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The Prevalence Of Hpv Associated Disease In Women Under Age 21: Who Will Be Missed Under The New Cervical Cancer Screening Guidelines?

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Who will be missed under the new cervical cancer screening guidelines?

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ABSTRACT

Objective: To quantify the number of adolescent females <21 with pre-cancerous cervical lesions or cervical intraepithelial neoplasia (CIN) 2+/AIS in the state of Connecticut and identify any correlates which may be associated with CIN 3.

Methods: CIN 2+/AIS precancerous cervical lesions are a reportable condition in the State of Connecticut for the purpose of public health surveillance. A subset of this data (681 women) under 21 years of age was analyzed for the years 2008-2010.

Results: Of the 681 records, 478 (70.2%) women had CIN 2, 92 had CIN 2/3 (13.5%), and 110 (16.2%) had CIN 3. The highest annual rates for CIN 2+/AIS were found in Litchfield (342.98/100,000) and New London (287.85/100,000) counties. CIN 3 occurred at an average rate statewide of 38.6/100,000 per year for women ages 13-20. The majority of adolescents with pre-cancerous cervical lesions CIN 2+/AIS (70%) were 19 and 20 years of age. CIN 3 vs. CIN 2 was not found to be associated with age, insurance status, specimen collection year, or living in a rural vs. urban county. However, the association between diagnosis and county level income was highly significant; adolescents with pre-cancerous lesions living in counties with lower median incomes were 2.3 times more likely to have CIN 3 vs. CIN 2.

Conclusion: Rates of CIN 2+/AIS and CIN 3 vary widely by geographic area. Practitioners should be reassured that the majority of cases of pre-cancerous cervical lesions are CIN 2 and therefore, likely to regress. CIN 3 rarely occurs in adolescent females under age 19; however, if young women do not initiate screening at age 21 or shortly thereafter, we may seen an increase in cervical cancer among young women in their twenties and thirties, especially among unvaccinated women and women living in low income areas.

Acknowledgments:

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Introduction

Biology and Natural History of HPV in the Adolescent

The Human Papillomavirus (HPV) is a necessary, but not sufficient cause of cervical cancer (Vesco et al., 2011). Transmission of the virus occurs during sexual intercourse, leading to an acute HPV infection. Most women (91%) will clear the virus within the first two years after infection. (Plummer et al., 2007). There are over 100 different strains of HPV, however types 16 and 18 are responsible for 70% of all cervical cancer cases and types 6 and 11 are responsible for 75-95% of genital warts. Types 16 and 18 are also the types associated with the highest grade of precancerous lesions (CIN) and persistence of HPV infection (Insinga et al., 2007). Adolescents are particularly vulnerable to HPV infection due to the difference in the cellular make-up of the cervix. The adolescent cervix is immature, consisting mainly of columnar and metaplastic cells, which are more vulnerable to lesions the site of the transformation zone. In contrast, the mature adult cervix is made up primarily of squamous epithelium cells (Mosciki, 2010a).

Condition Definition

Cervical intraepithelial neoplasia (CIN) represents pre-cancerous squamous cervical cellular changes that are diagnosed by histology. These changes can be divided into 3 tiers: CIN 1, CIN 2, and CIN 3 (with severity increasing in number). AIS is adenocarcinoma in situ of either the glandular or squamous tissue of the uterine cervix. CIN 2 and CIN 3 are generally considered precursors to cervical cancer, although CIN 2 is considered clinically challenging due to its frequent regression (Moscicki et al, 2010b). CIN 3 is universally considered to be a true precancerous lesion (Moscicki et al, 2010b). Estimates for the progression of CIN 3 to invasive cervical cancer are difficult to ascertain as it is considered

unethical to leave CIN 3 untreated. A review conducted in 1990 estimates a 20-30% risk of invasion over 5-10 years if CIN 3 is untreated (Chang, 1990). Another retrospective study looking at an unethical study conducted on women in New Zealand between 1965-1974 estimates that 31.3% of CIN will progress to cancer within 30 years (McCredie et al., 2008). However, it is unknown whether these estimates are applicable to the adolescent population.

