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Examining Stage at Diagnosis and Survival in Three Cancers with Definitive Screening Guidelines for Average-risk Adults: The Role of Marital Status

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A dissertation

presented to

the faculty of the Department of Biostatistics and Epidemiology

East Tennessee State University

In partial fulfillment

of the requirements for the degree

Doctor of Public Health with a concentration in Epidemiology

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by

David John Blackley

May 2013

_____

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Keywords: cancer, screening, survival, marital status

ABSTRACT

Examining Stage at Diagnosis and Survival in Three Cancers with Definitive Screening Guidelines for Average-risk Adults: The Role of Marital Status

by

David John Blackley

Each year there are more than 350 000 new cases and nearly 100 000 deaths attributed to colorectal, female breast, and cervical cancer in the United States. Screening tests can reduce morbidity and mortality associated with these cancers. Patient marital status has been associated with health outcomes, but no study has focused on the relationship of marriage with disease stage and survival for the 3 cancers with established screening guidance. It is critical to identify special populations that may be at risk for poor cancer outcomes.

The objective of this study was to examine the relationship of marital status with disease stage at the time of diagnosis and cancer-specific survival among population-based cohorts of patients diagnosed with invasive colorectal, breast, or cervical cancers. Subjects came from states or regions reporting to the Surveillance, Epidemiology, and End Results (SEER) tumor registries. The study included more than 243 500 patients diagnosed between January 1st 2004 and December 31st 2006 with 1 of these 3 cancers and who were followed for a minimum of 3 years. Descriptive statistics were calculated to summarize patient demographic and clinical characteristics. Baseline category logit models were fit to evaluate the association between marital status and disease stage. Kaplan-Meier survival curves and Cox proportional hazards models were developed to evaluate differences in patient survival across 4 marital status categories.

Married adults with colorectal, breast, and cervical cancer were diagnosed at an earlier disease stage than those who were divorced/separated, widowed, or single. After controlling for stage and demographic factors, married patients also experienced superior cancer-specific survival (range: 19-33% better) as compared to those in non-married groups.

Divorced/separated, widowed, and single adults are a subset of the population that may benefit from targeted prevention or care initiatives for cancers than can be detected early. Social support networks, selection effects, or other causal mechanisms likely moderate the protective association observed between marriage and cancer outcomes. These findings characterize a meaningful disparity in health outcomes. Additional person-level data on preventive health behaviors and treatment decisions could help solidify understanding of the issue and improve the ability to design effective research, interventions, and policy.

ACKNOWLEDGEMENTS

I'd like to thank my committee members--Deborah Slawson, Shimin Zheng, and James Anderson--for their guidance during the dissertation development process. I'd especially like to thank my chairman, Dr. Anderson, for his steady hand and thoughtful advice, and I wish him a happy and active retirement. I'd also like to express my sincere appreciation to 2 fellow students, Rachel Ward and Billy Brooks, for involuntarily serving as sounding boards for some of my early ideas. Finally, I'd like to thank the faculty and staff of the College of Public Health for fostering an environment that's gotten me interested in enough issues to keep busy for a lifetime.

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CHAPTER 1

INTRODUCTION

Burden of Cancer in the United States

Cancer is an ongoing public health problem in the United States (U.S.), and it is the second leading cause of death after heart disease. According to most recent estimates, there are about 1 640 000 new cancer cases and 577 000 cancer deaths in the U.S. each year.[1] Approximately 1 of every 4 deaths in the U.S. is a result of cancer, but it has been estimated that approximately one-third of these premature deaths could be avoided with proper adherence to screening recommendations.[2] Among males, lung/bronchus, prostate, and colorectal cancers account for about half of all incident cases; among females, lung/bronchus, breast, and colorectal cancers make up half of new cases.[1] Within the U.S. population, these 4 cancers account for about half of all deaths attributed to cancer, with lung cancer the leading cause of cancer death in males and females. Forty-five percent of males and 38% of females will be diagnosed with invasive cancer at some point in their lives, but females have a slightly higher likelihood than males of developing cancer before age 60 years due to breast cancer's tendency to be diagnosed at an earlier age relative to other cancer types.[1]

The U.S. population is likely experiencing its first sustained decline in overall cancer mortality since the 1930s. Among the U.S. male population, overall cancer incidence declined by an average of 0.6% per year between 1994 and 2008; an annual decline of 0.5% was observed among females until 2006, at which point the rate of decline moderated through 2008.[3] All-cancer mortality rates for both males and females appear to have peaked in the

early 1990s, and data suggest the annual decline in overall death rate was approximately 1.5% for both sexes from 2004 through 2008.[1,3] These decreases in the overall cancer death rate are likely a result of a variety of clinical and public health interventions and initiatives applied across the cancer continuum, including improvements in primary prevention, screening and treatment.[3] Incidence rates for 3 of the 4 leading tumor sites mentioned above have declined in recent years, with the lone exception being female breast cancer (Figures 1 and 2).[4] Research has linked changes in invasive female breast cancer incidence rates with variations in reproductive risk factors, mammography uptake and the prevalence of hormone replacement therapy among women.[3]

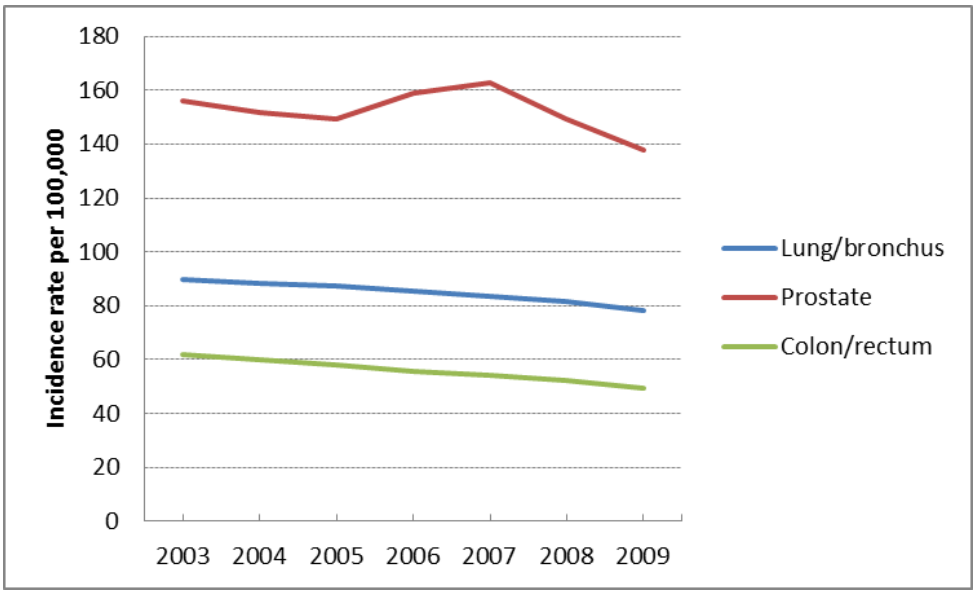


Figure 1: Age-adjusted incidence rates, lung/bronchus, prostate, and colorectal cancers diagnosed in males, all ages, United States, 2003 through 2009

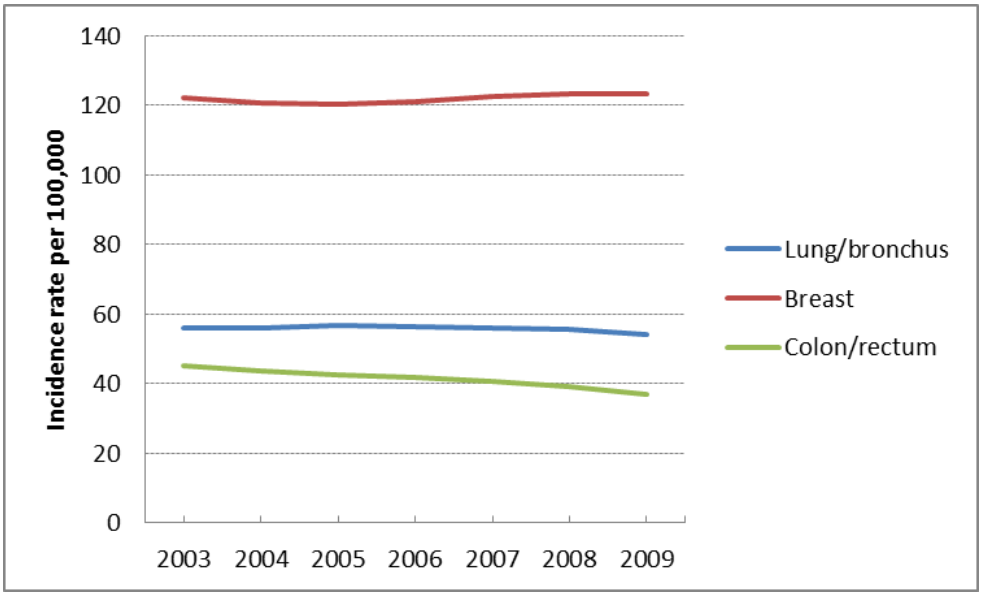


Figure 2: Age-adjusted incidence rates, lung/bronchus, breast, and colorectal cancers diagnosed in females, all ages, United States, 2003 through 2009

Reductions in lung cancer incidence are associated with historical declines in smoking prevalence, and declines in colorectal cancer incidence are partially attributed to improved uptake of endoscopic and radiologic screening methods capable of detecting, and then removing, precancerous growths.[5] Mortality rates for lung/bronchus, breast, colorectal, and prostate cancers are all decreasing (Figures 3 and 4), with reductions in lung cancer deaths accounting for 34%-40% of the overall decline, with slight variation by sex.[1,6] Among women substantial reductions in breast and colorectal cancer death rates account for more than half of the reduction in overall cancer mortality observed in recent years.[5,7] Among young men leukemia is the most common cause of cancer death, with lung cancer the leading cause after age 40 years. In women leukemia is the leading cause of cancer death until age 20 years, breast cancer between 21 and 59 years, and lung cancer after age 60 years.[1]

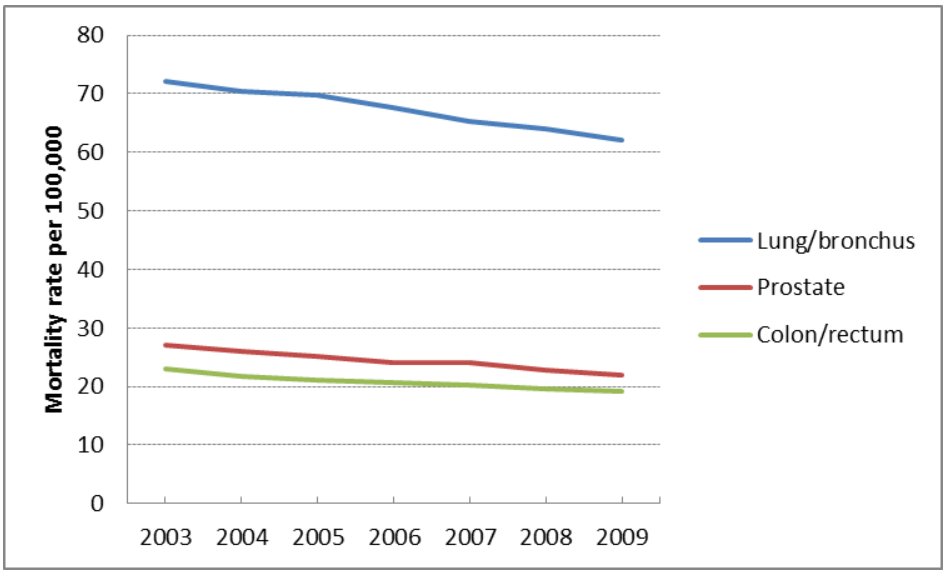


Figure 3: Age-adjusted mortality rates, lung/bronchus, prostate, and colorectal cancers diagnosed in males, all ages, United States, 2003 through 2009

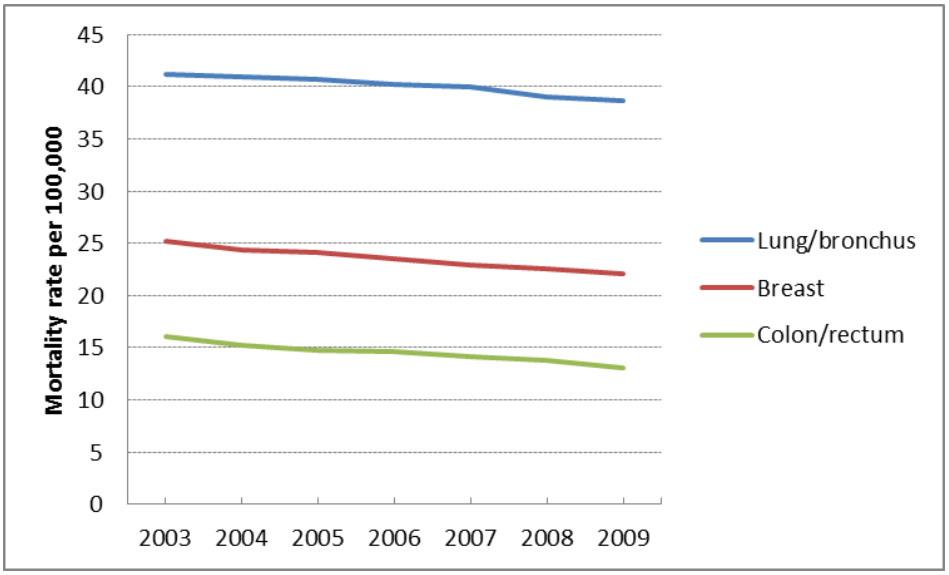


Figure 4: Age-adjusted mortality rates, lung/bronchus, breast, and colorectal cancers diagnosed in females, all ages, United States, 2003 through 2009

Cancer Disparities in the United States

There are large regional differences in overall cancer incidence and mortality in the U.S., and of the major tumor types, lung cancer has the most notable geographic variation.[1,8]

Regional variations are less pronounced for other tumor types, and for cancer that can be detected early, state-to-state differences in incidence and mortality usually reflect variations in screening uptake, although this doesn't entirely explain variations in rates.[1] In addition to region of residence, race/ethnicity is also associated with differences in population cancer outcomes. In the U.S. black men are 15% more likely than white men to get cancer, and 33% more likely to die from it; black women are 6% less likely than white women to get cancer, but 16% more likely to die from it.[1] Factors potentially contributing to disparities along racial lines vary by cancer type but may include differences in risk factor exposures, screening access, and timely and appropriate diagnosis and treatment.[9] Cancer incidence and mortality among smaller minority groups in the U.S. is lower than in non-Hispanic whites and blacks for most cancer types, with the exception of those frequently associated with infectious agents, such as cancers of the cervix, stomach, and liver.[1]

For lung/bronchus, prostate, colorectal, and breast cancers combined, African Americans are more likely than non-Hispanic whites to have regional or distant stage disease at diagnosis, most likely predisposing this minority group to a poorer prognosis before treatment can even be initiated.[10] For nearly every cancer type, 5-year survival is lower among African Americans than non-Hispanic whites independent of stage at diagnosis, which may be explained by racial disparities in access to care or differences in the presence of comorbidities and/or behavioral risk factors. Although disparities remain, both African Americans and whites have experienced marked improvements in 5-year cancer survival since 1975, which are likely a result of improved early detection and more effective cancer-directed treatments.[1] Two prominent cancers that have shown little-to-no improvement in 5-year survival rates in recent

years are lung/bronchus and pancreatic cancers, neither of which has widely accepted early detection methods.

Significance of Research

Survival following a cancer diagnosis largely depends on intrinsic tumor characteristics; however, socioeconomic, cultural, and demographic factors may also influence survival to varying degrees.[11] For cancers with definitive, evidence-based screening recommendations, it is critical for researchers and clinicians to be able to identify populations that may be at risk for presentation with advanced tumor stage and lower survival relative to the general population. National expert panels clearly recommend and provide evidence-based guidance for screening among average-risk adults for colorectal cancer, female breast cancer, and cervical cancer. These recommendations are based on peer-reviewed science demonstrating that proper screening for these cancers reduces morbidity and mortality.[12] The primary goal of this dissertation is to examine the association of patient marital status with tumor stage at diagnosis and survival for the 3 cancer types that have well established screening recommendations for the average-risk population. Research has identified an association between marital status and survival for multiple types of cancer, but results have not been entirely consistent. Given the dynamic nature of the institution of marriage (and its varying connotations and inherent responsibilities, depending on country of residence), many past findings may not be generalizable to the contemporary U.S. general population, because many of the studies were conducted in Europe and most are more than a decade old (and use data that are decades older still).[13]

No population-based study of marital status' association with tumor stage at diagnosis and survival has been conducted for the 3 cancers with established expert panel screening recommendations for the average-risk U.S. adult population. Developing clear and up-to-date information on these associations for each of the 3 cancers in population-based U.S. cohorts could increase our understanding of factors that may be associated with the risk of adverse prognoses and outcomes. These findings have the potential to improve the knowledge base necessary to appropriately design, implement, and evaluate cancer prevention and control efforts.

Research Aims

Research Aim #1: Assess differences in tumor stage at diagnosis and survival according to marital status among a population-based cohort of males and females diagnosed with invasive colorectal cancer between January 1st 2004 and December 31st 2006, while accounting for relevant demographic and clinical characteristics.

Research Aim #2: Assess differences in tumor stage at diagnosis and survival according to patient marital status among a population-based cohort of females diagnosed with invasive breast cancer between January 1st 2004 and December 31st 2006, while accounting for relevant demographic and clinical characteristics.

Research Aim #3: Assess differences in tumor stage at diagnosis and survival according to patient marital status among a population-based cohort of females diagnosed with invasive cervical cancer between January 1st 2004 and December 31st 2006, while accounting for relevant demographic and clinical characteristics.

