High-Grade Squamous Intraepithelial Lesion in Women Aged <30 Years Has a Prevalence Pattern Resembling Low-Grade Squamous Intraepithelial Lesion

Diama B. Vale, MD[1,2]; Maria C. Westin, MD[2,3]; and Luiz C. Zeferino, MD, PhD[2,3]

BACKGROUND: Cervical cytology is the cervical cancer screening test for women aged <30 years because of the low specificity of human papillomavirus tests in this age group. The Bethesda System classifies cervical intraepithelial neoplasia grade 2 (CIN 2) and grade 3 (CIN 3) as high-grade intraepithelial lesions (HSIL). In this study, the authors subclassified cytologic HSIL as suggestive of CIN 2 (HSIL-CIN 2) or CIN 3 (HSIL-CIN 3) and evaluated whether there was a correlation between these findings and age for screened and unscreened women. **METHODS:** The study included 2,002,472 cervical smears collected from women who had at least 1 previous test (screened) and 217,826 previously untested women (unscreened). The laboratory has been using the Bethesda System since 1998 with the subcategorization of HSIL-CIN 2 and HSIL-CIN 3. **RESULTS:** For unscreened women, the prevalence of low-grade intraepithelial lesion (LSIL) and HSIL-CIN 2 decreased with age, whereas the prevalence of HSIL-CIN 3 increased. The prevalence of HSIL-CIN 2 was greater than that of HSIL-CIN 3 for women up to age 29 years (prevalence ratio [PR], 4.73; 95% confidence interval [CI], 3.90-5.75) and lower for the groups ages 30 to 49 years (PR, 0.66; 95% CI, 0.50-0.87) and ≥50 years (PR, 0.21; 95% CI, 0.12-0.36). For screened women, the prevalence of HSIL-CIN 2 also was greater in the group aged ≤29 years (PR, 2.72; 95% CI, 2.49-2.97). **CONCLUSIONS:** The prevalence pattern of HSIL suggestive of CIN 2 resembled the pattern observed in LSIL and was more prevalent than HSIL suggestive of CIN 3 in younger women. The impact of screening was less evident when HSIL was suggestive of CIN 2. A conservative approach for younger women who have HSIL is important for management guidance. ***Cancer (Cancer Cytopathol)* 2013;121:576-81**. © *2013 American Cancer Society.*

KEY WORDS: screening; uterine cervical neoplasms; cervical intraepithelial neoplasm; human papillomavirus; cervical smear.

INTRODUCTION

The interpretation of cervical cytology smears is based on cytomorphologic changes, from which a histopathologic diagnosis is derived. The Bethesda System introduced the dichotomous terminology low-grade intraepithelial lesion (LSIL) and high-grade intraepithelial lesion (HSIL) and established that cytology results of cervical intraepithelial neoplasia grade 2 (CIN 2) and grade 3 (CIN 3) should be classified as HSIL.[1] A diagnosis of LSIL, which corresponds to CIN 1, represents a transient, productive infection with human papillomavirus (HPV). LSIL has a very low potential for progression to cancer and a higher prevalence among young women.[2–4] The diagnosis of CIN 3 represents a persistent and transforming infection by HPV and, thus, tends to increase with age.[5,6] There is currently no marker to distinguish between productive infection and transforming infection.[7–10]

Corresponding author: Luiz C. Zeferino, MD, PhD, Department of Obstetrics and Gynecology, Oncology Division, Universidade Estadual de Campinas, Rua Alexander Fleming 101, CEP 13083-881, Campinas-SP, Brazil; Fax: (011) 55-19-3521-9424; zeferino@fcm.unicamp.br

[1]School of Medicine, Rondonia Federal University, Rondonia, Brazil; [2]School of Medicine, Campinas State University, Campinas, Brazil; [3]Dr. Jose Aristodemos Pinotti Women's Hospital, Campinas State University, Campinas, Brazil

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Reasons for a change in nomenclature into the 2-tiered designation of SIL established by the Bethesda System were the low reproducibility of cytopathology results, mainly CIN 2 and CIN 3.[1,11,12] However, some members of the European cytopathology community in particular were in favor of the 3-tiered designation of CIN 1, CIN 2, and CIN 3 for cytology. The Bethesda System recognized that a differentiation between CIN 2 and CIN 3 might be helpful in managing some individual patients.[1]

Despite the limitations of cytology interpretation, it is interesting to add further knowledge to qualify reports. The prevalence of HSIL in young women is not negligible, but we know that transient or productive HPV infection is prevalent in this age group.[13] Thus, it is likely that an HSIL result does not represent a persistent or transforming HPV infection in young women and would not compromise these patients.

