Published in final edited form as:
Gynecol Oncol. 2012 November ; 127(2): 278–282. doi:10.1016/j.ygyno.2012.07.119.

Tubal Ligation Frequency in Oklahoma Women with Cervical Cancer

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Abstract

Objective—Infrequent Pap screening is an important risk factor for cervical cancer. We studied the association between contraceptive methods, screening frequency, and cancer.

Methods—Women (n=2,004) enrolled in the cross-sectional Study to Understand Cervical Cancer Endpoints and Determinants(SUCCEED) underwent colposcopy to evaluate an abnormal Pap test. Questionnaire data were compared between those with cervical intraepithelial neoplasia(CIN)3/adenocarcinoma in situ(AIS) and those with invasive cancer to identify factors associated with cancer. Logistic regression was used to calculate age-stratified measures of association between contraceptive method and Pap frequency as well as tubal ligation(TL) and cancer risk.

Results—In all age groups, women with TL were more likely to have had no Pap screening in the previous 5 years compared to women using other contraception: 26-35 years (OR 4.6, 95%CI 2.4 −8.6; p<0.001), 36-45 years (OR 3.8, 95%CI 2.1-7.0; p<0.001), and 46-55 years (OR 2.2, 95%CI 1.0-4.9; p=0.050). Subjects with cancer (n=163) were more likely to have had a TL (41%

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*Presented in part as an abstract at the 41st Meeting of the Society of Gynecologic Oncologists, March, 2010; San Francisco, CA

vs. 21%, p<0.001) than those with CIN3/AIS (n=370). Age-stratified analyses showed an increased odds of tubal ligation in women with cancer versus those with CIN3/AIS between 25 and 45 years, with a significant increase in women 26 to 35 years old (OR 3.3, 95%CI 1.4-8.1; p=0.009). Adjusting for Pap frequency changed the effect only slightly, suggesting increased risk was not fully mediated by lack of screening.

Conclusion—Contraceptive type is associated with Pap screening. Women with TLs obtain less frequent Pap testing and may be at increased risk for cervical cancer.

Introduction

The incidence of cervical cancer in the United States has markedly decreased over the last 50 years with widespread implementation of prevention efforts including Papanicolaou tests for screening, colposcopy for diagnosis, and excisional treatment for pre-invasive disease. Recent randomized trials have shown that the sensitivity of screening can be further increased with the inclusion of high-risk human papillomavirus (HPV) testing, which may also improve detection of adenocarcinoma in situ (AIS) and adenocarcinoma.[1-4] The majority of patients who now present with cervical cancer have no recent screening history; only a small fraction have a false negative cytology screening test within 3 years of cervical cancer diagnosis.[5-8]

Although the incidence of cervical cancer is still declining in the United States, a considerable number of women continue to be diagnosed and die unnecessarily each year; the American Cancer Society predicted that in 2010, there were 12,200 women detected with cervical cancer and 4,210 who died of this preventable disease.[9] Although the incidence declined among all women between 1992 and 2006, the burden of cancer remains significantly and disproportionately higher among some minority populations, particularly African-American and Hispanic women. [8, 10-13]

Concurrent with the widespread acceptance of Pap screening, the understanding of the etiology and pathogenesis of cervical cancer has evolved. HPV infection is necessary for development of cervical intraepithelial neoplasia (CIN), which may progress to invasive cancer over time. CIN 3 is considered a direct precancerous lesion, with approximately 30-50% of untreated CIN 3 proceeding to cancer within 10 years.[14-15] Many established risk factors for cervical cancer and CIN are related to the an increased risk of HPV infection and persistence: early age at sexual initiation, multiple sexual partners, high risk partners, high parity, smoking, immunosuppression, minority status, and lower socioeconomic status. [16-19]

Since screening and treatment of cancer precursors interrupts the natural history, lack of screening is an important risk factor for progression. Clinically, we observed that many women with cervical cancer had undergone tubal ligation (TL). Because of the traditional gynecologic link between Pap testing and family planning, specifically for oral contraceptive refills, we investigated the relationship between contraceptive history, screening frequency, and cervical pathology. Based on our clinical observations, we hypothesized that women presenting with invasive cancer would have higher rates of TL in comparison to women with CIN 3, and patients with TL would have less frequent screening than patients using other types of contraception.

