INFORMATION TO USERS

This manuscript has been reproduced from the microfilm master. UMI films the text directly from the original or copy submitted. Thus, some thesis and dissertation copies are in typewriter face, while others may be from any type of computer printer.

The quality of this reproduction is dependent upon the quality of the copy submitted. Broken or indistinct print, colored or poor quality illustrations and photographs, print bleedthrough, substandard margins, and improper alignment can adversely affect reproduction.

In the unlikely event that the author did not send UMI a complete manuscript and there are missing pages, these will be noted. Also, if unauthorized copyright material had to be removed, a note will indicate the deletion.

Oversize materials (e.g., maps, drawings, charts) are reproduced by sectioning the original, beginning at the upper left-hand corner and continuing from left to right in equal sections with small overlaps. Each original is also photographed in one exposure and is included in reduced form at the back of the book.

Photographs included in the original manuscript have been reproduced xerographically in this copy. Higher quality 6" x 9" black and white photographic prints are available for any photographs or illustrations appearing in this copy for an additional charge. Contact UMI directly to order.
RICE UNIVERSITY

Progress Against Cancer—A New Measure

by

Christopher M. Brauner

A THESIS SUBMITTED
IN PARTIAL FULFILLMENT OF THE
REQUIREMENTS FOR THE DEGREE

Master of Arts

APPROVED, THESIS COMMITTEE:

Marek Kimmel, Chairman
Professor of Statistics

James R. Thompson
Professor of Statistics

Paul E. Pfeiffer
Professor of Computational and Applied Mathematics

Barry W. Brown—Thesis Director
Chief of Computer Science, M.D.
Anderson Cancer Center

Houston, Texas
April, 1995
Abstract

Progress Against Cancer—A New Measure

by

Christopher M. Brauner

Measures of the impact of cancer on survival are often incomplete, and are subject to biases which cloud the assessment of progress against the disease.

A new measure, the proportion diagnosed with cancer and dead by a particular age, is proposed. This measure incorporates incidence, survival, and mortality, and improves upon other measures in several ways. The measure is examined separately by sex/race combinations for three periods of diagnosis.

To calculate the measure, long-term survival must be known or estimated. Only a limited period of followup is available for the population studied; therefore, a model expressing survival time as a function of age and diagnosis period is sought. The accelerated failure model is considered, but is poor at predicting later survival from early experience. Estimation is accomplished by projecting short-term survival experience from early diagnosis periods to later periods, and using the accelerated failure model to predict long-term survival.
Acknowledgements

Thanks go to all the people who contributed to this paper and to my experiences at Rice University. Special thanks go to Dr. Barry Brown, for assisting in the choice of topic and for whom it has been a sincere pleasure to work. I would like to thank Dr. Kimmel and Dr. Thompson and Dr. Pfeiffer for taking the time to serve on my thesis committee. And thanks also to Dr. Kathy Ensor, who has provided good guidance throughout my stay at Rice.

I would like to thank my fellow graduate students for the advice, friendship, and for providing a very comfortable working atmosphere. Thanks to Rachel B., Terri F-H, John S., David A., Ozgur B., Webster W., Mark O., Steve S. and the rest. Good luck to everyone.
# Contents

List of Tables vii
List of Illustrations vii

1 Introduction 1
1.1 The Data ................................................. 3
1.2 Calculation – Proportion Diagnosed and Dead by Age a .......... 5

2 Methods of Survival Calculation 6
2.1 The Accelerated Failure Model ................................ 6
2.2 Attempts at Applying the Accelerated Failure Model .......... 8
   2.2.1 Criterion 1 – Assessing Model-Based Survival Estimate . 8
   2.2.2 Criterion 2 – Testing Predictability of the Model ........ 10
2.3 Restructuring the Survival Estimate ............................. 12

3 Results 15
3.1 Proportion Diagnosed and Dead versus Year .................... 15
3.2 Checking the Results ......................................... 15
   3.2.1 Incidence and Survival ................................. 17
   3.2.2 Cumulative Incidence .................................... 17
   3.2.3 Proportion Diagnosed and Dead by Age within Time T .... 20

4 Supplementary Findings / Motivation for Research 23
4.1 Aids Bubble .................................................. 23
4.2 Underlying Problems – Accelerated Failure Model ............ 25
   4.2.1 Likelihood Contributions ............................... 25
   4.2.2 Variation of the Accelerated Failure Parameters (p, q) .... 26
4.3 Application to Single Cancers .................................. 28

5 Summary / Conclusions 30
A Progression of $P(a, T)$ versus $P(a)$

References
Tables

1.1 SEER Population .................................................. 4

2.1 Special Cases of the Accelerated Failure Model ............... 7
2.2 Accelerated Failure Model Parameters versus Age .............. 9
Chapter 1

Introduction

Assessing progress against cancer requires a measure which thoroughly reflects the relationship between humans and the disease. A complete measure should attempt to evaluate the full impact of cancer as observed from diagnosis through death. Many measures overlook certain aspects of the cancer experience, and are subjected to biases which cloud the assessment of progress.

For instance, when considering length of survival as a measure of the cancer impact, at least three problems arise. First, the measure is incomplete because cancer incidence is ignored. Second, the measure is subject to lead time bias associated with early detection. As the ability to detect cancers at earlier periods of development improves, the survival time after diagnosis may appear lengthened, even in the absence of successful treatment. Third, the measure is subject to the effect of false positive bias. Technological advancements have allowed for the detection of microscopic conditions which resemble early stage cancer but which do not develop as such; inclusion of such cases may inflate incidence and also give the impression of lengthened survival (Extramural Committee To Assess Measures of Progress Against Cancer, 1990).

An additional bias that hinders estimation of progress is false negative bias; that is, the failure to detect and diagnose an actual cancer. A decrease in such failure may inflate incidence rates, but its effect may not fully be understood because it is essentially unobservable.

Bailar and Smith (1986) examined recent trends in incidence, survival, and mortality and concluded that the best measure of cancer progress is the cancer-specific mortality rate. Foremost in their reasoning was the need to eliminate the effects of changing screening and detection standards, and for a direct measure of the most critical outcome, death. However, the cancer-specific death rate may be subject to reporting biases associated with attributing a specific cause of death (Brown, et al., 1993).

As cause of death may often not be substantiated and medical information may not be complete, Brown, et al. (1993) investigated the validity of the cancer-specific death
rate. Patients examined included white patients diagnosed with any cancer between the ages of 20 and 84 for each calendar year 1973-1987. The noncancer relative hazard (NCRH) was defined as the ratio of patient-to-general-population noncancer death rates, calculated by dividing the number of patient noncancer deaths per year by the number found in the matched U.S. population data. The study determined the existence of a significant excess of noncancer deaths in the cancer population compared to the population at large for common solid tumors (lung, colon, breast, prostate) and also for all combined cancers. This excess was deemed to be attributable not to an increased susceptibility to disease in general, but rather to the cancer experience itself, and most prominently to treatment of the disease. Of the leading causes of death other than cancer in the patient population, the most common causes were circulatory and respiratory failures, concentrated in the first few years after diagnosis. The argument that Brown, et al. make is that when assessing the outcome of cancer treatment, these deaths due to causes other than cancer may not be ignored.