Background

In November of 2009, the American Congress of Obstetricians and Gynecologists (ACOG) revised their guidelines for cervical cancer screening (ACOG, 2009). In March of 2012, two separate groups also released new recommendations: the United States Preventative Services Task Force (USPSTF) and a multidisciplinary partnership among the American Cancer Society/American Society for Colposcopy and Cervical Pathology/American Society for Clinical Pathology (ACS/ASCCP/ASCP) (Saslow et al., 2012; USPSTF, 2012). Prior to these changes in guidelines, women were advised to begin annual cervical cancer screening after onset of sexual activity. Under all of the new guidelines, no woman should begin cervical cytological screening (Papanicolaou test, commonly referred to as the pap smear) or HPV testing under age 21, regardless of risk factors or age of sexual debut (ACOG, 2009; Saslow et al., 2012; USPSTF, 2012).

These guidelines were changed in part due to the very low rate of cervical cancer among women under aged 21 and the number of potentially unnecessary treatment procedures such as loop electrosurgical excision procedures (LEEP) or endocervical curettage (ECC) performed on adolescents. Treatment procedures may be unnecessary in the adolescent, as studies have shown that CIN 2 can regress spontaneously in up to 65%-

68% percent of adolescent females within 3 years (Moore, 2007; Moscicki, 2010). Clinicians often want to treat these pre-cancerous lesions when found in order to err on the side of caution; however, conservative management is recommended as these procedures have been linked to pre-term birth and miscarriage in young women (Kyrgiou et al, 2006).

This research will quantify the number of women with precancerous lesions as well as their grade of lesion to determine who will be missed under the new practice guidelines. We will pay particular attention to CIN 3 to see if any correlates can be identified for having a diagnosis of CIN 3 vs. CIN 2, as this may aid clinicians in their decision of whether or not to adhere to the new screening guidelines within their own patient population.

Methods

Since 2008, the Centers for Disease Control and Prevention (CDC) have been monitoring the impact of the HPV vaccine through the Emerging Infections Program (EIP) network. This surveillance monitors cases of cervical intraepithelial neoplasia and higher (CIN 2+) and adenocarcinoma in situ (AIS) in women in order to determine the impact of the HPV vaccine at the population level. In 2008, the Connecticut Department of Public Health added the aforementioned pre-cancerous cervical lesions to its list of reportable diseases in order to facilitate the implementation of the surveillance. All 34 pathology laboratories statewide that process cervical biopsy specimens and diagnose CIN2+ and AIS are in compliance with this reporting requirement. Pathology reports included diagnostic information as well as limited patient demographics. Often, variables such as race and insurance were not available on the pathology report. The data are collected by trained Emerging Infections Program staff, de-identified and entered into a database. Accuracy of

the data was insured by numerous protocols including audit checks and double data entry for approximately one-third of the total cases.

The database was searched for all cases of CIN 2+ and AIS for women age 21 or under occurring between January 1, 2008 and December 31, 2010. The dataset was narrowed to include only unique women; when women had more than one event (i.e. more than one pathology report submitted during 2008-2010), the highest-grade lesion was recorded. For women with same grade lesions and multiple events, the first event was chosen to reflect the youngest age at which a woman was referred.

Measures

Patient demographics included age, race, ethnicity, insurance status and county. Age at diagnosis was dichotomized at the mean of 19 years of age. Race and ethnicity were not included in the analysis due to large percentages of missing data. Insurance was categorized as Medicaid and non-Medicaid, which included both military and private insurance. Those categorized as "unknown," "no coverage," or "self-pay" were not included in the analysis as we could not assume any relationship to income based upon these descriptors. Our primary dependent variable was final diagnosis, which was categorized as CIN 2, CIN 2/3, and CIN 3 and/or AIS. Other variables included specimen collection year and procedure that produced the specimen. Procedure was categorized as cervical biopsy, endocervical curettage (ECC), or loop electrocervical excision procedure (LEEP)/cone biopsy.

