Title: Cervical cancer survival in the United States by race and stage (2001-2009): findings from the CONCORD-2 study.

Running title*: Cervical cancer survival in the US by race and stage

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Precis: Five-year net survival from cervical in the US was 63.5% during 2001-2003 and remained constant during 2004-2009. However, survival in black women was 7% lower than survival in white women and this difference did not change over time.

ABSTRACT

Background: Overall, cervical cancer survival in the United States has been reported to be among the highest in the world, despite slight decreases over the last decade. The objective of the current study was to describe cervical cancer survival trends among US women and examine differences by race and stage.

Methods: We used data from the CONCORD-2 study to compare survival among women (age 15-99 years) diagnosed in 37 states covering up to 80% of the US population. Survival was adjusted for background mortality (net survival) using state- and race-specific life tables and age-standardized using the International Cancer Survival Standard weights. We compared five-year survival by race (all, black and white). Two time periods were considered, 2001-2003 and 2004-2009 due to changes in how the staging variable was collected.

Results: From 2001-2009, 90,620 women were diagnosed with invasive cervical cancer. The proportion of cancers diagnosed at regional or distant stage increased over time in most states. Overall, 5-year survival was 63.5% for 2001-2003 and 62.8% for 2004-2009. Survival was 7-8% lower for black women compared to white women in both calendar periods and in most states; black women had a higher proportion of distant stage cancers. **Conclusions:** The stability of the overall survival over time and persistent differences in survival between white and black women in all US states suggest that there is a need for targeted interventions and improved access to screening, timely treatment, and follow-up care, especially among black women.

INTRODUCTION

Cervical cancer screening has resulted in well-documented declines in incidence and mortality in the US.[1] Despite evidence that screening is effective in preventing invasive cervical cancer and cervical cancer death, many women are not screened as recommended, especially women in populations with limited access to preventive health services and a usual source of care.[2] Over half of all new cervical cancer cases are estimated to occur in women who have never or rarely been screened.[3] One recent study of cervical cancer in a sample of the US population noted improvements in survival from 1983 through 2009 among women diagnosed at earlier stages, but no improvements in survival for metastatic disease.[4] Disparities by race/ethnicity include higher incidence and mortality among Hispanic and black women, and poorer survival among black women compared to white women.[5] Population-based surveillance of cervical cancer survival trends by race and stage can provide insights into racial and geographic disparities that can be used to target cancer control efforts.

The CONCORD-2 study established worldwide cancer survival rates for 10 common cancers, producing estimates of 5-year survival for over 25 million patients in 67 countries and 279 cancer registries from 1995-2009.[6] Globally 5-year net survival for cervical cancer varied from less than 40% to more than 70%.[6] CONCORD-2 reported a slight decrease in 5-year net survival for cervical cancer in the US, from 64.2% in 1995-1999 to 62.8% in 2005-2009. Similar patterns were observed in other high-income countries. Disparities in cervical cancer survival, such as those seen between countries, represent profound health inequities because invasive cervical cancer is both potentially preventable and treatable if detected early with screening and followed by appropriate care. The present study used the US data from CONCORD-2, which included the most comprehensive and up-to-date population-based data, covering 80% of the US population. Survival was analyzed by race, stage and geographical area.

Materials and Methods

Data Source

We used data from 37 state-wide cancer registries that participated in the CONCORD-2 study,[6] covering approximately 80% of the US population. Registries consented to inclusion of their data in the more detailed analyses reported here. More details on data and methods are provided in the accompanying article by Allemani et al.[7] We analysed individual tumour records for 90,620 women (aged 15-99 years) who were diagnosed with primary, invasive cancer of the cervix (ICD-O-3:[8] C530-C531; C538-C539) from 2001 to 2009 and followed through December 31, 2009. If a woman was diagnosed with two or more cancers of the cervix during the same time period, only the first was considered in the survival analyses.