A more encompassing measure of cancer progress is the proportion diagnosed and dead by age; that is, the proportion of the U.S. population diagnosed with cancer and dying at or before a particular age. This measure incorporates both incidence and survival into its calculation, with the same emphasis on the event of death. Moreover, it is immune to the problems associated with early detection because when considering deaths at or before a certain age it does not matter when diagnosis occurred, but rather if it occurred and by what age death was observed. The proportion diagnosed and dead by age is also unaffected by unknown biases that may be associated with attributing a cause of death, because it incorporates all causes of death into its calculation. For the same reason, however, it is not immune to false positive bias, particularly at advanced ages of reference. It can also be affected by medical progress in general (e.g. heart disease), as well as progress against other causes of death.

The cancer-specific death rate considers those patients dying in a common time period. When cancer deaths are recorded for a particular year, those patients dying comprise a mix of many different years of diagnosis. Therefore, the experience of patients diagnosed in different time periods may not be directly compared. The proportion diagnosed and dead by a particular age considers those patients diagnosed in a common time frame.

To eliminate the effects of changes in size and age distribution of the population, the proportion diagnosed and dead should be age-adjusted to some standard population.
1.1 The Data

Data were obtained from the National Cancer Institute’s Surveillance, Epidemiology, and End Results (SEER) Program on patients diagnosed with any cancer between 1973 and 1990, with followup complete through December 1990. The SEER Program consists of 1.2 million records from nine population-based registries covering nine geographic regions of the United States *.

For this study, only those patients experiencing their first (or only) primary tumor were considered. *In-situ* cases were excluded from consideration, because such cases involve noninvasive tumors which generally do not develop and are not deadly. Also excluded were cases for whom the only report of the primary tumor appeared on a death certificate.

Only those patients diagnosed between ages 20 and 84 were studied, with ages grouped into the intervals 20-24, 25-29, …, 80-84. These groupings correspond to those in population and mortality tables. Persons under the age of 20 or over the age of 84 were excluded from the study. Only white and black patients were included as the number of cases of each other race was small.

Each patient record in SEER included the following: year of diagnosis, age at diagnosis, sex, race, and followup time in months. Data were examined separately by sex, race, and by year of diagnosis separated into three groups: 1975-6, 1980-1, and 1985-6. These groups were chosen to ensure that at least five years of known followup were available for each group. Table 1.1 shows the SEER population by the age categories used.

The outcome of interest is the change in the proportion diagnosed and dead from 1975-6 through 1985-6, for a range of particular ages.

---

*The SEER database is comprised of the cases submitted annually by each registry to the National Cancer Institute. The NCI edits the computer tapes on which the cases are submitted and releases them for analysis.*
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>White</td>
<td></td>
<td></td>
<td>Male</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>20-24</td>
<td>469</td>
<td>547</td>
<td>582</td>
<td>34</td>
<td>47</td>
<td>52</td>
</tr>
<tr>
<td>25-29</td>
<td>619</td>
<td>691</td>
<td>881</td>
<td>47</td>
<td>46</td>
<td>64</td>
</tr>
<tr>
<td>30-34</td>
<td>628</td>
<td>826</td>
<td>1288</td>
<td>38</td>
<td>77</td>
<td>87</td>
</tr>
<tr>
<td>35-39</td>
<td>723</td>
<td>914</td>
<td>1591</td>
<td>70</td>
<td>87</td>
<td>154</td>
</tr>
<tr>
<td>40-44</td>
<td>1093</td>
<td>1234</td>
<td>1751</td>
<td>152</td>
<td>178</td>
<td>203</td>
</tr>
<tr>
<td>45-49</td>
<td>2322</td>
<td>2099</td>
<td>2274</td>
<td>316</td>
<td>318</td>
<td>333</td>
</tr>
<tr>
<td>50-54</td>
<td>4046</td>
<td>3998</td>
<td>3706</td>
<td>476</td>
<td>586</td>
<td>546</td>
</tr>
<tr>
<td>55-59</td>
<td>5830</td>
<td>6463</td>
<td>6464</td>
<td>749</td>
<td>875</td>
<td>848</td>
</tr>
<tr>
<td>60-64</td>
<td>7803</td>
<td>8691</td>
<td>9551</td>
<td>761</td>
<td>1049</td>
<td>1124</td>
</tr>
<tr>
<td>65-69</td>
<td>8227</td>
<td>9806</td>
<td>11238</td>
<td>823</td>
<td>1081</td>
<td>1268</td>
</tr>
<tr>
<td>70-74</td>
<td>7804</td>
<td>9289</td>
<td>11133</td>
<td>632</td>
<td>881</td>
<td>985</td>
</tr>
<tr>
<td>75-79</td>
<td>6315</td>
<td>7384</td>
<td>8612</td>
<td>420</td>
<td>612</td>
<td>683</td>
</tr>
<tr>
<td>80-84</td>
<td>4481</td>
<td>4781</td>
<td>5442</td>
<td>215</td>
<td>304</td>
<td>424</td>
</tr>
<tr>
<td>Total</td>
<td>50360</td>
<td>56723</td>
<td>64513</td>
<td>4733</td>
<td>6141</td>
<td>6771</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td></td>
<td></td>
<td>Female</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>20-24</td>
<td>1331</td>
<td>1539</td>
<td>1768</td>
<td>341</td>
<td>249</td>
<td>195</td>
</tr>
<tr>
<td>25-29</td>
<td>2781</td>
<td>2735</td>
<td>3028</td>
<td>532</td>
<td>360</td>
<td>354</td>
</tr>
<tr>
<td>30-34</td>
<td>2640</td>
<td>2944</td>
<td>3238</td>
<td>460</td>
<td>425</td>
<td>373</td>
</tr>
<tr>
<td>35-39</td>
<td>2334</td>
<td>2750</td>
<td>3506</td>
<td>360</td>
<td>352</td>
<td>427</td>
</tr>
<tr>
<td>40-44</td>
<td>2894</td>
<td>2799</td>
<td>3788</td>
<td>377</td>
<td>351</td>
<td>486</td>
</tr>
<tr>
<td>45-49</td>
<td>4466</td>
<td>3552</td>
<td>4222</td>
<td>452</td>
<td>423</td>
<td>473</td>
</tr>
<tr>
<td>50-54</td>
<td>6188</td>
<td>5107</td>
<td>4970</td>
<td>541</td>
<td>560</td>
<td>527</td>
</tr>
<tr>
<td>55-59</td>
<td>7209</td>
<td>6739</td>
<td>6831</td>
<td>574</td>
<td>644</td>
<td>696</td>
</tr>
<tr>
<td>60-64</td>
<td>7330</td>
<td>7858</td>
<td>8793</td>
<td>535</td>
<td>667</td>
<td>849</td>
</tr>
<tr>
<td>65-69</td>
<td>7045</td>
<td>8103</td>
<td>9758</td>
<td>546</td>
<td>631</td>
<td>841</td>
</tr>
<tr>
<td>70-74</td>
<td>6222</td>
<td>7348</td>
<td>9083</td>
<td>421</td>
<td>548</td>
<td>720</td>
</tr>
<tr>
<td>75-79</td>
<td>5433</td>
<td>6444</td>
<td>7725</td>
<td>302</td>
<td>430</td>
<td>576</td>
</tr>
<tr>
<td>80-84</td>
<td>4144</td>
<td>4767</td>
<td>5628</td>
<td>206</td>
<td>281</td>
<td>369</td>
</tr>
<tr>
<td>Total</td>
<td>60077</td>
<td>62685</td>
<td>72338</td>
<td>5647</td>
<td>5921</td>
<td>6886</td>
</tr>
</tbody>
</table>

