



Published in final edited form as:

J Registry Manag. 2013 ; 40(2): 84–92.

Treatment Patterns for Cervical Carcinoma In Situ in Michigan, 1998–2003

Divya A. Patel, PhD^a, Mona Saraiya, MD^b, Glenn Copeland, MBA^c, Michele L. Cote, PhD^d, S. Deblina Datta, MD^e, and George F. Sawaya, MD^f

^aDepartment of Obstetrics, Gynecology, and Reproductive Sciences, Yale University School of Medicine

^bDivision of Cancer Prevention and Control, Centers for Disease Control and Prevention

^cMichigan Cancer Surveillance Program, Michigan Department of Community Health

^dPopulation Studies and Disparities Research, Karmanos Cancer Institute and Wayne State University School of Medicine

^eDivision of STD Prevention, Centers for Disease Control and Prevention

^fDepartment of Obstetrics, Gynecology, and Reproductive Sciences, University of California, San Francisco, California

Abstract

Objective—To characterize population-level surgical treatment patterns for cervical carcinoma in situ (CIS) reported to the Michigan Cancer Surveillance Program (MCSP), and to inform data collection strategies.

Methods—All cases of cervical carcinoma in situ (CIS) (including cervical intraepithelial neoplasia grade 3 and adenocarcinoma in situ [AIS]) reported to the MCSP during 1998–2003 were identified. First course of treatment (ablative procedure, cone biopsy, loop electrosurgical excisional procedure [LEEP], hysterectomy, unspecified surgical treatment, no surgical treatment, unknown if surgically treated) was described by histology, race, and age at diagnosis.

Results—Of 17,022 cases of cervical CIS, 82.8% were squamous CIS, 3% AIS/adenosquamous CIS, and 14.2% unspecified/other CIS. Over half (54.7%) of cases were diagnosed in women under age 30. Excisional treatments (LEEP, 32.3% and cone biopsy, 17.3%) were most common, though substantial proportions had no reported treatment (17.8%) or unknown treatment (21.1%). Less common were hysterectomy (7.2%) and ablative procedures (2.6%). LEEP was the most common treatment for squamous cases, while hysterectomy was the most treatment for AIS/adenosquamous CIS cases. Across histologic types, a sizeable proportion of women diagnosed 30 years of age underwent excision, either LEEP (20%–38.7%) or cone biopsy (13.7%–44%).

Conclusion—Despite evidence suggesting it may be safer and equally effective as excision, ablation was rarely used for treating cervical squamous CIS. These population-based data indicate some notable differences in treatment by histology and age at diagnosis, with observed patterns appearing consistent with consensus guidelines in place at the time of study, but favoring more aggressive procedures. Future data collection strategies may need to validate treatment information, including the large proportion of no or unknown treatment.

Keywords

adenocarcinoma; cervical carcinoma in situ; cervical intraepithelial neoplasia; hysterectomy; squamous cell carcinoma

Introduction

Despite dramatic declines in cervical cancer in the United States concurrent with widespread screening, about 12,280 women are diagnosed with invasive cervical cancer each year.¹ Cervical cancer is preceded by dysplastic changes of the cervical epithelium, known as cervical intraepithelial neoplasia (CIN). These CIN lesions are graded based on histological severity from 1 to 3, the latter including carcinoma in situ (CIS), a pre-invasive carcinomatous change of the cervix. High-grade CIN lesions (CIN 3) and CIS, often synonymous, are considered the most relevant cervical cancer precursors for diagnosis and treatment due to their heightened invasive potential.² Most cervical cancers (70%) are squamous cell carcinomas.³ While adenocarcinomas account for a smaller proportion (20%–25%) of all cervical cancers,^{3,4} registry-based studies indicate their incidence may be increasing.⁵ Adenocarcinoma in situ (AIS) is the most proximate precursor of cervical adenocarcinoma.

The systematic collection of data on high-grade CIN lesions could serve an important role in monitoring the impact of preventive measures such as newer cervical cancer screening guidelines and prophylactic human papillomavirus (HPV) vaccine on future disease burden.^{6,7} However, cervical cancer precursors are currently not routinely reported throughout the United States.⁶ Routine collection of CIS did occur by US cancer registries for several decades in the 1970s, 1980s, and early 1990s. In 1996, US cancer registries discontinued this practice due to concerns over the burden to reporting facilities; the quality of data, in light of changing diagnostic terminology for cervical cancer precursors⁸; and loss of comparability in incidence data over time and across registries.⁹

Despite the national decision in 1996 to stop collection of high-grade cervical cancer precursors, the Michigan Cancer Surveillance Program (MCSP) continued collection of cervical CIS/AIS data, with minimal additional resources, due to the increasing use of electronic case reporting.⁸ Because the Michigan program is the only population-based data source for high-grade cervical cancer precursors that has been continuously collected since 1985, it provides a unique resource for the long-term systematic monitoring of cervical cancer control efforts. Analysis of MCSP data found increasing rates of cervical carcinoma in situ (CIS) in Michigan that nearly doubled in less than 2 decades, increasing from 31.7 per 100,000 in 1985 to 59.2 per 100,000 in 2003. Furthermore, for every invasive cervical

cancer diagnosis reported during the same period, there were 7 in situ cases in white women and 4 in situ cases in black women.⁹

In women with a histological diagnosis of CIN, appropriate management is a critical component of cervical cancer prevention. However, very few population-based data exist on patterns of management for cervical cancer precursors. Surgical management options for CIN include ablative procedures that destroy the affected tissue in vivo (eg, cryotherapy, laser ablation), excisional procedures that remove the affected tissue (eg, loop electrosurgical excisional procedure [LEEP], laser conization, cold knife conization), and hysterectomy.^{10,11}

In a systematic review published in 2000, no substantive differences were found in the persistence or resolution of CIN among women treated with cone biopsy, cryotherapy, laser ablation, or LEEP.¹² A Cochrane review of the evidence through July 2004, from 28 randomized controlled trials of alternative surgical treatments for CIN, found no overwhelmingly superior technique for eradicating CIN.¹³ The authors concluded that the choice of treatment should therefore be based on cost, morbidity, and the value of obtaining biopsy specimens.

