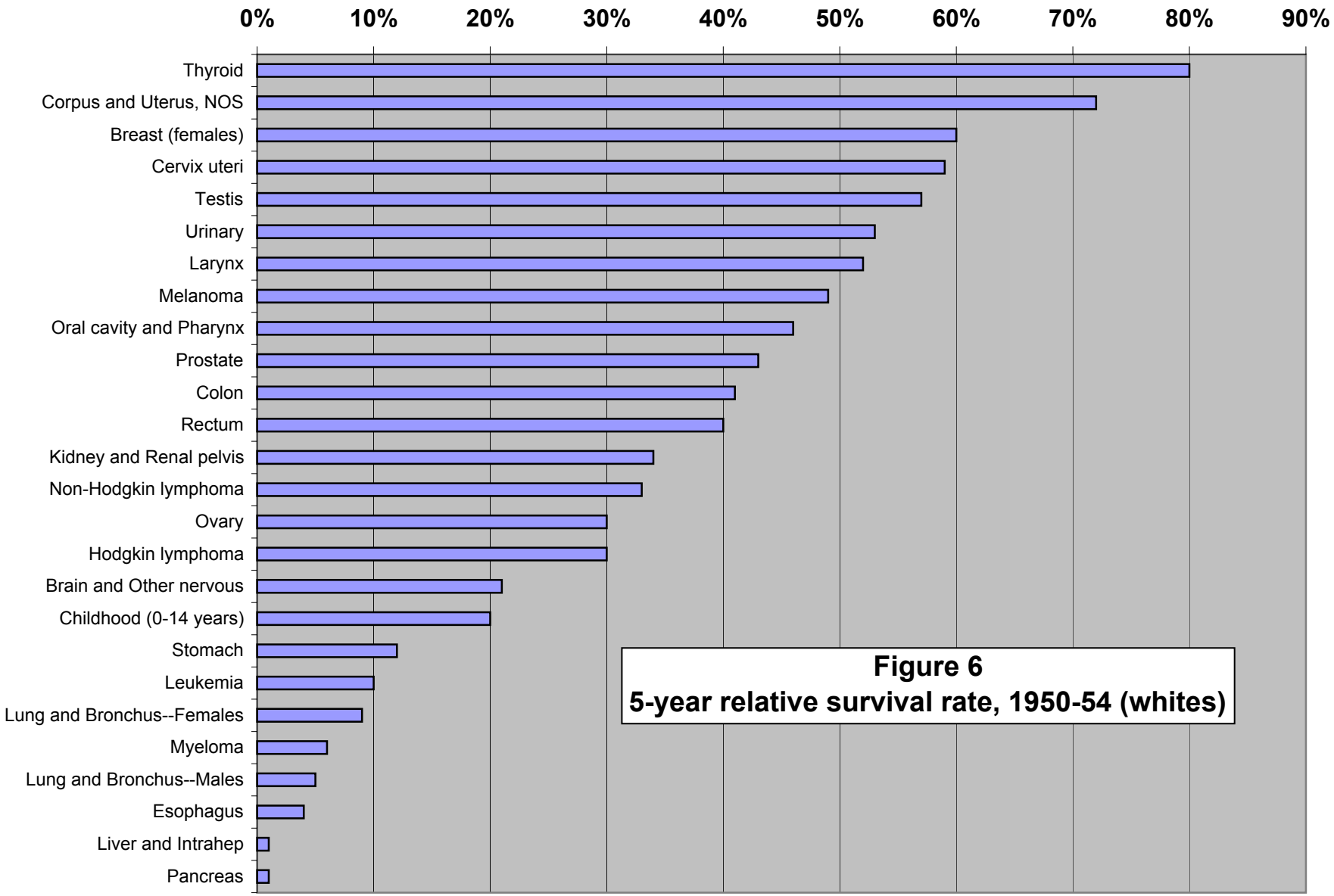

0%
10%
20%
30%
40%
50%
60%
70%
80%
90%
Thyroid
Corpus and Uterus, NOS
Breast (females)
Cervix uteri
Testis
Urinary
Larynx
Melanoma
Oral cavity and Pharynx
Prostate
Colon
Rectum
Kidney and Renal pelvis
Non-Hodgkin lymphoma
Ovary
Hodgkin lymphoma
Brain and Other nervous
Childhood (0-14 years)
Stomach
Leukemia
Lung and Bronchus--Females
Myeloma
Lung and Bronchus--Males
Esophagus
Liver and Intrahep
Pancreas
Figure 6
5-year relative survival rate, 1950-54 (whites)