Therefore, the objective of this study was to evaluate whether there is a correlation between patient age and cytology findings of HSIL, HSIL suggestive of CIN 2 (HSIL-CIN 2), and HSIL suggestive of CIN 3 (HSIL-CIN 3). We also analyzed the impact of screening on the reduction of prevalence in both categories of lesions. We hope that this study may provide some insights into cytopathology interpretation and selecting the best clinical management. A more judicious referral of young women for colposcopic assessment may reduce preventable interventions on the uterine cervix, avoiding future obstetric and neonatal morbidity.[14]

MATERIALS AND METHODS

This study was a cross-sectional assessment of the prevalence of cervical lesions in women undergoing cytology screening in Campinas, Sao Paulo State, Brazil. The sample consisted of all Papanicolaou smears performed in the Cytopathology Laboratory at the Dr. Jose Aristodemo Pinotti Women's Hospital, Campinas State University from January 2000 to December 2009 (10 years).

The cytopathology laboratory receives conventional smears collected for cancer screening from women in the public health system from approximately 70 towns in the Campinas region. Opportunistic screening is performed, although recommendations prioritize women ages 25 to 59 years with triennial intervals.[15] The laboratory does not receive tests performed by private health services.

We excluded tests that were incorrectly identified, those classified as unsatisfactory, and those obtained for a purpose other than screening. After exclusion criteria were applied, the study sample consisted of 2 groups: 2,002,472 tests from women who had at least 1 previous screening test (the screened group) and 217,826 tests from women without previous screening test (the unscreened group).

Cervical smears were collected by physicians or nurse practitioners in primary health care units. Those health professionals also identified and recorded clinical data on the patients. An optically read form for patient identification and recording of results was used as the data source for the laboratory information system.

In addition to patient identification, health professionals recorded clinical information, such as age, purpose of the test, and time since last screening test. If the woman had never undergone any previous screening test, then she was identified as having the first screening test. This recording allowed us to establish 2 groups for analysis: unscreened women (first screening test) and screened women (any time since the last screening test).

Cytologic scrutiny was conducted by cytotechnologists. Examinations with suspicious findings were reviewed by pathologists. For quality control, 30% of the negative results were randomly selected and submitted for rapid review, and 10% were submitted for a full review by senior cytotechnologists. The laboratory adopted the Bethesda System in 1998. However, for HSIL reports, categorization was dichotomized into HSIL-CIN 2 and HSIL-CIN 3, allowing us to conduct the current study. The cytomorphologic criteria used by the laboratory to characterize the interpretation of HSIL-CIN 2 and HSIL-CIN 3 are listed in Table 1.

The prevalence rates of the results were calculated for both groups (screened women and unscreened women). For trend analysis of prevalence rates according to age, the Cochrane-Armitage modified chi-square test was used. A statistical test with negative values indicated a trend toward decreased rates, whereas positive values indicated a trend toward increased rates. The impact of screening was assessed by calculating the prevalence ratio (PR) for the screened group divided by the unscreened group and for the HSIL-CIN 2 results divided by the HSIL-CIN 3 results, all of which were reported with 95% confidence intervals (CIs). Institutional Review Board approval was obtained before undertaking this study.

TABLE 1. Morphologic Criteria for Cytologic Squamous Cell Results

Morphologic Criteria	LSIL-CIN 1	HSIL-CIN 2	HSIL-CIN 3
Atypical cells	Superficial or intermediate	Intermediate or parabasal	Parabasal
Quantity of atypical cells	Moderate	Moderate	Marked
Atypical mature metaplastic cells	—	Present	Present
Atypical immature metaplastic cells	—	—	Present
Nuclear area (nuclear/cytoplasmic ratio)	Less than one-third	Less than half	Greater than half
Dense cytoplasmic border (koilocytosis)	Present	—	—
Anisokaryosis	Slight and Moderate	Moderate	Marked
Hyperchromasia	Slight and moderate	Moderate	Marked
Thick nuclear membrane	—	—	Present

Abbreviations: CIN 1, cytologic cervical intraepithelial neoplasia grade 1; CIN 2, cytologic cervical intraepithelial neoplasia grade 2; CIN 3, cytologic cervical intraepithelial neoplasia grade 3; HSIL, high-grade squamous intraepithelial lesion; LSIL, low-grade squamous intraepithelial lesion.