Excisional procedures are more widely used to treat CIN in the United States,¹⁴ largely due to its provision of a tissue specimen for assessment of histopathology and surgical margins,¹⁵ and perhaps because it is believed by clinicians to be more effective than ablation, despite evidence to the contrary.¹⁶⁻¹⁸ In contrast to these potential benefits, there is now evidence from meta-analyses of observational studies indicating potential increased risks for adverse pregnancy outcomes (ie, premature rupture of membranes, preterm delivery, low birth weight infant, and even perinatal mortality) among women treated with cold knife conization, LEEP, or laser conization.^{14,19}

The objectives of this study were to characterize population-level treatment patterns for cervical CIS by histology, age, and race in the MCSP, and to inform future data collection strategies.

Materials and Methods

Data Source and Case Selection

This study was approved as exempt by the Michigan Department of Community Health's Institutional Review Board. We used data collected by the MCSP, a statewide population-based registry which has been in operation since 1981, with legally mandated cancer reporting and statewide population coverage since 1985.⁹ Methods for collection of cervical CIS cases through the MCSP have been described in detail.⁹ Briefly, the MCSP covers a state population of approximately 10 million, consisting of 81.2% whites, 14.2% blacks, 2.4% Asians, 0.6% American Indians/Alaska Natives, and approximately 4.2% Hispanics.²⁰ All in situ and invasive cancers (other than basal or squamous cell carcinoma of nongenital skin) have been reportable to the MCSP as defined by the Michigan Administrative Code under the authority of Public Act 82 of 1984.

Cervical CIS is collected by MSCP in either of 2 diagnostic categories: carcinoma in situ, or grade 3 cervical intraepithelial neoplasia (CIN 3) without any qualifier. During the study period, a diagnosis of CIN 3 qualified with the term “severe dysplasia” was not reportable, an exclusion criterion intended to increase the specificity of cervical CIS cases. For our analysis, all cervical CIS cases reported between 1998 and 2003 were included. Cases were limited to ICD-O-3 topography code C53 (cervix uteri), histology codes 8010–8560, and behavior code 2 (in situ neoplasms).²¹ The majority of cases (63.6%) were ICD-O-3 histology code 8077, corresponding to squamous intraepithelial neoplasia grade III.²¹ The remaining cases included histology codes 8070 (squamous cell carcinoma in situ, not otherwise specified (NOS); 19%), 8010 (carcinoma in situ, NOS; 14.2%), 8140 (adenocarcinoma in situ, NOS; 2.8%),²¹ and other, less common codes.

Classification of Variables

Histology, demographic information (race and age at diagnosis), and first course of treatment were collected and reported according to SEER standards.²² Histologic subtypes were classified according to ICD-O-3 morphology codes,²¹ and categorized as squamous CIS, AIS/adenosquamous CIS, unspecified CIS, or other specified CIS. For analysis purposes, unspecified CIS and other specified CIS were grouped, so that the final categories for histologic subtype were as follows: squamous CIS, AIS/adenosquamous CIS, and unspecified CIS/other CIS. Race was categorized as white, black, other, or unknown. Age at diagnosis was categorized as <21, 21–30, 31–45, or >45 years.

Surgical procedures were classified according to SEER variable codes for first course of cancer-directed surgery, and categorized as ablative procedure, cone biopsy, LEEP, hysterectomy, unspecified surgical treatment, no surgical treatment, and unknown if surgically treated. Details of the surgical procedure classification, including SEER codes, procedure descriptions and frequencies, are shown in a supplemental table.

Ablative procedures included surgical techniques that destroy the affected tissue *in vivo*. The two most widely used excisional modalities that remove the affected tissue, LEEP and cone biopsy, were kept as separate categories. Hysterectomy included total, radical, modified radical, and extended hysterectomy. Trachelectomy, or surgical removal of the cervix, is a fertility-preserving surgical alternative to a radical hysterectomy. This procedure was reported in only a small number of cases (n=3) and was classified as hysterectomy because it may be viewed as having similar severity (though, unlike hysterectomy, trachelectomy does not preclude future childbearing). Unspecified surgical treatment included instances where it was assumed a surgical treatment occurred, but the procedure could not be readily classified with other surgical treatments on the basis of its limited description (ie, surgery, NOS [n=4]; local tumor excision, NOS [n=287]). The category of “no surgical treatment” was limited to a single SEER variable code for “none; no surgery of primary site; autopsy only.” It was unknown if surgically treated included the SEER variable code for “unknown if surgery performed; death certificate only” as well as procedures considered part of diagnostic workup rather than treatment (ie, dilation and curettage/endocervical curettage [n=1,685]; excisional biopsy, NOS [n=275]). The category of “no surgical treatment” was kept separate

from “unspecified surgical treatment” and “unknown if surgically treated” since some women may have had contraindications to surgery.