CHAPTER 2

LITERATURE REVIEW

Screening for Cancer

Effective cancer screening detects disease prior to clinical signs or symptoms.[14] Two necessary but not independently sufficient criteria for a screening modality to be considered effective are that it must identify cancer before it's detectable based on symptoms alone, and that treatment undertaken as a result is likely to elicit an improved outcome relative to if the cancer was discovered under normal circumstances.[2] Cancers amenable to screening should generally be diagnosed at an earlier stage and show an associated improvement in survival prognosis.[15] A disease-specific mortality reduction in a randomized, controlled prospective trial is the strongest form of evidence supporting the candidacy of any proposed screening modality.[16] Additionally, declines in overall mortality and incidence, improvements in tumor stage distribution, and reduced disease-related morbidity may also be considered when weighing the benefits and harms of cancer screening. At the population level, appropriate screening for colorectal, female breast, and cervical cancers reduces mortality from these diseases.[17]

The American Cancer Society (ACS) and the U.S. Preventive Services Task Force (USPSTF) develop and regularly update cancer screening recommendations, and guidance from these organizations is widely viewed as gold standards for cancer screening in the United States. Since 1980 the ACS has updated and published evidence-based guidelines and recommendations to foster informed decision-making on screening for cancers of the

colon/rectum, cervix, breast, prostate, endometrium, and most recently, lung. The ACS, in collaboration with outside experts, monitors the scientific literature on a continuous basis, and generally reviews and/or updates cancer screening guidance every 5 years, with summary reviews published annually.[12]

The USPSTF, formed in 1984 by the Public Health Service and formally supported by the Agency for Healthcare Research and Quality (AHRQ) since 1998, also publishes widely-adopted evidence-based cancer screening guidance. Public Law 106-129 mandates that USPSTF provide up-to-date scientific reviews to support evidence-based recommendations for preventive services, including cancer screening.[18] A screening method's benefits must outweigh its harms, among other criteria, in order for USPSTF to provide a recommendation. For the most part, USPSTF's recommendations closely resemble those made by ACS, although USPSTF guidance tends to be slightly more conservative (i.e. restrictive) with respect to upper and lower limits for age groups and recommended screening frequencies.

Based on the most recent ACS and USPSTF guidance, only 3 cancer sites--colon/rectum, female breast, and uterine cervix--have unequivocal screening recommendations for average-risk U.S. adults.[12,18] In 2009, 351 706 new cases of these cancers (133 160 colorectal cancers , 206 447 female breast cancers, and 12 099 cervical cancers) were diagnosed in the U.S. and during 2008 there were 97 454 deaths due to these 3 diseases, a large proportion of which could have been detected early or entirely prevented.[4] It has been estimated that anywhere from 3% to 35% of these premature cancer deaths could have been averted through proper use

of screening tests.[2] Table 1 presents the ACS's 2013 estimations for new cases and deaths from colorectal, female breast, and cervical cancers, as well as all cancers combined.[19]

Table 1: Estimated number of new invasive cases and cause-specific deaths, selected cancer sites, United States, 2013

Tumor Site		New cases	Deaths
Colon and rectum	Male	73 680	26 300
	Female	69 140	24 530
Breast (female only)		232 340	39 620
Cervix		12 340	4 030
All cancers combined	Male	854 790	306 920
	Female	805 500	273 430

Source: Siegel R, Naishadham D, Jemal A. Cancer statistics, 2013. *CA: a cancer journal for clinicians*. 2013;63(1):11-30.

Although screening for colorectal, female breast, and cervical cancer is clearly recommended for average-risk adults, each of these screening methods has distinct age, sex and frequency guidelines, which may differ based on which of the 2 organizations is making the recommendations. In addition, there are certain risks and benefits associated with each screening method that a patient should discuss with a clinical provider prior to having the screening.[12] Cancer screening should be viewed as a process rather than a series of isolated procedures, with multiple steps and points of contact between healthcare organizations,

clinicians, and patients.[17] Any disruptions of this process could lead to a failure to detect cancer and increase the likelihood of potentially avoidable morbidity and mortality. A recent literature review of cancer screening found that half of all cervical cancers are diagnosed in women who haven't kept up-to-date with screening, and half of all older women diagnosed with advanced breast cancer have never had a mammogram.[17] In addition, poor adherence to screening guidance likely contributes to the high levels of colorectal cancer mortality in populations with low socioeconomic status.[20]

Screening Guidance for Colorectal Cancer

ACS and USPSTF colorectal cancer screening recommendations for average-risk adults were each last updated in 2008. Both organizations recommend average-risk men and women begin screening at age 50 years. USPSTF recommends ceasing screening at age 75 years, while ACS does not define an upper age limit in its guidelines. There are several different colorectal cancer screening modalities garnering recommendations, which can be divided into 2 general categories: 1) tests that are capable of detecting cancer (includes fecal blood and DNA tests), and 2) tests than are capable of detecting cancer and advanced adenomatous polyps (includes endoscopic and radiological procedures).[12] The distinction between these 2 categories is provided to emphasize that prevention of colorectal cancer, and not just early detection, is possible, although modalities in each group have unique strengths and weaknesses that should be considered prior to choosing a screening method. ACS and USPSTF recommend an average-risk adult undergo one of the following: colonoscopy every 10 years, fecal occult blood test (FOBT) every year, or a flexible sigmoidoscopy every 5 years in conjunction with FOBT (every

year per ACS guidance and every 3 years per USPSTF). ACS approves additional alternatives, including double-contrast barium enema every 5 years or CT colonography (virtual colonoscopy) every 5 years.[12,21] USPSTF does not provide guidance on the use of barium enema or CT colonography. In 2010, 17.2% of U.S. adults age 50 years and over reported having had a blood stool test in the past 2 years, and 65.2% reported ever having a sigmoidoscopy or colonoscopy.[22] As of 2010, 58.3% of U.S. adults aged 50 to 75 years were currently meeting USPSTF guidelines for FOBT, colonoscopy, or sigmoidoscopy (95% CI 57.0-59.6).[23] In a British population, van Jaarsveld and colleagues reported that married adults were 23% more likely than non-married adults to report screening for colorectal cancer, and that inviting both members of a married couple to screen together further increases uptake.[24] Among 21 760 U.S. adults aged 50 to 85 years, Stimpson et al found that married individuals were 21% more likely than the unmarried to report ever having colorectal endoscopy (sigmoidoscopy, colonoscopy, or proctoscopy) and 49% more likely to report having an endoscopy during the 10 previous years.[25]

Screening Guidance for Female Breast Cancer

The ACS breast cancer screening recommendations for average-risk adult females were last updated in 2003; USPSTF recommendations were last updated in 2009. USPSTF recommends average-risk women start with screening mammography every 2 years beginning at age 50 years, and continue through age 74 years. ACS recommends average-risk women start with clinical breast examination (CBE) as part of periodic health exam (at least every 3 years) during their 20s and 30s. ACS guidance supports beginning annual mammography at age

40 years, in conjunction with annual CBE, as part of a regular preventive health appointment. ACS does not include an upper age limit for mammography in average-risk women.[12,26] In 2010, 75.2% of American women age 40 years and over, and 77.9% of women age 50 years and over reported having had a mammogram within the past 2 years.[22] Coughlin et al examined data on U.S. women age 40 years and over residing in metropolitan areas, and in unadjusted analysis found that currently married or cohabitating women (80.4%) were more likely than divorced/separated (75.5%), widowed (77.6%) and never married women (72.7%) to report receiving a mammogram in the previous 2 years.[27] The 95% confidence intervals for the married/cohabitating compared to the marriage status groups showed statistical significance ($p < 0.05$).

Screening Guidance for Cervical Cancer

The ACS cervical cancer screening recommendations for average-risk female adults were last updated in 2002; USPSTF recommendations were last updated in 2012. USPSTF and ACS both recommend women start screening for cervical cancer by age 21 years. USPSTF recommends a Papanicolaou (Pap) test every 3 years for women age 21 years to 65 years, or a Pap test/human papilloma virus (HPV) DNA test every 5 years for women age 30 years to 65 years. USPSTF doesn't recommend screening beyond age 65 years for women who have stayed current with appropriate screening, or for women who have had their cervix surgically removed. ACS recommends screening women with conventional Pap tests every year, or every 2 years if using liquid-based Pap tests. Upon reaching 30 years of age, ACS recommends women with 3 consecutive normal test results shift to a Pap test (either method) every 2 to 3

years, or every 3 years if a Pap test is done in conjunction with a HPV DNA test. ACS suggests halting screening in women over age 70 years who have had 3 consecutive normal Pap tests and no abnormal results during the previous 10 years, or women who have had their cervix completely removed.[12,28] In 2010, 81.3% of U.S. women age 18 years and over reported having had a Pap test in the past 3 years.[22] Coughlin et al examined data on self-reported rates of Pap testing among American women age 18 years and over living in metropolitan areas, and found in multivariate analysis that divorced/separated and widowed women were approximately 30% less likely to report a Pap test during the previous 3 years than those who were currently married or cohabitating (OR=0.72, 95% CI 0.61-0.85 for divorced/separated and OR=0.69, 95% CI 0.56-0.84 for widowed). Never-married women were much less likely than the currently married or cohabitating to report a Pap test in the previous 3 years (OR=0.29, 95% CI 0.25-0.34).[29] Hewitt et al examined a separate, nationally representative sample and came to a similar conclusion. In adjusted analysis, they found that formerly married women between the ages of 25 and 64 years were 25% less likely than currently married women to report a Pap test during the previous 3 years, and never married women were half as likely to report screening. The positive association between marriage and reported cervical cancer screening was even more pronounced in women 65 years of age and older.[30] Table 2 presents a summary of the prevalence of adults in the U.S. who report being 'up-to-date' with recommended evidence-based clinical preventive cancer guidelines, per the recommendations of 2 leading organizations.

Table 2: Prevalence (%) of U.S. adults up-to-date[a] with recommended cancer screening per U.S. Preventive Services Task Force (USPSTF) and American Cancer Society (ACS) guidance, 2010, with comparison to Healthy People 2020 goals[b]

	U.S. Preventive Services Task Force	American Cancer Society	Healthy People 2020 target
Colorectal cancer	58.6 (57.3-59.9)*	59.1 (57.9-60.3)	70.5
Breast cancer (female)	72.4 (70.7-74.0)	51.0 (49.6-52.4)	81.1
Cervical cancer	83.0 (82.0-84.0)	76.4 (75.4-77.4)	93.0

* % (95% confidence interval)

[a] Up-to-date according to most recent published USPSTF and ACS guidance

[b] Healthy People 2020 Goals screening prevalence goals refer to USPSTF recommendations

Although cancer develops within an individual person, its development is not independent of external factors. Decades of scientific literature have suggested that both patient-level and environmental factors can influence tumor characteristics and cancer outcomes.[31] Important factors directly affecting cancer survival, such as tumor stage, grade and lymph node involvement, are fundamental to the disease itself; other factors associated with survival may be external in nature.[13] Research exploring the determinants of disparities in stage at diagnosis and survival for various cancers has identified socioeconomic, cultural, geographic, biomedical, and genetic factors as associated with variations in outcomes across different population groups. Survival data broken down by racial and/or ethnic groups have

played an essential role in helping clinicians and public health researchers identify at-risk populations that may not be receiving adequate attention with respect to preventing and treating cancers that can be detected early.[15] It is also important to identify clinical and socioeconomic characteristics that may contribute to disparate survival patterns across groups, so as to improve the reach and cost-effectiveness of public health interventions.

Marriage in America

Marriage, and the responsibilities and expectations it entails, has different meanings in different contexts. Family structure norms in the U.S. have undergone radical change in recent decades. Economic and cultural forces have shifted societal standards for marriage, divorce, cohabitation, childbirth, sexual behavior, and women's roles in the home and workplace.[32] Nearly all Americans still consider marriage and married life the ideal family structure, but the institution is increasingly perceived as optional, and the notion of traditional marriage as a dominant family and social structure has been on the decline for decades.[32,33] Residents of the U.S. have an increasingly broad definition of what constitutes a 'family,' and nearly all adults cite their own family, in whatever form it takes, as the most important aspect of their lives. In recent decades, there has been a sharp decline in the proportion of American adults who are married, a trend shaped by opinions, attitudes, and behaviors that vary by age, race/ethnicity, and class. Fifty-one percent of all adults living in the U.S. are currently married, the lowest proportion in recorded domestic history. In 1960, 72% of U.S. adults were married.[34] The median age at first marriage in U.S. men (28.7 years) and women (26.5 years) has never been higher than it is now.[32,35] Researchers have observed declines in marriage rates among all age

groups, but these are most pronounced in the younger population, with only 20% of adults age 18 to 29 years currently married compared to 59% in 1960.[35] It is still impossible to know whether contemporary young adults are simply delaying marriage or increasingly abandoning it altogether, but contrary to widespread opinion, there is historical precedent for a reversal in the slope of the marriage curve.

Current social commentators, many of whom grew up in 1950s post-war America, often refer to that era as the normal "baseline" for the prevalence of marriage. However, average age at first marriage (for men and women) was at an historic low in the 1950s and is an anomaly compared to other time periods.[32] This does not diminish the cultural significance of the shifts observed in recent years. An increasingly egalitarian labor division has emerged between men and women, conferring new societal and individual benefits, as well as stressors.[33] Young adults, both married and unmarried, now have expanded options for housing, employment and education. The unmarried are currently much more likely than in the past to live alone, which could signify a major shift in the composition of important social support systems.[32] Childless unmarried cohabitation, as well as single-parent childrearing, has also become more prevalent, and decades of data suggest these trends are not related to economic cycles.[35] About half of U.S. adults cohabitate prior to nuptials, and increasingly, this arrangement evolves into an permanent informal substitute for marriage.[32] In a recent survey, nearly 40% of Americans said marriage is becoming obsolete, but more than 60% of the unmarried individuals in the same sample said they would like to marry someday.[35] Along with never-married adults, American communities have become increasingly supportive of single parents and divorcees.[33]

Although the broad societal trend has been towards a reduction in the overall prevalence of marriage, some researchers have identified the emergence and growth of a so-called "marriage gap" in America.[34] This "gap" exists between groups defined by race, income, and education. As of 2010, 51% of all U.S adults were married, 14% were divorced or separated, 6% were widowed, and the remaining 28% were never married. However, when stratified by race, 55% of white, 48% of Hispanic, and only 31% of black adults were married.[35] This gap is increasingly aligned with growing income disparities in the country.[34] The recent decline in the marriage rate has been much less precipitous among those with college educations, with current college graduates 17% more likely to be married than those with a high school education or less.[35] These underlying trends have led some to label this phenomenon as a "class-based" decline in marriage, highlighting systemic influences on the role of marriage in our society.[34] It has been hypothesized that additive effects of these complex societal changes, compounded over time, may be contributing to expanding mortality inequalities observed between married and unmarried populations.[33] Recent opinion polls asking about the acceptability of emerging nontraditional family structures found that the young were more accepting than the old, political liberals were more accepting than conservatives, and the secular were more accepting than the religious. Women have essentially achieved parity with men with respect to overall workforce composition and educational achievement, so it will be interesting to monitor how sex interacts with class-based variables to influence marriage trends.[34]

Recent declines in marriage rates have been substantial, but Americans are still more favorably inclined to marriage than residents of other developed countries.[32] Although

marriage rates are higher in the U.S. than in Europe and first world nations, the U.S also has substantially higher divorce rates, although these have diminished over the last 20 years after climbing consistently during the 1960s and 1970s.[35] One-third of marriages starting in the 1950s ultimately ended in divorce, compared to almost half in recent years; the nation has experienced something resembling a left-skewed bell curve over the past 60 years with respect to divorce rates.[32] Although the general public no longer sees marriage as the only path to a happy family life, or as a sacrament that can only be broken in extremely rare circumstances, the institution will no doubt continue to be promoted as a preferred lifestyle, both explicitly and implicitly.[33,34] Major religious institutions continue to promote marriage as the ideal family structure, and the U.S. Federal government has formally endorsed marriage in legislation. The Personal Responsibility and Work Opportunity Reconciliation Act of 1996, passed by the 104th Congress and signed by President Bill Clinton, clearly identified marriage as a foundation and essential institution of a successful society.[36]

Marital Status, Cancer Stage at Diagnosis, and Survival

Many researchers have identified an association between marital status and overall mortality. A recent international meta-analysis designed to estimate excess mortality in unmarried elderly individuals showed an overall relative risk of 0.88 [95 % CI: 0.85-0.91] in the married compared to the non-married, with minimal variation when results were stratified by sex.[37] The researchers found some evidence of publication bias, but ultimately their overall estimate was consistent across several methodological approaches and sensitivity analyses. It has been suggested that the protective association between marriage and mortality is likely a

result of enhanced support networks inherent to married and family life as well as the generally high regard for married relationships in modern Western society.[33] While this association has been documented in the U.S. and Europe for both overall and disease-specific mortality in past decades, the institution of marriage and its defining characteristics has undergone substantial change in recent years, with modern society becoming increasingly accepting of never-married adults, single parents, and divorcees.[33,38-40] Americans across the socioeconomic spectrum still view marriage as the ideal family structure, but increasingly this belief does not translate itself into practice.[32]

In 1987, Goodwin et al were among the first to identify a favorable association between marital status and likelihood of cancer diagnosis, treatment, and survival using population-based data.[41] It was already widely accepted that married individuals tended to live longer and experience lower all-cause mortality, but Goodwin and colleagues demonstrated that unmarried cancer patients were more likely to be diagnosed at an advanced tumor stage, more likely to remain untreated, and prone to poorer overall survival. Their approach of controlling for beneficial factors at the diagnostic, treatment, and response stages highlighted marriage's positive and independent influence at multiple stages of the disease process. The findings of this study will be discussed further in subsequent sections.

Most research focused on specific cancer types has found a protective effect of marriage, with cancer generally diagnosed at an earlier stage, and patients more likely to receive recommended therapy, but population-based research has also demonstrated conflicting findings about the association between marital status and stage, treatment, and/or

survival.[38,40] In fact, 2 separate research groups analyzed recent population based cancer registry data on bladder cancer patients, and arrived at contradictory conclusions.[11,13] Both studies examined outcomes in bladder cancer patients from the same nationally representative cancer registry during nearly identical timeframes (those diagnosed between 1973 and 2000 in the Gore study, 1973-2002 in the Nelles study), but Nelles considered all bladder cancer patients (n=127 015) while Gore restricted analysis to those who'd had radical cystectomy for transitional cell carcinoma of the bladder (n=7 262). Gore et al found that being married was associated with improved survival from bladder carcinoma relative to unmarried patients, independent of multiple factors known to influence survival, such as stage at diagnosis, gender, age, and race/ethnicity. In contrast, Nelles et al analyzed population-based data from the same registries and found that marriage did not seem to confer a definitive survival advantage for bladder cancer patients after controlling for relevant confounders. The differences observed in seemingly similar patient populations could be due in-part to potential lead time bias in Gore's subset population. There may be no true bladder cancer outcome benefit conferred by marital status, but married patients may be more likely to undergo cystectomy early, creating the illusion of longer survival when they could simply be experiencing better post-procedure survival. Nelles et al stratified their population to try to detect this same effect among those who'd had a cystectomy, but no such association was detected. Another factor potentially influencing this observed difference for the same tumor type was that Gore and colleagues considered overall survival, while Nelles et al calculated cancer-specific survival (death from any cancer). In other words, the marriage-survival benefit observed by Gore may have been

accounted for by deaths from 'other causes' in the non-married subsets of their bladder cancer patient populations.

