Cervical Cancer Trends in the United States: A 35-Year Population-Based Analysis

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Abstract

Purpose: To analyze trends in invasive cervical cancer incidence by age, histology, and race over a 35-year period (1973–2007) in order to gain insight into changes in the presentation of cervical cancer.

Methods: Data from the nine Surveillance, Epidemiology, and End Results (SEER) registries that continuously collected information on invasive cervical cancer were analyzed for trends. Standardized to the 2000 U.S. population, annual age-adjusted incidence rates were estimated by race and histologic subtype. Histologic subtype was classified into squamous, adenocarcinoma, and adenosquamous.

Results: Overall incidence rates for invasive cervical cancer decreased by 54% over the 35 years, from 13.07/100,000 (1973–1975) to 6.01/100,000 (2006–2007), and the incidence rates declined by 51% and 70.2%, respectively, among whites and blacks. The incidence rates for squamous carcinoma decreased by 61.1% from 10.2/100,000 (1973–1975) to 3.97/100,000 (2006–2007). Incidence rates for adenosquamous cell carcinomas decreased by 16% from 0.27/100,000 (1973–1975) to 0.23/100,000 (2006–2007), and incidence rates for adenocarcinomas increased by 32.2% from 1.09/100,000 (1973–1975) to 1.44/100,000 (2006–2007). This increase in adenocarcinomas was due to an increase in incidence in white women; a decrease in incidence was observed for black women.

Conclusions: Although marked reductions in the overall and race-specific incidence rates of invasive cervical cancer have been achieved, they mask important variation by histologic subtype. These findings suggest that alternatives to Pap smear-based screening, such as human papillomavirus (HPV) testing and HPV vaccination, need to be prioritized if adenocarcinomas of the cervix are to be controlled.

Introduction

CERVICAL CANCER IS THE THIRD MOST COMMON cancer in women worldwide.¹ Globally, the total cases of cervical cancer in 2011 were 529,800, with age-adjusted and sex-adjusted rates of 9.0/100,000 and 17.8/100,000, respectively, in more developed and less developed countries.^{1,2} In the United States, there were an estimated 12,200 new cases of cervical cancer diagnosed in 2010, translating to an incidence rate of 7.9/100,000 women.³

The introduction of the Pap smear in the 1940s led to significant reductions in the incidence of invasive squamous cervical cancer.^{4,5} However, Pap smear-based screening has been less effective at reducing invasive cervical adenocarcinomas.^{6,7} During the 1950s and 1960s, approximately 95% of all invasive cervical cancers were squamous cell carcinomas, and adenocarcinomas, the second most common histologic cell type, accounted for only 5% of cervical cancer cases.^{6,8,9} More recently, there has been a shift in the distribution of the

histologic subtypes of cervical cancer. At present, the squamous type accounts for approximately 75% of invasive cervical cancer, whereas adenocarcinomas account for the remaining 25%.^{10–12} The changes in the burden of cervical cancer by histologic type have been attributed to the Pap test and its ability to detect more squamous cell types than glandular (adeno) cell types. The anatomy of the cervix makes endocervical tissue more difficult to sample than the squamous epithelium of the ectocervix during a Pap test. This lack of anatomic accessibility has been suggested as the cause for reduced detection rates and late stage presentation of adenocarcinomas.^{13,14}

Over the last 35 years of cancer surveillance in the United States, there have been significant reductions in the incidence of invasive cervical cancer, but these reductions have not been similar for different racial groups and different histologic categories of cervical cancer. Characterizing differences in reductions by race and histologic category is vital for informing cervical cancer screening recommendations. Although

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previous studies have detailed differential reductions based on histologic subtypes other than the adenosquamous subtype, the longest time span for an analysis has been 24 years.^{6,11} Moreover, these studies did not exclude *in-situ* cases of cervical cancer. The aim of this study is to use the United States Surveillance, Epidemiology, and End Results (SEER) population data to analyze trends in the incidence of invasive cervical cancer by histology, age, and race between 1973 and 2007.

