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The Contributions of Improved Therapy and Earlier Detection to Cancer Survival Gains, 1988-2000

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The Contributions of Improved Therapy and Earlier Detection to Cancer Survival Gains, 1988-2000*

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Abstract

Prior literature has documented improvements in cancer survival over time. However, ambiguity remains over the relative contributions of improved treatment and earlier detection to survival gains. Using registry data, we developed a novel framework to estimate the relative contributions of advances in treatment and detection. Our approach compares changes in the probability of early detection, which we interpret as the effects of advances in detection, to improvements in stage-conditional survival, which we interpret as the effects of treatment. We applied this methodology using SEER data to estimate probabilities of early detection and stage-conditional survival curves for several cancers, by race, between 1988 and 2000. Survival increased for all of the cancers we examined, with blacks experiencing larger survival gains than whites for all cancers combined. Our baseline analysis found that treatment advances account for the vast majority of survival gains for all the cancers examined: breast cancer (83%), lung cancer (85%), colorectal cancer (76%), pancreatic cancer (100%), and non-Hodgkin's lymphoma (96%). Compared to whites, treatments appear to explain a lower percentage of survival gains for blacks for all cancers combined; breast cancer, NHL, and pancreatic cancer show a higher percentage of survival gains than lung cancer; and roughly the same percentage for the colorectal cancer. These results are robust to sensitivity analyses examining potential length and lead time bias. Overall, our results suggest that while improved treatment and early detection both contributed to the recent gains in survival, the majority of gains from 1988 to 2000 appear to have been driven by better treatment, manifested by improved stage-conditional survival. These results have important policy implications regarding investment in research and development and the evaluation of efforts to improve cancer screening.

KEYWORDS: survival analysis, breast neoplasms, lymphoma, non-Hodgkin's, colorectal neoplasms, pancreatic neoplasms, lung neoplasms

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Introduction

In the United States, cancer is the second leading cause of death overall and the leading cause of death for persons under the age of 85. Yet, cancer death rates have begun to decline in recent years (Jemal et al., 2008), particularly for certain tumor types, such as breast cancer, colorectal cancer, and lymphoma (Breen et al., 2001; Espey et al., 2007; Pulte et al., 2008). These improvements in survival have been driven by the combination of new technologies that permit earlier diagnosis, public health efforts to improve cancer screening rates, and advances in treatment. Earlier detection of the disease improves survival because local and systemic therapies may be more effective at earlier stages of the disease. In some cases, as with cervical cancer, screening may even reduce incidence, if the test identifies a pre-cancerous condition that can be treated prophylactically. Breast cancer illustrates the combined impact of earlier diagnosis and better therapy on improved survival rates, with the percentage of women receiving an annual mammogram increasing nearly three-fold between 1985 and 2000 (Berry, 2005). In addition, there have been numerous therapeutic advances in the treatment of breast cancer, including the development of new hormonal therapies (e.g., anastrozole, exemestane, and letrozole), chemotherapy (e.g., paclitaxel), and biologic agents (e.g. trastuzumab), which have improved disease-free or overall survival in patients diagnosed with early stage and metastatic disease (Clegg et al., 2001; Slamon et al., 2001; Berry et al., 2005; Piccart-Gebhart et al., 2005; Romond et al., 2005; Eisen et al., 2008). However, the greatest impact of these therapies may derive from their use as adjuvants. Both earlier detection due to screening campaigns and treatment advances (e.g. oxaloplatin, irinotecan, bevacizumab) have played a role in colorectal cancer survival improvements (American Cancer Society, 2008).

In contrast to the other cancers previously mentioned, lung cancer is more resistant to early detection despite improvements in imaging technology. Randomized controlled trials are ongoing in order to evaluate the effectiveness of screening with CT in high risk populations (Henschke et al., 2006). However, new chemotherapy regimens have been demonstrated to be effective at improving survival in patients with early stage lung cancer, and biologic therapies have improved outcomes in patients with advanced disease. The development of a number of novel treatments either have improved (e.g. rituximab for non-Hodgkin's lymphoma, imatinib for chronic myelogenous leukemia) or promise to improve survival for patients with many other types of cancer.

Given advances in both early detection and treatment, a natural question that arises is the degree to which each has contributed to the observed improvements in cancer survival. This question has important policy implications because of the substantial burden of illness associated with cancer, the sequelae of

its treatment, the tremendous resources expended to provide both screening and treatment, and the resources required to fund ongoing research and development of new technologies and therapies (Yabroff et al., 2004; Warren et al., 2008). Prior efforts to examine this question have relied primarily on microsimulation methods (Stockton et al., 1997; Webb et al., 2004; Berry et al., 2005; Mandelblatt et al., 2006; Chie et al., 2007; Imkampe and Bates, 2008). Typically, these methods create a random draw of cancer patients and simulate the course of their disease using data from the literature. Survival gains owing to improvements in treatment and detection can then be estimated by examining the evolution of these patients' diseases under various treatment and detection scenarios. Microsimulations provide a useful tool for examining the potential effects of screening and detection improvements.

In this paper, however, we develop a novel method for identifying the relative and absolute contributions of treatment and early detection in improving cancer survival, using data commonly available from cancer registries. We use data from the Surveillance, Epidemiology, and End Results (SEER) program. Our analysis includes all cancers combined, as well as separate evaluations of colorectal cancer, lung cancer, pancreatic cancer, breast cancer, and non-Hodgkin's lymphoma. These cancers were chosen for their significance, in terms of incidence and/or mortality. In addition, as previously discussed, they also show some heterogeneity in screening and/or treatment advances. For example, since there has been little change in screening or early detection methods for non-Hodgkin's Lymphoma and pancreatic cancer, our estimated effect of treatment's contribution to survival gains serves as a useful check for the methodology.

