Representativeness, Generalizability, and Diffusion of Cancer Clinical Trial Treatments

Joseph M. Unger

A dissertation submitted in partial fulfillment of the

requirements for the degree of

Doctor of Philosophy

University of Washington

2013

Reading Committee:

Diane P. Martin, Chair

Ruth Etzioni

William B. Barlow

Scott Ramsey

Dawn Hershman

Michael LeBlanc

Program Authorized to Offer Degree:

Health Services

University of Washington

Abstract

Representativeness, Generalizability, and Diffusion of Cancer Clinical Trial Treatments

Joseph Michael Unger

Chair of the Supervisory Committee:
Professor Emeritus Diane P. Martin
Health Services Research

The path from initial development of an anti-cancer agent to diffusion of a new cancer therapy into the cancer treatment community relies, crucially, on clinical trials. In this dissertation, we investigated the representativeness, generalizability, and diffusion of cancer clinical trial treatments. Representativeness was examined using a national, online survey sample of 5,499 patients enrolled from 2007-2011. Income independently predicted clinical trial participation ($p=.01$) and cost concerns were much more evident among lower income patients ($p<.001$). We concluded that a better understanding of why income is a barrier may help identify ways to make clinical trials better available to

all patients, and would increase the generalizability of clinical trial results across all income levels. To examine generalizability, we compared 5,190 trial patients from 21 SWOG studies from 1987-2007 to 69,187 corresponding non-trial controls selected from the Surveillance, Epidemiology, and End Results (SEER) program. The impact of trial participation on overall survival endured for only one year, and was therefore more likely to influence overall survival in poor prognosis studies (9/10) rather than good prognosis (0/11) studies ($p<.0001$). We concluded that the long term generalizability of standard arm outcomes improves confidence that trial treatment effects will translate to the real world setting, especially for good prognosis diseases. To examine diffusion, we analyzed docetaxel diffusion in metastatic prostate cancer patients diagnosed from 1995-2007 using the SEER-Medicare database. 6561 metastatic prostate cancer patients were identified; 1350 subsequently received chemotherapy (i.e. hormonal therapy failures). Diffusion was slower for socioeconomically disadvantaged patients. Eighty percent of docetaxel diffusion occurred prior to the release of phase III results showing superiority of docetaxel over standard-of-care in hormone-refractory prostate cancer. We concluded that efforts to increase the rate of diffusion of treatments among disadvantaged populations could lead to cancer population survival gains; also, diffusion prior to definitive phase III evidence suggests the widespread prevalence of off-label chemotherapy use. These results contribute to our understanding of the role of clinical trial results in the development of new treatments, and may help improve the speed and efficiency with which new cancer treatments are translated into clinical practice.

TABLE OF CONTENTS

LIST OF FIGURES

LIST OF TABLES

Chapter 1

INTRODUCTION

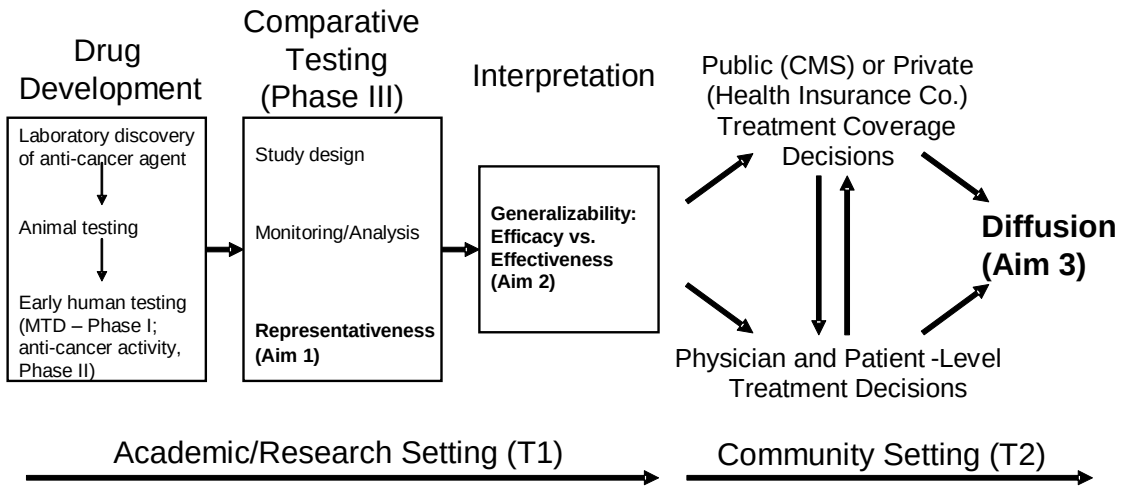
The path from initial development of an anti-cancer agent to diffusion of a new cancer therapy into the cancer treatment community involves, crucially, clinical trials, which represent the final step in evaluating the efficacy of new therapeutic approaches for malignancy. As such, the proper design, conduct and interpretation of cancer clinical trials are essential for informing not only future treatment decisions, but policy decisions pertaining to the coverage of new therapies.

Figure 1.1 shows a conceptual model of the pathway of development to diffusion of a new therapy. Early development includes lab discoveries of new agents through early human testing in phase I and phase II clinical trials. Comparative testing of a promising new drug to standard-of-care is conducted in a randomized phase III trial. Crucial elements for establishing the validity of the clinical trial experiment include the nature of the study design, appropriate trial monitoring and analysis, and the representativeness of the trial cohort compared to the intended treatment population. These factors will impact the generalizability of the study results; that is, the extent to which the impact of the new treatment, compared to standard-of-care, in the experimental setting (the "efficacy" of treatment) translates to the broader cancer treatment community (the "effectiveness" of treatment). Finally, the interpretation of results will impact patient and physician treatment decisions, as well as the decisions of public and private funding agencies, which will also interact with each other. Treatment and coverage decisions will influence the diffusion of the new therapy into the community setting. This pathway has

alternatively been decomposed into stages ***T1*** and ***T2***, where ***T1*** represents the translation of newly discovered agents from early laboratory testing through clinical testing and establishment of experimental efficacy and community effectiveness, and ***T2*** focuses on factors affecting the diffusion of a proven agent into clinical practice.[1]

Figure 1.1

Conceptual Model: Study to Diffusion of New Cancer Therapy



The conduct of cancer clinical trials, especially with regard to methodological issues of design, monitoring, and analysis, is firmly established and has evolved over decades.[2] But other elements along the pathway described above have received less attention. The representativeness of clinical trial cohorts with respect to race and ethnicity has received much attention; however, because patient-specific socioeconomic data are rarely collected for cancer patients enrolled on national clinical trials, the

influence of socioeconomic status on clinical trial participation has not been well studied.[3] A fuller understanding of the representativeness of clinical trial cohorts is especially important in light of the fact that only about 2-3% of adult cancer patients ultimately participate in cancer clinical trials;[4] thus extrapolation of clinical trial results from the experimental setting to the community setting takes on greater meaning. Along these lines, studies of the relationship between drug efficacy in a clinical trial versus drug effectiveness in the cancer treatment community ("generalizability") in cancer have not been comprehensive, relying instead on single-study comparisons with heterogeneous methodologic approaches.[5,6] Finally, although many studies of cancer treatment usage patterns for a snapshot in time have been conducted, studies of treatment usage patterns over time ("diffusion") are generally lacking.

Thus the objective of this dissertation is to investigate these three aspects – representativeness, generalizability, and diffusion – along the pathway from development to new treatment diffusion in cancer. Such investigations are crucial for understanding the context and nuances of clinical trial results, in order to better inform the funding and policy decisions that are driven by clinical trial results, and ultimately to help improve the speed and efficiency with which new cancer treatments are adopted into clinical practice.

1.1 REFERENCES

1. Dougherty D, Conway PH. The "3T's" road map to transform US health care: the "how" of high-quality care. JAMA. 2008 May 21;299(19):2319-21.

2. Green S, Benedetti J, Crowley J. *Clinical Trials in Oncology*. 2nd ed. CRC Press; 2003.

3. Ford JG, Howerton MW, Lai GY, et al. Barriers to recruiting underrepresented populations to cancer clinical trials: a systematic review. Cancer. 2008 Jan 15;112(2):228-42.

4. Tejeda HA, Green SB, Trimble EL, Ford L, High JL, Ungerleider RS, Friedman MA, Brawley OW. Representation of African-Americans, Hispanics, and whites in National Cancer Institute cancer treatment trials. J Natl Cancer Inst. 1996 Jun 19;88(12):812-6.

5. Peppercorn JM, Weeks JC, Cook EF, Joffe S. Comparison of outcomes in cancer patients treated within and outside clinical trials: conceptual framework and structured review. *Lancet*. 2004;363(9405):263-270.

6. Edwards SJ, Lilford RJ, Braunholtz DA, Jackson JC, Hewison J, Thornton J. Ethical issues in the design and conduct of randomised controlled trials. *Health Technol Assess*. 1998;2(15):1-132.

Chapter 2

PATTERNS OF DECISION-MAKING ABOUT CANCER CLINICAL TRIAL PARTICIPATION IN THE ONLINE CANCER TREATMENT COMMUNITY

2.1 INTRODUCTION

Clinical trials represent the final, critical step in evaluating the efficacy of new treatments for cancer. Continued access to and participation in cancer clinical trials are essential for reducing cancer mortality. However, only a small proportion of adult cancer patients participate in clinical trials.[1,2]

The decision about what cancer treatment to undergo is complex and personal. Even if patients are eligible for a trial, they often refuse to participate.[3,4] Patients express dislike of randomized treatment assignment, and may already have a particular treatment in mind.[4-7] Access factors (e.g. transportation, cost), disease status, and physicians' attitudes toward patient participation are also important.[3,4,7,8]

The generalizability of clinical trial results depends on how representative the trial population is of the cancer population. For instance, comorbid conditions may discourage older patients from trial participation, or may render patients clinically ineligible.[9] In 1999, investigators at SWOG, a national clinical trials consortium, showed that older patients were substantially underrepresented in cancer trials.[10] In 2000, Medicare changed its policy to cover the routine care costs of trial participation. A later SWOG study suggested that this policy change improved enrollment of older patients, but only for those with supplemental insurance to Medicare.[11]

Heightened awareness of socioeconomic disparities in access to medical, economic, or other resources is an important and current public policy issue, and provided the motivation to investigate potential socioeconomic barriers to clinical trial participation, which might also inform the age disparity. Because patient-specific socioeconomic data are rarely collected for cancer patients enrolled on national clinical trials, this topic has not been previously well studied.[12] In addition, participation in clinical trials is strongly influenced by the presence of comorbid illnesses, yet studies of clinical trial participation rarely include comorbidity data.[12] Therefore, to address the research question, SWOG collaborated with a provider of online treatment decision tools to assess patterns of clinical trial participation according to patient-level SES and demographic variables, accounting for comorbid illnesses.

2.2 METHODS

Administration

Investigators from SWOG collaborated with NexCura®, Inc. (The Woodlands, Texas, USA), a provider of proprietary Internet-based cancer treatment decision tools.[13] Patients were accessed through their registration to NexCura's treatment decision tool, which was embedded in multiple major cancer-oriented websites (e.g., American Cancer Society). An email was generated 3 months after each new registration (to allow patients time to make a treatment decision) offering the patient the opportunity to participate in the survey and providing a link to the survey website. The survey was completed online.

Patients were notified that information they provided would be reported in aggregate only. Since no individual identifiers were provided to researchers, the study was deemed IRB exempt.

Eligibility

To be eligible, patients must have been adults (≥18 years) living in the U.S. investigating treatment options for a first diagnosis of breast, colorectal, lung, or prostate cancer.

Design

The study design schema is shown in Figure 2.1.

All patients who agreed to participate were asked questions pertaining to their demographics, staging, and comorbid illnesses. Patients were asked whether they made a treatment decision within the prior three months. Patients who answered "No" were asked to indicate "Why". These patients were done with the survey.

Patients who answered "Yes" represented the evaluable patient cohort. These patients were asked whether they had discussed with their physician possible participation in a clinical trial. A brief description of a clinical trial was provided. Patients who answered either "No", or "Yes, but were not offered a clinical trial", were asked whether they thought clinical trials: 1) represented better treatment; 2) were more difficult to tolerate; 3) represented a gamble; 4) were inconvenient; and 5) were more difficult to pay for. These patients were done with the survey.

Patients who discussed a clinical trial with their physician *and* were offered trial participation were asked whether they participated in a clinical trial. Patients who answered "Yes" were asked about their attitudes toward clinical trials (as noted above) and were then done with the survey. Patients who answered "No" were asked about their reasons for declining trial participation based on 24 pre-specified questions from a prior

study of barriers to clinical trial participation.[7] These patients were then done with the survey.

The Appendix (Section 2.6) provides a full survey description.

Statistical Considerations

The primary objective was to assess, by SES and demographic factors: 1) rates of clinical trial enrollment; 2) patterns of enrollment to trials; 3) attitudes toward clinical trials; and 4) reasons for non-participation in clinical trials. Conditional logistic regression was used to assess the association between SES or demographic variables and a given outcome, conditioning on cancer type. All evaluable patients of any stage were included. Multivariable logistic regression was used to assess multiple factors associated with clinical trial participation simultaneously.

SES, Demographic, and Comorbidity Variables

The demographic factors were: age (<65 vs. ≥65 years), sex, and race (African American vs. other). Yearly household income was categorized as <$20,000 vs. $20,000-$34,999 vs. $35,000-$49,999 vs. $50,000-$99,999 vs. ≥$100,000 vs. "Don't know" vs. "Prefer not to answer". For the primary analysis, income was categorized as <$50,000/year vs. ≥$50,000/year (the nearest approximation to the median) and education was categorized as <2 year college degree vs. ≥2 year college degree. Binary indicator variables were used for consistency across factors and to aid interpretation. Further analyses explored other binary categorizations of income. Income analyses were limited to patients with a reported income value.

A comorbidity score was derived from data on 18 comorbid conditions.[14] Total travel distance to the clinic (a surrogate for convenience) was also obtained. Both factors were included as covariates in multivariable regression models, split at the median (comorbidity: 0-1 vs. ≥2; travel distance: <13 miles vs. ≥13 miles). In addition, each multivariable model included the SES and demographic variables.

2.3 RESULTS

Cohort Profile

A total of 77,752 survey invitations were sent; 6,259 were returned for a response rate of 8%, approximately twice that of a prior survey using NexCura's treatment decision tool.[13] Most patients, 5499 (88%), had made a treatment decision in the prior 3 months, representing the evaluable patient cohort; responses by cancer type included 2894 breast (53%), 1546 prostate (28%), 651 lung (12%), and 408 colorectal (7%).

Twenty-two percent of patients were ≥65 years, 2.5% were African American, and 62% were female (Table 2.1). In comparison, the U.S. adult cancer population with a similar cancer distribution was estimated to be older (58% ≥65 years) and to have more African Americans (10%), but the same proportion of females (62%).[11] There was good geographic representativeness compared to the U.S. adult population (Figure 2.2). Survey participants were similar to non-participants with respect to sex (female: 62% vs. 63%), income (>national median: 64% vs. 63%), and geographic region (Figure 2.2), but were more likely to have breast cancer (52% vs. 42%) and prostate cancer (28% vs. 20%) and less likely to have lung cancer (10% vs. 23%).

Income was reported by 83% of patients, of which 32% made <$50,000/year. Education was obtained for all patients; 34% reported less than a 2-year college degree.

Patterns of Decision-Making

Of the 5499 evaluable patients, 2174 (40%) reported discussing clinical trial participation with their physician; among these, 978 (45%) were offered a trial; and among these, 496 (51%) participated in a clinical trial and 482 (49%) did not (Figure 2.3). There were statistically significant differences in the proportion of patients discussing trial participation in multivariable analysis by age (42% <65 years vs. 29% $\geq$65 years, p<.001), income (36% <$50k/year vs. 42% $\geq$$50k/year, p<.001) and education (35% <2 year college degree vs. 42% $\geq$ 2 year college degree, p<.001). Given clinical trial participation was discussed, African Americans were more likely (57% vs. 45%, p=.03) and lower income patients less likely (40% vs. 47%, p=.05) to be offered a clinical trial. No other statistically significant differences by SES or demographic factors were found (see Table 2.3).

Univariate Estimation of Clinical Trial Participation

The overall rate of clinical trial participation among evaluable patients was 9.0% (496/5499; Figure 2.3). Conditioning on cancer type, clinical trial participation was less likely in older patients (5.4% vs. 10.0%, p=.002) and patients with lower income (7.6% vs. 10.0%, p=.001) and lower education (7.9% vs. 9.6%, p=.02; see Table 2.2). There were no statistically significant differences in trial participation by race or sex. Higher comorbidity scores and shorter distance to clinic were also associated with lower participation.

Multivariable Estimation of Clinical Trial Participation

In a multivariable conditional logistic regression model including all SES and demographic factors, plus the covariates comorbidity status and distance to clinic, income was the only SES or demographic factor that was statistically significantly associated with clinical trial participation (OR=0.73, p=.01; see Table 2.2).

Patients with lower income had lower clinical trial participation regardless of income cutpoint (see Table 2.2). For instance, patients with income <$20,000/year showed a 44% lower odds of participation.

Association of Income and Clinical Trial Participation in Subcategories

We explored the association of income with trial participation within subgroups of respondents using a forest plot (Figure 2.4). The odds of clinical trial participation are consistently lower in nearly all subcategories. Importantly, although there was a trend towards a stronger association of income with trial participation among those <65 years (test for interaction of age and income, p=.06), income was associated with participation in older patients as well.

Attitudes toward Clinical Trials

Patient attitudes toward clinical trials were similar for patients who did not discuss a trial (n=3325) versus those who discussed but were not offered a trial (n=1196; data not shown). These subsets were combined. Concern about how to pay for clinical trial participation was higher in lower income patients (OR=1.79, 95% CI: 1.53-2.10, p<.001) and lower education patients (OR=1.50, 95% CI: 1.29-1.75, p<.001), but was lower in older age patients (OR=0.54, 95% CI: 0.44-0.65, p<.001), likely due to Medicare access. Rates of concern about how to pay for trial participation were 53% for income

<$20,000, 46% for income $20,000-$34,999, 43% for income $35,000-$49,999, 36% for income $50,000-$99,999, and 24% for income ≥$100,000, indicating an inverse linear relationship (p<.001).

Among patients who participated in a clinical trial (n=496), older patients were more likely to consider trial participation a gamble (OR=2.51, 95% CI: 1.28-4.93, p=.008), lower education patients were less likely to think a clinical trial involved extra inconvenience (OR=0.56, 95% CI: 0.35-0.88, p=.01), and women (OR=4.02, 95% CI: 1.26-12.82, p.02) and lower income patients (OR=2.63, 95% CI: 1.53-4.51, p<.001) were more likely to worry about how clinical trial participation would be paid for. A strong linear association between income level and concern about how to pay for clinical trial participation was also evident in patients who participated in a clinical trial (p<.001; rates not shown).

Reasons for Non-Participation in Clinical Trials

Among those n=482 patients who were offered a clinical trial but declined, treatment-related concerns, especially dislike of randomized treatment (68%), were the most frequently cited reasons for nonparticipation (see Figure 2.5).

Each of the 24 questions in Figure 2.5 was analyzed in multivariable regression. Lower income was strongly associated with more concern about how to pay for clinical trial treatment (p=.01) and less concern that a research protocol would determine choice of treatment (p=.01). Other differences are shown with Figure 2.5.

A strong linear association between income level and concern about how to pay for clinical trial participation was also evident in patients who were offered a clinical trial but declined (p<.001; rates not shown).

2.4 DISCUSSION

In this large, national survey, patients with lower income were less likely to participate in a clinical trial, even accounting for comorbidity and education. Simultaneously, lower income patients were more likely than higher income patients to report concern about how to pay for clinical trial participation.

Proportional minority and female enrollment in cancer clinical trials, and inadequate older patient enrollment, have been observed in many studies.[6,10,11,15-17] Although distance to clinic has been cited as a reason for non-participation in clinical trials, in this study, trial participation was higher among patients who traveled a greater distance.[4] This may be due to the willingness of patients seeking trials to travel farther. Such patients may also be healthier, and could partly explain why travel distance has been found to be positively associated with improved survival in clinical trials even after accounting for cancer stage and performance status.[18]

Few studies have evaluated the association between income and clinical trial enrollment. Instead, some studies have used area-level surrogates for SES variables through Census data.(19-21) The associations found in these studies were sometimes not retained in multivariable modeling, perhaps due to a lack of patient-level data and corresponding loss of power.[20,21] A large study using a telephone survey to assess clinical trial recruitment patterns found that middle income individuals ($15k/yr-$50k/yr) were less likely to participate.[22] However, this study was limited to Maryland only, was not cancer-specific, and did not collect comorbidity data. Some studies have found associations of lower SES with surrogate outcomes for trial participation, such as willingness to participate or awareness of clinical trials.[23,24] Other studies have found no

SES association with trial participation, although these studies had small sample sizes[25,26] and high levels of missingness for SES factors.[27] In contrast, this study had patient-level SES data, assessed clinical trial enrollment (by patient report) rather than willingness to participate or awareness of clinical trials, and had a large number of patients.

One explanation for our study results might be that higher income individuals are better insured. Although insurance status was not collected in this survey, we observed that lower income predicted lower clinical trial participation in patients 65 or older, indicating an income disparity even in a population with universal access to Medicare. We also found no evidence that the association of lower income with trial enrollment differed between states with and without insurance mandates for coverage of clinical trials (interaction p-value=.32). Finally, lower income may be a selection factor for hospitals that are less likely to offer clinical trial participation. However, we observed that lower income patients were less likely to be offered a trial given a trial was discussed, suggesting an income disparity even when a clinical trial was explicitly under consideration.

This study also provides strong evidence that lower income patients are more likely than higher income patients to be concerned about how to pay for clinical trial participation. However the NCI, in summarizing the literature, has stated that "patient care costs for clinical trials are not appreciably higher than costs for patients not enrolled in trials."[28] The NCI cites in particular the *Costs of Cancer Treatment Study* by Goldman and colleagues at RAND, which found an overall small, non-statistically significant increase (6.5%) in trial versus non-trial costs, and no increase in prescription out-of-pocket costs.[29,30] Other studies have found similar results.[31-34]

One limitation of this study was the inability to assess concerns about cancer treatment costs in general. But even if treatment cost concerns are a general issue, public policy changes could reduce these concerns in the clinical trial setting specifically, with the potential to reduce the disparity in trial participation rates. One approach would be to cover excess costs for trial participation for all patients. Prior evidence suggests that even in an insured population, co-pays and co-insurance may deter clinical trial participation.[11] Similarly, payment to individuals to encourage clinical trial participation has been explored.[35-37] Such approaches would require careful calibration of the size of any monetary incentive attached to an offer of trial participation,[38] to avoid "undue influence" as indicated in the U.S. Common Rule for the Protection of Human Subjects. A different strategy could be direct-to-consumer-advertising (DTCA) targeted to lower income populations. DTCA has increased in recent years and awareness of oncology-related DTCA is generally high among cancer patients (>80%).[39,40] Finally, lower income patients may be more sensitive to indirect costs, such as having to take time off work for extra clinic visits. Certain low-cost considerations for patients related to time, convenience, or transportation, such as parking passes or bus fare, could improve participation for lower income patients in particular.[41] Interventions to provide more comprehensive information to patients about costs and benefits associated with clinical trial participation could also be useful. Jacobsen et al. recently reported that patients randomized to receive printed educational materials plus a multi-media DVD intervention had more positive attitudes about clinical trials and more willingness to participate in trials than patients who received printed education materials alone.[42]

Patient self-report may limit the reliability of certain types of data, for example comorbidity status. On the other hand, self-report is preferable for patient attitudes and

SES variables. Also, although all p-values $\leq$.05 are reported, those cases where .01$\leq$ p $\leq$.05 should be regarded with some suspicion because of the number of tests performed, while highly statistically significant p-values (p$\leq$.01) are less likely to be significant by chance alone. Further, inferences pertaining to African American patients were limited by the small proportion of African Americans in the survey. Finally, the survey was conducted among web-based users in order to obtain a national sample of patients with patient-level SES data. Although the survey response rate was low, it was similar to rates reported in other internet-based surveys.[13,43,44] The participant cohort was younger and less diverse than the general cancer population, but was comparable to non-participants for several factors examined, including income. Nonetheless, the most important issue is the extent to which the inference about the association between income and clinical trial participation is generalizable beyond this web-based cohort.[45] Because income may be found to have a different impact on clinical trial participation in different populations, such as those without internet access or non-respondents, the validity of this finding requires confirmation in different study settings.

Improving participation of lower income patients in clinical trials is important from multiple perspectives. Since clinical trials offer the newest cancer treatments, equal access to this important resource for patients of all income groups is essential. Also, improved lower income participation would allow clinical trials to be conducted more quickly, and would better ensure the applicability of trial results to all income levels (its "generalizability"). Understanding that income is related to clinical trial participation could help guide policy decisions aimed at increasing access for lower income patients.