Statistical Analysis

Average annual rates of CIN2+/AIS and CIN 3 were calculated per 100,000 females aged 13-20 in the state of Connecticut for 2008-2010. Denominator data for these rates

was taken from the U.S. Census Bureau, using county specific estimates from 2010. The data was analyzed using SAS 9.2 (SAS Institute, Cary, NC). A description of the sample was completed using most of the variables in the database including: age, diagnosis, patient county, patient insurance, specimen collection year and procedure. The variables of race and ethnicity were not included in the analysis due to large percentages of missing data. Chi square analysis was used to examine associations between categorical variables and CIN 2 vs. CIN 3; the Student t test (means) was used for continuous variables. All reported p-values were considered significant at <0.05 significance level. Univariate and multivariate logistic regression was completed on all significant associations. For this analysis, the categorical variable of county was combined into variables reflecting socioeconomic status of the county (> 65,000 or < 65,000) to provide sufficient numbers for regression analysis and to provide a more meaningful analysis. The income level of $65,000 was chosen as it represented the median of our counties by income level and it was at this level where there was a large income gap between the two county groups. Characteristics associated with CIN 3 and with p-values < 0.05 in the univariable analysis were included in the final model. Chi square analysis was also used to see if there were any associations between our variables that could lead to confounding.

Results

In all, 681 adolescent females had precancerous cervical lesions CIN 2+/AIS between 2008-2010. The majority of cases of CIN 2+/AIS were from three counties- Fairfield (21.7%), Hartford (27.6%), and New Haven (23.9%); these counties are generally considered to be urban, with much higher populations than the other counties. However, the rates per 100,000 females age 13-20 show that the highest rates of CIN 2+/AIS were

found in three of the rural counties: Litchfield (342.98), Middlesex (284.09), and New London (287.85). Rates of CIN 3 also varied widely by county. The highest rates per 100,000 females age 13-20 were found in Litchfield (71.79), New London (62.37) and Hartford (55.21).

The mean age of the study population was 19 (range, 14-20) years. The majority of the study population had a diagnosis of CIN 2 (70%). CIN 2/3 was found in 92 (13.5%) adolescents and CIN 3 in 110(16.2%); AIS was found in only one case. In our sample, 313 (46%) of adolescents had private insurance and 160 (23.5%) had Medicaid; 208 (30.5%) had missing insurance data. There was considerable variation in the number of cases reported per year; 315 (46.8%) in 2008, 236 (34.7%) in 2009, and 130 (19.1%) in 2010. The majority of the specimens (561 or 82.4%) were collected through cervical biopsy, with ECC accounting for only 13 cases (1.9%), and LEEP/Cone biopsy for 107 (15.7%) cases.

In our chi square analysis, patient county and procedure type were significantly associated with having CIN 3 vs. CIN 2 ($p<0.05$ for both comparisons). County level income showed that a median household income less than 65,000 was significantly associated with a diagnosis of CIN 3 vs. CIN 2 ($p<0.05$). CIN 3 occurred in nearly equal percentages in both the urban and rural groups (19.5% and 19.2 %) respectively, thus there was no significant association between living in an urban or rural county and having CIN 3 vs. CIN 2. There was no statistically significant association between age (<19 vs. ≥ 19), or specimen collection year and CIN 3 vs. CIN 2. Although not significant, a higher percentage of Medicaid patients were found among patients with CIN 3 vs. CIN2 (39.4% vs. 32.6%).

Univariate analysis was conducted for all variables and multivariate analysis was conducted on all variables significantly associated with CIN 3. In the adjusted analysis,

adolescents living in counties with a median household income of less than $65,000 were 2.31 times more likely to have CIN 3 vs. CIN 2 (OR=2.31, 95% CI [1.42-3.74]). Adolescents who had a LEEP/ECC treatment procedure were 2.83 times more likely to have CIN 3 than those who had a cervical biopsy (OR=2.83, 95% CI [1.69-4.72]).