Statistical Analysis

The distribution of age at diagnosis was tested for normality using the Shapiro-Wilk test, and because the resultant p-value was <0.05 , age at diagnosis was compared across histologic subtypes using the non-parametric Kruskal-Wallis test. First course of treatment was described overall and by histologic subtype, and was further stratified by race and age at diagnosis. Analyses by race were limited to white and black women, and excluded 109 (0.6%) women with other race due to small numbers as well as 1,865 (11%) women with unknown race. Analyses by age at diagnosis excluded 18 (0.1%) women for whom age at diagnosis was missing. The exact Cochran-Armitage trend test was used to evaluate trends in hysterectomy by age, stratified by histologic subtype. These trend tests compared the distribution of women undergoing hysterectomy with all individuals who did not undergo that treatment across age groups. Two-sided p-values <0.05 were considered statistically significant. All analyses were conducted using SAS version 9.2 (SAS Institute, Inc., Cary, NC).²³

Results

Characteristics of the Study Population

For the period 1998 through 2003, there were 17,022 cases of cervical CIS reported to the MSCP (Table 1). Median age at diagnosis was 29 years. Over half (54.7%) of cases were diagnosed under 30 years of age and 10.3% of cases were diagnosed under age 21. Most women were white (73.7%). The majority of cases diagnosed during this period were squamous CIS (82.8%). The distribution of age at diagnosis differed significantly across histologic subtypes (Kruskal-Wallis p-value <0.0001 ; data not shown); women with AIS/adenosquamous CIS were diagnosed at later ages (median: 33 years) than women with squamous CIS (median: 29 years) or unspecified/other CIS (median: 30 years). Overall, LEEP (32.3%) and cone biopsy (17.3%), both excisional modalities, were the most commonly used treatments. Fewer women underwent hysterectomy (7.2%), ablative procedures (2.6%) or unspecified surgical treatments (1.7%). In addition, a substantial proportion of women had no surgical treatment (17.8%), and for approximately one fifth of women (21.1%), it was unknown if they were surgically treated.

First Course of Surgical Treatment Stratified by Histologic Subtype

There were some notable differences in treatment across histologic subtypes (Table 2). LEEP was the most common treatment for women with squamous (33.6%) and unspecified/other CIS (29.2%). However, the most common form of treatment among women with AIS/adenosquamous CIS was hysterectomy (29.6%), a treatment received by only 6% of those with squamous CIS and 9% of those with unspecified/other CIS. Fewer women with AIS/adenosquamous CIS received no surgical treatment (9.5%), compared to 17.9% of those with squamous CIS and 19.3% of those with unspecified/other CIS. Ablation was the least common treatment across all histologic types (0.4%–2.7%).

First Course of Surgical Treatment Stratified by Race

Treatment patterns by race and histologic subtype, limited to 15,048 (88.4%) black and white women, are shown in Table 3. Among women with squamous CIS, treatments were similar by race, with the majority of white and black women undergoing LEEP (33.6% and 37.4%, respectively) and cone biopsy (17.8% and 17.3%, respectively). Treatments for unspecified/other CIS were also similar by race, with the majority of white and black women also undergoing LEEP (30.2% and 28%, respectively) and cone biopsy (19% and 20.5%, respectively). Some racial differences in treatment types were observed among women with AIS/adenosquamous CIS. White women had a higher proportion of hysterectomies (31.3%) than black women (34.8%), while black women had a higher proportion of cone biopsies (34.8%) than white women (23.3%). Among women with AIS/adenosquamous CIS, a larger proportion of black women (21.7%) underwent LEEP compared with white women (11.7%). Of note, because there were only 23 black women with AIS/adenosquamous CIS in this study population, these percentages and comparisons should be interpreted with caution.

First Course of Surgical Treatment Stratified by Age at Diagnosis

Treatment patterns by age at diagnosis and histologic subtype, among women for whom age at diagnosis was known (n=17,044; 99.9%), are shown in Table 4. For all histologic subtypes, the proportion of women undergoing hysterectomy increased significantly with increasing age at diagnosis (Cochran-Armitage trend test p-value <0.05 for each histologic subtype). Ablative procedures were performed in small proportions of women (<3.3%) regardless of age at diagnosis, and were used the least among those with AIS/adenosquamous CIS. Treatment patterns by age at diagnosis were similar for those with squamous CIS and unspecified/other CIS, with the majority of women with these histologic subtypes undergoing LEEP. However, treatment patterns were more variable among women with AIS/adenosquamous CIS. Among women diagnosed with this histologic subtype at <21 and 21–30 years of age, cone biopsy was the most common surgical treatment (44% and 35%, respectively). Among women diagnosed with this histologic subtype at later ages, hysterectomy was the predominant form of surgical treatment (42.2% for those diagnosed at age 31–45 years and 44.6% for those diagnosed at age >45 years), with substantially fewer women diagnosed in these age groups undergoing cone biopsy or LEEP.