Registry data provide the ability to empirically estimate the effects of detection and treatment using a sample of actual cancer patients. However, registry data face two serious limitations. First, they are vulnerable to lead time bias, which occurs because increases in detection lead to the inclusion of patients at earlier stages of disease, who will have higher survival even in the absence of treatment advances. Second, registry data are vulnerable to changes in unobserved tumor characteristics. For example, length bias states that increases in detection will tend to sample tumors with more favorable survival characteristics, which can also cause an apparent increase in survival with registry data. While it is difficult to directly identify the size of these two biases, we perform several sensitivity analyses to address how the limitations of registry data may affect our results.

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Methods

Conceptual Framework

If better detection shifts patients to earlier, more treatable stages of disease, while advances in treatment improve survival *conditional* on disease stage, one can mathematically decompose survival improvements into the contributions of better detection and better treatment. Formally, consider a patient whose diease begins in year t, and suppose that the disease progresses through n stages. Let p_i^t represent the probability that the patient is eventually diagnosed at stage i, S_i^t represent the life expectancy conditional on being diagnosed at stage i, and S_t the unconditional life expectancy.[1] The increase in life expectancy between two years t and t' can be written as

$$S^{t'} - S^t = \sum_i p_i^t \left(S_i^{t'} - S_i^t\right) + \sum_i \left(p_i^{t'} - p_i^t\right) S_i^{t'} \qquad (1)$$

Equation (1) provides the decomposition required. The first term in the sum is the absolute contribution of improvements in treatment, which is simply a weighted average of the survival improvement at each stage, $\left(S_i^{t'} - S_i^t\right)$, where the weights are the probability (or proportion of patients) of detection at each stage. Therefore, the relative importance of survival improvements for a particular stage rises proportionally with the number of patients diagnosed at that stage.

The second term in the sum represents the absolute contribution of detection improvements. The anatomy of this term implies that increases in the probability of detection at a particular stage contribute more to overall survival, when earlier detection has larger therapeutic benefits. Indeed, if early detection has no therapeutic benefit and no effect on stage-conditional survival, equation (1) implies that improvements in detection will have no effect on overall survival gains.

Estimating each term in the decomposition requires data on the probabilities of detection at each stage of the disease, as well as stage-specific survival data.

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[1] Note that $S^t = \sum_i p_i^t S_i^t$.

Data

We use data from the Surveillance, Epidemiology, and End Results (SEER) program to estimate gains in cancer survival. The SEER program collects tumor site, histology, demographic, and survival data from all patients living in an area covered by a registry. We restricted our focus to tumors from the nine original SEER registries present in 1973, which cover roughly 10% of the US population.

Using the SEER Site Recode (ICD-O-3) variable to identify tumor site, we focused our analysis on the following cancers: breast, colorectal, lung, pancreas, and non-Hodgkin's lymphoma. We used the SEER Historic Stage A variable to identify tumor stage for all tumors except non-Hodgkin's lymphoma. SEER Historic Stage A provides four classifications for stage: in situ, localized, regional metastasis, and distal metastasis. Because the proportion of patients diagnosed with in situ cancer was relatively small for most of the cancers we examined, we combined the in-situ and localized stages, except in the case of breast cancer. The probability of cure with true in situ cancer should be close to 100%, and the number of cases detected with in situ disease was relatively small compared to other stages. Therefore, this simplification should sacrifice little generality. We modeled breast cancer as proceeding through four stages: in situ, localized, regional and distal metastasis, and modeled most of the remaining cancers cancers as proceeding through three stages: in situ/localized, regional, and metastatic. For non-Hodgkin's lymphoma (NHL) and all cancers combined, differences in coding across cancers and years require us to model disease in two stages: a late stage comprising of metastatic disease and an early stage consisting of all earlier stages combined. For all cancers combined and NHL, we used the Extent of Disease-Extension variable to identify distal metastasis for tumors diagnosed after 1987. For tumors diagnosed between 1983 and 1987, we use the 4-digit Extent of Disease code to identify metastatic disease.

Patient Population

We conducted analyses for patients diagnosed with any kind of cancer, as well as separate analyses for patients with colorectal cancer, lung cancer, pancreatic cancer, breast cancer, and non-Hodgkin's lymphoma. We excluded from our analysis cases that were lost to active follow-up, cases with more than one primary cancer, and cases lacking histologic confirmation of the tumor. In addition, we excluded cases where the stage of the tumor at diagnosis was unknown, as well as cases with hematopoietic or miscellaneous cancers, as neither of these cancers is staged. Appendix table 1 summarizes the codes used to identify tumor site and stage for each of the cancers we examined. Our final

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sample consists of 3,225,546 tumors. Each patient was followed for a mean of 4.2 years (s.d. 5.5 years).

Estimating Stage-Conditional Survival

Using the SEER data, we produced Kaplan-Meier survival curves in order to estimate the stage-conditional life expectancies for a given year, S_i^t. We used the period approach outlined by Brenner and Gefeller (Brenner and Gefeller, 1996), as well as included all-cause mortality to estimate our curves rather than disease-specific mortality. While all-cause mortality will be affected by gains from treatment of competing risks for cancer, it also avoids issues associated with cause-of-death misattribution (Moy et al., 2001; Black et al., 2002). Following several prior studies (Rutqvist, 1985; Royston, 2001; Tai et al., 2005; Qazi et al., 2007), for each cancer, stage, and subpopulation (see below), we estimated a lognormal survival regression model which includes indicator variables for each year of incidence. Our final survival curves are constructed as follows. First, we use the survival probabilities directly estimated from SEER for the time periods available. Second, we use the estimated probabilities from the survival regression model described above to extrapolate survival probabilities for the periods that we cannot directly estimate from SEER, up to thirty years post-diagnosis. Since neither the observed nor extrapolated probabilities lead to a zero probability of survival, even at longer time periods, we truncated the survival curves by assuming that cancer patients at thirty years post-diagnosis have survival probabilities similar to that for 89 year-old persons in 2000 (Philipson and Jena, 2006). Our results are not sensitive to either this truncation or the use of a wide variety of alternative methods for extrapolating the survival curves, such as the use of exponential or weibull models of survival.[2]