Population counts for thirteen age groups in SEER, for those diagnosed in the years 1975-6, 1980-1, and 1985-6.
1.2 Calculation–Proportion Diagnosed and Dead by Age $a$

Let $a$ index the age category so that for ages 20-24, $a = 1$, for ages 25-29, $a = 2$, $\ldots$, and for ages 80-84, $a = 13$. Let $\text{Prop}(i)$ be the proportion of the reference population for age group $i$. In this study the age-adjustment is in reference to the 1980 U. S. population between the ages of 20 and 84. Then the probability diagnosed and dead by age $a$ is given by

$$P(a) = \sum_{i=1}^{a} \text{Prop}(i) \times \text{Incidence}(i) \times (1 - S(a - i|a)),$$

where $S(a - i|a)$ is the probability of surviving to age $a$ given diagnosis at age $i$. $\text{Incidence}(i)$ is the probability of being diagnosed with cancer while in group $i$. The incidence for one year is taken to be the number of patients in SEER for age group $i$ divided by the number in the SEER population file for age group $i$. Since each age group is a five year interval, $\text{Incidence}(i)$ is taken to be the incidence for one year multiplied by five.

To calculate the proportion diagnosed and dead by a particular age for any given year, long-term survival must be either available or approximated. For instance, if one is to determine the probability of being diagnosed and dead by the age of 82 (corresponding to the midpoint of the oldest age group in the data), then part of the calculation requires knowledge of the probability that a patient diagnosed at age 22 survives for at least 60 years to reach 82 years of age. Unfortunately, such a long period of followup is not available—indeed the largest followup period in the data ranges from fifteen years for 1975-6 cases down to only five years for 1985-6 patients. When $a - i$ is suitably small (less than 4 for 1975-6 patients, $\ldots$, less than 2 for 1985-6), $S(a - i|a)$ may be calculated directly from the Kaplan-Meier survival estimate, as formulated in Kalbfleisch and Prentice (1980). For larger values of $a - i$, a suitable approximation to the survival curve is required, for times extending well beyond what is observable in the data.
Chapter 2

Methods of Survival Calculation

The initial goal of this study is to express cancer survival time as a function of age and year of diagnosis. To meet this requirement, a very generalized and versatile parametric model must be applied. Once the model is fit to survival data, survival probabilities may be determined from the values of the relevant parameters. They may be calculated for as long a period after diagnosis as desired. The long-term survival probabilities \( S(a - i|i) \) with \( a - i \) suitably large may then be determined from the model-based survival estimate.

2.1 The Accelerated Failure Model

The accelerated failure time model was chosen because of its flexibility of form as it serves as a generalized version of many well-known log-linear models. The following discussion formulates the model as described in Kalbfleisch and Prentice (1980).

The accelerated failure model has the following parameters: \( a \) and \( b \), the half-degrees of freedom of the \( F \) distribution; \( \mu \) and \( \sigma \), the constant and scaling term for the logarithm of survival time; and a coefficient \( \beta_j \) for each covariate considered. Let the values of the covariates for the \( i \)th subject be \( z_{ij} \), \( j = 1, \ldots, p \) and define

\[
\alpha_i = \mu + \sum_{j=1}^p z_{ij} \beta_j.
\]

If \( Y_i \) is a random variable distributed as the logarithm of the time-to-event for the \( i \)th subject, then

\[
Y_i = \alpha_i + \sigma \cdot W,
\]

where \( W \) is distributed as the logarithm of an \( F \)-variate with \( 2a \) and \( 2b \) degrees of freedom. If no covariates are modeled, then all \( \alpha_i = \mu \) and \( Y_i \) are identically distributed.

Since covariates have an additive effect on the distribution of the logarithm of time, they have a multiplicative effect on time itself. The term, accelerated failure, expresses
this consequence of the model: time to failure is traversed at a rate that depends multiplicatively on covariate values. The appeal of this model is largely due to the diversity of forms of the survival time distribution as the degrees of freedom vary. Many widely used parametric distributions are obtained for particular values of \( a \) and \( b \). In several cases the value of \( a \) or \( b \) is infinite. Prentice's (1980) reparameterization from half-degrees of freedom, \((a, b)\), to \((p, q)\) is given by

\[
p = \frac{2}{a + b}
\]

and

\[
q = \frac{\frac{1}{a} - \frac{1}{b}}{\sqrt{\frac{1}{a} + \frac{1}{b}}}
\]

In this parameterization, the log-likelihood has finite, not identically zero derivatives everywhere on the boundary \( a = \infty \) or \( b = \infty \) and also on the interior of the \((a, b)\) plane. Thus, the reparameterization regularizes the likelihood and eliminates testing problems associated with infinities. Table 2.1 shows the log-normal, Weibull, log-logistic, reciprocal Weibull, and generalized gamma models in time (not in the logarithm of time) as given by \((p, q)\) and corresponding \((a, b)\) values.

<table>
<thead>
<tr>
<th>Model</th>
<th>((p, q))</th>
<th>((a, b))</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Log-normal</td>
<td>(0,0)</td>
<td>((\infty, \infty))</td>
<td></td>
</tr>
<tr>
<td>Weibull</td>
<td>(0,1)</td>
<td>((1,\infty))</td>
<td></td>
</tr>
<tr>
<td>Exponential</td>
<td>(0,1)</td>
<td>((1,\infty))</td>
<td></td>
</tr>
<tr>
<td>Log-logistic</td>
<td>(1,0)</td>
<td>((1,1))</td>
<td>(\sigma = 1)</td>
</tr>
<tr>
<td>Reciprocal Weibull</td>
<td>(0,1)</td>
<td>((\infty,1))</td>
<td></td>
</tr>
<tr>
<td>Generalized Gamma</td>
<td>(p=0)</td>
<td>(a \text{ or } b \text{ or both } \infty)</td>
<td></td>
</tr>
</tbody>
</table>

Cancer cases discovered during an autopsy and patients who did not survive a full month after diagnosis were assigned zero months survival time. Therefore, to avoid taking logarithms of zero, the survival time of each patient was increased by one month. Essentially, then, the problem is to model \( \log(\text{time} + 1) \), where time is in months.