Marital Status and Colorectal Cancer

In 1987 Goodwin et al were among the first to study the association between marital status and stage, treatment, and survival in patients diagnosed with cancer. They examined tumor registry data representing all Hispanic and non-Hispanic white New Mexico adults (age 20+ years) diagnosed between 1969 and 1982. They separated cancers of the colon and rectum for statistical analysis and found that unmarried patients had slightly higher likelihood of nonlocal (regional or distant) disease at diagnosis for both cancers, but the odds ratio was not statistically significant. After controlling for tumor stage at diagnosis, unmarried rectal (but not colon) cancer patients were significantly less likely to receive definitive treatment. Upon controlling for stage and treatment, unmarried colon cancer patients had a significantly elevated risk of death (RR=1.27, 95% CI 1.11-1.45), but risk was not elevated in rectal cancer patients (RR=0.97, 95% CI 0.84-1.28).[41] In 1996 Johansen et al studied a cohort of Danish patients diagnosed with colon or rectal cancer between 1968 and 1972, which allowed for follow-up of more than 2 decades. Of the 7 302 individuals eligible for the study, married colon cancer patients demonstrated significantly better 5-year survival than unmarried patients, even after controlling for extent of disease (RR=0.85, 95% CI 0.78-0.93), but there was no survival difference observed in rectal cancer patients in the same cohort.[42] In 2010 Lai et al analyzed the association between marital status and stage and diagnosis and survival in 72 214 U.S. colon (rectum excluded) cancer patients (adults age 50 to 75 years) diagnosed between 1992

and 2003. After adjusting for stage at diagnosis, they found that single patients had a 23% higher risk of death compared to married patients, but this elevated risk was less pronounced among widowed, separated, and divorced patients. Unmarried patients were also more likely than married patients to be diagnosed with advanced stage colon cancer. The apparent survival benefit in married individuals diminished once researchers controlled for stage at diagnosis in survival models, suggesting that the protective benefit of marriage on cancer survival may be explained in-part by its impact on stage at diagnosis.[43] In 2011 Wang et al examined this association in a U.S. population, again only in colon cancer patients. They analyzed national data on 127 753 patients diagnosed with colon cancer between 1992 and 2006 and found that married patients were more likely to be diagnosed at an earlier stage compared to single, separated, and divorced patients, and they were more likely to receive definitive surgery than all unmarried (including widowed) individuals. Controlling for age, race, tumor stage, and receipt of surgery, married colon cancer patients had lower risk of death than single patients (hazard ratio (HR) in males, 0.86, 95% CI 0.82-0.90; in females, HR 0.87, 0.83-0.91).[38]

Marital Status and Female Breast Cancer

Goodwin and colleagues also examined the effect of marital status on female breast cancer survival. They found that unmarried women had an increased likelihood of nonlocal disease at the time of diagnosis (OR 1.24, 95% CI 1.09-1.42) and of failing to receive definitive treatment (OR 1.34, 95% CI 1.02-1.76). However, after controlling for these 2 factors, there was no association between marriage status and risk of death in female breast cancer patients

(RR 1.03, 95% CI 0.92-1.16).[41] In 2005, Osborne at al published nationally representative data on U.S.-resident women diagnosed with breast cancer between 1991 and 1995. Of the 32 268 women age 65 years and older in the study population, unmarried women were more likely than married to be diagnosed with late-stage (II-IV) cancer compared to early stage (I or in situ) cancer (OR 1.17, 95% CI 1.12-1.23). Unmarried women with early stage disease were also less likely than married women to receive definitive treatment. Upon controlling for stage at diagnosis and treatment received, unmarried women were 25% more likely than married women to die from breast cancer during the study period (95% CI 1.14-1.37). These data were linked with Medicare records, which increased the amount of individual-level data available for each patient. However, within this large cohort, patient socioeconomic status and comorbidities ultimately had minimal impact on the independent association between marital status and breast cancer survival.[44]

Marital Status and Cervical Cancer

Goodwin et al also examined data on New Mexico's Hispanic and non-Hispanic white women diagnosed with cervical cancer between 1969 and 1982, and found a marginally significantly increased likelihood of nonlocal disease at time of diagnosis in the unmarried (OR 1.35, 95% CI 1.00-1.84). However, after controlling for stage at diagnosis, unmarried women were much less likely than married to receive definitive treatment for cervical cancer (OR 3.41, 95% CI 1.77-6.55). Finally, when controlling for stage at diagnosis and receipt of treatment, there was no statistically significant difference in risk of death between married and unmarried women (RR 1.25, 95% 0.96-1.60).[41] In 1990, Murphy et al published research examining

survival among 1 728 women in southeastern England diagnosed with cervical cancer between 1972 and 1981. Although the researchers observed an apparent difference in crude survival by marital status, this difference was accounted for after controlling for variations in age and stage by marital status, at which point it became clear that there was no significant difference in survival by marriage category.[45] In 2010 Patel et al similarly found that among 7 997 women in a nationally-representative U.S. sample of patients diagnosed with cervical cancer between 1992 and 1996, being married initially seemed to be associated with better 5-year survival among the married compared to the unmarried. However, this advantage vanished once the researchers corrected for tumor stage at diagnosis and receipt of definitive treatment, suggesting that marriage's role may be more pronounced in the portion of the cancer continuum associated with early diagnosis and/or treatment decisions. In other words, most of the observed survival benefit in this married population could be attributed to earlier stage at diagnosis and/or higher likelihood of receiving radiation therapy.[46]

Mechanisms Potentially Explaining the Association

Several mechanisms have been suggested to explain the association between marriage and improved cancer outcomes, but the *selection effect* and *social causation* are 2 theories frequently mentioned in the literature.[33,38,40] The selection effect, sometimes called *health selection* or *marriage selection*, is based on the premise that healthy people may be more likely than unhealthy people to get and stay married.[33,38] In other words, good health may not be a result of being married, but rather, marriage a result of good health.[38] Kaplan et al suggested that those who are seriously ill, or more likely to become seriously ill, may be perceived by

others as less suitable marriage partners than those with a history of good health. Their findings offer support for this idea, because within the population they studied, the disadvantageous association between marriage status and mortality was stronger in those who were never married than in those who had been married but had divorced or been widowed at a later date.[47]

Social causation is the idea that social networks, or in this case marriage and the close familial bonds that commonly come with it, provide important emotional support, cultivate positively influential relationships, and encourage healthful behaviors.[33,38] In as much as these benefits are gained through transition into the married state, it has also been suggested that loss of some of this support system, whether through divorce or widowing, could increase risk of cancer-related morbidity and mortality.[33] In a more tangible sense, encouragement from a spouse may influence someone to elect to undergo screening, or pursue a more aggressive treatment, which could advantageously influence stage at the time of diagnosis and survival respectively.[38] In those who've been diagnosed with a potentially treatable cancer, the presence and support of a spouse may convince them that there is "more to live for."

The Surveillance, Epidemiology, and End Results (SEER) Program

The Surveillance, Epidemiology, and End Results (SEER) program collects data from tumor registries across the U.S. SEER is a standard of quality in the field of cancer outcomes research and is the definitive source for population-based cancer incidence and survival data in the United States.[38,48] SEER disseminates population-based cancer data on patient demographics, tumor site and morphology, extent of disease and treatment course, with

follow-up to monitor vital status.[49] The broad goals of the SEER Program are 4-fold: 1) report regularly and accurately on U.S. cancer incidence, mortality, prevalence, and survival, 2) identify and monitor unusual cancer incidence trends in demographic and geographic subpopulations, 3) report on trends in cancer stage at diagnosis and treatment/therapy decisions, and 4) encourage research that promotes identification of factors to improve effectiveness of comprehensive cancer control initiatives.[49] The SEER Program is financially supported by the National Cancer Institute (NCI) and the Centers for Disease Control and Prevention (CDC). SEER's Public Use Database is maintained by personnel from NCI's Division of Cancer Control and Population Sciences, Surveillance Research Program, Cancer Statistics Branch.[40,48]

In 1971 the National Cancer Act established the authority to collect, analyze, and share national data relevant to cancer prevention, diagnosis, and treatment.[49] In early 1973 the SEER program started collecting data in 5 states and 2 metropolitan areas, and it has since expanded to include tumor registries around the country. SEER now reports cancer-related data for residents of Connecticut, Hawaii, Iowa, New Mexico, Utah, California, Georgia, Kentucky, Louisiana, New Jersey, the Detroit and Seattle/Puget Sound metropolitan areas, and Alaska Natives and American Indians in Arizona.[48] Participating SEER regions and states were chosen because they contained epidemiologically important and/or representative population groups and possessed the capacity to maintain a population-based tumor registry system and regularly report accurate data. Currently, SEER-participating registries collect and report cancer-related data covering 28% of the U.S. population, with some oversampling for recognized racial/ethnic minorities. Seventy-one percent of Hawaiian/Pacific islanders, 54% of Asian Americans, 43% of

American Indians/Alaska natives, 41% of Hispanics, and 26% of African Americans residing in the country are covered by SEER-participating registries. As of the most recently reported diagnosis year, SEER registries have reported detailed information on more than 7 million diagnosed cancer cases, with cases diagnosed since 2001 having tumor site and histology coded according to International Classification of Diseases for Oncology, third edition (ICD-O-3) standards.[49,50]

Collectively, the sub-populations comprising the SEER registries are nearly identical to the broader U.S. population with respect to education and poverty levels, but the SEER population has a higher proportion of foreign-born (17% vs. 11%) and urban (88% vs. 79%) participants than the broader populace.[48] State and regional registries participating in SEER report all incident cancers diagnosed in their geographic areas each year.[49] Participating registries regularly conduct both passive and active cancer case follow-up; patient vital status is verified through state and national death records, Health Care Financing Administration and Social Security Administration files, voting, credit, and driver license records, and hospital/physician records.[15] The SEER Program complements these data with annual mortality reports from the National Center for Health Statistics (NCHS). NCHS data include information on deceased individuals in the geographic areas of interest, including age, sex, and underlying/contributing causes of death.[49] To assure accurate reporting of cancer incidence and outcomes, SEER allows 22 months to elapse between the end of a diagnosis year and the time of report to NCI. With each annual spring data release, existing case records from previous years are updated if new patient information is available or entirely new diagnoses from that time period (i.e. missed cases) are reported to registries. Historically, an initial annual

SEER case count is about 2% below the total count that will eventually be registered for that year.[49]

Cancer Staging in SEER

Extent of disease at the time of diagnosis is an important determinant of cancer treatment course and is often a useful outcome predictor. Two prominent cancer staging systems used in the U.S. include the American Joint Committee on Cancer's (AJCC) *Cancer Staging Manual,* commonly referred to as the TNM (tumor-node-metastasis) System, and the Summary Staging System.[51] The AJCC-maintained TNM System is predominantly used by clinicians, with the 'tumor' component describing the invasiveness and size of the primary tumor, the 'node' component describing the presence or absence of the cancer in nearby lymph nodes, and the 'metastasis' component indicating whether or not there are distant metastases and/or distant lymph node involvement.[52]

The SEER Program has developed a modified version of the Summary Staging System, made possible through its consistent documentation of various characteristics relevant to extent of disease. Data on extent of disease are more specific than stage alone, which allows a cancer staged in the SEER system to remain comparable across multiple generations of AJCC stage definitions.[53] This characteristic of the SEER system is well suited to its primary use, because SEER staging is used for population-based longitudinal research, while AJCC staging is more commonly used in the clinical setting to inform decisions related to individual patient prognosis. SEER staging can be used for all solid tumors but not for leukemias. It combines information from medical records, clinical findings, and pathological reports.[52] SEER summary

staging consists of 5 categories: in situ, localized, regional, distant, and unstaged. A separate localized/regional category applies only to prostate cancer cases and is not used in this study.[54] Cancers coded in SEER as in situ are non-invasive tumors without malignant behavior that haven't extended through the basement membrane or beyond the epithelium. A localized cancer is confined to the organ of origin, with rare exceptions, such as limited intraluminal extension in colon cancer, assuming no lymph node involvement. Regional cancer has spread in one of the following ways: 1) directly into surrounding tissue or organ(s), 2) into nearby lymph nodes via the lymphatic system, or 3) via a combination of these 2 routes. Cancer classified as distant has spread to parts of the body away from the primary tumor, via direct growth, discontinuous metastasis to other organs, or to distant lymph nodes via the lymphatic system.[54]

Summary Statement

Much of the research described in preceding sections focused on the association between marital status and stage, treatment, and outcomes for cancers originating in the prostate, brain, bladder, kidney, and pancreas.[11,13,31,39,40,55-57] While the findings are certainly interesting and informative, those cancers do not have evidence-based early detection methods likely to reduce mortality or morbidity. The focus of the current study is limited to the 3 cancer types for which there are screening methods proven to reduce mortality. Any findings on protective associations for colon, cervical, and breast cancer have more potential for translation to practices that could improve actual health outcomes. An enhanced understanding of the effect of marital status on stage at diagnosis and ultimately cancer survival could help clinicians and public health professionals identify subset(s) of the U.S.

population at risk for adverse cancer-related outcomes, or who could stand to benefit from targeted cancer prevention and control efforts.

CHAPTER 3

METHODS

Based on a review of the literature, this appears to be the first population-based study examining the association of marital status with tumor stage at diagnosis and survival for cancers with definitive screening recommendations for the average-risk adult population. The SEER Program, described previously, collects cancer patient data which is used for the analysis in this study. Upon signing a data-use agreement, these data were made accessible through the SEER Limited-Use database. The East Tennessee State University Office for the Protection of Human Research Subjects has determined that this research proposal does not meet established definitions for research involving human subjects and does not require Institutional Review Board (IRB) approval. The University has issued a letter of exemption regarding human subjects' research.

The methods consist of the 3 following major components:

1. Descriptive statistics characterizing the 3 distinct patient populations

2: Bivariate and baseline category logit analysis of the association between marital status and disease stage at the time of diagnosis; the latter will include steps to control for confounding and assess effect modification

3: Development of Kaplan-Meier survival curves and Cox proportional hazards models describing differences in patient survival across marriage categories while accounting for potential confounders

Overall Patient Population

Using the Case Listing Session function of the National Cancer Institute's SEER*Stat software version 8.0.1, all invasive primary site colon/rectum, female breast, and uterine cervix cancers diagnosed between January 1st 2004 and December 31st 2006 in adults residing in a SEER-participating state or region are identified and followed through November 2011. These diagnosis dates are chosen to allow for up to 6 years and no less than 3 years of survival follow-up for all patients, depending on the date of diagnosis. Case data are downloaded using SEER*Stat and the results matrix containing patient records is imported into SAS version 9.2 (Cary, North Carolina) for analysis. De-identified patient records include information on patient demographics, tumor characteristics, and outcomes. The minimum age for patient inclusion in the cohorts reflects the most liberal guidance for initiation of screening (specific to each tumor site) within the average risk adult population according to evidence-based recommendations made by ACS and USPSTF. Cancer anatomic site is categorized according to International Classification of Diseases for Oncology, 3rd Edition (ICD-O-3) standards.

Colorectal Cancer Cases

ICD-O-3 tumor site codes C18.0-C18.9, C19.9 and C20.9 are designated cancers of the colon/rectum.[54] These site codes include tumors originating in the cecum, appendix, ascending colon, hepatic flexure, transverse colon, splenic flexure of the colon, descending colon, sigmoid colon, rectosigmoid junction, overlapping lesions of the colon, and those originating in the colon or rectum that are not otherwise specified (NOS). Lymphomas originating in lymphatic

tissue of the colon/rectum are excluded. Minimum age for inclusion in the cohort is 50 years. There is no upper age limit for inclusion.

Female Breast Cancer Cases

ICD-O-3 tumor site codes C50.0-C50.9 are designated cancers of the female breast.[54] These include tumors originating in the nipple, central breast, upper-inner, lower-inner, upper-outer and lower-outer quadrants, and axillary tail of the breast, as well as overlapping lesions of the breast and breast tumors not otherwise specified (NOS). All male breast cancers and skin cancers originating in breast tissue are excluded from analysis. Minimum age (at the time of diagnosis) for inclusion in the cohort is 40 years. There is no upper age limit for inclusion.

Cervical Cancer Cases

ICD-O-3 tumor site codes C53.0-C53.9 are designated cancers of the uterine cervix.[54] Only females are included in analysis. These site codes include tumors originating in the endocervix, exocervix, cervix uteri, and overlapping lesions of the cervix uteri. Minimum age for inclusion in the cohort is 20 years. There is no upper age limit for inclusion.

Independent Variable

The independent variable is patient marital status at the time of diagnosis report to the registry for the referent tumor. During the time frame of this study, there were 6 possible categories in the SEER database for marital status: 1) married (including common law marriage), 2) single (never married), 3) separated, 4) divorced, 5) widowed, and 6) unknown.[58] If a patient declares him/herself married at the time of diagnosis, then it is reported as such (SEER defines

marriage as a self-reported state). Separated and divorced are combined into one category (divorced/separated) per research precedent, but other categories remain as defined by the SEER program.[11] Completeness of the marital status variable within SEER was 95% for patients diagnosed from 1973-2007, with minimal variation in completeness by patient vital status.

Stage at Diagnosis

SEER Historic Stage A, a unique summary stage for tumors, is used to categorize cancer stage at the time of diagnosis.[54] Historic Stage A is created by collapsing comprehensive extent of disease information collected by the SEER Program, and stage categories relevant to this analysis include in situ, localized, regional, distant, and unstaged. Patients with tumors lacking malignant behavior and those with tumors left unstaged are excluded from analysis.

Covariates

Other patient variables included in analysis are sex (for colorectal cancer only), race, age, education, household income, and residential status. Modeled small area estimates of the percentage of the female population with a mammography in the past 2 years and a Pap test within the past 3 years are also available for breast and cervical cancer patients.