Notably, across histologic subtypes, a sizeable proportion of women diagnosed ≥30 years of age underwent an excisional procedure, either a LEEP (20%–38.7%) or cone biopsy (13.7%–44%). In the subgroup of 1,749 (10.3%) women diagnosed at the youngest ages (<21 years), approximately one fourth (23.2%) received no surgical treatment. Excisional procedures were common among women diagnosed <21 years of age, for squamous CIS (36.1% LEEP, 13.7% cone biopsy), AIS/adenosquamous CIS (20% LEEP, 44% cone biopsy), and unspecified/other CIS (38.7% LEEP, 17% cone biopsy).

Discussion

In this population-based study of 17,022 women diagnosed with cervical CIS in Michigan during 1998–2003, excisional procedures (LEEP and cone biopsy) were the most commonly

used treatments. Cervical ablation was rarely performed, with less than 3.3% of women across all histological subtypes treated with these procedures. Consensus guidelines in place during the time frame of our study recommended both excision or ablation of the transformation zone as acceptable treatment options for women with biopsy-confirmed CIN^{2,3} and a satisfactory colposcopy.²⁴ In women with recurrent CIN,^{2,3} excisional treatment modalities were recommended.²⁴ We also found that hysterectomies increased significantly with age, and were most commonly performed for AIS/adenosquamous CIS, in line with the existing recommendations against hysterectomy as primary therapy for CIN^{2,3} but the recommended treatment for women with AIS who have completed childbearing.²⁴ We observed some potential differences in treatment for AIS/adenosquamous CIS by race, which may be due in part to confounding by differences in desires for future childbearing and/or preferences for definitive risk-eliminating surgery compared to continued surveillance.

There are few other population-based registry studies with which to compare the treatment patterns observed in our study. A small study conducted by the Romagna Cancer Registry in northern Italy found that, among 264 women with biopsy-confirmed CIN 3 reported to the registry during 1986–1993, the first course of treatment involved conization (59%), hysterectomy (35%), and local destructive therapy (6%).²⁵ The authors attributed the limited role of conservative therapy and high prevalence of hysterectomy to a lack of ensuring follow-up with repeat smears and/or colposcopy.²⁵ We observed similar proportions of women undergoing LEEP or conization (49.6%), but fewer women undergoing hysterectomy (7.2%) and ablative therapy (2.6%). The lower percentage of hysterectomies and ablative therapy could reflect misclassification or the preferred and popular choice of treatment during the study period.

A study linking the British Columbia Cancer Agency cytology database with cancer registry and vital statistics data found women with CIN 3 most often underwent cone biopsy¹⁸; however, as the purpose of their study was to examine rates of CIN^{2,3} and invasive cervical cancer following treatment, their exclusion criteria precludes direct comparison with our findings. Perhaps the most methodologically comparable study is an analysis published in 1990 of the Surveillance, Epidemiology, and End Results (SEER) Program's New Mexico Tumor Registry.²⁶ Overall, of the 4,585 women diagnosed with cervical CIS during 1969–1985, 31.1% underwent conservative treatment (conization, laser treatment, cryosurgery or trachelectomy), while 65.5% underwent hysterectomy.²⁶ By the end of the 17-year period, the proportion of women undergoing hysterectomy had declined to 45.8% while the proportion of women who underwent more conservative treatments had increased to 50.3%.²⁶ The use of conservative treatments increased in all age groups with the largest increase in women under age 30.²⁶ Interestingly, these dramatic shifts in surgical practice occurred in the absence of any consensus guidelines for the management of women with CIN, but may have reflected the advent of LEEP which could be easily performed in an outpatient setting.

In our study, the median age at diagnosis was 29 years, coinciding with peak childbearing age among American women.²⁷ The few available registry-based studies have reported later ages at diagnosis, both in areas with organized cervical cancer screening such as in

Romagna, Italy (median: 38.5 years)²⁵ and in areas with opportunistic cervical cancer screening such as in Israel (mean: 38.4 years),²⁸ which may reflect differences in risk factors for CIN, socioeconomic characteristics, access to cervical cancer screening, and management of abnormal screening test results. In our study, a small proportion (10.3%) of cervical CIS cases was diagnosed at ages under 21 years. However, newer guidelines for screening start age combined with HPV vaccine initiatives are likely to affect diagnoses among the youngest women. Recent cervical cancer screening guidelines issued by both the American Cancer Society²⁹⁻³¹ and the US Preventive Services Task Force³² recommend that screening start at age 21, regardless of sexual history. Typically, CIN 3 lesions grow slowly over many years before invasion³³ and less than half (30%-50%) of CIN 3 lesions will progress to cancer³⁴; treatment of lesions which may ultimately regress could put women at unnecessary risk for treatment-related side effects as well as for potential adverse outcomes in future pregnancies. Ongoing surveillance data are needed to inform our understanding of the epidemiology of cervical CIS, and registry-based studies may be helpful in evaluating the population-level impact of evolving screening guidelines and of HPV vaccination on the burden of disease, particularly among young women.

During the time frame of our study, LEEP and cone biopsy were commonly performed in young women with cervical squamous CIS, despite the evidence that had accumulated during that period for adverse obstetric effects associated with excisional treatments. Across histologic subtypes, a sizeable proportion of women diagnosed 30 years of age underwent either LEEP (20%–39%) or cone biopsy (14%–44%). Even in the youngest subgroup of women (diagnosed under age 21), excisional procedures were common. It is conceivable that these young women may have undergone repeat excisional procedures over their reproductive life span, potentially further increasing their risk of adverse outcomes in future pregnancies. A meta-analysis showing consistent evidence linking excisional treatments for CIN and adverse outcomes in future pregnancies, with risks of preterm delivery, low birth weight, and preterm premature rupture of membranes increased approximately twofold, was published after the time frame of our study (2006).¹⁹ Risks of adverse pregnancy outcomes were not shown for women undergoing ablative treatment.¹⁹ In the United States, practitioners may choose more aggressive management options even for the youngest women due to concerns about access to care and compliance with follow-up.

