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# The Effect of Marriage on Stage at Diagnosis and Survival in Women with Cervical Cancer

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# THE EFFECT OF MARRIAGE ON STAGE AT DIAGNOSIS AND SURVIVAL IN WOMEN WITH CERVICAL CANCER

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## ABSTRACT

Marriage is associated with improved health outcomes for many conditions. Married persons enjoy financial stability, social and emotional support, and tend to have better control of health risk behaviors compared to the unmarried. The marriage scene is changing continuously. Americans are marrying less or delaying the engagement to an older age. They are divorcing more, they choose cohabitation as an alternative to marriage, or engage in premarital relationships. As a consequence, barely half of Americans were married in 2011 compared to close to three quarters of Americans were married in the sixties. With the increase of the unmarried population - including those who cohabitate, the never married, the divorced, and the widowed - understanding whether marriage is an independent determinant of health outcomes is an important public health matter.

The relationship of marriage and health outcomes has been studied for many health conditions and cancer sites. However, this association has not been fully explored for cervical cancer outcomes. In addition, studies with recent data are lacking. This study aimed at investigating whether marriage has a protective effect from late stage of diagnosis and whether it independently improves survival in women with cervical cancer with more recent population-based data.

The National Cancer Institute program Surveillance, Epidemiology, and End Results (SEER) was used to identify women with cervical cancer diagnosed between 2000 and 2010. Statistical analyses were conducted to assess the effect of marriage on stage and survival. The Logistic regression modeling was used to calculate the odds ratios of advanced stage - defined as regional and distant - accounting for socio-demographic and clinical covariates. Hazard ratios were obtained by the Cox Proportional Hazards modeling to compare death risk between married and unmarried women. Additional modeling was conducted with cases diagnosed between 2007 and 2010 to account for insurance status at diagnosis. Kaplan Meier survival curves and Log Rank

test of difference in survival between marital groups were executed. Interactions between marital status and age; between marital status and race; and between marital status and stage were tested.

In terms of stage of diagnosis, Single [adjusted odds ratio (aOR) 1.41; 95% CI = 1.33-1.49], separated/divorced [aOR 1.44; 95% CI = 1.34-1.55], and widowed women [aOR 1.43; 95% CI = 1.31-1.58] were significantly more likely to be diagnosed at an advanced stage compared to married women after controlling for age, race/ethnicity, period of diagnosis, histology, and SEER area. Marital status was found to be an independent factor for survival. Single (aHR 1.35; 95% CI = 1.28-1.43), separated (aHR 1.22; 95% CI = 1.15-1.29), and widowed women (aHR 1.28; 95% CI = 1.19-1.36) had increased death risk compared to married women adjusted for socio-demographic (age, race/ ethnicity) and clinical factors (stage, histology, and period of diagnosis). Even after controlling for insurance status, married women continued to be more likely to be diagnosed early and have favorable survival over the unmarried.

Findings from this study support the rising body of literature of the protective effect of marriage on cancer outcomes. Particularly for cervical cancer, based on its sexually transmitted etiology, unmarried women are more likely to have multiple sexual partners and are, therefore, at increased risk of developing this cancer. Moreover, unmarried women are more likely to have inadequate access to health care, which reduces their chance of receiving recommended cervical screening services and timely treatment. In addition, unmarried women lack spousal emotional and social support, which contribute to psychosocial stress and unfavorable health outcomes.

National guidelines on cervical cancer risk factors may need to be revised to include marital status as an independent predictor for stage of diagnosis and survival. Further qualitative and quantitative research is needed to determine how to improve health outcomes for the unmarried population in the clinical and the community settings.

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To my dear parents, husband and son

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# CHAPTER 1 BACKGROUND AND SIGNIFICANCE

## SECTION 1 INTRODUCTION

### Marriage

#### *Marriage trends*

Marriage is a social institution that affects individuals' lives in many aspects. Marriage is associated with family life, wellbeing, and mutual support in times of hardship. In most cultures and populations, entering adulthood is closely related to finding the significant other and starting a family. Raising children, achieving physical, mental and economic happiness and stability are some of the traditional reasons to exchanging vows.

In recent times, especially for the new generations, marriage is decreasingly attractive. Marriage rates in the United States are steadily falling. In 2011, less than half of American households were composed of married couples compared with over three quarter of households in the 1950s (US Census Bureau, 2011). Reasons for this trend may stem from economic hardships, pursuit of higher education, and other complex social patterns. These trends are similar for men and women.

While women were gaining emancipation entering the work force and seeking higher degrees, their family plans were being placed on hold. Women are getting married later and prefer premarital cohabitation. In 2010, one of every two young females age 25 to 29 had never married compared to one in five women in 1970 (US Census Bureau, 2011). The median age at first marriage in women increased from 20 in 1970 to 26 years of age in 2009. While 88 percent of women were married by the age of 24 in the 1970s, only 38

percent were married by the age 24 in 2009 (Elliott & Simmons, 2011). On the other hand, premarital cohabitation increased from 3% in 1995 to 11% in 2010 (Copen, Daniels, Vespa, & Mosher, 2012).

In combination with decreasing marriage rates, marriage termination is on the rise. Compared to a very low baseline (less than 1%) of separated or divorced women in 1920, the proportion of married has increased to 15% in 2011 (US Census Bureau, 2011) (Figure 1.1).

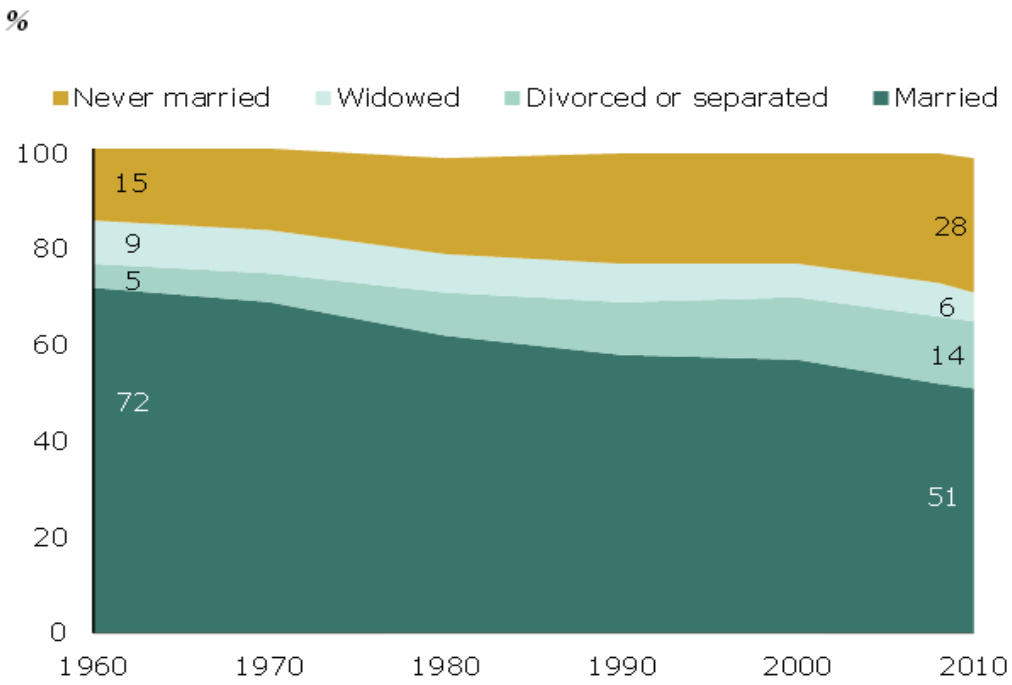


**Figure 1.1.** Current marital status 1960-2010
Source: Pew Research Center analysis of Decennial Census (1960-2000) and American Community Survey data (2008, 2010), IPUMS.

### *Marriage and health*

Marriage has been traditionally found to improve many health outcomes for both spouses. Although healthier persons may be selectively more likely to marry, overall, marriage has been found to be health protective (Bailey, 2009; Chandra, Szklo, Goldberg, & Tonascia, 1983; Schoenborn, 2004).

There are many factors that work synergistically to provide married persons with financial, social, emotional, and even physical safety nets that ultimately promote health and prolong life:

#### Financial stability

Some of the health benefits conferred by marriage are mediated through increased financial stability for the spouses. Married persons generally profit from combination of their earnings and can rely on each other in times of hardship. In addition, unemployed married persons have the opportunity to gain health insurance coverage under the spouse's employer-sponsored plan; this greatly improves access to healthcare services (Bernstein, Cohen, Brett, & Bush, 2008).

#### Social and emotional support

The literature is increasingly exploring the effect of social and emotional support on health outcomes (Ell, Nishimoto, Mediansky, Mantell, & Hamovitch, 1992; Kroenke, Kubzansky, Schernhammer, Holmes, & Kawachi, 2006; Zhang, Norris, Gregg, & Beckles, 2007). Outcomes from life-threatening conditions are particularly affected by the extent of social networks (Brummett et al., 2001). Marriage offers a safety net against

social isolation through strong ties between spouses and other family members. These ties are especially beneficial in times of illness. For instance, married breast cancer patients have been consistently shown to enjoy better survival relative to their unmarried counterparts (Ell, Nishimoto, Mediansky, Mantell, & Hamovitch, 1992; Neale, Tilley, & Vernon, 1986; Osborne, Ostir, Du, Peek, & Goodwin, 2005).