Materials and Methods

Questionnaire data were analyzed from the Study to Understand Cervical Cancer Early Endpoints and Determinants (SUCCEED), a cross-sectional study conducted at the University of Oklahoma Health Sciences Center (OUHSC) sponsored by the National Cancer Institute. IRB approval was obtained at both institutions and all subjects signed

informed consent. The study design has been described previously, but in brief, subjects were standard patients referred for care at OUHSC with cervical cancer or abnormal cervical screening results and were recruited starting in November 2003.[20-21] The catchment area for cervical cancer patients includes most of Oklahoma and parts of western Missouri, northern Texas, and southern Kansas; this geographical area has a population of nearly two million women. Patients referred to dysplasia clinic also travel from a large region comprising most of the state of Oklahoma, with the exception of the greater Tulsa area, and are largely uninsured. They are referred by private physicians, county health clinics, federally-funded community clinics, the OUHSC hospital-based clinic, Planned Parenthood, and other private medical facilities. Patients from all referral groups were asked to participate. Inclusion criteria included a recent history of abnormal Pap test or presentation with cervical cancer and referral to OUHSC for management and evaluation. Exclusion criteria were age less than eighteen, pregnancy, HIV positivity, prior diagnosis of cancer or radiation therapy, and prior hysterectomy.

A study nurse administered a standardized questionnaire to collect demographic data including age, ethnicity, socioeconomic status, insurance status, obstetric history, prior sexually transmitted infection, contraceptive history, sexual history, smoking history, cervical dysplasia history, and frequency of Pap screening. Standard colposcopy, with biopsies and endocervical curettage as indicated, was then performed by an OUHSC physician. Participants were subsequently managed according to the American Society for Colposcopy and Cervical Pathology (ASCCP) guidelines.[20-21] Laboratory methods have been previously described.[22-23] The clinical outcome evaluated was the worst final pathologic diagnosis made by the study pathologist.

Questionnaire data were examined to identify demographic risk factors among patients with cancer compared to those with CIN 3. Specifically, age, self-reported race/ethnicity, education level, insurance status, contraceptive history, and frequency of Pap screening, were analyzed. Women who did not indicate Hispanic ethnicity were considered non-Hispanic in the race indicated. Contraception included all methods used previously. Both squamous cell cancer and adenocarcinoma were included for analysis; CIN 3 and adenocarcinoma in situ (AIS) were grouped as precancerous lesions (CIN 3/AIS) while adenocarcinoma was analyzed with squamous cell cancer (cancer). Variables considered are listed in Table 1.

Analysis was performed using SAS version 9.1.3 (SAS Institute Inc., Cary, NC). All hypotheses were two-sided, with an alpha of 0.05 considered statistically significant. Descriptive statistics were used to summarize demographic characteristics and medical history among groups of subjects. A chi-square test or Fisher's exact test, when more than 20% of expected cross-tabulation cell counts were less than 5, was used to compare the distribution of categorical characteristics among disease groups. A Mantel-Haenszel test was used to estimate an overall odds ratio, summarized across age groups, describing the association between categorical demographic and clinical characteristics and invasive cancer status. The Mantel-Haenszel test result was not reported when the Breslow-Day test for homogeneity of the odds ratio was significant at the 0.10 alpha level or could not be calculated due to small cell sizes. Logistic regression models were used to investigate the age-stratified association between cancer versus CIN 3/AIS and the odds of tubal ligation among subjects reporting birth control use with and without adjustment for Pap screening frequency. Regression models were also adjusted for condom use and number of pregnancies, as potential confounding factors, but given very similar results to models without adjustment, the results are not presented. Similar models with age stratification were used to evaluate the association between lack of Pap screening and contraceptive method (TL vs. other). Odds ratios and 95% confidence intervals were calculated using non-tubal

ligation contraceptive methods as the reference group when investigating the association between lack of Pap screening and birth control use. Subgroup-specific odds ratio values were only estimated when there were at least 20 subjects in each disease category (invasive cancer or CIN 3/AIS) or Pap screening frequency category (no Pap tests in the past 5 years versus at least 1 Pap test).