While the MCSP represents some of the best available population-level data for cervical CIS, several limitations must be considered. The current study likely underestimates the true burden of cervical CIS because CIN 3 qualified with “severe dysplasia” was not reportable in Michigan during the study period. As the MCSP began collecting “severe dysplasia” in 2009, additional studies using more recent data could be useful for evaluating the sensitivity and specificity of the reporting definition for cervical CIS and the potential need for modifying or standardizing the definition. We were not able to evaluate the observed racial differences in surgical treatment for AIS/adenosquamous CIS for potential confounding (eg, by age at diagnosis) due to the small number of black women with this histological subtype (n=23) in our study population. As management guidelines in place at the time of study recommended cryotherapy, laser ablation, and LEEP as acceptable treatment modalities even for biopsy-confirmed CIN 1,²⁴ reasons for the high proportion of women (17.8%) with

CIS that had no surgical treatment or unknown treatment (21.1%) warrant further investigation.

There is potential misclassification of some diagnostic procedures as treatment in the registry. For example, in this study, dilation and curettage or endocervical curettage was recorded in the registry as the first course of treatment for 1,685 (9.9%) women; for the purposes of our analyses, these women were included in the “unknown if surgically treated” category, as these procedures are generally considered part of the diagnostic workup rather than treatment. Data collection and coding manuals should be reviewed and, if needed, modified to distinguish between procedures used for diagnostic workup and those used therapeutically, taking into account the sequence of treatments. This process will also involve efforts to train the medical chart abstraction staff to improve data quality. Finally, choice of treatment may have been influenced by medical history (eg, remote history of treated CIN) that we could not capture in our analysis.

Looking forward, future changes being proposed by pathology organizations to standardize classification of HPV-related neoplasia of the lower genital tract³⁵ may impact the interpretation of data from long-standing surveillance systems like the MCSP. Further, with our improving understanding of treatment-associated outcomes, the collection of relevant treatment details (eg, cone excised depth) could be considered. While it may be prohibitively burdensome to add this to existing cancer registries, newer population-based cancer registries and sentinel surveillance systems that begin collecting cervical cancer precursors to monitor the effects of HPV vaccination may be able to enhance their overall impact by also collecting data on relevant treatment characteristics and clinical outcomes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

This work was supported by the National Program of Cancer Registries, Centers for Disease Control and Prevention (grant number 5U58DP000812). Dr. Patel was supported in part through a career development award from the National Cancer Institute, National Institutes of Health (grant number K07CA120040). Dr. Sawaya was supported in part through an interprofessional agreement with the Centers for Disease Control and Prevention. The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the funding agencies.

References

1. U.S. Cancer Statistics Working Group. United States Cancer Statistics: 1999–2007 Incidence and Mortality Web-based Report. U.S. Department of Health and Human Services, Centers for Disease Control and Prevention and National Cancer Institute; Atlanta: 2010.
2. McIndoe WA, McLean MR, Jones RW, Mullins PR. The invasive potential of carcinoma in situ of the cervix. *Obstet Gynecol.* 1984; 64(4):451–458. [PubMed: 6483293]
3. Ries, LAG.; Melbert, D.; Krapcho, M., et al. SEER Cancer Statistics Review, 1975-2005. National Cancer Institute; Bethesda, MD: 2008. Based on November 2007 SEER data submission, posted to the SEER Web site Available at: http://seer.cancer.gov/csr/1975_2005/