#### Effect on health behaviors

Other mechanisms by which marriage might influence health outcomes include its effect on some health risk factors through the motivation to adopt healthier behaviors. The interaction of self-motivation and/or spousal-motivation in married persons is likely to have a positive impact on health. For example, smoking is more prevalent in unmarried persons than those who are married regardless of gender. A similar pattern is found in terms of heavy drinking with married persons having the lowest rates (Schoenborn, 2004). Even persons who live with a partner have worse risky health behaviors indicators than married persons, more comparable to divorced or widowed persons suggesting an intrinsic protective effect of marriage beyond living together under the same roof (Schoenborn, 2004).

### *Marital status and health outcomes*

#### Effect on death risk from various health conditions

The effect of marital status has been studied for many health conditions. Eaker and colleagues found married men in the Framingham Offspring Study had almost a 50% decreased risk of death from cardiovascular disease compared to unmarried men (Eaker,

Sullivan, Kelly-Hayes, D'Agostino, & Benjamin, 2007). Likewise, using longitudinal data from the National Longitudinal Mortality Study, Johnson and colleagues found middle aged non-married men and women, regardless of marital status subgroup and race, to be at significant increased mortality risk. This finding was upheld even after accounting for social and economic factors such as education, income, and employment status (Johnson, Backlund, Sorlie, & Loveless, 2000). In another study, never married males aged 19 to 44 had a two-fold increase in death risk from pulmonary disease and accidents compared to married males in the same age group. The risk increased to nine-fold for death caused by infectious diseases (Kaplan & Kronick, 2006).

### Effect on death risk from cancer

The protective effect of marriage has also been extensively studied for cancer outcomes. Although there were a few studies that were not able to detect a relationship between marriage and cancer outcomes (Jatoi et al., 2007; Kroenke, Kubzansky, Schernhammer, Holmes, & Kawachi, 2006), most other studies established a protective effect of marriage (Table 1.1 & 1.2). Separated or divorced breast cancer patients from the Detroit metropolitan area had unfavorable survival compared to their married counterparts (Neale, Tilley, & Vernon, 1986). Widowed breast cancer patients from the Houston area had a significanty lower survival compared to married patients (30% ten year-survival vs. 45% ten year-survival respectively) (Neale, 1994).

Several authors have used national population-based data from the Surveillance, Epidemiology and End Results to study survival differentials between marital groups. Married patients with common cancers such as lung, colorectal, breast, pancreatic,

prostate, liver, non-Hodgkin lymphoma, head/neck, ovarian, or esophageal cancers had a consistently significant survival advantage over unmarried patients with males having even greater benefits from marriage compared to females (Aizer et al., 2013; Baine et al., 2011; Lai et al., 1999; Mahdi et al., 2013; Wang, Wilson, Stewart, & Hollenbeak, 2011). The protective effect of marriage was also experienced by Norwegian cancer patients (Kravdal, 2001; Kravdal, 2013).

**Table 1.1.** Death risk for unmarried vs. married – various sources of data

| Cancer Site | Period | N | Data source | HR | 95% CI | Authors |
|---|---|---|---|---|---|---|
| Breast Cancer | 1973-1978 | 10,778 | Detroit Cancer Surveillance System | 1.12 | 1.00-1.26 | Neale V. Anne |
| Multiple cancers | 2005-2007 | 21,694 | Norwegian Cancer Registry | 1.47 | 1.29-1.67 | Kravdal Oystein |
| Multiple cancers | 1970-2007 | 441,556 | Norwegian Cancer Registry | 1.17 | 1.15-1.20 | Kravdal et al. |

**Table 1.2.** Death risk for married vs. unmarried – studies that used SEER data

| Cancer site | Period | N | HR | 95% CI | Authors |
|---|---|---|---|---|---|
| Multiple cancers | 2004-2008 | 1,260,898 | 0.80 | 0.79-0.81 | Aizer et al. |
| Colon | 1992-2006 | 127,753 | 0.87 | 0.83-0.91 | Wang et al. |
| Ovarian | 1988-2006 | 49,777 | 0.80 | 0.78-0.83 | Mahdi et al. |
| Pancreatic | 1998-2003 | 34,555 | 0.87 | 0.85-0.89 | Baine et al. |

### Effect on cancer stage at diagnosis

Some studies have also examined whether marital status affects cancer stage at diagnosis. These studies have found that unmarried cancer patients are at a disadvantage of being diagnosed at an advanced stage compared to married patients (Aizer et al., 2013;

Goodwin, Hunt, Key, & Samet, 1987; Ortiz, Freeman, Kuo, & Goodwin, 2007; Osborne, Ostir, Du, Peek, & Goodwin, 2005) (Table 1.3).

**Table 1.3.** Effect of marriage on odds ratios of advanced stage of diagnosis - various sources of data

| Cancer Site | Period | N | Data source | OR | 95% CI | Authors |
|---|---|---|---|---|---|---|
| Breast Cancer | 1991-1995 | 32,268 | SEER-Medicare | 1.17* | 1.12-1.23 | Osborne et al. |
| Melanoma | 1991-1999 | 5,835 | SEER-Medicare | 1.31* | 1.13-1.52 | Ortiz et al. |
| Multiple | | 27,779 | New Mexico | 1.19* | 1.12-1.25 | Goodwin et al. |
| Multiple cancers | 2004-2008 | 1,260,898 | SEER | 0.83** | 0.82-0.84 | Aizer et al. |

*Odds ratio of unmarried vs. married.
**Odds ratio of married vs. unmarried.

## Cervical cancer in the U.S.

### *Risk factors*

Cervical cancer is cancer that starts in the tissues of the cervix. It is the second most common cancer in women worldwide (World Health Organization. Department of Reproductive Health, World Health Organization. Department of Chronic Diseases, & Health Promotion, 2006). The main cause of cervical cancer is infection with human papillomavirus (HPV). Some other risk factors include: smoking history; immunosuppression such as HIV infection; multiple sexual partners; early sexual activity; young age at first pregnancy; and history of cervical dysplasia (American Cancer Society, 2013).

### *Incidence and mortality trends*

In 2013, it was estimated that 12,340 new cases of invasive cervical cancer will be diagnosed and that 4,030 women would die of the disease in the United States (Siegel, Naishadham, & Jemal, 2013).

Cervical cancer incidence and mortality in the U.S. have been declining by 2% per year in the last decade, with a remarkable decrease of 54% in incidence in the last 35 years (Adegoke, Kulasingam, & Virnig, 2012; CDC, 2012). This decline is largely attributed to the wide spread use of screening with cervical cytology screening (Papanicolaou test), which can detect precancerous lesions, and thus, prevent the disease or can detect cervical neoplasm at a treatable stage (CDC, 2012).

### *Cervical cancer screening*

The US Preventive Services Task Force and the American Cancer Society recommend cervical cancer screening every three years with Pap test in women with average risk starting at age 21 to 29 years of age. Women aged 30 to 65 can be screened with a combination of cytology and HPV DNA tests every five years. Annual screening is not recommended for any age (Smith, Brooks, Cokkinides, Saslow, & Brawley, 2013; US Preventive Services Task Force, 2013).

### *Stage at diagnosis and survival*

Stage at diagnosis is used to guide selection of primary or adjuvant treatment and to evaluate treatment results. Therefore, cancer stage of presentation is a major predictor of prognosis. For cervical cancer, regional and distant stages have the poorest outcomes in

terms of survival. The five-year survival rate for cervical cancer drops from 91% for localized stage, to 57% and 16% for regional and distant stages respectively (Siegel, Naishadham, & Jemal, 2013).

### *Effect of marriage in cervical cancer patients*

In contrast to other cancers, the association between marriage and cervical cancer outcomes has not received adequate attention. An early study found that in both Black and White women, the age-adjusted incidence rates of cervical cancer were lowest in married women compared to single, divorced, or widowed (Swanson, Belle, & Satariano, 1985)

In terms of late stage at diagnosis, Ferrante and colleagues found that unmarried women from Florida had a significant 63% increase in likelihood of being detected at an advanced stage compared to married women (OR 1.63; 95% CI = 1.18-2.25) (Ferrante, Gonzalez, Roetzheim, Pal, & Woodard, 2000).

In a study that assessed racial differences in survival among cervical cancer patients from SEER areas between 1988 and 1994, the authors found that widowed, divorced, or separated women had poorer survival (aHR 1.15; 95% CI = 1.02-1.29) compared to married women. Single women had a 10% increase in death risk, although, this risk did not approach statistical significance (aHR 1.10; 95% CT = 0.93-1.29) (Howell, Chen, & Concato, 1999). Lai et al. showed similar poorer survival in single women in relation to married women in the 1973-1990 period (HR 1.25; 95% CI = 1.04-1.5) (Lai et al., 1999).

In his study of the Norwegian cancer population, Kravdal found the never-married and the separated or divorced cervical cancer patients had almost 30% increase in excess mortality compared to the married. However, widowed patients had excess mortality comparable to married patients (Kravdal, 2001).

## SECTION 2 STUDY PURPOSE AND HYPOTHESES

### Study purpose

The literature review of the association of marital status and cervical cancer survival shows inconsistent findings for some of the unmarried categories. On the other hand, marital differentials in terms of stage at diagnosis have not been fully explored. Further, there is a lack of studies of this association with more recent data. In the present study, we investigated whether marriage has a protective effect from late stage of diagnosis and whether it independently improves survival in women with cervical cancer with more recent population-based data.

### Hypotheses

**H1:** Unmarried women (single, separated, or widowed) are more likely to be diagnosed with cervical cancer at an advanced stage compared to married women adjusted for socio-demographic and clinical characteristics.