Stage at diagnosis was defined based on SEER Summary Stage 2000 (SS2000) and categorized as localized, regional, distant, or unknown. Women were grouped by year of diagnosis into two calendar periods (2001-2003, 2004-2009) to reflect changes in the methods used by U.S. registries to collect data on stage at diagnosis beginning in 2004. . From 2001 to 2003, most registries coded SEER Summary Stage (SS) 2000 directly from the medical records.[9] From 2004 to 2009, registries derived SS2000 using the Collaborative Staging System.[10]

Survival analyses

We estimated net survival by state, race (all, black, white), SS2000 (local, regional, distant and unknown) and calendar period of diagnosis. Net survival is the probability of survival up to a given time since diagnosis after controlling for other causes of death (background mortality). To control for wide differences in background mortality among participating states, we constructed life tables of all-cause mortality in the general population of each state from the number of deaths and the population, by single year of age, sex, calendar year and, where possible, by race (black, white).[7]

These life tables have been published elsewhere.[12] We estimated net survival up to 5 years after diagnosis and 95% confidence intervals (CI) using the Pohar Perme estimator.[13]

We estimated net survival using the cohort approach for patients diagnosed from 2001-2003, since all patients had been followed up for at least five years by December 31, 2009. We used the complete approach to estimate net survival for patients diagnosed from 2004-2009, because five years of follow-up

data were not available for all patients. Net survival was estimated for five age groups (15-44, 45-54, 55-64, 65-74, 75-99 years). We obtained age-standardized survival estimates using the International Cancer Survival Standard (ICSS) weights.[14] If two or more of the five age-specific estimates could not be obtained, we present only the pooled, unstandardized survival estimate for all ages combined. Unstandardized estimates are italicized in Tables 2 and 3. Trends, geographic variations and differences in age-standardized survival by race are presented graphically in bar charts and funnel plots.[15] Funnel plots of net survival for 2001-2003 and 2004-2009 provide insight into the variability of cancer survival in the US by race and state and show how much a particular survival estimate deviates from the pooled estimate of US registries (horizontal line) given the precision of each estimate.

RESULTS

For 2001-2003, 48.8% of cervical cancers were diagnosed with localized stage, 31.8% with regional stage and 9.6% with distant stage. The proportion of cancers at the localized stage fell by 4% for 2004-2009, but increased for cancers at regional (35.5%) and distant (11.5%) stages. The percentage of unknown stage decreased from 9.8% to 8.4% (Table 1). The proportion of cancers diagnosed with local stage cervical cancer for black women was 10% lower than for white women, and this difference did not change over time (40.9% vs. 50.4% for 2001-2003; 36.6% vs. 46.2% for 2004-2009). In comparison, a higher proportion of cancers were diagnosed at regional (35.6% vs. 31.2%; 38.6% vs. 35.0%) and distant stage (11.0% vs. 9.4%; 13.5% vs. 11.3%).

For all women diagnosed with cervical cancer, the 1-, 3-, and 5-year net survival estimates are presented in Table 2 by race and calendar period. The 1- and 5-year net survival were 83.4% and 63.5%, respectively, for 2001-2003 and 82.9% and 62.8%, respectively, for 2004-2009. Net survival was lower among black women than among white women overall and in the majority of the US states (Table 2, Supplemental Table 2). Among women diagnosed during 2004-2009, 1-year survival was 3.5% lower in black women than white women, and 8.0% lower at 5 years.

Figure 1 depicts the 5-year net survival among states grouped by US Census Region. Survival ranged from 55.7% to 71.8% for 2001-2003 and from 52.5% to 73.9% for 2004-2009 (Figure 1, Supplemental Table 2). Survival decreased in 22 states and increased in 13 states. In the US southern Census region, 12 out of 14 states in 2001-2003 and 10 out of 14 states in 2004-2009 showed a 5-year net survival lower than the US value.

Figure 2 reports funnel plots of net survival for 2001-2003 and 2004-2009 to obtain further insight into the variability of cervical cancer survival in the US by race and state. These plots show striking racial and geographical variation in survival. Five-year survival from cervical cancer was lower for black women than for white women in most states, both for 2001-2003 and 2004-2009. In all 15 states for which a survival estimate could be obtained for black women, survival was systematically lower than the US value.

Table 3 provides the 5-year net survival by stage, race and calendar year. There was a slight increase observed for women diagnosed with a localized (84.5% to 85.9%) or a regional cancer (53.2% to 55.8%). Survival for women diagnosed with a distant cervical cancer remained constant (Table 3). Survival trends were similar for white women between the two time periods. Survival for black women was steady for cancers diagnosed at localized stage (79.1% to 79.2%), and increased slightly for cancer diagnosed at regional (47.4% to 51.1%) and distant (13.4% to 14.4%) stage. However, black women had lower survival than white women for all stages and in both time periods (Table 2, Figure 2). Substantial variation in five-year net survival by stage was observed among states and over time. For 2004-2009, the 5-year survival range for localized stage was 69.3% to 97.1%; for regional stage, 38.9% to 68.3% and for distant stage, 8.1% to 25.7% (Supplemental Table 2).