4. Smith HO, Tiffany MF, Qualls CR, Key CR. The rising incidence of adenocarcinoma relative to squamous cell carcinoma of the uterine cervix in the United States—a 24-year population-based study. *Gynecol Oncol.* 2000; 78(2):97–105. [PubMed: 10926787]
5. Wang SS, Sherman ME, Hildesheim A, Lacey JV Jr, Devesa S. Cervical adenocarcinoma and squamous cell carcinoma incidence trends among white women and black women in the United States for 1976–2000. *Cancer.* 2004; 100(5):1035–1044. [PubMed: 14983500]
6. Markowitz LE, Hariri S, Unger ER, Saraiya M, Datta SD, Dunne EF. Post-licensure monitoring of HPV vaccine in the United States. *Vaccine.* 2010; 28(30):4731–4737. [PubMed: 20188681]
7. World Health Organization. Report of the meeting on HPV Vaccine Coverage and Impact Monitoring, 16–17 November 2009. Geneva, Switzerland: Available at: http://whqlibdoc.who.int/hq/2010/WHO_IVB_10.05_eng.pdf
8. Saraiya M, Goodman MT, Datta SD, Chen VW, Wingo PA. Cancer registries and monitoring the impact of prophylactic human papillomavirus vaccines: the potential role. *Cancer.* 2008; 113(suppl 10):3047–3057. [PubMed: 18980287]
9. Copeland G, Datta SD, Spivak G, Garvin AD, Cote ML. Total burden and incidence of in situ and invasive cervical carcinoma in Michigan, 1985–2003. *Cancer.* 2008; 113(suppl 10):2946–2954. [PubMed: 18980278]
10. Wright TC Jr, Massad LS, Dunton CJ, Spitzer M, Wilkinson EJ, Solomon D. 2006 consensus guidelines for the management of women with abnormal cervical cancer screening tests. *Am J Obstet Gynecol.* 2007; 197(4):346–355. [PubMed: 17904957]
11. Vesco, KK.; Whitlock, EP.; Eder, M., et al. Screening for Cervical Cancer: A Systematic Evidence Review for the U.S. Preventive Services Task Force. Agency for Healthcare Research and Quality; Rockville, MD: May. 2011 Evidence Synthesis No.86 AHRQ Publication No. 11-05156-EF-1
12. Nuovo J, Melnikow J, Willan AR, Chan BK. Treatment outcomes for squamous intraepithelial lesions. *Int J Gynaecol Obstet.* 2000; 68(1):25–33. [PubMed: 10687833]
13. Martin-Hirsch PPL, Paraskevaidis E, Kitchener HC. Surgery for cervical intraepithelial neoplasia. *Cochrane Database of Systematic Reviews.* 2009:3.
14. Arbyn M, Kyrgiou M, Simoons C, et al. Perinatal mortality and other severe adverse pregnancy outcomes associated with treatment of cervical intraepithelial neoplasia: meta-analysis. *BMJ.* 2008; 337:a1284. [PubMed: 18801868]
15. Ang C, Mukhopadhyay A, Burnley C, et al. Histological recurrence and depth of loop treatment of the cervix in women of reproductive age: incomplete excision versus adverse pregnancy outcome. *BJOG.* 2011; 118(6):685–692. [PubMed: 21429068]
16. Chirenje ZM, Rusakaniko S, Akino V, Mlingo M. A randomised clinical trial of loop electrosurgical excision procedure (LEEP) versus cryotherapy in the treatment of cervical intraepithelial neoplasia. *J Obstet Gynaecol.* 2001; 21(6):617–621. [PubMed: 12521783]
17. Dey P, Gibbs A, Arnold DF, Saleh N, Hirsch PJ, Woodman CB. Loop diathermy excision compared with cervical laser vaporisation for the treatment of intraepithelial neoplasia: a randomised controlled trial. *BJOG.* 2002; 109(4):381–385. [PubMed: 12013158]
18. Melnikow J, McGahan C, Sawaya GF, Ehlen T, Coldman A. Cervical intraepithelial neoplasia outcomes after treatment: long-term followup from the British Columbia Cohort Study. *J Natl Cancer Inst.* 2009; 101(10):721–728. [PubMed: 19436026]
19. Kyrgiou M, Koliopoulos G, Martin-Hirsch P, Arbyn M, Prendiville W, Paraskevaidis E. Obstetric outcomes after conservative treatment for intraepithelial or early invasive cervical lesions: systematic review and meta-analysis. *Lancet.* 2006; 367(9509):489–498. [PubMed: 16473126]
20. U.S. Census Bureau. [Accessed April 20, 2011] State and County QuickFacts. Available at: <http://quickfacts.census.gov/qfd/states/26000>
21. Fritz, A.; Percy, C.; Jack, A., et al. International Classification of Diseases for Oncology. 3rd ed. World Health Organization; Geneva: 2000.
22. Fritz, A.; Ries, L. The SEER Program Code Manual. 3rd ed. Cancer Statistics Branch, Surveillance Program, Division of Cancer Control and Population Sciences, National Cancer Institute, National Institutes of Health; 1998.
23. SAS (for Windows) [computer program]. Version 9.2. The SAS Institute; Cary, NC: 2008.

24. Wright TC Jr, Cox JT, Massad LS, Carlson J, Twigg LB, Wilkinson EJ. 2001 consensus guidelines for the management of women with cervical intraepithelial neoplasia. *Am J Obstet Gynecol.* 2003; 189(1):295–304. [PubMed: 12861176]
25. Serafini M, Cordaro C, Montanari E, Falcini F, Bucchi L. Diagnosis and treatment of cervical intraepithelial neoplasia grade 3: a registry-based study in the Romagna region of Italy (1986-1993). *Int J Epidemiol.* 1999; 28(2):196–203. [PubMed: 10342679]
26. Goodwin JS, Hunt WC, Key CR, Samet JM. Changes in surgical treatments: the example of hysterectomy versus conization for cervical carcinoma in situ. *J Clin Epidemiol.* 1990; 43(9):977–982. [PubMed: 2213085]
27. Livingston, G.; Cohn, D. The new demography of American motherhood. Pew Research Center; 2010.
28. Kogan L, Menczer J, Shejter E, Liphshitz I, Barchana M. Selected demographic characteristics of Israeli Jewish women with high-grade cervical intraepithelial neoplasia (CIN3): a population-based study. *Arch Gynecol Obstet.* 2011; 283(2):329–333. [PubMed: 20191281]
29. Saslow D, Solomon D, Lawson HW, et al. American Cancer Society, American Society for Colposcopy and Cervical Pathology, and American Society for Clinical Pathology screening guidelines for the prevention and early detection of cervical cancer. *J Low Genit Tract Dis.* 2012
30. Saslow D, Solomon D, Lawson HW, et al. American Cancer Society, American Society for Colposcopy and Cervical Pathology, and American Society for Clinical Pathology screening guidelines for the prevention and early detection of cervical cancer. *CA Cancer J Clin.* 2012; 62(3):147–172. [PubMed: 22422631]
31. Saslow D, Solomon D, Lawson HW, et al. American Cancer Society, American Society for Colposcopy and Cervical Pathology, and American Society for Clinical Pathology screening guidelines for the prevention and early detection of cervical cancer. *Am J Clin Path.* 2012; 137(4): 516–542. [PubMed: 22431528]
32. Moyer VA. Screening for Cervical Cancer: U.S. Preventive Services Task Force Recommendation Statement. *Ann Intern Med.* Mar 14.2012
33. Schiffman M, Wentzensen N, Wacholder S, Kinney W, Gage JC, Castle PE. Human papillomavirus testing in the prevention of cervical cancer. *J Natl Cancer Inst.* 2011; 103(5):368–383. [PubMed: 21282563]
34. Yang HP, Zuna RE, Schiffman M, et al. Clinical and pathological heterogeneity of cervical intraepithelial neoplasia grade 3. *PLOS ONE.* 2012; 7(1):e29051. [PubMed: 22253702]
35. College of American Pathologists. [Accessed November 17, 2011] HPV-related neoplasia of lower anogenital tract. 2011. Available at: http://www.cap.org/apps/cap.portal?_nfpb=true&cntvwrPtl_t_actionOverride=%2Fportlets%2FcontentViewer%2Fshow&_windowLabel=cntvwrPtl_t&cntvwrPtl_t%7BactionForm.contentReference%7D=cap_today%2F0911%2F0911f_hpv_related.html&_state=maximized&_pageLabel=cntvwr