Materials and Methods

Data source

The SEER cancer registries were used for this analysis. SEER is a network of population-based tumor registries that collect information on all newly diagnosed cancer cases that occur in their areas. The information collected about each incident cancer diagnosis includes demographic characteristics, date of diagnosis, data about the cancer (histology, stage, and grade), follow-up of vital status, and cause of death if applicable. We use information from the SEER 9 registries that continuously collected cancer surveillance data between 1973–1975 and 2008. They are Atlanta, Connecticut, Detroit, Hawaii, Iowa, New Mexico, San Francisco-Oakland, Seattle-Puget Sound, and Utah. Data are available for cases diagnosed from 1973 and later for these registries, with the exception of Seattle-Puget Sound and Atlanta. The Seattle-Puget Sound and Atlanta registries joined the SEER program in 1974 and 1975, respectively.³

Analysis

A cohort of all cases of invasive cervical cancer diagnosed between January 1, 1973, and December 31, 2007, was created. Over the 35-year period, there were 37,776 cases of invasive cervical cancer. The analysis excluded women aged ≤ 20 years and subsequently restricted race to white and black women. The final cohort used for the analysis included 33,928 women diagnosed with invasive cervical cancer with specified histology, which represents approximately 90% of the population over a 35-year period. Table 1 shows the criteria used to derive the final cohort.

TABLE 1. COHORT CREATION OF INVASIVE CERVICAL CANCER DIAGNOSED IN SURVEILLANCE, EPIDEMIOLOGY, AND END RESULTS 9 REGISTRIES, 1973–2007

Criteria	Cases	%	Exclusions
Cases of invasive cervical cancer	37,776	100	166
Exclude cases without microscopic confirmation	37,610	99.56	31
Exclude cases with death certificates and autopsy confirmation	37,579	99.48	86
Exclude children, i.e., <20 years	37,493	99.25	3,565
Limit race to whites and blacks	33,928	89.81	0
Limit histologic type to squamous, adenocarcinomas, and adenosquamous	33,928	89.81	
Final cohort	33,928		

Inclusion criteria: All cases of invasive cervical cancer diagnosed in the SEER 9 registries between 1973 and 2007.

Age was categorized into 5-year groups (20–24, 25–29, 30–34, 35–39, 40–44, 45–49, 50–54, 55–59, 60–64, 65–69, 70–74, 75–79, 80–84, and >85). Race was classified into whites and blacks, as these were the only classifications used since the commencement of the cancer registries. Histologic subtypes were classified based on the *International Classification of Disease for Oncology*, 2nd ed. (ICD-02).¹⁵ Squamous cell carcinomas were coded as 8050–8130, adenocarcinomas as 8140–8147, 8160–8162, 8180–8221, 8250–8506, 8520–8550, 8570–8573, and 8940–8941, and adenosquamous carcinomas as 8560–8570.¹⁶ The stage at presentation of invasive cervical cancer was based on the historic staging used by SEER: localized, regional, and distant.

Annual crude incidence rates were calculated using the age-specific absolute counts and age-specific female population provided by the SEER registries. The population estimates used to calculate cancer incidence rates represent a modification of the Vintage 2009 annual time series of July 1 county population estimates by age, sex, race, and Hispanic origin produced by the U.S. Census Bureau's Population Estimates Program, in collaboration with the National Center for Health Statistics.

The crude rates were standardized to the 2000 U.S standard population and expressed as cases per 100,000 women. Analyses were conducted with SAS version 9.2 (SAS Institute Inc., Cary, NC). Join point regression, which involves fitting a series of joined straight lines on a log scale to the trends in the annual age-adjusted rates, was used to identify significant changes in incidence rates and trends in the data. In our analysis, a maximum of three join points (four line segments) was used for each model.

Results

A total of 37,776 cases of invasive cervical cancer in the SEER registry dataset were diagnosed between 1973 and 2007. The overall incidence of invasive cervical cancer was highest in the 45–49-year age group. However, peak age group varied by histologic types. Squamous cell incidence peaked in the 45–49-year age groups. The peak ages for adenocarcinoma and adenosquamous carcinoma were both in the 35–39-year age group (Fig. 1).

Overall

Over the 35-year period, age-adjusted incidence rates for all invasive cervical cancer decreased by 54% from 13.07/100,000 women in 1973–1975 to 6.01/100,000 women in 2006–2007. Join-point analysis showed that, on an annual basis, invasive cervical cancer declined by 6.4% between 1973 and 2007. This rate of change was not constant over the 35-year study period, with a 9.9% decrease between 1973 and 1983. The decline stabilized between 1983 and 1992; since then, the incidence rate decreased by a rate of 7.7% annually.

By race

Of note, the age-adjusted incidence rates for all invasive cervical cancers for black women declined by 72.2% from 22.79/100,000 women in 1973–1975 to 6.8/100,000 women in 2006–2007. A decline of 54% was experienced among whites, from an annual incidence rate of 13.07/100,000 women in 1973–1975 to 6.01/100,000 women in 2006–2007 (Fig. 2).

FIG. 1. Age distribution of invasive cervical cancer histologic subtypes, 1973–2007.