2.5 REFERENCES

1. Murthy VH, Krumholz HM, Gross CP. Participation in cancer clinical trials: race-, sex-, and age-based disparities. JAMA. 2004 Jun 9;291(22):2720-6.

2. Tejeda HA, Green SB, Trimble EL, et al. Representation of African-Americans, Hispanics, and whites in National Cancer Institute cancer treatment trials. J Natl Cancer Inst. 1996 Jun 19;88(12):812-6.

3. Comis RL, Miller JD, Aldigé CR,. Public attitudes toward participation in cancer clinical trials. J Clin Oncol. 2003 Mar 1;21(5):830-5.

4. Lara PN Jr., Higdon R, Lim N, et al. Prospective evaluation of cancer clinical trial accrual patterns: identifying potential barriers to enrollment. JCO, 2001 Mar 15; 19(6): 1728-33.

5. Hunter CP, Frelick RW, Feldman AR, et al. Selection factors in clinical trials: results from the Community Clinical Oncology Program Physician's Patient Log. Cancer Treat Rep. 1987; 71: 559-65.

6. Klabunde CN, Springer BC, Butler B, et al. Factors influencing enrollment in clinical trials for cancer treatment. South Med J, 1999; 92;1189-93.

7. Javid SH, Unger JM, Gralow JR, et al. A prospective analysis of the influence of older age on physician and patient decision-making when considering enrollment to breast cancer clinical trials (SWOG S0316). The Oncologist. 2012 Jun 20. [Epub ahead of print]

8. Ross S, Grant A, Counsell C,. Barriers to participation in randomised controlled trials: a systematic review. J Clin Epidemiol. 1999 Dec;52(12):1143-56.

9. Bergman L, Dekker G, van Kerhoff EH,. Influence of age and comorbidity on treatment choice and survival in elderly patients with breast cancer. Breast Cancer Res Treat 1991;18:189-198.

10. Hutchins LF, Unger JM, Crowley JJ,. Underrepresentation of patients 65 years of age or older in cancer-treatment trials. N Engl J Med. 1999 Dec 30;341(27):2061-7.

11. Unger JM, Coltman CA Jr, Crowley JJ, et al. Impact of the year 2000 Medicare policy change on older patient enrollment to cancer clinical trials. J Clin Oncol. 2006 Jan 1;24(1):141-4. Epub 2005 Dec 5.

12. Ford JG, Howerton MW, Lai GY, et al. Barriers to recruiting underrepresented populations to cancer clinical trials: a systematic review. Cancer. 2008 Jan 15;112(2):228-42.

13. Markman M, Luce R. Impact of the cost of cancer treatment: an internet-based survey. J Oncol Pract. 2010 Mar;6(2):69-73. Epub 2010 Feb 19.

14. Katz JN, Chang LC, Sangha O,et al. Can comorbidity be measured by questionnaire rather than medical record review? Med Care. 1996 Jan;34(1):73-84.

15. Trimble EL, Carter CL, Cain D, et al. Representation of older patients in cancer treatment trials. Cancer. 1994 Oct 1;74(7 Suppl):2208-14.

16. Lewis JH, Kilgore ML, Goldman DP, et al. Participation of patients 65 years of age or older in cancer clinical trials. J Clin Oncol. 2003 Apr 1;21(7):1383-9.

17. Talarico L, Chen G, Pazdur R. Enrollment of elderly patients in clinical trials for cancer drug registration: a 7-year experience by the US Food and Drug Administration. J Clin Oncol. 2004 Nov 15;22(22):4626-31.

18. Lamont EB, Hayreh D, Pickett KE, et al. Is patient travel distance associated with survival on phase II clinical trials in oncology? J Natl Cancer Inst. 2003 Sep 17;95(18):1370-5.

19. Gross CP, Filardo G, Mayne ST, et al. The impact of socioeconomic status and race on trial participation for older women with breast cancer. Cancer. 2005 Feb 1;103(3):483-91.

20. Du W, Gadgeel SM, Simon MS. Predictors of enrollment in lung cancer clinical trials. Cancer. 2006 Jan 15;106(2):420-5.

21. Sateren WB, Trimble EL, Abrams J, et al. How sociodemographics, presence of oncology specialists, and hospital cancer programs affect accrual to cancer treatment trials. J Clin Oncol. 2002 Apr 15;20(8):2109-17.

22. Baquet CR, Commiskey P, Daniel Mullins C, et al. Recruitment and participation in clinical trials: socio-demographic, rural/urban, and health care access predictors. Cancer Detect Prev. 2006;30(1):24-33. Epub 2006 Feb 21.

23. Brown DR, Topcu M. Willingness to participate in clinical treatment research among older African Americans and Whites. Gerontologist. 2003 Feb;43(1):62-72.

24. Lara PN Jr, Paterniti DA, Chiechi C, et al. Evaluation of factors affecting awareness of and willingness to participate in cancer clinical trials. J Clin Oncol. 2005 Dec 20;23(36):9282-9.

25. Avis NE, Smith KW, Link CL,et al. Factors associated with participation in breast cancer treatment clinical trials. J Clin Oncol. 2006 Apr 20;24(12):1860-7.

26. Kemeny MM, Peterson BL, Kornblith AB, et al. Barriers to clinical trial participation by older women with breast cancer. J Clin Oncol. 2003 Jun 15;21(12):2268-75. Erratum in: J Clin Oncol. 2004 Dec 1;22(23):4811.

27. Chang SM, Barker FG 2nd, Schmidt MH, et al. Clinical trial participation among patients enrolled in the Glioma Outcomes Project. Cancer. 2002 May 15;94(10):2681-7.

28. National Cancer Institute website: at http://www.cancer.gov/clinicaltrials/conducting/cost

29. Goldman DP, Berry SH, McCabe MS, et al. Incremental treatment costs in national cancer institute-sponsored clinical trials. JAMA. 2003 Jun 11;289(22):2970-7.

30. Kilgore ML, Goldman DP. Drug costs and out-of-pocket spending in cancer clinical trials. Contemp Clin Trials. 2008 Jan;29(1):1-8. Epub 2007 May 6.

31. Barlow W, Taplin S, Seger D, et al. Medical care costs of cancer patients on protocol. NCI meeting, Bethesda, MD: July 7, 1998.

32. Bennett CL, Stinson TJ, Vogel V, et al. Evaluating the financial impact of clinical trials in oncology: Results from a pilot study from the association of American Cancer Institutes/Northwestern University Clinical Trials Costs and Charges Project. J Clin Oncol. 2000 Aug;18(15):2805-10.

33. Fireman BH, Fehrenbacher L, Gruskin EP, et al. Cost of care for patients in clinical trials. J Natl Cancer Inst. 2000 Jan 19;92(2):136-42.

34. Wagner JL, Alberts SR, Sloan JA, et al. Incremental costs of enrolling cancer patients in clinical trials: A population-based study. J Natl Cancer Inst. 1999 May 19;91(10):847-53. (Published erratum appears in J Natl Cancer Inst. 2000;92:164-5.)

35. Macklin R. On paying money to research subjects: 'due' and 'undue' inducements. IRB. 1981 May;3(5):1-6.

36. McNeill P. Paying people to participate in research: why not? A response to Wilkinson and Moore. Bioethics. 1997 Oct;11(5):390-6.

37. Wilkinson M, Moore A. Inducement in research. Bioethics. 1997 Oct;11(5):373-89.

38. Viens, AM. Socio-economic status and inducement to participate. The American Journal of Bioethics. 2001; 1:2, 1f-2f.

39. Donohue JM, Cevasco M, Rosenthal MB. A decade of direct-to-consumer advertising of prescription drugs. N Engl J Med. 2007 Aug 16;357(7):673-81.

40. Abel GA, Burstein HJ, Hevelone ND, et al. Cancer-related direct-to-consumer advertising: awareness, perceptions, and reported impact among patients undergoing active cancer treatment. J Clin Oncol. 2009 Sep 1;27(25):4182-7. Epub 2009 Aug 3.

41. McCabe MS, Varricchio CG, Padberg RM. Efforts to recruit the economically disadvantaged to national clinical trials. Semin Oncol Nurs. 1994 May;10(2):123-9.

42. Jacobsen PB, Wells KJ, Meade CD, et al. Effects of a brief multimedia psychoeducational intervention on the attitudes and interest of patients with cancer regarding clinical trial participation: a multicenter randomized controlled trial. J Clin Oncol. 2012 Jul 10;30(20):2516-21. Epub 2012 May 21.

43. Hollowell CM, Patel RV, Bales GT, et al. Internet and postal survey of endourologic practice patterns among American urologists. J Urol. 2000 Jun;163(6):1779-82.

44. Kim HL, Gerber GS, Patel RV, et al. Practice patterns in the treatment of female urinary incontinence: a postal and internet survey. Urology. 2001 Jan;57(1):45-8.

45. Krosnick, J. (1999). Survey research. Annual Review of Psychology, 50, 537-67.

Table 2.1: Characteristics of the Survey Sample (N=5,499)

Demographic Factors	N	%		**Other Factors**	N	%
Age				Comborbidity Score		
<65 Years	4300	78%		0-1	3629	59%
≥65 Years	1199	22%		≥2	2230	41%
Gender				Distance to Clinic		
Female	3420	62%		<13 Miles	2726	50%
Male	2079	38%		≥13 Miles	2727	50%
Race				Cancer Type		
White	5192	94.4%		Breast	2894	53%
African American	135	2.5%		Colorectal	408	7%
Asian/Pacific Islander	62	1.1%		Lung	651	12%
Native American	20	0.4%		Prostate	1546	28%
Other	90	1.6%				
SES Factors				Geographic Region		
Income*				West	1388	25%
<$20,000	342	7%		Midwest	1151	21%
$20,000-$34,999	483	11%		Northeast	1063	19%
$35,000-$49,999	631	14%		South	1893	34%
$50,000-$99,999	1679	37%				
≥$100,000	1444	32%				
Don't know	24					
Prefer not to answer	896					
Education						
≤High School Deg.	660	12%				
Some college	1223	22%				
2-Year College Deg.	627	11%				
4-Year College Deg.	1288	23%				
Graduate School	1701	31%				

* Percentages are based on the total of 4579 respondents (83% of evaluable patients) who reported an income value.

Table 2.2: Rates of Clinical Trial Enrollment

Factor	Categories (codes)	% Enrolled in CT*	OR (95% CI)	p-value
Univariate Model Results				
Age	<65 (=0) ≥65 (=1)	10.0% 5.4%	0.64 (0.48-0.85)	.002
Sex**	Male (=0) Female (=1)	5.6% 11.1%	0.97 (0.63-1.48)	.88
Race	White (=0) African American (=1)	9.1% 11.1%	1.25 (0.72-2.16)	.43
Income	≥$50,000/year (=0) <$50,000/year (=1)	10.0% 7.6%	0.68 (0.54-0.86)	.001
Education	≥College (=0) <College (=1)	9.6% 7.9%	0.78 (0.64-0.96)	.02
CS	0 or 1 (=0) ≥2 (=1)	10.1% 7.5%	0.78 (0.64-0.95)	.01
DTC	≥13 Miles (=0) <13 Miles (=1)	10.5% 7.6%	0.66 (0.55-0.80)	<.001
Multivariable Model Results				
Age			0.79 (0.58-1.08)	.14
Sex			0.93 (0.58-1.49)	.75
Race			1.31 (0.74-2.33)	.35
Income			0.73 (0.57-0.94)	.01
Education			0.92 (0.73-1.16)	.49
CS			0.81 (0.65-1.02)	.07
DTC			0.66 (0.54-0.81)	<.001
Multivariable Model Results for Different Income Cutpoints				
$20,000/yr			0.56 (0.35-0.91)	.02
$35,000/yr			0.73 (0.54-0.98)	.04
$50,000/yr			0.73 (0.57-0.94)	.01
$100,000/yr			0.79 (0.63-0.98)	.04

CT=Clinical trial; OR=Odds Ratio; CI=Confidence Interval; CS=Comorbidity Score; DTC=Distance To Clinic

* Participation coded as 1; non-participation coded as 0.

** Although the observed participation rate for women was almost twice as that for men (11.1% vs. 5.6%), the difference was not statistically significant after conditioning on

cancer type due to the relatively high rate of enrollment among breast cancer patients. In the non-sex-specific diseases only (lung and colorectal), the rates were 8.4% for males and 8.0% for females.

Table 2.3: Patterns of Clinical Trial Decision-Making by SES and Demographic Subgroups

		By SES and Demographic Subgroups				
	Overall	Age	Sex	Race	Income	Education
Decision-Making Level		≥65 v. <65	F v. M	AA v. O	<$50k v. ≥$50k	<CD v. ≥CD
Discussed CT	40% (2174/5499)	29% v. 42% P<.001	45% v. 31% P=.36	33% v. 40% P=.12	36% v. 42% P<.001	35% v. 42% P<.001
Offered CT*	45% (978/2174)	38% v. 46% P=.70	50% v. 32% P=.27	57% v. 45% P=.04	40% v. 47% P=.05	42% v. 46% P=.59
Participated in CT**	51% (496/978)	51% v. 49% P=.15	49% v. 57% P=.48	60% v. 51% P=.43	52% v. 51% P=.91	54% v. 50% P=.38

* Conditional on having discussed a CT.
** Conditional on having been offered a CT.

CT = Clinical Trial; F = Female; M = Male; AA = African American; O = Other; CD = College Degree

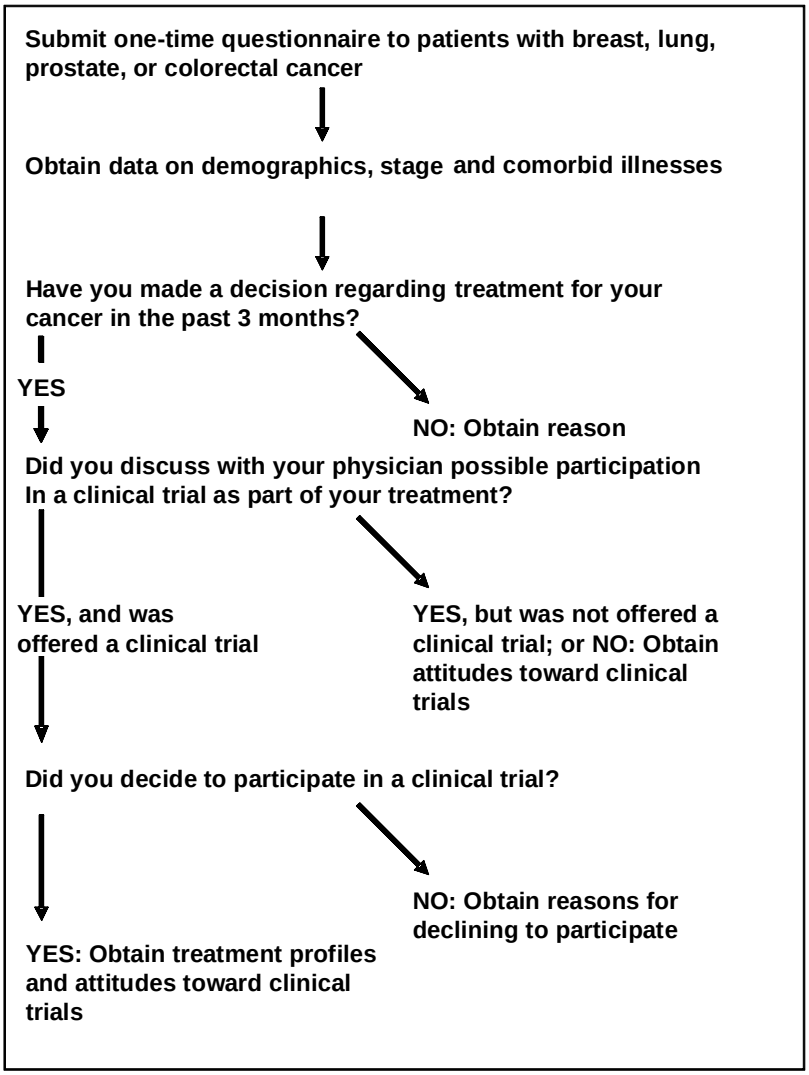
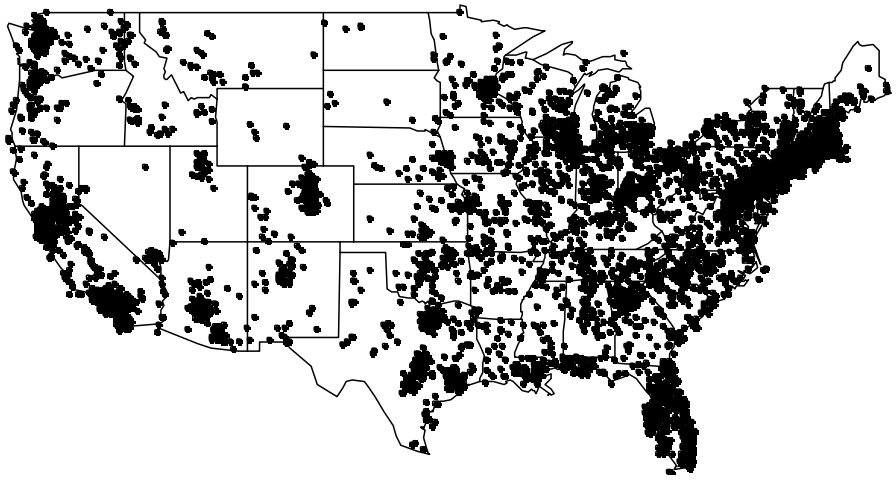


Figure 2.1. Survey schema.



Region	% in Participants	% in Non-Participants	% in U.S.
West	25%	23%	23%
Midwest	21%	22%	22%
Northeast	19%	19%	18%
South	34%	36%	37%

Figure 2.2. Geographic distribution of NexCura survey respondents. The legend shows the proportion of survey participants by geographic region compared to proportions in non-participants and in the U.S. adult population.

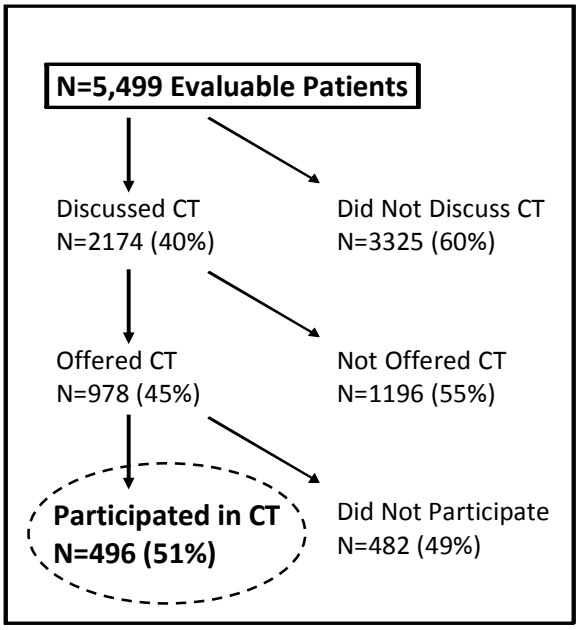


Figure 2.3: Patient flow diagram indicating decision-making patterns about clinical trial participation. A total of 77,752 survey invitations were sent and 6,259 were returned, of which n=760 had not made a treatment decision within the 3 months since their initial registration to the NexCura website, leaving N=5499 evaluable patients. For the 760 respondents who had not made a treatment decision within the 3 months since their initial registration, most had made a treatment decision prior to 3 months ago (65%) or were recently diagnosed but still undecided about treatment (15%). CT=Clinical Trial.

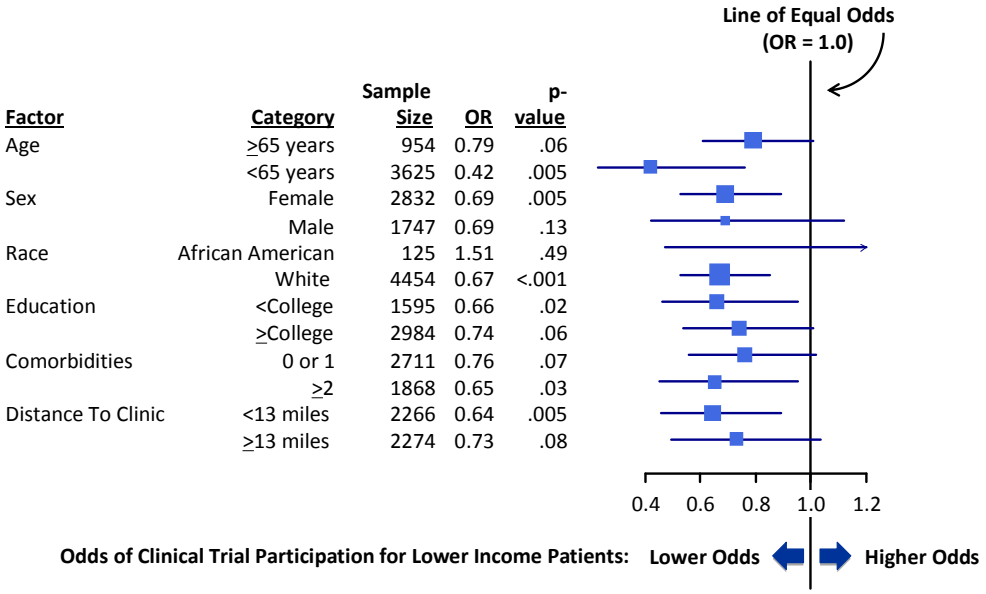


Figure 2.4: Forest plot of the association of income and clinical trial participation by each study factor. Each square represents an Odds Ratio (OR) and each horizontal line is the 95% confidence interval. The vertical line is the line of equal odds. For lower income individuals, the odds of clinical trial participation are consistently lower (that is, to the left of the line of equal odds) within nearly all subgroups of all the factors included in this analysis, indicating that the association between income and participation is independent of subgroup membership.

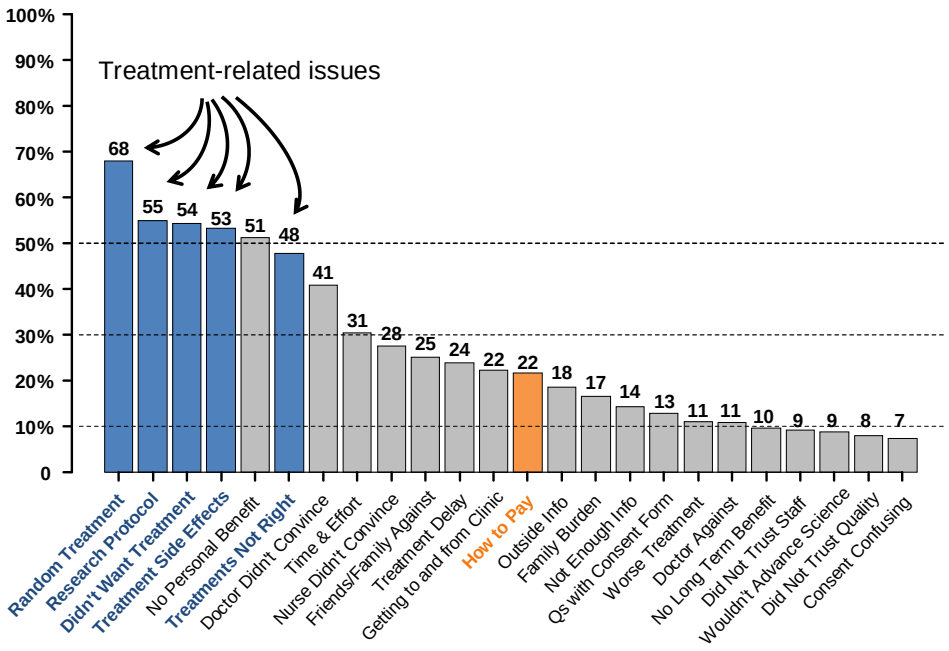


Figure 2.5: Reasons for declining to participate in clinical trials. Among patients who were offered a clinical trial but did not participate (n=482), the most common reasons cited for non-participation were treatment related concerns (i.e. fear of randomization, did not want the specified protocol treatment, etc.). Other reasons that differed by SES or demographic factors included the following. AGE: Older patients were less concerned about travel related to clinical trial participation (p=.02), less concerned about how to pay for clinical trial participation (p=.04), and less concerned about time and effort related to clinical trial participation (p=.04). SEX: Women were less likely to have family and friends opposed to their clinical trial participation (p=.03). INCOME: Lower income patients were more concerned about how to pay for clinical trial participation (p=.01), less concerned that a research protocol would determine their treatment choice (p=.01), less likely to have family/friends opposed to their clinical trial participation (p=.03), and less concerned about random treatment assignment in a clinical trial (p=.04). EDUCATION: Lower education patients were less concerned about clinical trial side effects (p=.05).