**H2:** Unmarried women are more likely to die of cervical cancer compared to married women adjusted for socio-demographic and clinical characteristics.

**Conceptual model**

In the hypothesized model (Figure 1.2), we present the multidimensional association between being married and having better cervical cancer outcomes. Marriage improves women's financial, health access, and emotional status in addition to providing ground for protection from HPV infection risk factors, assuming mutual monogamous relationships.

**Significance to public health**

Results from this study might inform whether unmarried women have a differential risk for late diagnosis and poorer prognosis for cervical cancer. In this case, clinicians and public health professionals may need to develop targeted guidelines and programs to reduce unfavorable outcomes for unmarried women.

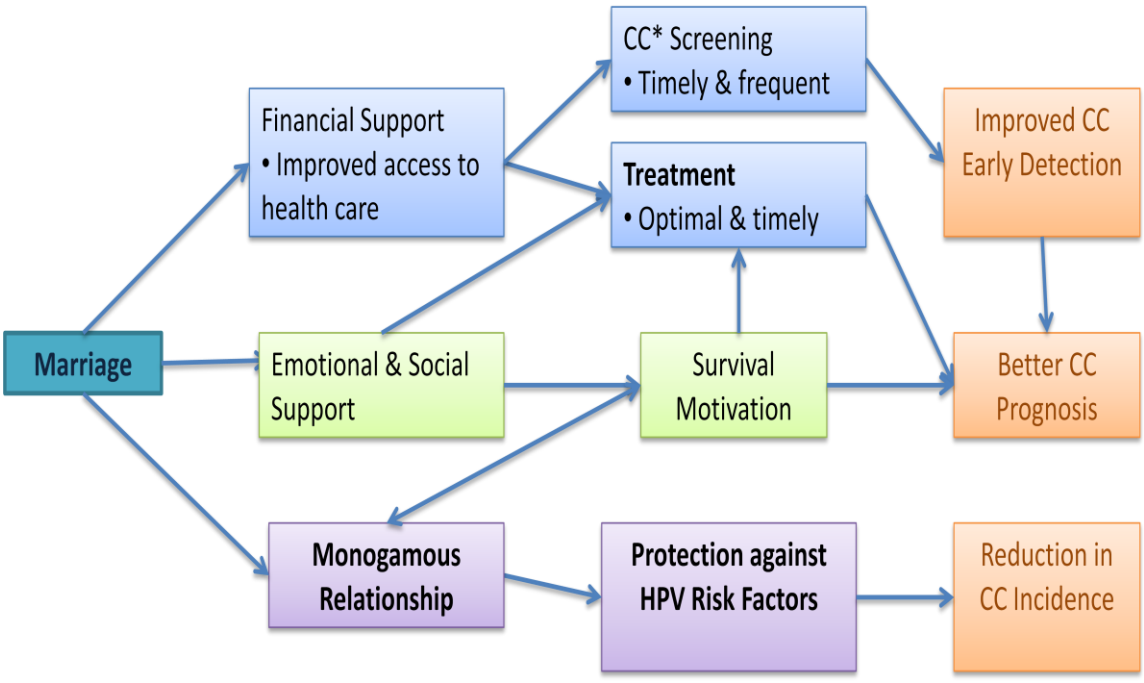


**Figure 1.2.** Conceptual model: marital status and cervical cancer outcomes

# CHAPTER 2 METHODS

## SECTION 1 STUDY DESIGN

### Design method

In the present study, a cross-sectional design was used to assess the association of marital status and late stage at diagnosis. For this purpose, the logistic regression modeling was used to calculate the odds ratios of advanced stage accounting for socio-demographic and clinical covariates. To assess differences in survival between married and unmarried cervical cancer cases, a longitudinal design was used. In this design, the Cox Proportional Hazards modeling was conducted to obtain hazard ratios for death risk adjusted for the selected covariates.

### Study population

This study used population-based data from the Surveillance, Epidemiology and End Results 18 (SEER) program of the National Cancer Institute (NCI). The SEER program was funded by NCI since 1973 as a result of the National Cancer Act of 1971.

The Surveillance, Epidemiology and End Results 18 geographic areas represent approximately 28% of the US population. There are nine states (New Mexico, Hawaii, Utah, Iowa, Connecticut, Greater California, Kentucky, Louisiana, New Jersey), five metropolitan areas (Metro Atlanta plus a sample of rural Georgia, the Greater Bay Area [San Francisco-Oakland and San-Jose Monterey], Los Angeles, Seattle, Detroit), and the Alaska Native Tumor Registry (Figure 2.1).

The SEER registries maintain high quality standards and report timely, accurate, and continuous data. They monitor cancer trends and provide information about patient demographics, primary tumor site, specific cancer markers, cancer stage at diagnosis, first course of treatment, and patient survival (Surveillance, Epidemiology, and End Results (SEER) Program, 2013).

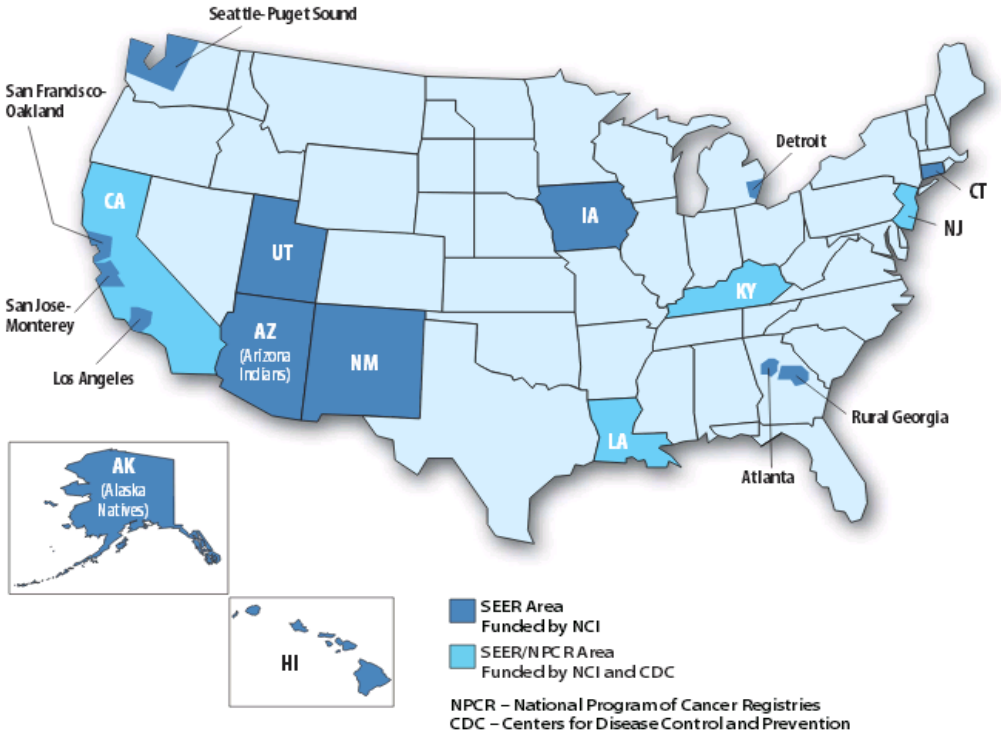


**Figure 2.1.** SEER registries areas
Source: US department of Health and Human Services, National Cancer Institute.

### Inclusions and exclusions

Cases diagnosed with primary invasive cervical cancer between 2000 and 2010 were identified using the International Classification of Diseases for Oncology, Third Edition, (ICD-O-3) codes: C53.0, C53.1, C53.8, and C53.9.

Patients diagnosed at less than 15 years old, diagnosed at the time of death, reported through a death certificate, or diagnosed with sarcoma cell type were excluded from the study. Only cases with one primary cervical cancer were included, cases with two or more malignancies of any kind were excluded.

Other observations were selectively excluded depending on the statistical analysis. For instance, patients with unknown marital status were excluded from the bivariate analysis and cases with unknown stage were excluded from the logistic regression.

## Variables and recodings

### *Marital status*

The original marital status variable included these categories: single (never married), married (including common law), separated, divorced, widowed, unmarried or domestic partner, and unknown. Married was then brought as the first category, then single and unmarried or domestic partner were combined in the single category. Separated and divorced were also combined in one category. The last categories were widowed and unknown marital status at diagnosis.

### *Age at diagnosis*

Age at diagnosis was categorized from the continuous variable to the traditionally used five age groups in survival analysis: 15-44; 45-54; 55-64; 65-74; and older than 75 years old.

### *Race/ethnicity*

The race/ethnicity variable was created by combining information from race (Whites, Blacks, American Indians/Alaskan Natives, and Asians/ Pacific Islanders) with ethnicity (Hispanic, non-Hispanic). This created a new variable with the following categories: non-Hispanic (NH) Whites, NH Blacks, NH American Indians/Alaskan Natives, and NH Asians/ Pacific Islanders in addition to Hispanics of all races.

### *Period of diagnosis*

The year of diagnosis was used to create the period of diagnosis. Three mutually exclusive periods were generated: 2000 to 2003; 2004 to 2007; and 2008 to 2010.

### *Histology*

A new histology variable was created from the histology ICD-O-3 broad grouping by adding the number 8000 to the original variable. This allowed for easy categorization. Then this very detailed cell type variable was categorized into five major histology types: squamous cell carcinomas, adenocarcinomas, adenosquamous, carcinomas, sarcomas, in addition to other types.