The sex variable categorizes the patient as either male or female at the time of diagnosis. For publication purposes, the SEER Program collapses specific racial categories into white, black, other (defined as American Indian/Alaska Native, Asian/Pacific Islander), unspecified, and unknown. The age variable refers to the patient's age in years at the time of tumor diagnosis. The age variable is treated as a categorical variable and stratified according to research

precedent and the recommended age range for each screening modality. For colorectal cancer patients, age is categorized into 4 groups: 50-59 years, 60-69 years, 70-79 years, and 80 years of age or greater. Female breast cancer patients are categorized in 5 age groups: 40-49 years, 50-59 years, 60-69 years, 70-79 years, and 80 years of age or greater. Cervical cancer patients are also divided into 5 age groups: less than 40 years, 40-49 years, 50-59 years, 60-69 years, and 70 years of age or greater. Residential status, income, and education are county-level attributes using U.S. Census Bureau data.[59] For the educational attainment variable, percentage of county residents age 25 years and older with less than a high school education was linked to the individual patient record. For the income level variable, median household income in the county of residence was linked with the patient record. For residential status, the Rural-Urban Continuum Code, developed by the U.S. Department of Agriculture, is used to characterize the population size of the patient's county of residence. Rural-Urban Continuum Codes characterize metropolitan counties by the population size of the metropolitan area(s) within their borders, and nonmetropolitan counties by the degree of urbanization within and adjacent to metropolitan area(s) in neighboring counties. Codes developed in 2003 are used for analysis. Rural-Urban Continuum Codes have 9 categories ranging from counties in metropolitan areas with greater than 1 million residents to completely rural counties with less than 2 500 residents not adjacent to a metropolitan area.[59] Categories 1 through 3 are metropolitan with populations of at least 250 000 persons, and categories 4 through 9 are nonmetropolitan, ranging from small urban areas adjacent to metropolitan areas down to sparsely populated rural and frontier areas not adjacent to metropolitan centers. Due to limitations of Rural-Urban Continuum Code availability for the state of Alaska, all patients from this SEER registry are

classified as nonmetropolitan for analysis. The modeled small area estimates for breast and cervical cancer screening are developed by the National Cancer Institute using Behavioral Risk Factor Surveillance System (BRFSS) and National Health Interview Survey (NHIS) data. These estimates are ecological and available at the health service area (HSA) level.

Descriptive Statistics

Descriptive statistics and clinical characteristics of the patient population for male and female colorectal, female breast, and cervical cancer patients are summarized in table format, and chi-square tests are used to assess unadjusted associations between categorical variables. Ecological county-level attributes are not characterized descriptively because they don't represent individual-level characteristics. Patients with missing information for marital status, tumor stage, age and/or race are excluded.[38]

Baseline Category Logit Models

Following the descriptive analysis, the next step is determination of the likelihood of advanced stage cancer (regional or distant) at the time of diagnosis. Bivariate associations between potential covariates and the outcome variable stage at diagnosis are calculated, with those covariates showing independent statistically significant associations (at p=0.05) with the outcome eligible for inclusion in the multiple regression models. Baseline category logit models are then fit for each of the 3 patient cohorts. This is an unconditional, nominal logistic multiple regression model with the dependent variable stage. The 2 non-reference categories (regional and distant disease) are contrasted with the baseline referent (localized disease). The Logistic Procedure in SAS software fits these models using a maximum likelihood estimation when the

generalized logit option (LINK=GLOGIT) is specified in the MODEL statement. Analysis includes assessment for effect modification between marital status and relevant covariates such as sex and race.

Patient Survival Time and Follow-up

Survival time can't be analyzed as a simple continuous outcome variable because time to event is not known for all patients. Because patients are diagnosed with cancer at different points in the study period, follow-up time differs across each of the 3 cohorts. By taking follow-up time into account, the power and precision of results are improved. Survival time is measured in months from the time of cancer diagnosis with adjustment for censoring from any of the following conditions: 1) patient is lost to follow-up; 2) patient dies from any non-cancer cause; 3) patient survives to the end of the follow-up portion of the study period. Patients are followed for up to 6 years, and for a minimum of 3 years, to allow for sufficient data for survival analyses while still assuring a contemporary patient population. It is necessary to restrict analysis to patients diagnosed after January 1st, 2004, because before that time the SEER Program derived summary tumor stages (including SEER Historic Stage A) using outdated extent of disease information that have limited comparability across time. The 2011 SEER Program data submission, made public in April 2012, contained a patient follow-up cutoff date of December 31st, 2009.[54]

Survival Analysis

Separate survival analyses are conducted for each of the 3 cancer patient cohorts. Each survival analysis specifies death resulting from any cancer as the outcome of interest (patient failure). This outcome is used because death from any cancer may not be independent of the primary tumor in a population already diagnosed with invasive cancer, especially when considering that post-diagnosis follow-up consists of no more than 6 years for any given patient.[13] Population-based research evaluating agreement between initial cancer diagnosis and coded cause of death found that approximately 85% of deaths within the first decade of follow-up were attributed to the tumor-specific diagnosis listed in SEER, but an additional 8% of deaths were attributed to another type of cancer.[60] A portion of this 8% could be attributed to distant metastases, or could be due to physicians reporting nonspecific tumor sites on death certificates. The reliability of relative (overall) survival as an outcome measure for cancer patients is questionable if life tables don't accurately portray true mortality in all sub-groups of the population. Reliability of a standard life table could vary by group because of differences in the distribution of "other causes" of mortality due to socioeconomic, lifestyle, or genetic risk factors. The SEER Program oversamples certain American minority populations (e.g. Alaska Natives, Cherokee Nation) to allow for improved cancer incidence and outcome data in these relatively small populations. The NCHS doesn't publish life tables for Asian Americans or American Indians, and racial/ethnic misclassification on death certificates has been found to be high within minority populations.[53] In cancer research, it is common to focus on overall survival rather than cancer-specific survival. This approach may be most useful when evaluating effectiveness of cancer-directed therapies that place patients at risk for non-cancerous adverse

events. However, when evaluating cancer outcomes in populations with older age distributions, as is the case with breast, cervical, and colorectal cancer patients, it is advantageous to calculate cancer-specific survival because older individuals are also at increased risk of death from unrelated causes. Minority (blacks and non-white Hispanics) cancer patients are also more likely than white cancer patients to die of diseases or conditions other than cancer.[60]

SEER*Stat software allows users to request a cause of death recode. Deaths within the 3 patient cohorts are stratified by "cancer causes of death" and "non-cancer causes of death" to allow development of a cancer-specific cause of death category in survival analyses. Thus, at the time of failure or censoring, patients are classified as either alive, dead from any malignant cancer, or dead from all other causes combined (e.g. diseases of the heart, septicemia, suicide, etc.), including in situ, benign, or unknown behavior neoplasms.

An important early step during the analysis of survival data is the estimation of the distribution of patient failure times. The LIFETEST procedure in the SAS software package can be used to compute nonparametric estimates of the cancer-specific survival function using the product-limit method. Kaplan-Meier product limit estimators for survival functions by each marital status category are assessed, with differences tested using the log-rank test. Death from any malignant cancer (referred to as cancer-specific death) is considered the event of interest, while non-cancer deaths and those who survived through follow-up are censored. 36-month cancer-specific survival probabilities are calculated and compared across each marital status category.

The PHREG procedure in SAS software allows users to perform multiple regression analysis of patient survival data based on the semiparametric Cox proportional hazards model. Cox proportional hazards analysis can help quantify the effect of predictor variables on hazard rates within a population. In the current study the model is used to quantify the risk of death from any cancer during the follow-up period and to estimate the independent association between marital status and cancer death for colorectal, female breast, and cervical cancer patients. A backward elimination process with p=0.20 set as cut-off level for covariates is used to determine those that may have a meaningful effect on cancer-specific survival among colorectal, female breast, and cervical cancer patients. Tests for violations of the proportional hazards assumption are conducted through assessment of Shoenfeld residuals.

CHAPTER 4

RESULTS

Patient Population Characteristics

Of the 103 144 colorectal cancer patient records retrieved from the SEER database, 92 705 had complete demographic and clinical information. Of the 151 155 female breast cancer patients, 141 561 complete records were available; of the 10 267 cervical cancer patients, 9 239 complete records were available. Descriptive tables in this section characterize each of the 3 patient populations, stratified by marital status (married, divorced/separated, widowed and single).

Colorectal Cancer Patient Characteristics

The 92 705 colorectal cancer patients eligible for analysis represent 89.9% of the total original cohort downloaded from the 18 participating SEER cancer registries. Those excluded comprise 529 patients listed as unknown race, 6 115 with unknown stage at diagnosis and 4 754 with unknown marital status. The total number of missing values for these variables amounts to slightly more than the total number of patients excluded because a small number of observations (individuals) had missing values for more than one measure. Colorectal cancer patients with unknown marital status were not substantially different from those with known marital status with regards to several important variables. Those with unknown marital status were 1.5% more likely to be younger than age 70 years, 2.9% more likely to be female, 0.8% more likely to be black, and 3.2% less likely to be diagnosed with distant stage disease.

Fifty-two thousand six hundred thirty-one (56.8%) of the patients eligible for analysis were married at the time of diagnosis, 8 703 (9.4%) were divorced or separated, 21 234 (22.9%) were widowed and 10 137 (10.9%) were single (Table 3).

Table 3: Demographic and clinical characteristics of colorectal cancer patients, SEER cancer registries, 2004-2006 diagnoses, n=92 705

Characteristics	No. married (%)	No. divorced/ separated (%)	No. widowed (%)	No. single (%)	Row Total	*p* value
Total no. patients	52 631 (56.8)	8 703 (9.4)	21 234 (22.9)	10 137 (10.9)	92 705	
Age in years						
50-59	119 00 (65.6)	2 435 (13.4)	642 (3.5)	3 154 (17.4)	18 131	<0.0001
60-69	150 66 (65.5)	2 939 (12.8)	2 245 (9.8)	2 769 (12.0)	23 019	
70-79	16 193 (58.7)	2 312 (8.4)	6 659 (24.1)	2 422 (8.8)	27 586	
80+	9 472 (39.5)	1 017 (4.2)	11 688 (48.8)	1 792 (7.5)	23 969	
Sex						
Male	33 326 (70.1)	4 039 (8.5)	4 807 (10.1)	5 352 (11.3)	47 524	<0.0001
Female	19 305 (42.7)	4 664 (10.3)	16 427 (36.4)	4 785 (10.6)	45 181	
Race						
White	44 123 (57.9)	6 814 (8.9)	17 900 (23.5)	7 378 (9.7)	76 215	<0.0001
Black	4 198 (42.4)	1 438 (14.5)	2 097 (21.2)	2 163 (21.9)	9 896	
Other	4 310 (65.4)	451 (6.8)	1 237 (18.8)	596 (9.0)	6594	
Residence						
Metropolitan	44 911 (56.4)	7 579 (9.5)	18 049 (22.7)	9 072 (11.4)	79 611	<0.0001
Nonmetropolitan	7 720 (59.0)	1 124 (8.6)	3 185 (24.3)	1 065 (8.1)	13 094	
Disease Stage						
Localized	23 922 (58.7)	3 534 (8.7)	9 179 (22.5)	4 154 (10.2)	40 789	<0.0001
Regional	18 872 (56.4)	3 124 (9.3)	7 843 (23.5)	3 602 (10.8)	33 441	
Distant	9 837 (53.2)	2 045 (11.1)	4 212 (22.8)	2 381 (12.9)	18 475	

Statistically significant ($p<0.0001$) differences existed between the 4 marital status categories as defined by patient age, sex, race, residential status, and disease stage. Single colorectal cancer

patients were more likely to be in the youngest (50-59 years) age group, while widowed patients were far more likely than others to be 80 years of age or older; divorced/separated patients were least likely to be 80 years of age or older at diagnosis. Widowed patients were more likely than others to be female, while married patients were predominantly male. The divorced/separated and single populations had approximately equal distributions of males and females. A majority of these colorectal cancer patients was white (82.2%), and whites were more likely than other groups to be widowed. Black patients were approximately twice as likely as whites to be divorced/separated or single. Proportionally, patients classified as 'other' race were more likely to be married than any other marital status category. At least 85% of colorectal cancer patients in each of the 4 marital status categories lived in metropolitan areas, with single patients more likely to be metropolitan and widowed patients most likely to be nonmetropolitan. Married patients were more likely than others to be diagnosed with localized disease; divorced/separated and single patients were less likely than those who were married or widowed to have localized disease at diagnosis and more likely to have distant stage disease. Married patients were least likely among the 4 categories to have distant stage disease at the time of diagnosis.

Female Breast Cancer Patient Characteristics

The 141 561 female breast cancer patients eligible for analysis comprise 93.7% of the total cohort downloaded from the SEER registries. Those excluded consist of 706 patients listed as unknown race, 3 500 with unknown disease stage at diagnosis and 6 298 with unknown marital status. There were no apparent major differences between those included in and

excluded from analysis with regards to several important covariates. Female breast cancer patients with unknown marital status were 3.6% less likely to be younger than age 60 years; there was no difference in the racial composition of the groups. Those with unknown marital status were 1.3% more likely to be diagnosed with distant stage disease than those who had known marital status recorded in the SEER registries.

Seventy-nine thousand seven hundred twenty-two (56.3%) of the patients included in analysis were married at the time of diagnosis, 16 969 (12.0%) were divorced/separated, 27 118 (19.2%) were widowed and 17 752 (12.5%) were single (Table 4). Statistically significant ($p<0.0001$) differences existed between the 4 marital status categories by patient age, race, residential status, and disease stage. Proportionally, single female breast cancer patients were more likely than others to be in the youngest (40-49 years) age category; widowed patients were more likely to be in the oldest (80+ years) age group. Married and divorced/separated patients were more likely than those in other marital status groups to be between 50 and 59 years of age at diagnosis. A clear majority of patients in all 4 marital categories was white, with those of 'other' race most likely to be married and those who were black most likely to be divorced/separated or single. Black patients were more likely to be single (26.3%) than those in the other 2 marital status groups, and patients classified as 'other' race were more likely to be married (65.3%). Breast cancer patients in all marital categories predominantly lived in areas classified as metropolitan, with single patients most likely to reside in metropolitan areas, and widowed patients most likely to live in nonmetropolitan areas.

Table 4: Demographic and clinical characteristics of female breast cancer patients, SEER cancer registries, 2004-2006 diagnoses, n=141 561

Characteristics	No. married (%)	No. divorced/ separated (%)	No. widowed (%)	No. single (%)	Row Total	*p* value
Total no. patients	79 722 (56.3)	16 969 (12.0)	27 118 (19.2)	17 752 (12.5)	141 561	
Age in years						
40-49	18 502 (67.1)	3 468 (12.6)	369 (1.3)	5 242 (19.0)	27 581	<0.0001
50-59	24 177 (65.8)	5 330 (14.5)	1 722 (4.7)	5 528 (15.0)	36 757	
60-69	19 684 (60.3)	4 653 (14.2)	4 733 (14.5)	3 601 (11.0)	32 671	
70-79	12 839 (47.7)	2 600 (9.7)	9 347 (34.7)	2 118 (7.9)	26 904	
80+	4 520 (25.6)	918 (5.2)	10 947 (62.0)	1 263 (7.2)	17 648	
Race						
White	68 166 (57.8)	13 738 (11.7)	23 063 (19.6)	12 940 (11.0)	117 907	<0.0001
Black	5 042 (36.9)	2 384 (17.4)	2 661 (19.5)	3 590 (26.3)	13 677	
Other	6 514 (65.3)	847 (8.5)	1 394 (14.0)	1 222 (12.3)	9 977	
Residence						
Metropolitan	70 576 (56.0)	15 327 (12.2)	23 580 (18.7)	16 449 (13.1)	125 932	<0.0001
Nonmetropolitan	9 146 (58.5)	1 642 (10.5)	3538 (22.6)	1 303 (8.3)	15 629	
Disease Stage						
Localized	51 484 (57.3)	10 272 (11.4)	17 645 (19.6)	10 446 (11.6)	89 847	<0.0001
Regional	24 273 (56.7)	5 422 (12.7)	7 389 (17.3)	5 743 (13.4)	42 827	
Distant	3 965 (44.6)	1 275 (14.4)	2 084 (23.5)	1 563 (17.6)	8 887	

Married and widowed patients were more likely than others to have localized breast cancer at the time of diagnosis; single patients were least likely to have localized disease. Single females were also more likely than others to have regional or distant stage breast cancer at the time of diagnosis; married patients were least likely to be diagnosed with distant stage disease.

Cervical Cancer Patient Characteristics

The 9 239 cervical cancer patients eligible for analysis comprise 90% of the original cohort downloaded from the SEER registries. Those excluded were 82 patients listed as unknown race, 523 with unknown stage at diagnosis, and 567 with unknown marital status. Cervical cancer patients with unknown marital status did not differ markedly from those with known marital status with respect to age (54.62% of those with known marriage and 54.63% of those with unknown marriage younger than age 50 years). Patients with unknown marital status were 0.6% less likely to be black, as well as 0.6% less likely to have distant stage cervical cancer at the time of diagnosis.

Four thousand three hundred seventeen (46.7%) of these patients were married at the time of diagnosis, 1 343 (14.5%) were separated/divorced, 1 063 (11.5%) were widowed and 2 516 (27.2%) were single (Table 5). Statistically significant ($p<0.0001$) differences existed between the 4 marital status categories as defined by patient age, race, residential status, and disease stage. Proportionally, single cervical cancer patients were more likely than those in other marital status groups to be younger than 40 years of age. Widowed patients were the most likely of the 4 marital status groups to be age 70 years or older at the time of diagnosis. Married patients were more likely than others to be between 40 and 49 years of age at diagnosis. As with the colorectal and female breast cancer cohorts, a majority of cervical cancer patients in this population was white. Black patients were more likely to be single (46.0%), while white patients were more likely than others to be divorced/separated (15.6%). Those patients classified as 'other' race (50.1%) were more likely than others to be married.

Table 5: Demographic and clinical characteristics of cervical cancer patients, SEER cancer registries, 2004-2006 diagnoses, n=9 239

Characteristics	No. married (%)	No. divorced/ separated (%)	No. widowed (%)	No. single (%)	Row Total	*p* value
Total no. patients	4 317 (46.7)	1 343 (14.5)	1 063 (11.5)	2 516 (27.2)	9 239	
Age in years						
<40	1 258 (50.3)	255 (10.2)	24 (1.0)	962 (38.5)	2 499	<0.0001
40-49	1 366 (53.6)	385 (15.1)	67 (2.6)	729 (28.6)	2 547	
50-59	871 (47.7)	368 (20.1)	130 (7.1)	459 (25.1)	1 828	
60-69	500 (42.1)	208 (17.5)	254 (21.4)	225 (19.0)	1 187	
70+	322 (27.3)	127 (10.8)	588 (49.9)	141 (12.0)	1 178	
Race						
White	3 443 (48.7)	1 103 (15.6)	747 (10.6)	1 777 (25.1)	7 070	<0.0001
Black	350 (27.7)	151 (12.0)	182 (14.4)	581 (46.0)	1 264	
Other	524 (57.9)	89 (9.8)	134 (14.8)	158 (17.5)	905	
Residence						
Metropolitan	3 781 (46.3)	1 187 (14.5)	902 (11.0)	2 300 (28.2)	8 170	<0.0001
Nonmetropolitan	536 (50.1)	156 (14.6)	161 (15.1)	216 (20.2)	1 069	
Disease Stage						
Localized	2 342 (52.6)	559 (12.6)	334 (7.5)	1 214 (27.3)	4 449	<0.0001
Regional	1 563 (41.6)	620 (16.5)	578 (15.4)	993 (26.5)	3 754	
Distant	412 (39.8)	164 (15.8)	151 (14.6)	309 (29.8)	1 036	

Most cervical cancer patients lived in metropolitan areas. Proportionally, single patients were more likely to live in metropolitan areas, and widowed were more likely to live in nonmetropolitan areas. Married patients were more likely than others to have localized disease at diagnosis and were least likely to have distant stage disease. Conversely, widowed patients were least likely to have localized disease at diagnosis and more likely than those in the other 3 marital status groups to be diagnosed with regional or distant disease.