2.6 APPENDIX

Survey Description

The following represents the verbatim wording to the web-based survey. The survey was administered to all breast, colorectal, lung, and prostate cancer patients 3 months after patient registration to the Nexcura online treatment decision tool.

Section 1: Demographic and SES Data

"The following survey is designed to assess patterns of treatment decision-making for patients with a diagnosis of breast, colon or rectal, lung, or prostate cancer. Patients must be 18 years or older and must reside in the United States."

Question: "When were you first diagnosed with cancer?"
Response option: text entry – year of diagnosis

Question: "What is your current age?"
Response option: text entry – age in years

Question: "What is your gender?"
Response options:

Male
Female

Question: "What is your race?"
Response options:

• African American
• Asian/Pacific Islander
• Native American
• Other
• White/Caucasian

Question: "What is your ethnic background?"
Response options:

• Hispanic
• Non-Hispanic

Question: "What is your activity level and self-care ability?"
Response options:

- Able to carry on normal activity and work
- Have some symptoms of the cancer but able to walk about (ambulatory) and carry out activities of personal self-care and daily living, e.g., bathing, dressing, meal preparation, household chores, etc.
- Able to care for self but unable to work; occasionally may need assistance with personal needs or activities of daily living
- Disabled; need special care and assistance with personal needs and activities of daily living
- Completely disabled with no self-care ability; unable to get out of bed; may need hospitalization

Question: "What is your marital status?"
Response options:

- Married
- Living with partner
- Single
- Separated
- Divorced
- Widowed

Question: "What is your highest level of education?"
Response options:

- 8th grade or less
- Some high school
- High school diploma
- Some vocational or college credit
- 2-year diploma or degree
- 4-year college degree
- Graduate school training and/or degree

Question: "Approximately how many miles do you have to travel to receive your care at your clinic?"
Response option: text entry – travel distance to clinic in miles

Question: "What kind of transportation do you use most often to get to this clinic?"
Response options:

- Personal car
- Bus
- Taxi
- Someone else drives me
- Senior citizen transportation
- Other

Question: "What is your household income?"
Response options:

- Less than $20,000
- $20,000 to $34,999
- $35,000 to $49,999
- $50,000 to $99,999
- $100,000 or more
- Don't know
- Prefer not to answer

Question: "Do you live in the United States?"
Response options:

- Yes
- No

Question: "What is your zip code?"
Response options: text entry – 5-digit zip code

"Please continue to next page"

Section 2: Stage Data

Question: "What type of cancer have you been diagnosed with?"
Response options:

- Breast cancer
- Colorectal cancer
- Non-small cell lung cancer
- Prostate cancer
- Small cell lung cancer
- Other:
- Not diagnosed with cancer

If breast cancer:

Question: "What was the stage of your breast cancer at the time of diagnosis?"
Response options:

- **Stage 0**, noninvasive breast cancer, ductal and lobular carcinoma in-situ
- **Stage I**, tumor is less than 2 cm, no cancer in lymph nodes
- **Stage II**, meaning one of the following: cancer is no larger than 2 centimeters but has spread to the lymph nodes in the armpit (the axillary lymph nodes); cancer is between 2 and 5 centimeters (from 1 to 2 inches) and may have spread to the lymph nodes in the armpit; cancer is larger than 5 centimeters (larger than 2 inches) but has not spread to the lymph nodes in the armpit.
- **Stage III**, meaning one of the following: cancer is larger than 5 cm (larger than 2 inches) with axillary lymph node involvement; cancer is any size with significant involvement of lymph nodes, the nodes stick together or are attached to nearby structures
- **Stage IV**, cancer spread beyond the breast and axilla, to lymph nodes above the collarbone, or to distant parts of the body
- I don't know

Question: "If you do not know the stage of your breast cancer at diagnosis, please indicated the extent of your cancer by checking one of the following:"
Response options:

- Local (confined to breast only)
- Regional (in breast and lymph nodes)
- Metastatic (tumor in other parts of the body)

If non-small cell lung cancer:

Question: "What was the stage of your lung cancer at the time of diagnosis?"
Response options:

- **Stage I**, very early stage cancer, no spread to lymph nodes
- **Stage II**, cancer has spread to nearby areas or lymph nodes within the same lung
- **Stage III**, additional spread of the cancer to areas within the chest or other lymph nodes on the other side of the chest
- **Stage IV**, cancer of any size within the lung with spread to other sites of the body
- I don't know

If small cell lung cancer:

Question: "What was the stage of your lung cancer at the time of diagnosis?"
Response options:

- **Limited stage**, cancer is located only in one lung. If any lymph nodes are involved, they are on the same side of the chest
- **Extensive stage**, cancer has spread to the other lung, to lymph nodes on the other side of the chest, or to distant organs. Many people with small cell lung cancer will already have extensive disease when it is found
- **I don't know**

If prostate cancer:

Question: "What was the extent of your prostate cancer at the time of your diagnosis?"
Response options:

- **Cancer was confined to my prostate** (organ confined, no cancer outside the prostate capsule)
- **Cancer was spread outside of my prostate**, but not to other organs in my body (the cancer may have spread to the nearby seminal vesicles, or other nearby tissues within the pelvic area)
- **Cancer was spread outside of my prostate to areas far from my prostate**, such as lymph nodes or bone
- **I don't know**

If colorectal cancer:

Question: "What was the stage of your colorectal cancer at the time of diagnosis?"
Response options:

- **Stage 0**, the cancer is in its earliest stage. It has not grown beyond the inner lining of the colon or rectum. Other names for this stage are carcinoma in situ (IS), or intramucosal carcinoma
- **Stage I**, the cancer has grown into the inner layers of the lining of the colon or rectum, but has not spread outside the wall of the colon/rectum or into surrounding tissue
- **Stage II**, the cancer has grown into the outermost wall of the colon or rectum (the serosa) or beyond, but does not involve any lymph nodes
- **Stage III**, meaning one of the following: cancer has grown into the inner layers of the lining of the colon, but has not spread outside the wall of the colon or into surrounding tissue AND 1-3 lymph nodes are involved; cancer has grown into the outermost wall of the colon (the serosa), or locally beyond AND 1-3 lymph nodes are involved; any size or depth of tumor AND 4 or more lymph nodes involved
- **Stage IV**, the cancer has spread to other parts of the body, such as liver or lungs

- **I don't know**

Question: "Is this the first time you have been diagnosed with cancer, or is this a recurrence of a previously treated cancer"?
Response options:

- First diagnosis
- Recurrence

"Please continue to next page"

Section 3: Comorbid Illnesses Data

Question: "Other Health Conditions: Do you currently have, or have you ever had or been treated for, any of the following (please select a response for each condition):"

Response options:

	Yes	No	Don't know
Heart attack			
Heart failure			
Coronary bypass surgery			
Hypertension (high blood pressure)			
Stroke or transient ischemic attack (TIA)			
Poor kidney function			
History of another type of cancer			
Blood clots			
Asthma			
Emphysema, chronic bronchitis, or obstructive lung disease			
Stomach ulcers or peptic ulcer disease			
Diabetes			
Moderate to severe arthritis			
Alzheimer's disease or other dementia			
Cirrhosis or serious liver damage			
Hearing loss or impairment			
Visual loss or impairment			
Degenerative joint disease			

"Please continue to next page"

Section 4: Decision Making for All Patients

Question: "Have you made a decision regarding treatment for your cancer in the past 3 months?"

Response options:

- Yes
- No

If response is "No":

Question: "Please indicate the reason why you did not make a decision regarding treatment for your cancer in the past 3 months:

Response options:

- Recently diagnosed but still undecided about treatment
- Decided about treatment prior to 3 months ago
- Decided on no treatment
- Other reason

"You are done with this questionnaire. Thank you for participating in this important research project."

Section 5: Decision-Making for Patients Who Had Made a Treatment Decision in Prior 3 Months

If response is "Yes":

Question: "In making your decision, did you discuss with your physician participation in a clinical trial as part of your treatment?"

<The following text was provided to describe a clinical trial>

"What is a clinical trial? Clinical trials are carefully controlled scientific research studies to test new treatments for people with cancer. The goal of this medical research is to find better ways to treat cancer and improve the lives of cancer patients. Clinical trials test the safety and potential benefits of new treatments before they are approved for widespread use. They investigate many types of approaches such as new drugs, new surgical or radiological procedures, and new ways to reduce the side effects of treatment. All medications, procedures, and treatments currently used were once investigated in clinical trials."

Response options:

- **No**
- **Yes**, but not offered participation in a clinical trial
- **Yes**, and was offered participation in a clinical trial

Section 6: Attitudes toward Clinical Trials among Patients Who Did Not Discuss a Clinical Trial with Their Physician, or Who Discussed a Clinical Trial with Their Physician but Were Not Offered Participation in a Clinical Trial

If response is "No" or "Yes", but not offered participation in a clinical trial:

Question: "Would you have been interested in participating in a clinical trial if you had been offered one?"
Response options:

- Yes
- No
- Don't Know

Question: "Do you believe patients get better treatment when they are in a clinical trial?"
Response options:

- Yes
- No
- Don't Know

Question: "Do you think the treatment given in a clinical trial might be more difficult to tolerate than non-clinical trial treatment?"
Response options:

- Yes
- No
- Don't Know

Question: "Do you think that a treatment trial sounds like a gamble?"
Response options:

- Yes
- No
- Don't Know

Question: "Do you think a clinical trial might involve extra inconvenience?"
Response options:

- Yes
- No
- Don't Know

Question: "Do you worry about how your treatment would be paid for on a clinical trial?"
Response options:

- Yes
- No
- Don't Know

Question: "You may not have been offered participation in a clinical trial because you were not eligible for an available trial; that is, you did not meet the health criteria for participation in the trial. As far as you know, did any of the following reasons prevent you from being offered participation in a clinical trial? (check all that apply)"
Response options:

- I had a previous cancer.
- I have two different types of cancer.
- I am not feeling well enough to participate.
- I have another illness (noted previously under "other health conditions").
- Other reason (specify):
- None of the above

"You are done with this questionnaire. Thank you for participating in this important research project."

Section 7: Treatment Profiles and Attitudes toward Clinical Trials in Patients Who Participated in a Clinical Trial

If response is "Yes":

Question: "Did you decide to participate in a clinical trial?"
Response options:

- Yes
- No

If response is "Yes":

Question: "What type of trial are you currently participating in or will be participating in?"
Response options:

- **Phase I:** Researchers test a new drug or treatment in a small group of people for the first time to evaluate its safety, determine a safe dosage range, and identify side effects.
- **Phase II or pilot:** The drug or treatment is given to a larger group of people to see if it is effective and to further evaluate its safety.
- **Phase III:** The drug or treatment is given to large groups of people to compare it to commonly used treatments, as well as to confirm its effectiveness, monitor side effects, and collect information that will allow the drug or treatment to be used safely.
- **Don't know**

Question: "What type of treatment are you currently receiving or will be receiving as part of the clinical trial? (Check all that apply)"
Response options:

- Surgery
- Radiation therapy
- Hormonal therapy
- Chemotherapy
- Targeted therapies (ie monoclonal antibodies, enzyme inhibitors, or angiogenesis inhibitors)
- Other
- Don't know

Question: "Do you believe patients get better treatment when they are in a clinical trial?"
Response options:

- Yes
- No
- Don't know

Question: "Do you think the treatment given in a clinical trial might be more difficult to tolerate than non-clinical trial treatment?"
Response options:

- Yes
- No
- Don't know

Question: "Do you think that a treatment trial sounds like a gamble?"
Response options:

- Yes
- No
- Don't know

Question: "Do you think a clinical trial might involve extra inconvenience?"
Response options:

- Yes
- No
- Don't know

Question: "Do you worry about how your treatment will be paid for on a clinical trial?"
Response options:

- Yes
- No
- Don't know

Question: "Do you know who sponsors the trial?"
Response options:

- Government
- Industry or pharmaceutical company
- Other
- Don't know

"You are done with this questionnaire. Thank you for participating in this important research project."

"If you answered NO, please continue to next page."

Section 8: Reasons for Not Participating in a Clinical Trial among Patients Who Were Offered a Trial But Declined to Participate

"You indicated you did discuss with your physician the possibility of participating in a clinical trial as part of your treatment and were offered a trial, but you declined participation. We would like to ask you some questions about why you decided not to participate in a clinical trial. Answers to these questions will assist us in better understanding patient attitudes and concerns about clinical trials, which could help to better design research studies."

"Please indicate true or false and, if true, the extent to which the following reasons influenced your decision not to participate in a clinical trial.

At the time I decided against being in a clinical trial:

	For me…			If a reason was True for you, please rate how important that reason was in your decision not to participate in a clinical trial		
	False	True	NA	Very Important	Somewhat Important	Not Important
1 – I was concerned that the treatment offered by the clinical trial had too many side effects.						
2 – I was not sure that any of the treatments were right for my cancer.						
3 – I did not want one of the treatments that was part of the clinical trial.						
4 – The consent form did not answer my questions about treatment risks and side effects.						
5 – The doctor did not convince me that any of the study treatments would be good for me.						
6 – The nurse did not convince						

me that any of the study treatments would be good for me.						
7 – My doctor recommended against participation in a clinical trials.						
8 – I did not really trust the medical staff where I was treated						
9 – I did not trust the quality of the treatment provided where I was treated						
10 – My family was against my participating in a clinical trials.						
11 – My friends were against my participating in a clinical trial.						
12 – I did not like the idea that a research protocol would say what my treatment would be.						
13 – I thought that by being on a clinical trial I would get worse treatment and follow-up care.						
14 – I thought that my participation would not advance the science of cancer treatment.						
15 – I thought that I would not benefit personally from the study.						
16 – I thought that my participation in a clinical trial would not help my children or future generations.						
17 – I thought I would not receive enough information about my cancer and its treatment on a clinical trial.						
18 – I was concerned about						

how my treatment would be paid for if I was on a clinical trial.						
19 – Information I had received on the internet or from media reports made me concerned about getting treated on a clinical trial.						
20 – I thought that being on a clinical trial would be a burden for my family.						
21 – Getting to and from the clinical center for treatment would be a problem for me.						
22 – The tests and procedures for a clinical trial would take too much time and effort.						
23 – The study requirements might delay the start of treatment.						
24 – I did not like the idea of being randomly assigned to a treatment.						
25 – The consent form was confusing.						

"You are done with this questionnaire. Thank you for participating in this important research project."

(Note: For the analysis, items 10 and 11 were combined.)

Chapter 3

COMPARISON OF SURVIVAL OUTCOMES AMONG CANCER PATIENTS TREATED IN AND OUT OF CLINICAL TRIALS

3.1 INTRODUCTION

Randomized cancer clinical trials represent the final step in evaluating the efficacy of new treatments. However, utilization of clinical trials as a vehicle for delivering cancer treatment is low (<3%).[1,2] Reasons for low rates of clinical trial participation are numerous.[3-5] Sometimes trials may not be available for patients willing to participate; or, when they are available, patients are often excluded due to not meeting eligibility criteria.[6-9]

Eligibility criteria are designed to meet the stated objectives of the trial, and must satisfy two opposing factors.[10] They must be sufficiently narrow to establish a homogeneous sample, so that the effect of treatment is roughly consistent across the cohort. Eligibility criteria that are too broad risk including patients for which the treatment is not optimal, which could mask the overall treatment effect. Eligibility should also be sufficiently broad in order that the results are generalizable to a broader population. One possible difference between trial and non-trial patients is that trial eligibility criteria rule out poor prognosis patients with prior comorbid conditions. Yet if the trial cohort is otherwise representative of the general cancer population with respect

to cancer histology and stage, any differences in survival induced by ruling out poor prognosis patients may not endure over time.

Despite attempts by clinical trialists to establish equipoise between homogeneity and generalizability, clinical trials are sometimes criticized in particular for sacrificing generalizability.[11] To assess generalizability in a systematic fashion, we evaluated whether presenting characteristics and survival outcomes for patients on the standard arms of a large series of randomized phase III cancer clinical trials were representative of outcomes in patients receiving non-clinical trial treatment.

3.2 METHODS

Cancer clinical trial data were from SWOG, formerly the Southwest Oncology Group, a national clinical trials consortium sponsored by the National Cancer Institute. Non-trial data were from the Surveillance, Epidemiology, and End Results (SEER) registry,[12] which registers cancer patients from geographic regions representing 26% of the US population.

A survey of studies from the SWOG historical phase III database over a 25 year period (1987-2011) was conducted. The SWOG study must have been a published randomized phase III study and must have had up-front randomization in order to avoid post-registration filtering of patients prior to receipt of standard treatment, since such filtering could not be reproduced using SEER data. Data to replicate the essential primary site, histology, and stage specifications from the SWOG study must have been available in SEER. Staging criteria included both TNM staging and, where appropriate,

surgical and nodal staging. Studies which relied on tumor characteristics not available in SEER were excluded. SWOG studies of patients with recurrent disease were excluded since SEER indexes reported cases according to first diagnosis of a unique tumor type. Positive SWOG studies for which a trend towards improved survival over time was evident in corresponding cancer population patients were also excluded. Finally, corresponding SEER patients must have had a diagnosis date during the SWOG study's enrollment period. Assuming the SWOG standard arm represented standard-of-care in the general cancer population during the study enrollment period, this allowed comparison between trial and non-trial patients with approximately similar treatments. The age limits specified in SWOG study eligibility were applied to the corresponding SEER datasets.

Statistical Considerations

Comparisons between SWOG and SEER patients with respect to demographic factors and stage were conducted across the panel of SWOG studies. Demographic factors were age (<65 years vs. $\geq$65 years), sex, and race (African American vs. white vs. other). For a given study, stage was split into two categories based on the closest categorization to the median value (i.e. $\geq$median stage vs. <median stage). In some instances, further distinctions by stage were not feasible (i.e. metastatic disease only). To test whether there was a global trend in SES or demographic rates across the panel of studies, the study-specific rates for both SEER and SWOG were converted to z-scores

(one for each study), and a one-sample t-test was conducted on the difference in the z-scores between SEER and SWOG.

Kaplan-Meier plots were generated to explore patterns of survival between SEER and SWOG patients across the panel of studies.[13] Cox regression was used to estimate the hazard ratio and 95% confidence intervals for the impact of trial participation, accounting for the demographic factors, stage, and year of enrollment.[14] Studies were categorized as good vs. poor prognosis based on average 2-year Kaplan-Meier survival estimates, split at 50%.

To further explore differences in survival patterns, SWOG and, separately, SEER patients were combined across the panel of studies, by prognosis. To construct an equally-weighted sample, a random sample of 50 patients from each SWOG study and each corresponding SEER cohort was selected. This process was averaged across 1000 repeat random samples. Kaplan-Meier plots and corresponding smoothed hazard functions (using Kernel-based methods) of the aggregate datasets were examined.[15-17]

The contributions of cancer-related and non-cancer-related deaths to survival patterns were investigated using the same aggregate datasets. SEER codes cause-of-death (COD) according to the International Classification of Diseases (ICD-10). In SWOG, a death was deemed cancer-related if it followed a documented cancer progression. SWOG rates were adjusted using COD data available for a subset of patients. (See the Appendix for further details).

Finally, we assessed the extent to which study factors determined variation in survival outcomes. We estimated components of variation of the factors by comparing

the log-likelihoods from nested models. We took the average of both forward and backward nesting approaches, with factors rank-ordered for model inclusion according to their chi-square statistic in a multivariable model.

All analyses were limited to survival in the first five years after diagnosis in order to emphasize outcome related to cancer and its treatments. Two-sided p-values are reported.

3.3 RESULTS

Study Selection

We examined 102 SWOG studies. Of these, 64 were initially excluded (Figure 3.1). Of the remaining 38 studies, 17 were excluded due to inadequate SEER data on essential tumor characteristics.

Study Profiles and Eligibility

Twenty-one studies (21/38=55%) met the specified study inclusion criteria (Table 3.1).[18-38] The study sample included both early and late stage cancers from a range of cancer types. A total of 5,190 SWOG patients and 69,187 SEER patients were analyzed. Among SWOG patients, 36% were from academic centers, 33% were from local affiliates to academic centers, and 31% were from community-based sites. Enrollment spanned 21 years, from 1987-2007.

Table 3.2 summarizes additional eligibility criteria from the SWOG study that do not specifically pertain to histology or tumor characteristics. The minimum age was 18 for several but not all studies. Nearly all SWOG studies excluded patients with prior malignancies; for comparability, only SEER patients with first primaries were included.

None of the remaining criteria in Table 3.2 could be accounted for using SEER data. Nearly all studies had prior systemic therapy exclusions, and nearly all studies required adequate kidney, liver, and hematologic function. The majority of studies required no current evidence or history of cardiac dysfunction. The maximum performance status – a measure of a patient's activity level – was 1 in 8 studies, 2 in 8 studies, 3 in 4 studies, and unspecified in one study. Other common exclusion criteria included other serious medical conditions, diseases, or active infections.

The mean total number of eligibility criteria for a given study was 16.1. The majority of eligibility criteria were related to comorbidity or performance status, with a mean of 9.8 per study (60% of total).

Demographic Factors and Stage

Figure 3.2 shows horizontal barplots of the difference between SEER and SWOG patients for each demographic and stage factor. The SEER cohort was consistently more likely to be older and, to a lesser degree, female, but there were no panel-wide trends in the proportion of patients with higher stage or African-American race.

Overall Survival Comparisons between SWOG and SEER

The forest plot in Figure 3.3 shows both univariate (unadjusted) and multivariable (adjusted) hazard ratios comparing overall survival between SWOG and SEER cohorts, in descending order of average 2-year survival. Eleven studies had average 2-year survival of $\geq$50% ("good prognosis") and 10 studies had 2-year survival of <50% ("poor prognosis"). For none of the good prognosis studies did survival for SWOG patients differ significantly from survival for SEER patients in multivariable analysis, whereas for 9 of 10 poor prognosis studies, SWOG patients had statistically significantly greater risk of death ($p<.0001$). Results by prognosis based on univariate analyses were similar though not as extreme ($p=.002$).

Differences in Aggregate Survival Patterns between SWOG and SEER Patients

Examination of the individual study-specific survival curves (Figure 3.4) indicated a frequent pattern of an early survival advantage for SWOG patients that waned over time for both early and late stage cancers. To further examine this, Kaplan-Meier plots of overall survival, and the corresponding smoothed hazard functions, were plotted using an aggregate dataset as described in the Methods (Figure 3.5). For both good and poor prognosis patients, the hazard function for SWOG patients started low, then increased, reaching a maximum around Year 1 and nearly merging with the hazard function for SEER patients. Thus the influence of trial participation on survival patterns endured only for one year.

Average Effect Accounting for the First Year Survival Difference

For good prognosis patients, the mean of the multivariable hazard ratios for overall survival comparing SWOG to SEER patients shown in Figure 3.3 was not statistically different from 1.0 (mean=0.96, 95% CI: 0.92-1.01, p=.12). We analyzed the subset of patients who survived one year using conditional survival analysis. The results were similar (mean=1.05, 95% CI: 0.96-1.14, p=.22). On the other hand, for poor prognosis patients, the mean of the multivariable hazard ratios shown in Figure 3.3 was much less than 1.0 (mean=0.74, 95% CI: 0.64-0.84, p=.0003). Conditioning on one year survival, this difference was no longer evident (mean=1.05, 95% CI: 0.95-1.15, p=.27), reinforcing the observation that the impact of trial participation endured for only about one year.

Analysis of Cancer-Specific and Non-Cancer-Specific Events

The proportion of patients experiencing cancer-related and non-cancer-related deaths – relative to the number of patients at risk – was analyzed by year. Non-cancer-related deaths were lower in SWOG patients, although this difference was small and relatively stable across all five years of follow-up (Figure 3.6). In contrast, cancer-related deaths were notably lower in the first year in SWOG patients, but similar to SEER patients in later years. Therefore the difference in the patterns of death for trial vs. non-trial patients between Year 1 vs. Years 2-5 is largely attributable to different patterns of cancer-related deaths.

Attributable Variation

In the non-sex-specific studies, disease and stage explained 92.2% of the variation in survival outcomes, followed by age (5.2%), trial participation (1.5%), race (0.6%), and sex (0.5%). In the first year only, estimates of variation in survival outcomes attributable to disease and stage was 88.4% and to trial participation was 4.9%, compared to 92.7% and 1.2%, respectively, after one year.

3.4 Discussion

Short term estimates (e.g. <1 year) of absolute survival probabilities from clinical trials are more likely than not to be optimistic, especially for poor prognosis diseases. Patients and physicians who use clinical trial results to assist in making treatment decisions should be aware of this phenomenon. Better short-term survival for trial patients is likely related to the exclusion of sicker patients from trials through eligibility criteria pertaining to comorbidity and performance status. These exclusions also resulted in trial cohorts that were notably younger, as previously observed.[39] In contrast, long-term survival patterns (e.g. >1 year) for trial patients appeared similar to those for patients in the general cancer population.