### *Stage at diagnosis*

SEER historic stage was used, which is a simpler version, compared to the American Joint Commission on Cancer (AJCC) staging (Surveillance, Epidemiology, and End Results (SEER) Program, 2013). Although the SEER Historic stage contains an "in situ" category, in situ cervical cancer is not reported. Therefore, there were no cases in this

category and it was omitted from the stage variable. The final stage variable contained the following categories: localized, regional, distant, and unstaged. The advanced stage category was then created combining regional and distant. The dichotomized version of stage (localized/advanced) was used in the Logistic regression modeling.

### *SEER registry*

Since the creation of the SEER program in 1973, several cancer registries have joined throughout the years. Currently, there are eighteen participating cancer registries in the program. Because of geographical population variations in terms of heath care access and survival outcomes, the SEER registry variable was included in the models.

Frequency tables were generated continuously to test for any coding errors or missing observations.

This study was deemed exempt by the Biomedical Institutional Review Board of the University of Nevada, Las Vegas under Protocol # 1308-4542M.

## SECTION 2 STATISTICAL ANALYSES

### Model diagnostics

The Akaike Information Criterion (AIC) was used to select the best-fitted model. Logistic and Cox regression models with the smallest AIC were retained. The Variance Inflation Factor (VIF) was used to test for multicolinearity between covariates. Each covariate was regressed on the other ones and the VIF was verified at each step. A VIF >10 is indicative

of multicolinearity. Linearly correlated variables may inflate the errors of the estimated parameters.

**Bivariate analysis**

Frequencies of patient characteristics by marital status were generated. These frequencies informed about the proportion of each covariate distributed by marital status categories except for unknown marital status. Differences between groups were assessed using Likelihood Chi-square test.

**Logistic regression**

In the logistic regression analysis, a model was fitted to predict advanced stage of diagnosis (regional & distant) vs. localized stage by marital status while controlling for age, race/ethnicity, period of diagnosis, SEER area, and histology. Odds ratios were obtained and their 95% confidence intervals (CI) were estimated. SAS PROC LOGIT procedure was used to generate the logistic model.

**Kaplan-Meier survival curve**

The Kaplan-Meier survival curve was generated using the SAS Output Delivery System (ODS). To test whether survival was different between marital status groups, the Log-Rank test in the LIFETEST Procedure was used.

## Cox proportional hazards modeling

The Cox proportional hazards regression was used to estimate hazard ratios of death for unmarried (single, separated or divorced, and widowed) cases compared to married cases while controlling for age, race/ethnicity, period of diagnosis, stage, SEER area, and histology. This model is considerably robust in terms of survival analysis. It does not require assumptions about the shape of the distribution of survival times, it has different methods to handle tied data, it accommodates for continuous and discrete variables, it allows for time-dependent covariates, and it is flexible in terms of stratification (Allison, 2012).

The SAS procedure used for the Cox regression was PROC PHREG.

### *Tied data*

Data are tied when events occur at the same time. It is very likely that our data have cases that died at the same time given the very large number of observations. The EXACT method handles tied data; however, because our dataset is large, this method would need a substantial amount of mathematical computations and, therefore, computer time. For this reason, the Efron approximation was used in the Proportional Hazard model to remedy tied data.

## Interactions

Interactions between marital status and age; and marital status and race were tested in the Logistic regression model. Interactions were also tested between marital status and stage; marital status and age; and marital status and race in the Cox Regression model. Where

interaction terms were found significant at $p<0.05$, the model was stratified by the covariate.

## Additional analyses

### *Unmarried comparisons*

The "CONTRAST" statement in SAS was used to examine advanced stage and survival differential between the unmarried categories:

- Singles vs. separated or divorced
- Singles vs. widowed
- Widowed vs. separated or divorced

Results from these comparisons inform which one of the unmarried categories has increased likelihood of advanced stage and higher death risk compared to the other unmarried categories.

### *Combined marital status*

Marital status was also tested with combined unmarried categories. Single, separate or divorced, and widowed categories were combined in one category called "unmarried". Advanced stage and survival differentials were then tested between married and unmarried cervical cancer cases.

### *Sub-analyses*

In April 2013, the SEER program released data about insurance status at diagnosis for cancer cases diagnosed from 2007 through 2010. The insurance variable includes the

following categories: Insured, uninsured, insured under Medicaid, and unknown insurance status.

Sub-analyses were conducted to include insurance information in order to assess whether adjusting for insurance status will affect the odds for stage at diagnosis and hazard ratios for survival. The sub-analyses included cases from 2007 to 2010 and consisted of the models describes above (logistic regression and survival) with the added insurance covariate.

All analyses were conducted using version 9.2 of the SAS statistical software (SAS Institute, Cary, NC)

# CHAPTER 3 RESULTS

## SECTION 1 MODELING

### Model diagnostics

In both the logistic and Cox regression models, the selection methods resulted in the same AIC and therefore all the covariates were kept in the final models (Table 3.1).

No multicolinearity was found between the covariates according to the Variance Inflation Factor (VIF).

**Table 3.1.** Model selection

| Model | Selection method | AIC |
|---|---|---|
| **Logistic regression** | Forward | 38574.99 |
| | Backward | 38574.99 |
| | Stepwise | 38574.99 |
| **Cox regression** | Forward | 187255.8 |
| | Backward | 187255.8 |
| | Stepwise | 187255.8 |

### Bivariate analysis by marital status

Results of the bivariate analysis of patients' demographic and clinical characteristics by marital status (married, single, separated/divorced, and widowed) are presented in Table 3.2. The binary analysis excluded unknown marital status cases. Our study consisted of 31425 women with cervical cancer diagnosed between 2000 and 2010. Overall, most cases were married at the time of diagnosis; 14513 cases (46.3%). Almost 1 out of every

3 cases were single; 8851 cases (28%). Separated/divorced or widowed patients represented 15% (4652) and 11% (3379) of the total sample respectively.

Married and single patients were younger (less than 44 years old) at the time of diagnosis compared to separated and widowed patients (48.1% and 57% vs. 35% and 4% respectively, $p<0.001$). Widowed women had the highest proportion (84%) of elder cases aged 65 and older.

The majority of cases were White (16840, 54%) followed by Hispanics (7230, 23%), and Blacks (4348, 14%). Of the married, single, and widowed cases over half were White. Compared to other race/ethnic groups, Blacks women had the largest proportion of the combined unmarried subgroups – single, separated/divorced, and widowed - (3252, 74.8%).

The percentage of cases diagnosed at localized and advanced stage was similar (48% and 48% respectively). However, significant differences were found between marital status groups. More married patients were diagnosed at a localized stage (7984, 55%) than patients in other marital groups (47% of singles, 42% of separated/divorced, and 28% of widowers, $p<0.001$). Advanced stage, including regional and distant, was highest among widowed women (2201, 65%).

After summarizing year of diagnosis into three mutually exclusive periods (2000-2003, 2004-2007, 2008-2010), there seems to be a general downward trend in number of cases diagnosed in more recent years. This trend was somewhat similar across marital status groups with married women experiencing a considerable drop in number of cases of 12% points from the first period (2000-2003) to the third period (2008-2010).

**Table 3.2.** Cervical cancer cases characteristics by marital status

| Patient Characteristics | Total | | Married | | Single | | Separated/ Divorced | | Widowed | | P** value |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | n | % | n | % | n | % | n | % | n | % | |
| Total | 31425 | 100 | 14543 | | 8851 | | 4652 | | 3379 | | |
| **Age at Diagnosis** | | | | | | | | | | | <0.001 |
| 15-44 | 13751 | 44 | 6991 | 48 | 5011 | 57 | 1615 | 35 | 134 | 4 | |
| 45-54 | 7509 | 24 | 3786 | 26 | 2034 | 23 | 1365 | 29 | 324 | 10 | |
| 55-64 | 4776 | 15 | 2143 | 15 | 1044 | 12 | 942 | 20 | 647 | 19 | |
| 65-74 | 2993 | 9 | 1121 | 8 | 465 | 5 | 503 | 11 | 904 | 27 | |
| 75+ | 2396 | 8 | 502 | 21 | 297 | 12 | 227 | 9.5 | 1370 | 57 | |
| **Race/Ethnicity** | | | | | | | | | | | <0.001 |
| Whites | 16840 | 54 | 8441 | 58 | 3731 | 42 | 2860 | 62 | 1808 | 54 | |
| Blacks | 4348 | 14 | 1096 | 7 | 2036 | 23 | 597 | 13 | 619 | 18 | |
| Hispanics | 7230 | 23 | 3271 | 23 | 2493 | 28 | 914 | 20 | 552 | 16 | |
| AI/AN | 193 | 0.6 | 75 | 0.5 | 67 | 0.8 | 32 | 0.7 | 19 | 0.6 | |
| A/PI | 2655 | 8 | 1576 | 11 | 466 | 5 | 237 | 5 | 376 | 11 | |
| Unknown | 159 | 0.5 | 84 | 0.6 | 58 | 0.7 | 12 | 0.7 | 5 | 0.2 | |
| **Stage at Diagnosis** | | | | | | | | | | | <0.001 |
| Localized | 15,022 | 48 | 7984 | 55 | 4167 | 47 | 1938 | 42 | 933 | 28 | |
| Regional | 11677 | 37 | 4784 | 33 | 3271 | 37 | 1955 | 42 | 1667 | 49 | |
| Distant | 3536 | 11 | 1360 | 9 | 1046 | 12 | 596 | 13 | 534 | 16 | |
| Unstaged | 1190 | 4 | 415 | 3 | 367 | 4 | 163 | 3 | 245 | 7 | |
| Advanced* | 15213 | 48 | 6144 | 42 | 4317 | 49 | 2551 | 55 | 2201 | 65 | |
| **Period of diagnosis** | | | | | | | | | | | <0.001 |
| 2000-2003 | 11704 | 37 | 5517 | 38 | 3077 | 36 | 1658 | 36 | 1168 | 35 | |
| 2004-2007 | 11295 | 36 | 5303 | 36 | 3166 | 36 | 1658 | 36 | 1168 | 35 | |
| 2008-2010 | 8426 | 27 | 3723 | 26 | 2608 | 30 | 1281 | 28 | 814 | 24 | |
| **Histology** | | | | | | | | | | | <0.001 |
| SCC | 21519 | 69 | 9354 | 64 | 6386 | 72 | 3386 | 73 | 2393 | 71 | |
| ADK | 6619 | 21 | 3745 | 26 | 1528 | 17 | 803 | 17 | 543 | 16 | |
| ADS | 1303 | 4 | 658 | 4 | 350 | 5 | 189 | 4 | 106 | 3 | |
| Carcinomas | 1367 | 4 | 514 | 4 | 409 | 5 | 194 | 4 | 250 | 7 | |
| Others | 617 | 2 | 272 | 2 | 178 | 2 | 80 | 2 | 87 | 3 | |