Between 1973 and 2007, join-point analysis showed an overall decrease in the incidence of invasive cervical cancer among whites by 5.9%. Among blacks, however, there was an even greater (10.4%) decrease over the same period. Table 2 shows the decrease in incidence among blacks and whites between 1974 and 1983. Incidence decreased at a statistically significant rate of 10% among white women per year between 1974 and 1983. Among black women, the decrease was greater (14.1% annually) when compared to white women.

By histologic type

Table 3 shows a decline in the age-adjusted incidence rates of squamous cell carcinomas of 61.1%, from 10.28/100,000 women in 1973–1975 to 3.97/100,000 women in 2006–2007. Age-adjusted incidence rates for adenosquamous carcinoma declined by 16%, from 0.27/100,000 women in 1973–1975 to 0.23/100,000 women in 2006–2007. However, the age-adjusted incidence rates for adenocarcinomas increased by 32.2%, from 1.09/100,000 women in 1973–1975 to 1.44/100,000 women in 2006–2007.

The trend in incidence by histologic type varied over the 35 years. The overall incidence of squamous cell cancer

decreased annually between 1973 and 2007 by 8%, and the incidence of adenocarcinoma increased by an average of 2.9% per year over the same period. The trend analysis indicates that the incidence of squamous and adenosquamous carcinoma decreased between 1973 and 1983 by 10.4% and 4.6% per year, respectively, but there was a subtle increase in squamous cell carcinomas between 1983 and 1992 of 5.4% annually. Between 1992 and 2001, there was an 8.9% annual decrease in squamous cell carcinoma incidence and a 9.2% annual decrease between 2001 and 2007 (Table 4).

By race and histologic type

Between 1973 and 2007, the age-adjusted incidence rates of squamous cell cancer among white women declined by 60.6%, from 9.49/100,000 women in 1973–1975 to 3.74/100,000 women in 2006–2007 (Fig. 3A). Among black women, there was a 72.2% decline, from 18.90/100,000 women to 5.25/100,000 women during the same period. Figure 3B shows that the age-adjusted incidence rates of adenocarcinomas among white women increased by 41.8%, from 1.1/100,000 women in 1973–1975 to 1.56/100,000 women in 2006–2007. This increase

TABLE 2. TREND ANALYSIS OF INVASIVE CERVICAL CANCER BY RACE, 1973–2007

Join point ^a	White women			Black women	
	APC	95% CI	Join point	APC	95% CI
1974–1983	–10 ^b	(–14.7, –5.2)	1974–1980	–8.4	(–48.2, 62.1)
1983–1992	–1.8	(–11.7, 9.1)	1980–1989	–14.1	(–51.4, 52.0)
1992–2001	–7.4	(–16.6, 3.0)	1989–1998	–6.9	(–47.4, 64.7)
2001–2007	–7	(–16.3, 3.4)	1998–2007	–11.3	(–33.3, 18.0)

^aEach join point denotes a statistically significant ($p=0.05$) change in trend.

^bAnnual percent change (APC) is significantly different from zero (two-sided $p<0.05$).
CI, confidence interval.

TABLE 3. INVASIVE CERVICAL CANCERS BY HISTOLOGIC SUBTYPE, 1973–2007

Year	<i>Squamous carcinoma</i>			<i>Adenocarcinoma</i>			<i>Adenosquamous carcinoma</i>		
	Cases	AAIR	95% CI	Cases	AAIR	95% CI	Cases	AAIR	95% CI
1973–1975	2462	10.28	4.99, 18.76	259	1.09	0.04, 5.72	68	0.27	0, 4.23
1976–1978	2588	9.56	4.49, 17.82	306	1.15	0.04, 5.84	72	0.26	0, 4.21
1979–1981	2442	8.53	3.80, 16.47	348	1.23	0.06, 5.96	67	0.24	0, 4.17
1982–1984	2238	7.55	3.16, 15.16	334	1.12	0.04, 5.79	94	0.32	0, 4.32
1985–1987	2140	6.83	2.71, 14.19	402	1.24	0.06, 5.90	89	0.29	0, 4.27
1988–1990	2288	6.95	2.78, 14.36	478	1.44	0.10, 6.32	136	0.40	0, 4.48
1991–1993	2202	6.36	2.42, 13.55	448	1.32	0.07, 6.11	134	0.37	0, 4.43
1994–1996	2069	5.69	2.02, 12.63	540	1.50	0.11, 6.41	134	0.37	0, 4.43
1997–1999	2052	5.44	1.87, 12.29	570	1.53	0.11, 6.46	122	0.32	0, 4.33
2000–2002	1838	4.77	1.49, 11.34	568	1.49	0.10, 6.40	129	0.32	0, 4.34
2003–2005	1730	4.36	1.28, 10.76	550	1.41	0.09, 6.27	94	0.24	0, 4.18
2006–2007	1075	3.97	1.08, 10.21	384	1.44	0.09, 6.31	62	0.23	0, 4.15

Rates are per 100,000 women adjusted to the U.S. 2000 standard population.