Discussion

Although we found a CIN 2+/AIS rate of 238.4/100,000 adolescents per year, clinicians can be re-assured that the majority of precancerous cervical lesions in adolescents are CIN 2 (70%) and therefore, have a high chance of regression (Moore et al, 2007; Moscicki, 2010b). Overall, CIN 3 is a rare finding in the adolescent, especially among females under age 19. In total, there were only 33 cases of CIN 3 in the lower age group (<19) over the course of the 3 years. If these numbers are generalized beyond Connecticut, for every 1,000 adolescent patients seen by an individual clinician, 0.38% will have CIN 3. Approximately 30-40 adolescents per year with CIN 3 will be missed in Connecticut under the new cervical cancer screening guidelines recommended by the American College of Obstetricians and Gynecologists, the American Cancer Society, the American Society for Colposcopy and Cervical Pathology, and the American Society for Clinical Pathology (ACOG, 2009; Saslow et al., 2012; USPSTF, 2012).

However, these rates are likely to be underestimated. First, the numerator represents only those adolescents that underwent cervical cancer screening, so the rate among the general population is likely much larger. Second, in examining the rate of CIN 3, it is important to note that 92 women (13.5%) in the sample were diagnosed with CIN 2/3, a gray area between CIN 2 and 3, which to our knowledge has not been studied with regard to regression/progression. It is also important to note that studies have shown that 15% of

CIN 2 will progress to CIN 3 within 3 years (Moscicki et al., 2010b). In our study, 15% of the CIN 2 population (478) would amount to another 37 cases of CIN 3 per year (within 3 years of diagnosis) on average.

Our study showed that living in a county with a lower median household income was predictive of having CIN 3 versus CIN 2 among adolescents. Although not significant, we also saw a higher percentage of Medicaid patients with CIN 3 lesions versus. CIN 2. This finding is consistent with findings by Niccolai et al. (2011) who found a strong association between poverty and increasing rates of CIN 2+/AIS This association is important for several reasons. First, publicly insured women and uninsured women are more likely to be unvaccinated (against HPV) than privately insured women (Mehta et al., 2011). Low-income adolescents may be at risk for having higher-grade lesions as well as poor vaccination coverage against the two most highly oncogenic strains (16, 18) of HPV. Second, in Connecticut and many other states, all adolescents are eligible for health insurance coverage either under Medicaid and the Children's Health Insurance Program until age 19. They also are routinely seen free of charge in school based health centers. Low-income adolescents may lose insurance coverage once they turn 19 and therefore, may delay seeking care in their twenties and initiating cervical cancer screening.

Clinicians should also be reassured that the majority of cases (68.8%) occurred in adolescents aged 19 and 20 who theoretically will be initiating screening within the following two years. Only four total cases of CIN 3 were found in women under age 17 between 2008 and 2010. However, it is important to take into consideration that the Pap smear test has imperfect sensitivity, with false negative results from a one-time pap smear ranging from 28-41 percent (Fahey, Irwig &Macaskill, 2011). For example, if a 19 year old

adolescent (the median age from our study) with CIN 3 initiates screening at age 21 and has a false negative cervical cytology screening, she may not be re-screened until age 24 if her clinician follows the new guidelines released by the USFTF and ACS/ASCCP/ASCP that now recommend screening every three years for women aged 21-29 without a history of abnormal Pap smear testing.

The essential question is: how quickly can CIN 3 develop into invasive cervical cancer? Estimates for the progression of CIN 3 to invasive cervical cancer are difficult to ascertain as it is considered unethical to leave CIN 3 untreated. A review conducted in 1990 estimates a 20-30% risk of invasion over 5-10 years if CIN 3 is untreated (Chang, 1990). Another retrospective study looking at an unethical study conducted on women in New Zealand between 1965-1974 estimates that 31.3% of CIN will progress to cancer within 30 years (McCredie et al., 2008). However, it is unknown whether these estimates are applicable to the adolescent population.