Estimating Detection Probabilities

We used the SEER data to calculate the annual number of patients diagnosed in each of the stages defined above. We then calculated the probability that the disease is detected in the early stage as the number of patients diagnosed in the early stages divided by the number of incident cases in a year.[3]

[2] Results using these alternative specifications are available from the authors upon request.

Subpopulation Analyses

Our baseline analyses were performed for all cancer patients as a whole. However, we also performed similar analyses for black and white race subpopulations using the SEER Race variables to identify race.

Sensitivity Analyses

Using registry data to implement our methodology leads to two important sources of bias. First, registry data report survival from the date of diagnosis as opposed to the date of actual cancer incidence. This could potentially overstate the importance of detection improvements, due to lead time bias. Second, cancer stages, particularly with SEER, are broadly defined, so a given stage can encompass a variety of tumors with varying characteristics and survival patterns. This raises concerns about length bias: to the degree that improved screening shifts patients to more favorable tumors within a given stage, our methodology will incorrectly attribute these detection gains to improved treatment.

Lead Time Bias

We calculate the impact of lead time bias on our estimates by explicitly modeling the length of time elapsed between incidence and diagnosis, which coincides with entry into the SEER database. Since the transition time between incidence and diagnosis is generally unknown, we examine the degree to which variability in the transition time impacts our findings. For our analysis, we assume that (a) for in situ/local patients, the date of diagnosis and the date of incidence are the same, and that (b) for later stage patients, the transition time is one year between stages. These transition times affect our empirical calculation of the total number of incident cases in a given year, since our model defines the number of incident cases as the number of cases that *start* in a given year, regardless of when they are eventually detected. Under a one year transition time between stages, the total number of incident cases in a given year t for cancers modeled in three stages is therefore calculated as the sum of (a) the number of in situ/localized cases in year t, (b) the number of regional cancers in year $t+1$, and (c) the number of metastatic cases in year $t+2$. We take this approach to reflect the fact that, with a one year transition time between stages, metastatic diseases which are found in year $t+2$ actually began in year t. Finally, note that this adjustment also affects the number of *prevalent* cases: our estimates of incident but undetected cases are added to diagnosed prevalence, in order to construct an estimate of true prevalence.

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For cancers with three designated stages, such as colon, pancreatic, and lung cancer, our assumed one year transition time between stages amounts to an assumed two year transition time between early and late disease. Therefore, a key issue is the plausibility of a two year transition time, in the absence of treatment, from early stage to metastatic disease. Transition times are likely to vary across tumor types and individuals. However, for the purpose of this analysis, our primary concern is whether a two year transition time is a reasonable upper bound on the transition from early to late stage disease. While there are few studies that have assessed the progression of cancer *in the absence of treatment*, the extant literature suggests the transition time between early stage and malignant disease is roughly two years or less. If correct, this provides an approximate bound on the error in measuring the true date of incidence.

For lung cancer, Raz et al. (2007) examined survival among 1,324 California patients who were untreated for stage I disease due to patient refusal, death prior to surgery, or contraindications due to risk factors, and found a median survival of 9 months. In the case of breast cancer, Bloom et al (1962) found the median survival for stage 1, stage 2, and stage 3 breast cancer to be 47.3 months, 39.2 months, and 22 months, respectively. Based on these numbers, the average time to transition between stages is about one year, although the staging system used by Bloom, the Manchester system, is a clinical system which differs slightly from the AJCC system used in SEER.

For the other cancers, there is indirect evidence supporting our assumption. In the case of pancreatic cancer, converting 5-year survival probabilities into annual rates and then assuming an exponential survival function, life expectancy was calculated for early stage pancreatic patients at 2.6 years (15% 5-yr survival) Advanced stage and metastatic pancreatic disease are known to have life expectancy of 6-12 months and 2-6 months, respectively (Androulakis et al., 1999; Graziano and Cascinu, 2000; Cancer Research UK, 2009). In the case of non-Hodgkin's lymphoma, Horning and Rosenberg (1984) found that 82 percent of patients with low grade disease were alive at five years. We were unable to find any studies examining the natural history of untreated early stage colorectal cancer. However, in a study analyzing the cost-effectiveness of colon cancer screening, Frazier et al. (2000) assume the annual transition probability from local to regional disease to range from 0.10-0.50, with a baseline probability of 0.28, and the annual transition probability from regional to distant disease to be 0.32-0.80, with a baseline probability of 0.63. Using the baseline estimates, these transition probabilities imply that at the end of two years, nearly 38% of patients in early stage disease will have transitioned to metastatic disease, with a minimum of 8% and a maximum of 68%, given the ranges listed above. Thus, our assumed two-year transition time is well within this range for colorectal cancer. In the case of non-Hodgkin's lymphoma, this assumption may understate the transition time

for low grade cancers, but we were unable to find studies examining the natural history of higher grade cancers, which tend to grow more rapidly.