Figure 7
Relationship between initial survival rate and incidence growth

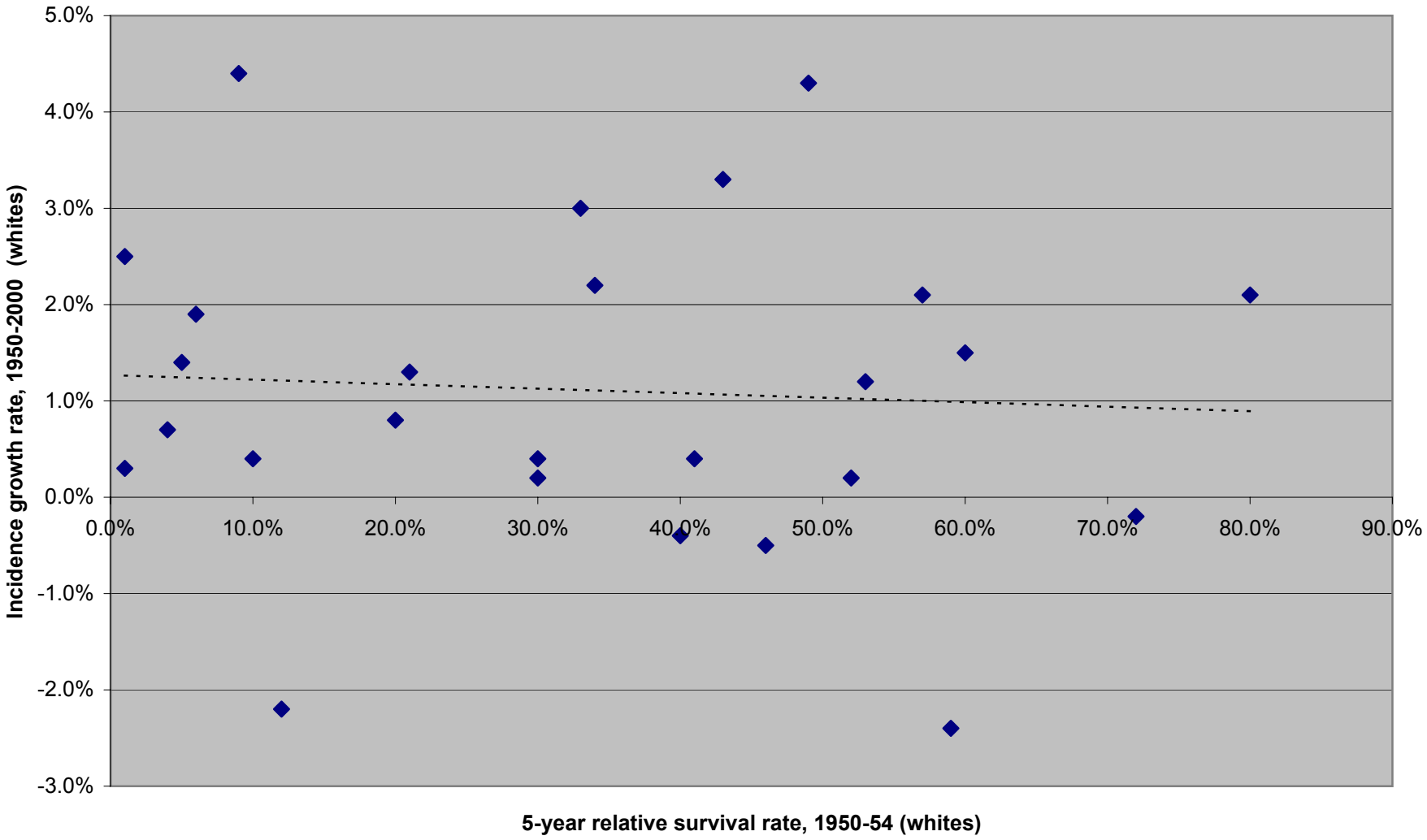


Figure 8
Survival rates, 1992-99 vs. 1950-54

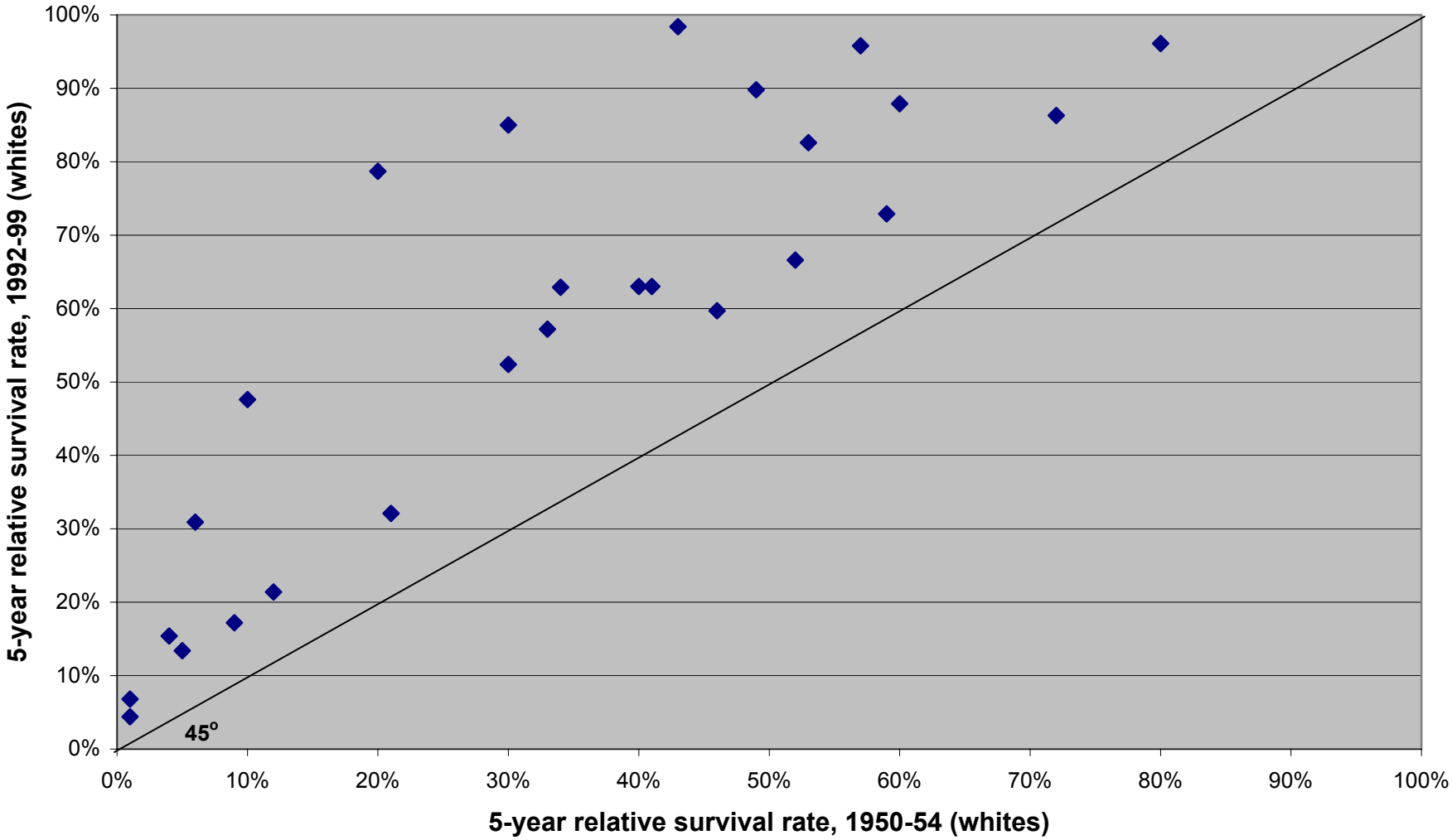
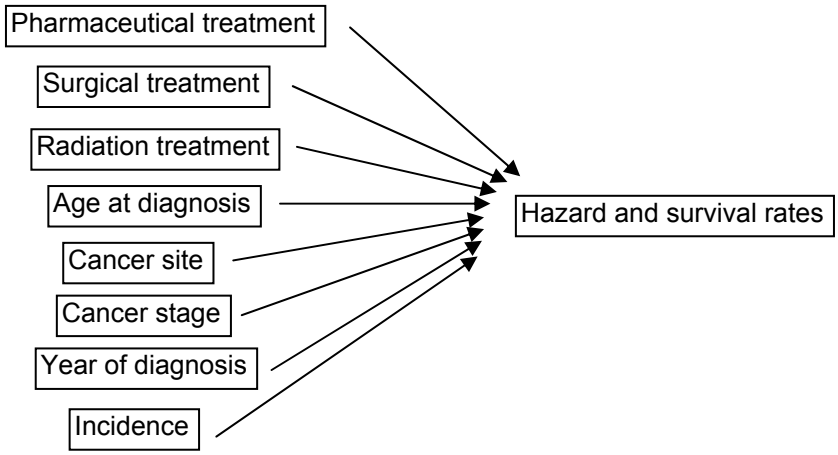
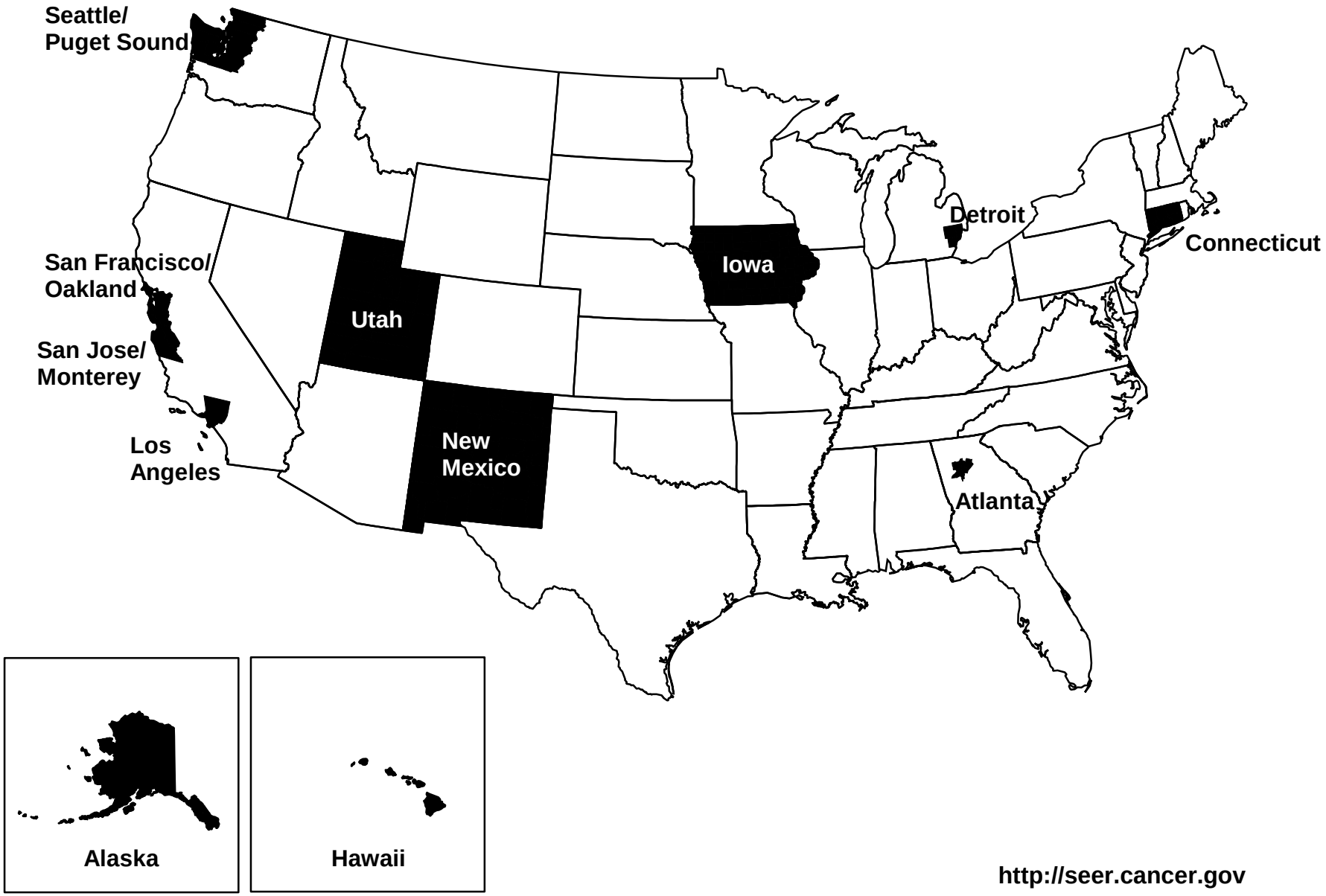