Abbreviations: AI/AN, American Indian/Alaskan Natives; A/PI, Asians/Pacific Islanders; SCC, Squamous Cell Carcinoma; ADK, Adenocanrcinoma; ADS, Adenosquamous.
*Advanced includes regional + distant.
**Likelihood ratio p value, significant at p<0.05.

Histological types differed between married and unmarried patients ($p$<0.001). Unmarried patients had a higher proportion of scquamous cell carcinomas (12165, 72%) and a lower proportion of adenocarcinomas (2874, 17%) compared to the married (9354, 64% and 3745, 26% respectively). Widowed women had the highest proportion of carcinoma cell type compared to other marital status groups (250, 7.4%).

## Logistic regression

### *Univariate logistic model*

Differences in stage of diagnosis between married and unmarried cervical cancer cases were examined by fitting logistic regression modeling. In the univariate Logistic model, unmarried women (single, separated or divorced, and widowed) were more likely to be diagnosed at an advanced stage compared to married women. Widowed women had the highest increased risk of being detected late, a 3-fold increase, compared to married women (HR 3.06; 95% CI = 2.82-3.33) (Table 3.3).

**Table 3.3.** Unadjusted odds ratios of advanced stage of diagnosis

| Variable | | 95% CI | |
|---|---|---|---|
| | **OR** | **Lower limit** | **Upper limit** |
| Marital status | | | |
| Married (Ref.) | 1 | | |
| Single | 1.35 | 1.25 | 1.42 |
| Sep./Div. | 1.71 | 1.59 | 1.83 |
| Widowed | 3.06 | 2.82 | 3.33 |
| Unknown | 0.79 | 0.79 | 0.88 |

### *Multivariate logistic model*

Marital differentials in stage at diagnosis continued to be significant after controlling for age, race/ethnicity, period of diagnosis, histology, and SEER area. Single [adjusted odds ratio (aOR) 1.41; 95% CI = 1.33-1.49], separated/divorced [aOR 1.44; 95% CI = 1.34-1.55], and widowed women [aOR 1.43; 95% CI = 1.31-1.58] were all significantly more likely to be diagnosed at an advanced stage compared to married women (Table 3.4).

## Survival analysis

### *Kaplan–Meier survival curve*

The number of deaths and censored cases by marital status are presented in Table 3.5.

The Kaplan-Meier procedure was used to produce survival curves by marital status (Figure 3.1). These curves are not age-adjusted; therefore, they do not reflect the accurate survival representation and direct comparisons are not appropriate. The unadjusted Log Rank test of survival difference between marital groups was significant ($p<0.001$).

**Table 3.4** Adjusted odds ratios of advanced stage of diagnosis

| Variable | | OR | 95% CI | |
|---|---|---|---|---|
| | | | Lower limit | Upper limit |
| Marital status | | | | |
| | Married | 1 | | |
| | Single | 1.41 | 1.33 | 1.49 |
| | Separated Divorced | 1.44 | 1.34 | 1.55 |
| | Widowed | 1.43 | 1.31 | 1.58 |
| | Unknown | 0.74 | 0.66 | 0.83 |
| Age at Diagnosis | | | | |
| | 15-44 | 1 | | |
| | 45-54 | 2.24 | 2.11 | 2.37 |
| | 55-64 | 3.28 | 3.06 | 3.52 |
| | 65-74 | 3.71 | 3.39 | 4.16 |
| | 75+ | 4.71 | 4.21 | 5.26 |
| Race/Ethnicity | | | | |
| | Whites | 1 | | |
| | Blacks | 1.28 | 1.19 | 1.39 |
| | Hispanics | 1.06 | 1.00 | 1.13 |
| | AI/AN | 1.17 | 0.85 | 1.61 |
| | A/PI | 1.17 | 1.04 | 1.26 |
| | Unknown | 0.22 | 0.15 | 0.37 |
| Diagnosis period | | | | |
| | 2000-2003 | 1 | | |
| | 2004-2007 | 1.15 | 1.09 | 1.21 |
| | 2008-2010 | 1.15 | 1.08 | 1.22 |
| Histology | | | | |
| | SSC | 1 | | |
| | ADK | 0.56 | 0.53 | 0.59 |
| | Adenosquamous | 1.11 | 0.98 | 1.24 |
| | Carcinomas | 0.95 | 0.82 | 1.09 |
| | Others | 2.01 | 1.66 | 2.42 |

Abbreviations: AI/AN, American Indian/Alaskan Natives; A/PI, Asians/Pacific Islanders; SCC, Squamous Cell Carcinoma; ADK, Adenocanrcinoma; ADS, Adenosquamous.

**Table 3.5.** Number of deaths by marital status

| Marital status | Total | No. of deaths | Censored | % censored |
|---|---|---|---|---|
| Married | 14543 | 3366 | 11177 | 76.8 |
| Single | 8851 | 2660 | 6191 | 69.9 |
| Separated /Divorced | 4652 | 1563 | 3089 | 66.4 |
| Widowed | 3379 | 1897 | 1482 | 43.9 |

***Univariate Cox regression model***

Cox proportional hazard model was fitted to assess the association of marital status and risk of death after cervical cancer diagnosis. In this model, compared to married women, single women had 44% increase risk of death (HR 1.44; 95% CI 1.37-1.54) and separated/divorced had a 57% (HR 1.57; 95% CI 1.48-1.67) increase risk of death. The survival di sadvantage was more pronounced in widowed women with a 3-fold increase in death risk (HR 3.26; 95% CI 3.08-3.45) compared to married women (Table 3.6).

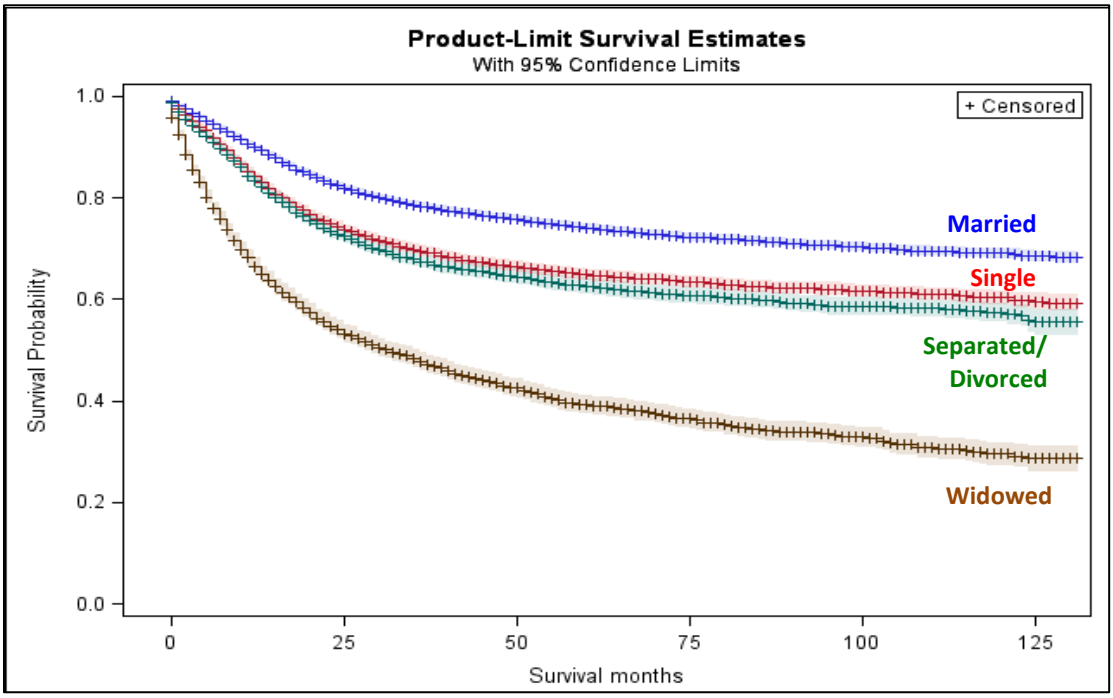


**Figure 3.1.** Unadjusted survival curve by marital status

**Table 3.6.** Univariate model of death risk by marital status

| Variable | | 95% CI | |
|---|---|---|---|
| | HR | Lower limit | Upper limit |
| Marital status | | | |
| Married (Ref.) | 1 | | |
| Single | 1.44 | 1.37 | 1.54 |
| Sep./Div. | 1.57 | 1.48 | 1.67 |
| Widowed | 3.26 | 3.08 | 3.45 |
| Unknown | 1.17 | 1.07 | 1.29 |

### *Multivariate Cox regression model*

After adjusting for socio-demographic (age, race/ ethnicity) and clinical factors (stage, histology, and period of diagnosis), married women continued to have a significant survival advantage. Single women (aHR 1.35; 95% CI 1.28-1.43), separated women (aHR 1.22; 95% CI 1.15-1.29), and widowed women (aHR 1.28; 95% CI 1.19-1.36) had significant increased risk of death compared to married women (Table 3.7).