Length Bias

We took a similar approach to length time bias, by evaluating the extent to which such bias could impact our results. In particular, for each cancer in our analysis, we divided each SEER stage into two artificial substages: a "favorable" subtype and a "non-favorable" subtype. We then examined how the estimated percentage of survival gains due to treatment improvements changed with differing values for: (a) the magnitude of mortality improvements associated with the "favorable" substage, (b) the initial fraction of patients in the "favorable" substages, and (c) increases in the fraction of patients being detected in the "favorable" substage. Because the literature on the distribution of survival times within a cancer stage is sparse, we were unable to directly apply the literature to inform these values. For (a), we assumed that the "favorable" subtype conferred a survival advantage of 25% relative to the overall survival for the given stage, a number which likely overstates the true value (and the likely bias), given data from the CONCORD study which finds that racial and international differences in survival for the cancers we examine are generally around 10% (Coleman et al., 2008). For (b), we considered a wide range of values from 10-40% for the proportion of patients in the favorable subtype. Since we think of this as a "more favorable than average" subtype, it makes sense to view it as a proportion below 50%. Our baseline analysis adopted a rate of 30%. We examined how increasing the number of patients in the favorable subtype to 34% and 40% affected our results. For (c), our analysis suggests that movement *across* SEER stages between 1988 and 2000 was at most 10%, and was generally much lower, so these two ranges provide likely bounds on movement of patients within a stage. Thus, our sensitivity analysis addresses the issue of length bias by evaluating the degree to which our results are affected by within-stage movements towards more favorable tumors. In addition to conducting separate analyses for lead time and length bias as described above, we also performed analyses examining the joint effect of lead time and length bias. Specifically, we performed our length bias analysis in conjunction with a one-year transition between stages.

Results

Figure 1 shows the gains in overall survival across tumor types, based on our estimated survival curves. Between 1988 and 2000, overall survival increased the most for breast cancer (3.6 years) and non-Hodgkin's lymphoma (3.5 years), with pancreatic cancer experiencing the most modest gains (0.5 years). For all cancers combined, overall survival increased by 3.9 years. The increase in life

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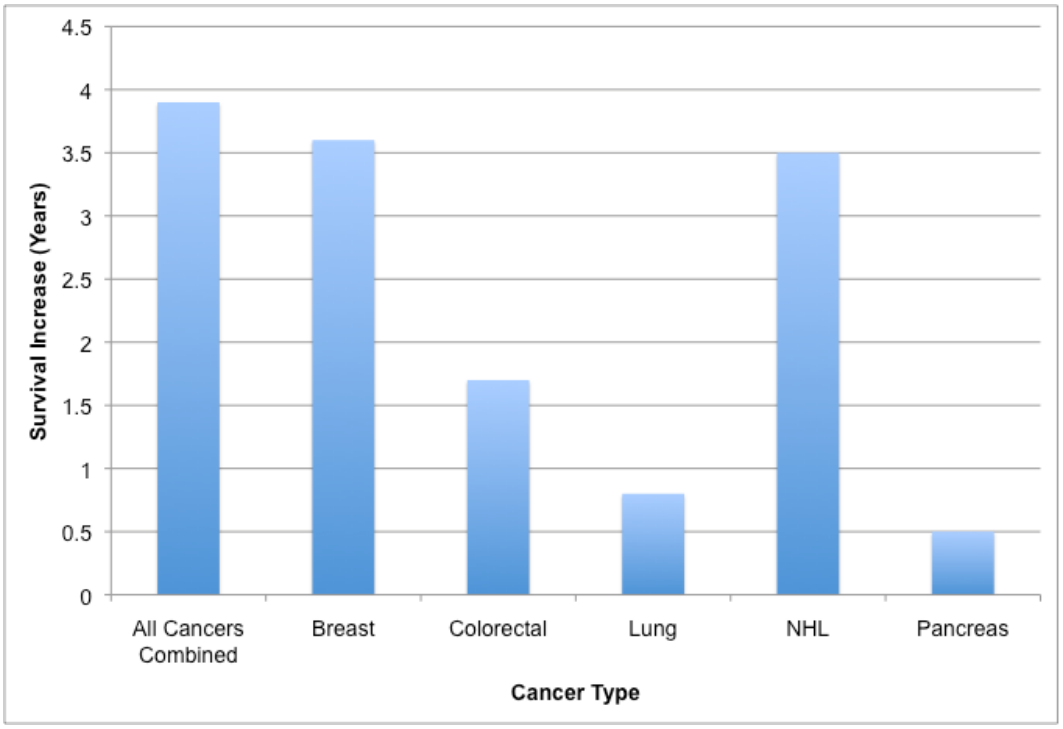
expectancy for all cancers combined is higher than for each of the individual cancers, because the "all cancers combined" numbers include additional cancers besides the specific ones we examine.

Table 1 shows detection improvements, as measured by changes in the stage at diagnosis. Between 1988 and 2000, the percent of breast cancer patients diagnosed at the in situ stage increased by 8.1 percentage points, and the percent of patients diagnosed at an early stage for non-Hodgkin's lymphoma increased by 4.1 percentage points . For all cancers combined, the percent of patients diagnosed with early stage disease increased by 5.5 percentage points. By contrast, the remaining cancers we studied (colorectal, lung and pancreatic) saw more modest increases in the percent of patients diagnosed at earlier stages.

Figure 1 - Gains in Overall Survival by Cancer Type, 1988-2000



Notes: Figure 1 shows the estimated increase in unconditional life expectancy between 1988-2000 for each of the cancers in our analysis, as well as all cancers combined. NHL=non Hodgkin's Lymphoma

For the most part, all the cancers we examined had increases in survival at earlier disease stages, with generally little improvement in survival for patients who were diagnosed with metastatic disease (Table 2). However, one notable exception is non-Hodgkin's lymphoma, where survival gains for patients with

stage IV disease (3.4 years) are similar to gains in survival for early stage disease. It is worth nothing that for many cancers, the overall improvement in life expectancy is greater than the increases at individual stages. For example, for all cancers combined, the increase in overall life expectancy is 3.9 years, compared to gains of 3.7 years for in situ/local/regionalized cancers and 0.8 years for metastatic cancer. The fact that the overall improvement is greater than the improvement at individual stages may seem counterintuitive, but is explained by increases in the number of patients who are found at earlier stages and therefore experience the larger survival improvements associated with moving across stages.