Marital Status and Advanced Tumor Stage at Diagnosis

The proportional odds assumption was not met with these data, so the dependent variable tumor stage at diagnosis could not be treated as ordinal. Table 6 presents results of the baseline category logit model assessing marital status and other factors' relationships with stage of colorectal cancer at the time of diagnosis. The 2 results columns (labeled 'Regional' and 'Distant') contain odds ratios comparing patients in categories of the primary predictor and each covariate to a category-specific baseline referent with respect to their likelihood of being diagnosed with the later stages of either regional or distant as compared to the basline outcome of localized cancer. Ecological variables serving as proxies for educational level and income did not meaningfully improve the model, and were not included as covariates in the final model.

Patients in each of the 3 'non-married' categories (divorced/separated, widowed, single) were significantly more likely to have regional (vs. localized) and distant (vs. localized) stage colorectal cancer at the time of diagnosis compared to married patients (*p*-value range: <0.0001-0.0007). Divorced/separated patients had the highest likelihood of later stage disease relative to married patients for both stage comparisons (OR=1.11, 95% CI 1.05-1.17 for regional vs. localized and OR=1.36, 95% CI 1.28-1.44 for distant vs. localized). Females were slightly more likely than males to have regional stage disease at diagnosis (OR=1.06, 95% CI 1.03-1.09), but there was no discernible female vs. male difference for the distant vs. localized stage disease comparison (p=0.0626).

Table 6: Baseline category logit analysis of marital status and other factors predicting colorectal cancer stage at diagnosis, SEER cancer registries, 2004-2006 diagnoses, n=92 705

	Tumor stage at diagnosis			
Characteristic	**Regional**	*p*-value	**Distant**	*p*-value
Marital status				
Married	1.00		1.00	
Divorced/separated	1.11 (1.05-1.17)*	0.0001	1.36 (1.28-1.44)	<0.0001
Widowed	1.08 (1.04-1.13)	0.0002	1.23 (1.17-1.29)	<0.0001
Single	1.09 (1.04-1.14)	0.0007	1.33 (1.26-1.41)	<0.0001
Sex				
Male	1.00		1.00	
Female	1.06 (1.03-1.09)	0.0004	0.97 (0.93-1.00)	0.0626
Age in years				
50-59	1.00		1.00	
60-69	0.99 (0.94-1.03)	0.5258	0.94 (0.89-0.99)	0.0112
70-79	0.94 (0.90-0.99)	0.0082	0.79 (0.75-0.84)	<0.0001
80+	0.95 (0.90-0.99)	0.0224	0.78 (0.73-0.82)	<0.0001
Race				
White	1.00		1.00	
Black	0.99 (0.94-1.04)	0.6007	1.25 (1.18-1.32)	<0.0001
Other	1.09 (1.03-1.15)	0.0034	1.00 (0.93-1.07)	0.9477
Residence				
Metropolitan	1.00		1.00	
Nonmetropolitan	0.93 (0.89-0.97)	0.0008	0.94 (0.90-0.99)	0.0176

* Odds ratio (95% confidence interval)

There was no apparent trend in effect size change with advancing patient age (ORs 0.99, 0.94 and 0.95 for 60-69, 70-79, and 80 years of age and older, respectively) for the regional vs.

localized comparison, while for the distant vs. localized comparison progressively higher age groups seemed to enjoy modestly larger protective effects (OR=0.94, 95% CI 0.89-0.99, OR=0.79, 95% CI 0.75-0.84, and OR=0.78, 95 % CI 0.73-0.82 for 60-69, 70-79, and 80 years of age and older, respectively). There was no significant difference between black and white patients for the regional vs. localized comparison (p=0.6007) or between those classified as 'other' race and whites for the distant vs. localized comparison (p=0.9477). Those of 'other' race were slightly more likely than whites to have regional vs. localized disease (OR=1.09, 95% CI 1.03-1.15), and blacks were 25% more likely than whites to have distant vs. localized stage colorectal cancer at diagnosis (OR=1.25, 95% CI 1.18-1.32). Residing in a nonmetropolitan area seemed to be marginally protective, but the odds ratios for these measures were close to null for both regional vs. localized and distant vs. localized comparisons (0.93, 95% CI 0.89-0.97 and OR=0.94, 95% CI 0.90-0.99 respectively). The variable for patient sex appeared to modify the relationship between marital status and stage (p=0.0003), and the data were subsequently stratified (See Appendix A). After stratifying by sex, divorced/separated, widowed, and single males were more likely to be diagnosed with distant vs. localized disease than females, with the disparity in effect sizes most pronounced among the divorced/separated (OR 1.49, 95% CI 1.37-1.62 in males compared to OR 1.22, 95% CI 1.12-1.33 in females) and single patients (OR 1.46, 95% CI 1.36-1.58 in males compare to OR 1.17, 95% CI 1.07-1.27 in females). It would appear that among colorectal cancer patients, the protective association between marriage and disease stage at diagnosis is stronger in men than women.

Table 7 presents results of the baseline category logit model characterizing the association of marital status and other factors with later stage breast cancer at diagnosis.

Table 7: Baseline category logit analysis of marital status and other factors predicting female breast cancer statge at diagnosis, SEER cancer registries, 2004-2006 diagnoses, n=141 561

	Tumor stage at diagnosis			
Characteristic	**Regional**	*p*-value	**Distant**	*p*-value
Marital status				
Married	1.00		1.00	
Divorced/separated	1.11 (1.07-1.15)*	<0.0001	1.52 (1.42-1.63)	<0.0001
Widowed	1.12 (1.08-1.17)	<0.0001	1.50 (1.41-1.60)	<0.0001
Single	1.09 (1.05-1.13)	<0.0001	1.77 (1.66-1.88)	<0.0001
Age in years				
40-49	1.00		1.00	
50-59	0.83 (0.80-0.86)	<0.0001	1.13 (1.06-1.21)	0.0004
60-69	0.66 (0.64-0.69)	<0.0001	1.05 (0.97-1.12)	0.2274
70-79	0.56 (0.54-0.58)	<0.0001	0.94 (0.87-1.01)	0.0995
80+	0.55 (0.52-0.58)	<0.0001	1.13 (1.03-1.23)	0.0080
Race				
White	1.00		1.00	
Black	1.33 (1.28-1.38)	<0.0001	1.83 (1.72-1.95)	<0.0001
Other	1.01 (0.97-1.06)	0.6616	0.93 (0.85-1.02)	0.1276

* Odds ratio (95% confidence interval)

Ecological variables for education, income, and screening mammography did not meaningfully improve the model and were excluded from the final version. Residential status was also excluded as a covariate during model development due in part to a low Wald χ^2 value noted during analysis of effects. The variable exceeded the 0.2 significance level specified for

removal of potential covariates during backward model selection. Marital status, age, and race were included as predictor variables in the final model.

Women in the divorced/separated, widowed, and single categories were significantly more likely than those in the married category to have regional vs. localized breast cancer at the time of diagnosis, with the effect size more considerable across these same categories for the distant vs. localized disease comparison. Single women were most likely to be diagnosed with tumors at the lastest stage; they had a 77% higher likelihood of distant vs. localized disease than those who were married (OR=1.77, 95% CI 1.66-1.99). Advanced age had a progressively larger protective effect for the regional vs. localized disease comparison, while the 4 older (compared to the referrent) age groups in the distant vs. localized comparison demonstrated no uniform trend, with 2 of the outcome measures (for ages 60-69 and 70-79 years) failing to reach statistical significance. Black patients had higher likelihood than whites of regional vs. localized (OR=1.33, 95% CI 1.28-1.38) and distant vs. localized disease (OR=1.83, 1.72-1.95) at diagnosis, while those classified as 'other' race were not significantly different from whites at either level of comparison. An interaction term for race by marital status was marginally significant (p=0.0430), and data were stratified by race (See Appendix B). Once stratified by race, the only substantial departures from effect sizes observed in the full model were among divorced/separated and single women classified as 'other' race. These women had more than twice the likelihood of distant vs. localized disease at diagnosis compared to married peers (OR=2.05, 95% CI 1.54-2.73 and OR=2.29, 95% CI 1.81-2.91 for divorced/separated and single, respectively). Smaller sample sizes and less precise estimates within this stratification scheme, evidenced by wider confidence intervals, could play a role in

these observed differences, although a majority of the effect size estimates for white and 'other' race patients are statistically significant.

Table 8 presents results of the baseline category logit model describing the association of marital status and age with later stage cervical cancer at the time of diagnosis.

Table 8: Baseline category logit analysis of marital status and other factors predicting cervical cancer stage at diagnosis, SEER cancer registries, 2004-2006 diagnoses, n=9 239

	Tumor stage at diagnosis			
Characteristic	**Regional**	*p*-value	**Distant**	*p*-value
Marital status				
Married	1.00		1.00	
Divorced/separated	1.49 (1.31-1.71)*	<0.0001	1.44 (1.17-1.78)	0.0005
Widowed	1.44 (1.22-1.71)	<0.0001	1.34 (1.05-1.72)	0.0191
Single	1.38 (1.23-1.53)	<0.0001	1.68 (1.42-1.98)	<0.0001
Age in years				
<40	1.00		1.00	
40-49	1.79 (1.59-2.03)	<0.0001	2.27 (1.83-2.83)	<0.0001
50-59	2.88 (2.52-3.30)	<0.0001	4.61 (3.69-5.76)	<0.0001
60-69	3.37 (2.88-3.96)	<0.0001	5.64 (4.40-7.23)	<0.0001
70+	4.19 (3.51-5.00)	<0.0001	5.78 (4.39-7.61)	<0.0001

* Odds ratio (95% confidence interval)

Ecological variables for education, income, and Pap test prevalence, as well as individual-level variables for race and residential status did not meaningfully improve the model and were excluded either prior to full model development or during a backward elimination process. Women in each of the 3 non-married categories were more likely than those who were married to have regional vs. localized cervical cancer at diagnosis, with divorced/separated women having the greatest increased likelihood (OR=1.49, 95% CI 1.31-1.71). The same is true for the distant vs. localized comparison, except that single women had the highest likelihood of distant disease relative to the married (OR=1.68, 95% CI 1.42-1.98). While controlling for patient marital status, there was a distinct age gradient, with elevated likelihoods of later stage disease relative to the youngest age group for both baseline stage comparisons. The adverse association with advanced age was more pronounced within each categorical stratum in the distant vs. localized compared to the regional vs. localized column. Those who were 70 years of age or older had more than 4 times (OR=4.19, 95% CI 3.51-5.00) higher likelihood of being diagnosed with regional vs. localized cervical cancer than those younger than age 40 years, while the oldest patients were nearly 6 times more likely than the youngest (OR=5.78, 95% CI 4.39-7.61) to have distant vs. localized disease at the time of diagnosis.

Marital Status and Cancer-specific Survival

Colorectal Cancer and Survival

Figure 5 shows cancer-specific survival probability curves comparing colorectal cancer patient survival by marital status category. Unadjusted Kaplan-Meier survival analysis

demonstrated that throughout follow-up, married patients had better cancer-specific survival than those who were divorced/separated, single, and widowed.

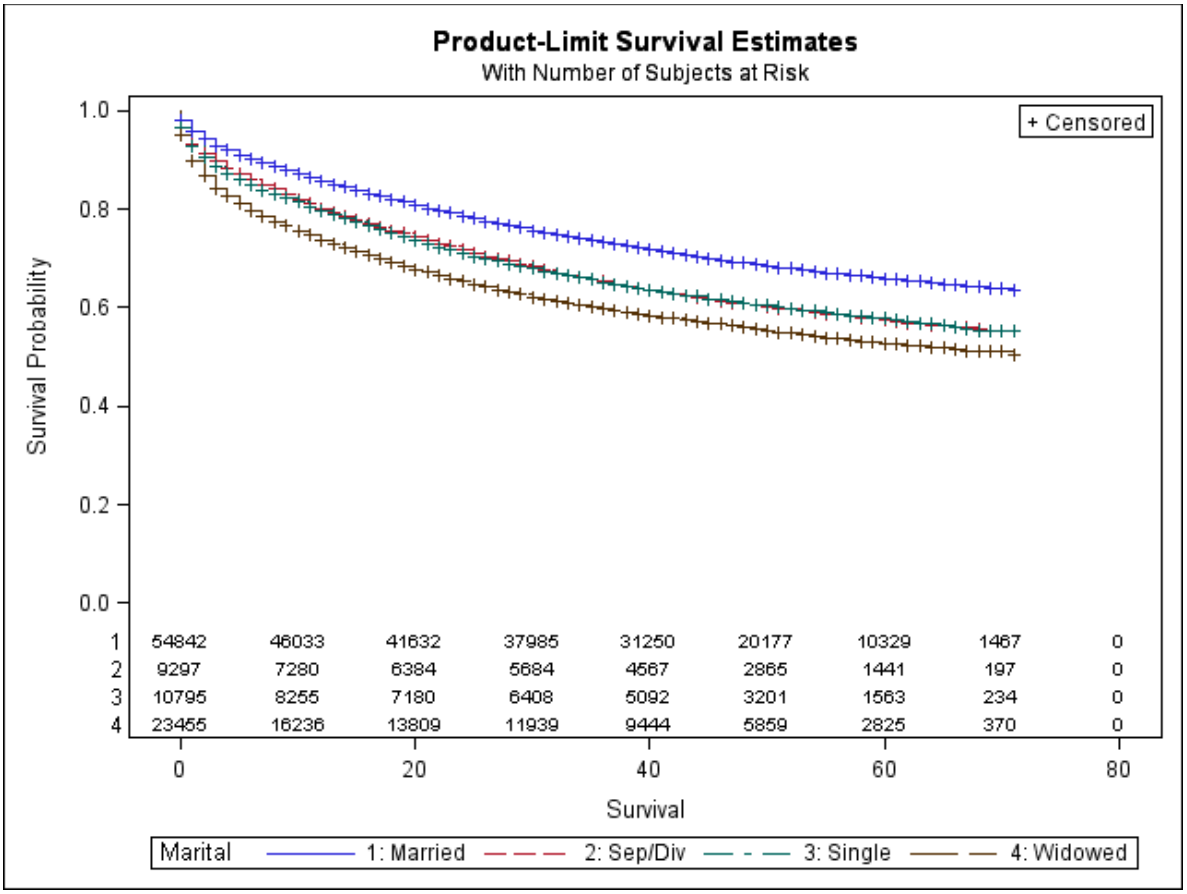


Figure 5: Kaplan-Meier plot, colorectal cancer patient survival, in months, stratified by marital status, SEER cancer registries, 2004-2006 diagnoses

The log-rank test for equality across marital status strata was statistically significant ($p<0.0001$). Of the 33 547 patients who died of any cancer during follow-up, 16 557 (49.4%) were married, 3 488 (10.4%) were divorced/separated, 3 986 (11.9%) were single, and 9 516 (28.4%) were widowed. 64 842 patients were right censored (survived or died of a non-cancer cause), of whom 38 285 (59.0%) were married, 5 809 (9.0%) were divorced/separated, 6 809 (10.5%) were

single, and 13 939 (21.5%) were widowed. At 36 months, the longest uniform follow-up time for all individuals, cancer-specific survival was 73.3% for married, 65.4% for divorced/separated, 65.2% for single, and 59.7% for widowed patients.

Among patients diagnosed with invasive colorectal cancer, being married at the time of diagnosis was associated with superior cancer-specific survival during the follow-up period, independent of sex, age, race, and disease stage (Table 9). Ecological variables for education level and household income, as well as a variable characterizing patient residential (metropolitan vs. nonmetropolitan) status did not meaningfully improve the multiple regression model, and were excluded from the final version. Divorced/separated and single patients had approximately 30% higher risk of death during follow-up (Hazard Ratio=1.29, 95% CI 1.24-1.34 and HR=1.30, 95% CI 1.25-1.35, respectively) than those who were married at the time of diagnosis; widowed patients had 24% higher risk of death during follow-up than married patients (HR=1.24, 95% CI 1.20-1.28). Controlling for other relevant factors, females had a lower risk of death during follow-up (HR=0.88, 95% CI 0.85-0.90), and advancing age was consistently associated with increased risk of cancer-specific death, with a nearly 3-fold increase in risk among those who were 80 years of age or older compared to those in the youngest age group (HR=2.70, 95% CI 2.60-2.80). Black colorectal cancer patients had a 20% higher risk of death than whites at any point during follow-up, while being classified as 'other' race was associated with slightly better survival. Having regional stage colorectal cancer at diagnosis was associated with more than 2-fold higher risk compared to those with localized disease (HR=2.31, 95% CI 2.24-2.39), while those with distant stage disease were nearly 13.5 times more likely to die of any cancer during the follow-up period (HR=13.43, 95% CI 13.01-

13.86). Patient sex modified the association between marital status and cancer-specific survival, and data were stratified by sex to assess the effect this interaction may have on hazard ratios in the full model (See Appendix C).

Table 9: Multivariate Cox proportional hazards model for marital status and other variables predicting death from any cancer among colorectal cancer patients, SEER cancer registries, 2004-2006 diagnoses

Characteristic	Hazard Ratio (95% CI)	*p*-value
Marital status		
Married	1.00	
Divorced/separated	1.29 (1.24-1.34)	<0.0001
Widowed	1.24 (1.20-1.28)	<0.0001
Single	1.30 (1.25-1.35)	<0.0001
Sex		
Male	1.00	
Female	0.88 (0.85-0.90)	<0.0001
Age in years		
50-59	1.00	
60-69	1.20 (1.16-1.25)	<0.0001
70-79	1.71 (1.65-1.78)	<0.0001
80+	2.70 (2.60-2.80)	<0.0001
Race		
White	1.00	
Black	1.20 (1.16-1.24)	<0.0001
Other	0.91 (0.87-0.96)	0.0001
Tumor stage		
Localized	1.00	
Regional	2.31 (2.24-2.39)	<0.0001
Distant	13.43 (13.01-13.86)	<0.0001

Although a term included in the model to assess for interaction between patient sex and marital status was statistically significant (p=0.0045), following stratification, the changes in hazard ratios across marital status categories were relatively minor. However, it appears that being married was more protective among male colorectal cancer patients than among females, as hazard ratios for divorced/separated, widowed, and single patient groups were 1.34 (95% CI 1.27-1.42), 1.26 (95% CI 1.20-1.33), and 1.37 (95% CI 1.31-1.44) respectively, all modestly higher than those observed among female counterparts. This aside, it's clear that while controlling for relevant factors available in the SEER registry database, colorectal cancer patients in each of the 3 'non-married' categories were at significantly higher risk of cancer-specific death during the years immediately following their diagnoses.