TABLE 2. Impact of Age on the Prevalence of Cytology Results for Screened and Unscreened Women[a]

	LSIL, %		HSIL-CIN 2, %		HSIL-CIN 3, %		HSIL, %	
Age, y	Unscreened	Screened	Unscreened	Screened	Unscreened	Screened	Unscreened	Screened
≤19	1.81	1.62	0.33	0.32	0.03	0.03	0.36	0.35
20–24	1.35	1.03	0.35	0.33	0.08	0.10	0.43	0.42
25–29	1.00	0.68	0.39	0.26	0.24	0.14	0.64	0.40
30–34	0.68	0.42	0.39	0.18	0.35	0.15	0.73	0.33
35–39	0.47	0.33	0.41	0.14	0.67	0.13	1.07	0.28
40–44	0.50	0.30	0.32	0.13	0.53	0.12	0.84	0.25
45–49	0.43	0.20	0.20	0.10	0.86	0.10	1.05	0.20
50–54	0.18	0.14	0.18	0.05	0.46	0.10	0.64	0.15
55–59	0.04	0.08	0.08	0.07	0.49	0.09	0.57	0.16
60–64	0.18	0.07	0.09	0.04	0.84	0.10	0.93	0.14
65–69	0.00	0.03	0.10	0.04	0.49	0.12	0.59	0.17
≥70	0.08	0.06	0.11	0.06	0.57	0.16	0.68	0.22
P	< .0001	< .0001	.0005	< .0001	< .0001	.83	< .0001	< .0001
ST[b]	−19	−66	−3.5	−29	+21	—	+8.9	−23

Abbreviations: CIN 2, cytologic cervical intraepithelial neoplasia grade 2; CIN 3, cytologic cervical intraepithelial neoplasia grade 3; HSIL, high-grade squamous intraepithelial lesion; LSIL, low-grade squamous intraepithelial lesion-cytologic cervical; ST, statistic test.
[a] Prevalence is based on screening tests from 2,002,472 screened women and 217,826 unscreened women for the period from 2000 to 2009.
[b] For the ST, positive (+) Cochrane-Armitage chi-square values correspond to increasing trends, and negative (−) values correspond to decreasing trends.

RESULTS

For unscreened women, the prevalence rates of LSIL tended to decrease with age, whereas HSIL rates tended to increase with age (Table 2). Analyzing HSIL categories separately, the prevalence of HSIL-CIN 2 had a trend similar to that of LSIL, whereas HSIL-CIN 3 rates had a clear increase in prevalence with age. For previously screened women, the prevalence rates of LSIL and HSIL-CIN 2 tended to decrease with increasing age, but HSIL-CIN 3 rates did not vary with statistical significance. Figure 1 illustrates the trends in these diagnoses.

The impact of age on the prevalence of both categories of HSIL (HSIL-CIN 2 and HSIL-CIN 3) was analyzed according to the PR. For unscreened women, the prevalence of HSIL-CIN 2 was greater than that of HSIL-CIN 3 for women aged ≤29 years (PR, 4.73; 95% CI, 3.90-5.75). This relation was reversed in the groups ages 30 to 49 years (PR, 0.66; 95% CI, 0.50-0.87) and aged ≥50 years (PR, 0.21; 95% CI, 0.12-0.36); whereas, in the latter age group, the prevalence of HSIL-CIN 3 was approximately 5 times greater than the prevalence of HSIL-CIN 2 (Table 3). For screened women, the prevalence of HSIL-CIN 2 was greater than that of HSIL-CIN 3 in the groups aged ≤29 years (PR, 2.72; 95% CI, 2.49-2.97) and ages 30 to 49 years (PR, 1.11; 95% CI, 1.02-1.19); however, in women aged >50 years, this relation was reversed (PR, 0.50; 95% CI, 0.43-0.60) (Table 3).

Comparing screened women with unscreened women, the prevalence rates for HSIL and HSIL-CIN 3 cytology results did not vary among women aged <19 years and ages 20 to 24 years. However, in the screened