Our study has several limitations to consider. First, we could not control for variability in diagnostic technique/expertise between laboratories. It is possible that some pathologists are more likely to repeatedly use one diagnosis over the other, for example, CIN 2/3 versus CIN 2 or CIN 3. Another limitation of this study is that we were limited by the amount of missing data, specifically with race, ethnicity, and insurance. Although the association was strong between county level income and CIN 3 vs. CIN 2, we were unable to include an individual level measure for poverty/income.

One notable strength of this study is that in contrast to previous studies, which have looked at the prevalence of CIN 2 and CIN 3 within a small population limited to one hospital or laboratory, this study is able to draw upon surveillance conducted within an

entire state, providing a more accurate absolute number of cases one could expect to see within the state of Connecticut per year as well as a more accurate rate per 100,000 population of CIN 2+/AIS and CIN 3 (among adolescents engaged in care and receiving screening). Drawing upon surveillance data (where 100% of laboratories are compliant in their reporting) also limits selection bias. Given the variability in rates between counties, our findings may not generalize to other states; therefore, we encourage researchers to examine these topics in their geographic areas.

We observed a much higher number of cases of CIN 3 reported in 2008 than 2010 (53 vs. 19). This observed decrease may be due to early clinician adoption of the 2009 ACOG recommendations to stop adolescent cervical cancer screening, but is also likely due to the impact of the HPV vaccine, which has initiation rates of 61% in Connecticut (CDC, 2010). With the continued uptake of the two HPV vaccines among adolescent females and the introduction of the quadrivalent vaccine for the adolescent male population, we anticipate that the rates of precancerous cervical lesions in adolescent females will continue to decline. However, if women have poor access to care and/or do not initiate screening after age 21, we may seen an increase in the short-term of cervical cancer rates among young women in their twenties and thirties.

In closing, previous studies have shown that risk factors associated with non-regression of CIN 2+ included use of combined (estrogen/progesterone) oral contraceptives, and persistence of HPV infection (Mosciki et al, 2010b). Having greater than four sexual partners has also been shown to be associated with having CIN 3 versus. CIN 1 (Clements, Raker, Cooper, & Boardman, 2011). Taken together with our results that show a correlation between lower county level income and CIN 3, these risk factors can

help clinicians to identify adolescents who may be at greater risk for CIN 3, in order to initiate close follow-up and timely cervical cancer screening at age 21. It is important to recognize that this age (21) represents a time of transition in most young women's lives. It is therefore imperative that during comprehensive care visits pediatric providers educate adolescents and parents not only about the new screening guidelines, but also regarding the importance of establishing a regular primary care provider during the young adult years. College health providers, urgent care providers, and any other point of care for adolescent females should also reinforce these goals in order to prevent delayed cervical cancer screening in young women.

Table 1. Description of the sample: Connecticut statewide women under age 21 with pre-cancerous cervical lesions (CIN 2+/AIS) from 2008-2010 (N=681)

Characteristic	N (%)
Age (years) mean ± SD	18.9 ± 1.2
Age	
<19	206 (30.6)
≥ 19	475 (69.8)
Final Diagnosis	
CIN 2	478 (70.2)
CIN 2 and AIS	1 (0.2)
CIN 2/3	92 (13.5)
CIN 3	110(16.2)
Patient County	
Fairfield	147 (21.7)
Hartford	189 (27.6)
Litchfield	43 (6.3)
Middlesex	33 (4.9)
New Haven	163 (23.9)
New London	60 (8.8)
Tolland	25 (3.7)
Windham	13 (1.9)
Missing	8 (1.2)
Patient insurance	
Medicaid	160 (23.5)
Non-Medicaid	313 (46.0)
Missing	208 (30.5)
Specimen collection year	
2008	315 (46.3)
2009	236 (34.7)
2010	130 (19.1)
Procedure	
Cervical biopsy	561 (82.4)
ECC	13 (1.9)
LEEP	107 (15.7)

Table 2: Description of the sample by diagnosis CIN 2 vs. CIN 3: Connecticut statewide women under age 21 with pre-cancerous cervical lesions from 2008-2010