Other predictors independently associated with excess risk of death from cervical cancer were increased age, Black race, advanced stage, and carcinoma malignancy cell type. Hispanics and Asians/Pacific Islander had a lower risk of death than Whites. Cases diagnosed between 2008 and 2010 were less likely to die compared to those diagnosed between 2000 and 2003.

**Table 3.7.** Multivariate model to estimate hazard ratios

| Variable | | HR | 95% CI | |
|---|---|---|---|---|
| | | | Lower limit | Upper limit |
| Marital status | | | | |
| | Married | 1 | | |
| | Single | 1.35 | 1.28 | 1.43 |
| | Separated/ Divorced | 1.22 | 1.15 | 1.29 |
| | Widowed | 1.28 | 1.19 | 1.36 |
| | Unknown | 1.06 | 0.96 | 1.17 |
| Age at Diagnosis | | | | |
| | 15-44 | 1 | | |
| | 45-54 | 1.34 | 1.27 | 1.42 |
| | 55-64 | 1.69 | 1.59 | 1.8 |
| | 65-74 | 2.10 | 1.96 | 2.25 |
| | 75+ | 4.10 | 3.82 | 4.4 |
| Race/Ethnicity | | | | |
| | Whites | 1 | | |
| | Blacks | 1.16 | 1.09 | 1.23 |
| | Hispanics | 0.84 | 0.79 | 0.89 |
| | AI/AN | 1.16 | 0.89 | 1.49 |
| | A/PI | 0.79 | 0.73 | 0.86 |
| | Unknown | 0.42 | 0.28 | 0.64 |
| Stage at Diagnosis | | | | |
| | Localized | 1 | | |
| | Regional | 4.36 | 4.11 | 4.62 |
| | Distant | 15.27 | 14.31 | 16.29 |
| | Unstaged | 4.11 | 3.72 | 4.53 |
| Diagnosis period | | | | |
| | 2000-2003 | 1 | | |
| | 2004-2007 | 0.98 | 0.93 | 1.02 |
| | 2008-2010 | 0.92 | 0.87 | 0.98 |
| Histology | | | | |
| | SSC | 1 | | |
| | ADK | 0.97 | 0.92 | 1.03 |
| | Adenosquamous | 1.04 | 0.94 | 1.15 |
| | Carcinomas | 1.67 | 1.53 | 1.74 |
| | Others | 1.92 | 1.73 | 2.13 |

Abbreviations: AI/AN, American Indian/Alaskan Natives; A/PI, Asians/Pacific Islanders; SCC, Squamous Cell Carcinoma; ADK, Adenocanrcinoma; ADS, Adenosquamous.

## SECTION 2 ADDITIONAL ANALYSES

### Interactions and stratification in the logistic model

Significant interactions were found between marital status and age. Interaction between marital status and race in terms of odds of advanced stage were not significant. The Logistic regression was then stratified by age.

#### *Stratification by age*

Stratification of the logistic regression by age showed that elder unmarried women, except widowed women aged 65 to 74 years old, were as likely to be diagnosed with cervical cancer at an advanced stage as married women (Table 3.8).

### Interactions and stratification in the Cox regression model

Testing interactions between marital status and age; marital status and race; and marital status and stage in the Cox regression model revealed significant associations. The model was then stratified by these covariates.

#### *Stratification by age*

Separated or divorced older women had comparable survival as older married women. Single and widowed older patients continued to have poorer survival compared to married older patients. Younger and middle aged married women had favorable survival compared to younger and middle aged unmarried women (Table 3.9).

**Table 3.8.** Odds ratios of advanced stage stratified by age

| Marital status | Age 15-44 n=14,135 | | Age 45-54 n=7652 | | Age 55-64 n=4862 | | Age 65-74 n=3001 | | Age 75+ n=2264 | |
|---|---|---|---|---|---|---|---|---|---|---|
| | aOR* | 95% CI | aOR | 95% CI | aOR | 95% CI | aOR | 95% CI | aOR | 95% CI |
| Married | | | | | | | | | | |
| Single | 1.42 | 1.32-1.55 | 1.55 | 1.37-1.74 | 1.27 | 1.08-1.50 | 1.18 | 0.92-1.56† | 1.08 | 0.76-1.53† |
| Separated/ Divorced | 1.59 | 1.42-1.79 | 1.45 | 1.27-1.65 | 1.35 | 1.14-1.59 | 1.23 | 0.97-1.56† | 0.94 | 0.64-1.37† |
| Widowed | 1.91 | 1.34-2.72 | 1.32 | 1.04-1.68 | 1.71 | 1.39-2.08 | 1.23 | 1.01-1.50 | 1.19 | 0.93-1.53† |

*Odds ratios were adjusted for race, period of diagnosis, SEER area, and histology in each stratum.
† Non-significant at $p<0.05$

**Table 3.9.** Hazard ratios of marital status by age

| Marital status | Age 15-44 n=14664 | | Age 45-54 n=7951 | | Age 55-64 n=5078 | | Age 65-74 n=3187 | | Age 75+ n=2560 | |
|---|---|---|---|---|---|---|---|---|---|---|
| | aHR | 95% CI | aHR | 95% CI | aHR | 95% CI | aHR | 95% CI | aHR | 95% CI |
| Married | 1 | | 1 | | 1 | | 1 | | 1 | |
| Single | 1.32 | 1.21-1.448 | 1.41 | 1.27-1.56 | 1.39 | 1.27-1.57 | 1.28 | 1.09-1.52 | 1.22 | 1.02-1.47 |
| Separated/ Divorced | 1.2 | 1.06-1.36 | 1.23 | 1.09-1.38 | 1.32 | 1.17-1.49 | 1.08† | 0.92-1.27 | 1.15† | 0.94-1.39 |
| Widowed | 1.48 | 1.06-2.08 | 1.41 | 1.16-1.70 | 1.29 | 1.12-1.49 | 1.27 | 1.11-1.45 | 1.28 | 1.11-1.43 |

*Hazard ratios were adjusted for race, period of diagnosis, stage, and histology in each stratum.
† Non-significant at $p<0.05$

### *Stratification by race*

Stratifying the proportional hazard model by race produced varying hazard ratios of unmarried cases compared to married depending on the race/ethnic group they belong to. For instance, single, separated or divorced and widowed American Indian/Alaskan Native women were as likely to die as their married counterparts.

Other categories that had comparable survival to married women after race stratification were widowed Hispanics and Asians/Pacific Islanders and separated or divorced Asians/ Pacific Islanders (Table 3.10).

**Table 3.10.** Hazard ratios of marital status by race/ethnicity

| Marital status | Whites | | Blacks | | Hispanics | | AI/AN | | A/PI | |
|---|---|---|---|---|---|---|---|---|---|---|
| | n= 16,840 | | n= 4,348 | | n= 7,230 | | n= 193 | | n= 2,655 | |
| | HR | 95% CI | HR | 95% CI | HR | 95% CI | HR | 95% CI | HR | 95% CI |
| Married | 1 | | 1 | | 1 | | 1 | | 1 | |
| Single | 1.35 | 1.25-1.45 | 1.5 | 1.32-1.72 | 1.23 | 1.09-1.37 | 1.79 | 0.94-3.45† | 1.31 | 1.07-1.6 |
| Sep. or Div. | 1.21 | 1.12-1.31 | 1.35 | 1.14-1.59 | 1.15 | 1.00-1.33 | 0.61 | 0.24-1.54† | 1.17 | 0.90-1.54† |
| Widowed | 1.33 | 1.22-1.45 | 1.54 | 1.31-1.82 | 1.06 | 0.89-1.26† | 0.8 | 0.33-1.96† | 0.94 | 0.75-1.16† |

Abbreviations: AI/AN, American Indian/Alaskan Natives; A/PI, Asians/Pacific Islanders
*Hazard ratios were adjusted for age, stage, period of diagnosis, and histology in each stratum.
† Non-significant at $p<0.05$

### *Stratification by stage*

After stratification by stage, the impact of marital status was not significantly different between separated or divorced and widowed women diagnosed at a distant stage and their married counterparts (Table 3.11).

**Table 3.11.** Hazard ratios of marital status by stage

| Marital status | Localized | | | Regional | | | Distant | | |
|---|---|---|---|---|---|---|---|---|---|
| | n= 16,065 | | | n= 12,155 | | | n=3,694 | | |
| | HR* | 95% CI | | HR | 95% CI | | HR | 95% CI | |
| Married | 1 | | | 1 | | | 1 | | |
| Single | 1.66 | 1.46 | 1.90 | 1.36 | 1.26 | 1.46 | 1.19 | 1.08 | 1.31 |
| Separated/Divorced | 1.26 | 1.07 | 1.48 | 1.25 | 1.15 | 1.36 | 1.10 | 0.98 | 1.22† |
| Widowed | 1.66 | 1.41 | 1.95 | 1.34 | 1.23 | 1.47 | 1.04 | 0.91 | 1.18† |

*Hazard ratios were adjusted for age, race, period of diagnosis, and histology in each stratum.
† Non-significant at $p<0.05$

## Analyses with combined unmarried

After the unmarried categories were combined, the Logistic and Cox regression models were run again to assess whether combining all the unmarried groups would have an effect on the risk of being diagnosed late and risk of death from cervical cancer.