Table 1 - Changes in Detection (Stage of Diagnosis), 1988-2000

CANCER	PATIENT POPULATION	%CHANGE IN DIAGNOSIS			
		In Situ/Local/Regional			Distant
All Cancers	All	5.5%			(5.5%)
	White	5.4%			(5.4%)
	Black	8.7%			(8.7%)
NHL	All	4.1%			(4.1%)
	White	3.4%			(3.4%)
	Black	9.3%			(9.3%)
		In Situ/Local		Regional	Distant
CRC	All	2.4%		0.9%	(3.3%)
	White	2.6%		0.9%	(3.5%)
	Black	4.1%		(2.4%)	(1.7%)
Lung	All	1.4%		0.7%	(2.1%)
	White	1.8%		0.7%	(2.5%)
	Black	(0.5%)		1.1%	(0.6%)
Pancreas	All	(1.8%)		1.4%	0.4%
	White	(2.2%)		1.8%	0.4%
	Black	(1.2%)		1.2%	0%
		In Situ	Local	Regional	Distant
Breast	All	8.1%	(1.5%)	(5.2%)	(1.3%)
	White	7.9%	(1.2%)	(5.6%)	(1.1%)
	Black	7.9%	(0.8%)	(4.0%)	(3.1%)

Notes: Table 1 shows changes in the proportion of canecers detected at various stages between 1988 and 2000, using data from the SEER registries. NHL=non-Hodgkin's lymphoma. Numbers in parentheses indicate negative values.

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Table 2 – Change in Cancer Life Expectancy, 1988-2000

CANCER	PATIENT POPULATION	CHANGE IN LIFE EXPECTANCY (YEARS)				
		In Situ/Local/Regional			Distant	Overall
All Cancers	All	3.7			0.8	3.9
	White	3.6			0.9	3.8
	Black	4.7			0.4	4.6
NHL	All	3.3			3.4	3.5
	White	2.0			2.2	3.4
	Black	3.2			3.4	2.5
		In Situ/Local		Regional	Distant	Overall
CRC	All	0.9		2.3	0.6	1.7
	White	0.7		2.2	0.6	1.6
	Black	1.0		0.9	0.6	1.2
Lung	All	1.9		0.8	0.3	0.8
	White	1.9		0.8	0.2	0.8
	Black	0.9		0.7	0.3	0.5
Pancreas	All	1.1		0.8	0.2	0.5
	White	1.0		0.9	0.2	0.5
	Black	0.7		(0.11)	0.0	0.0
		In Situ	Local	Regional	Distant	Overall
Breast	All	0	2.1	4.8	1.2	3.6
	White	0	2.1	4.8	1.5	3.6
	Black	1.8	2.2	4.4	0.7	4.1

Notes: Table 2 shows changes in cancer life expectancy, conditional on stage, between 1988 and 2000. Results based on data obtained from the SEER registries. NHL=non-Hodgkin's lymphoma; CRC=Colorectal cancer Numbers in parentheses indicate negative values.

Table 3 presents our estimates of the share of survival gains due to improved treatment. The first column shows our baseline estimates. Overall, we find that treatment advances explain nearly all of the observed gains in survival for non-Hodgkin's lymphoma and pancreatic cancer (roughly nine-tenths of survival gains for lung cancer, and roughly four-fifths of survival gains for all cancers combined, breast cancer, and colorectal cancer). Given that there have been no efforts to increase early detection for pancreatic cancer, lung cancer, or non-Hodgkin's lymphoma, it is reassuring to see that our estimates suggest that treatment has accounted for nearly all of the survival gains for these diseases. The second two columns show the range of estimates from our sensitivity analyses. The second column in table 3 shows the sensitivity of our results to potential lead time bias. Overall, we find that adjusting for lead time bias has little effect on our baseline results—for example, for all cancers combined, we

find that treatment accounts for 81-86% of survival improvements, which is similar to our baseline estimate of 81%. It should be noted, however, that accounting for potential length bias generally leads to higher than baseline estimates.

Table 3 – Share of Survival Gains Attributable to Treatment Advances, 1988-2000

CANCER	% OF SURVIVAL GAINS DUE TO TREATMENT			
All Patients		*Sensitivity Analyses*		
	Baseline	Lead Time	Length	Length+Lead Time
All Combined	80.9	81.3-85.6	67.3-76.1	67.5-76.3
Breast	82.5	82.5-88.4	51.9-65.5	49.7-65.8
Colorectal	77.9	77.9-81.2	53.5-69.1	48.7-68.6
Lung	87.9	90.2-93.7	77.2-84.1	76.1-85.1
NHL	95.1	96.6-97.4	82.9-90.1	85.1-95.2
Pancreas	100	100	97.1-100	91.0-97.6
Whites		*Sensitivity Analyses*		
	Baseline	Lead Time	Length	Length+Lead Time
All Combined	80.9	80.5-84.7	66.6-75.7	66.2-75.3
Breast	83.0	83-89.3	53.1-66.8	49.5-65.8
Colorectal	75.5	75.5-78.6	50.2-66.2	46.3-66.7
Lung	84.7	89.0-92.9	73.9-80.8	74.9-83.9
NHL	95.9	96.5-97.3	83.6-91.6	84.9-92.7
Pancreas	100	100	97.6-100	91.8-97.7
Blacks		*Sensitivity Analyses*		
	Baseline	Lead Time	Length	Length+Lead Time
All Combined	77.9	82.9-89.5	68.8-74.5	73.2-79.4
Breast	79.1	79.1-87.9	51.4-61.6	59.0-69.6
Colorectal	74.4	58.5-75.2	43.9-63.3	31.0-48.5
Lung	100	99.9-100	89.1-97.4	76.3-91.3
NHL	80.1	81-100	67.6-76.6	87.4-96.3
Pancreas	71.3	94.9-100	14.0-70.1	81.6-89.5