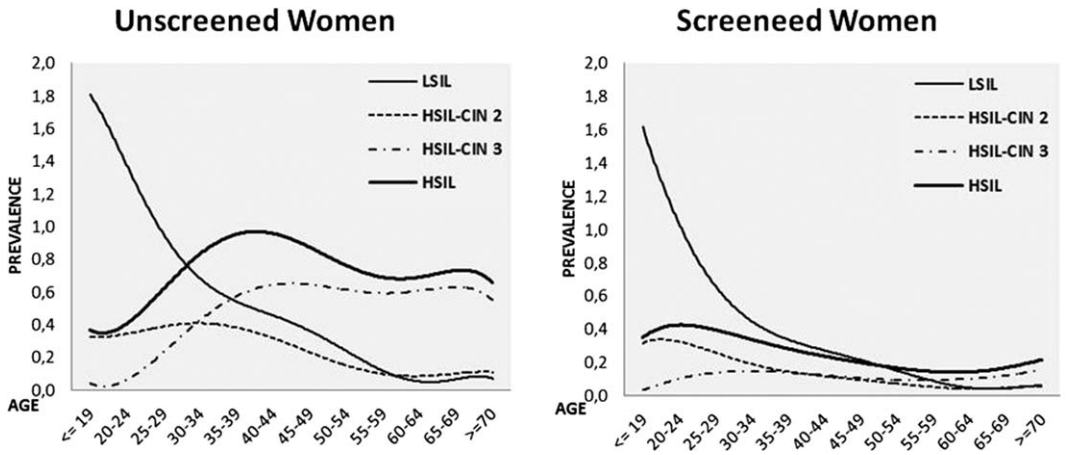

FIGURE 1. The impact of age on the prevalence of cytology results is illustrated for screened and unscreened women. Prevalence was based on screen tests from 2,002,472 screened women and 217,826 unscreened women during the period from 2000 to 2009. LSIL indicates low-grade squamous intraepithelial lesion; HSIL, high-grade squamous intraepithelial lesion; CIN 2, cytologic cervical intraepithelial neoplasia grade 2; CIN 3, cytologic cervical intraepithelial neoplasia grade 3.

TABLE 3. Prevalence Ratio of Cytological Cervical Intraepithelial Neoplasia Grade 2/Grade 3

	Unscreened		Screened	
Age, y	PR	CI 95%	PR	CI 95%
≤29	4.73	3.90–5.75	2.72	2.49–2.97
30–49	0.66	0.50–0.87	1.11	1.02–1.19
≥50	0.21	0.12–0.36	0.50	0.43–0.60

Abbreviations: CI, confidence interval; PR, prevalence ratio.

group, prevalence rates decreased with age in women ages 25 to 29 years. Among women ages 35 to 39 years, there was a greater than 70% decrease in prevalence. The prevalence rates for LSIL and HSIL-CIN 2 cytology results did not have a homogeneous pattern, even in different age groups in which prevalence rates were lower in previously screened women (Table 4).

DISCUSSION

According to this study, results from the HSIL group identified lesions with 2 distinct behaviors: 1 that reflected transient HPV infection and another that may be associated with persistent infection. The prevalence of lesions in unscreened women may be considered representative of the natural history of cervical neoplasm, because they were not subjected to diagnostic or therapeutic interventions. In this group of women, the prevalence rates of HSIL-CIN 2 cytology results decreased with increasing age, similar to the tendency observed for LSIL. These cytologic findings reflect a transient HPV infection with high potential for clearance with higher prevalence rates, a behavior similar to the pattern of HPV infection.[2,13,16]

Conversely, the prevalence rates of HSIL-CIN 3 results clearly increased with age for unscreened women, but not in the presence of screening because of diagnostic and therapeutic intervention. The prevalence of CIN 3 in countries that have implemented screening program peaks at approximately age 30 years and decreases in older women,[6,17,18] a pattern similar to that observed in this study for HSIL-CIN 3 in previously screened women.

The results from this study highlight the finding that HSIL-CIN 2 had a tendency similar to that of LSIL and dissimilar to the pattern of persistent and transforming HPV infection. Screening is not efficient at reducing the prevalence of LSIL and HSIL-CIN2 associated with transient HPV infection. In fact, screening does not prevent the acquisition of HPV infection. Moreover, the current study demonstrates that it is highly probable that HSIL findings corresponded to HSIL-CIN 2 rather than HSIL-CIN 3 in previously screened women. This can be explained by the greater protective effect of screening against lesions associated with persistent HPV infection, or against HSIL-CIN 3.

For countries in which screening is opportunistic, a large number of tests are focused on young women. This

TABLE 4. Protective Effect of Screening in Low-Grade Squamous Intraepithelial Lesion, High-Grade Squamous Intraepithelial Lesion (HSIL), HSIL-Cytologic Cervical Intraepithelial Neoplasia Grade 2 (CIN 2), and HSIL-CIN 3 Cytology Results: Prevalence Ratio of Screened Women Versus Unscreened Women