For this study, then, the desired model is:

\[
Y_i = \mu + \beta_1 \text{age} + \beta_2 \text{age}^2 + \beta_3 I_{1980-1} + \beta_4 I_{1985-6} + \sigma \cdot W
\]  

(2.1.1)
where $Y_i$ is a random variable distributed as $\log(time + 1)$ for the $i$th subject; $\beta_1$, $\beta_2$, $\beta_3$, $\beta_4$, $\sigma$, and $(p,q)$ are to be determined. The indicator variables $I_{1980-1}$ and $I_{1985-6}$ correspond to diagnosis in 1980-1 and 1985-6, respectively. One model was fit for each sex (male, female) and race (white, black) combination.

The program (ACCFLF) of Brown, et al. (1994) at M. D. Anderson Cancer Center was used to fit the accelerated failure model to all relevant data sets.

### 2.2 Attempts at Applying the Accelerated Failure Model

Obtaining useful survival estimates proved to be a more complicated task than anticipated. Application of the accelerated failure model given by (2.1.1) met with resounding failure, which forced consideration of various additional accelerated failure model setups.

In order for predicted survival to be accepted for the study, a model had to meet two criteria: (1) to produce a survival estimate which agreed with the Kaplan-Meier estimate within the time frame encompassed by the data, and (2) to demonstrate the ability to predict survival fairly well for times beyond what was observed in the data. Since the interest lay in detecting small changes in survival, the model had to be as accurate as possible.

#### 2.2.1 Criterion 1–Assessing Model-Based Survival Estimate

Producing an adequate survival estimate proved particularly problematic for the model given by (2.1.1). Comparisons between survival given by this model and the Kaplan-Meier estimates for most subpopulations showed that the estimates differed by several percent at most time points, and that the general shapes of the two curves were dissimilar.

The main reason for rejecting the model given by (2.1.1) lay in the apparently changing shape of the survival curve with age. To address this possibility, a separate model was fit for each age group and year. Table 2.2 shows the parameters and log likelihoods for the thirteen models fit to followup for white males diagnosed in 1975-6. The table demonstrates the changing shape of the survival curve; the parameter $q$ in particular increased linearly ($p$-value $< 0.0001$) with age. Since (2.1.1) assumed constant $(p,q)$ for each age group, its predicted survival could not satisfy criterion (1).
Table 2.2 Accelerated Failure Model Parameters versus Age

<table>
<thead>
<tr>
<th>Age</th>
<th>p</th>
<th>q</th>
<th>σ</th>
<th>μ</th>
<th>log likelihood</th>
</tr>
</thead>
<tbody>
<tr>
<td>20-24</td>
<td>486.982</td>
<td>-31.980</td>
<td>0.004</td>
<td>2.570</td>
<td>-616.5</td>
</tr>
<tr>
<td>25-29</td>
<td>2.749</td>
<td>-3.481</td>
<td>0.424</td>
<td>2.723</td>
<td>-827.3</td>
</tr>
<tr>
<td>30-34</td>
<td>1.719</td>
<td>-2.888</td>
<td>0.529</td>
<td>3.096</td>
<td>-814.1</td>
</tr>
<tr>
<td>35-39</td>
<td>0.000</td>
<td>-2.074</td>
<td>1.055</td>
<td>2.730</td>
<td>-1108.0</td>
</tr>
<tr>
<td>40-44</td>
<td>0.000</td>
<td>-1.682</td>
<td>1.257</td>
<td>2.816</td>
<td>-1758.2</td>
</tr>
<tr>
<td>45-49</td>
<td>0.000</td>
<td>-1.793</td>
<td>0.998</td>
<td>2.265</td>
<td>-4008.2</td>
</tr>
<tr>
<td>50-54</td>
<td>0.000</td>
<td>-1.462</td>
<td>1.181</td>
<td>2.344</td>
<td>-7195.6</td>
</tr>
<tr>
<td>55-59</td>
<td>0.000</td>
<td>-1.064</td>
<td>1.720</td>
<td>2.570</td>
<td>-19065.0</td>
</tr>
<tr>
<td>60-64</td>
<td>0.000</td>
<td>-0.761</td>
<td>2.354</td>
<td>2.655</td>
<td>-14535.1</td>
</tr>
<tr>
<td>65-69</td>
<td>0.000</td>
<td>-0.445</td>
<td>3.981</td>
<td>2.767</td>
<td>-15533.4</td>
</tr>
<tr>
<td>70-74</td>
<td>0.000</td>
<td>-0.600</td>
<td>27.555</td>
<td>2.955</td>
<td>-14611.4</td>
</tr>
<tr>
<td>75-79</td>
<td>0.000</td>
<td>0.132</td>
<td>11.961</td>
<td>2.808</td>
<td>-11751.4</td>
</tr>
<tr>
<td>80-84</td>
<td>0.000</td>
<td>0.238</td>
<td>6.601</td>
<td>2.705</td>
<td>-8196.7</td>
</tr>
</tbody>
</table>

Parameters and likelihoods determined by fitting a separate accelerated failure model to white male followup (with diagnosis in 1975-6) for each of thirteen given age classes.

The left panel of Figure 2.1 shows the model-based survival estimates obtained from the parameter values in Table 2.2. Model-based estimates agreed with the corresponding Kaplan-Meier estimates only for the first year or two after diagnosis. Beyond those times the estimates strayed considerably.

The largest discrepancies between the model-based survival estimates and the Kaplan-Meier estimates occurred in age groups experiencing many deaths within the first year or two after diagnosis. In an attempt to improve the fit for these cases, an additional model was fit for each age group by bypassing the first year of followup. First-year survival was taken from the Kaplan-Meier estimate, and the followup starting at one year after diagnosis was fit. The right panel of Figure 2.1 shows the resulting survival estimates. Although model-based survival was somewhat pessimistic compared to Kaplan-Meier survival, the two estimates showed some similarity, with great improvement seen in the older age groups. The largest difference between the model-based estimate and Kaplan-Meier estimate was 2.9 percent.

The procedure was repeated by bypassing two and then three years followup. The accelerated failure estimates continued to approach the Kaplan-Meiers as more followup was bypassed. However, since patients diagnosed in 1985-6 had only five years of available followup, it was feared that bypassing too many years of followup would present problems in predicting long-term survival. To be useful, predicted survival based on three or fewer years of followup would have to be accurate for distant times. Therefore, modeling survival after one year was considered to be adequate for estimating survival within the time frame encompassed by the data,
Figure 2.1 Survival Estimates versus Age, White Males, 1975-6
Estimated survival for white males diagnosed in 1975-6 in four selected age groups. The solid
lines represent survival given by the accelerated failure model. The dotted lines represent the
 corresponding Kaplan-Meier estimates. The vertical line in the right panel represents the one year
point.

since the discrepancies between predicted survival and Kaplan-Meier survival were
reasonably small.