Results

There were 2,004 women with non-missing Pap history, age, and contraceptive history who were enrolled in SUCCEED prior to October 1, 2009. Of these, 533 women were diagnosed with CIN 3/AIS (n=370) or invasive cancer (n=163). Table 1 shows demographic data comparing subjects with CIN 3/AIS versus those with cancer. Women with cancer were older ($p<0.001$), had higher incomes ($p=0.005$), were more likely to have private insurance ($p<0.001$), and were less likely to be current smokers ($p<0.001$) in comparison to women with CIN 3/AIS. Women with cancer also underwent less frequent Pap screening ($p<0.001$).

Pap frequency among the 2,004 subjects enrolled in SUCCEED was analyzed with regards to contraceptive method, specifically comparing tubal ligation status to other contraception types (Table 2). This group included women with all histologic diagnoses. The odds of having no Pap test in the past 5 years were higher among women with tubal ligation versus non-tubal ligation methods: 25 to 35 years (OR 4.6, 95% CI 2.4 to 8.6; $p<0.001$), 36 to 45 years (OR 3.8, 95% CI 2.1 to 7.0; $p<0.001$), and 46 to 55 years (OR 2.2, 95% CI 1.0 to 4.9; $p=0.050$). The odds of no recent Pap test among reproductive age women were also higher among those with no contraceptive use versus those using a non-tubal ligation contraceptive method.

Birth control method was then compared among women with cancer and women with CIN 3/AIS (Table 3.) Spermicides ($p=0.048$), injectable medications ($p<0.001$), the patch ($p=0.007$), oral contraceptive pills ($p<0.001$), and condoms ($p<0.001$) were more frequently used by women with CIN 3/AIS. On the other hand, women with cancer were more likely to have a TL ($p<0.001$), to have used an intrauterine device (IUD) ($p=0.003$), or to have never used contraception ($p<0.001$). The overall frequency of women using IUDs, the patch, and no birth control were low.

Because increased age is related to both cervical cancer and the likelihood of having a TL, the association between TL and cancer was evaluated after stratifying by age group (Table 4). Among subjects reporting prior birth control use, the odds of TL for women 26 to 35 years old with invasive cancer were 3.3 times (95% CI 1.4 to 8.1, $p=0.009$) the odds among those with CIN 3/AIS. There were too few cases to measure the association in women between the ages of 18 and 25 and in women older than 55 years, but there was no association in other age groups. To determine whether the association between tubal ligation and cervical cancer was a result of decreased Pap screening in women with tubal ligation, the odds ratio was adjusted for the frequency of Pap testing. If the relationship was caused by a decline in Pap testing among women with tubal ligation, there would be no expected association between tubal ligation and cervical cancer when adjusted for Pap frequency. In subjects between 26 and 35 years after adjustment for Pap frequency, the odds of TL among subjects with invasive cancer remained elevated at 2.9 times (95% CI 1.1 to 7.5, $p=0.025$) higher than the odds of TL among women with CIN 3/AIS. When invasive cancer was limited to squamous cell histology (n=138) and pre-invasive lesions were limited to CIN 3 (n=356), the odds of TL remained higher among 26 to 35-year-olds with cancer compared to those with CIN 3 (OR 2.7, 95% CI 1.0 to 7.4; $p=0.046$). The association was not statistically significant after adjustment for Pap frequency in the SCC/CIN 3 sub-group (OR 2.2, 95% CI 0.8 to 6.3; $p=0.14$).

Discussion

Here, we report findings from a cross-sectional study based in Oklahoma showing that type of contraception was associated with participation in Pap-based cervical cancer screening. Most notably, tubal ligation was associated with less frequent Pap screening compared to other contraceptive methods such as OCPs, injections, patches, and IUDs in the overall study population. TL is a definitive method of contraception that does not require further physician visits, in contrast to the other contraceptive methods that require continuous replenishment or monitoring.