Table 1
Characteristics of Cervical Carcinoma In Situ (CIS) Cases* in Michigan, 1998-2003
(n=17,022)

<i>Characteristic</i>	<i>n (%)</i>
Age at diagnosis (years)	
<21	1,749 (10.3)
21-30	7,552 (44.4)
31-45	59,92 (35.2)
>45	1,711 (10.1)
Missing	18 (0.1)
Median (range)	29 (8-103)
Race	
White	12,540 (73.7)
Black	2,508 (14.7)
Other	109 (0.6)
Unknown	1,865 (11.0)
Histologic subtype	
Squamous CIS	14,096 (82.8)
AIS or adenosquamous CIS	514 (3.0)
Unspecified or other CIS	2,412 (14.2)
First course of cancer-directed surgery	
Ablative procedure	446 (2.6)
Cone biopsy	2,942 (17.3)
LEEP	5,504 (32.3)
Hysterectomy	1,221 (7.2)
Unspecified surgical treatment	291 (1.7)
No surgical treatment	3,032 (17.8)
Unknown if surgically treated	3,586 (21.1)

AIS = adenocarcinoma in situ, LEEP = loop electrosurgical excisional procedure.

* All cases reported to the Michigan Cancer Surveillance Program during 1998-2003 and limited to ICD-O-3 topography code C53 (cervix uteri), histology codes 8010-8560, and behavior code 2 (in situ neoplasms). The majority of cases (63.6%) were ICD-O-3 histology code 8077, corresponding to squamous intraepithelial neoplasia grade III.

Table 2
First Course of Treatment for Cervical Carcinoma In Situ (CIS) Cases* by Histologic Subtype, Michigan, 1998-2003 (n=17,022)

	<i>Histologic subtype</i>			<i>Overall</i>
	Squamous CIS	AIS or adenosquamous CIS	Unspecified or other CIS	
	(n=14,096; 82.8%)	(n=514; 3.0%)	(n=2,412; 14.2%)	
Treatment	n (%)	n (%)	n (%)	n (%)
Ablative procedure	380 (2.7)	2 (0.4)	64 (2.7)	446 (2.6)
Cone biopsy	2,370 (16.8)	124 (24.1)	448 (18.6)	2,942 (17.3)
LEEP	4,733 (33.6)	66 (12.8)	705 (29.2)	5,504 (32.3)
Hysterectomy	851 (6.0)	152 (29.6)	218 (9.0)	1,221 (7.2)
Unspecified surgical treatment	232 (1.7)	16 (3.1)	43 (1.8)	291 (1.7)
No surgical treatment	2,518 (17.9)	49 (9.5)	465 (19.3)	3,032 (17.8)
Unknown if surgically treated	3,012 (21.4)	105 (20.4)	469 (19.4)	3,586 (21.1)

AIS = adenocarcinoma in situ, LEEP = loop electrosurgical excisional procedure.

* All cases reported to the Michigan Cancer Surveillance Program during 1998–2003 and limited to ICD-O-3 topography code C53 (cervix uteri), histology codes 8010–8560, and behavior code 2 (in situ neoplasms). The majority of cases (63.6%) were ICD-O-3 histology code 8077, corresponding to squamous intraepithelial neoplasia grade III.