We did not explicitly assess whether the treatment effect in a clinical trial translates (i.e. generalizes) to the broader cancer population. Such a study would be difficult, since it would require a comparison between experimental and standard arm treatments occurring in the general cancer population at the same time as the clinical trial is conducted. However, similar standard arm outcomes beyond the first year

improve confidence that efficacy of treatment in a trial translates to the real world setting, in particular for good prognosis malignancies, for which the differences in standard arm survival in the first year comprise a smaller portion of overall followup. In the classic definition of confounding, if trial participation is only weakly or transiently related to survival outcomes from treatment, the confounding influence of trial participation on the association between treatment and outcome will be limited.

Given the difficulty in assessing the generalizability of the treatment effect, studies in the literature also focus on presenting characteristics and absolute survival differences between trial and non-trial patients. The most reliable way to establish the causal relationship between trial participation and outcome would be to randomize patients to be offered a clinical trial vs. not offered a clinical trial.[40] Such a study would be practically and ethically difficult. Instead, the literature is based on observational studies. In these, identification of the appropriate non-trial control group is crucial to inference, since any observational design will be limited by unmeasured confounding, whether trial patients are compared to eligible non-trial controls (bias with respect to factors associated with refusing trial participation), ineligible controls (bias with respect to prognosis), or population controls (multiple biases).[40] These studies most often focused on single trial vs. non-trial comparisons, raising the issue of subjective study selection.

Both Peppercorn et al. and, separately, Edwards et al. have reviewed the historical literature.[40-41] Both found that a majority of comparisons from cancer studies showed evidence of better outcomes for trial patients, with no evidence of harm. Peppercorn concluded there was no strong evidence of a benefit for trial patients, in part

due to methodological issues with the non-trial comparator groups, while Edwards concluded there was positive, albeit weak, evidence that participation in trials improves outcomes. The conclusions from other reviews, and recent individual studies, range from strong evidence, to no evidence, that trial participation is related to improved outcome.[42-45]

The inconclusive picture offered by the literature could be related to the transient impact of trial participation on survival found in this study. We re-examined the cancer studies included in two prior reviews.[40-41] Studies were categorized as good or poor prognosis as defined in this study. In total, there were 36 comparisons from 27 studies (see Table 3.3).[46-72] Fifty-six percent of good prognosis studies showed univariate or multivariable evidence of survival benefit for trial patients, compared to 82% of poor prognosis studies, a pattern consistent with, but not as extreme as, the pattern found in this study. A similar pattern was found among comparisons that included multivariable analyses only[46,48,50-57,59-61,66-69] and adult cancers only.[46-56,59,60,63-65,71,72] This assessment is limited by the inclusion of analyses with different methodologies compared to the approach used in this study, including different factors in the multivariable models and a heterogeneous set of comparator groups.

The differences in overall survival between trial and non-trial patients in this study may be due in part to a "trial effect" – that is, an implicit benefit of trial participation.[73] Since this study included only standard arm treatments, we can rule out a benefit due to superior experimental therapies. Trial patients could also benefit from changes in behavior or outlook associated with being under observation,[73] although that is less likely to impact survival. Trial patients could benefit from care that is

administered according to strict protocol.[74] Alternatively, trial patients may exhibit better outcomes because eligibility criteria (see Table 3.2) prevent sicker patients from enrolling on study. These enrollment restrictions appear to primarily limit early cancer deaths. Unfortunately, most of the eligibility factors in Table 3.2, the majority of which relate to comorbidity or performance status, could not be replicated using SEER data. Therefore, the extent to which the survival differences are related to a trial effect and/or patient selection cannot be estimated with these data.

We were unable to account for obesity and socioeconomic status, both of which have been associated with higher cancer-specific mortality,[75-78] since these variables cannot be derived from SEER data. In addition, the actual treatments of the non-trial control patients were unknown. It is inevitable that not all non-trial patients in SEER received standard-of-care for their histology and stage, and may have received no treatment. Further, a different composition of physicians involved in trial participation might impact outcomes; however, about 2/3 of SWOG patients in this analysis were from community or affiliate institutions, indicating a broad spectrum of physicians. The use of different databases with different methods of data collection may induce different patterns of endpoint assessment. This is likely less of an issue for overall survival than for cancer-specific events. Finally, these results may not apply to other clinical settings (i.e., screening).

This study also has particular strengths compared to prior studies. The approach of systematically examining an entire cooperative group Phase III clinical trial database limited potential subjective selection of studies. It also provided a large panel of studies for comparison. Because these studies were from the same cooperative group, other

potential sources of variation (e.g., data collection methods, payment methods, study designs) were implicitly controlled for. These advantages allowed us to aggregate data across studies and thus distinguish the different behaviors of the survival functions between trial and non-trial patients.

These results may serve as a stimulus to design randomized trials with less strict eligibility criteria. In the panel of studies we analyzed, eligibility pertaining to comorbid conditions comprised approximately 60% of all criteria. Despite this, histology and stage were primarily determinative of survival outcomes, even in the first year when the influence of trial participation was strongest. Eligibility criteria in clinical trials are clearly required to maintain patient safety, however consideration should be given to relaxing or eliminating criteria where possible. One concern is that broader eligibility will introduce heterogeneity into the clinical trial cohort, which could reduce statistical power. However, since histology and stage are the dominant predictors of outcome, sufficient homogeneity will be retained even if less impactful criteria are softened. Expanding eligibility would have the further advantage of increasing access to clinical trials for a broader cross-section of patients. Ultimately, identification of only a transient survival benefit associated with trial participation improves confidence in the generalizability of clinical trial treatment results.

3.5 REFERENCES

1. Tejada HA, Green SB, Trimble EL, et al. Representation of African-Americans, Hispanics, and whites in National Cancer Institute cancer treatment trials. J Natl Cancer Inst. 1996;88(12):812-816.

2. Murthy VH, Krumholz HM, Gross CP. Participation in cancer clinical trials: race-, sex-, and age-based disparities. JAMA. 2004;291(22):2720-2726.

3. Ford JG, Howerton HW, Lai GY, et al. Barriers to recruiting underrepresented populations to cancer clinical trials: a systematic review. Cancer. 2008;112(2):228-242.

4. Ross S, Grant A, Counsell C, Gillespie W, Russell I, Prescott R. Barriers to participation in randomised controlled trials: a systematic review. J Clin Epidemiol. 1999;52(12):1143-1156.

5. Unger JM, Green S, Albain KS. Under-representation of elderly patients in cancer clinical trials: causes and remedial strategies. In: L Balducci, GH Lyman, WB Ershler, M extermann, eds. Comprehensive Geriatric Oncology. 2nd ed. Taylor and Francis;2004:464-491.

6. Begg CB, Zelen M, Carbone PP, et al. Cooperative groups and community hospitals. Measurement of impact in the community hospitals. Cancer. 1983;52(9):1760-1767.

7. Hunter CP, Frelick RW, Feldman AR, et al. Selection factors in clinical trials: results from the Community Clinical Oncology Program Physician's Patient Log. Cancer Treat Rep. 1987;71:559-565.

8. Javid SH, Unger JM, Gralow JR, et al. A prospective analysis of the influence of older age on physician and patient decision-making when considering enrollment in breast cancer clinical trials (SWOG S0316). Oncologist. 2012;17(9):1180-1190.

9. Klabunde CN, Springer BC, Butler B, White MS, Atkins J. Factors influencing enrollment in clinical trials for cancer treatment. South Med J. 1999;92:1189-1193.

10. Green S, Benedetti J, Crowley J. Clinical Trials in Oncology. 2nd ed. CRC Press; 2003.

11. Newhouse JP, McClellan M. Econometrics in outcomes research: The use of instrumental variables. Annu Rev Public Health. 1998;19:17-34.

12. Ries LAG, Melbert D, Krapcho M, Stinchcomb DG, Howlader N, Horner MJ, Mariotto A, Miller BA, Feuer EJ, Altekruse SF, Lewis DR, Clegg L, Eisner MP, Reichman M, Edwards BK (eds). "SEER Cancer Statistics Review, 1975-2005." 2008. National Cancer Institute, Bethesda, MD. <http://seer.cancer.gov/csr/1975_2005/, based on November 2007 SEER data submission, posted to the SEER web site, 2008>.

13. Kaplan E, Meier P. Nonparametric estimation from incomplete observations. J Am Stat Assoc. 1958;53:457-481.

14. Cox D. Regression models and life tables. J R Stat Assoc. 1972;34:187-220.

15. Gefeller O, Dette H. Nearest neighbor kernel estimation of the hazard function from censored data. J Statist Comput Simul. 1992;43:93-101.

16. Hess KR, Serachitopol DM, Brown BW. Hazard function estimators: a simulation study. Stat Med. 1999;18(22):3075-3088.

17. Mueller HG, Wang JL. Hazard rates estimation under random censoring with varying kernels and bandwidths. Biometrics. 1994;50:61-76.

18. Anderson JE, Kopecky KJ, Willman CL, et al. Outcome after induction chemotherapy for older patients with acute myeloid leukemia is not improved with mitoxantrone and etoposide compared to cytarabine and daunorubicin: a Southwest Oncology Group study. Blood. 2002;100(12):3869-3876.

19. Blumenthal DT, Wade M, Rankin C, et al. MGMT methylation in newly-diagnosed glioblastoma multiforme (GBM): from the S0001 phase III study of radiation therapy (RT) and O-benzylguanine (O BG) plus BCNU versus RT and BCNU alone for newly diagnosed GBM. Proc of the Amer Soc Clin Oncol, J Clin Oncol. 2006;24(18S):#1512.

20. Eisenberger MA, Blumenstein BA, Crawford ED, et al. Bilateral orchiectomy with or without flutamide for metastatic prostate cancer. N Eng J Cancer. 1998;339:1036-1042.

21. Ellis GK; Barlow WE; Gralow JR, et al. Phase III comparison of standard doxorubicin and cyclophosphamide versus weekly doxorubicin and daily oral cyclophosphamide plus granulocyte colony-stimulating factor as neoadjuvant therapy for inflammatory and locally advanced breast cancer: SWOG 0012. J Clin Oncol. 2011;29(8):1014-1021.

22. Flanigan RC, Salmon SE, Blumenstein BA, et al. Nephrectomy followed by interferon alfa 2-b compared with interferon alfa-2b alone for metastatic renal-cell cancer. N Eng J Med. 2001;345(23):1655-1659.

23. Gandara DR, Crowley J, Livingston RB, et al. Evaluation of cisplatin intensity in metastatic non-small cell lung cancer: A phase III study of the Southwest Oncology Group. J Clin Oncol. 1993;11(5):873-878.

24. Godwin JE, Kopecky KJ, Head DR, et al. A double-blind placebo-controlled trial of granulocyte colony-stimulating factor in elderly patients with previously untreated acute myeloid leukemia: A Southwest Oncology Group study (9031). Blood. 1998;91(10):3607-3615.

25. Grossman HB, Natale RB, Tangen CM, et al. Neoadjuvant chemotherapy plus cystectomy compared with cystectomy alone for locally advanced bladder cancer. N Eng J Med. 2003;349(9):859-866.

26. Kelly K, Crowley J, Bunn PA, et al. Randomized phase III trial of paclitaxel plus carboplatin versus vinorelbine plus cisplatin in the treatment of patients with advanced non-small cell lung cancer: a Southwest Oncology Group trial. J Clin Oncol. 2001;19(13):3210-3218.

27. Lamm DL, Blumenstein BA, Crawford ED, et al. Randomized intergroup comparison of bacillus calmette-guerin immunotherapy and mitomycin C chemotherapy prophylaxis in superficial transitional cell carcinoma of the bladder. A Southwest Oncology Group study. Urol Oncol. 1995;1:119-126.

28. Lara PN Jr, Natale R, Crowley J, et al. Phase III trial of irinotecan/cisplatin compared with etoposide/cisplatin in extensive-stage small-cell lung cancer: clinical and pharmacogenomic results from SWOG S0124. J Clin Oncol. 2009;27(15):2530-5.

29. Linden HM, Haskell CM, Green S, et al. Sequenced compared with simultaneous anthracycline and cyclophosphamide in high-risk stage I and II breast cancer: final analysis from INT-0137 (S9313). J Clin Oncol. 2007;25(6):656-661.

30. Macdonald JS, Smalley SR, Benedetti J, Hundahl SA, Estes NC, Stemmermann GN, Haller DG, Ajani JA, Gunderson LL, Jessup JM, Martenson JA. Chemoradiotherapy after surgery compared with surgery alone for adenocarcinoma of the stomach or gastroesophageal junction. N Eng J Med. 2001;345(10):725-730.

31. Meyskens Jr FL, Kopecky KJ, Taylor CW, et al. Randomized trial of adjuvant human interferon gamma versus observation in high-risk cutaneous melanoma: A Southwest Oncology Group study. J Natl Cancer Inst. 1995;87(22):1710-1713.

32. Peters III WA, Liu PY, Barrett RJ, et al. Concurrent chemotherapy and pelvic radiation therapy compared with pelvic radiation thereapy alone as adjuvant therapy after radical surgery in high-risk early stage cancer of the cervix. J Clin Oncol. 2000;18(8):1606-1613.

33. Philip PA, Benedetti J, Corless CL, et al. Phase III study comparing gemcitabine plus cetuximab versus gemcitabine in patients with advanced pancreatic adenocarcinoma: Southwest Oncology Group-directed intergroup trial S0205. J Clin Oncol. 2010;28(22):3605-10.

34. Pisters KM, Vallières E, Crowley JJ, et al. Surgery with or without preoperative paclitaxel and carboplatin in early-stage non-small-cell lung cancer: Southwest Oncology Group Trial S9900, an intergroup, randomized, phase III trial. J Clin Oncol. 2010 Apr 10;28(11):1843-9.

35. Salmon SE, Crowley JJ, Grogan TM, Finley P, Pugh RP, Barlogie B. Combination chemotherapy, glucocorticoids, and interferon alfa in the treatment of multiple myeloma: A Southwest Oncology Group study. J Clin Oncol. 1994;12(11):2405-2414.

36. Sondak VK, Liu PY, Tuthill RJ, et al. Adjuvant immunotherapy of resected, intermediate-thickness, node-negative melanoma with an allogeneic tumor vaccine: Overall results of a randomized trial of the Southwest Oncology Group. J Clin Oncol. 2002;20(8):2058-2066.

37. Williamson SK, Crowley JJ, Lara Jr PN, et al. Phase III trial of paclitaxel plus carboplatin with or without tirapazamine in advanced non-small-cell lung cancer: Southwest Oncology Group trial S0003. J Clin Oncol. 2005;23(36):9097-9104.

38. Wozniak AJ, Crowley JJ, Balcerzak SP, et al. Randomized trial comparing cisplatin with cisplatin plus vinorelbine in the treatment of advanced non-small-cell lung cancer: A Southwest Oncology Group study. J Clin Oncol. 1998;16(7):2459-2465.

39. Hutchins LF, Unger JM, Crowley JJ, Coltman Jr CA, Albain KS. Underrepresentation of patients 65 of age or older in cancer-treatment trials. N Eng J Med. 1999;341(27):2061-2067.

40. Peppercorn JM, Weeks JC, Cook EF, Joffe S. Comparison of outcomes in cancer patients treated within and outside clinical trials: conceptual framework and structured review. Lancet. 2004;363(9405):263-270.

41. Edwards SJ, Lilford RJ, Braunholtz DA, Jackson JC, Hewison J, Thornton J. Ethical issues in the design and conduct of randomised controlled trials. Health Technol Assess. 1998;2(15):1-132.

42. Elting LS, Cooksley C, Bekele BN, et al. Generalizability of cancer clinical trial results: prognostic differences between participants and nonparticipants. Cancer. 2006;106(11):2452-2458.

43. Stiller CA. Centralised treatment, entry to trials and survival. Br J Cancer. 1994;70(2):352-362.

44. Tanai C, Nakajima TE, Nagashima K, et al. Characteristics and outcomes of patients with advanced gastric cancer who declined to participate in a randomized clinical chemotherapy trial. J Oncol Pract. 2011;7(3):148-153.

45. Vist GE, Hagen KB, Devereaux PJ, Bryant D, Kristoffersen DT, Oxman AD. Systematic review to determine whether participation in a trial influences outcome. BMJ. 2005;330(7501):1175-1181.

46. Antman K. A comparison of randomized vs concurrent controls." Proceedings of the American Association of Cancer Research. 1983;24:146.

47. Bertelsen K. Protocol allocation and exclusion in two Danish randomized trials in ovarian cancer. British J Cancer. 1991;64:1172-1176.

48. Boros L, Chuang C, Butler FO, Bennett JM. Leukemia in Rochester (NY). A 17-year experience with an analysis of the role of cooperative group (ECOG) participation. Cancer. 1985;56(9):2161-2169.

49. Burgers JA, Arance A, Ashcroft L, Hodgetts J, Lomax L, Thatcher N. Identical chemotherapy schedules given on and off trial protocol in small cell lung cancer: response and survival results. Br J Cancer. 2002;87(5):562-566.

50. Cottin V, Arpin D, Lasset C, et al. Small-cell lung cancer: patients included in clinical trials are not representative of the patient population as a whole. Ann Oncol. 1999;10(7):809-815.

51. Dahlberg M, Glimelius B, Pahlman L. Improved survival and reduction in local failure rates after preoperative radiotherapy: evidence for the generalizability of the results of Swedish Rectal Cancer Trial. Ann Surg. 1999;229(4):493-497.

52. Davis S, Wright PW, Schulman SF, et al. Participants in prospective, randomized clinical trails for resected non-small cell lung cancer have improved survival compared with nonparticipants in such trials. Cancer. 1985;56(7):1710-1718.

53. Dowling AJ, Czaykowski PM, Krahn MD, Moore MJ, Tannock IF. Prostate specific antigen response to mitoxantrone and prednisone in patients with refractory prostate cancer: prognostic factors and generalizability of a multicenter trial to clinical practice. J Urol. 2000;163(5):1481-1485.

54. Feuer EJ, Frey CM, Brawley OW, Nayfield SG, Cunningham JB, Geller NL, Bosl GJ, Kramer BS. After a treatment breakthrough: a comparison of trial and population-based data for advacned testicular cancer. J Clin Oncol. 1994;12(2):368-377.

55. Greil R, Holzner B, Kemmler G, et al. Retrospective assessment of quality of life and treatment outcome in patients with Hodgkin's disease from 1969 to 1994. Eur J Cancer. 1999;35(5):698-706.

56. Karjalainen S, Palva I. Do treatment protocols improve end results? A study of survival of patients with multiple myeloma in Finland. BMJ. 1989;299(6707):1069-1072.

57. Lennox EL, Stiller CA, Jones PH, Wilson LM. Nephroblastoma: treatment during 1970-73 and the effect on survival of inclusion in the first MRC trial. Br Med J. 1979;2(6190):567-569.

58. Link MP, Goorin Am, Miser AW, et al. The effect of adjuvant chemotherapy on relapse-free survival in patients with osteosarcoma of the extremity. N Engl J Med. 1986;314(25):1600-1606.

59. Marubini E, Mariani L, Salvadori B, et al. Results of a breast-cancer-surgery trial compared with observational data from routine practice. Lancet. 1996;347(9007):1000-1003.

60. Mayers C, Panzarella T, Tannock IF. Analysis of the prognostic effects of inclusion in a clinical trial and of myelosuppression on survival after adjuvant chemotherapy for breast carcinoma. Cancer. 2001;91(12):2246-2257.

61. Meadows AT, Kramer S, Hopsono R, Lustbader E, Jarrett P, Evans AE. Survival in childhood acute lymphocytic leukemia: effect of protocol and place of treatment. Cancer Invest. 1983;1(1):49-55.

62. MRC Working Group on Leukaemia. Duration of survival of children with acute leukemia. Report to the Medical Research Council from the Committee on Leukaemia and the Working Party on Leukaemia in Childhood. BMJ. 1971;4(5778):7-9.

63. Roy P, Vaughan Hudson G, Vaughan Hudson B, Esteve J, Swerdlow AJ. Long-term survival in Hodgkin's disease patients. A comparison of relative survival in patients in trials and those recorded in population-based cancer registries. Eur J Cancer. 2000;36(3):384-389.

64. Schea RA, Perkins P, Allen PK, Komaki R, Cox JD. Limited-stage small-cell lung cancer: patient survival after combined chemotherapy and radiation therapy with and without treatment protocols. Radiology. 1995;197(3):859-862.

65. Schmoor C, Olschewski M, Schumacher M. Randomized and non-randomized patients in clinical trials: experiences with comprehensive cohort studies. Stat Med. 1996;15(3): 263-271.

66. Stiller CA, Benjamin S, Cartwright RA, et al. Patterns of care and survival for adolescents and young adults with acute leukaemia—a population-based study. Br J Cancer. 1999;79(3-4):658–665.

67. Stiller CA, Draper GJ. Treatment centre size, entry to trials, and survival in acute lymphoblastic leukaemia. Arch Dis Child. 1989;64(5):657-661.

68. Stiller CA, Eatock EM. Survival from acute non-lymphocytic leukaemia, 1971-88: a population based study. Arch Dis Child. 1994;70(3):219-223.

69. Stiller CA, Eatock EM. Patterns of care and survival for children with acute lymphoblastic leukaemia diagnosed between 1980 and 1994. Arch Dis Child. 1999;81(3):202-208.

70. Wagner HP, Dingeldein-Bettler I, Berchthold W, et al. Childhood NHL in Switzerland: incidence and survival of 120 study and 42 non-study patients. Med Pediatr Oncol. 1995;24(5):281-286.

71. Ward LC, Fielding JW, Dunn JA, Kelly KA. The selection of cases for randomised trials: a registry survey of concurrent trial and non-trial patients. The British Stomach Cancer Group. Br J Cancer. 1992;66(5):943-950.

72. Winger MJ, Macdonald DR, Schold Jr SC, Cairncross JG. Selection bias in clinical trials of anaplastic glioma. Ann Neurol. 1989;26(4):531-534.

73. Braunholtz DA, Edwards SJ, Lilford RJ. Are randomized clinical trials good for us (in the short term)? Evidence for a "trial effect". J Clin Epidemiol. 2001;54(3):217-224.

74. Grimshaw JM, Russell IT. Effect of clinical guidelines on medical practice: a systematic review of rigorous evaluations. Lancet. 1993;342(8883):1317-1322.

75. Calle EE, Rodriguez C, Walker-Thurmond K, Thun MJ. Overweight, obesity, and mortality from cancer in a prospectively studied cohort of U.S. adults. N Engl J Med. 2003;348(17):1625-1638.

76. Harper S, Lynch J, Meersman SC, Breen N, Davis WW, Reichman MC. Trends in area-socioeconomic and race-ethnic disparities in breast cancer incidence, stage at diagnosis, screening, mortality, and survival among women ages 50 years and over (1987-2005). Cancer Epidemiol Biomarkers Prev. 2009;18(1):121-131.

77. Singh GK, Miller BA, Hankey BF, Edwards BK. Persistent area socioeconomic disparities in U.S. incidence of cervical cancer, mortality, stage, and survival; 1975-2000. Cancer. 2004;101(5):1051-1057.

78. Ward E, Jemal A, Cokkinides V, et al. Cancer disparities by race/ethnicity and socioeconomic status. CA Cancer J Clin. 2004;54(2):78-93.