When we analyzed the association between tubal ligation and cancer risk, comparing women with cancer to women with CIN3/AIS, we observed an increased odds of tubal ligation in women ages 26-35, but not in other age groups. Adjusting for Pap screening history did not change this association, however, suggesting that Pap screening frequency does not fully mediate the association between TL and cervical cancer in young women. These findings are surprising, as we showed a clear relationship between TL and less screening, and lack of screening has been demonstrated as a major risk factor for developing cervical cancer.[24] A further limitation of the study was that the participants with cancer were derived from a larger population base than the dysplasia patients. While women with dysplasia were enrolled through colposcopy clinics, women with cancer were referred from a larger area in the state of Oklahoma and adjacent states. These referral pattern differences may also explain why women with cancer were more likely to have health insurance. A majority of women recruited from the university dysplasia clinic are uninsured. In contrast, all women with cervical cancer, regardless of insurance status, are treated by university gynecologic oncologists and were subject to recruitment. Furthermore, women who decide to undergo permanent sterilization at a young age may differ from their peers in some way that was not appreciated in our questionnaire, but that also increases their risk for cervical cancer.

While contraceptive use was found to be associated with cervical cancer risk when compared to women without cervical disease in multiple studies, we found different effects by type of contraception when comparing women with cancer to women with CIN3/AIS. The mechanism by which contraceptive use causes increased cervical cancer risk is poorly understood and hypotheses include increased HPV exposure, persistence of HPV infection, or transformation of premalignant lesions among OCP users.[25] Here, we show that different types of contraceptives are associated with different screening behaviors. This new finding of decreased Pap screening among sterilized women is of particular importance to the physicians performing the sterilization procedure and the group of medical providers who may serve as the only point of contact in the health care system for these patients in the primary care setting, in urgent care centers, and in the emergency room.. It is important that gynecologists performing tubal ligations are aware of the risk association between the procedure and non-compliance with of future cervical cancer screening. Obviously, in an opportunistic screening program, more gynecology visits are associated with more frequent Pap screening. We do not have evidence that there is an increased biological risk of developing cervical cancer after tubal ligation. Therefore, based on current data, women with tubal ligation should not be considered at higher risk of developing cancer compared to women choosing other methods of contraception, but at higher risk of non-compliance with screening. Women need to be educated about the importance of compliance with current screening guidelines, even if there are no other reasons for gynecologic visits. If recommended by current guidelines, screening should be integrated into the pre- or post-operative routine. Serious consideration should be given to co-testing with cytology and HPV DNA, an approach that is FDA approved in women 30 years and older, at the time of tubal ligation. The risk of disease in women testing negative for both cytology and HPV DNA is extremely low for the next 5-10 years.[26] Further studies are necessary to better

understand the association between tubal ligation, contraception, Pap screening, and cervical cancer development.

Acknowledgments

**The research was supported in part by the Intramural Research Program of the NIH and the National Cancer Institute Tubal Ligation Frequency in Oklahoma Women with Cervical Cancer