2.2.2 Criterion 2–Testing Predictability of the Model
The only model satisfying criterion (1) bypassed the first year of followup and de-
scribed survival after the first year. To determine if such a model could reasonably
predict survival for times beyond those observed in the data, the following procedure
was performed.

Patients diagnosed in 1975-6 had fifteen years of available followup. For each
age group, an accelerated failure model was fit to the only the first five years of fol-
lowup, with first year survival replaced by the corresponding Kaplan-Meier estimate.
Patients surviving more than five years were assigned censoring times of five years,
and the resulting followup was fit. Survival was then calculated out to fifteen years
after diagnosis. If model-based survival followed the Kaplan-Meier estimate reason-
ably well out to fifteen years after diagnosis, then the model was considered to satisfy criterion (2).

![Graph showing survival rates for different age groups.](image)

**Figure 2.2** Survival Estimates Based on First Five Years Followup

Estimated survival for white males diagnosed in 1975-6 in four selected age groups. The solid lines represent survival given by the accelerated failure model fitting only the first five years followup, bypassing the first year. The dashed lines represent survival given by the accelerated failure model fitting all followup after 1 year. The dotted lines represent the corresponding Kaplan-Meier estimates. The vertical line represents the five year point.

Figure 2.2 shows the model-based survival estimates for white males. The estimates determined by fitting all followup are presented for comparison. Survival estimated by fitting the first five years of followup was generally more optimistic than the other estimates (most notably for those aged 60-64 of those shown). In all but one of the thirteen age groups, the model based on the first five years of followup predicted higher (from 1.0 to 8.4 percent) fifteen year survival. Similar results were seen when the model was fit to the first ten years of followup. Because predicted survival based on limited early followup did not reasonably follow Kaplan-Meier survival, the accelerated failure model as formulated could not satisfy criterion (2).

**Fitting Followup Well Removed From Diagnosis**

It was hoped that ignoring early survival and fitting an interval of followup far removed from diagnosis would allow for more predictive quality. To test this assessment
for each age group (diagnosed in 1975-6), an accelerated failure model was fit to followup between five and ten years after diagnosis. Those surviving more than ten years were assigned censoring times of ten years, and the resulting followup was fit. Survival estimates were calculated and compared to the corresponding Kaplan-Meier estimates over the interval of five to fifteen years after diagnosis.

![Graph showing survival estimates](image)

**Figure 2.3** Survival Estimates Based on Five to Ten Year Followup
Estimated survival for white males diagnosed in 1975-6, fitting followup between five and ten years after diagnosis. The solid lines represent survival given by the accelerated failure model. The dotted lines represent the corresponding Kaplan-Meier estimates.

Figure 2.3 shows this comparison for selected age groups of white males. The two estimates seemed to agree for most of the period, with the discrepancies between the estimates not exceeding one or two percent. Similar results for the other sex and race combinations suggested that later survival may be better predicted in this manner.

### 2.3 Restructuring the Survival Estimate

The difficulty in obtaining an acceptable model-based survival estimate forced a tailoring of the survival calculation. The accelerated failure model proved troublesome for estimating survival, as the changing shape of the survival curve with age and the influence of deaths at or near diagnosis prevented the model from displaying much
predictive quality. There was some evidence, however, that the model may be able
to adequately predict survival if based on followup years removed from diagnosis.

The new strategy for calculating survival involved using observed survival whenever possible. Survival for times beyond those observed was to be estimated by an accelerated failure model fit to an interval of followup as far removed from diagnosis as possible. Accordingly, the survival estimate (for each sex, race, and age) was restructured as follows:

- For patients diagnosed in 1975-6, survival for the first fifteen years after diagnosis was taken from the appropriate Kaplan-Meier estimate. For times beyond fifteen years, survival was taken from an accelerated failure model fit to ten to fifteen year followup.

- For patients diagnosed in 1980-1, survival for the first ten years after diagnosis was taken from the Kaplan-Meier estimate. Survival for ten to fifteen years after diagnosis was assumed to follow the ten to fifteen survival experience of patients diagnosed in 1975-6. Survival for times beyond fifteen years was assumed to follow the long-term survival given by the model for patients diagnosed in 1975-6.

- For patients diagnosed in 1985-6, survival for the first five years after diagnosis was taken from the Kaplan-Meier estimate. Ten to fifteen year survival was assumed to follow the ten to fifteen year experience of patients diagnosed in 1975-6. Survival for times beyond fifteen years after diagnosis was assumed to follow the long-term survival given by the model for patients diagnosed in 1975-6. For five to ten year survival, two options were considered:
  (a). Assume that patients diagnosed in 1985-6 follow the five to ten year survival experience of patients diagnosed in 1980-1.
  (b). Assume that patients diagnosed in 1985-6 continue the trend seen from 1975-6 to 1980-1. For example, five to ten year survival for white males diagnosed in 1980-1 improved by 1.2 percent across age groups from 1975-6. Therefore, the assumption is that five to ten year survival for white males diagnosed in 1985-6 improves another 1.2 percent across age. There was 1.5 percent decrease across age in the five to ten year survival for white females diagnosed in 1980-1, a 4.9 percent decrease for black males, and a 5.9 percent decrease for black females.

Results obtained under both assumptions showed that assumption (b) only slightly altered the numbers found under assumption (a), while the comparisons between the three time intervals were unaffected. Therefore, all results presented in the following chapter are presented under assumption (a).
In a few instances, particularly for age groups with relatively few observations, the model predicted survival which exceeded that of the general population. Therefore, survival for times greater than fifteen years after diagnosis was bounded above by the survival of the general population, as obtained from the National Center for Health Statistics for years 1985-6.
Chapter 3

Results

3.1 Proportion Diagnosed and Dead versus Year

Figure 3.1 shows the proportion diagnosed and dead (in number per 100000) by particular ages for each sex and race combination. The scale is the same for each rate and difference plot. Ages range from 22 to 82, which correspond to the midpoints of the thirteen age groups.

For white males ages 72 and above the proportion increased moderately in 1980-1, with little change occurring at any other ages. In 1985-6, however, the proportion showed much more prominent increases, with ages below 47 and above 72 experiencing the most significant changes.

For white females, the proportion dropped slightly in 1980-1 for ages above 62, with other ages experiencing little change. By 1985-6, however, the proportion rose to its highest levels for ages above 67, with little change elsewhere.

The proportion of black males diagnosed and dead increased for almost every age in 1980-1, with large increases occurring at ages 62 and higher. There were only minor changes between 1980-1 and 1985-6.

Conversely, black females experienced a lower proportion diagnosed and dead for most ages in 1980-1, particularly for ages 47 and above. Some increases were seen from 1980-1 to 1985-6 for ages 72 and higher, but for the ten year period the proportion showed an overall decrease across age.