Table 3.1: SWOG Studies Included for Comparison to SEER

SWOG Criteria					Corresponding SEER Criteria		
Cancer: Study No.	Years of Accrual	Histology	Major Tumor Characteristic Criteria from SWOG Studies[1]	SWOG N	SEER N	ICD-O-3 Primary Site	Histology Code
Brain S0001	01-05	Glioblastoma multiforme/ gliosarcoma	▪ Biopsy or surgical resection prior to registration	89	2264	C710-725	9440-9444
Breast S9313	94-97	Adenocarcinoma[2]	▪ Stage T1-3, N0, M0 (selected stages I-III; no locally advanced disease) ▪ Axillary dissection required ▪ ≥6 nodes removed and examined ▪ ≤3 positive nodes ▪ Tumor >2cm and ER/PR (-) or (+); or, 1-3 (+) axillary nodes ▪ Prior mastectomy or breast sparing surgery	1423	9941	C500-509	8500-8530
Breast S0012	01-05	Locally advanced or inflammatory breast carcinoma	▪ Stage IIB-IIIB (M0)	391	2855	C500-506, C508-509	Any
GI-Gastric S9008	91-98	Adenocarcinoma[3]	▪ Stage IB-IV (M0) ▪ Prior en bloc surgery	283	2487	C150-155, 58-66, 68-69	8140-8800
GI-Pancreas S0205	04-06	Adenocarcinoma[4]	▪ Locally advanced (not surgically resectable, i.e. no prior surgery) or metastatic	82	1943	C250-254, C257-259	8140

			disease				
GU-Bladder S8710	88-97	Transitional cell carcinoma	▪ Stage T2-T4A (no metastasis)	148	2377	C670-679	8120-8124
GU-Bladder S8795	88-92	Transitional cell carcinoma (including papillary)	▪ Stage Ta-T1 and Grade I-IV ▪ Completely resected	191	5059	C670-679	8120-8124, 8130
GU-Prostate S8894	89-94	Adenocarcinoma	▪ Stage D2	534	5961	C619	8140
GU-Renal S8949	91-98	Carcinoma	▪ Metastatic ▪ No nephrectomy (standard arm)	95	1569	C649	8312
GYN-Cervix S8797	90-96	Squamous cell carcinoma, adenocarcinoma, or adenosquamous carcinoma	▪ Stages IA2, IB, or IIA ▪ Radical hysterectomy with total pelvic lymphadenectomy ▪ Positive pelvic or parametrial, and negative para-aortic, nodal involvement	130	137	C530-531, C538-539	8070-8, 8140-7, 8260-3, 8310-84, 8560-62
LEUK-AML S9031	91-94	AML	▪ FAB classes M0-M2, M4-M7 (excluded M3s beginning in August, 1992)	85	1672	C420-1, C424	9801, 9840, 9861, 9866-7, 9871-74, 9891, 9896, 9910
LEUK-AML S9333	95-98	AML	▪ FAB classes M0-M2, M4-M7 (excluded M3s)	129	2320	C420-1, C424	9801, 9840, 9861, 9867, 9871-74, 9891, 9896, 9910
Lung-NSCLC S8738	88-90	Squamous cell carcinoma, adenocarcinom	▪ M1 disease (including lung metastasis). Exclude patients with mets only to ipsilateral	94	4084	C340-3, C348-9	8012, 8070-78, 8140-47

		a, and large cell carcinoma	hilar nodes (N1) and/or mediastinal nodes (N2) or supraclavicular nodes (N3) ONLY				
Lung-NSCLC S9308	93-95	Any NSCLC	▪ Stage IIIB (based on positive pleural effusions or ipsilateral lung involvement) or Stage IV	178	4755	C340-3, C348-9	8012, 8046, 8070-8, 8140-7, 8240-50, 8560, 9050-3
Lung-NSCLC S9509	96-97	Any NSCLC (except bronchioalveolar)	▪ Stage IIIB with either 1) T4 disease due to malignant pleural effusion; 2) multiple lesions in a single lobe containing a T3 or T4 primary; or 3) lesions in multiple lobes of the ipsilateral lung for which one such lesion is T3 or T4;[5] or Stage IV	205	4817	C340-3, C348-9	8012, 8046, 8070-8, 8140-7, 8240-9, 8560, 9050-3
Lung-NSCLC S9900	99-04	Any NSCLC	▪ Selected Stages IB (T2N0), II (T1-2, N1; or T3N0), or IIIA (T3N1) ▪ Limited to surgery type specified in protocol: lobectomy, sleeve resection, bilobectomy, or pneumonectomy (excludes limited resection or NOS)	168	829	C340-3, C348-9	8012, 8046, 8070-8, 8140-7, 8240-50, 8560, 9050-3
Lung-NSCLC S0003[6]	00-02	Squamous, adeno-, large cell, or NSC-NOS carcinoma	▪ Use newly diagnosed, selected Stage IIIB (based on positive pleural effusions) or Stage IV	165	7727	C340-3, C348-9	8012, 8046, 8070-8, 8140-7

Lung-SCLC S0124	02-07	Any SCLC	▪ Extensive disease	266	2790	C340-3, C348-9	8041-5
Melanoma S8642	87-90	Any melanoma	▪ Stage II (thickness ≥1.5, N0, M0) or III (any T, N1-2, M0) ▪ Complete wide-excision of tumor (≥1 cm margin)[7]	96	738	C440-9	8720-72
Melanoma S9035	92-96	Any melanoma	▪ Stage T3N0M0 (thickness 1.51-4.00 mm or Clark IV if thickness unknown) ▪ Complete wide-excision of tumor (≥1 cm margin)[7]	299	1347	C440-9	8720-72
Myeloma S8624	87-90	Multiple myeloma	▪ Previously untreated	139	3515	C421	9732
TOTAL 21 Studies	**22 yrs (87-07)**			**5190**	**60187**		

N=Sample size; ER=estrogen receptor; PR=progesterone receptor; GI=gastrointestinal; GU=genitourinary; GYN=gynecologic; LEUK=leukemia; AML=acute myeloid leukemia; FAB=French-American-British; NSCLC=non-small cell lung cancer; SCLC=small cell lung cancer

1 – All criteria listed in the table were explicitly accounted for in SEER. Additional tumor characteristic criteria that could not be accounted for explicitly in SEER include: Brain, S0001) Patients with ≥3 non-contiguous sites are ineligible; GI-Gastric, S9008) No ascites; no peritoneal seeding; no liver metastases or extra-abdominal metastases; GU-Bladder, S8710) ≥1 kidney and proximal ureter free of tumor and all other disease resectable; GU-Bladder, S8795) No recurrent tumor on cystoscopy within 4 weeks if first TURBT >4 weeks prior to registration; and, random biopsy or a negative urinary cytology; GU-Renal, S8949) Primary cancer must be amenable to surgery if patient did not otherwise have metastatic disease; Leukemia-AML, S9031 and S9333) Exclude blastic transformation of chronic myelogenous leukemia; Lung-NSCLC, S9509) Exclude Stage IIIB tumors involving the superior sulcus; Lung-NSCLC, S9900) No patients with symptomatic tumors (T3,N0-N1) involving the superior sulcus; Melanoma, S9035) Lympadenctomy must have resolved; patients with suspicious nodes must have regional lymph node dissection with negative nodes; Myeloma, S8642) Specific protein criteria; and, patients with IgM myeloma not eligible.

2 – Excluding tubular, mucinous, papillary, sarcoma, lymphoma, apocrine, adenocystic, or squamous cell carcinoma; ductal or lobular carcinoma in situ allowed if 1-3 positive nodes. Patients with tumor >1cm and ER/PR(-) excluded from both SWOG and SEER datasets due to lack of ER/PR data in SEER during the study period.
3 – Stomach and esophagogastric junction
4 – Exclude endocrine tumors, lymphoma of pancreas, or ampullary cancer
5 – For IIIB definition in SEER, simplified as IIIB with T3 or T4 extent-of-disease.
6 – Although S0003 allowed recurrent patients, these were excluded. Comparison to SEER relied on newly diagnosed patients only.
7 – Detailed surgical resection criteria were specified.

Table 2.2: Eligibility Criteria for SWOG Clinical Trials

Cancer Type and Study Number	Min (Max) Age	No Prior Cancer[1]	Prior Treatment Exclusions	Organ Function Criteria[2]	Max PS[3]	Other PS	Pregnant/ Contra-ception	Serious Medical Condition[4]	HIV	Prior TX Timing	Other on-study therapy	No Brain Mets	Study Drug Allergy	Scan Timing	Other [5]
Brain, S0001	18	X	Ch, RT	K, P	2		X	X	X		X		X	X	0
Breast, S9313	NS		Ch, R, S	K, L, H, C		LTFU	X	X		X				X	1
Breast, S0012	NS	X	Ch, Hr, RT, S	K, L, H, C	2		X		X		X			X	0
GI-Gastric, S9008	NS	X	Ch, B, RT	K, L, H	2		X	X		X				X	1
GI-Pancreas, S0205	NS	X	Ch	K, L, H, C	2		X		X	X	X	X		X	0
GU-Bladder, S8710	NS	X	RT[6]	K, L, H, C	1	Cure	X	X		X				X	1
GU-Bladder, S8795	NS	X	Ch	K, L, H	2	LE	X			X	X			X	1
GU-Prostate, S8894	NS	X	Ch, Hr, B	K, L, H	3			X			X			X	0
GU-Renal, S8949	NS	X	Ch, Hr, B, RT[7]	K, L, H, C	2		X				X	X		X	0
GYN-Cervix, S8797	NS	X	Ch, Hr, B, RT[6]	K, L, H	2			X		X				X	1
LEUK-AML, S9031	56	X	Ch	K, L, C	3		X							X	0
LEUK-AML, S9333	56	X	Ch	K, L, C	3		X							X	1
Lung-NSCLC,	NS	X	Ch	K, H, C	2	LE	X				X	X		X	0

S8738															
Lung-NSCLC, S9308	18	X	Ch, B	K, L, H	1		X	X		X		X		X	1
Lung-NSCLC, S9509	18	X	Ch, B	K, L, H, C	1		X	X				X	X	X	1
Lung-NSCLC, S9900	18	X	Ch, RT	K, L, H, P	1		X	X			X		X	X	1
Lung-NSCLC, S0003	NS	X	Ch, B	K, L, H	1		X			X		X	X	X	0
Lung-SCLC, S0124	18	X	Ch, RT[8]	K, L, H	1		X		X	X				X	1
Melanoma, S8642	18 (70)	X	Ch, Hr, B, RT	K, L, H, C	1		X	X			X			X	2
Melanoma, S9035	18	X	Ch, Hr, B, RT	K, L, H, C	1		X			X	X			X	0
Myeloma, S8624	NS	X	Ch	H[9], C	3			X						X	1

PS=Performance Status; Ch=Chemotherapy; Hr=Hormonal Therapy; B=Biologic therapy; RT=Radiation Therapy; S=Surgery; K=kidney; L=Liver; P=Pulmonary; H=Hematologic; C=Cardiac; NS=Not Specified; LTFU=Adequate health for Long Term Follow Up; CURE=potentially curable; LE=minimum life expectancy

Only the first two criteria listed (age and prior cancer) were explicitly accounted for in SEER. All other criteria could not be accounted for based on SEER data. Eligibility criteria that related to comorbidity or performance status included prior treatment exclusions, prior malignancy exclusion, performance status, organ function status, HIV status, serious medical conditions, brain metastases, study drug allergy, and maximum age limit.

1 – Typically requires no prior malignancy except adequately treated non-melanoma skin cancer, in situ cervical cancer, or other cancer for which the patient has been disease free for 5 or more years.

2 – Organ function criteria were based primarily on the following tests: for kidney, creatinine clearance and/or serum creatinine; for liver bilirubin, SGOT and/or SGPT; and for hematologic, white blood count and platelets.
3 – Performance status is a measure of the patient's well-being and activity level. In SWOG, the coding scheme is: 0 = asymptomatic or fully active; 1 = Symptomatic but completely ambulatory; 2 = Symptomatic but in bed <50% of day; 3 = Symptomatic, >50% in bed, but not bedbound; 4 = Completely disabled or bedbound.
4 – Including active infections
5 – Other eligibility criteria include: Breast, S9313) Patients with breast-sparing surgery must plan RT after chemotherapy; GI-Gastric, S9008) Good caloric intake of $\geq$1500/day required; GU-Bladder, S8710) Normal organ function required; GU-Bladder, S8795) Must be at increased risk of papillary tumor recurrence; GYN-Cervix, S8797) No pelvic inflammatory disease; Leukemia-AML, S9333) Exclude if marrow unaspirable and WBC and blasts + promyelocytes + promonocytes outside normal limits; Lung-NSCLC, S9308) No $\geq$Grade 2 neuropathy; Lung-NSCLC, S9509) No $\geq$Grade 2 neuropathy; S9900) No $\geq$Grade 2 neuropathy; Lung-SCLC, S0124) Prior brain metastases must have been treated; Melanoma, S8642) No known seizure disorder or known CNS disease; no prior organ transplant; Myeloma, S8624) Patients must have objective evidence, or be symptomatic from, AML.
6 – Pelvic
7 – Except palliative
8 – Except brain
9 – Based on M-component

Table 3.3: Main Results and Prognosis for Individual Studies Included in Reviews by Edwards et al. and Peppercorn et al.

				Evidence	
Article[1]	Cancer Type	Results[2]	Prognosis Group[3]	Any (U or M)	M[4,5]
Antman (E) JCO, 1985[6]	Sarcoma	No U result; no SS difference in M DFS (p=.15); OS not reported	Good	No	No
Bertelsen (E) Br J Cancer, 1991	Ovarian	Difference in OS in U setting (p<.001) but not M setting w/same tx (p=.98)	Good	Yes	No
Boros (P) Cancer, 1985	AML	Difference in OS in U setting (p<.001) and in M setting (p=.02)	Poor	Yes	Yes
Burgers (P) Br J Cancer, 2002	SCLC	No SS difference in OS in U (no p-value given); M not done	Poor	No	-
Cottin (P) Ann Oncol, 1999	SCLC	SS difference in the U (p=.01) but not M setting (unknown p-value); adjusted for PS	Poor	Yes	No
Dahlberg (P) Ann Surg, 1999	Rectal	No differences between trial and non-trial pts of similar tx (surgery)	Good	No	No
Davis (B) Cancer, 1985	NSCLC	SS difference in both U (p<.001) and M setting (p<.002)	Good	Yes	Yes
Dowling (P) J Urol, 2000	Prostate	SS difference in U (p=.003) but not M setting after adjusting for PS (p=.42)	Poor	Yes	No
Feuer (P) JCO, 1994	i) Testicular	Minimal disease: SS diff in both U and M	Good	Yes	Yes
	ii) Testicular	Advanced disease: No diff in U or M	Good	No	No
Greil (P) Euro J Cancer, 1999	Hodgkin's	No difference in OS in either U (p=.67) or M (p=.65) settings	Good	No	No
Karjalainen (B) Br Med J, 1989	i) Myeloma	1979-85: SS difference in favor of trial pts	Good	Yes	Yes
	ii) Myeloma	1959-78: NS trend in favor of non-trial pts	Good	No	No
Lennox (B) Br Med J, 1979	Wilms[7]	SS difference in OS in both U (p<.01) and M settings (p<.001)	Good	Yes	Yes
Link (P)	Osteo-	No difference in OS in U (no p-	Good	No	-

NEJM, 1986	sarcoma[7]	value)			
Marubini (P) Lancet, 1996	Breast	SS in U setting (no p-value given) but not M setting (p=.50)	Good	Yes	No
Mayers (P) Cancer, 2001	Breast	SS in U setting (p=.02) but not M setting (p=.09)	Good	Yes	No
Meadows (P) Cancer Invest, 1983	ALL[7]	SS differences in U (p<.001) and M (no p-value) settings	Good	Yes	Yes
MRC (E) Br Med J, 1971	Leukemia[7]	Difference in OS (p-value not given)	Poor	Yes	-
Roy (P) Euro J Cancer, 2000	Hodgkin's	No p-values given. OS appears worse for non-trial pts in older (≥45) but not younger pts	Good	Yes	-
Schea (P) Radiology, 1995	SCLC	SS difference in U (p=.002)	Poor	Yes	-
Schmoor (B) Stat Med, 1996	Breast	Trial 2) No difference in DFS in U	Good	No	-
		Trial 3) NS DFS trend in favor of trial pts in U	Good	No	-
Stiller (B) Arch Dis Child, 1989	ALL[7]	SS diff for both U (no p-value given) and M (p<.0001)	Good	Yes	Yes
Stiller (B) Arch Dis Child, 1994	AML[7]	1975-83: U not done; SS diff in M (p<.001)	Poor	Yes	Yes
		1984-88: U not done; No diff in M	Good	No	No
Stiller (P) Arch Dis Child, 1999	ALL[7]	1980-84: U not done; No in M (p=.62)	Good	Yes	No
		1985-89: U not done; Yes in M (p=.02)	Good	Yes	Yes
		1990-94: U not done; Yes in M (p<.0001)	Good	Yes	Yes
Stiller (P) Br J Cancer, 1999	ALL[7]	No diff in U (p=.63)	Good	No	-
	AML[7]	SS diff in U (p=.04); in M, No in 84-88, Yes in 89-94	Poor	Yes	Yes
Wagner (P) Med Ped Oncol, 1995	NHL[7]	SPOG v non-study: No SS in U (p=.07)	Good	No	-
		POG v non-study: SS diff in U (p<.0001)	Good	Yes	-
Ward (B) Br J Cancer, 1992	Stomach	5/10 analyses were SS (p≤.05; Table III)	Poor	Yes	-

Winger (P) Ann Neurol, 1989	Glioma	SS in U (p=.00001) vs all non-study pts	Poor	Yes	-
	Glioma	NS for U (p=.12) vs. all non-study pts	Poor	No	-

SS = Statistically significant; U=Univariate; M=Multivariable; OS=Overall Survival; NR=Not reported; ACM=All cause mortality; AS=Actuarial survival; NHL=Non-Hodgkin's Lymphoma; AML=Acute Myeloid Leukemia; SCLC=Small Cell Lung Cancer; NSCLC=Non Small Cell Lung Cancer; tx=treatment; pts=patients

1- "E" indicates article was included in Edwards et al., "P" indicates article was included in Peppercorn et al., and "B" indicates article was included in both reviews.

2 - Results based on overall survival for all studies except Antman et al. and Schmoor et al.

3 – Prognosis groups: Good prognosis is defined as ≥50% average estimated 2 year survival; Poor prognosis is defined as <50% average estimated 2 year survival.

4 – Consistent with our own analysis, studies were categorized according to whether there was a statistically significant (p<.05) difference between trial and non-trial patients.

5 – Among studies where multivariable analyses were conducted.

6 – Based on full published article for the conference abstract cited by both authors.

7 – Childhood cancer

Figure 3.1. Study identification flow diagram. One hundred two phase III SWOG studies were examined over the 25 year period 1987-2011. Among these, 64 were excluded from further consideration, 33 due to early closure (of which 30 were closed early due to poor accrual, two were closed early due to changed relationship with the drug manufacturer, and one was a positive study based on PFS), 12 were still active or recently closed, seven did not have up-front randomization, six had non-survival endpoints, and six were studies for recurrent disease. Of the 38 considered for comparison to SEER data, 17 were excluded because SEER did not have essential staging criteria to replicate the SWOG study. In the end, 21/38 studies (55% of those considered for stage comparison) were identified.

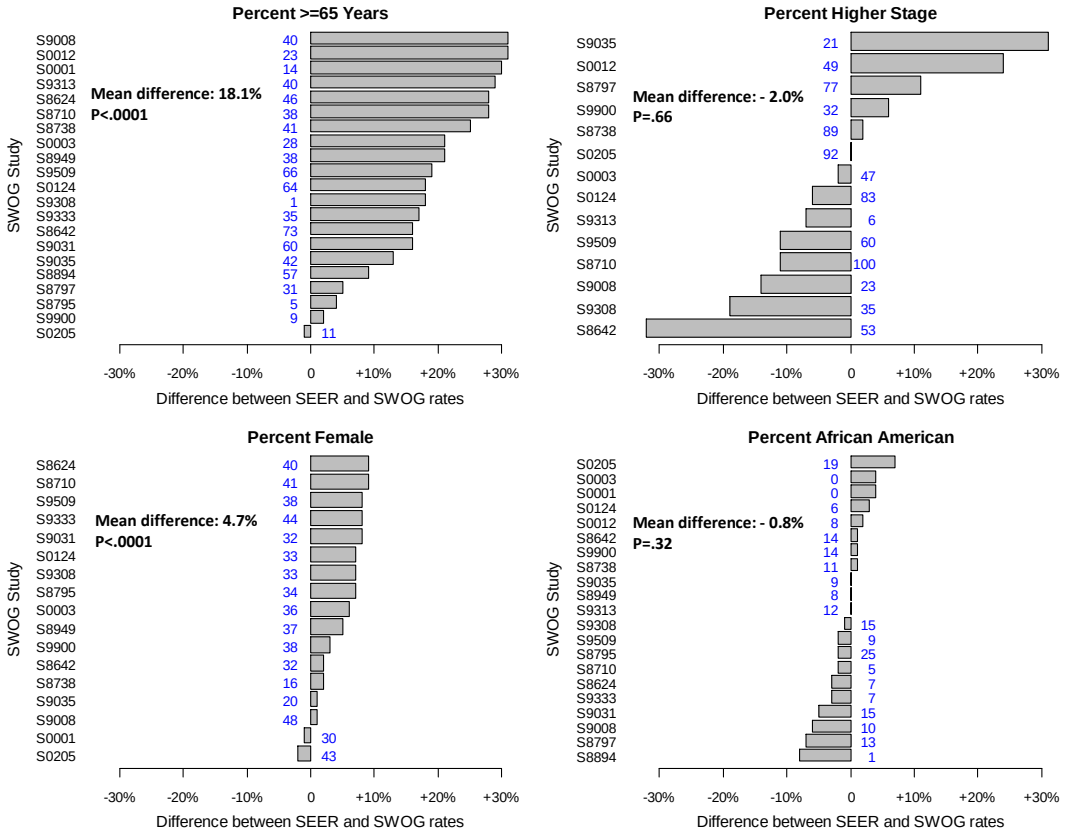


Figure 3.2. Differences in stage and demographic rates, SEER vs. SWOG. Horizontal barplots of the difference between SEER and SWOG patients for each demographic and stage factor, in descending order of the absolute difference in percentages between SWOG and SEER cohorts. The SWOG percentage is also shown in each figure. Bars to the right of center indicate a higher proportion in SEER, and to the left of center a higher proportion in SWOG.

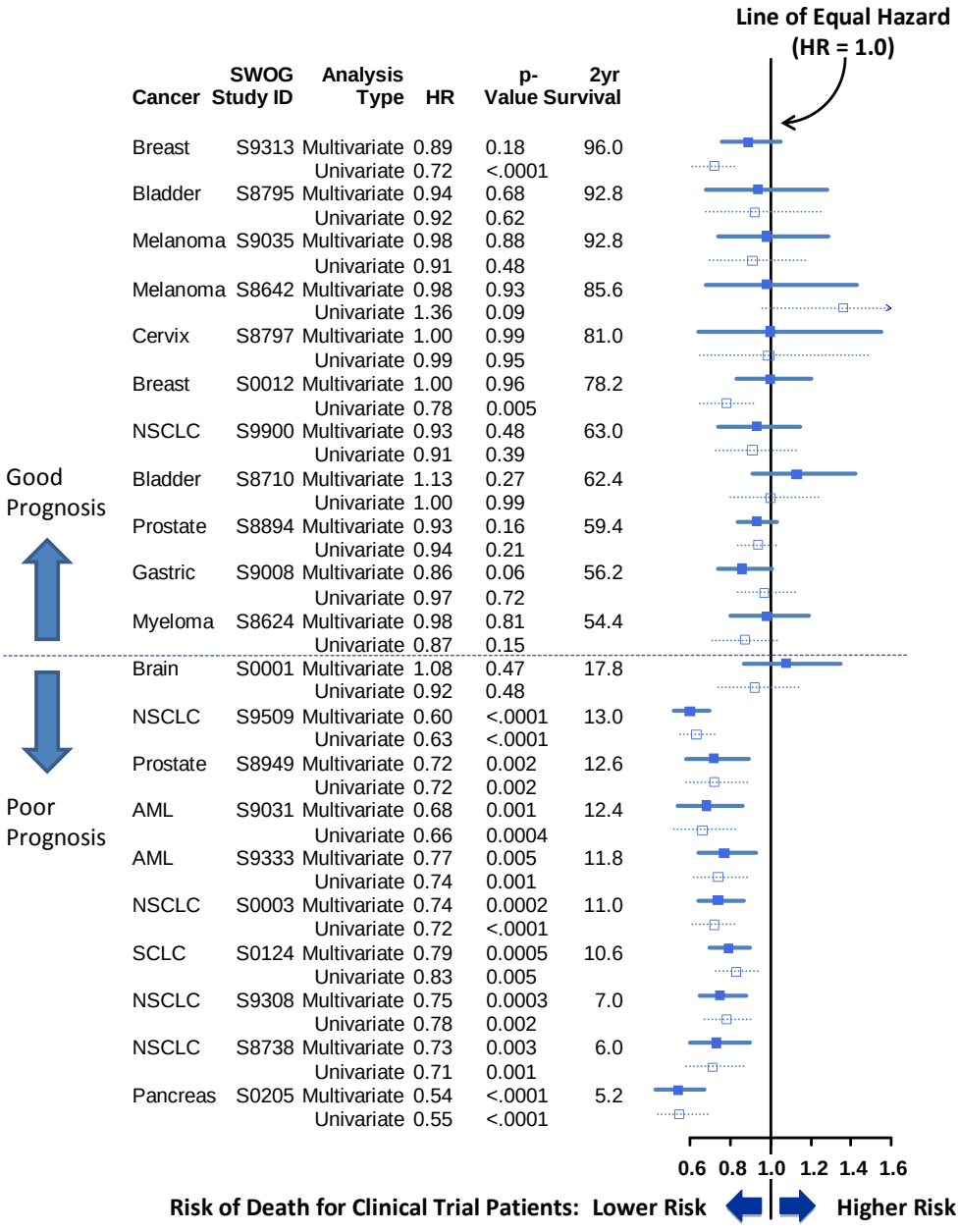


Figure 3.3. Forest plot of univariate and multivariate hazard ratios for overall survival, by study, in descending order of average 2-year overall survival. In univariate analyses, 2/11 (18%) of good prognosis studies and 9/10 (90%) poor prognosis studies show evidence of a survival benefit for trial patients (p=.002 by Fisher's exact test). In multivariable analyses, 0/11 of good prognosis studies and 9/10 poor prognosis studies show evidence of a survival benefit for trial patients (p<.0001).