	LSIL		HSIL-CIN 2		HSIL-CIN 3		HSIL	
Age, y	PR	95% CI	PR	95% CI	PR	95% CI	PR	95% CI
≤19	0.89	0.83–0.96	0.97	0.82–1.14	0.95	0.58–1.57	0.97	0.83–1.13
20–24	0.76	0.70–0.82	0.94	0.80–1.10	1.22	0.88–1.68	0.99	0.86–1.14
25–29	0.68	0.59–0.79	0.66	0.52–0.84	0.58	0.43–0.78	0.63	0.52–0.76
30–34	0.63	0.50–0.80	0.48	0.35–0.65	0.43	0.31–0.60	0.45	0.36–0.57
35–39	0.70	0.46–1.07	0.35	0.22–0.56	0.20	0.14–0.29	0.26	0.19–0.35
40–44	0.60	0.42–0.87	0.40	0.25–0.63	0.23	0.16–0.33	0.29	0.22–0.39
45–49	0.47	0.28–0.79	0.49	0.23–1.04	0.12	0.08–0.17	0.19	0.13–0.26
50–54	0.79	0.35–1.77	0.28	0.12–0.63	0.22	0.13–0.38	0.24	0.15–0.37
55–59	2.04	0.28–14.63	0.82	0.20–3.35	0.18	0.10–0.33	0.27	0.16–0.47
60–64	0.37	0.13–1.02	0.45	0.11–1.91	0.12	0.07–0.19	0.15	0.09–0.24
65–69	—	—	0.43	0.10–1.87	0.25	0.13–0.49	0.28	0.15–0.52
≥70	0.78	0.23–2.60	0.53	0.18–1.55	0.27	0.17–0.45	0.32	0.20–0.50

Abbreviations: CI, confidence interval; LSIL, low-grade squamous intraepithelial lesion; PR, prevalence ratio.

shift in care reveals an excessive number of abnormal results in this age group, because these women would not be prioritized in an organized screening program.[19–21] In young women, in addition to a high prevalence of LSIL results, most HSIL diagnoses may represent transient HPV infection.

Because we observed that a woman aged <30 years who had an HSIL result had a high risk of presenting with HSIL-CIN 2 (unscreened women: PR, 4.73; 95% CI, 3.90-5.75; screened women: PR, 2.72; 95% CI, 2.49-2.97), it seems reasonable to consider a less interventionist approach for adolescents and young women with HSIL, so that indication for treatment can be individualized. The long period of development and transformation into cervical lesions,[22,23] the very low potential for progression to CIN 3 in this age group,[2,4,23] and the risk of obstetric and neonatal morbidity[14] are further arguments to support the adoption of conservative protocols.

The Bethesda System nomenclature was opted for the 2-tiered designation of HSIL and LSIL because of the poor reproducibility of cytopathology results. In fact, the criteria and application of the same criteria may vary among observers. For example, in the past, authors described CIN 2 for cervical cytology smears when the core area corresponded to 50% of the total area of the cell, whereas others described the same result when the core area corresponded to up to 66% of the total area.[24,25] In our study, the first understanding prevailed. Thus, as expected, the results revealed that selected HSIL-CIN 2 lesions had characteristics closer to those of low-grade lesions. Cytology diagnosis is based on a set of criteria, and the lesions corresponded to low-grade cervical smears that had changes confined to cells with mature or surface-type cytoplasm, but changes in nuclear intensity also play an important role in discriminating between LSIL and HSIL. Nuclear alterations of atypical cells and metaplastic cells in cervical smears are predictive criteria of high-grade CIN.[26]

A British study examined data from annually collected National Health Service Cervical Screening Program laboratory Korner returns (KC61 returns) for the screening years before and after conversion from conventional smears to liquid-based cytology and observed that the histologic correspondence for moderate dyskaryosis in conventional smears and in liquid-based cytology was poorer than that for mild and severe dyskaryosis. Taking into account the new cytologic classification, high-grade dyskaryosis had a higher positive predictive value for CIN2+, but not for CIN3+. These results highlight the finding that the intermediate cytologic category had lower agreement with CIN 2.[27]

The limitation of this study is the lack of available histopathologic diagnoses. However, the results are powerful, because we included a sample of approximately 2 million cervical cytology tests among screened women and 200,000 among unscreened women, which allowed us to analyze trends according to age group.

Cytology interpretation is very important in young women, because HPV-DNA testing is not indicated as a screening test in this population.[28,29] Therefore, we

conclude that most HSIL results in young women clearly do not correspond to a truly high-grade lesion, and this is a weakness of the 2-tiered classification of SIL.

The objective of this study was to demonstrate a specific weakness of the 2-tiered cytologic classification relevant for younger women, and not to corroborate the 3-tiered classification of SIL. The finding of HSIL may not have the same clinical significance in young woman, and what matters is the clinical differentiation between lesions associated with transient HPV infection and those associated with persistent infection. In this context, the cytomorphologic criteria between low-grade and high-grade intraepithelial lesions need to be adjusted within possible limits.

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