Figure 9
Model of hazard and survival rates



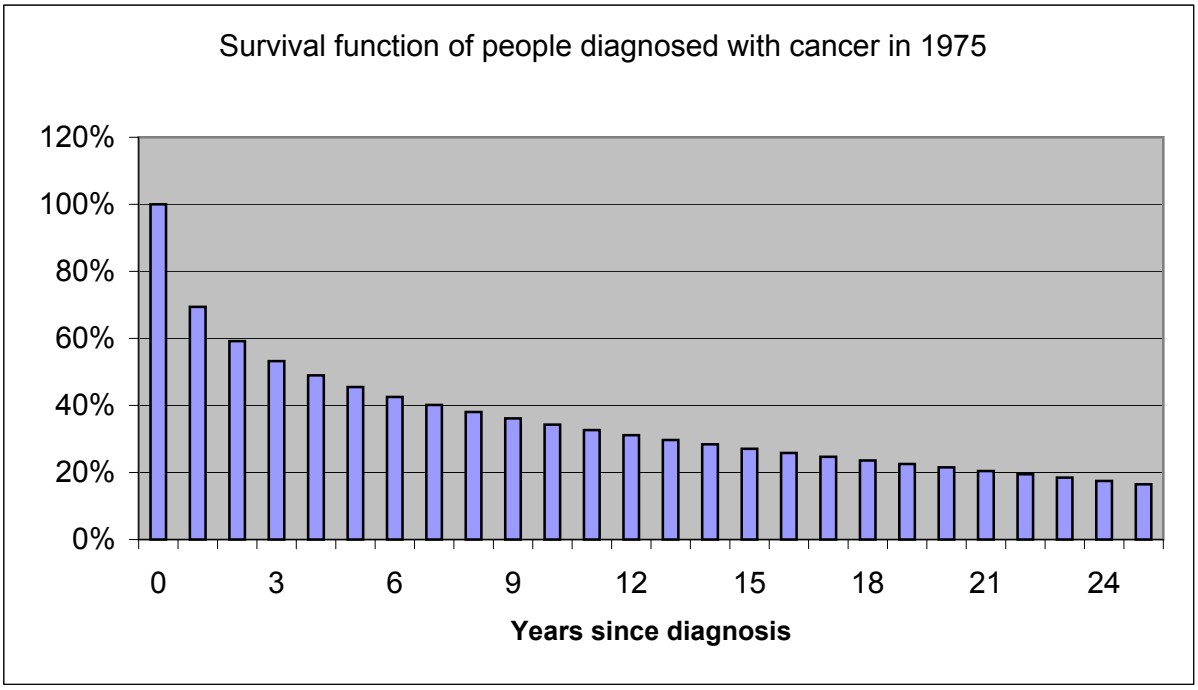
Surveillance, Epidemiology, and End Results Program, 2003
National Cancer Institute
U.S.A