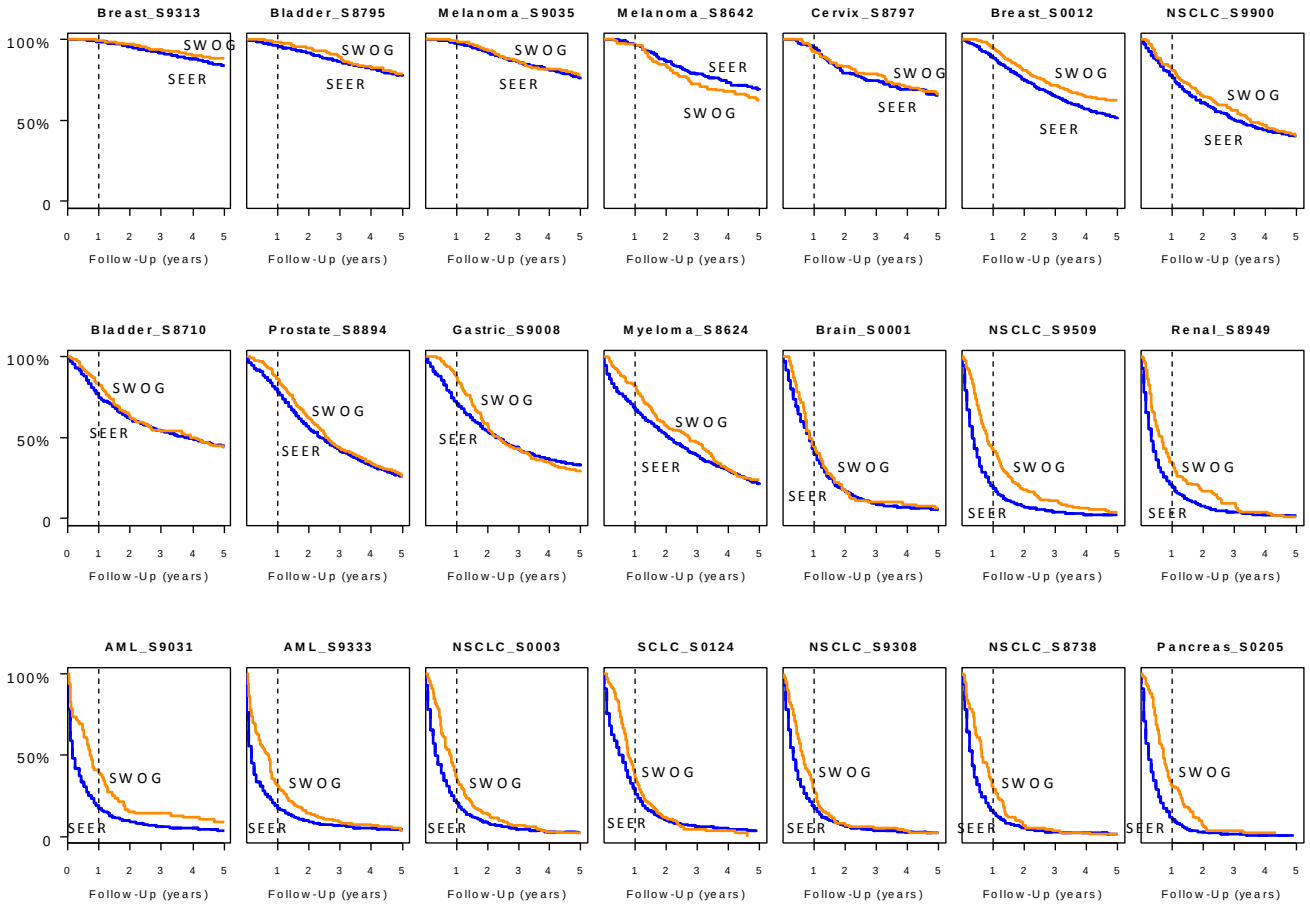


Figure 3.4: Study-specific survival plots. Ordered in descending order of average 2 years survival. The dashed line indicates the 1-year followup timepoint.

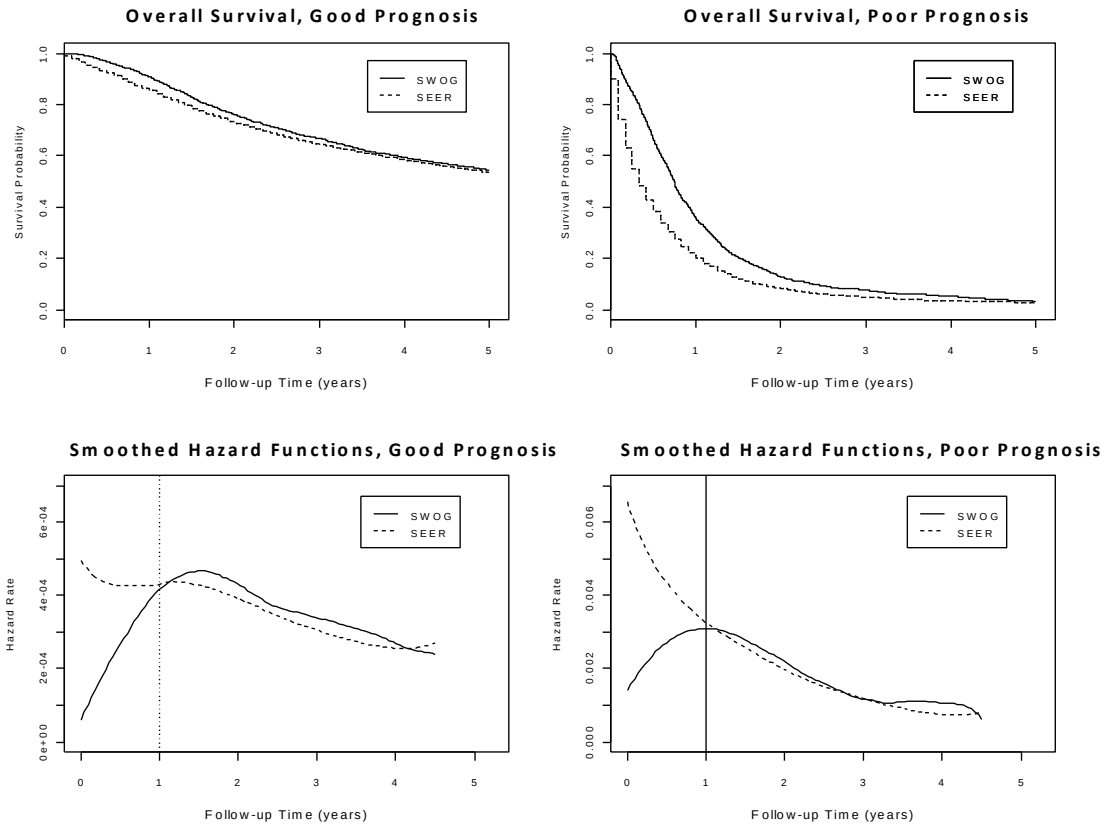


Figure 3.5. Overall survival and hazard functions for aggregate study data, by prognosis.

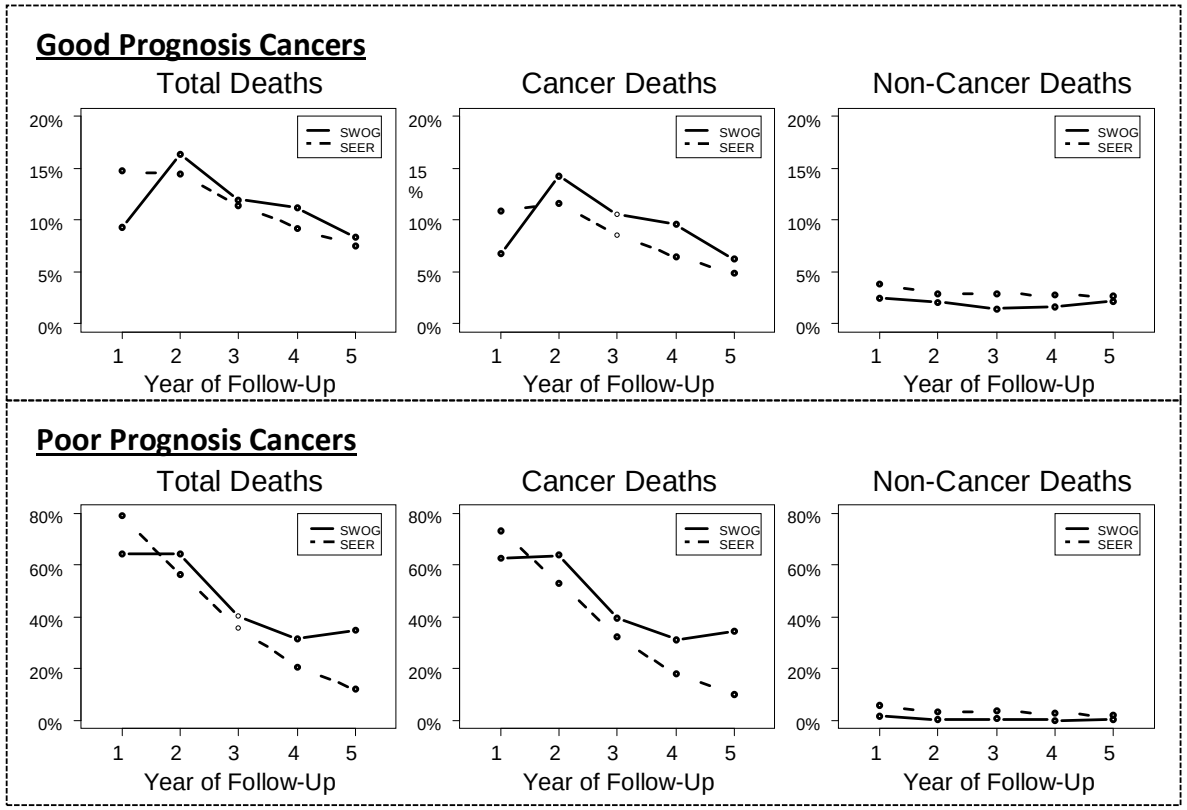


Figure 3.6: Total, cancer-specific, and non-cancer-specific deaths by year of follow-up.

3.5 Appendix: Analysis of Cancer-Related and Non-Cancer-Related Events

The contributions of cancer-related and non-cancer-related deaths to survival patterns were investigated using the aggregate (equally weighted) datasets. SEER codes cause-of-death (COD) according to the International Classification of Diseases (ICD-10). In SWOG, a death was deemed cancer-related if it followed a documented cancer progression. SWOG also collected cause-of-death data beginning in 2001, and thus COD were also available for a fraction (11.2%) of SWOG cases.

The proportion of patients experiencing cancer-related and non-cancer-related deaths – relative to the number of patients at risk – was analyzed by year using documented progression only. These proportions were then adjusted. In SWOG patients with COD data, we calculated the percentage of those without documented progression that were actually specified to have had a cancer-related death according to the COD data. The initial estimates based on documented progression alone were then adjusted (inflated) based on these estimates. This analysis was conducted separately by prognosis (good vs. poor).

Figure 5 shows the pattern of events for both good and poor prognosis studies over time. For each of the first five years, the proportion of patients experiencing death of any kind, cancer-specific death, and non-cancer death – relative to the number of patients at risk in each year – is plotted for both SWOG and SEER patients. Consistent with the Kaplan-Meier survival plots in Figure 4, the total event rate is notably lower in SWOG patients in the first year. In Years 2-5, in contrast, the proportions of total events

in SWOG and SEER patients are more similar and are decreasing as the risk of death decreases. For both good and poor prognosis patients, the pattern of a relatively lower event rate for SWOG patients in Year 1 is mostly reflective of a diminished rate of cancer-related deaths in Year 1; although non-cancer-related deaths are also lower in SWOG patients, this difference was small and relatively stable across all five years of follow-up. Indeed in good prognosis patients, the unweighted ratio of the rate of SEER cancer deaths to SWOG cancer deaths is 1.60 in Year 1, but is less than one – only 0.78 – in Years 2-5. For non-cancer deaths, the ratios are very similar whether in Year 1 (1.57) or Years 2-5 (1.52), indicating the pattern change over time occurs in cancer-related deaths only. A similar pattern held for poor prognosis cancers. In summary, the difference in the patterns of death for trial vs. non-trial patients between Year 1 vs. Years 2-5 is largely attributable to different patterns of cancer deaths.

Chapter 4

THE DIFFUSION OF DOCETAXEL USE IN PATIENTS PRESENTING WITH METASTATIC PROSTATE CANCER

4.1 INTRODUCTION

The diffusion of new health care innovations can be inefficient, despite often ample evidence supporting the use of new treatments or procedures. For this reason, study of diffusion has been a major focus of agencies within the NIH.[1] In cancer, the past several decades have witnessed the introduction of multiple new therapies. Unfortunately treatments with proven benefit sometimes permeate slowly through the treatment community,[2] while in other cases, uptake of new drugs occurs prior to definitive evidence.[3] Appropriate and rapid adoption of proven new cancer treatments could impact population survival.[4,5]

Diffusion is the transmission of a new innovation over time within a social system and is driven by three factors: perceptions of the innovation, characteristics of adopters, and contextual factors (i.e., social ties).[6,7] Perceptions of an innovation pertain to (often qualitative) assessments of the risks and benefits of the new innovation. Presentation of efficacy findings for a new drug at a scientific conference or in a journal influence the perception of a new treatment.[8] Drugs with clearly positive benefit/risk ratios may be taken up immediately into clinical practice. One question is whether adoption follows definitive evidence of a new treatment in a phase III study. Finally, adopter characteristics can apply to patients as well as physicians. For instance, older patient age

is associated with the diffusion of doxorubicin-based chemotherapy in patients with lymphoma, and with chemotherapy for advanced ovarian cancer.[2,9]

Current primary treatment for patients with metastatic prostate cancer is androgen deprivation therapy (ADT), achieved most frequently in the form of luteinizing hormone-releasing (LHRH) antagonists,[10] with response durations of 18-24 months.[11,12] Standard secondary therapy for patients with hormone refractory metastatic prostate cancer was mitoxantrone combined with prednisone following positive clinical trials in the 1990s.[13,14] Mitoxantrone provided palliative relief but no survival benefit. More recently, docetaxel (Taxotere®) was shown to provide both pain relief and improved survival, though with higher levels of treatment toxicity. In 2004, docetaxel became the new standard of care.[15,16] In this analysis, we investigated the association of drug efficacy information and patient socioeconomic status (SES) and demographic factors with diffusion patterns of docetaxel in metastatic prostate cancer.

4.2 METHODS

The linked SEER-Medicare database was the data source.[17] The primary analysis included men $\geq$65 years diagnosed with metastatic prostate cancer from 1995-2007 (inclusive). Medicare claims through 2008 were analyzed. To avoid attributing receipt of chemotherapy to another cancer, men must have had no other prior or subsequent cancers. To ensure that patients had a minimum amount of Medicare claims coverage, we required patients to have had continuous Medicare Parts A and B, with no HMO participation, for $\geq$1 years after diagnosis.

Receipt of chemotherapy was identified at any time after diagnosis using Medicare claims according to ICD-9 Healthcare Common Procedure Coding System (HCPCS) J-codes from hospital outpatient and physician reimbursement records. Hospital inpatient records were also used to identify diagnostic and surgical procedures for establishing comorbidity status.[18,19] Docetaxel use was defined based on HCPCS J-code J9170 (first implemented on January 1, 1998) and mitoxantrone use was based on HCPCS J-code J9293 (first implemented on January 1, 1990).[20] Other potential chemotherapy types are shown in Table 4.1. Although docetaxel did not receive a J-code until 1998, we included metastatic prostate cancer patients diagnosed from 1995 onward to allow 3 years of follow-up time from diagnosis for those who received chemotherapy early in the period. Unspecified J-codes (J8999, J9999) were not used because they may identify unanticipated procedures.[21]

Dependent Variable

A challenge for this analysis is that prostate cancer patients who have failed ADT therapy (hormone failures) are the candidate population for chemotherapy. However, hormone failures are not explicitly identifiable using SEER data. Rather, SEER patients are indexed according to the stage of their presenting diagnosis (local, regional, or distant metastatic). Thus the denominator of patients with hormone refractory prostate cancer cannot be explicitly identified.

Therefore, we assessed the receipt of chemotherapy using two different approaches. First, we analyzed the 5-year cumulative incidence of first docetaxel use from diagnosis of metastatic prostate cancer. Following a closed cohort over time using cumulative incidence accounts for competing events (i.e. death) and is therefore useful

for assessing patterns according to SES and demographic factors.[22] However, the estimates represent docetaxel use among patients diagnosed with metastatic prostate cancer, not hormone refractory disease.

Secondly, we analyzed the subset of patients who received chemotherapy from 1998-2008. This subset represents hormone failures, because chemotherapy is typically not used in prostate cancer prior to hormone failure, and because we limited the population to only those patients with prostate cancer, so receipt of chemotherapy would not be for a different type of cancer. Within each yearly interval, among those who received their first chemotherapy, we calculated the proportion that received docetaxel. This approach mimics a series of cross-sectional yearly cohorts[23] and has the advantage of assessing docetaxel usage rates over calendar time. First receipt of chemotherapy was used because it is consistent with the cumulative incidence analysis and in the real-world represents the chemotherapy of first choice.

The Model

In diffusion analyses, cumulative adoption over time typically adheres to an S-shaped or sigmoid curve, representing a pattern of bounded geometric growth in which adoption occurs infrequently at first, accelerates as more individuals adopt, then slows as adoption reaches a natural ceiling.[7,24-26] To model yearly docetaxel use rates, we used the classic "mixed influence" deterministic diffusion model, which describes the instantaneous change in the shape of the diffusion curve by the differential equation:

$$\frac{dF(t)}{d(t)} = \left(k_1 + k_2 * F(t)\right) * (\bar{F} - F(t))$$

where *F(t)* is the cumulative number of adopters at time *t*, F-bar is the total potential number of adopters, and k_1 and k_2 are coefficients representing a mix of influences both *external* to the social system (k_1) and *internal* to the social system (k_2).[24,27] Conceptually, the behavior of this function indicates the influence of social dynamics on diffusion, since, if the magnitude of k_2 is non-trivial, then the instantaneous rate of change of diffusion with respect to time is proportional, in part, to the interaction between prior adopters (k_2*F(t)) and potential adopters (F-bar - *F(t)*).[28] Thus the magnitude of k_2 relative to k_1 suggests the extent to which an underlying social process influences diffusion.

Independent Variables

SES, Demographic, Comorbidity, and Geographic Variables

We analyzed the 5-year cumulative incidence of docetaxel by demographic variables including age, split at 75 years, and race (black vs. other). Cumulative incidence by ethnicity was not analyzed due to the small subset of Hispanic patients. SES factors were income and education, based on whether the patient's Year 2000 census tract median income and percentage with some college education were higher or lower than the study sample median. Poverty status was based on individual-level data reflecting prior Medicaid participation (yes vs. no).[29] Differences by baseline comorbidity index within 1 year prior to diagnosis were analyzed using the Charlson index, modified as per Klabunde.[18,19,30] Binary indicator variables were used for consistency across variables and to aid interpretation, with the exception of geographic region, which was analyzed

according to SEER registry area (East vs. Midwest vs. West). Differences between cumulative incidence curves were tested using Gray's test.[31]

Landmark Events

We estimated the proportion of total diffusion occurring prior to October, 1999, the period prior to the first phase I and II conference and journal article reports regarding docetaxel efficacy;[32-36] from October, 1999 to May, 2004, the period between the first phase I and II conference and journal article reports and phase III conference reports and FDA approval (which occurred nearly simultaneously);[37-39] and after May, 2004.

Docetaxel Use over Time in Prostate Cancer Compared to Other Cancers

To evaluate whether docetaxel diffusion patterns for prostate cancer were unique, we compared them to those in advanced breast, gastric, ovarian, and non-small cell lung cancer (NSCLC). For these other cancers, docetaxel is often indicated after failure of initial chemotherapy. Therefore, rather than using first chemotherapy, within each year a patient received chemotherapy, we coded patients as "1" if docetaxel was received, "0" if other chemotherapy was received, and "0.5" if both were received. We compared patterns across all cancers to FDA approval times.

4.3 RESULTS

Cohort Characteristics

We identified 6,561 patients with metastatic prostate cancer meeting the inclusion criteria (Table 4.2). The majority of patients (58%) were 75 or older, 14% were black and 7% were Hispanic. Poverty status was reported in 21% of patients. Median Census tract income, $42,654, higher than the median U.S. Year 2000 income for this age cohort.[40] Thirty percent of patients had evidence of prior comorbidity.

We identified 1,350 patients who subsequently received chemotherapy. Compared to the 5211 patients without subsequent chemotherapy, chemotherapy patients were younger, less likely to be black, had higher income, and had less comorbidity.

Cumulative Incidence by Year of Diagnosis

Five year cumulative incidence of docetaxel use after diagnosis of metastatic prostate cancer increased from 2% for patients diagnosed in 1996-1997 to 33% for patients diagnosed in 2004-2005 (Figure 4.1). The use of mitoxantrone decreased in conjunction with the increased use of docetaxel, although 5-year cumulative incidence of mitoxantrone use even early in the period never exceeded 7%.

Cumulative Incidence by Factors

Figure 4.2 shows 5-year cumulative incidence of docetaxel use combined over all years of diagnosis (1995-2007) by SES, demographic, comorbidity, and geographic factors. The cumulative incidence was slower for older patients, black patients, lower income patients, patients who experienced poverty, and patients from Western and Midwestern SEER regions. There were no observed differences in diffusion rates by education level or comorbidity level.

Association of Landmark Events with Docetaxel Use over Time

As shown in Figure 4.3, among metastatic prostate cancer patients who received chemotherapy, the maximum observed proportion whose first chemotherapy was docetaxel was 95% in 2008, the last year of the period. Docetaxel uptake in this patient population began well before the results for the phase III trials were reported. Thirteen percent of total (i.e. maximum) diffusion occurred between initial phase I and II conference reports and journal reports, 67% between phase I and II journal reports and initial phase III conference reports and FDA approval, and 20% after the phase III reports/FDA approval.

Model Fit for Four Year Cumulative Incidence

Figure 4.4 shows the observed yearly docetaxel usage rates along with the model fitted curve, indicating an S-shaped trajectory. The model explained 99.2% of total variation. Importantly, the regression coefficient for the internal influence factor (k_2 as described in the methods) was about 7.2x greater than the coefficient for the external influence factor (k_1), suggesting that social dynamics within the prostate cancer treatment community contributed to diffusion.

Use of Docetaxel for Multiple Cancers in Relation to FDA Drug Approval

Figure 4.5, top panel, compares yearly rates of docetaxel use in metastatic prostate cancer to those in metastatic breast, NSCLC, gastric, and ovarian cancer. Uptake of docetaxel began, and achieved maximums, at similar times for all cancers, regardless of whether FDA approval was received early in the period (breast and NSCLC), late in the

period (prostate and gastric), or never (ovarian cancer). Maximum diffusion was notably higher among prostate cancer patients, likely due to fewer effective chemotherapy options.

The bottom panel of Figure 4.5 shows the observed diffusion rates for prostate cancer compared to all other cancers combined, with model fitted curves superimposed. For each curve, the inflection point – representing the time of maximum increase in the use of docetaxel – was identified. The inflection points for prostate cancer and for all other cancers combined both occurred in February, 2000. Therefore docetaxel diffusion patterns with respect to time were very similar.

4.4 DISCUSSION

We found that by 2008, nearly all metastatic prostate cancer patients who underwent chemotherapy received docetaxel as their first treatment. Docetaxel uptake was slower for socioeconomically and demographically disadvantaged patients. The absence of differences in cumulative incidence by comorbidity status is surprising, but may be due to sicker patients failing hormone treatment more quickly, hastening receipt of chemotherapy. Notably, docetaxel diffusion largely preceded definitive phase III evidence of efficacy in hormone refractory prostate cancer. Indeed the diffusion of docetaxel appeared to be a drug-wide phenomena rather than a disease-specific phenomena.