Breast Cancer and Survival

Unadjusted Kaplan-Meier survival curves showed married breast cancer patients with the highest survival probability, divorced/separated and single with nearly identical curves and widowed patients with the lowest cancer-specific survival probability (Figure 6). The log-rank test for equality across strata was statistically significant (p<0.0001). Of the 18 320 female breast cancer patients who died of any cancer during follow-up, 7 651 (41.8%) were married, 2 486 (13.6%) were separated/divorced, 2 756 (15.0%) were single, and 5 427 (29.6%) were widowed. Of the 126 537 patients who were censored, 73 171 (57.8%) were married, 14 876 (11.8%) were separated/divorced, 15 466 (12.2%) were single, and 23 024 (18.2%) were widowed. After 36 months of follow-up, cancer-specific survival was 93.1% for married, 88.8% for divorced/separated, 87.7% for single, and 83.6% for widowed patients.

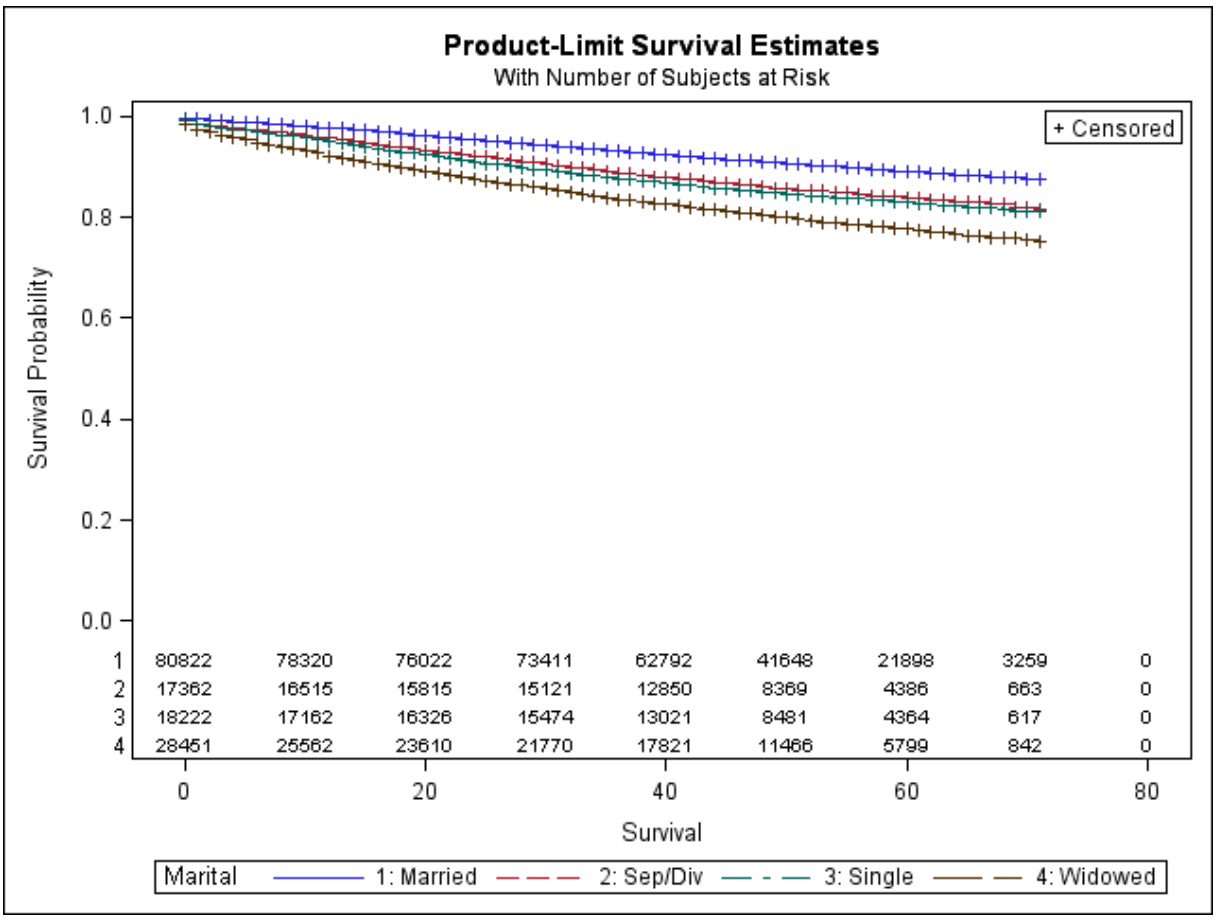


Figure 6: Kaplan-Meier plot, female breast cancer patient survival, in months, stratified by marital status, SEER cancer registries, 2004-2006 diagnoses

Married females diagnosed with invasive breast cancer had lower risk of death than those in all 3 non-married categories, independent of age, race, and tumor stage at diagnosis (Table 10). Ecological variables serving as proxies for patient household income, education and mammography screening prevalence, as well as an individual-level variable describing residential status, didn't improve the model and were excluded from the final version.

Table 10: Multivariate Cox proportional hazards model for marital status and other variables predicting death from any cancer among female breast cancer patients, SEER cancer registries, 2004-2006 diagnoses

Characteristic	Hazard Ratio (95% CI)	*p*-value
Marital status		
Married	1.00	
Divorced/separated	1.29 (1.23-1.36)	<0.0001
Widowed	1.31 (1.26-1.37)	<0.0001
Single	1.33 (1.27-1.39)	<0.0001
Age in years		
40-49	1.00	
50-59	1.17 (1.11-1.23)	<0.0001
60-69	1.34 (1.27-1.41)	<0.0001
70-79	1.82 (1.73-1.92)	<0.0001
80+	2.94 (2.77-3.12)	<0.0001
Race		
White	1.00	
Black	1.66 (1.59-1.73)	<0.0001
Other	0.88 (0.82-0.95)	0.0004
Tumor stage		
Localized	1.00	
Regional	2.90 (2.80-3.02)	<0.0001
Distant	20.69 (19.90-21.50)	<0.0001

The elevated risk of cancer-specific death was nearly uniform across the divorced/separated, widowed, and single groups with hazard ratios of 1.29 (95% CI 1.23-1.36), 1.31 (95% CI 1.26-1.37), and 1.33 (95% CI 1.27-1.39) respectively. Risk of cancer-specific death was progressively higher with increasing age, with those patients age 80 years and older having nearly 3 times the risk of those between the ages of 40 and 49 years (HR=2.94, 95% CI 2.77-3.12). As was the case

in colorectal cancer patients, but within this cohort to a greater extent, black female breast cancer patients had higher risk of cancer-specific death (HR=1.66, 95% CI 1.59-1.73 compared to whites), while those classified as 'other' race enjoyed a small protective association (HR=0.88, 95% CI 0.82-0.95). Once again, disease stage was inversely proportional to cancer-specific survival during follow-up, with nearly 3-fold and more than 20-fold higher risk of death from any cancer among those with regional and distant stage breast cancer respectively (HR=2.90, 95% CI 2.80-3.02, HR=20.69, 95% CI 19.90-21.50). Upon inclusion of a model term assessing interaction, it appeared that the variable race modified the association between patient marital status and cancer-specific survival during follow-up (p=0.0002). Data were stratified by race and the new models were interpreted (See Appendix D). Effect sizes across each of the 3 non-married categories remained essentially unchanged among whites (HR=1.30, 95% CI 1.23-1.37, HR=1.31, 95% CI 1.25-1.37, and HR=1.27, 95% CI 1.20-1.34 for divorced/separated, widowed, and single breast cancer patients respectively). Among the black female breast cancer patient population, the protective effect was slightly lower among the divorced/separated and widowed patients relative to the married (HR=1.20, 95% CI 1.07-1.35 and HR=1.28, 95% CI 1.14-1.45 respectively), while risk of death among single patients was modestly higher relative to the entire population (HR=1.36, 95% CI 1.23-1.50 in blacks compared to HR=1.33, 1.27-1.39 in the full model). The protective association with marriage appears to be most pronounced among those classified as 'other' race. Those who were divorced/separated had a corresponding hazard ratio of 1.64 (95% CI 1.32-2.02) compared to their married counterparts, a marked departure from that of 1.29 (95% CI 1.23-1.36) observed in the full population. Single patients in the 'other' race category (HR=1.55, 95% CI 1.28-1.87)

also experienced higher risk relative to married patients compared to the same measure in the full model (HR=1.33, 95% CI=1.27-1.39). For effect size estimates in the models stratified by race, the confidence intervals were wider and the corresponding p-values were larger, although each hazard ratio for the non-married categories across all 3 race strata remained statistically significant.

Cervical Cancer and Survival

Among cervical cancer patients, unadjusted Kaplan-Meier survival analysis showed clear differences in cancer-specific survival probabilities between the 4 marital status categories, with married patients having the best survival, followed by single, divorced/separated, and widowed patients respectively (Figure 7). The log-rank test for equality across strata was significant ($p<0.0001$). Of the 2 739 cervical cancer patients who died of any malignant cancer during follow-up, 1 021 (37.3%) were married, 462 (16.9%) were separated/divorced, 727 (26.5%) were single, and 529 (19.3%) were widowed. Of the 6 960 who were censored, 3 445 (50.0%) were married, 960 (13.8%) were separated/divorced, 1 916 (27.5%) were single, and 639 (9.2%) were widowed. After 36 months of post-diagnosis follow-up, cancer-specific survival in this cohort was 78.8% among married, 69.1% among separated/divorced, 73.3% among single, and 54.4% among widowed patients.

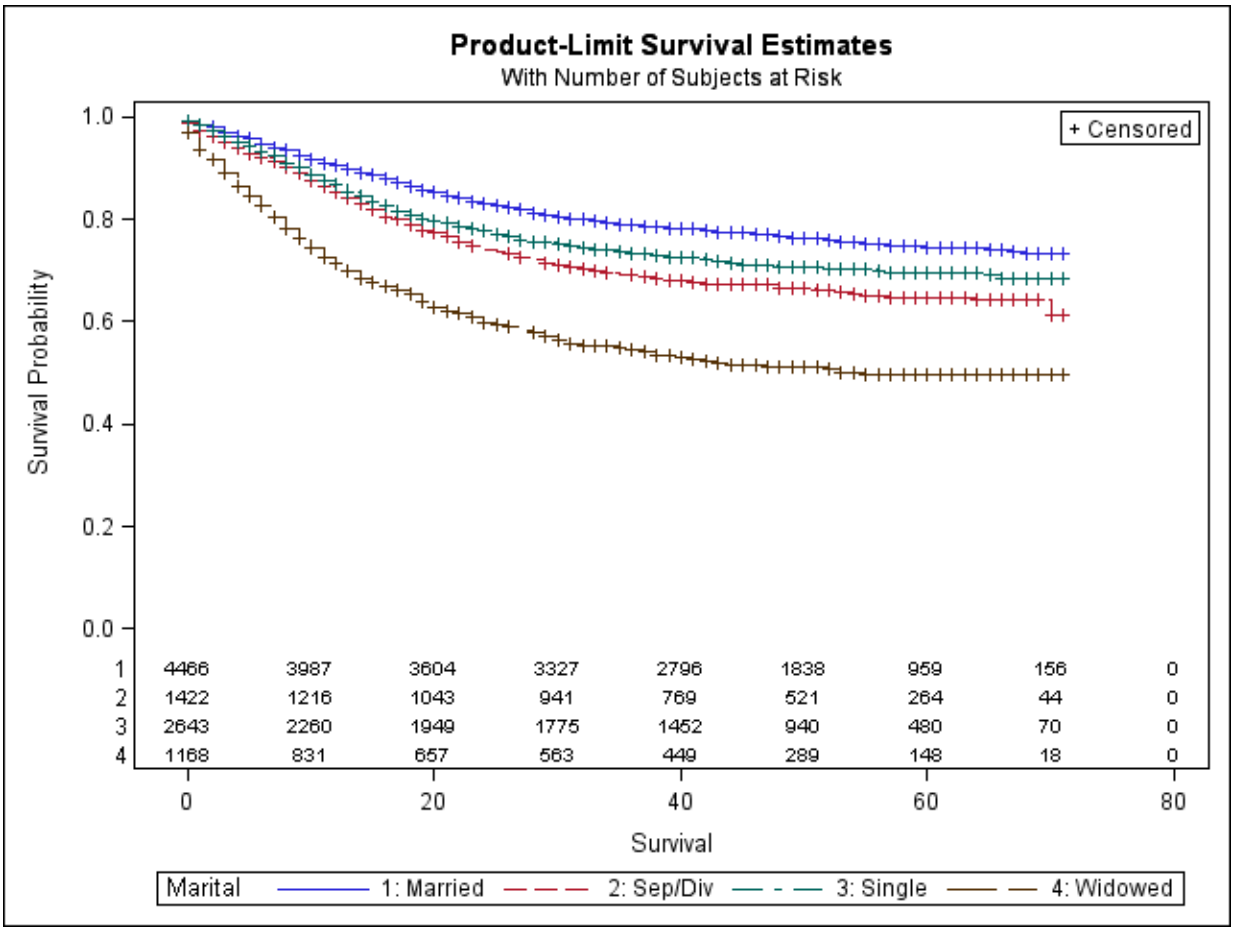


Figure 7: Kaplan-Meier plot, cervical cancer patient survival, in months, stratified by marital status, SEER cancer registries, 2004-2006 diagnoses

Among women diagnosed with invasive cervical cancer, being married at the time of diagnosis was associated with lower risk of death from any cancer during follow-up compared to those who were divorced/separated (HR=1.21, 95% CI 1.07-1.35), widowed (HR=1.32, 95% CI 1.16-1.50), and single (HR=1.19, 95% CI 1.07-1.31) (Table 11). Ecological variables substituted as proxies for patient household income, education and Pap testing prevalence did not meaningfully improve the model and weren't included in the final version.

Table 11: Multivariate Cox proportional hazards model for marital status and other variables predicting death from any cancer among cervical cancer patients, SEER cancer registries, 2004-2006 diagnoses

Characteristic	Hazard Ratio (95% CI)	*p*-value
Marital status		
Married	1.00	
Divorced/separated	1.21 (1.07-1.35)	0.0016
Widowed	1.32 (1.16-1.50)	<0.0001
Single	1.19 (1.07-1.31)	0.0009
Age in years		
<40	1.00	
40-49	1.06 (0.93-1.20)	0.4123
50-59	1.24 (1.09-1.41)	0.0010
60-69	1.33 (1.15-1.53)	<0.0001
70+	2.30 (1.99-2.66)	<0.0001
Race		
White	1.00	
Black	1.27 (1.14-1.41)	<0.0001
Other	0.89 (0.78-1.02)	0.1027
Residence		
Metropolitan	1.00	
Nonmetropolitan	1.16 (1.03-1.30)	0.0120
Tumor stage		
Localized	1.00	
Regional	4.98 (4.42-5.60)	<0.0001
Distant	19.03 (16.74-21.65)	<0.0001

There was no significant difference in risk of death among those age 40 and 49 years compared to those younger than age 40 years (p=0.4123), but patients who were 50-59 (HR=1.24, 95% CI 1.09-1.41), 60-69 (HR=1.33. 95% CI 1.15-1.53), and older than age 70 years (HR=2.30, 95% CI 1.99-2.66) had increased risk of death compared to the youngest patients. Black patients with

cervical cancer in this cohort had a higher risk of death from any cancer than whites (HR=1.27, 95% CI 1.14-1.41); there was no statistically significant difference between those classified as 'other' race and whites (p=0.1027). Women who lived outside metropolitan areas had slightly higher risk of death during follow-up (HR=1.16, 95% CI 1.03-1.30). As was the case with colorectal and female breast cancer patients, cervical cancer patients with regional (HR=4.98, 95% CI 4.42-5.60) and distant stage disease (HR=19.03, 95% CI 16.74-21.65) had substantially higher risk of death from any cancer during the follow-up period.

CHAPTER 5

DISCUSSION

Primary Findings

In this population-based study, married patients with colorectal, breast, and cervical cancer experienced better cancer-related outcomes than those who weren't married. These findings have certain limitations, but this much is clear: 1) married adults with colorectal, breast, and cervical cancer (all of which can be detected early with routine screening) were diagnosed at an earlier disease stage than their non-married counterparts, and 2) even after controlling for stage and important demographic factors, married patients experienced better all-cancer survival than those who were divorced/separated, widowed, or single.

Within the 3 non-married groups, differences existed in cancer stage distribution and survival, but the disparity between the 2 broader groups (married and non-married) was remarkably consistent across each of the 3 anatomic cancer sites and multiple levels of analysis. Even with limited information about the screening and treatment behaviors of the patients in these 3 cohorts, unmarried adults are a subset of the population that may stand to benefit from targeted prevention or care initiatives throughout the natural course of preventable and/or detectable cancers. Given the consistently protective association between marriage and superior cancer outcomes observed in this study, researchers focusing on patients with 1 of these 3 cancers should consider marital status as a meaningful determinant of stage at diagnosis and cancer-specific survival. In the meantime, additional research examining the

mechanisms underlying the association between marriage and cancer-specific survival in patients diagnosed with these 3 cancers is important.

Distant Stage Cancer at Diagnosis

In looking at colorectal and female breast cancer stage at diagnosis outcomes, the protective association among those who were married compared to that of patients in the 3 non-married groups was consistently stronger for the distant vs. localized than for the regional vs. localized stage comparisons (Tables 6 and 7). The same was true in the stratified analyses (Appendices A and B), with the protective association especially pronounced among the male colorectal cancer patients. This was not the case among cervical cancer patients, with the exception of those in the single (never married) group (Table 8). It is possible that differences in social network support may explain some of variation in the associations. For example, perhaps less adherence (e.g. lower prevalence or frequency of screening) to early detection guidance for colorectal and breast cancer in the 3 non-married groups could result in discovery at a later stage disease by virtue of clinical symptomatology. The result would be a stronger net protective effect of marriage through its influence on the use of clinical preventive services. The largest difference observed in the regional/distant vs. localized comparisons was among single patients. This was true for all 3 cancer sites (and was the only of the non-married categories to have a stronger distant vs. localized comparison within the cervical cancer cohort). Those who have never been married may be less likely to have some of the residual familial support network (e.g. adult children, or lasting friendships developed with or through an ex-spouse, etc.) enjoyed by those in the divorced/separated and widowed groups. Smaller

support networks could result in lower overall levels of external encouragement to adhere to recommended early detection schedules for these cancers. In cancers that can potentially be detected early, stage at diagnosis data are often evaluated within the context of population screening rates broken down by variable(s) of interest. According to the most recent Centers for Disease Control and Prevention (CDC) data linked to USPSTF guidelines, non-married (divorced/separated, widowed, and single) individuals are more likely to fail to meet guidelines for colorectal, breast, and cervical cancer screening compared to those who are currently married.[61] In 2010, 62.9% of married adults were up-to-date with USPSTF guidelines for colorectal cancer screening, compared to 54.1% of divorced/separated, 54.7% of widowed, and 49.6% of single men and women. Similar differences were reported among women screening for breast and cervical cancers. Greater than 76% of married women were meeting USPSTF guidelines for breast cancer screening in 2010, compared to 63.7% of divorced/separated, 71.8% of widowed, and 66.1% of single women. Nearly 86% of married women were current with USPSTF guidance for cervical cancer guidance during the same time period, compared to 81.3% of divorced/separated, 78.0% of widowed, and 77.2% of single women.[61] These CDC data were derived from a nationally population-based representative sample from the SEER registries although the data did not incorporate the entire U.S. population. With this in mind, the marked differences in national cancer screening rates between married and non-married individuals are still consistent with the findings in the current study that non-married colorectal, breast, and cervical cancer patients tend to be diagnosed with later stage disease compared to married counterparts.