http://seer.cancer.gov

Figure I-1

Figure 11
Survival and hazard functions of people diagnosed with cancer in 1975



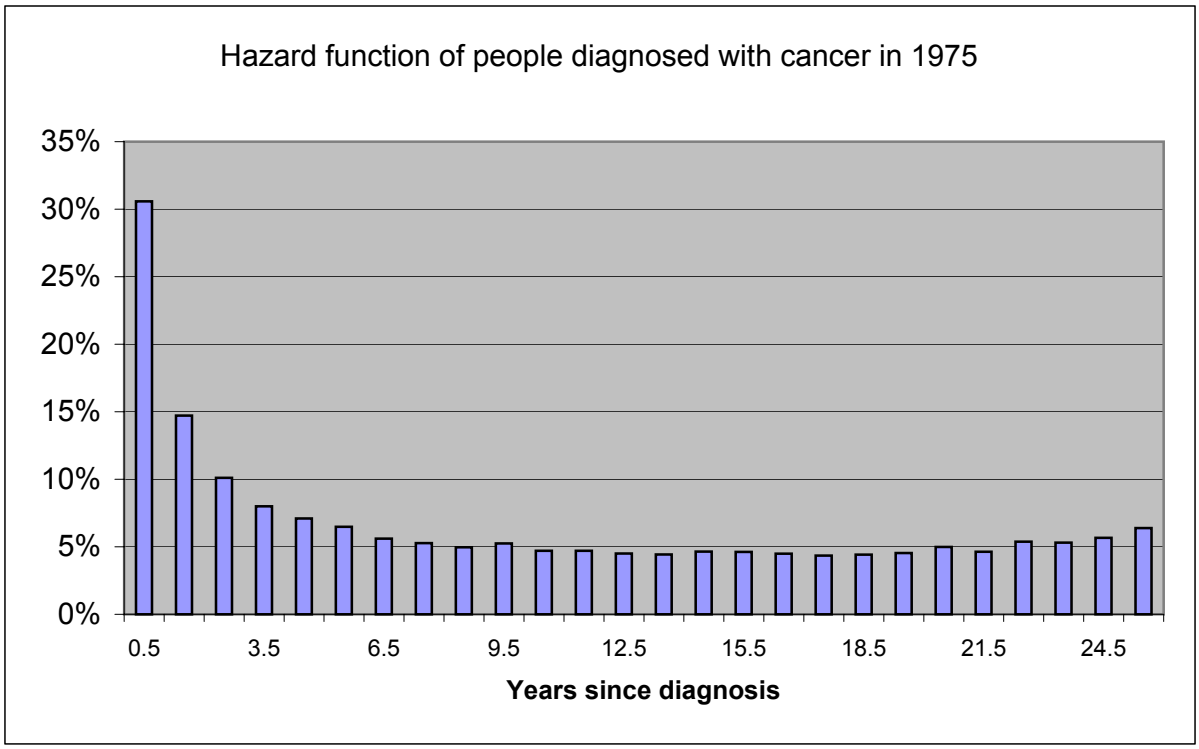


Figure 12
Log change since 1969 in stock of drugs approved for selected cancer sites