Notes: Table 3 shows the estimated share of 1988-2000 cancer survival gains due to treatment advances Baseline estimates are based on values shown in tables 1 and 2, using equation (1), as discussed in the Methods section. Details of the sensitivity analyses for length and lead time bias are discussed in the Methods section. NHL=non-Hodgkin's lymphoma.

The third column of Table 3 shows the sensitivity of our results to length bias. As may be expected, our sensitivity analyses show that accounting for

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length bias lowers the estimated effect of treatment improvements. Nonetheless, it remains the case that treatment improvements account for the majority of survival advances, and, with the single exception of breast cancer, they account for the large majority. In the case of all cancers combined, for example, we find that, after adjusting for within-stage movements, treatment advances still account for 67-76% of survival gains. In the final colum of table 3, we show the sensitivity of our results to lead time and length bias. For the most part, these results are similar to the analyses shown for length bias, suggesting that accounting for both sources of bias has little effect on our results beyond the effects of length bias alone.

Racial Subpopulation Analysis

Compared to white patients, black patients experienced less improvement in survival for non-Hodgkin's lymphoma (2.5 versus 3.4 years), but experienced larger improvements in survival than whites for breast cancer (4.1 versus 3.6 years). For the colorectal, lung, and pancreatic cancers, blacks experienced survival improvements that were close to but smaller than improvements for whites. However, for all cancers combined, blacks experienced survival improvement greater than whites (4.6 versus 3.8 years), although some of this difference may reflect changes in the mix of cancers for the two groups over time. Relative to whites, blacks experienced larger gains in earlier detection for all cancers combined, NHL, and colorectal cancer. However, for lung cancer, the probability of detection at the in situ/local stage actually fell for blacks over this time period, even as it increased slightly for whites. Compared to whites, treatments appear to explain a lower percentage of survival gains for blacks for all cancers combined, as well as individually for breast cancer, NHL, and pancreatic cancer. Conversely, treatments seem to explain a higher percentage of lung cancer survival gains for blacks, but roughly the same percentage of colorectal cancer gains.

Discussion

Overall, our results suggest that advances in treatment have been the primary force driving observed improvements in cancer survival between 1988 and 2000. For each of the cancers we examined, we find that treatment advances explain roughly 80-90% of observed survival gains between 1988 and 2000 in our baseline scenario. Overall, blacks experienced larger gains than whites for all cancers combined, but there is marked heterogeneity across cancers, with blacks experiencing larger gains for breast cancer and smaller gains than whites for non-Hodgkin's Lymphoma. Moreover, we find some evidence that treatment

improvements are less important in generating survival improvements for blacks than for whites.

Our results are in rough alignment with the timing of advances in treatment and detection outlined earlier. For lung cancer, NHL, and pancreatic cancer, it is not surprising that treatment accounts for all of the observed survival gains, since there have been few advances in screening for these cancers. In the case of breast and colorectal cancer, which have been the subject of many technological advances and public health efforts to promote screening, we find that while detection advances have played an important role, the gains due to treatment advances have been significant. These results seem in line with screening and treatment advances for the specific time period we consider (1988-2000). For example, CDC reports suggest little increase in colorectal cancer screening over this time period (CDC, 2001). Swan et al find that the use of mammography trended sharply upwards until 1991 and then grew at a slower rate afterwards (Swan et al., 2003). In addition, several studies suggest that increased use of screening mammograms has modest effects on breast cancer mortality (Gotzsche and Olsen, 2000; Armstrong et al., 2007). By contrast, breast and colorectal cancer both experienced significant therapeutic advances during this time.

Table 4 – Prior Studies Examining the Effect of Treatment on Survival Gains

STUDY	COUNTRY	CANCERS EXAMINED	TIME PERIOD	%SURVIVAL GAINS DUE TO TREATMENT
Berry et al. (7)	USA	Breast Cancer	1975-2000	35-72%
Chie et al. (12)	Taiwan	Breast, Cervical, Colorectal, Gastric, Liver, Prostate	1989-1998	Breast 23%; Cervical 50%; Colorectal 48%; Gastric 24%; Liver 34%; Prostate 70%
Imkampe and Bates (13)	UK	Breast	1980-2002	*
Stockton et al. (14)	UK	Breast	1982-1989	<50%
Webb et al. (15)	Australia	Breast	1981-1994	*
Mandelblatt et al. (16)	US	Breast	1975-2000	54%
Notes:*=No explicit calculation				

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Several prior studies have examined the degree to which treatment and detection advances have driven survival gains (Table 4) (Stockton et al., 1997; Webb et al., 2004; Berry et al., 2005; Mandelblatt et al., 2006; Chie et al., 2007; Imkampe and Bates, 2008). Our baseline estimates for the proportion of survival gains due to treatment advances are in the upper range of the estimates from these prior studies. Several factors could account for these differences. First, several studies looked at cancer survival in countries other than the US. Second, the two US studies examined the case of breast cancer between 1975 and 2000 (Berry et al., 2005; Mandelblatt et al., 2006), while our study examines a more recent time period (1988-2000), in which screening advances were much less common than in the preceding period beginning in 1975 (Swan et al., 2003). Therefore, it may be possible that detection advances may explain a larger share of survival gains prior to 1991, while treatment advances account for a larger share of survival gains during the time period we consider.