Discussion

Cervical cancer survival in the US remained stable between 2001 to 2009 at around 63%. We documented persistent racial and geographical disparities with lower 5-year survival (55.5%) for 2004-2009 and proportionately more later staged cancers among black women compared to white women.

Slight decreases[6] or no change in survival occurred despite decreasing incidence and death rates[1, 2] related to long-standing screening activities within the population. Cervical cancer screening mostly detects pre-invasive cervical cancers, and follow-up treatment of abnormal cells can prevent invasive cancers that would otherwise have arisen. As such, decreasing incidence for cervical cancer can be used as a marker for effective screening, because most cervical cancers are preventable with early detection and appropriate follow-up of pre-invasive lesions.[16] As most women with access to health services are screened and malignant lesions are removed before they become invasive, the incidence of invasive cervical cancer may become skewed toward cases arising in the unscreened population[3], interval cancers with a faster doubling time and thus a shorter sojourn time in the pre-clinical detectable phase, and those with lack of adequate follow-up[17]. This results in an increase in the proportion of women diagnosed at regional and distant stages, and thus in a decrease in survival for all women with cervical combined, as found in this study. Additionally, as reported in this study and elsewhere, black women have higher incidence and mortality and lower survival than white women.[4] As we noted, lower stage-specific survival and higher proportions of later stage cancers among black women contribute to these disparities.

Clinical Implications

Significant advances in cervical cancer prevention, screening, and treatment have occurred in the past decade. In the area of primary prevention, the first human papillomavirus (HPV) vaccine was approved for use in the United States in 2006.[18] Both the quadrivalent and bivalent HPV vaccines target infection from two oncogenic types, HPV 16 and 18, which are responsible for 66% of cervical cancers.[19] In 2014, the 9-valent vaccine, which includes five additional oncogenic types, was approved

for use and can potentially prevent an additional 14% of cervical cancers.[20] HPV vaccines have the potential to lower the risk for a woman to ever develop and subsequently die from cervical cancer.[21] However, the coverage in the US in 2015 was less than optimal, with only about 62% of girls aged 13-17 receiving at least one dose.[22] Screening programs remain imperative to preventing cervical cancer as we move into an era of more HPV vaccine coverage.

During the past decade, several improvements were also made for cervical cancer screening including a gradual paradigm shift from cytology-based screening to HPV-based screening, allowing for greater sensitivity and potential for less frequent screening.[23] HPV-based screening has the potential to detect abnormal cervical lesions at an earlier stage, ideally prior to invasion. Significant developments in treatment (adding chemotherapy to radiation therapy for cervical cancer as a standard of treatment in the late 1990s, fertility-sparing surgery for early stage disease, and adding bevacizumab to advanced or recurrent disease) can result in improved survival and better quality of life.[24] Timely access to optimal treatment is important to increase the chance of survival; these factors go beyond the treatment itself to address system and access barriers.[25]

Cancer Control Implications

Population-based survival trends are crucial for developing and prioritizing cancer control strategies, as well as evaluating the impact of cancer control activities and progress towards meeting national objectives. Using surveillance data to plan interventions is one activity that the Centers for Disease Control and Prevention (CDC)'s National Comprehensive Cancer Control Program is strongly encouraged to complete on a routine basis.[26] These cancer control plans include using information on the region's cancer burden to inform goals and potential activities to improve primary cancer prevention such as increasing HPV vaccination, cervical cancer screening, and cervical cancer survival in the community. Additionally, direct clinical services have been provided by CDC's National Breast and Cervical Cancer Early Detection Program (NBCCEDP) for cervical cancer screening to low income, uninsured, and underinsured women.[26] Women diagnosed with cancer through this program are eligible

for Medicaid coverage to cover treatment costs and other healthcare-related needs.[27] This program

reaches approximately 7% of all eligible women across the US,[28] and has shown reduction in mortality

from cervical cancer among low income women.[29]

Many of these CDC programs have worked collaboratively to reach women in underserved

populations, including: (1) working with federally qualified health centers to monitor and increase

cervical cancer screening utilization;(2) developing culturally competent action plans to reach African

American, American Indian, and Latino women; (3) conducting group educational sessions and

outreach, and (4) using community health workers or patient navigators to provide education and entry

into screening (personal communication J. Townsend). CDC also funds national networks that serve

racial/ethnic minorities, people living with mental illness and addictions, and rural residents to address

cancer-related health disparities (http://www.cdc.gov/cancer/ncccp/dp13-1314.htm). One network is

addressing the high cervical cancer incidence rates among Hispanic and Latina women by providing

technical assistance on evidence-based programs to increase screening and vaccination rates

(http://www.nuestrasvoces.org/). However even with these comprehensive interventions, women

continue to develop this largely preventable disease and health disparities exist. CDC is leading a

national study to understand the barriers to timely screening and follow-up to help understand these

persistent disparities; study findings will be in the literature early next year.