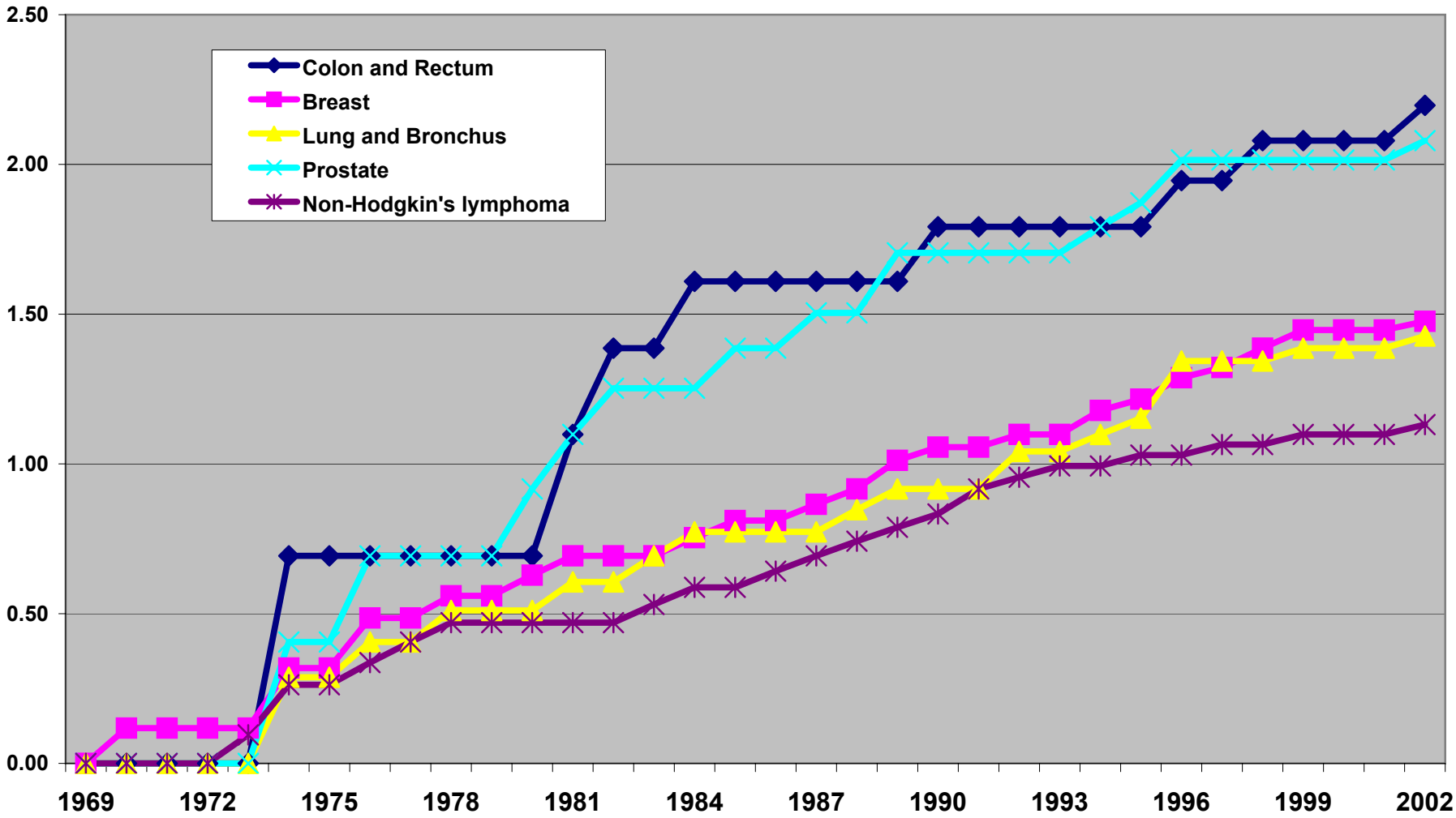


Figure 13
Actual vs. predicted survival functions

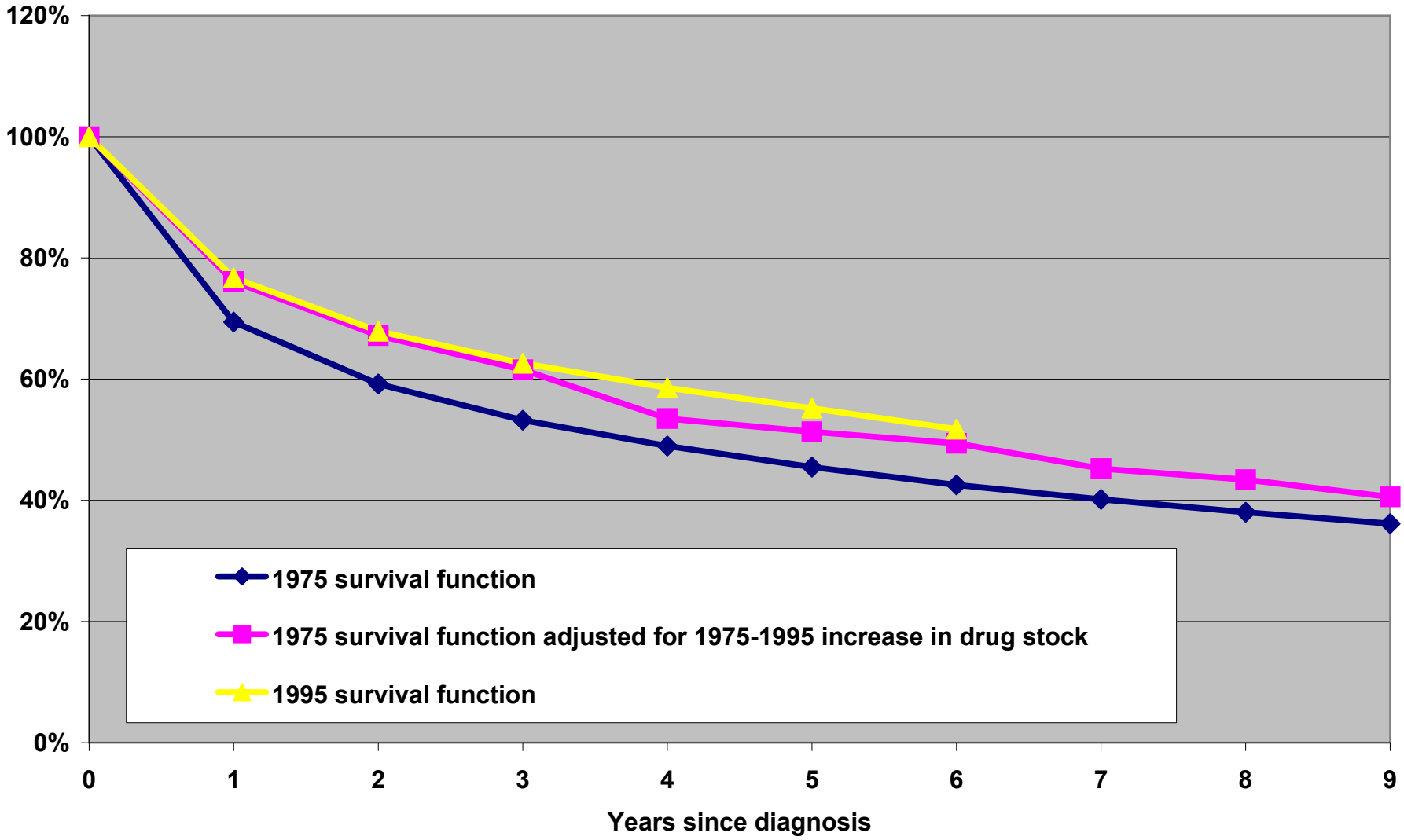


Figure 14
Hypothetical effect on new drugs on time-QOL profile

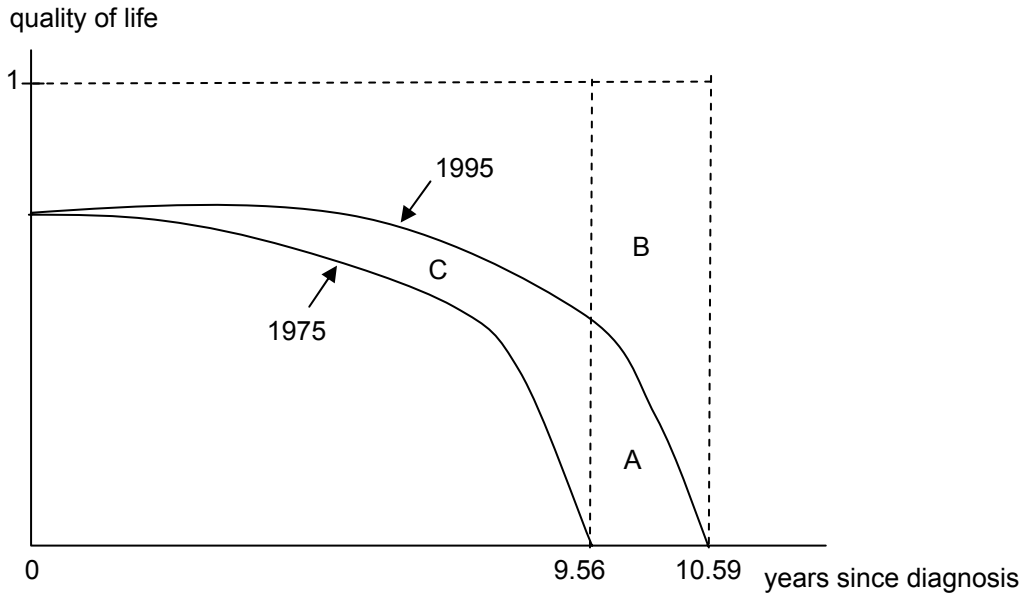


Table 1
5-year relative survival rates, by primary cancer site, 1950-54 and 1992-99