### *Logistic regression with combined unmarried*

The multivariate logistic regression model with combined unmarried categories maintained significance. Overall, unmarried women were 42% more likely to be diagnosed at an advanced stage compared to married women (aOR 1.42; 95% CI = 1.36-1.49). The Odds ratios were adjusted for age, race, period of diagnosis, and histology.

### *Survival with combined unmarried*

Unmarried women had a 32% increased risk of death compared to married women (aHR 1.32; 95% CT = 1.27-1.38). The hazard ratios were adjusted for age, race, period of diagnosis, stage, and histology.

## Contrast between unmarried

### *Contrast in stage*

Within the unmarried categories, no significant differences in stage at diagnosis were observed (Table 3.12).

**Table 3.12.** Odds ratios between unmarried groups

| Unmarried categories | Odds of late stage | |
|---|---|---|
| | **OR** | **95% CI** |
| Singles vs. separated or divorced | 0.97 | 0.90-1.05 |
| Singles vs. widowed | 0.97 | 0.87-1.08 |
| Widowed vs. separated or divorced | 1.00 | 0.89-1.11 |

### *Contrast in survival*

When comparing survival between the unmarried categories, singles were 11% more likely to die compared to separated or divorced women (HR 1.11; 95% CI = 1.04-1.18). Widowed women were as likely to die as single and separated or divorced women (Table 3.13).

**Table 3.13.** Hazard ratios between unmarried groups

| Unmarried categories | Hazard Ratios | |
|---|---|---|
| | **HR** | **95% CI** |
| Singles vs. separated or divorced | 1.11 | 1.04-1.18 |
| Singles vs. widowed | 1.06 | 0.99-1.13 |
| Widowed vs. separated or divorced | 1.04 | 0.97-1.12 |

## Sub-analysis with insurance status

### *Distribution of insurance by marital status*

Insurance status at diagnosis was significantly difference between marital groups ($p<0.001$). Overall, 60% of patients diagnosed between 2007 and 2010 were insured while only 8% of cases were uninsured. Married women had a much higher proportion of insurance (74%) compared to single (46%), separated or divorced (56%), or widowed

(64%) women. Single women had the highest percentage of uninsurance (12%). Almost 1 of every 3 unmarried women were insured under Medicaid while only 1 of 5 married women were insured under Medicaid (Table 3.14).

**Table 3.14.** Distribution of insurance status by marital status – SEER 2007-2010

| | Total | | Married | | Single | | Separated/ Divorced | | Widowed | | Unknown | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | n | % | n | % | n | % | n | % | n | % | n | % |
| Total | 12040 | 100 | 5092 | 42.29 | 3418 | 28.39 | 1717 | 14.26 | 1082 | 8.99 | 731 | 6.07 |
| Insured | 7295 | 60.59 | 3751 | 73.66 | 1569 | 45.9 | 970 | 56.49 | 689 | 63.68 | 316 | 43.23 |
| Uninsured | 947 | 7.87 | 277 | 5.44 | 416 | 12.17 | 143 | 8.33 | 65 | 6.01 | 46 | 6.29 |
| Medicaid | 3241 | 26.92 | 916 | 17.99 | 1323 | 38.71 | 570 | 33.2 | 295 | 27.26 | 137 | 18.74 |
| Unknown | 557 | 4.63 | 148 | 2.91 | 110 | 3.22 | 34 | 1.98 | 33 | 3.05 | 232 | 31.74 |

### *Logistic regression with insurance*

The effect of marriage on advanced stage of diagnosis was modeled in patients diagnosed between 2007 and 2010 while accounting for insurance status in addition to the other demographic and clinical factors. Although the odds ratios were reduced after adjusting for insurance, unmarried women were still at higher risk of advanced diagnosis compared to married women. Single women had a 25% increased risk of advanced diagnosis and separated /divorced and widowed women had about a 30% higher likelihood of being detected late compared to married women (Table 3.15).

### *Survival analysis with insurance*

Unmarried women continued to have poorer survival compared to their married counterparts even after adjusting for insurance status (Table 3.16).

**Table 3.15.** The odds of advanced diagnosis accounting for insurance

| Marital status | | 95% CI | |
|---|---|---|---|
| | OR* | Lower limit | Upper limit |
| Married | 1 | | |
| Single | 1.25 | 1.13 | 1.38 |
| Sep./Div. | 1.30 | 1.15 | 1.47 |
| Widowed | 1.33 | 1.12 | 1.58 |

*Odds ratios adjusted for age, race, insurance, SEER area, and histology

**Table 3.16.** Hazard ratios accounting for insurance

| Marital status | | 95% CI | |
|---|---|---|---|
| | HR* | Lower limit | Upper limit |
| Married | 1 | | |
| Single | 1.30 | 1.07 | 1.45 |
| Sep./Div. | 1.29 | 1.08 | 1.37 |
| Widowed | 1.19 | 1.03 | 1.36 |

*Hazard ratios adjusted for age, race, insurance, SEER area, stage, and histology

# CHAPTER 4 DISCUSSION

Marriage is an independent predictor of stage at diagnosis and survival in women with cervical cancer. Unmarried women including single, separated or divorced, and widowed have a disadvantage of being diagnosed late and have poorer survival compared to married women. The survival advantage of married women was sustained after accounting for demographic and clinical factors such as age, race/ethnicity, period of diagnosis, SEER area, histology, and stage. Even after adjusting for insurance status at diagnosis, unmarried women were still at a higher risk of being detected at an advanced stage and at an increased risk of death in relation to married women.

Significant interactions were found between marital status and age; marital status and race; and marital status and stage. The effect of marital status was attenuated in older separated or divorced women. Relative to married American Indian/Alaskan Native women, their unmarried counterparts did not have a survival disadvantage. Similar results were found for widowed Hispanics and Asians/Pacific Islanders and separated or divorced Asians/ Pacific Islanders. When stratified by stage, separated or divorced and widowed women diagnosed at a distant stage had comparable survival as their married counterparts.

When unmarried categories were combined, unmarried women remained at a disadvantage of late diagnosis and unfavorable survival compared to the married. After comparing stage at diagnosis and survival within the unmarried categories, only single women were at higher death risk in relation to separated or divorced women. Overall, single women have the poorest outcomes compared to other marital groups.

This study adds to the emerging body of literature on the benefit of marriage on cancer health outcomes. The mechanisms of the marriage advantage have yet to be fully understood, however, there are some possible explanations particularly for cervical cancer.

**Marriage and cervical cancer incidence**

In very early studies, investigators reported that cervical cancer incidence rates in married women are lowest compared to other marital status groups and higher rates exist among separated white women compared to the married (Ernster, Sacks, Selvin, & Petrakis, 1979). Reasons for higher incidence of cervical cancer in unmarried women may be related to HPV infection.

Prevalence of any type of HPV is lowest in married women (27.8%) and highest in never married (53.9%). Women living with a partner (44.8%) and divorced/separated or widowed (50.6%) have higher prevalence of HPV compared to married women (Peyton et al., 2001). The same pattern was seen when comparing the prevalence of the high-risk HPV that is likely to cause cervical cancer. Even when accounting for many other factors, married women had a 40% decrease in the prevalence odds ratio compared to the never married (Peyton et al., 2001). In another study that used data from the National Health and Nutrition Examination Survey, widowed women and women living with a partner had over a three-fold increase risk of being infected with HPV compared to married women (Dunne et al., 2007).

**Marriage and health behaviors**

Being in a marital relationship is likely to affect lifestyle and health behaviors. Spouses are likely to positively influence each other's behaviors in terms of diet, screening exams, smoking, and exercise. This might explain the low cervical screening rates in unmarried women compared to the married (Hewitt, Devesa, & Breen, 2004; Hsia et al., 2000). Moreover, childbearing women have a greater encounter with the gynecologist which increases their chance of receiving cervical cancer screening as part of their prenatal care.

**Marriage and insurance**

Marital status is an important predictor of having health insurance coverage for working-age women in most income or poverty levels. Unmarried working-age women have greater prevalence of lack insurance (21%) than married women (13%). In addition, married women have the advantage of health insurance coverage under their spouses' plan. In 2007, approximately 1 of every 3 married women had insurance through their spouses' employer-sponsored coverage (Bernstein, Cohen, Brett, & Bush, 2008).

Uninsurance is widely accepted as a predictor of having poor health. Although married women have a higher percentage of insurance than the unmarried, controlling for insurance status in our study reduced the effect of marriage; however, marriage remained protective. Likewise, Osborne and colleagues showed that unmarried breast cancer patients have higher mortality compared to married patients although these patients were all Medicare beneficiaries (Osborne, Ostir, Du, Peek, & Goodwin, 2005b). Melanoma widowed patients insured under Medicare, were also found to have poorer survival in relation to married patients (Ortiz, Freeman, Kuo, & Goodwin, 2007).

**Marriage and socio-economic status**

Another mechanism by which marriage may confer health benefits is the improved socio-economic status of married individuals. This benefit is substantial especially for women. For instance, recently divorced women are more likely to be living in poverty and be receiving public assistance compared to men (Elliott & Simmons, 2011). In our study we were not able to control for individual level socio-economic (SES) status as this information does not exist in the SEER data. Other studies have used ecological measures as proxies for SES (Aizer et al., 2013; Neale, 1994; Osborne, Ostir, Du, Peek, & Goodwin, 2005a). In all these studies, married cancer patients had a survival advantage over the unmarried.