Strengths and Limitations

This study of cervical cancer survival, which included high-quality data from 37 states covering

over 80% of the population in the US, is the most comprehensive study of population-based cancer

survival in the US to date. We also document racial disparities in stage at diagnosis and five-year

survival, highlighting areas for future public health interventions to achieve health equity. Net survival

was estimated using state- and race-specific life tables. However, we were only able to construct white-

and black-specific life tables and therefore not able to report the data for other races or ethnic groups. In

addition, unusually high survival in some areas may result from incorrect vital status information because of data quality variations related to data linkages.[30]

Conclusions

Although cervical cancer survival has been relatively stable over time, reflecting improvements in screening,[31] racial and geographical disparities in survival still exist. By understanding the status of cervical cancer survival and the opportunities available to continue to decrease incidence and improve survival, CDC programs are working to determine the most effective ways to close the gaps and ensure that all women benefit from the latest advances in cervical cancer prevention, early diagnosis and timely treatment.

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Figures and Tables

Figure 1: 5-year age-standardized net survival (%) for female (15-99 years) diagnosed during 2001-2003 and 2004-2009, and absolute change (%): states grouped by US Census Region.

Note: States are ranked within Census Region by the survival estimate for 2004-2009.

Note: Dark colors – states affiliated with the National Program of Cancer Registries (NPCR); pale colors – states affiliated with the Surveillance, Epidemiology and End Results (SEER) Program. * Registries affiliated with both federal surveillance programs. Change (%) not plotted because at least one calendar period estimate was not age-standardized.

Figure 2. Cervical cancer: 5-year age-standardized net survival (%) for females (15-99 years), by state, race and calendar period of diagnosis.

Note: the pooled (US) survival estimates for each calendar period are shown by the horizontal (solid) line with corresponding 95.0% and 99.8% control limits (dotted lines).

Table 1. Cervical cancer: number of cases for females (15-99 years) diagnosed 2001-2009 and distribution (%) by summary stage 2000 at diagnosis, by race and calendar period of diagnosis.

Table 2. Cervical cancer: age-standardized net survival (%) at 1-, 3- and 5-years for females (15-99 years) diagnosed 2001-2009, by race and calendar period of diagnosis.

Table 3. Cervical cancer: 5-year age-standardized net survival (%) for females (15-99 years) diagnosed 2001-2009, by, stage at diagnosis, race and calendar period of diagnosis.

Supplement Table 1. Cervical cancer: number of cases for females (15-99 years) diagnosed 2001-2009 and distribution (%) by SEER Summary Stage 2000 at diagnosis, by race, calendar period of diagnosis, and US Census Region and States.

Note: NPCR indicates National Program of Cancer Registries; SEER indicates Surveillance, Epidemiology, and End Results program. Information on stage was not available for two states (Maryland and Wisconsin), or for Rhode Island for cases diagnosed during 2004- 2009. This is the same information that appears in Table 1.

Supplement Table 2. Cervical cancer: age-standardized net survival (%) at 1-, 3- and 5-years for females (15-99 years) diagnosed 2001-2009, by race, calendar period of diagnosis, and US Census Region and States.

Note: NPCR indicates National Program of Cancer Registries; SEER indicates Surveillance, Epidemiology, and End Results program. Unstandardized estimates are italicized. This is the same information that appears in Table 2.

Supplement Table 3. Cervical cancer: 5-year age-standardized net survival (%) for females (15-99 years) diagnosed 2001-2009, by SEER Summary Stage 2000 at diagnosis, race, calendar period of diagnosis and US Census Region and States.

Note: NPCR indicates National Program of Cancer Registries; SEER indicates Surveillance, Epidemiology, and End Results program. Information on stage was not available for two states (Maryland and Wisconsin), or for Rhode Island for cases diagnosed during 2004- 2009. Unstandardized estimates are italicized.
This is the same information that appears in Table 3.