Primary Site	5-year relative survival rate, 1950-54 (whites)	5-year relative survival rate, 1992-99 (whites)
All	35.0%	64.4%
Oral cavity and Pharynx	46.0%	59.7%
Esophagus	4.0%	15.4%
Stomach	12.0%	21.4%
Colon and Rectum	37.0%	63.0%
Colon	41.0%	63.0%
Rectum	40.0%	63.0%
Liver and Intrahep	1.0%	6.8%
Pancreas	1.0%	4.4%
Larynx	52.0%	66.6%
Lung and Bronchus	6.0%	15.1%
Lung and Bronchus--Males	5.0%	13.4%
Lung and Bronchus--Females	9.0%	17.2%
Melanoma	49.0%	89.8%
Breast (females)	60.0%	87.9%
Cervix uteri	59.0%	72.9%
Corpus and Uterus, NOS	72.0%	86.3%
Ovary	30.0%	52.4%
Prostate	43.0%	98.4%
Testis	57.0%	95.8%
Urinary	53.0%	82.6%
Kidney and Renal pelvis	34.0%	62.9%
Brain and Other nervous system	21.0%	32.1%
Thyroid	80.0%	96.1%
Hodgkin lymphoma	30.0%	85.0%
Non-Hodgkin lymphoma	33.0%	57.2%
Myeloma	6.0%	30.9%
Leukemia	10.0%	47.6%
Childhood (0-14 years)	20.0%	78.7%

http://seer.cancer.gov/csr/1975_2000/results_single/sect_01_table.03.pdf

Table 2
Summary statistics from SEER Public Use File

year of diagnosis	number of people diagnosed	mean age at diagnosis	surgery treatment rate	radiation treatment rate	stage0%	stage1%	stage2%	stage4%	stage8%	stage9%
1973	55,382	61.4	55.1%	33.2%	7.1%	26.2%	17.9%	19.8%	4.7%	24.3%
1974	67,297	61.5	59.0%	31.2%	7.6%	29.3%	20.0%	20.7%	5.1%	17.4%
1975	73,608	61.4	63.4%	27.0%	8.5%	29.5%	19.2%	20.4%	5.5%	16.8%
1976	75,617	61.5	63.4%	26.4%	8.3%	29.4%	20.1%	20.6%	5.8%	15.8%
1977	76,591	61.8	63.3%	26.2%	7.9%	29.1%	21.0%	20.7%	6.2%	15.1%
1978	77,890	62.0	63.3%	26.5%	7.7%	29.6%	21.1%	21.2%	6.1%	14.4%
1979	80,126	62.3	63.4%	26.7%	7.5%	29.6%	21.3%	21.1%	6.6%	13.9%
1980	82,694	62.6	63.2%	26.3%	7.3%	29.4%	21.1%	21.3%	6.7%	14.0%
1981	85,364	62.7	63.6%	26.2%	7.3%	29.4%	21.4%	20.9%	6.8%	14.2%
1982	86,577	62.8	63.4%	26.3%	7.3%	29.0%	21.2%	21.3%	6.9%	14.5%
1983	89,724	63.0	63.7%	26.4%	7.6%	29.0%	23.0%	22.0%	6.6%	11.9%
1984	93,224	63.0	63.3%	26.4%	7.8%	28.9%	22.7%	22.0%	6.4%	12.3%
1985	97,498	62.9	64.5%	26.7%	8.5%	29.5%	22.0%	21.3%	6.5%	12.2%
1986	100,078	62.9	64.3%	26.1%	8.9%	29.9%	21.3%	20.4%	6.7%	12.8%
1987	105,871	63.2	64.4%	26.4%	9.2%	29.6%	20.7%	20.1%	7.6%	12.8%
1988	107,403	63.0	64.3%	26.2%	9.7%	29.7%	20.3%	20.1%	7.7%	12.4%
1989	110,185	63.0	63.7%	26.0%	9.9%	29.1%	19.8%	20.1%	8.2%	13.0%
1990	116,033	63.0	64.2%	26.3%	10.4%	28.7%	19.4%	19.3%	9.4%	12.8%
1991	123,115	63.2	63.5%	27.2%	10.4%	27.6%	18.2%	18.7%	11.7%	13.4%
1992	127,775	63.3	62.1%	27.9%	10.4%	27.5%	18.0%	17.8%	13.4%	12.9%
1993	125,917	63.1	61.6%	27.6%	10.7%	28.2%	18.2%	17.8%	12.4%	12.7%
1994	125,715	62.9	62.1%	27.4%	11.0%	29.3%	18.8%	17.7%	11.5%	11.7%
1995	127,069	62.7	62.6%	27.5%	11.8%	29.7%	18.5%	17.7%	11.3%	10.9%
1996	121,258	64.7	61.1%	30.0%	6.1%	32.1%	19.9%	18.8%	12.2%	11.0%
1997	125,352	64.8	61.3%	30.5%	6.4%	31.9%	19.9%	18.7%	12.5%	10.6%
1998	128,279	64.9	62.6%	31.7%	7.0%	32.2%	20.3%	18.3%	12.3%	9.8%
1999	129,930	64.8	62.8%	31.3%	7.2%	31.9%	20.4%	17.9%	13.4%	9.2%
2000	129,053	64.5	63.1%	30.9%	7.4%	32.3%	20.5%	18.1%	13.8%	7.9%

Table 3
Estimates of eq. (1)