Citations

1. Mayrand MH, Duarte-Franco E, Rodrigues I, et al. Human papillomavirus DNA versus Papanicolaou screening tests for cervical cancer. N Engl J Med. Oct 18; 2007 357(16):1579–1588. [PubMed: 17942871]
2. Liao SY, Rodgers WH, Kauderer J, et al. Carbonic anhydrase IX and human papillomavirus as diagnostic biomarkers of cervical dysplasia/neoplasia in women with a cytologic diagnosis of atypical glandular cells: a Gynecologic Oncology Group study in United States. Int J Cancer. Nov 15; 2009 125(10):2434–2440. [PubMed: 19670419]
3. Zappa M, Visioli CB, Ciatto S, Iossa A, Paci E, Sasieni P. Lower protection of cytological screening for adenocarcinomas and shorter protection for younger women: the results of a case-control study in Florence. Br J Cancer. May 4; 2004 90(9):1784–1786. [PubMed: 15150597]
4. Naucler P, Ryd W, Tornberg S, et al. Human papillomavirus and Papanicolaou tests to screen for cervical cancer. N Engl J Med. Oct 18; 2007 357(16):1589–1597. [PubMed: 17942872]
5. Abed Z, O'Leary M, Hand K, et al. Cervical screening history in patients with early stage carcinoma of the cervix. Ir Med J. May; 2006 99(5):140–142. [PubMed: 16892918]
6. Janerich DT, Hadjimichael O, Schwartz PE, et al. The screening histories of women with invasive cervical cancer, Connecticut. Amer J Pub Health. Jun; 1995 85(6):791–794. [PubMed: 7762711]
7. Parazzini F, Negri E, La Vecchia C, Bocciolone L. Screening practices and invasive cervical cancer risk in different age strata. Gyn Onc. Jul; 1990 38(1):76–80.
8. Health NIo. Cervical Cancer. NIH Consensus Statement 1996. 1996; 14(1):1–38.
9. Jemal A, Siegel R, Xu J, Ward E. Cancer statistics, 2010. CA Cancer J Clin. 2010; 60:277–300. [PubMed: 20610543]
10. 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. Mar 1; 2004 100(5):1035–1044. [PubMed: 14983500]
11. Group USCSW. [Accessed July 6, 2009] United States Cancer Statistics: 1999–2005 Incidence and Mortality Web-based Report 2009. 2009. http://www.cdc.gov/cancer/cervical/statistics/
12. Watson M, Saraiya M, Benard V, et al. Burden of cervical cancer in the United States, 1998-2003. Cancer. Nov 15; 2008 113(10 Suppl):2855–2864. [PubMed: 18980204]
13. Group USCSW. United States Cancer Statistics: 1999-2005 Incidence and Mortality Web-based Report. US Department of Health and Human Services, Centers for Disease Control and Prevention and National Cancer Institute; Atlanta: 2009. http://www.cdc.gov/npcr/uscs
14. Ostor AG. Natural history of cervical intraepithelial neoplasia: a critical review. Int J Gynecol Pathol. Apr; 1993 12(2):186–192. [PubMed: 8463044]
15. McCredie MR, Sharples KJ, Paul C, et al. Natural history of cervical neoplasia and risk of invasive cancer in women with cervical intraepithelial neoplasia 3. Lancet Oncol. May; 2008 9(5):425–434. [PubMed: 18407790]
16. Ferris, DG.; Cox, J.; Thomas; O'Connor; Dennis, M.; Wright, V.; Cecil; Foerster; John, editors. Modern Colposcopy Textbook and Atlas. Second ed. Kendal/Hunt; Dubuqe, Iowa: 2004.
17. Kruger-Kjaer S, van den Brule AJ, Svare EI, et al. Different risk factor patterns for high-grade and low-grade intraepithelial lesions on the cervix among HPV-positive and HPV-negative young women. Int J Cancer. May 29; 1998 76(5):613–619. [PubMed: 9610715]
18. Thomas DB, Qin Q, Kuypers J, et al. Human papillomaviruses and cervical cancer in Bangkok. II. Risk factors for in situ and invasive squamous cell cervical carcinomas. Am J Epidemiol. Apr 15; 2001 153(8):732–739. [PubMed: 11296144]

19. Thomas DB, Ray RM, Qin Q. Risk factors for progression of squamous cell cervical carcinoma in-situ to invasive cervical cancer: results of a multinational study. Cancer Causes Control. Sep; 2002 13(7):683–690. [PubMed: 12296516]

20. Wright TC Jr, Cox JT, Massad LS, et al. 2001 Consensus guidelines for the management of women with cervical intraepithelia neoplasia. J Low Genit Tract Dis. 2003; 7:154–67. [PubMed: 17051063]

21. Wright TC Jr, Massad LS, Dunton CJ, et al. 2006 Consensus guidelines for the management of women with abnormal cervical screening tests. J Low Genit Tract Dis. 2007; 11:201–22. [PubMed: 17917566]

22. Wang SS, Zuna RE, Wentzensen N, et al. Human papillomavirus cofactors by disease progression and human papillomavirus types in the study to understand cervical cancer early endpoints and determinants. Cancer Epidemiol Biomarkers Prev. Jan; 2009 18(1):113–120. [PubMed: 19124488]