Interestingly, among breast cancer patients, advancing age was increasingly protective in older age women, who had a lower likelihood of regional compared to localized disease. There was essentially no age trend in associations for the distant vs. localized comparison. This was not the case among cervical cancer patients, where increased age was a risk factor for later tumor stage at diagnosis, with an increase in likelihood of both regional and distant stage disease from the youngest to the oldest age groups. One potential explanation for this finding among breast cancer patients could be that the younger women in this cohort may be more likely than older women to have genetic mutations predisposing them to more aggressive types of breast cancer than their older counterparts. Research has found that younger women with breast cancer are more frequently diagnosed with non-localized disease and their tumors may be more likely to show characteristics unfavorable to prognosis.[62] However, this hypothesis is complicated by the absence of the same trend among those diagnosed with distant stage disease, but it's possible that breast cancers associated with certain mutations in younger women may be more frequently discovered (through mammography or clinical exam) at the regional stage.

Among colorectal cancer patients, a similar, though less pronounced trend was observed with advancing age in the distant vs. localized stage comparison although the same association was not seen for age and regional vs. localized disease, which was null or close to null. However, for the distant vs. localized comparison, women 70 years of age or older had greater than 20% lower likelihood of distant stage disease than those in the youngest age group (OR=0.79, 95% CI 0.75-0.84 and OR=0.78, 95% CI=0.73-0.82 for 70-79 year-olds and 80+ year-olds respectively). One potential explanation for this finding may be that older individuals who

perceive that they are at risk for colorectal cancer based on personal history or familial risk factors are more likely to pursue gold-standard screening, such as colonoscopy, to catch this disease early. Research has shown that younger individuals are more likely to be diagnosed with less differentiated and later stage colorectal cancer, which may be partially attributed to higher rates of screening in older age groups.[5] Colonoscopies are expensive procedures, but Medicare began covering them for average-risk beneficiaries in 2001, whereas previously coverage had been limited to those who were deemed high-risk.[63] Removal of a substantial cost barrier, and the subsequent effect on screening behavior, could have increased the likelihood that those old enough to qualify for this benefit generally detect the disease at an earlier stage. It is unclear what could be influencing the difference in the protective associations of age for the regional and distant stage comparisons, but it may be worth examining differences in primary tumor site and histology to see if variations in these factors are disproportionately associated with either younger or older patients.

Black patients had had 25% higher likelihood of distant vs. localized stage disease at diagnosis compared to whites and those classified as 'other' race. In part because of historically high rates of disease and death, colorectal cancer awareness has been heavily promoted within African American communities in the United States in recent years; research published just prior to the period when patients in this cohort were diagnosed found that blacks were actually more likely to be current with colorectal cancer screening guidelines than whites.[64] However, blacks are still more likely than whites to be diagnosed with advanced stage colorectal cancer, but disparities in anatomic sub-site (e.g. proximal vs. distal disease) of diagnosis and potential differences in tumor aggressiveness by race render it difficult to disentangle truly independent

effects of screening, race, genetics, and exposures on differential outcomes in stage at diagnosis.[65] Black female breast cancer patients were more likely than those of other races to have regional and distant stage disease at the time of diagnosis. Researchers have long held that black women are more likely than whites to be diagnosed with late stage breast cancer.[66] Factors beyond racial differences in mammography screening rates likely influence this disparity; some of the most notable possibilities include socioeconomic status, lifestyle factors, and biologic tumor characteristics.[67]

Survival Following Cancer Diagnosis

In unadjusted analysis, widowed colorectal cancer patients experienced the lowest 3-year survival of all the marital status categories, but single patients had the largest corresponding hazard ratio in the adjusted Cox proportional hazards model (Table 9). It is difficult to make direct comparisons between the findings of our study and the results from past studies. In prior studies researchers only considered colon cancer,[38,43] conducted their work in foreign countries with considerably different health care systems,[42] or published their findings decades ago.[41] Also, there were differences in how the outcome 'event' of interest (e.g. death from one cancer, death from any cancer, death from any cause, etc.) was defined. These variations could limit the comparability of the effect sizes determined by using survival analyses. Keeping these limitations in mind, it is valuable to compare the findings of the current study with those of past related research studies in order to consider consistencies, discrepancies, and potential strategies to improve the validity of this type of outcomes research.

Within the United States, colon cancer is far more prevalent than rectal cancer, and the hazard ratio for colorectal cancer patients who are single (HR=1.30, 95% CI 1.25-1.35) was slightly larger than that observed in colon cancer patients in Lai's study (HR=1.23, 95% CI 1.18-1.29) although the association was in the same direction and of similar magnitude.[43] Interestingly, the patients in the other non-married categories (divorced, separated, widowed) in Lai's study had hazard ratios closer to the referent (married patients) than did non-married patients in the cohort analyzed for the current study. The difference between risk of death in other non-married patient categories in Lai's cohort (HR range: 1.11-1.15) and the same categories in the current study (HR range 1.24-1.29) is meaningful when one considers the number of total cases of colorectal cancer (more than 133 000 diagnosed in the United States each year).[4] The true difference in risk of death by marital status may be slightly larger in rectal cancer patients than colon cancer patients, which could mean Lai's technique of treating the two as distinct tumors during analysis may mask some of the actual risk present in the broader patient population, but this would be difficult to determine without further stratification and analysis. Results from Goodwin's study, however, do not support the idea that marital status is more protective among rectal compared to colon cancer patients, although the methods are not entirely analogous. Their results do not display effect sizes for specific tumors by non-married subgroups, but rather present them as unmarried vs. married. These do show higher risk of nonlocal disease and failure to receive treatment among unmarried rectal compared to colon cancer patients, but the relative risk of dying is lower in unmarried rectal cancer patients after controlling for disease stage and receipt of treatment (RR=0.97, 95% CI 0.84-1.28 in rectal cancer patients, RR=1.27, 95% CI 1.11-1.45 in colon cancer patients).[41] The current study does

not consider receipt of definitive treatment which would have been difficult to define across each of the 3 tumor types and multiple years. On the other hand, Goodwin et al controlled for this factor which could influence their final effect size estimations.

Wang et al used single patients as the referent in their Cox proportional hazards model and found that married patients were 14% less likely (HR 0.86, 95% CI 0.82-0.90) to die from cancer than those who were single. They used a similar definition for the event of interest (death from any cancer), which should enhance the comparability of results. However, only colon cancer patients were considered, and they were also able to control for receipt of cancer-directed surgery.[38] Other researchers studying cancer-specific survival have suggested that never-married (single) men's higher likelihood of substance abuse and risky behaviors may result in an increased prevalence of comorbidities relative to women, which could negatively influence health status as well as disease progression.[39] After stratifying by sex, the proportional hazards model in Appendix C provided some support for this hypothesis, with an elevated hazard ratio in single men (relative to other non-married groups) while the hazard ratio in women was essentially identical across the 3 non-married groups. Methodological differences notwithstanding, the existence of a clear protective association between marriage and survival after colorectal cancer diagnosis, even after controlling for tumor stage, is consistent between the current study and those done in the past. The effect of 'receipt of definitive surgery' as a potential confounder is not entirely known, but results of the current study suggest the effect of marriage on survival may be slightly more pronounced than has been previously reported, further emphasizing the importance of expanded research into the behavioral or immunologic mechanisms influencing this phenomenon.

As was the case with colorectal cancer patients, widowed female breast cancer patients experienced the lowest 3-year cancer-specific survival during unadjusted analysis, but those who were single had the largest corresponding hazard ratio in proportional hazards analysis (HR=1.33, 95% CI 1.27-1.39), during which age, race, and cancer stage were controlled. Effect sizes across the 3 non-married categories (divorced/separated, widowed, single) were nearly identical (HR range: 1.29-1.33), potentially lending support to a hypothesis that the mechanisms influencing marriage's association with survival in breast cancer patients may equally induce a protective effect regardless of the particular way an individual enters (or remains in) the non-married state. Among those classified as 'other' race, divorced/separated, and single patients, but not those who were reported as widowed, had markedly higher risk of cancer-specific death during follow-up than that which was observed in the full model. The reason widowed patients did not also experience higher risk of death during follow-up is unclear, but it could mean that among certain racial minorities, widowed individuals are more likely to have either the self-efficacy and/or support network necessary to make it more likely that they will pursue aggressive cancer-directed treatment. Age was controlled for in the regression models, so it is unlikely that differences in age distribution between those who were widowed and others had any influence on the relatively superior outcomes of the widowed patients under these specific circumstances.

During unadjusted analysis, widowed cervical cancer patients had substantially lower 3-year cancer-specific survival than those who were married (54.4% vs. 78.8% respectively), the largest survival difference between married patients and a non-married group for any of the 3 cohorts. In Cox proportional hazards analysis, widowed patients retained the highest risk of

cancer-specific death during follow-up even after adjusting for confounders; this was the only instance among the 3 cohorts when the group with the poorest survival during unadjusted analysis also had the largest corresponding hazard ratio in the Cox model. Research has shown that widowed women are less likely than married, cohabitating, divorced/separated, and single women to report being up-to-date with Pap testing.[29] Controlling for disease stage likely accounts for some of the survival difference attributable to disparities in cervical cancer screening; receipt of definitive treatment was not controlled for in the current study. However, if widowed women are less likely to stay current with appropriate preventive guidelines, they may also be less likely to seek and receive cervical cancer treatment, or they may not address their disease as aggressively as those in other marital status categories. In a study of factors associated with untreated cervical cancer in the United States, patients who were unmarried and older were less likely to receive any treatment following their diagnosis.[68] Other researchers have found that older patients were more likely to eschew treatment altogether or choose less aggressive treatment options.[69] While the current study controlled for age, it's clear that widowed patients have the oldest age distribution (Table 5), with more than 55% falling into the 70 years of age or older category. If old age is indeed associated with a lower likelihood of receiving appropriate cancer-directed treatment, then widowed patients in this SEER cohort may not be receiving the level of post-diagnostic care enjoyed by those in other marital status categories. The distinct age/hazard gradient observed in Table 11 suggests that even while controlling for other factors, advanced age is still associated with a lower likelihood of survival following cervical cancer diagnosis. While on the surface this may not appear to be a very surprising finding, Coker et al suggest that there is still controversy over whether age is

associated with survival after controlling for relevant confounders.[69] The protective effect of younger age, even after controlling for stage and race, was consistent with the general findings reported by Coker, although they also controlled for receipt of cancer-directed treatment.

The observational, retrospective nature of the current study prohibits definitive conclusions on whether the differences in survival between married and non-married patients were a result of patient health before the development of cancer, patient post-diagnosis behavior related to clinical decisions and familial interactions, immunologic differences, or some combination of these factors. A logical next step to begin addressing this question could be to define 'best practices' in cancer-directed treatment during the time period in which these patients were diagnosed and followed (2004 through 2009), and determine whether being married influenced the likelihood of patients in the 3 tumor cohorts receiving appropriate therapy.

Proponents of the selection effect commonly emphasize that healthier individuals may be more fit (and desirable) for marriage in the first place, which could account for some of the observed survival advantage among married patients.[38] Kaplan et al suggested that lower survival in the never married compared to the divorced/separated and widowed may provide evidence supporting the presence of this effect, because never entering marriage may increase the likelihood for more severe social isolation and reduced social connectedness.[47] In the current study, the never married (single) patients had lower adjusted survival than the divorced/separated and widowed for 2 of the 3 cancer patient cohorts (colorectal and female

breast), although the differences in effect sizes were not very pronounced. Single patients had the longest adjusted survival of the 3 non-married groups in the cervical cancer cohort.

Further consideration raises an interesting prospect, however, in that it's clear that the selection effect and the social causation effect, 2 of the leading theories proposed to explain the protective health effect of marriage, usually cannot be totally disentangled. While the selection effect may limit the marriage prospects of less healthy individuals (resulting in fewer 'unfit' individuals getting married), the relative deficiency of social networks in those left out of marriage is likely to exacerbate the disparity in health outcomes between the 2 groups. It seems likely that the presence or absence of one effect in combination with the other could modify the cumulative impact on health incomes. If there does prove to be a larger negative effect on cancer survival in never-married individuals, then it could be worthwhile to investigate the potential mediating factors, because recent research on all combined types in a European cancer patient population suggests that the excess mortality in single compared to married individuals has increased in recent years, especially among men, while the excess mortality observed in divorced/separated men and women has remained stable.[70] While the aforementioned research was conducted in a country with universal access to healthcare, as well as different societal norms for marriage, increasing health outcome disparities between the single and the previously-married could be an early indication of reduced society-level cohesion, which may leave single individuals especially vulnerable due to limited social support networks. The current study does not compare survival estimates across time, so from these data it is impossible to know whether a similar trend of excess never-married mortality is occurring in patients diagnosed with these cancers in the United States.

The findings in the current study that non-married cancer patients were diagnosed at later disease stage, and subsequently (while controlling for age) had poorer survival than married counterparts, fits with components of the social causation theory, although we can't know how much of the effect sizes are attributable to this factor. Enhanced social networks present during married life may positively influence decisions related to physical activity, diet, tobacco and alcohol use, and health-seeking behaviors, all of which influence tumor development and/or cancer prognosis.[71] Children from a current (or previous) marriage may also play a positive role in helping elders navigate the health care system.[70]

Others who have researched social support networks' potential to serve as 'stress buffers' through the effects of natural killer cells (cytotoxic cells of the immune system that respond to tumor growth) have suggested that social support also boosts the body's ability to fight the disease. Levy et al found that a substantial amount of the variance in natural killer cell activity in 25 to 70 year old women diagnosed with localized and regional stage breast cancer was explained by the presence or absence of quality emotional support from a spouse or intimate partner.[72] Cortisol, a reliable measure of physiologic stress, which has been shown to accelerate tumor cell growth in humans, has also been studied as a potential pathway for the influence of social support on cancer survival. The clinical implications are not entirely clear, but among women with distant stage breast cancer, those reporting stronger social support (based on size and quality of networks) had lower mean salivary cortisol levels, likely an indication of better neuroendocrine functioning.[73] While stress associated with limited social support networks may or may not have any influence on the initial development of a tumor, it appears that there are plausible pathways through which the presence of support in a time of

need may serve to diminish or blunt the influences of endocrine system changes associated with tumor cell proliferation.[71]

Limitations

There are certain limitations that should be considered while interpreting these results. Enhanced availability of patient-level information would increase the potential to draw more definitive conclusions from the findings in each of the 3 cancer patient cohorts. The SEER registry data do not provide individual-level socioeconomic variables, such as personal or household income, educational attainment, or occupational class. Ecological variables may serve as proxies for these variables, an approach others have implemented in similar studies, but this method increases the potential for bias.[39,40,43,74] Nonetheless, ecological variables for income, education, and select cancer screening behaviors were considered during the formative stages of analysis for this study and they did not meaningfully contribute to the explanatory models and therefore were excluded from the final versions presented in the tables in this document. Information on personal medical history, comorbidities and insurance status would also be extremely useful, but these variables were not available in the dataset. A SEER-Medicare data linkage exists that could provide a richer collection of patient-level information for patients who were Medicare enrollees. The Medicare files also contain records on matched 'non-cancer' enrollees who can be included in analysis for comparative purposes. Collectively, these linked datasets constitute one of the only domestic resources making it possible to incorporate quality of cancer care measures into population-based research.[75] However, the costs and administrative logistics associated with acquiring these additional data

for the current study proved to be prohibitive. In the future, augmenting these analyses with Medicare data may help address certain concerns associated with confounding and effect modification related to medical history and comorbidities, although eligibility for--and inferences from--such a study would be restricted to those older than age 65 years at the time of diagnosis (with rare exceptions).

The current study did not control for receipt of definitive treatment. Although other researchers have taken this approach to address potential confounders, their work usually focused on a single tumor type.[31,38] The complexities associated with determining treatment best practices (e.g. surgery, radiation, chemotherapy, etc.) for different cancer types when there is limited information available on individual medical history and tumor characteristics, combined with the dynamic nature of what is considered 'best practice' for a specific condition, influenced the decision to exclude this as a covariate in the current study. If the association between marital status and cancer outcomes is investigated further for any of these 3 cancer types individually, it might be more feasible and would be useful to assess what is considered best practice treatment during the study period and incorporate that variable into multiple regression models.

An additional limitation is the lack of information related to marital transitions (e.g. divorce, widowing, and marriage) that occur after the baseline status measurement but prior to the end of the follow-up period. The recorded value of the primary predictor variable does not vary with time in this study, even if the patient undergoes a marital transition. However, given that most of these patients are relatively advanced in age, it's likely that the majority of the

marital transitions in these cohorts would be in the direction of widowhood, or perhaps to a lesser extent, divorce or separation.[38] Assuming that there is such misclassification and that the findings in the current study are accurate, then the true size of marriage's protective effect would be underestimated. Research has suggested that failure to update patient marital status in longitudinal studies of its association with health outcomes does actually diminish the effect size observed in statistical analysis.[76]

Another important issue to consider is a lack of information on the actual quality of any given marriage for patients in this dataset. If social support is one of the mechanisms moderating the positive association between marriage and these cancer outcomes, then there is the assumption that support offered within the context of a marriage generally has positive health effects. Patients in healthy relationships are more capable of averting depression associated with a cancer diagnosis than those in relationships regarded as less emotionally healthy; this can mean detrimental effects on health-related quality of life (for both partners) for those in lower quality marriages.[11,77] For those individuals in a marriage with pre-existing high levels of stress, strife, or depression, the net negative influence of these factors may negate any positive effects resulting from social support inherent to a marriage. Future studies that are able to incorporate some validated measure to assess self-reported quality of marriage may be able to better address this concern.