Studies of cancer treatment use by patient SES, demographic levels, and health status have frequently shown lower usage for disadvantaged patients.[8,9,41-53] Differences by geographic region have also been found.[54] Diffusion, which tracks patterns of usage

over time, has been explicitly studied in some instances. Slower diffusion for older patients, minorities, and patients with lower SES were identified.[22,55,56]

The observation that disadvantaged patients have slower diffusion presents opportunities to improve uptake of proven new therapies in subpopulations. For instance, direct-to-consumer-advertising (DTCA) has recently been shown to improve the appropriate use of aromatase inhibitors.[57] Since oncology patients are frequently aware of DTCA, DTCA could be a useful tool to promote the use of proven new therapies in certain target populations.[58] Cost concerns might dissuade lower income patients in particular from getting treatment, especially newer treatments.[59] If newer treatments require higher out-of-pocket costs, financial assistance for patients in lower SES categories may help alleviate disparities in the uptake of new drugs. Even if patient out-of-pocket costs for newer treatments are similar, anxiety about how to pay may exist,[60] in which case improved communication between physicians and patients is crucial for clarifying treatment costs.[61]

Evidence of a sigmoid shape for use of docetaxel over time is consistent with prior observations that social dynamics accelerate new innovation diffusion.[7,25] The inference that social relationships among physicians are important suggests that enhancing communication channels among physicians, especially between key opinion leaders and their colleagues, would encourage more rapid adoption of treatments. One factor that has been repeatedly identified as influential in increasing adoption rates is attendance at scientific symposia,[8,62] which serve as forums for disseminating information about new treatments. Unfortunately, the nature of the relationships among physicians was not analyzable in this study due to lack of data on their social links.

The rapid uptake of docetaxel in hormone refractory prostate cancer prior to definitive evidence from a phase III trial is a concern. On its face, adoption prior to definitive evidence violates the clinical trial paradigm, which relies on randomized comparisons between the new treatment and current standard-of-care. Considerations that may have lead to early adoption of docetaxel include prior FDA indications in other solid tumors and the fact that conventional treatment, mitoxantrone, provided only palliative relief, whereas early pilot trials for docetaxel held promise of a survival benefit.[63] However, despite the early evidence, the positive result for docetaxel in randomized trials was not a foregone conclusion. Indeed, multiple phase III trials for drugs already in wide use have returned negative results.[64-66] In some instances, phase III evidence lead to an appropriate diminution in the use of the new drug,[3,67] though not in all.[47,68]

The evidence in Figure 4.5 indicates that uptake of docetaxel diffusion occurred across different cancers approximately simultaneously, in all cases prior to FDA approval, suggesting the prevalence of off-label prescriptions for reimbursement. Off-label drug use is considered appropriate in many instances.[69] Indeed it is typically estimated that 25-50% of cancer drug prescriptions are off label.[69-72] Denials of off-label use by Medicare and Medicaid lead Congress, in 1993, to deem that Medicare contractors pay for cancer drug prescriptions if their use is supported by selected standard medical compendia.[73] Currently four compendia are recognized by the Center for Medicare and Medicaid services.[74] However, questions about the quality of the medical compendia have been raised. A recent review found that compendia "lack transparency, cite little current evidence, and lack systematic methods to review or update evidence."[75] For docetaxel in particular, the review found that "the methodologies and actual practice

diverge, predominantly due to subjective assessments of the value and volume of the data, subjective assessments of current practice, and omission of recent citations."[76] The questionable quality of medical compendia is astonishing in light of the role compendia play in determining reimbursement. A recent study found that nearly 40% of total U.S. sales for a set of anti-cancer drugs were based on off-label prescriptions, about half of which were supported, and half unsupported, by compendia guidelines.[70]

A notable limitation in this study is the inability to identify the true denominator of patients with hormone refractory prostate cancer. Identifying hormone failures based on chemotherapy does not capture patients with hormone refractory disease who received no chemotherapy. Such patients may be too sick to receive chemotherapy. Thus diffusion estimates for hormone refractory prostate cancer are likely biased high. An alternative approach would be to identify metastatic prostate cancer patients according to their cause of death. This approach might preferentially exclude patients with longer survival by selectively choosing those with suboptimal therapy. The necessity of using Medicare claims to identify relapse or recurrence is often problematic,[21] but especially when treatment is itself the endpoint, since it raises the question whether patients not identified as relapse/recurrent by Medicare claims (i.e. HMO patients) may be different, limiting generalizability of the findings. Also, the use of Medicare data limits the analysis to patients $\geq$65 years. However prostate cancer occurs primarily in patients $\geq$65 years (~70% of cases)[77] and older patients may receive suboptimal care and thus represent a critical target population.[78,79]

These results provide an example of widespread diffusion of a new therapy occurring prior to publication of definitive phase III evidence. Fortunately, phase III results ultimately supported docetaxel use in hormone-refractory prostate cancer. In

other instances, however, they will not. Early use of docetaxel was likely enabled by compendia supporting its off-label use. Reliance on compendia to facilitate treatment reimbursement represents an attempt to balance tradeoffs. On the one hand, the requirement that every variation in target population for a drug require a separate FDA indication would overwhelm available resources. On the other hand, reliance on compendia of potentially questionable quality may lead to inappropriate use, with potential costs in increased morbidity and mortality if a different drug may have been more appropriate. Inappropriate use also places an unnecessary financial burden on health care payers. Off-label drug use may also discourage clinical trial participation, which slows the very research that could render off-label prescriptions less necessary. In part for these reasons, the American Society of Clinical Oncology has stated that the "system for identifying medically appropriate cancer therapies, including those that involve off-label uses… requires attention."[69]

4.5 REFERENCES

1. Agency for Healthcare Research and Quality. Translating Research into Practice [on-line]. Available at: http://grants.nih.gov/grants/guide/pa-files/PA-02-066.html.

2. Grann VR, Hershman D, Jacobson JS, et al. Outcomes and diffusion of doxorubicin-based chemotherapy among elderly patients with aggressive non-Hodgkin lymphoma. Cancer. 2006 Oct 1;107(7):1530-41.

3. Haas JS, Kaplan CP, Gerstenberger EP, et al. Changes in the use of postmenopausal hormone therapy after the publication of clinical trial results. Ann Intern Med. 2004 Feb 3;140(3):184-8.

4. Booth CM, Shepherd FA, Peng Y, et al. Adoption of adjuvant chemotherapy for non-small-cell lung cancer: a population-based outcomes study. J Clin Oncol. 2010 Jul 20;28(21):3472-8.

5. Unger JM, LeBlanc M, Crowley JJ, et al. Estimating the impact of new clinical trial proven cancer therapy and cancer chemoprevention on population mortality: the Karnofsky Memorial lecture. J Clin Oncol. 2003 Dec 1;21(23 Suppl):246s-252s.

6. Berwick DM. Disseminating innovations in health care. JAMA 2003;289: 1969-1975.

7. Rogers EM. Diffusion of Innovations. (5 th ed.), 2003, New York: Free Press

8. Giordano SH, Duan Z, Kuo YF, et al. Impact of a scientific presentation on community treatment patterns for primary breast cancer. J Natl Cancer Inst. 2006 Mar 15;98(6):382-8.

9. Sundararajan V, Hershman D, Grann VR, et al. Variations in the use of chemotherapy for elderly patients with advanced ovarian cancer: a population-based study. J Clin Oncol. 2002 Jan 1;20(1):173-8.

10. Perlmutter MA, Lepor H. Androgen Deprivation Therapy in the Treatment of Advanced Prostate Cancer. Rev Urol. 2007;9(Suppl 1): S3-S8.

11. Crawford ED, Eisenberger MA, McLeod DG, et al. A controlled trial of leuprolide with and without flutamide in prostatic carcinoma. N Engl J Med 1989;321:419-24. [Erratum, N Engl J Med 1989;321:1420.]

12. Eisenberger MA, Blumenstein BA, Crawford ED, et al. Bilateral orchiectomy with or without flutamide for metastatic prostate cancer. N Engl J Med 1998;339: 1036-42.

13. Tannock IF, Osoba D, Stockler MR, et al. Chemotherapy with mitoxantrone plus prednisone or prednisone alone for symptomatic hormone-resistant prostate cancer: a Canadian randomized trial with palliative end points. J Clin Oncol. 1996;14: 1756-1764.

14. Kantoff PW, Halabi S, Conaway M, et al. Hydrocortisone with or without mitoxantrone in men with hormone-refractory prostate cancer: results of the Cancer and Leukemia Group B 9182 study. J Clin Oncol 1999; 17:2506-13.

15. Petrylak DP, Tangen CM, Hussain MH, et al. Docetaxel and estramustine compared with mitoxantrone and prednisone for advanced refractory prostate cancer. N Engl J Med. 2004 Oct 7;351(15):1513-20.

16. Tannock IF, de Wit R, Berry WR, et al. Docetaxel plus prednisone or mitoxantrone plus prednisone for advanced prostate cancer. N Engl J Med. 2004;351(15):1502-12.

17. Potosky AL, Riley GF, Lubitz JD, et al. Potential for cancer related health services research using a linked Medicare-tumor registry database. Med Care. 1993 Aug;31(8):732-48.

18. Charlson ME, Pompei P, Ales KL, et al. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis 1987;40(5):373-83.

19. Klabunde CN, Legler JM, Warren JL, et al. A refined comorbidity measurement algorithm for claims-based studies of breast, prostate, colorectal, and lung cancer patients. Ann Epidemiol. 2007 Aug;17(8):584-90. Epub 2007 May 25.

20. ICD9Data.com, available at: http://www.icd9data.com/HCPCS/2011/J/J9170.htm

21. Earle CC, Nattinger AB, Potosky AL, et al. Identifying cancer relapse using SEER-Medicare data. Med Care 2002;40(Suppl. 8):S75-81.

22. Sima CS, Panageas KS, Heller G, et al. Analytical strategies for characterizing chemotherapy diffusion with patient-level population-based data. Appl Health Econ Health Policy. 2010;8(1):37-51.

23. Cronin KA, Binbing Y, Krapcho M, et al. Modeling the dissemination of mammography in the United States. Cancer Causes and Control. 2005;16:701-712.

24. Bass FM. A new-product growth model for consumer durables. Management Science. 1969 January;15:215-227.

25. Coleman, J., Katz, E., & Menzel H. (1957). The diffusion of an innovation among physicians. Sociometry, 20, 253-270.

26. Mansfield E. Technical change and the rate of imitation. Econometrica. 1961;29:741-766.

27. Sharif MN, Ramanathan K. Binomial innovation diffusion models with dynamic potential adopter population. Technological Forecasting and Social Change. 1981;20:63-87.

28. Mahajan V, Peterson RA. "Models for innovation diffusion." Sage University Paper Series on Quanitative Applications in the Social Sciences, CA: Sage. 1985.

29. Bach PB, Guadagnoli E, Schrag D, et al. Patient demographic and socioeconomic characteristics in the SEER-Medicare database: Applications and Limitations. Med Care. 2002 Aug;40(8 Suppl):IV-19-25.

30. National Cancer Institute website. SEER-Medicare: Calculation of comorbidity weights. Online at: http://healthservices.cancer.gov/seermedicare/program/comorbidity.html

31. Gray, R. A Class of K-Sample Tests for Comparing the Cumulative Incidence of a Competing Risk. Annals Statis. 1998;16:1141–1154.

32. Beer TM, Pierce WC, Lowe BA, et al. Phase II study of weekly docetaxel in symptomatic androgen-independent prostate cancer. Ann Oncol. 2001 Sep;12(9):1273-9.

33. Berry W, Dakhil S, Gregurich MA, et al. Phase II trial of single-agent weekly docetaxel in hormone-refractory, symptomatic, metastatic carcinoma of the prostate. Semin Oncol. 2001 Aug;28(4 Suppl 15):8-15. PMID: 11685723 [PubMed - indexed for MEDLINE]

34. Friedland D, Cohen J, Miller R Jr, et al. A phase II trial of docetaxel (Taxotere) in hormone-refractory prostate cancer: correlation of antitumor effect to phosphorylation of Bcl-2. Semin Oncol. 1999 Oct;26(5 Suppl 17):19-23.

35. Picus J, Schultz M. Docetaxel (Taxotere) as monotherapy in the treatment of hormone-refractory prostate cancer: preliminary results. Semin Oncol. 1999 Oct;26(5 Suppl 17):14-8.

36. Savarese D, Taplin ME, Halabi S, et al. A phase II study of docetaxel (Taxotere), estramustine, and low-dose hydrocortisone in men with hormone-refractory prostate cancer: preliminary results of cancer and leukemia group B Trial 9780. Semin Oncol. 1999 Oct;26(5 Suppl 17):39-44.

37. Dagher R, Li N, Abraham S, et al. Approval summary: Docetaxel in combination with prednisone for the treatment of androgen-independent hormone-refractory prostate cancer. Clin Cancer Res. 2004 Dec 15;10(24):8147-51.

38. Eisenberger MA, De Wit R, Berry W, et al. A multicenter phase III comparison of docetaxel (D) + prednisone (P) and mitoxantrone (MTZ) + P in patients with hormone-refractory prostate cancer (HRPC). ASCO 2004: #4. June 2004

39. Petrylak DP, Tangen C, Hussain M, et al. Randomized phase III trial of docetaxel (D)/estramustine (E) versus mitoxantrone(M)/prednisone(p) in men with androgen-independent prostate cancer (AIPCA). ASCO 2004: #3. June 2004

40. U.S. Census Bureau, Current Population Reports, P60-213, *Money Income in the United States: 2000,* U.S. Government Printing Office, Washington, DC, 2001.

41. Giordano SH, Lin YL, Kuo YF, et al. Decline in the use of anthracyclines for breast cancer. J Clin Oncol. 2012 Jun 20;30(18):2232-9.

42. Hershman DL, Buono D, Jacobson JS, et al. Surgeon characteristics and use of breast conservation surgery in women with early stage breast cancer. Ann Surg. 2009 May;249(5):828-33.

43. Hershman DL, Richards CA, Kalinsky K, et al. Breast Cancer Res Treat. 2012 Nov;136(2):535-45.

44. Matushansky I, Dela Cruz F, Insel BJ, et al. Chemotherapy use in elderly patients with soft tissue sarcoma: A population-based study. Cancer Invest. 2013 Feb;31(2):83-91.

45. Neugut AI, Hillyer GC, Kushi LH, et al. Noninitiation of adjuvant chemotherapy in women with localized breast cancer: the breast cancer quality of care study. J Clin Oncol. 2012 Nov 1;30(31):3800-9.

46. Neugut AI, Becker DJ, Insel BJ, et al. Uptake of oxaliplatin and bevacizumab for treatment of node-positive and metastatic colon cancer. J Oncol Pract. 2012 May;8(3):156-63.

47. Schrag D, Rifas-Shiman S, Saltz L, et al. Adjuvant chemotherapy use for Medicare beneficiaries with stage II colon cancer. J Clin Oncol. 2002 Oct 1;20(19):3999-4005.

48. Spencer BA, Insel BJ, Hershman DL, et al. Racial disparities in the use of palliative therapy for ureteral obstruction among elderly patients with advanced prostate cancer. Support Care Cancer. 2013 Jan 6. [Epub ahead of print]

49. Strauss J, Hershman DL, Buono D, et al. Use of adjuvant 5-fluorouracil and radiation therapy after gastric cancer resection among the elderly and impact on survival. Int J Radiat Oncol Biol Phys. 2010 Apr;76(5):1404-12.

50. Sundararajan V, Grann VR, Jacobson JS, et al. Variations in the use of adjuvant chemotherapy for node-positive colon cancer in the elderly: a population-based study. Cancer J. 2001 May-Jun;7(3):213-8.

51. Temple LK, Hsieh L, Wong WD, et al. Use of surgery among elderly patients with stage IV colorectal cancer. J Clin Oncol. 2004 Sep 1;22(17):3475-84.

52. Wright JD, Burke WM, Wilde ET, et al. Comparative effectiveness of robotic versus laparoscopic hysterectomy for endometrial cancer. J Clin Oncol. 2012 Mar 10;30(8):783-91.

53. Zafar SY, Malin JL, Grambow SC, et al. Early dissemination of bevacizumab for advanced colorectal cancer: A prospective cohort study. BMC Cancer. 2011 Aug 16;11:354.

54. Nattinger AB, Gottlieb MS, Veum J, et al. Geographic variation in the use of breast-conserving treatment for breast cancer. *N Engl J Med*. 1992;326:1102–1107.

55. Chen AY, Halpern MT, Schrag NM, et al. Disparities and trends in sentinel lymph node biopsy among early-stage breast cancer patients (1998-2005). J Natl Cancer Inst. 2008 Apr 2;100(7):462-74.

56. Flowers CR, Fedewa SA, Chen AY, et al. Disparities in the early adoption of chemoimmunotherapy for diffuse large B-cell lymphoma in the United States. Cancer Epidemiol Biomarkers Prev. 2012 Sep;21(9):1520-30.

57. Abel GA, Chen K, Taback N, et al. Impact of oncology-related direct-to-consumer advertising: Association with appropriate and inappropriate prescriptions. Cancer. 2013 Mar 1;119(5):1065-72.

58. Abel GA, Burstein HJ, Hevelone ND, et al. Cancer related direct-to-consumer advertising: Awareness, perceptions, and reported impact among patients undergoing active cancer treatment. J Clin Oncol 27:4182-4187, 2009

59. Kim P. Cost of cancer care: the patient perspective. J Clin Oncol. 2007 Jan 10;25(2):228-32.

60. Unger JM, Hershman DL, Albain KS, et al. Patient income level and cancer clinical trial participation. J Clin Oncol. 2013 Feb 10;31(5):536-42.

61. Schrag D, Hanger M. Medical oncologists' views on communicating with patients about chemotherapy costs: A pilot survey. J Clin Oncol. 2007 Jan 10;25(2):233-7.

62. Buban GM, Link BK, Doucette WR. Influences on oncologists' adoption of new agents in adjuvant chemotherapy of breast cancer. J Clin Oncol. 2001 Feb 15;19(4):954-9.

63. Petrylak DP. Chemotherapy for advanced hormone refractory prostate cancer. Urology. 1999 Dec;54(6A Suppl):30-5.

64. Hughes KS, Schnaper LA, Berry D, et al. Lumpectomy plus tamoxifen with or without irradiation in women 70 years of age or older with early breast cancer. N Engl J Med. 2004 Sep 2;351(10):971-7.

65. Rossouw JE, Anderson GL, Prentice RL, et al. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results From the Women's Health Initiative randomized controlled trial. JAMA. 2002 Jul 17;288(3):321-33.

66. Stadtmauer EA, O'Neill A, Goldstein LJ, et al. Conventional-dose chemotherapy compared with high-dose chemotherapy plus autologous hematopoietic stem-cell transplantation for metastatic breast cancer. Philadelphia Bone Marrow Transplant Group. N Engl J Med. 2000 Apr 13;342(15):1069-76.

67. Bekelman JE, Rosenzweig KE, Bach PB, et al. Trends in the use of postoperative radiotherapy for resected non-small-cell lung cancer. Int J Radiat Oncol Biol Phys. 2006 Oct 1;66(2):492-9.

68. Soulos PR, Yu JP, Roberts KB, et al. Assessing the impact of a cooperative group trial on breast cancer care in the medicare population. J Clin Oncol. 2012 May 10;30(14):1601-7.

69. American Society of Clinical Oncology. Reimbursement for cancer treatment: coverage of off-label drug indications. J Clin Oncol. 2006 Jul 1;24(19):3206-8.

70. Conti RM, Bernstein AC, Villaflor VM, et al. Prevalence of Off-Label Use and Spending in 2010 Among Patent-Protected Chemotherapies in a Population-Based Cohort of Medical Oncologists. J Clin Oncol. 2013 Mar 20;31(9):1134-9.

71. United States General Accounting Office: Off-Label Drugs: Reimbursement Policies Constrain Physicians in Their Choice of Cancer Therapies. September 1991: GAO/PEMD-91-14. http://archive.gao.gov/d18t9/144933.pdf

72. Van Allen EM, Miyake T, Gunn N, et al. Off-label use of rituximab in a multipayer insurance system. J Oncol Pract. 2011 Mar;7(2):76-9. doi: 10.1200/JOP.2010.000042.

73. Omnibus Budget Reconciliation Act of 1993. Available at: www.gpo.gov/fdsys/pkg/BILLS-103hr2264enr/pdf/BILLS-103hr2264enr.pdf

74. Center for Medicare and Medicaid Services regulations and guidance transmittal. Subject: “Compendia and Authoritative Sources for use in the Determination of a ‘Medically Accepted Indication’ of Drugs and Biologicals Used Off-Label in an Anti-Cancer Chemotherapeutic Regimen.” Available online at:

http://www.cms.gov/Regulations-and-Guidance/Guidance/Transmittals/downloads/r96bp.pdf. October 24, 2008.

75. Abernethy AP, Raman G, Balk EM, et al. Ann Intern Med. 2009 Mar 3;150(5):336-43.

76. Agency for Healthcare Research and Quality Technology Assessment Program. Compendia for coverage of off-label uses of drugs and biologics in an anticancer chemotherapeutic regiment. Final report. May 7, 2007. Available online at: http://www.cms.gov/Medicare/Coverage/DeterminationProcess/downloads/id46ta.pdf

77. Unger JM, Coltman CA Jr, Crowley JJ, et al. Impact of the year 2000 Medicare policy change on older patient enrollment to cancer clinical trials. J Clin Oncol. 2006 Jan 1;24(1):141-4. Epub 2005 Dec 5.

78. Bennett CL, Greenfield S, Aronow H, et al. Patterns of care related to age of men with prostate cancer. Cancer. 1991 May 15;67(10):2633-41.

79. Greenfield S, Blanco DM, Elashoff RM, et al. Patterns of care related to age of breast cancer patients. JAMA. 1987 May 22-29;257(20):2766-70.

Table 4.1: J-Codes for Chemotherapies Used in Breast, Lung, Ovarian, and Prostate Cancer

		Typically Used in Cancer Setting			
Drug Names	**J-Codes**	**Breast**	**Lung**	**Ovarian**	**Prostate**
Drug of Interest					
Docetaxel	J9170	X	X	X	X
Other Drugs					
5-FU	J9190	X			
Cabazitaxel	J9043				X
Capcitabine	J8520, J8521	X			
Carboplatin	J9045		X	X	X
Cisplatin	J9060, J9062			X	
Cyclophosphamide	J8530, J9070, J9080, J9090, J9091, J9092, J9093, J9094, J9095, J9096, J9097	X	X		
Doxorubicin	J9000	X	X	X	X
Etoposide	J9181, J9182, J8560			X	X
Gemcitabine	J9201	X	X	X	
Halaven	J9179	X			
Ifosfamide	J9208		X		
Irinotecan	J9206		X		
Ixabepilone	J9207	X			
Methotrexate	J9250, J9260	X			
Mitoxantrone	J9293				X
Paclitaxel	J9265	X	X	X	X
Pemetrexed	J9305, C9213		X		
Topotecan	J9350		X	X	
Unspecified*	J8999, J9999	X	X	X	X
Vinblastine	J9360		X		X
Vinorelbine	J9390	X	X	X	X

* Unspecified antineoplastic drugs.

Table 4.2: Cohort Characteristics

	Percent	Subsequently Received Chemotherapy?	
Factor	Metastatic Prostate Cancer (N=6,561)	Yes (i.e. Hormone Refractory Prostate Cancer) (N=1,350)	No (N=5,211)
Age ≥75	58%	41%	63%**
Black	14%	10%	16%**
Asian/Pacific Islander	6%	5%	6%
Hispanic origin	7%	8%	6%
Income			
≥$50,000/year	37%	46%**	35%
Poverty	21%	15%	23%**
Median	$42,654	$47,344**	$41,692
Median proportion with some college	28%	28%	28%
Site			
East	18%	20%*	17%
Midwest	37%	35%	37%
West	45%	44%	46%
Comorbidity index ≥1	30%	25%	31%**

* Statistically significantly higher, .01≤p≤.05

** Statistically significantly higher, p<.0001

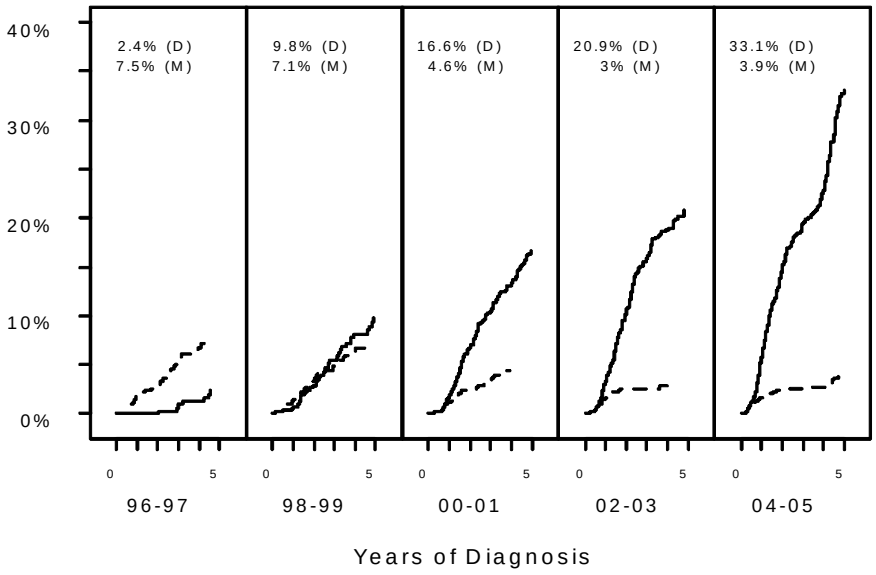


Figure 4.1: Five-year cumulative incidence of docetaxel (solid line) and mitoxantrone (dashed line) use from diagnosis, by year of diagnosis, among patients presenting with metastatic prostate cancer. Five-year cumulative incidence estimates are shown. D=docetaxel; M=mitoxantrone.