3.2 Checking the Results

Since survival was estimated under assumptions, a closer look may be needed to interpret the changes in the proportion diagnosed and dead by age. Examining different components of the measure separately should clarify the results.
Figure 3.1 Proportions Diagnosed and Dead by Age
The proportion diagnosed with cancer and dead by particular ages. The solid lines represent the quantities for 1975-6, the dotted lines for 1980-1, and the dashed lines for 1985-6. In the difference plots, the solid lines represent the 1975-6 quantities as a base line for comparison.
3.2.1 Incidence and Survival

The interplay between incidence and survival was examined separately for each sex and race. Figure 3.2 shows the five year incidence for each sex and race combination. Likewise, Figure 3.3 shows five year survival for each sex and race. Five year survival is shown because those diagnosed in all three time periods have at least five years of observed survival. The scale is the same for each rate and difference plot.

For white males, incidence increased moderately in 1985-6 for people between the ages of 22 and 47. At the same time, survival dropped sharply for patients diagnosed between 22 and 42. The result was a swift upturn in the proportion diagnosed and dead from age 22 to age 47. The incidence increases seen for older white males (ages 62+ in 1980-1, ages 52+ in 1985-6) were large enough to counter the mild survival improvements for those diagnosed at those ages. As a result, the proportion diagnosed and dead for older ages increased in both 1980-1 (ages 72+) and 1985-6 (ages 62+).

White female incidence for those aged 62 and above increased significantly enough to offset any survival increases and push the proportion diagnosed and dead up in 1985-6 (ages 67+). The incidence and survival changes in 1980-1 were small, and the proportion dipped only slightly for ages above 52.

Black male incidence shot up in 1980-1 for those above the age of 47, and especially for those aged 62 and higher. Likewise, the proportion diagnosed and dead was pushed up at those ages in 1980-1. Neither the incidence nor the proportion diagnosed and dead showed much change from 1980-1 to 1985-6. Survival fluctuations did not significantly affect the measure in either time period.

Black female survival dropped gradually between 1975-6 and 1985-6 for those diagnosed below the age of 47. However, incidence decreases seen for those same age groups were enough to lower the proportion diagnosed and dead in both 1980-1 and 1985-6 for those young ages. Incidence for those above the age of 57 showed a marked increase, while survival remained relatively stable for those ages. However, the proportion diagnosed and dead continued to drop across age.

3.2.2 Cumulative Incidence

The potentially confusing interplay between black female incidence and survival may be clarified by examining changes in the cumulative incidence.

The proportion diagnosed and dead includes all causes of death into its calculation. As age increases, the probability of dying of any cause approaches one. This implies
Figure 3.2  Cancer Incidence
Five year cancer incidence. The solid line represents incidence for 1975-6, the dotted line for 1980-1, and the dashed line for 1985-6. In the difference plots, the solid lines represent the 1975-6 incidence as a base line for comparison.
Figure 3.3  Five Year Survival
Proportion of those diagnosed surviving to five years after diagnosis. The solid line represents five year survival for 1975-6, the dotted line for 1980-1, and the dashed line for 1985-6. In the difference plots, the solid lines represent the 1975-6 five year survival as a base line for comparison.
that the proportion diagnosed and dead by age \( a \) should approach the cumulative incidence as \( a \) increases, since \( S(a - i|i) \) goes to zero with \( a \) suitably large. Changes in the cumulative incidence should be comparable to changes in \( P(a) \) for large \( a \).

The age-adjusted cumulative incidence for white males ages 20-84 rose from 2258 to 2369 to 2517 per 100000 people. For white females, the cumulative incidence increased from 2514 to 2457 to 2688 per 100000 people. Black males aged 20-84 experienced an increase from 2185 to 2505 to 2514 out of every 100000. For black females the numbers were 2326, 2068, 2112.

Figure 3.1 shows that the change in the proportion diagnosed and dead by age 82 (the highest age considered) corresponded with changes in the cumulative incidence for each sex and race combination, with the exception of only a very slight decrease of \( P(82) \) for black males from 1980-1 to 1985-6.

### 3.2.3 Proportion Diagnosed and Dead by Age within Time \( T \)

An upper time limit on survival may be imposed on the proportion diagnosed and dead by a particular age so that the new measure is calculated directly from observed survival, independent of any modeling. This measure is defined and calculated as follows.

Again let \( a \) index the age category so that for ages 20-24, \( a = 1 \), for ages 25-29, \( a = 2 \), ..., and for ages 80-84, \( a = 13 \). Let \( T = 1, 2, 3, \ldots \) correspond to time limits of 5, 10, 15, ..., years. Then for each sex and race, the proportion diagnosed and dead within time \( T \) by age \( a \) is

\[
P(a, T) = \sum_{i=1}^{a} Prop(i) \times Incidence(i) \times (1 - S'(a - i|i)),
\]

where

\[
S'(a - i|i) = \begin{cases} 
S(a - i|i) & \text{if } a - i \leq T \\
S(T|i) & \text{if } a - i > T
\end{cases}
\]

Therefore, \( P(a, T) \) is the proportion of the population diagnosed with cancer and dead by age \( a \), with death occurring within \( 5T \) years of diagnosis.

\( Prop(i) \) and \( Incidence(i) \) are defined as in the calculation of \( P(a) \), and \( S'(a - i|i) \) is taken from the restructured survival estimate as described previously. Since the maximum available followup for any group is fifteen years, only values of \( T \) up to 3 may be considered. Since cancer causes many deaths within fifteen years of diagnosis, changes in \( P(a, 3) \) should reflect changes in \( P(a) \).
The proportions diagnosed and dead by age within time limits of $T$ up to 3 were calculated for each sex and race combination; the progression of $P(a, T)$ as $T = 1, 2, 3$ was compared to $P(a)$ with age ranging from 22 to 82.

This progression is shown for white males in Figure 3.4. The change in each proportion from 1975-6 was practically identical for ages below 67. The changes from 1975-6 became steadily larger for ages above 67. Since the progression of the changes in each measure agreed with changes in the proportion diagnosed and dead, the $P(a)$ results were considered acceptable. The progressions of $P(a, 1)$ through $P(a)$ for the other sex and race combinations are shown and discussed in the appendix.
Figure 3.4 Proportions Diagnosed and Dead
Within Time Limit T, White Males
The proportion diagnosed with cancer and dead by particular ages, within time limits of 5, 10 and 15 years after diagnosis, and also with no time limit. The solid lines represent the quantities for 1975-6, the dotted lines for 1980-1, and the dashed lines for 1985-6. In the difference plots, the solid lines represent the 1975-6 quantities as a base line for comparison.
Chapter 4

Supplementary Findings / Motivation for Research

4.1 Aids Bubble

In their study of noncancer deaths in white adult cancer patients, Brown, et al. (1993) detected a large increase in noncancer deaths for patients aged 20-59 for years 1983-7, especially for males. The increase was attributed primarily to the rising number of patients with human immunodeficiency virus (HIV) infections during the same time period. Further evidence of the AIDS influence was seen in the results obtained in this study, with higher incidence, lower five year survival, and a greater proportion of white males diagnosed in 1985-6 and dead by ages 22 to 47.