23. Wentzensen N, Schiffman M, Dunn ST, et al. Grading the severity of cervical neoplasia based on combined histopathology, cytopathology, and HPV genotype distribution among 1,700 women referred to colposcopy in Oklahoma. Int J Cancer. Feb 15; 2009 124(4):964–969. [PubMed: 19030188]

24. Nygard JF, Nygard M, Skare GB, Thoresen SO. Screening histories of women with CIN 2/3 compared with women diagnosed with invasive cervical cancer: a retrospective analysis of the Norwegian Coordinated Cervical Cancer Screening Program. Cancer Causes Control. May; 2005 16(4):463–474. [PubMed: 15953989]

25. International Collaboration of Epidemiological Studies of Cervical Cancer. Cervical cancer and hormonal contraceptives. Lancet. 2007; 370:1609–21. [PubMed: 17993361]

26. Dillner J, Reboli M, Birembaut P, et al. Long term predictive values of cytology and human papillomavirus testing in cervical cancer screening. BMJ. 2008; 337:a1754. [PubMed: 18852164]

Highlights

- We compare contraception type and Pap frequency among women with cervical cancer and dysplasia.
- Women with tubal ligation underwent less frequent pap screening.
- Young women with tubal ligation have an increased risk of cervical cancer.

Table 1

Demographic Information by Histology Diagnosis*

	All Subjects (n=2,004)	CIN 3/AIS** (n=370)	Invasive Cancer (n=163)	p-value (CIN 3/AIS vs. Cancer)
Median Age at Worst Diagnosis (Interquartile Range) (IQR)	26 (22-34)	27 (24-34)	45 (37-56)	<0.001
Age at Worst Diagnosis (years)				<0.001
18-25 yrs.	984 (49%)	146 (39%)	4 (2%)	
36-45 yrs.	257 (13%)	53 (14%)	53 (33%)	
46-55 yrs.	122 (6%)	18 (5%)	38 (23%)	
56-65 yrs	60 (3%)	9 (2%)	30 (18%)	
>65 yrs.	15 (<1%)	0	12 (7%)	
Race/Ethnicity				0.51 (white vs. non white)
Black	229 (11%)	21 (6%)	9 (6%)	
Hispanic	295 (15%)	49 (13%)	12 (7%)	
White/Non-Hispanic	1292 (65%)	270 (73%)	124 (76%)	
Other	180 (9%)	28 (8%)	18 (11%)	
Health Care Coverage				<0.001
Employer/Self-Insured	205 (10%)	28 (8%)	55 (36%)	
Medicare/Medicaid/Health Dept	1226 (63%)	232 (66%)	65 (43%)	
None	518 (27%)	93 (26%)	31 (21%)	
Household Income				0.005
$10,000 or less	689 (40%)	116 (36%)	40 (27%)	
$10,001 - $20,000	549 (32%)	103 (32%)	41 (28%)	
$20,001 - $40,000	356 (20%)	69 (22%)	34 (23%)	
More than $40,000	138 (8%)	33 (10%)	32 (22%)	
Marital Status				0.001
Single	836 (43%)	117 (33%)	28 (18%)	
Married or living as married	796 (41%)	173 (49%)	86 (57%)	
Separated or divorced	299 (15%)	59 (17%)	29 (19%)	
Widowed	30 (2%)	6 (2%)	9 (6%)	
Smoking Status				<0.001
Current	897 (45%)	216 (60%)	63 (39%)	
Former	281 (14%)	46 (13%)	39 (24%)	
Never	794 (40%)	99 (27%)	58 (36%)	
Number of Pregnancies				0.001
0	482 (24%)	59 (16%)	15 (9%)	
1	415 (21%)	74 (20%)	15 (9%)	
2	410 (21%)	77 (21%)	35 (21%)	

	All Subjects (n=2,004)	CIN 3/AIS** (n=370)	Invasive Cancer (n=163)	p-value (CIN 3/AIS vs. Cancer)
3	322 (16%)	72 (19%)	43 (26%)	
4-14	369 (19%)	88 (24%)	55 (34%)	
Frequency of Pap Test (last 5 years)				<0.001
2+ times/year	294 (15%)	44 (12%)	6 (4%)	
Yearly	298 (15%)	58 (16%)	7 (4%)	
Every 2 years	988 (49%)	180 (49%)	42 (26%)	
Every 3+ years	157 (8%)	26 (7%)	20 (12%)	
None	267 (13%)	62 (17%)	88 (54%)	
Median Number of Paps (last 5 years) (IQR)	4 (2-5)	4 (2-5)	0 (0-3)	<0.001