**Marriage and treatment**

Survival is largely dependent on timely and effective treatment. Osborne et al. assessed whether there were therapy differentials by marital status in Medicare breast cancer patients. The authors found that unmarried women diagnosed with more localized stage were less likely to receive definitive therapy such as breast conserving surgery or mastectomy (Osborne, Ostir, Du, Peek, & Goodwin, 2005a). Other authors reported that widowed Lung cancer patients had a greater proportion of not receiving any treatment after cancer diagnosis compared to other marital groups (Jatoi et al., 2007).

Unmarried women may have concerns about treatment cost and concerns about long term care in case of treatment complications. In contrast, married women are more likely to have spousal and immediate family support for transportation to treatment appointments,

help with medication compliance, support in coping with medication side effects, and choice of more aggressive therapies.

In the present study we found married women have a survival advantage even after accounting for stage. Clinicians use stage of diagnosis to plan the course of treatment. However, it is ultimately up to the patient to decide on the therapy they would choose depending on different factors such as cost and the related physical and emotional stress. Marriage may be beneficial in terms of having the support on making these types of decisions and providing a survival motivation for patients with family dependents. Further, married persons who experience a fulfilling and joyful marital relationship may have a stronger drive and desire to lead a healthy life.

In this study we were not able to control for comorbidities that might influence death risk; however, in other investigations that did include information about other conditions marital status remained a predictor of survival (Ortiz, Freeman, Kuo, & Goodwin, 2007; Osborne, Ostir, Du, Peek, & Goodwin, 2005a).

**Marriage and social support**

The body of literature has yet to understand how marriage imparts health benefits especially in terms of protection from social isolation and psychosocial stress. Some studies have even found biological plausibility of the effect of social support on better survival in the form of improved immunologic function (Levy et al., 1990).

Reasons for psychosocial stress and social isolation are likely to be differential between the unmarried categories. Single women may suffer from social isolation because of

autonomous life style and, therefore, they may have less opportunities or willingness to engage in social networks. Kroenke et al. reported that breast cancer patients did not have mortality differentials by marital status, however, they found those who were socially isolated (were not married, had few friends or relatives, and were not associated with any church or community groups) before diagnosis had a two-fold increased risk of breast cancer mortality compared to those socially integrated (Kroenke, Kubzansky, Schernhammer, Holmes, & Kawachi, 2006).

Separated or divorced women may suffer from psychosocial stress from the divorce process and from the loss of material support especially for women who were stay-at-home mothers or those who were absent from the job field while married. For instance, divorced lung cancer patients reported increased financial concerns compared to other marital groups (Jatoi et al., 2007).

Bereavement form the loss of a significant other may cause widowed women to fall into depression, have less motivation to care for their own health and may have lost their caregiver (Jacobs & Ostfeld, 1977).

**Marriage trends and their impact on cervical cancer**

There are several trends in sexual behaviors that may contribute to an increased risk of HPV infection and, consequently, of cervical malignancy. Age at first intercourse is decreasing. For example, median age at first premarital sex dropped from 20 in the 1960s to 17 years old in the early 2000 (Finer, 2007). Studies have shown HPV infection is more prevalent in girls who had their first intercourse before age 16 (Dunne et al., 2007). This increases the risk of developing cervical cancer at a younger age. In fact, cervical

cancer is the second most common cancer in young women aged 20 to 39 years old (Siegel, Naishadham, & Jemal, 2013).

**Cervical cancer prevention**

The introduction of cervical cancer vaccine for both young girls and boys has been shown to decrease HPV infection in teens (CDC Newsroom, 2013). Nevertheless, the impact of the vaccine on cervical cancer incidence is yet to be determined. Future studies will need to examine how the vaccine will affect the distribution of incidence, stage, and survival from cervical malignancy.

**Future studies**

The association of marital status and health outcomes should be further studied. There are many aspects that merit investigation. For example, as the cohabitating phenomenon is becoming more and more popular, researchers would need to compare health outcomes between married persons and those living with a partner. Likewise, same-sex marriage is gaining acceptance and made legal in a number of states. A research question that arises is - do same-sex married couples have the same health benefits as heterosexual married persons?

With the implementation of the Affordable Care Act, millions of uninsured Americans will have health insurance including unmarried persons. Consequently, how will the increased access to health care services, especially preventive services, affect the marriage advantage? Will the marriage benefits weaken or remain?

Researchers will also need to study health behaviors by marital status in depth. Is marriage beneficial because married persons are less likely to engage in risky health behaviors than the unmarried? And how is cancer screening distributed by marital status? If the unmarried are less likely to get screened, what are the barriers? How can public health professionals intervene to reduce these barriers? Finally, how can health outcomes of the unmarried be improved?

# CHAPTER 5 STRENGTHS AND LIMITATIONS

## SECTION 1 STRENGTHS

This study is one of the very few that examined the relationship of marriage and cervical cancer outcomes. This study opened the discussion about marital trends and their possible effect on women's health. It is important to bring attention to the increase of age at first marriage and its positive association with HPV infection and occurrence of cervical cancer in young females. It is important to bring awareness to young females about their susceptibility to the disease if they don't follow the Pap test screening recommendations.

The use of population-based data from the SEER geographic areas is another strength. This program covers approximately 28% of the U.S. population. It is one of the only comprehensive sources of cancer data in the U.S. that includes patient demographics, primary tumor site, morphology, stage at diagnosis, first course of treatment, and follow-up for vital status.

## SECTION 2 LIMITATIONS

Results of this study should be considered in light of some limitations. First, data are not available on some other important factors such as individual level of social-economic status, individual Pap test history, and co-morbidities. Cancer registries do not collect these variables as part of the surveillance system. Second, marital status is recorded at the time of diagnosis; any later changes in marital status are not reported. Moreover, the insurance status variable is not available for the full study period.

# CHAPTER 6 CONCLUSION

Cervical cancer is largely preventable through prevention and early detection. The association of marriage and cervical cancer outcomes is particularly important because this disease affects younger women and its major risk factors are related to sexual behaviors.

In this study we assessed two main outcomes: stage at diagnosis and survival. We found that young and middle-aged unmarried women are at higher risk of an advanced stage at diagnosis compared to married women in the same age group. In terms of survival, marriage was, overall, protective. However, the association between marriage and survival varied depending on age, race, and stage. Marriage provides a survival advantage to young and middle-aged women; White, Black, and Hispanic women; and women diagnosed at localized or regional stages. Among all categories of marital status, single women had the poorest outcomes. Furthermore, this effect of marriage on stage of diagnosis and survival remained after adjusting for insurance status.

In light of marriage trends in the U.S., there is a strong need to focus on cancer prevention and control of cervical cancer in unmarried women, especially single women. Moreover, our study showed higher risk of death for unmarried women compared to married women. Further studies are needed to examine the causes of this differential.

In the United States there are approximately 150 million unmarried adults. Inferior health of the unmarried constitutes a sizable public health issue. With less and less people exchanging vows or choosing to cohabitate, the issue is gaining momentum and merits attention from the public health community.

Solutions to poorer outcomes for unmarried women are multidimensional and many stakeholders need to be involved.

First, we need to target unmarried women to improve screening rates especially young females. Although under the Affordable Care Act health insurance plans must provide preventive services free of cost sharing, it is still possible that unmarried persons have other barriers to access these services such as remoteness from care providers, lack of transportation, or attitude of fear towards a disease diagnosis. Moreover, current screening guidelines lack the marital status factor and, therefore, could take into account marital status disparities.

Second, efforts are needed to ensure that unmarried women have the support network that will allow them to adhere to treatment regiments and to reduce the stress related to coping with the disease. This is important especially in the case of disease reoccurrence.

Third, clinicians need to have special consideration when providing services to unmarried patients. Clinicians have a major role in guiding unmarried patients, who may lack social and emotional support, to adhere to screening and to opt for timely and effective treatments. Moreover, continuous counseling and active surveillance systems using the Electronic Medical Records are needed to provide optimal care for the unmarried.

Lastly, the most important solution that needs to be consistently emphasized is prevention. This study constitutes further evidence to the need of immunization of both girls and boys with the HPV vaccine. As teen girls and boys are increasingly engaging in sexual relationships at an early age, the vaccine will protect them from infection with the most prevalent HPV types.

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## APPENDIX

UNLV
UNIVERSITY OF NEVADA LAS VEGAS

### Biomedical IRB – Exempt Review
### Deemed Exempt

**DATE:** September 12, 2013

**TO:** **Dr. Paulo Pinheiro,** Environmental & Occupational Health

**FROM:** Office of Research Integrity – Human Subjects

**RE:** Notification of IRB Action
Protocol Title: The Effect of Marriage on Stage at Diagnosis and Survival in Women with Cervical Cancer.
Protocol # 1308-4542M

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This memorandum is notification that the project referenced above has been reviewed as indicated in Federal regulatory statutes 45CFR46 and deemed exempt under 45 CFR 46.101(b)4.

*Any* changes to the application may cause this project to require a different level of IRB review. Should any changes need to be made, please submit a **Modification Form**. When the above-referenced project has been completed, please submit a **Continuing Review/Progress Completion report** to notify ORI – HS of its closure.

If you have questions or require any assistance, please contact the Office of Research Integrity - Human Subjects at IRB@unlv.edu or call 895-2794.

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