line	Years after diagnosis	Regressor	Estimate	Std. Error	t Value	Pr > |t|
1	1	$\ln(DRUG\_STOCK_{i,t-3})$	-0.167	0.044	-3.78	0.0002
2	1	$\ln(N_{i,t-k})$	-0.328	0.048	-6.88	<.0001
3	1	$AGE\_MEAN_{i,t-k}$	0.075	0.006	13.35	<.0001
4	1	$SURGERY\%_{i,t-k}$	-1.494	0.213	-7.02	<.0001
5	1	$RADIATION\%_{i,t-k}$	0.071	0.104	0.69	0.4921
6	1	$STAGE0\%_{i,t-k}$	-1.381	0.389	-3.55	0.0004
7	1	$STAGE1\%_{i,t-k}$	-2.820	0.199	-14.16	<.0001
8	1	$STAGE2\%_{i,t-k}$	-1.935	0.266	-7.27	<.0001
9	1	$STAGE4\%_{i,t-k}$	2.855	0.236	12.11	<.0001
10	1	$STAGE8\%_{i,t-k}$	-1.658	0.419	-3.96	<.0001
11						
12	2	$\ln(DRUG\_STOCK_{i,t-3})$	-0.156	0.049	-3.16	0.0016
13	2	$\ln(N_{i,t-k})$	-0.249	0.055	-4.50	<.0001
14	2	$AGE\_MEAN_{i,t-k}$	0.057	0.006	8.89	<.0001
15	2	$SURGERY\%_{i,t-k}$	-1.145	0.241	-4.75	<.0001
16	2	$RADIATION\%_{i,t-k}$	0.410	0.104	3.95	<.0001
17	2	$STAGE0\%_{i,t-k}$	-1.221	0.412	-2.96	0.0032
18	2	$STAGE1\%_{i,t-k}$	-2.740	0.215	-12.75	<.0001
19	2	$STAGE2\%_{i,t-k}$	-1.362	0.274	-4.97	<.0001
20	2	$STAGE4\%_{i,t-k}$	2.562	0.253	10.14	<.0001
21	2	$STAGE8\%_{i,t-k}$	-1.350	0.499	-2.70	0.0071
22						
23	3	$\ln(DRUG\_STOCK_{i,t-3})$	-0.129	0.074	-1.73	0.084
24	3	$\ln(N_{i,t-k})$	-0.391	0.073	-5.36	<.0001
25	3	$AGE\_MEAN_{i,t-k}$	0.040	0.009	4.65	<.0001
26	3	$SURGERY\%_{i,t-k}$	-1.092	0.321	-3.40	0.0007
27	3	$RADIATION\%_{i,t-k}$	0.160	0.132	1.21	0.2257
28	3	$STAGE0\%_{i,t-k}$	-3.170	0.515	-6.15	<.0001
29	3	$STAGE1\%_{i,t-k}$	-2.517	0.267	-9.41	<.0001
30	3	$STAGE2\%_{i,t-k}$	-2.215	0.337	-6.56	<.0001
31	3	$STAGE4\%_{i,t-k}$	2.436	0.312	7.80	<.0001
32	3	$STAGE8\%_{i,t-k}$	-2.581	0.704	-3.67	0.0003
33						
34	4	$\ln(DRUG\_STOCK_{i,t-3})$	0.484	0.132	3.66	0.0003
35	4	$\ln(N_{i,t-k})$	-0.276	0.128	-2.15	0.032
36	4	$AGE\_MEAN_{i,t-k}$	0.034	0.015	2.30	0.0217
37	4	$SURGERY\%_{i,t-k}$	0.408	0.572	0.71	0.4763
38	4	$RADIATION\%_{i,t-k}$	0.678	0.237	2.86	0.0044
39	4	$STAGE0\%_{i,t-k}$	-1.247	0.906	-1.38	0.1693
40	4	$STAGE1\%_{i,t-k}$	-4.328	0.454	-9.53	<.0001
41	4	$STAGE2\%_{i,t-k}$	-1.336	0.584	-2.29	0.0227
42	4	$STAGE4\%_{i,t-k}$	4.043	0.532	7.60	<.0001
43	4	$STAGE8\%_{i,t-k}$	1.222	1.300	0.94	0.3477

Table 3 (continued)
Estimates of eq. (1)

line	Years after diagnosis	Regressor	Estimate	Std. Error	t Value	Pr > |t|
44	5	$\ln(DRUG\_STOCK_{i,t-3})$	-0.323	0.098	-3.30	0.001
45	5	$\ln(N_{i,t-k})$	-0.010	0.098	-0.10	0.9221
46	5	$AGE\_MEAN_{i,t-k}$	0.013	0.011	1.23	0.2174
47	5	$SURGERY\%_{i,t-k}$	0.454	0.430	1.06	0.2913
48	5	$RADIATION\%_{i,t-k}$	0.090	0.173	0.52	0.6026
49	5	$STAGE0\%_{i,t-k}$	1.256	0.679	1.85	0.0648
50	5	$STAGE1\%_{i,t-k}$	-1.213	0.347	-3.50	0.0005
51	5	$STAGE2\%_{i,t-k}$	1.302	0.437	2.98	0.003
52	5	$STAGE4\%_{i,t-k}$	-0.011	0.419	-0.03	0.9791
53	5	$STAGE8\%_{i,t-k}$	-1.867	1.030	-1.81	0.0706
54						
55	6	$\ln(DRUG\_STOCK_{i,t-3})$	-0.327	0.120	-2.73	0.0066
56	6	$\ln(N_{i,t-k})$	0.024	0.118	0.20	0.8377
57	6	$AGE\_MEAN_{i,t-k}$	-0.006	0.013	-0.43	0.6664
58	6	$SURGERY\%_{i,t-k}$	0.573	0.514	1.11	0.2654
59	6	$RADIATION\%_{i,t-k}$	-0.360	0.211	-1.71	0.0882
60	6	$STAGE0\%_{i,t-k}$	-4.545	0.843	-5.39	<.0001
61	6	$STAGE1\%_{i,t-k}$	-1.840	0.400	-4.60	<.0001
62	6	$STAGE2\%_{i,t-k}$	-1.877	0.549	-3.42	0.0007
63	6	$STAGE4\%_{i,t-k}$	1.454	0.489	2.97	0.0031
64	6	$STAGE8\%_{i,t-k}$	-3.811	1.338	-2.85	0.0046
65						
66	7	$\ln(DRUG\_STOCK_{i,t-3})$	0.385	0.134	2.88	0.0042
67	7	$\ln(N_{i,t-k})$	-0.325	0.139	-2.33	0.0203
68	7	$AGE\_MEAN_{i,t-k}$	0.078	0.015	5.09	<.0001
69	7	$SURGERY\%_{i,t-k}$	-0.628	0.590	-1.06	0.2879
70	7	$RADIATION\%_{i,t-k}$	0.786	0.247	3.18	0.0015
71	7	$STAGE0\%_{i,t-k}$	2.080	0.971	2.14	0.0327
72	7	$STAGE1\%_{i,t-k}$	-0.295	0.446	-0.66	0.509
73	7	$STAGE2\%_{i,t-k}$	2.131	0.576	3.70	0.0002
74	7	$STAGE4\%_{i,t-k}$	-0.708	0.546	-1.30	0.1951
75	7	$STAGE8\%_{i,t-k}$	-2.602	2.023	-1.29	0.199
76						
77	8	$\ln(DRUG\_STOCK_{i,t-3})$	-0.179	0.193	-0.93	0.3551
78	8	$\ln(N_{i,t-k})$	-0.456	0.172	-2.66	0.0082
79	8	$AGE\_MEAN_{i,t-k}$	0.038	0.020	1.90	0.0575
80	8	$SURGERY\%_{i,t-k}$	-1.613	0.707	-2.28	0.0229
81	8	$RADIATION\%_{i,t-k}$	-0.709	0.319	-2.22	0.0269
82	8	$STAGE0\%_{i,t-k}$	2.593	1.198	2.16	0.031
83	8	$STAGE1\%_{i,t-k}$	-0.441	0.509	-0.87	0.386
84	8	$STAGE2\%_{i,t-k}$	1.069	0.701	1.52	0.128
85	8	$STAGE4\%_{i,t-k}$	-0.339	0.629	-0.54	0.5908
86	8	$STAGE8\%_{i,t-k}$	-2.679	2.994	-0.89	0.3713