Characteristic	CIN 2	CIN 3	P-value	Unadjusted OR (95% CI)	Adjusted OR (95% CI)
Age (N=588)			0.8106		N/A
<19	149 (31.2)	33 (30.0)		1.00	
≥ 19	329 (68.8)	77 (70.0)		1.06 (0.63-1.66)	
County (N=580)			0.0079	N/A	N/A
Fairfield	120 (25.5)	15 (13.6)			
Hartford	118 (25.1)	38 (34.6)			
Litchfield	27 (5.7)	9 (8.2)			
Middlesex	24 (5.1)	0 (0.0)			
New Haven	112 (23.8)	32 (29.1)			
New London	43 (9.2)	13 (11.8)			
Tolland	19 (4.0)	1 (0.9)			
Windham	7 (1.5)	2 (1.8)			
County, median household income (N=580)			0.0005		
>65,000	190 (40.4)	25 (22.7)		1.00	1.00
<65,000	280 (59.6)	85 (77.3)		2.31(1.42-3.74)*	2.31 (1.42-3.76)*
County (N=580)			0.5409		N/A
Urban	350 (74.5)	85 (77.3)		1.00	
Rural	120 (25.5)	25 (22.7)		1.17 (0.71-1.90)	
Insurance (N=385)			0.2414		N/A
Non-Medicaid	205 (67.4)	49 (60.5)		1.00	
Medicaid	99 (32.6)	32 (39.5)		1.35 (0.82-2.24)	
Specimen collection year (N=588)			0.5729		N/A
2008	211 (44.1)	53 (48.2)		1.00	
2009	164 (34.3)	38 (34.5)		1.01 (0.65-1.56)	
2010	103 (21.6)	19 (17.3)		0.76 (0.44-1.31)	
Procedure (N=588)			<0.0001		
Cervical Biopsy	422 (88.3)	80 (72.7)		1.00	1.00

ECC/LEEP	56 (11.7)	30 (27.3)		2.83 (1.71-4.68)**	2.83 (1.69-4.72)**

*P=<0.001, **P=< 0.0001

Table 3: Average Annual Rates of CIN 2+/AIS and CIN 3 per 100,000 in Females aged 13-20 in the State of Connecticut, 2008-2010.

County	CIN 2+/AIS	CIN 3
Fairfield	215.19	21.90
Hartford	274.60	55.21
Litchfield	342.98	71.79
Middlesex	284.09	0
New Haven	117.33	44.28
New London	287.85	62.37
Tolland	124.25	4.97
Windham	124.80	19.20
Connecticut (average)	238.40	38.60

Figure 1: Cases of CIN 2+/AIS in adolescent females by age-Connecticut, 2008-2010