SEER is an observational database; in the current study it was possible to assess associations between proposed risk factors and late stage disease/risk of death, but it was not feasible to make conclusions about the causal nature or directionality of observed correlations.

Simply put, it is impossible to say with any certainty whether being unmarried causes inferior colorectal, breast, and cervical cancer outcomes. It can only be stated that being unmarried is associated with these outcomes, and then provide evidence supporting the existence of plausible causal mechanisms involved in these associations.

Cancer-specific survival was the primary outcome measure used in this study. Determining the appropriate method for defining patient failure in survival analysis can be difficult.[53] One argument against using cause-specific survival is the potential for misclassification of the cause of death, which could bias survival estimates.[78] While acknowledging the potential for this problem in the current study, research has found SEER registry cause of death designations to be highly accurate and death from any cancer (as opposed to tumor-specific) to be an appropriate survival measure in older patient populations with a relatively high risk of death from competing non-cancer conditions, which would not be censored in analysis assessing overall survival.[60]

Conclusions

The association between marital status and health outcomes is complex, and it is likely that whether an individual is married or not can affect health, and in turn be affected by it.[79] Research that does not acknowledge and investigate this complex relationship could result in erroneous results and lead to faulty conclusions regarding the influence of marriage on health. There is broad public and scientific interest in determining whether social factors such as marriage influence the development or progression of cancer.[71] Researchers have long held that marriage is favorably associated with health, with most acknowledging some combination

of selection and social causation effects as the primary drivers of the beneficial association.[41,79,80] Goodwin and colleagues are generally credited with first identifying a protective effect of marriage on survival in cancer patients.[39] However, much of the research on this topic has been devoted to cancers for which there are no proven early detection methods recommended for average-risk adults.[11,13,31,39,40,74,81] Based on a review of the literature, the current study appears to be the first in which this relationship has been assessed in a contemporary United States population for the 3 cancers with definitive screening recommendations. If differing forms of social causation play a role in the protective associations observed in current study, then it's likely that we as a society can reduce this disparity through tailored interventions and educational programs. While these data do not allow for conclusions on causal mechanisms, simply knowing that the presence or absence of marriage can have a substantial impact on cancer-specific survival at the population level could serve as a motivator for action.

There are numerous factors influencing the association between marriage and cancer outcomes. These may include substance abuse, diet, physical activity, insurance status, mental health, and hospital care. Because this study focused on cancers detectable through routine screening, these data coupled with complementary behavioral research may be most useful when viewed through the lens of preventive health services' influence on the marital status/cancer relationship. In a comprehensive literature review of the effects of marriage on general health, Wood et al found limited research on relationships between marital status and utilization of preventive health services.[79] While there are no nationally representative data connecting marital transitions and changes in the use of cancer-related preventive services, Lee

at al found that among female nurses age 46 to 71 who had received a mammogram during the previous 2 years, transitions out of marriage (widowing or divorce) were associated with an approximately 25% higher likelihood of women skipping regular breast cancer screening during the next 4 years (adjusted OR=1.27, 95% CI 0.94-1.73 in divorced, OR=1.24, 95% CI 1.07-1.44 in widowed).[82] Interestingly, remarrying did not alter the already lower likelihood that these women would skip routine breast cancer screening in the near future. This finding suggests that the likelihood of screening for cancer may not simply be associated with getting and staying married, but also (or perhaps, rather) with the presence or absence of anguish or stress resulting from the loss of a spouse or partner. Wood's contemporary literature review of the topic suggests that there is some support for this theory in research focused on other types of cancer screening, but most other methodologies are cross-sectional and/or descriptive. They conclude by calling for an expansion of the representativeness of research on marital status and use of cancer-related preventive services.[79] While the results of the current study certainly enhance our ability to characterize the disparity in outcomes between married and the non-married colorectal, breast, and cervical cancer patients, additional person-level information on use of preventive services as well as other important variables could certainly solidify our understanding of the issue, and improve our ability to find actionable items in the causal pathway(s) for future research, policy and interventions.

Ongoing implementation of healthcare reform creates an opportunity for public health to enhance its role as a national leader in cancer prevention and control. Screening for colorectal, breast, and cervical cancer saves lives, but there are still disparities in the uptake of clinical preventive health services. There has been no improvement in national rates of

screening for breast and cervical cancer during the last decade, and scarcely more than half of adults adhere to recommended colorectal cancer screening guidelines.[23,83] While the current study does not account for differences in screening rates, we know that within this population, non-married adults are generally diagnosed with later stage cancer and have shorter survival, suggesting that early detection plays a role. The Patient Protection and Affordable Care Act will address traditional barriers such as lack of insurance through expansion of social safety nets for the poor and subsidized insurance exchanges for those in the working class, but complementary initiatives could target those who still do not actively pursue clinical preventive services.[83] The limitations of the current study may actually highlight opportunities for improvements in the infrastructure of cancer prevention. Currently, the best data available on the prevalence of cancer screening in the United States come from self-reported telephone-based surveys administered regularly over time. Registries such as SEER, however, comprehensively document events (in SEER's case, cancer outcomes) as they occur. With the substantial expansion of insurance coverage promised by health reform, there may be an opportunity to link Medicare, Medicaid, state insurance exchange, and other health benefits data to monitor preventive health behavior comprehensively at the individual level, and in real time. Special populations with poor health outcomes (such as non-married adults within the age range for cancer screening) might benefit from targeted programs designed to improve screening uptake and clinical follow-up while also monitoring treatment decisions and cancer-specific outcomes.

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APPENDICES

APPENDIX A

Assessing Sex as an Effect Modifier of Stage at Diagnosis in Colorectal Cancer Patients

Baseline category logit analysis of marital status and other factors predicting colorectal cancer stage at diagnosis in male patients, SEER cancer registries, 2004 through 2006 diagnoses, n=47 524

	Tumor stage at diagnosis			
Characteristic	Regional	*p*-value	Distant	*p*-value
Marital status				
Married	1.00		1.00	
Divorced/separated	1.14 (1.06-1.23)*	0.0006	1.49 (1.37-1.62)	<0.0001
Widowed	1.06 (0.99-1.14)	0.1023	1.27 (1.17-1.38)	<0.0001
Single	1.15 (1.07-1.23)	<0.0001	1.46 (1.36-1.58)	<0.0001
Age in years				
50-59	1.00		1.00	
60-69	0.96 (0.91-1.02)	0.1868	0.94 (0.88-1.00)	0.0631
70-79	0.92 (0.87-0.98)	0.0061	0.79 (0.73-0.84)	<0.0001
80+	0.94 (0.88-1.00)	0.0424	0.76 (0.70-0.82)	<0.0001
Race				
White	1.00		1.00	
Black	1.06 (0.99-1.14)	0.0884	1.29 (1.19-1.39)	<0.0001
Other	1.05 (0.97-1.14)	0.2007	1.08 (0.98-1.19)	0.1060
Residence				
Metropolitan	1.00		1.00	
Nonmetropolitan	0.94 (0.89-1.00)	0.0511	0.96 (0.89-1.02)	0.2011

* Odds ratio (95% confidence interval)

Baseline category logit analysis of marital status and other factors predicting colorectal cancer stage at diagnosis in female patients, SEER cancer registries, 2004 through 2006 diagnoses, n=45 181

	Tumor stage at diagnosis			
Characteristic	Regional	*p*-value	Distant	*p*-value
Marital status				
Married	1.00		1.00	
Divorced/separated	1.07 (1.00-1.15)*	0.0576	1.22 (1.12-1.33)	<0.0001
Widowed	1.07 (1.02-1.13)	0.0088	1.16 (1.08-1.23)	<0.0001
Single	1.02 (0.95-1.10)	0.5208	1.17 (1.07-1.27)	0.0003
Age in years				
50-59	1.00		1.00	
60-69	1.02 (0.95-1.09)	0.5594	0.94 (0.87-1.01)	0.1086
70-79	0.98 (0.91-1.04)	0.4390	0.81 (0.75-0.88)	<0.0001
80+	0.97 (0.91-1.04)	0.3992	0.81 (0.75-0.88)	<0.0001
Race				
White	1.00		1.00	
Black	0.93 (0.86-0.99)	0.0254	1.22 (1.13-1.32)	<0.0001
Other	1.12 (1.03-1.21)	0.0054	0.91 (0.82-1.01)	0.0694
Residence				
Metropolitan	1.00		1.00	
Nonmetropolitan	0.92 (0.86-0.97)	0.0045	0.92 (0.86-0.99)	0.0273

* Odds ratio (95% confidence interval)

APPENDIX B

Assessing Race as an Effect Modifier of Stage at Diagnosis in Female Breast Cancer Patients

Baseline category logit analysis of marital status and other factors predicting female breast cancer stage at diagnosis in white patients, SEER cancer registries, 2004-2006 diagnoses, n=117 907

	Tumor stage at diagnosis			
Characteristic	Regional	*p*-value	Distant	*p*-value
Marital status				
Married	1.00		1.00	
Divorced/separated	1.11 (1.07-1.16)*	<0.0001	1.51 (1.40-1.63)	<0.0001
Widowed	1.12 (1.08-1.16)	<0.0001	1.51 (1.40-1.62)	<0.0001
Single	1.09 (1.04-1.14)	<0.0001	1.68 (1.56-1.81)	<0.0001
Age in years				
40-49	1.00		1.00	
50-59	0.82 (0.79-0.85)	<0.0001	1.11 (1.03-1.21)	0.0081
60-69	0.65 (0.62-0.68)	<0.0001	1.04 (0.96-1.13)	0.3481
70-79	0.55 (0.53-0.57)	<0.0001	0.92 (0.84-1.00)	0.0462
80+	0.53 (0.51-0.56)	<0.0001	1.13 (1.02-1.24)	0.0172

* Odds ratio (95% confidence interval)

Baseline category logit analysis of marital status and other factors predicting female breast cancer stage at diagnosis in black patients, SEER cancer registries, 2004-2006 diagnoses, n=13 677

	Tumor stage at diagnosis			
Characteristic	Regional	*p*-value	Distant	*p*-value
Marital status				
Married	1.00		1.00	
Divorced/separated	1.01 (0.91-1.13)*	0.7973	1.42 (1.20-1.69)	<0.0001
Widowed	1.08 (0.96-1.22)	0.1809	1.38 (1.15-1.66)	0.0007
Single	1.09 (0.99-1.19)	0.0733	1.89 (1.63-2.19)	<0.0001
Age in years				
40-49	1.00		1.00	
50-59	0.96 (0.88-1.06)	0.4690	1.21 (1.03-1.42)	0.0233
60-69	0.78 (0.70-0.87)	<0.0001	1.08 (0.91-1.29)	0.3781
70-79	0.68 (0.60-0.78)	<0.0001	1.15 (0.94-1.41)	0.1661
80+	0.73 (0.62-0.86)	0.0001	1.12 (0.87-1.44)	0.3754

* Odds ratio (95% confidence interval)

Baseline category logit analysis of marital status and other factors predicting female breast cancer stage at diagnosis in patients classified as 'other' race, SEER cancer registries, 2004-2006 diagnoses, n=9 977

	Tumor stage at diagnosis			
Characteristic	Regional	*p*-value	Distant	*p*-value
Marital status				
Married	1.00		1.00	
Divorced/separated	1.22 (1.04-1.42)*	0.0143	2.05 (1.54-2.73)	<0.0001
Widowed	1.21 (1.05-1.41)	0.0108	1.57 (1.17-2.10)	0.0026
Single	1.09 (0.95-1.25)	0.2007	2.29 (1.81-2.91)	<0.0001
Age in years				
40-49	1.00		1.00	
50-59	0.80 (0.72-0.89)	<0.0001	1.22 (0.96-1.56)	0.1094
60-69	0.65 (0.57-0.74)	<0.0001	1.10 (0.84-1.44)	0.4901
70-79	0.57 (0.49-0.67)	<0.0001	0.87 (0.63-1.21)	0.4054
80+	0.56 (0.45-0.69)	<0.0001	1.15 (0.76-1.73)	0.5127

* Odds ratio (95% confidence interval)

APPENDIX C

Assessing Sex as an Effect Modifier of Survival in Colorectal Cancer Patients

Multivariate Cox proportional hazards model for marital status and other variables predicting death from any cancer among male colorectal cancer patients, SEER cancer registries, 2004-2006 diagnoses, n=47 524

Characteristic	Hazard Ratio (95% CI)	*p*-value
Marital status		
Married	1.00	
Divorced/separated	1.34 (1.27-1.42)	<0.0001
Widowed	1.26 (1.20-1.33)	<0.0001
Single	1.37 (1.31-1.44)	<0.0001
Age in years		
50-59	1.00	
60-69	1.19 (1.13-1.25)	<0.0001
70-79	1.72 (1.64-1.80)	<0.0001
80+	2.79 (2.65-2.93)	<0.0001
Race		
White	1.00	
Black	1.27 (1.21-1.33)	<0.0001
Other	0.93 (0.87-0.99)	0.0266
Tumor stage		
Localized	1.00	
Regional	2.25 (2.15-2.35)	<0.0001
Distant	13.08 (12.53-13.66)	<0.0001

Multivariate Cox proportional hazards model for marital status and other variables predicting death from any cancer among female colorectal cancer patients, SEER cancer registries, 2004-2006 diagnoses, n=45 183

Characteristic	Hazard Ratio (95% CI)	*p*-value
Marital status		
Married	1.00	
Divorced/separated	1.23 (1.16-1.30)	<0.0001
Widowed	1.21 (1.17-1.26)	<0.0001
Single	1.22 (1.15-1.29)	<0.0001
Age in years		
50-59	1.00	
60-69	1.23 (1.16-1.30)	<0.0001
70-79	1.72 (1.63-1.81)	<0.0001
80+	2.64 (2.49-2.79)	<0.0001
Race		
White	1.00	
Black	1.14 (1.08-1.20)	<0.0001
Other	0.89 (0.83-0.96)	0.0013
Tumor stage		
Localized	1.00	
Regional	2.38 (2.27-2.49)	<0.0001
Distant	13.81 (13.19-14.46)	<0.0001

APPENDIX D

Assessing Race as an Effect Modifier of Survival in Female Breast Cancer Patients

Multivariate Cox proportional hazards model for marital status and other variables predicting death from any cancer among white female breast cancer patients, SEER cancer registries, 2004-2006 diagnoses, n=117 907

Characteristic	Hazard Ratio (95% CI)	*p*-value
Marital status		
Married	1.00	
Divorced/separated	1.30 (1.23-1.37)	<0.0001
Widowed	1.31 (1.25-1.37)	<0.0001
Single	1.27 (1.20-1.34)	<0.0001
Age in years		
40-49	1.00	
50-59	1.19 (1.12-1.27)	<0.0001
60-69	1.42 (1.34-1.51)	<0.0001
70-79	1.94 (1.82-2.06)	<0.0001
80+	3.12 (2.92-2.24)	<0.0001
Tumor stage		
Localized	1.00	
Regional	2.92 (2.90-3.05)	<0.0001
Distant	21.10 (20.21-22.04)	<0.0001

Multivariate Cox proportional hazards model for marital status and other variables predicting death from any cancer among black female breast cancer patients, SEER cancer registries, 2004-2006 diagnoses, n=13 677

Characteristic	Hazard Ratio (95% CI)	*p*-value
Marital status		
Married	1.00	
Divorced/separated	1.20 (1.07-1.35)	0.0015
Widowed	1.28 (1.14-1.45)	<0.0001
Single	1.36 (1.23-1.50)	<0.0001
Age in years		
40-49	1.00	
50-59	1.09 (0.98-1.21)	0.1109
60-69	1.07 (0.95-1.20)	0.2904
70-79	1.44 (1.27-1.64)	<0.0001
80+	2.14 (1.84-2.49)	<0.0001
Tumor stage		
Localized	1.00	
Regional	2.68 (2.43-2.96)	<0.0001
Distant	17.03 (15.42-18.80)	<0.0001

Multivariate Cox proportional hazards model for marital status and other variables predicting death from any cancer among female breast cancer patients classified as 'other' race, SEER cancer registries, 2004-2006 diagnoses, n=9 977

Characteristic	Hazard Ratio (95% CI)	*p*-value
Marital status		
Married	1.00	
Divorced/separated	1.64 (1.32-2.02)	<0.0001
Widowed	1.34 (1.09-1.64)	0.0054
Single	1.55 (1.28-1.87)	<0.0001
Age in years		
40-49	1.00	
50-59	1.19 (0.98-1.45)	0.0782
60-69	1.34 (1.12-1.71)	0.0023
70-79	1.84 (1.45-2.32)	<0.0001
80+	3.66 (2.80-4.80)	<0.0001
Tumor stage		
Localized	1.00	
Regional	3.33 (2.81-3.94)	<0.0001
Distant	27.65 (23.20-32.97)	<0.0001

APPENDIX E

Institutional Review Board Determination Letter



East Tennessee State University
Office for the Protection of Human Research Subjects • Box 70565 • Johnson City, Tennessee 37614-1707
Phone: (423) 439-6053 Fax: (423) 439-6060

November 14, 2012

David J. Blackley
507 E. Unaka Ave. Apt. 2
Johnson City, TN 37601

Dear Mr. Blackley,

Thank you for recently submitting information regarding your proposed project "Tumor stage at diagnosis and survival for three cancers with screening recommendations for average-risk adults: Does marital status play a role? (tentative)."

I have reviewed the information, which includes a completed Form 129.

The determination is that this proposed activity as described meets neither the FDA nor the DHHS definition of research involving human subjects. Therefore, it does not fall under the purview of the ETSU IRB.

IRB review and approval by East Tennessee State University is not required. This determination applies only to the activities described in the IRB submission and does not apply should any changes be made. If changes are made and there are questions about whether these activities are human subject research in which the organization is engaged, please submit a new request to the IRB for a determination.

Thank you for your commitment to excellence.

Sincerely,
Chris Ayres
Chair, ETSUIRB



Accredited Since December 2005

VITA

DAVID JOHN BLACKLEY

Personal Data: Date of Birth: September 28, 1983

Place of Birth: Shelby, NC

Education: Public Schools, Shelby, NC 2002

B.S. Zoology, North Carolina State University, Raleigh, NC 2006

M.P.H. with a concentration in Analysis and Management, East Carolina University, Greenville, NC 2010

Dr.P.H. with a concentration in Epidemiology, East Tennessee State University, Johnson City, TN 2013

Experience: Cytogenetic oncology laboratory technologist, Laboratory Corporation of America, Research Triangle Park, NC 2006-2008

Epidemic Intelligence Service Officer, Centers for Disease Control and Prevention, Atlanta, GA, start 2013

Honors: Eagle Scout, Boy Scouts of America, 1999