AAIR, age-adjusted incidence rates.

was not reflected among black women, where we observed a 15.2% decline from 0.92/100,000 women in 1973–1975 to 0.78/100,000 women in 2006–2007. The age-adjusted incidence rates of invasive adenosquamous cervical cancer for whites was relatively stable (0.25/100,000 women) over the study period. However, among blacks, there was a 59.4% decline from 0.69/100,000 women in 1973–1975 to 0.28/100,000 women in 2006–2007.

Table 5 shows the incidence trend for cell types by race. Among whites, squamous cell incidence decreased 7.7% per year, whereas for blacks, there was a greater decrease (10.9%) per year; both declines were statistically significant. Among whites, adenocarcinoma incidence increased by 3.6% per year, and for blacks, the opposite (a decrease of 2.1% annually) occurred. Similar results were seen in the incidence trends of adenosquamous cell types, with the incidence for

white women increasing by 1.3% annually, and that for black women decreasing by 6.1% per year.

By stage

Approximately, 56.45% of all invasive cervical cancers were diagnosed at the localized stage, regional stage cancer accounted for 34.36%, and the remaining 9.29% of total invasive cervical cancer cases were diagnosed at the distant stage. There was an overall decline in the age-adjusted rates among those with squamous cell histology irrespective of stage of diagnosis. A similar decline was seen among the two racial groups. For adenocarcinoma, however, white women had increased rates irrespective of stage of diagnosis, and a corresponding decline was reported in the overall and black age-adjusted incidence rates irrespective of stage of diagnosis.

FIG. 2. Invasive cervical cancer incidence rates by race, 1973–2007.

TABLE 4. TREND ANALYSIS OF INVASIVE CERVICAL CANCER HISTOLOGIC SUBTYPES, 1973–2007

<i>Squamous carcinoma</i>			<i>Adenocarcinoma</i>			<i>Adenosquamous carcinoma</i>		
<i>Join point^a</i>	<i>APC</i>	<i>95% CI</i>	<i>Join point</i>	<i>APC</i>	<i>95% CI</i>	<i>Join point</i>	<i>APC</i>	<i>95% CI</i>
1974–1983	10.4	–23, 4.3	1974–1980	2.8	–40.6, 78.1	1974–1980	–4.6	–67.4, 179.4
1983–1992	–5.4	–30.1, 28.1	1980–1989	4.8	–319.98, 81.6	1980–1989	16.2	–60.3, 240.3
1992–2001	–8.9	–32.7, 23.3	1981–1998	4.2	–39.9, 80.5	1989–2001	–4.9	–44.4, 62.7
2001–2007	–9.2	–32.9, 22.9	1998–2007	–2.3	–25.8, 28.6	2001–2005	16.9	–71.6, 141.98

^aEach join point denotes a statistically significant ($p=0.05$) change in trend.

Finally, incidence rates for adenosquamous cancers for white women increased for regional stage, with an overall decline in other stages.

Discussion

Our 35-year population-based analysis of the SEER database indicates that invasive cervical cancer rates for black women decreased more rapidly than for white women over this timeframe. Recent studies have reported similar rates of Pap smear-based screening for black and white women.¹⁷ These comparable rates probably account for the overall decline in invasive cervical and squamous cancer rates among black women.¹⁸ Although rates for black women have shown greater declines than for white women, the absolute incidence of invasive cancer remains higher for black women than for white women. This may be because even though rates of screening are similar, black women may be less likely than white women to seek follow-up and treatment after abnormal Pap test results.¹⁹

The apparent difference between black and white women in terms of overall invasive cervical cancer incidence can partially be explained by the variation in histologic types of invasive cervical cancer. Consistent with other studies, our study shows a shift in the distribution of cervical cancer by histologic type.^{20,21} Although squamous cell carcinoma incidence rates have continued to decline, adenocarcinoma rates have gradually increased, especially among white women. Several studies have attributed the increasing incidence of adenocarcinomas to an increase in the detection of lesions that were previously undiagnosed or were not categorized as adenocarcinomas.^{6,11,21} Other studies suggest that cytology-based screening may be more effective for squamous cell cervical cancer screening than for adenocarcinoma screening.^{7,22,23}

An analysis by Sigurdsson,²⁴ using data from a cervical cancer screening program in Iceland, calculated a sensitivity of 81% for cytology for preinvasive squamous cell carcinoma after a 3-year interval and a sensitivity of 42% for preinvasive adenocarcinoma. Schiffman et al.,²⁵ in a case-control study in Australia, observed that the risk of adenocarcinoma was not reduced by screening.