An examination of the ninth revision of the International Classification of Diseases (ICD)-coded causes of death for the SEER data showed that code 042 (HIV infection) and code 279 (deficiency of cell-mediated immunity) made up 0 cases in 1975-6, 4 cases in 1980-1, and 212 cases in 1985-6. In addition, code 136 (other unspecified infectious and parasitic diseases) comprised 8, 18 and 75 cases over the three time periods. An examination of site codes in SEER for the cancers with which these patients were diagnosed showed that codes 25020 (Other non-epithelial skin cancer) and 33041 (Nodal non-Hodgkin's lymphomas) were responsible for 3, 7, and 235 (82%) of the cases whose causes of death are given above. The counts for patients with either of these two cancers were 1240, 1680, and 3009 for all age groups; 186, 288, and 1219 for ages 20-45 only. When patients diagnosed with either of these two cancers were excluded from consideration, the results changed appreciably.

The AIDS influence is summarized in Figure 4.1. The upper panels show the incidence change for white males both with and without the two cancers associated with HIV. Likewise, the middle panels show the change in five year survival, and the lower panels show the change in the proportion of white males diagnosed and dead by ages ranging from 22 to 82. The figure shows that, without the HIV-related cancers, the outcome in 1985-6 is much more optimistic than previous results had indicated.
Figure 4.1 The Impact of AIDS, White Males

Five year incidence, five year survival and the proportion diagnosed and dead for white males. The panels on the left show the quantities for all combined cancers. The panels on the right show the quantities for all cancers except the two HIV-related cancers. The solid lines represent the quantities for 1975-6, the dotted lines for 1980-1, and the dashed lines for 1985-6. In the difference plots, the solid lines represent the 1975-6 quantities as a baseline for comparison.
For age as high as 72, in fact, the proportion diagnosed and dead held practically steady from 1975-6 to 1985-6. Elimination of patients diagnosed with either of the HIV-related cancers was not enough to significantly alter cumulative incidence trends, so for the oldest ages the proportion increased with time period as before. Removal of the HIV cancers also resulted in a flattening of the incidence "bubble" for ages 20 to 49, as well as a decrease in cumulative incidence from 2517 to 2401 per 100000 (the cumulative incidence likewise decreased from 2258 to 2292 per 100000 in 1975-6 and from 2369 to 2298 in 1980-1). Similarly, the dip in five year survival for ages 27 to 47 disappeared, and the pattern of survival increase across age and time period resumed.

It should be noted that while the exclusion of the two cancers associated with HIV allowed for a verification of the AIDS presence, it certainly could not account for the entire AIDS influence. The process also undoubtedly ensured that some patients who were not infected with HIV were also removed. Nevertheless, the results do clearly suggest that the AIDS impact on the proportion diagnosed and dead (as on any other measure of progress) is real and significant.

4.2 Underlying Problems—Accelerated Failure Model

The main problems encountered in the various accelerated failure model setups considered were: (1) no model based on all available followup could produce survival probabilities similar to the Kaplan-Meier estimate within the first fifteen years after diagnosis, and (2) even when a model was found which seemed to overcome the first problem (bypassing the first year of followup), it did not demonstrate the ability to accurately predict survival based on fitting early followup.

4.2.1 Likelihood Contributions

An examination of likelihood contributions shows that the deaths occurring shortly after diagnosis heavily influenced how each model was fit. Figure 4.2 shows the contribution to the likelihood at each time point for the model fit to the followup of white males aged 80-84 diagnosed in 1975-6. Patients diagnosed in this age group experienced many early deaths, as the survival was only 51.9 percent after one year. The likelihood contribution for censoring events increased across time and fluctuated at larger times where most of the losses to followup occurred. Likewise, the contribution to the likelihood for deaths was largest for the earliest times where the most deaths
occurred. The magnitude of the death contribution, however, was much larger (on the order of 100) than the contribution for censored events, especially at times immediately after diagnosis. For this particular age group, deaths occurring within the first year after diagnosis accounted for 51 percent of the likelihood contribution. Since the contribution to the likelihood was dominated by the deaths occurring shortly after diagnosis, the accelerated failure models were able to describe early survival accurately. However, the models were not useful in estimating survival at later times because they assumed that the shape of the survival curve was the same for distant times as observed for times immediately following diagnosis.

![Censored Observations](image1.png) ![Observed Deaths](image2.png)

**Figure 4.2** Likelihood Contribution versus Time
Contribution to the likelihood at each time point after diagnosis for censored cases and observed death cases, white males ages diagnosed in 1975-6 at ages 80-84.

Once the initial year of followup was bypassed, the models produced more acceptable survival estimates, as the influence of the many deaths within the first year of followup was diminished somewhat. Of those surviving one year in the above age group, 76.3 percent survived to the two year point.

### 4.2.2 Variation of the Accelerated Failure Parameters \((p, q)\)

Table 2.2 evidences the change with age of the shape parameters \((p, q)\). A similar age-dependence was seen in each of the model setups that were examined. Parameter
q in particular appeared to show dependence on age, since in most cases the value of $p$ was found to be 0. Figure 4.3 shows a plot of $q$ versus age group for three different models fit to followup of white males diagnosed in 1975-6: in each, the value of $p$ was determined to be 0 across age. The first model was fit to the first five years followup, the second to the first ten years followup, and the third to all fifteen years available followup; in each model the first year of followup was bypassed. There is evidence of a linear increase of $q$ with age for each fit ($p$-values < 0.0001). Since $(p, q)$ changed with age, no covariates for age could not be included in the model, since such a model assumed constant $(p, q)$ across age.

![Graph](image)

**Figure 4.3** Accelerated Failure Parameter $q$ versus Age, Amount of Followup

The value of the accelerated failure model parameter $q$ versus age for various amounts of followup fit for white males diagnosed in 1975-6. The dotted line represents the values of $q$ fitting only the first 5 years followup. The dashed line represents the $q$ values fitting the first 10 years followup. The solid line represents the $q$ values fitting all available followup. In each case, the value of the parameter $p$ is zero.

Figure 4.3 also shows an increase in $q$ (across age) with the amount of followup fit by the model. Since the amount of available followup differed for each year group, the dependence of $q$ with available followup would prevent a direct comparison of different years of interest. Even if the shapes of the survival curves were similar for the years studied, the changing $(p, q)$ values associated with modeling the differing
amounts of followup would disallow the inclusion of indicator variables for year of diagnosis.

The change of the shape parameter $q$ with amount of followup fit provides further evidence that the shape of the survival curve changed with time after diagnosis. Consequently, the model had difficulty accurately predicting survival for times extending beyond what was modeled, since the model assumed constant $(p, q)$ values for all times.

### 4.3 Application to Single Cancers

The mix of all combined cancers no doubt contains some cancers which produce primarily short survival times and others which allow generally long survival. Perhaps the mix of such cancers is more difficult to model than a single cancer which behaves in a more "regular" way. The applicability of the accelerated failure model to single cancers was investigated by fitting the model to survival times of both white male lung cancer and white female breast cancer.