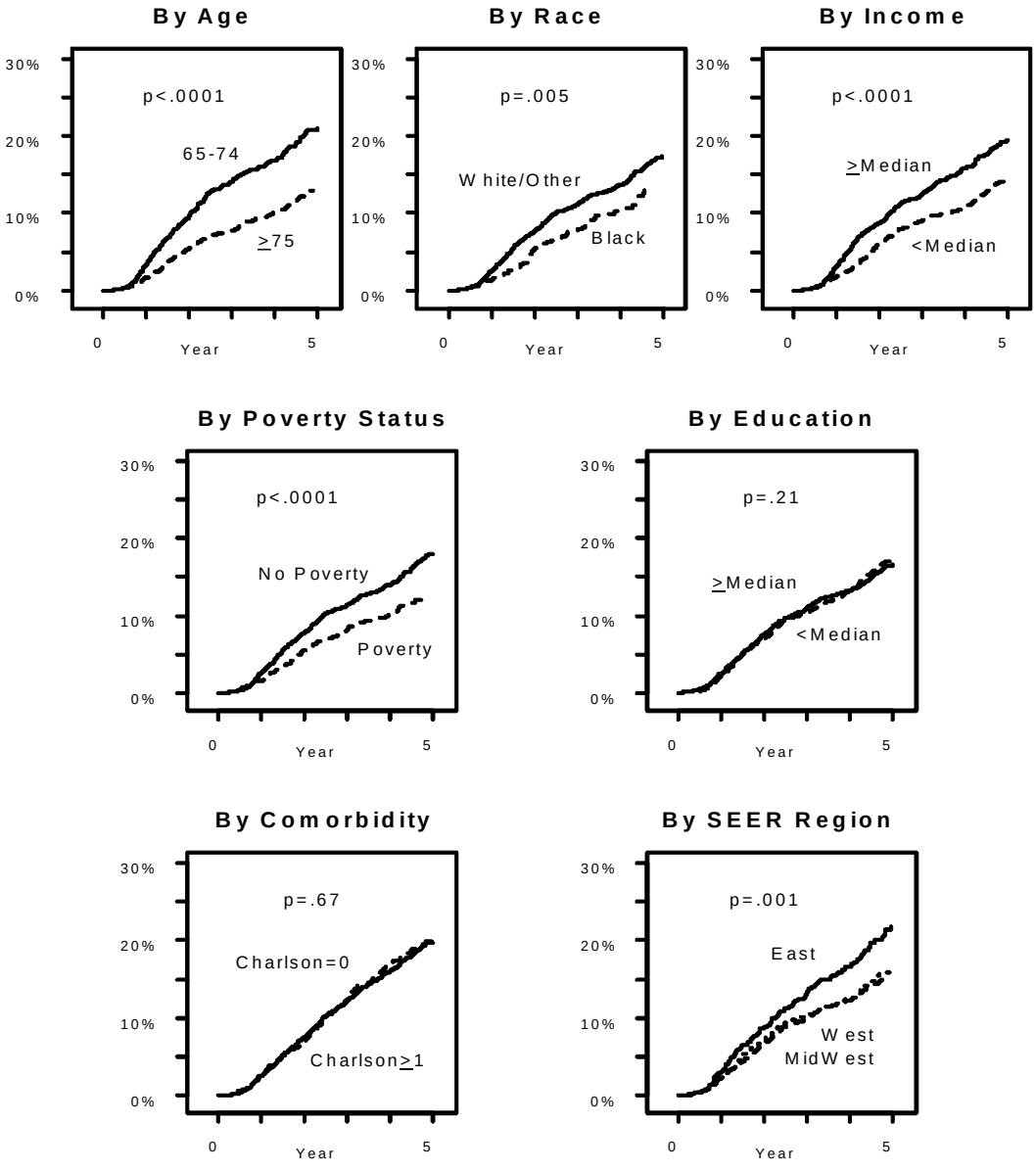

By Age
p<.0001
65-74
≥75
By Race
p=.005
White/Other
Black
By Income
p<.0001
≥Median
<Median
By Poverty Status
p<.0001
No Poverty
Poverty
By Education
p=.21
≥Median
<Median
By Comorbidity
p=.67
Charlson=0
Charlson≥1
By SEER Region
p=.001
East
West
MidWest
30%
20%
10%
0%
0
5
Year

Figure 4.2. Five-year cumulative incidence of docetaxel use from diagnosis among patients presenting with metastatic prostate cancer by SES, demographic, comorbidity, and geographic factors. Patients for all years of diagnosis were included. Five year cumulative incidence estimates by factor were: BY AGE: 24.8% for patient 65-74 versus 15.4% for patients $\geq$75; BY RACE: 20.3% for white/other patients versus 16.9% for black patients; BY INCOME: 22.8% for patients from Census tract regions with income >median versus 16.9% for patients from Census tract regions with income <median; BY POVERTY STATUS: 21.2% for patients with no evidence of poverty and 14.5% for patients with evidence of poverty; BY EDUCATION: 20.2% for patients from Census tract regions with education >median versus 19.6% for patients from Census tract regions with education <median; BY COMORBIDITY STATUS: 19.8% for patients with a Charlson score of 0 versus 20.1% for patients with a Charlson score of $\geq$1; BY SEER REGION: 25.6% for patients from Eastern regions versus 18.8% for patients from Western regions versus 18.5% for patients from Midwestern regions.

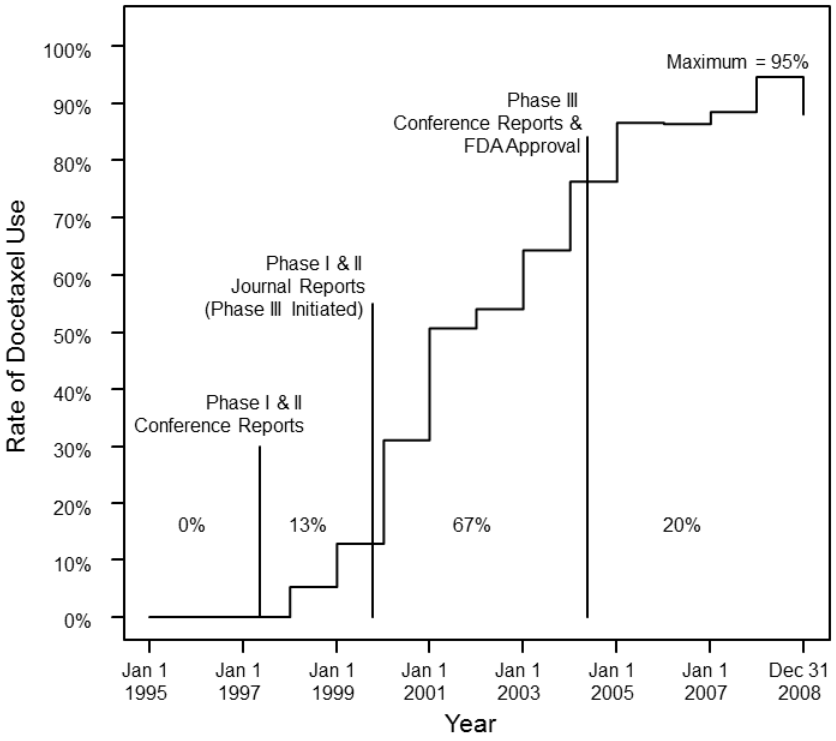


Figure 4.3. Proportion using docetaxel over time with landmark events. Thirteen percent of total (i.e. maximum) diffusion occurred between initial phase I and II conference reports and journal reports, 67% between phase I and II journal reports and initial phase III conference reports and FDA approval, and 20% after the phase III reports/FDA approval.

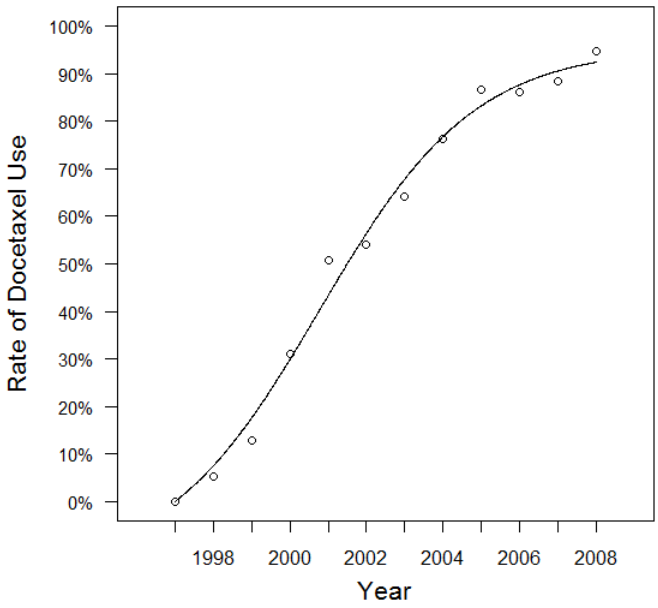


Figure 4.4. Mixed influence diffusion model fit of proportion using docetaxel over time by year. The model explained 99.2% of total observed variation. The coefficient for k_2 (=0.462), the measure of internal influence, was 7.2x the magnitude of the coefficient for k_1 (=0.064), consistent with hypothesis that social dynamics played a significant role in the diffusion of docetaxel.

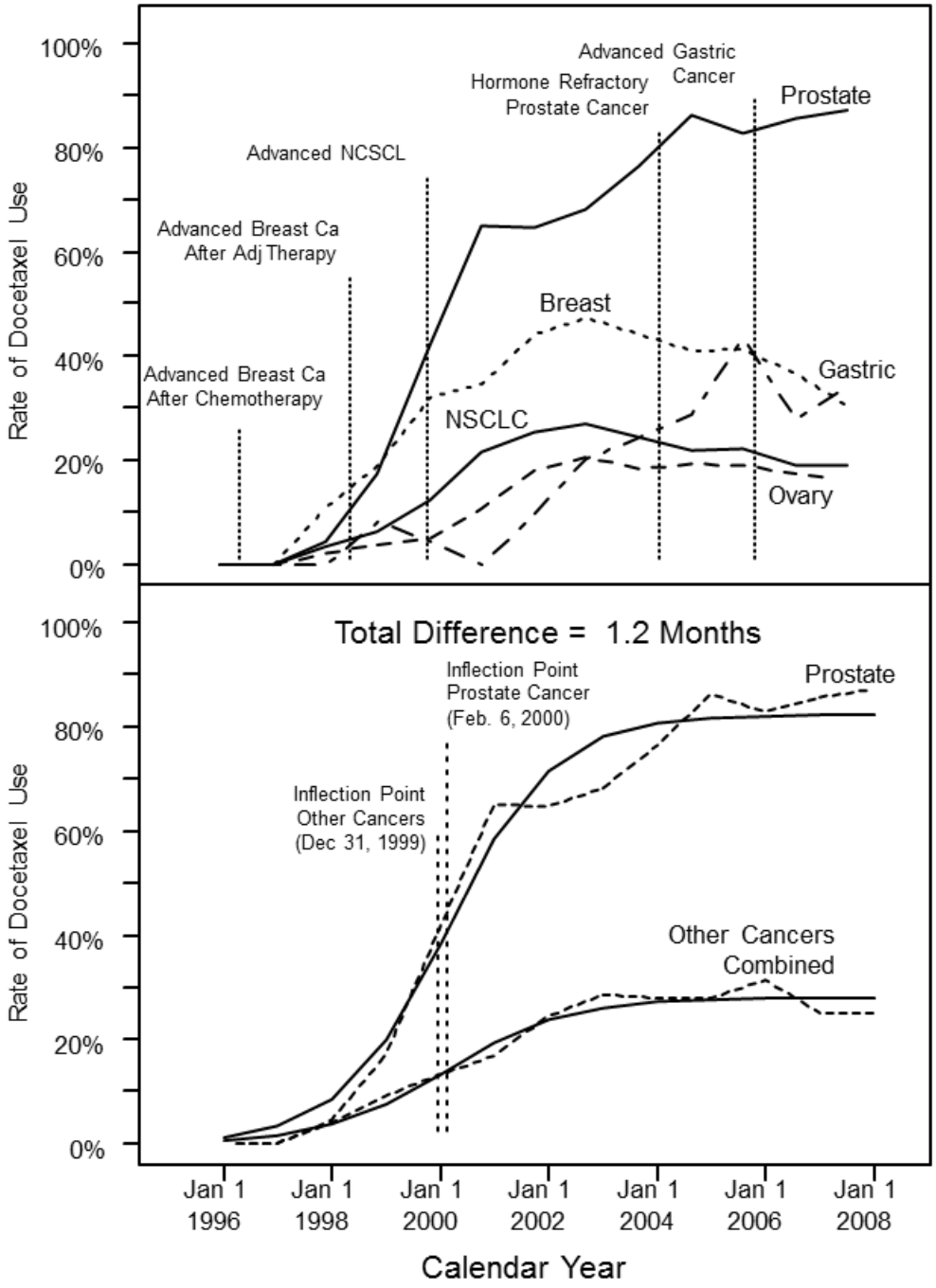

100%
80%
60%
40%
20%
0%
Rate of Docetaxel Use
Advanced Gastric Cancer
Hormone Refractory Prostate Cancer
Prostate
Advanced NCSCL
Advanced Breast Ca After Adj Therapy
Breast
Advanced Breast Ca After Chemotherapy
Gastric
NSCLC
Ovary
Total Difference = 1.2 Months
Inflection Point Prostate Cancer (Feb. 6, 2000)
Prostate
Inflection Point Other Cancers (Dec 31, 1999)
Other Cancers Combined
Jan 1 1996
Jan 1 1998
Jan 1 2000
Jan 1 2002
Jan 1 2004
Jan 1 2006
Jan 1 2008
Calendar Year

Figure 4.5. Proportion using docetaxel over time, by cancer type, with landmark events and model-fitted curves. **Top panel:** The proportion using docetaxel over time for metastatic prostate cancer is compared to rates in advanced breast, lung, gastric, and ovarian cancers. FDA approval times for each cancer are shown. Docetaxel was approved for use in patients with locally advanced or metastatic breast cancer after failure of prior chemotherapy in May, 1996; in patients with metastatic breast cancer who failed adjuvant therapy in June, 1998; in patients with NSCLC who failed cisplatin-based treatment in December, 1999; and in patients with advanced gastric cancer (in combination with 5-FU and cisplatin) in March, 2006. Docetaxel has not received an FDA indication for use in ovarian cancer patients, but is included to convey the similarity of diffusion patterns of docetaxel for a cancer in which prescriptions are strictly off-label. **Bottom panel:** The observed proportions using docetaxel over time for metastatic prostate cancer are compared to the combined rates from advanced breast, lung, gastric, and ovarian cancers. Fitted model-based estimates are superimposed. The inflection points for the fitted curves indicate the time of maximum increase in the rate of docetaxel use, and are approximately the same (10 days difference) between the two curves.

Chapter 5

CONCLUSIONS

The design, monitoring, and analysis of clinical trials has been established over decades.[1] Other topics of study regarding the role of clinical trials in establishing community-based treatments have had less study. In this dissertation, we investigated the representativeness, generalizability, and diffusion of cancer clinical trial treatments. Prior investigations of these topics have been limited by the available data or have been evaluated in a non-comprehensive fashion.

To analyze the representativeness of cancer clinical trial cohorts, we assessed clinical trial participation patterns according to important SES and demographic factors in a large sample of patients surveyed via an Internet-based treatment decision tool.[2] This approach allowed collection of patient-level socioeconomic and comorbidity data from a large sample of patients, the absence of which limited prior investigations.[3] In addition, attitudes toward clinical trials were assessed using pre-specified items about treatment, treatment tolerability, convenience, and cost.[4] In total, 5,499 patients were successfully surveyed from 2007-2011. We found that income was the only socioeconomic or demographic factor that was independently associated with clinical trial participation. Even in patients $\geq$65, who have universal access to Medicare, lower income predicted lower trial participation. We also found that cost concerns were much more evident among lower income patients.[2]

To investigate generalizability, we examined whether cancer clinical trial patients were similar to non-trial, "real world" patients with respect to presenting characteristics and survival outcomes. We reviewed the phase III database of SWOG over a 25 year period to identify candidate trials, and compared patients from the standard arms of those trials to non-trial controls selected from the Surveillance, Epidemiology, and End Results program. This comprehensive approach limited the potential impact of subjective selection of studies for analysis,[5,6] and, given key similarities across studies within SWOG, allowed the aggregation of study arms within prognosis groups ($\geq$50% vs. <50% average 2-year survival). We found that the impact of trial participation on overall survival endured for only one year, and was therefore more likely to independently influence overall survival in poor prognosis studies (9/10) rather than good prognosis studies (0/11; $p<.0001$). As long as the underlying mechanism(s) causing improved outcomes for trial patients are independent of treatment, trial participation will be associated with a similar one year improvement in outcomes for patients on the experimental arms of trials as well.

Finally, we examined patterns of diffusion in a database of metastatic prostate cancer patients diagnosed from 1995-2007 using SEER-Medicare. Treatment usage patterns for a snapshot in time have previously been described, but changes in treatment usage over time (diffusion) have not been well studied. We assessed cumulative incidence of docetaxel by socioeconomic, demographic, and comorbidity variables, and compared diffusion patterns to landmark events including release of phase III results and FDA approval dates. In phase III studies, docetaxel use reduced risk of death by about 20-25%. We found that diffusion was notably slower in socioeconomically

disadvantaged groups, including patients with lower income. We also found that most of the diffusion of docetaxel occurred prior to the release of definitive phase III results showing superiority of docetaxel over standard-of-care for hormone-refractory prostate cancer, and that docetaxel diffusion patterns with respect to time were similar across multiple cancers.

Although the topics covered in this dissertation all fall along the pathway from early study to diffusion of cancer treatments, taken together, they comprise largely non-overlapping data, conceptual, and analytic domains. This represents both a strength and a weakness. On the positive side, these disparate topics gave experience using multiple different data sources, required the study of multiple literature domains, and required facility with multiple analytic approaches. On the negative side, this approach reduced the depth of examination into any particular domain. For instance, examination of the diffusion of docetaxel for hormone-refractory prostate cancer represents a single example which may not be generalizable. Early diffusion in this setting may well have been driven by the urgency of the clinical prognosis, strong positive evidence in early stage trials, and the lack of alternative treatments with survival benefits. An alternative set of examinations may have investigated not just chemotherapy in refractory disease but perhaps in other cancer types or disease stages. Or, further methodologic examinations of diffusion might have been possible, such as devising a method to estimate loss (whether in person-years, dollars, or etc.) due to inefficient diffusion.

Given the disparate nature of the topics in this dissertation, the implications are varied. With respect to clinical trial representativeness, the main finding is that lower income patients were less likely to participate in clinical trials, even when considering

age group. Thus a better understanding of why income is a barrier may help identify ways to make clinical trials better available to all patients, and would increase the generalizability of clinical trial results across all income levels. Importantly as well, improved participation by lower income patients could help clinical trials be completed more quickly. Suggested policy approaches for improving lower income participation in clinical trials included covering excess costs for trial participation for all patients; direct payments to individuals to encourage clinical trial participation; and direct-to-consumer advertising about clinical trials to the target population. Certain low-cost considerations for patients related to time, convenience, or transportation, such as parking passes or bus fare, could also improve participation for lower income patients.

The main finding of the generalizability paper was that the impact of trial participation on overall survival endured for only one year. This was likely due to eligibility criteria that excluded higher comorbidity patients from trials. In the long term, histology and stage, not trial participation, primarily determined survival. If histology and stage determine survival – despite the fact that the average SWOG phase III clinical trial had 16 eligibility criteria over and above those pertaining to histology and stage, and that 60% of these pertained to comorbid conditions – then consideration should be given to relaxing or eliminating criteria where possible. Given the dominance of histology and stage in determining outcomes, this should not notably reduce statistical power, and would have the advantage of increasing access to clinical trials for a broader cross-section of patients. Additionally, improved confidence in the long-term generalizability of clinical trial results, especially in the good prognosis setting, could hasten adoption of new, proven treatments into the community setting.

Finally, we found that diffusion of docetaxel for hormone refractory prostate cancer largely preceded the release of phase III results showing superiority of docetaxel over standard-of-care. Rapid diffusion prior to definitive phase III evidence suggested the widespread prevalence of off-label chemotherapy use. These results also provided an example wherein the clinical trial paradigm – which relies on randomized comparisons between the new treatment and current standard-of-care prior to diffusion into the cancer treatment community – was not adhered to. Indeed diffusion of a new therapy may in some cases be not so much a disease-specific phenomenon as a drug-wide phenomenon. Importantly, also, diffusion was slower for socioeconomically disadvantaged groups, including lower income patients and patients in poverty. Efforts to improve access to new treatments for socioeconomically disadvantaged populations might include financial assistance or targeted advertising – in other words, similar policy prescriptions as those that might improve clinical trial participation for these populations.

The tradition of health services research has famously been described as emphasizing equity, effectiveness, and efficiency in health care.[7] The main results and conclusions of this dissertation fit squarely within this tradition, insofar as the analysis of Representativeness (Chapter 2) investigated *equity* of access to a health care resource according to income; the analysis of Generalizability (Chapter 3) investigated the translation of efficacy of a treatment in a clinical trial to *effectiveness* of the new treatment in the treatment community; and the analysis of Diffusion (Chapter 4) investigated the *efficiency* with which a new proven treatment is taken up by the treatment community. In addition, we observed a common, if unanticipated, theme that

links these analyses above and beyond their inclusion in the pathway from early study to diffusion. Namely, socioeconomic status appears to be a limiting factor in access to medical resources, be they clinical trial participation or new, proven treatments. Thus the findings are also highly topical, given the current emphasis in the public discourse about how disparities in economic resources may affect health and health care use. Most importantly, these investigations contribute to our understanding of the context and nuances of clinical trial results, and may therefore help improve the speed and efficiency with which new cancer treatments are translated into clinical practice.

5.1 REFERENCES

1. Green S, Benedetti J, Crowley J. Clinical Trials in Oncology. 2nd ed. CRC Press; 2003.

2. Unger JM, Hershman DL, Albain KS, Moinpour CM, Petersen JA, Burg K, Crowley JJ. Patient income level and cancer clinical trial participation. J Clin Oncol. 2013 Feb 10;31(5):536-42. doi: 10.1200/JCO.2012.45.4553. Epub 2013 Jan 7.

3. Ford JG, Howerton MW, Lai GY, et al. Barriers to recruiting underrepresented populations to cancer clinical trials: a systematic review. Cancer. 2008 Jan 15;112(2):228-42.

4. Javid SH, Unger JM, Gralow JR, et al. A prospective analysis of the influence of older age on physician and patient decision-making when considering enrollment to breast cancer clinical trials (SWOG S0316). The Oncologist. 2012 Jun 20. [Epub ahead of print]

5. Peppercorn JM, Weeks JC, Cook EF, Joffe S. Comparison of outcomes in cancer patients treated within and outside clinical trials: conceptual framework and structured review. *Lancet*. 2004;363(9405):263-270.

6. Edwards SJ, Lilford RJ, Braunholtz DA, Jackson JC, Hewison J, Thornton J. Ethical issues in the design and conduct of randomised controlled trials. *Health Technol Assess*. 1998;2(15):1-132.

7. Aday LA, et al. Evaluating the Healthcare System: Effectiveness, Efficiency, and Equity. 3rd Ed. Chicago: Health Administration Press, 2004.

ACKNOWLEDGEMENTS

First, I would also like to thank my parents, Mike and Cheri, for their support and encouragement over 5 years of both work and school.

I would also like to acknowledge and thank my Dissertation Committee. When you told me my dissertation was too ambitious, I should have listened.

I would like to thank my colleagues at SWOG, for their support.

I would like to thank my friends for not forgetting about me during my long absence.

I would like to thank my sisters, Rachel and Karen, for teaching me to work well with others.

I would like to thank my grandma, Margie, for the wonderful cookie recipe that saw me through several years of grind.

And finally, I would like to thank my nephews James and Alex, and my niece Kelly, for forgiving me for not visiting as much as I wanted to these past 5 years.