It is important to note several limitations to our study. First, the use of registry data leads to the possibility of lead time and length bias, and our sensitivity analyses have addressed the impact of these limitations. Second, we cannot exclude the possibility that changes in observed demographic variables may be affecting our results. For example, our observed changes in survival and detection for all cancers combined may also reflect changes in the mix of cancers over time. Similarly, changes in survival and detection for other cancers may also reflect changes in the age distribution of cancer over time. Our results also do not take into account any changes in quality of life during the period under investigation. Finally, our analysis is not intended to be a comprehensive cost-benefit analysis of recent survival gains, as we do not account for either the value or cost of observed survival gains.

As noted above, our results also suggest some differences across races. The reasons for this discrepancy, such as differences in access to optimal care, tumor biology, and/or the presence of co-morbidities, remain an area for further research. Intriguingly, for certain cancers, detection improvements appear to play a larger role for improvement in survival for black patients, suggesting that they have benefited more than whites from efforts to increase screening. However, as shown in tables 2 and 3, the small number of black patients for some of the cancers in our analysis means that those estimates of the probability of early detection and the share of survival gains due to treatment lack precision, and warrant caution in interpretation.

These results have important policy implications. New treatments appear to have been important in generating cancer survival gains. Indeed, the period from 1988-2000 saw the introduction of many new therapies, such as hormonal therapies (e.g., anastrozole, exemestane, and letrozole), biologic agents (e.g. trastuzumab, rituximab), and chemotherapeutic agents (e.g., paclitaxel, docetaxel,

gemcitabine, etc.). In addition, given that treatment advances account for a large share of recent survival gains, our results highlight the importance of ensuring access to cancer therapy, particularly given the high costs of cancer therapy and concerns that these costs may limit access to care (Ayanian et al., 1993; Hewitt and Simone, 1999; Thorpe and Howard, 2003; Schrag, 2004; American Cancer Society, 2008; Halpern et al., 2008).

References

American Cancer Society (2008). "Cancer Facts and Figures 2008." American Cancer Society. Atlanta.

Androulakis, N., C. Kourousis, M. A. Dimopoulos, et al. (1999). "Treatment of pancreatic cancer with docetaxel and granulocyte colony-stimulating factor: a multicenter phase II study." J Clin Oncol **17**(6): 1779-85.

Armstrong, K., E. Moye, S. Williams, et al. (2007). "Screening mammography in women 40 to 49 years of age: a systematic review for the American College of Physicians." Annals of Internal Medicine **146**(7): 516-26.

Ayanian, J. Z., B. A. Kohler, T. Abe, et al. (1993). "The relation between health insurance coverage and clinical outcomes among women with breast cancer." N Engl J Med **329**(5): 326-31.

Berry, D. A., K. A. Cronin, S. K. Plevritis, et al. (2005). "Effect of screening and adjuvant therapy on mortality from breast cancer." New England Journal of Medicine **353**(17): 1784-92.

Berry, J. (2005). "Are all aromatase inhibitors the same? A review of controlled clinical trials in breast cancer." Clinical Therapeutics **27**(11): 1671-84.

Black, W. C., D. A. Haggstrom and H. G. Welch (2002). "All-cause mortality in randomized trials of cancer screening." J Natl Cancer Inst **94**(3): 167-73.

Bloom, H. J., W. W. Richardson and E. J. Harries (1962). "Natural history of untreated breast cancer (1805-1933). Comparison of untreated and treated cases according to histological grade of malignancy." Br Med J **2**(5299): 213-21.

Breen, N., D. K. Wagener, M. L. Brown, et al. (2001). "Progress in cancer screening over a decade: results of cancer screening from the 1987, 1992, and 1998 National Health Interview Surveys." Journal of the National Cancer Institute **93**(22): 1704-13.

DOI: 10.2202/1558-9544.1195

Brenner, H. and O. Gefeller (1996). "An alternative approach to monitoring cancer patient survival." Cancer **78**(9): 2004-10.

Cancer Research UK. (2009, November 10, 2008). "Statistics and Outlook for Pancreatic Cancer." Retrieved July 23, 2009, from http://www.cancerhelp.org.uk/help/default.asp?page=7519.

CDC (2001). "Trends in screening for colorectal cancer -- United States, 1997 and 1999." Morbidity and Mortality Weekly Report **50**(9): 162-6.

Chie, W. C., Y. H. Chang and H. H. Chen (2007). "A novel method for evaluation of improved survival trend for common cancer: early detection or improvement of medical care." Journal of Evaluation in Clinical Practice **13**(1): 79-85.

Clegg, A., D. A. Scott, M. Sidhu, et al. (2001). "A rapid and systematic review of the clinical effectiveness and cost-effectiveness of paclitaxel, docetaxel, gemcitabine and vinorelbine in non-small-cell lung cancer." Health Technology Assessment **5**(32): 1-195.

Coleman, M. P., M. Quaresma, F. Berrino, et al. (2008). "Cancer survival in five continents: a worldwide population-based study (CONCORD)." Lancet Oncol **9**(8): 730-56.

Eisen, A., M. Trudeau, W. Shelley, et al. (2008). "Aromatase inhibitors in adjuvant therapy for hormone receptor positive breast cancer: a systematic review." Cancer Treatment Reviews **34**(2): 157-74.

Espey, D. K., X. C. Wu, J. Swan, et al. (2007). "Annual report to the nation on the status of cancer, 1975-2004, featuring cancer in American Indians and Alaska Natives." Cancer **110**(10): 2119-52.