The breast cancer model with covariates $age$ and $age^2$ seemed to give a much better fit than did the one for all cancers combined. The largest discrepancy between any of the survival estimates given by the model and the corresponding Kaplan-Meier estimates was 0.8 percent. For the lung cancer model, the difference was larger—as much as 6.5 percent during a steep survival drop shortly after diagnosis. In both cases, however, fitting age and year separately as before showed that the accelerated failure parameter $q$ once again appeared to change (although not linearly) with both age and with length of available followup. Therefore, modeling these single cancers separately did not eliminate any existing predictability problems.

After restructuring the survival estimate as described earlier, the proportion diagnosed and dead by age was calculated for white male lung cancer and for white female breast cancer.

Figure 4.4 shows the proportion for each single cancer. The proportion of white males diagnosed with lung cancer and dead dropped from 1980-1 to 1985-6 for ages above 47, but was still higher over the ten year period for ages 72 and up. The proportion of white females diagnosed with lung cancer and dead increased across age in 1985-6 after showing slight improvement in 1980-1. The increase was most pronounced for ages above 62. Much of the change in each measure for higher ages may be attributed to cumulative incidence increases seen over the same time frame.
Figure 4.4 Proportions Diagnosed and Dead by Age, Selected Single Cancers
Number per 100000 diagnosed and dead by age. The upper panels show the quantities for white males diagnosed with lung cancer. The lower panels show the quantities for white females diagnosed with breast cancer. The solid line represents the quantity for 1975-6, the dotted line for 1980-1, and the dashed line for 1985-6. In the difference plots, the solid lines represent the 1975-6 quantities as a base line for comparison.

It is of interest to note that the ten year change in the proportion diagnosed and dead by age 82 for white female breast cancer (56.5 per 100000) was largely responsible for the increase of the measure for all combined cancers (a change of 83.0 per 100000).
Chapter 5

Summary / Conclusions

In this study, the proportion diagnosed and dead was considered an appropriate measure for assessing the impact of cancer on survival. The measure improves upon many existing measures for several reasons. First, it includes both incidence and survival, with equal emphasis on the event of death. Second, it is immune to lead time bias, because only the age at death is considered. Third, it does not rely on the attributed cause of death, since all causes of death are included; therefore is not affected by any associated reporting biases. The measure also allows one to directly compare the experience of patients diagnosed in different years.

The main problems associated with its calculation were in extrapolating survival beyond observation. Model-based survival for early times was often adequate, but for distant times survival prediction proved to be difficult. Therefore, survival had to be reestimated from both observed survival and from that estimated by a model fit to followup times well removed from diagnosis. Changes in incidence, five year survival, and proportions diagnosed and dead within convenient upper time limits were examined to interpret and support the $P(a)$ results.

Assessment of Progress

In their examination of cancer-specific mortality trends over a 35 year period, Bailar and Smith (1980) concluded that recent attempts to improve cancer treatment had to be deemed a failure, since the measure of interest increased in the period of study for almost all sex and race combinations considered.

Doll (1991) focused attention on incidence and mortality trends in young adults, which he considered to be more indicative of progress. Doll's assessment of progress was more encouraging, with his conclusion that progress has been made in reducing cancer fatality, and that this progress has not been outweighed by spread of new hazards.
The conclusions of this study fall somewhere in the middle of those above. There is no evidence of resounding progress, nor evidence of disaster. For white males, it seems that rising incidence and improvements in survival largely canceled each other out for ages under 72, when cancers associated with HIV were excluded from consideration. For ages above 72, rising cumulative incidence rates led to a gradual increase in the proportion diagnosed and dead. For white females, the proportion diagnosed and dead also held steady for ages under 72, with cumulative incidence increases again pushing the measure up in 1985-6. Black males showed no evidence of progress whatsoever, due mostly to sharp incidence increases from 1975-6 to 1980-1. The proportion diagnosed and dead did hold steady from 1980-1 to 1985-6. For black females, the picture was more optimistic, with smaller proportions diagnosed and dead in 1980-1 and again in 1985-6.
Appendix A

Progression of $P(a, T')$ versus $P(a)$

Figure A.1 shows the progression of $P(a, T)$ as $T = 1, 2, 3$ compared to $P(a)$ for white females. The proportion diagnosed and dead by age $a$ within fifteen years ($P(a, 3)$) was slightly more pessimistic than $P(a)$ for ages above 75 in 1980-1; otherwise all of the measures seemed to agree.

Figure A.2 shows the progression for black males. The changes in the proportions with and without time limits were practically identical.

Figure A.3 shows the progression for black females. The changes in each measure agreed for ages under 50. For older ages, however, each proportion with a time limit steadily increased with time, whereas $P(a)$ actually showed an overall decrease. This result was initially surprising, but upon further investigation of incidence and survival changes, it became easily explainable.

Consider both $P(a, 3)$ and $P(a)$ as weighted sums of the age-adjusted incidence, with weights determined by survival at appropriate times after diagnosis. For black females, incidence for younger ages declined over the period of study, while incidence for older ages increased (as Figure 3.2 indicates). At fifteen years after diagnosis, survival for those diagnosed at young ages was good (at least 60 percent for ages under 40 in all three year groups), so in the calculation of $P(a, 3)$ smaller weights were given to the ages where incidence decreased. Conversely, survival to age 82 was much lower for those diagnosed at young ages (only as high as 32 percent), so in the calculation of $P(a)$ larger weights were given to the ages where incidence decreased. Fifteen year survival and survival to age 82 were comparable in older ages, and thus the weights given those ages changed little between $P(a, 3)$ and $P(a)$. Therefore, the decreasing incidence of younger black females was able to affect $P(a)$ more than $P(a, 3)$, enough to counter the incidence increases seen in older ages and produce an overall decrease in $P(a)$. A similar situation was seen for white females.
Figure A.1 Proportions Diagnosed and Dead
Within Time Limit $T$, White Females

The proportion diagnosed with cancer and dead by particular ages, within time limits of 5, 10 and 15 years after diagnosis, and also with no time limit. The solid lines represent the quantities for 1975-6, the dotted lines for 1980-1, and the dashed lines for 1985-6. In the difference plots, the solid lines represent the 1975-6 quantities as a baseline for comparison.
Figure A.2 Proportions Diagnosed and Dead

Within Time Limit $T$, Black Males

The proportion diagnosed with cancer and dead by particular ages, within time limits of 5, 10 and 15 years after diagnosis, and also with no time limit. The solid lines represent the quantities for 1975-6, the dotted lines for 1980-1, and the dashed lines for 1985-6. In the difference plots, the solid lines represent the 1975-6 quantities as a baseline for comparison.
Figure A.3  Proportions Diagnosed and Dead
Within Time Limit $T$, Black Females

The proportion diagnosed with cancer and dead by particular ages, within time limits of 5, 10 and 15 years after diagnosis, and also with no time limit. The solid lines represent the quantities for 1975-6, the dotted lines for 1980-1, and the dashed lines for 1985-6. In the difference plots, the solid lines represent the 1975-6 quantities as a baseline for comparison.
References