Table 4
Actual vs. predicted hazard and survival rates

Column	1	2	3	4	5	6	7	8	9
Year	β_{ik}	Error	t Value	Pr > |t|	HAZ_ACT	HAZ_PRE	SURV_ACT	SURV_PRE	1995 SURV_ACT
0							100.0%	100.0%	100.0%
1	-0.167	0.044	-3.78	2E-04	30.6%	23.9%	69.4%	76.1%	76.7%
2	-0.156	0.049	-3.16	0.002	14.7%	11.7%	59.2%	67.2%	67.9%
3	-0.129	0.074	-1.73	0.084	10.1%	8.4%	53.2%	61.5%	62.6%
4	0.484	0.132	3.66	3E-04	8.0%	13.1%	49.0%	53.5%	58.6%
5	-0.323	0.098	-3.30	0.001	7.1%	4.1%	45.5%	51.3%	55.2%
6	-0.327	0.120	-2.73	0.007	6.5%	3.7%	42.5%	49.4%	51.8%
7	0.385	0.134	2.88	0.004	5.6%	8.4%	40.1%	45.2%	
8	-0.179	0.193	-0.93	0.355	5.3%	4.0%	38.0%	43.4%	
9	0.247	0.191	1.29	0.197	5.0%	6.6%	36.1%	40.6%	
10	0.098	0.187	0.53	0.599	5.3%	5.9%	34.2%	38.1%	
11	-0.709	0.240	-2.96	0.003	4.7%	0.3%	32.6%	38.0%	
12	-0.467	0.247	-1.89	0.059	4.7%	1.8%	31.1%	37.3%	
13	0.436	0.240	1.82	0.07	4.5%	7.1%	29.7%	34.7%	
14	0.084	0.236	0.36	0.723	4.4%	4.9%	28.4%	33.0%	
15	-0.088	0.318	-0.28	0.782	4.6%	4.1%	27.1%	31.6%	
16	-0.567	0.358	-1.58	0.115	4.6%	1.2%	25.8%	31.2%	
17	0.095	0.320	0.30	0.766	4.5%	5.0%	24.7%	29.7%	
18	0.984	0.327	3.01	0.003	4.3%	9.9%	23.6%	26.7%	
19	0.943	0.483	1.95	0.053	4.4%	9.9%	22.5%	24.1%	
20	1.114	0.517	2.16	0.033	4.5%	11.2%	21.5%	21.4%	
21	-0.344	0.534	-0.64	0.522	5.0%	2.7%	20.4%	20.8%	
22	0.112	0.587	0.19	0.849	4.6%	5.3%	19.5%	19.7%	
23	-1.306	1.076	-1.21	0.23	5.4%	-3.8%	18.4%	20.5%	
24	1.290	0.613	2.10	0.046	5.3%	14.3%			

Appendix Table 1
Drugs listed in British Columbia Cancer Drug Manual, by year of FDA approval

FDA approval year	drug	FDA approval year	drug
before 1938	ASPARAGINASE	1987	MITOXANTRONE
before 1938	BCG	1988	IFOSFAMIDE
1949	MECHLORETHAMINE	1988	MESNA
1953	METHOTREXATE	1988	OCTREOTIDE
1954	BUSULFAN	1989	CARBOPLATIN
1955	DIETHYLSTILBESTROL	1989	FLUTAMIDE
1955	FLUDROCORTISONE	1989	GOSERELIN
1958	FLUOXYMESTERONE	1990	IDARUBICIN
1959	CYCLOPHOSPHAMIDE	1990	LEVAMISOLE
1959	THIOTEPA	1991	FLUDARABINE
1961	VINBLASTINE	1991	PAMIDRONATE
1962	FLUOROURACIL	1991	PENTOSTATIN
1962	MEDROXYPROGESTERONE	1992	PACLITAXEL
1963	MERCAPTOPURINE	1992	TENIPOSIDE
1964	DACTINOMYCIN	1993	CLADRIBINE
1966	THIOGUANINE	1994	TAMOXIFEN
1967	HYDROXYUREA	1994	VINORELBINE
1969	CHLORAMBUCIL	1995	ANASTROZOLE
1969	CYTARABINE	1995	BICALUTAMIDE
1969	PROCARBAZINE	1995	DAUNORUBICIN
1970	MELPHALAN	1995	PORFIMER
1970	MITOTANE	1996	DOCETAXEL
1970	PLICAMYCIN	1996	GEMCITABINE
1971	TRETINOIN	1996	IRINOTECAN
1973	BLEOMYCIN	1996	NILUTAMIDE
1974	DOXORUBICIN	1996	TOPOTECAN
1974	LEUCOVORIN	1997	LETROZOLE
1975	DACARBAZINE	1997	RITUXIMAB
1976	LOMUSTINE	1998	CAPECITABINE
1976	MEGESTROL	1998	TRASTUZUMAB
1977	CARMUSTINE	1999	EPIRUBICIN
1978	CISPLATIN	1999	EXEMESTANE
1980	AMINOGLUTETHIMIDE	1999	TEMOZOLOMIDE
1981	ESTRAMUSTINE	2002	OXALIPLATIN
1981	MITOMYCIN	not FDA approved	AMSACRINE
1982	STREPTOZOCIN	not FDA approved	BUSERELIN
1983	ETOPOSIDE	not FDA approved	CLODRONATE
1984	VINCRISTINE	not FDA approved	CYPROTERONE
1985	LEUPROLIDE	not FDA approved	RALTITREXED
1986	INTERFERON ALFA	not FDA approved	VINDESINE

Appendix Table 2

Distribution of drugs listed in British Columbia Cancer Drug Manual, by drug class

Drug class	Number of drugs
ALKYLATING AGENT	12
ANTITUMOUR ANTIBIOTIC	9
ANTIMETABOLITE	8
ENDOCRINE HORMONE	8
ENDOCRINE ANTIHORMONE	5
MITOTIC INHIBITOR	4
ALKYLATING AGENT, CYTOTOXIC	3
ANTIMETABOLITE, CYTOTOXIC	3
AROMATASE INHIBITOR, NONCYTOTOXIC	3
BIOLOGICAL RESPONSE MODIFIER	3
BONE METABOLISM REGULATOR, NONCYTOTOXIC	2
MITOTIC INHIBITOR, CYTOTOXIC	2
MONOCLONAL ANTIBODY, NONCYTOTOXIC	2
TOPOISOMERASE I INHIBITOR, CYTOTOXIC	2
ANTITUMOUR ANTIBIOTIC (EMERGENCY RELEASE)	1
DIFFERENTIATION INDUCING AGENT, NONCYTOTOXIC	1
ENDOCRINE ANTIHORMONE, NONCYTOTOXIC	1
ENDOCRINE HORMONE, NONCYTOTOXIC	1
MISCELLANEOUS	10