Frazier, A. L., G. A. Colditz, C. S. Fuchs, et al. (2000). "Cost-effectiveness of screening for colorectal cancer in the general population." JAMA **284**(15): 1954-61.

Gotzsche, P. and O. Olsen (2000). "Is screening for breast cancer with mammography justifiable?" Lancet(355): 129-34.

Graziano, F. and S. Cascinu (2000). "Docetaxel chemotherapy for pancreatic cancer: Do results support certainty? Italian Group for the Study of Gastrointestinal Tract Carcinomas." J Clin Oncol **18**(2): 445-6.

Halpern, M. T., E. M. Ward, A. L. Pavluck, et al. (2008). "Association of insurance status and ethnicity with cancer stage at diagnosis for 12 cancer sites: a retrospective analysis." Lancet Oncol **9**(3): 222-31.

Henschke, C. I., D. F. Yankelevitz, D. M. Libby, et al. (2006). "Survival of patients with stage I lung cancer detected on CT screening." N Engl J Med **355**(17): 1763-71.

Hewitt, M. and J. V. Simone, Eds. (1999). Ensuring Quality of Cancer Care. Washinton DC, National Academy Press.

Horning, S. J. and S. A. Rosenberg (1984). "The natural history of initially untreated low-grade non-Hodgkin's lymphomas." N Engl J Med **311**(23): 1471-5.

Imkampe, A. K. and T. Bates (2008). "Improvements in breast cancer survival over time, related to adjuvant treatment and node status." European Journal of Surgical Oncology.

Jemal, A., M. J. Thun, L. A. Ries, et al. (2008). "Annual report to the nation on the status of cancer, 1975-2005, featuring trends in lung cancer, tobacco use, and tobacco control." J Natl Cancer Inst **100**(23): 1672-94.

Mandelblatt, J., C. B. Schechter, W. Lawrence, et al. (2006). "The SPECTRUM population model of the impact of screening and treatment on U.S. breast cancer trends from 1975 to 2000: principles and practice of the model methods." Journal of the National Cancer Institute. Monographs.(36): 47-55.

Moy, C. S., D. M. Albert, M. Diener-West, et al. (2001). "Cause-specific mortality coding. methods in the collaborative ocular melanoma study coms report no. 14." Control Clin Trials **22**(3): 248-62.

Philipson, T. J. and A. B. Jena (2006). "Who benefits from new medical technologies? Estimates of consumer and producer surpluses for HIV/AIDS drugs." Forum for Health Economics & Policy **9**(2).

Piccart-Gebhart, M. J., M. Procter, B. Leyland-Jones, et al. (2005). "Trastuzumab after adjuvant chemotherapy in HER2-positive breast cancer." New England Journal of Medicine **353**(16): 1659-72.

DOI: 10.2202/1558-9544.1195

Pulte, D., A. Gondos and H. Brenner (2008). "Improvements in survival of adults diagnosed with acute myeloblastic leukemia in the early 21st century." Haematologica **93**(4): 594-600.

Qazi, S., D. DuMez and F. M. Uckun (2007). "Meta analysis of advanced cancer survival data using lognormal parametric fitting: a statistical method to identify effective treatment protocols." Curr Pharm Des **13**(15): 1533-44.

Raz, D., J. Zell, I. Ou, et al. (2007). "Natural history of stage I non-small cell lung cancer." Chest **132**: 193-199.

Romond, E. H., E. A. Perez, J. Bryant, et al. (2005). "Trastuzumab plus adjuvant chemotherapy for operable HER2-positive breast cancer." New England Journal of Medicine **353**(16): 1673-84.

Royston, P. (2001). "The lognormal distribution as a model for survival time in cancer, with an emphasis on prognostic factors." Statistica Neelandica **55**(1): 89-104.

Rutqvist, L. E. (1985). "On the utility of the lognormal model for analysis of breast cancer survival in Sweden 1961-1973." Br J Cancer **52**(6): 875-83.

Schrag, D. (2004). "The price tag on progress--chemotherapy for colorectal cancer." N Engl J Med **351**(4): 317-9.

Slamon, D. J., B. Leyland-Jones, S. Shak, et al. (2001). "Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that overexpresses HER2." New England Journal of Medicine **344**(11): 783-92.

Stockton, D., T. Davies, N. Day, et al. (1997). "Retrospective study of reasons for improved survival in patients with breast cancer in east Anglia: earlier diagnosis or better treatment." BMJ **314**(7079): 472-5.

Swan, J., N. Breen, R. J. Coates, et al. (2003). "Progress in cancer screening practices in the United States: results from the 2000 National Health Interview Survey." Cancer **97**(6): 1528-40.

Tai, P., E. Yu, R. Shiels, et al. (2005). "Long-term survival rates of laryngeal cancer patients treated by radiation and surgery, radiation alone, and surgery alone: studied by lognormal and Kaplan-Meier survival methods." BMC Cancer **5**: 13.

Thorpe, K. and D. Howard (2003). "Health Insurance and Spending among Cancer Patients." Health Affairs(Web Exclusive): W3-189.

Warren, J. L., K. R. Yabroff, A. Meekins, et al. (2008). "Evaluation of trends in the cost of initial cancer treatment." J Natl Cancer Inst **100**(12): 888-97.

Webb, P. M., M. C. Cummings, C. J. Bain, et al. (2004). "Changes in survival after breast cancer: improvements in diagnosis or treatment?" Breast **13**(1): 7-14.

Yabroff, K. R., W. F. Lawrence, S. Clauser, et al. (2004). "Burden of illness in cancer survivors: findings from a population-based national sample." J Natl Cancer Inst **96**(17): 1322-30.

DOI: 10.2202/1558-9544.1195