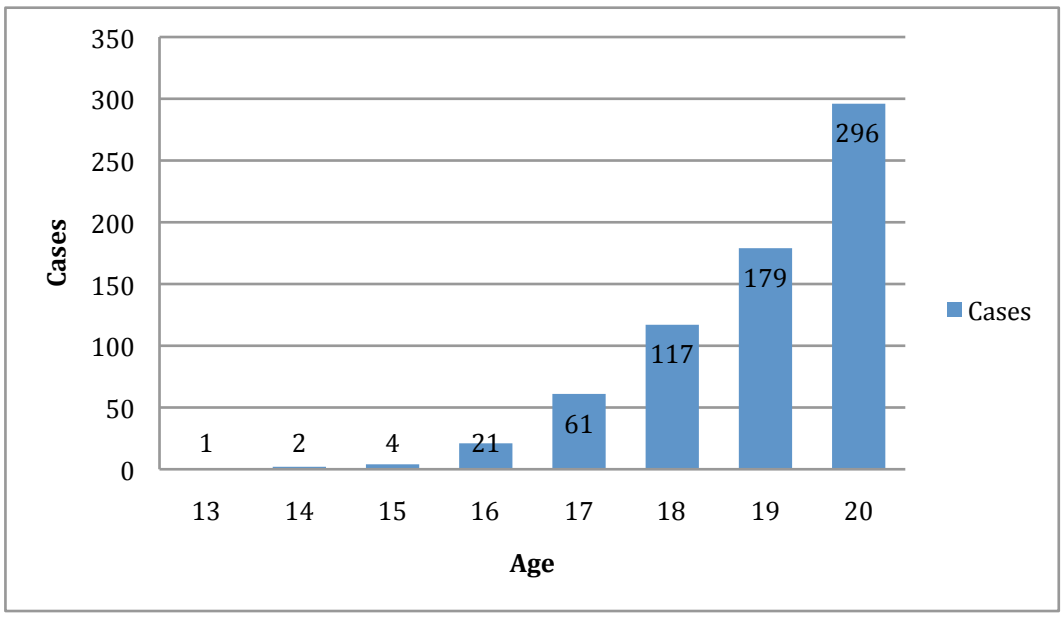
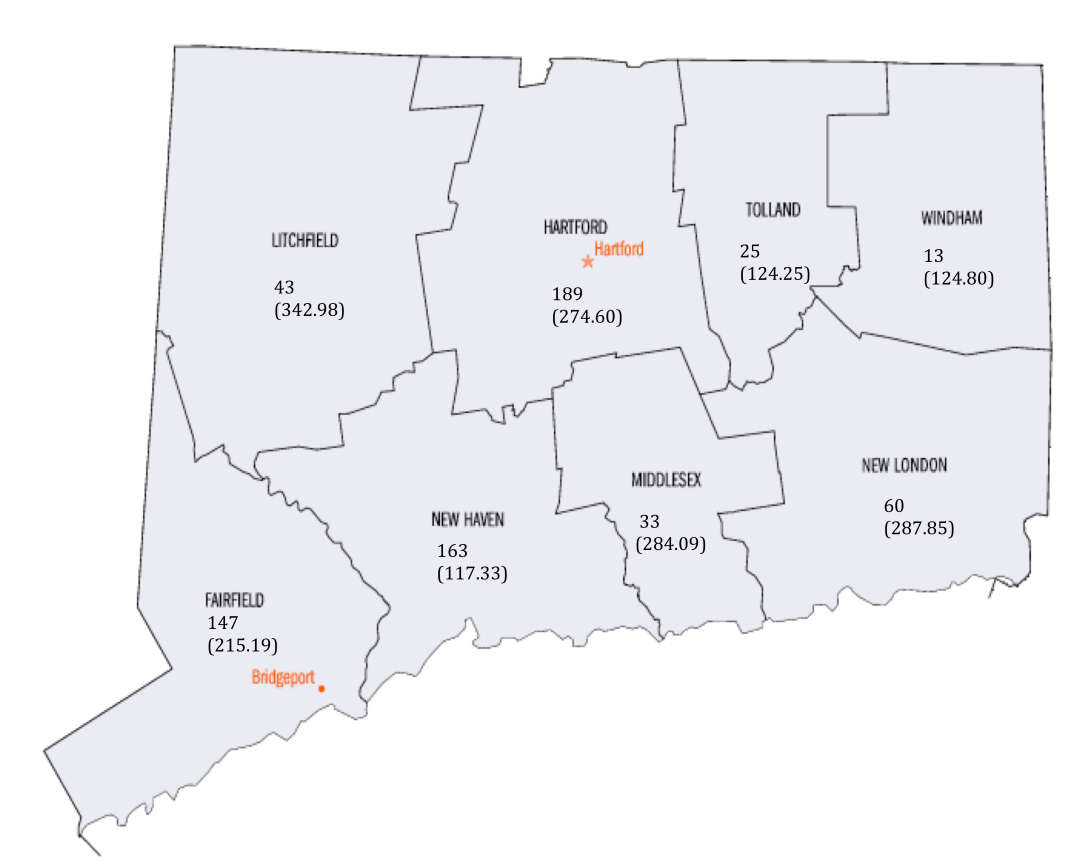


Figure 2: CIN 2+/AIS cases (annual rates) per 100,000 female population age 13-20 by county-Connecticut, 2008-2010



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