*Percentiles may not sum to 100 because of rounding; number of subjects in each demographic category may not sum to column because of missing data

**CIN = cervical intraepithelial neoplasia, AIS = adenocarcinoma in situ

Table 2

Odds of No Pap Test in Past 5 years by Tubal Ligation Status

	Frequency No Pap in 5 years	OR	95% CI	p-value
18-25 yrs.				
Other Birth Control Method	47/950	1 (ref)		
Tubal	0/21	(not estimable)		
No Birth Control	4/13	8.5	2.5 to 28.7	<0.001
26-35 yrs.				
Other Birth Control Method	26/458	1 (ref)		
Tubal	20/93	4.6	2.4 to 8.6	<0.001
No Birth Control	3/15	4.2	1.1 to 15.6	0.035
36-45 yrs.				
Other Birth Control Method	20/121	1 (ref)		
Tubal	48/112	3.8	2.1 to 7.0	<0.001
No Birth Control	11/24	4.3	1.7 to 10.9	0.002
46-55 yrs.				
Other Birth Control Method	17/56	1 (ref)		
Tubal	25/51	2.2	1.0 to 4.9	0.050
No Birth Control	10/15	4.6	1.4 to 15.5	0.014
>55 yrs.				
Other Birth Control Method	21/43	1 (ref)		
Tubal	12/27	0.8	0.3 to 2.2	0.72
No Birth Control	3/5	1.6	0.2 to 10.4	0.64

Table 3

Contraception History by Severity of Diagnosis

	CIN 3/AIS* (n=370)	Invasive Cancer (n=163)	p-value
Ever Used Birth Control	361 (98%)	145 (89%)	<0.001
Median Number of Types of Birth Control Used (Interquartile Range)	3 (2-3)	2 (1-3)	<0.001
Birth Control Method Used **			
Diaphragm	8 (2%)	7 (4%)	0.25
IUD	20 (5%)	21 (13%)	0.003
Sponge	4 (1%)	5 (3%)	0.14
Spermicide	52 (14%)	13 (8%)	0.048
Injectable Medication	156 (42%)	11 (7%)	<0.001
Patch	30 (8%)	1 (<1%)	0.007
Pill	317 (86%)	113 (69%)	<0.001
Tubal	76 (21%)	67 (41%)	<0.001
Male Sterilization	26 (7%)	18 (11%)	0.12
Norplant	2 (<1%)	1 (<1%)	>0.9
Condom	281 (76%)	70 (43%)	<0.001
No Birth Control	9 (2%)	18 (11%)	<0.001

* CIN = cervical intraepithelial neoplasia, AIS = adenocarcinoma in situ

** Subjects may report more than one method of birth control.

Table 4

Odds of Tubal Ligation (TL) Associated with Invasive Cancer Among Women Reporting Contraception Use

Age Group	CIN 3/AIS* cases with TL	Cancer cases with TL	OR (95%CI) (cancer vs. CIN 3/AIS)	p-value	Adjusted OR** (95%CI) (cancer vs. CIN 3/AIS)	p-value
18-25 yrs.	6/146	1/4	(not estimated)			
26-35 yrs.	27/141	11/25	3.3 (1.4 to 8.1)	0.009	2.9 (1.1 to 7.5)	0.025
36-45 yrs.	28/50	27/45	1.2 (0.5 to 2.7)	0.69	1.0 (0.4 to 2.3)	0.96
46-55 yrs.	10/16	14/31	0.5 (0.1 to 1.7)	0.26	0.4 (0.1 to 1.4)	0.16
56-65 yrs.	5/8	9/28	(not estimated)			
>65 yrs.	0/0	5/12	(not estimated)			

*AIS = adenocarcinoma in situ, CIN = cervical intraepithelial neoplasia

**Adjusted for Pap Frequency