Although endocervical sampling is recommended to address shortcomings in current techniques, reductions in the rate of adenocarcinomas have not yet been reported. This may be so for a number of reasons, including a lag in detection. The prevention of invasive cervical adenocarcinomas presents challenges²³; the morphology of the earliest precursors is unclear, adenocarcinoma *in situ* typically involves areas of the cervix that are difficult to sample (i.e., endocervix), and in-

vasive adenocarcinomas are thought to develop from small foci of adenocarcinomas *in situ*.^{21,26}

Studies have shown a strong correlation between risk factors for adenocarcinomas of the cervix and endometrial cancer, suggesting a potential independent effect of hormones on disease incidence.^{13,27} Studies have shown an increased risk of adenocarcinoma associated with parity and use of oral contraceptives among white women.²⁸ The increase in the incidence of adenocarcinomas has also been explained in part as a birth cohort effect as a result of increased use of oral contraceptive pills reported in the 1960s.^{27,29} Consistent with this theory, Piccinino and Mosher,³⁰ using the National Survey of Family Growth, showed that the rates of oral contraceptive use were statistically lower among black women than white women, providing a potential explanation for the decreased rates of adenocarcinoma in blacks compared to whites.

Our analyses are limited by a lack of data on the incidence of carcinoma *in-situ* (CIS) and adenocarcinoma *in-situ* (AIS), the precursor of invasive cervical cancer. Such data would help to clarify the impact of detecting these precursor lesions on rates of invasive cancer. Another limitation is the lack of long-term data to describe trends in cervical cancer incidence for women from other racial and ethnic subgroups. As data with a longer timeframe become available, we will be able to determine if trends are occurring similar to those currently seen in white and black women. There is also a lack of information about human papillomavirus (HPV) type-specific infection; this would help quantify the role of type-specific infection in the development of specific histologic subtypes in the U.S. population. Recent studies, using pooled data from different countries, suggest that HPV types 16 and 18 cause approximately 70% of squamous cervical cancers and close to 80% of adenocarcinomas.³¹ These high proportions suggest that current HPV vaccines, which are targeted against HPV types 16 and 18, may eventually have a significant impact on squamous and adenocervical cancers. Recent studies also suggest that HPV test-based screening may be more effective than cytology-based screening for detection of adenocarcinoma. A study by Katki et al.^{7,23} concluded that HPV testing in a cohort of U.S. women detected more than three times the amount of adenocarcinoma than that detected by cytology (77.78% compared to 17.39%). Further, many of the adenocarcinomas that were HPV positive were detected earlier with HPV testing compared to cytologic study, suggesting that use of HPV testing may have a significant impact on the incidence of adenocarcinoma. Thus, recommendations for the use of HPV test-based screening and expanded vaccine coverage may eventually cause a decreased incidence in adenocarcinomas over the coming years.

FIG. 3. (A) Squamous cell carcinoma histology incidence rate by race, 1973–2007. **(B)** Adenocarcinoma and adenosquamous histology incidence rates by race, 1973–2007.

TABLE 5. TREND ANALYSIS OF CELL TYPES BY RACE, 1973–2007

	White women		Black women	
	APC	95% CI	APC	95% CI
Squamous	-7.7 ^a	-8.5, -7	-10.9 ^a	-12, -9.8
Adenocarcinoma	3.6 ^a	2.3, 4.9	-2.1 ^a	-4.1, -0.1
Adenosquamous	1.3	-3.5, 5.3	-6.1 ^a	-10.7, -1.4

Each join point denotes a statistically significant ($p=0.05$) change in trend.

^aAPC is significantly different from zero (two-sided $p < 0.05$).

Conclusions

Our analysis suggests that although cytology-based screening has been successful in reducing disparities in overall and squamous cell cervical cancer incidence between black women and white women, adenocarcinomas remain a significant component of cancer incidence, especially among white women in the United States. Attention should be given to the evaluation of alternatives to reduce false-negative results in detecting cervical adenocarcinomas. HPV test-based screening and HPV vaccines may be more effective approaches than cytology-based screening for achieving across the board reductions in cervical cancer.

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Disclosure Statement

The authors declare no competing financial interests exist.

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