Table 3
First Course of Treatment for Cervical Carcinoma In Situ (CIS) Cases* by Histologic Subtype, Overall and by Race, Michigan, 1998-2003 (n=15,048[†])

<i>Treatment</i>	<i>Race</i>		
	White (n=12,540; 83.3%) n (%)	Black (n=2,508; 16.7%) n (%)	Overall (n=15,048) n (%)
Squamous CIS (n=12,420)			
Ablative procedure	313 (3.0)	38 (1.9)	351 (2.8)
Cone biopsy	1862 (17.8)	342 (17.3)	2204 (17.8)
LEEP	3509 (33.6)	741 (37.4)	4250 (34.2)
Hysterectomy	714 (6.8)	109 (5.5)	823 (6.6)
Unspecified surgical treatment	200 (1.9)	25 (1.3)	225 (1.8)
No surgical treatment	1744 (16.7)	276 (13.9)	2020 (16.3)
Unknown if surgically treated	2096 (20.1)	451 (22.8)	2547 (20.5)
AIS or adenosquamous CIS (n=483)			
Ablative procedure	2 (0.4)	0 (0)	2 (0.4)
Cone biopsy	107 (23.3)	8 (34.8)	115 (23.8)
LEEP	54 (11.7)	5 (21.7)	59 (12.2)
Hysterectomy	144 (31.3)	5 (21.7)	149 (30.9)
Unspecified surgical treatment	16 (3.5)	0 (0)	16 (3.3)
No surgical treatment	41 (8.9)	0 (0)	41 (8.5)
Unknown if surgically treated	96 (20.9)	5 (21.7)	101 (20.9)
Unspecified or other CIS (n=2,145)			
Ablative procedure	49 (3.0)	8 (1.6)	57 (2.7)
Cone biopsy	312 (19.0)	103 (20.5)	415 (19.4)
LEEP	496 (30.2)	141 (28.0)	637 (29.7)
Hysterectomy	174 (10.6)	39 (7.8)	213 (9.9)
Unspecified surgical treatment	38 (2.3)	1 (0.2)	39 (1.8)
No surgical treatment	261 (15.9)	111 (22.1)	372 (17.3)
Unknown if surgically treated	312 (19.0)	100 (19.9)	412 (19.2)

LEEP = loop electrosurgical excisional procedure, AIS = adenocarcinoma in situ.

* All cases reported to the Michigan Cancer Surveillance Program during 1998-2003 and limited to ICD-O-3 topography code C53 (cervix uteri), histology codes 8010-8560, and behavior code 2 (in situ neoplasms). The majority of cases (63.6%) were ICD-O-3 histology code 8077, corresponding to squamous intraepithelial neoplasia grade III.

[†] Does not include 109 (0.6%) women of other race and 1865 (1 1.0%) women with unknown race.

Table 4
First Course of Treatment for Cervical Carcinoma In Situ (CIS) Cases* by Age at
Diagnosis and Histologic Subtype, Michigan, 1998-2003 (n=17,004[†])

<i>Treatment</i>	<i>Age at diagnosis (years)</i>			
	<i><21</i> (n=1,749; 10.3%) n (%)	<i>21-30</i> (n=7,552; 44.4%) n (%)	<i>31-45</i> (n=5,992; 35.2%) n (%)	<i>>45</i> (n=1,711; 10.1%) n (%)
Squamous CIS				
Ablative procedure	47 (3.1)	207 (3.3)	110 (2.3)	16 (1.2)
Cone biopsy	209 (13.7)	1,026 (16.2)	878 (18.0)	255 (19.2)
LEEP	552 (36.1)	2,383 (37.6)	1,512 (31.0)	285 (21.4)
Hysterectomy	1 (0.1)	111 (1.8)	508 (10.4)	231 (17.4)
Unspecified surgical treatment	20 (1.3)	102 (1.6)	82 (1.7)	28 (2.1)
No surgical treatment	351 (22.9)	1,166 (18.4)	765 (15.7)	231 (17.4)
Unknown if surgically treated	350 (22.9)	1,344 (21.2)	1,031 (21.1)	283 (21.3)
AIS or adenosquamous CIS				
Ablative procedure	0 (0)	1 (0.6)	1 (0.4)	0 (0)
Cone biopsy	11 (44.0)	62 (35.0)	41 (17.3)	10 (13.5)
LEEP	5 (20.0)	37 (20.9)	21 (8.9)	3 (4.1)
Hysterectomy	1 (4.0)	18 (10.2)	100 (42.2)	33 (44.6)
Unspecified surgical treatment	0 (0)	6 (3.4)	8 (3.4)	2 (2.7)
No surgical treatment	1 (4.0)	16 (9.0)	21 (8.9)	10 (13.5)
Unknown if surgically treated	7 (28.0)	37 (20.9)	45 (19.0)	16 (21.6)
Unspecified or other CIS				
Ablative procedure	5 (2.6)	31 (3.0)	22 (2.5)	6 (2.0)
Cone biopsy	33 (17.0)	191 (18.4)	171 (19.7)	53 (17.2)
LEEP	75 (38.7)	339 (32.7)	241 (27.7)	50 (16.2)
Hysterectomy	0 (0)	27 (2.6)	119 (13.7)	71 (23.1)
Unspecified surgical treatment	3 (1.6)	21 (2.0)	17 (2.0)	2 (0.7)
No surgical treatment	53 (27.3)	200 (19.3)	136 (15.7)	72 (23.4)
Unknown if surgically treated	25 (12.9)	227 (21.9)	163 (18.8)	54 (17.5)

LEEP = loop electrosurgical excisional procedure, AIS = adenocarcinoma in situ.

* All cases reported to the Michigan Cancer Surveillance Program during 1998-2003 and limited to ICD-O-3 topography code C53 (cervix uteri), histology codes 8010–8560, and behavior code 2 (in situ neoplasms). The majority of cases (63.6%) were ICD-O-3 histology code 8077, corresponding to squamous intraepithelial neoplasia grade III.

[†] Does not include 18 (0.1%) women with missing age at diagnosis.