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Updated Guidelines for Papanicolaou Tests, Colposcopy, and Human Papillomavirus Testing in Adolescents

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Abstract

Worldwide, cervical cancer is a major health concern for women of all ages; however the epidemiology and biology of human papillomavirus (HPV) infection differs in female adolescents and adults. In the United States, 50% of adolescent and young women acquire HPV within 3 years after initiating sexual intercourse, resulting in relatively high prevalence rates. Most infections, however, are transient and clear within several months. Consequently HPV infections detected in adolescents are likely to reflect benign disease, whereas infections detected in older women are likely to reflect persistent infections and a higher risk of advanced cervical intraepithelial lesions that can lead to invasive cervical cancer. This article reviews the most recently published guidelines for the prevention of cervical cancer through screening and management of abnormal cervical cytologic and histologic findings, which have been updated to reflect the differences in HPV infections and cervical abnormalities in female adolescents and adults.

Keywords

HPV; Uterine cervical neoplasm; Uterine cervical dysplasia; Cervical intraepithelial neoplasia; Adolescent; Screening; Guidelines; Evidence-based medicine

Cervical cancer is a preventable disease that continues to occur worldwide. For decades, screening for cervical cancer precursors with Papanicolaou (Pap) tests and colposcopy has been the mainstay of prevention efforts. Cervical cancer screening programs are an effective prevention measure when they are able to be fully implemented by health care systems and used by all women. However this has proved to be a formidable task, and nearly half a million women continue to be diagnosed with cervical cancer each year [1]. After recognition that persistent infection with oncogenic types of human papillomavirus (HPV) is a necessary cause of cervical cancer, further developments in prevention efforts have emerged, including the use of HPV-DNA testing in older women and the immunization of younger women to prevent HPV infection.

With respect to cervical cancer prevention efforts, adolescent women are increasingly being recognized as a population distinct from adult women. An increased understanding of HPV virology, as well as the epidemiology and natural history of HPV and cervical cancer precursors in adolescents compared with adults has had an impact on all aspects of cervical cancer prevention. This understanding has informed the recommendations for HPV vaccination in

female individuals as well as the evidence-based guidelines for screening, management, and treatment of cancer precursors.

HPV Virology

The HPVs are DNA viruses that infect epithelium. Within the family of HPV, there are more than 100 genotypes (types) that differ in their tissue tropism and oncogenic potential. HPV types are defined based on the homology of the viral genome. Different types have more than 10% difference in their DNA sequence, including the L1 gene [2]. Epidemiologic research has identified that certain HPV types generally infect either the cutaneous or mucosal epithelium. Cutaneous types most commonly cause plantar, palmar, and other skin warts. Mucosal HPV types can cause benign papillomas of the conjunctiva, oral, nasal, and genital mucosa, or rare malignancies of the genital and aerodigestive mucosa. Mucosal types that have been linked to malignancies in large epidemiology studies are categorized as high-risk types. Low-risk types are types included in these studies that are not linked to malignancies; thus they confer a low oncogenic risk [3,4].

Life Cycle of HPV

The HPV infects the cells of the basal epithelium. Trauma or inflammation can expose these cells to infection. The virus remains intraepithelial and is not blood borne. Its infection does not induce a typical inflammatory response as seen with other cervical infections, such as *Chlamydia trachomatis* infection. After a virus enters the cell, it makes its way to the cell nucleus, where it uses the host cell's nuclear material for its own replication. HPV gene expression depends on epithelial cell maturation. Early in infection, at the parabasal cell layer, expression of viral genes E (early) 6 and E7 results in abnormal cell proliferation. As the cell matures through the epithelium, other viral proteins are expressed, leading to more abnormal histologic features [2]. The continued viral gene expression in maturing cells results in cytologic features that define squamous intraepithelial lesions (SIL), including abnormal cell proliferation, nuclear enlargement, abnormal mitotic figures, and perinuclear halos (Figure 1). In mature epithelial cells, late viral genes, L1 and L2, are expressed, forming structural proteins responsible for DNA packaging and virion assembly. Terminal differentiation of the epithelial cells allows final production of infectious virions and release of infectious virus through normal cell desquamation [2].

Role of HPV Infection in Cervical Cancer

Although multiple factors influence the development of cancer, persistent infection with high-risk HPV is a necessary cause of cervical cancer (Figure 2). Persistence has no precise definition; it refers to the repeated detection of the same HPV type over time. It can also be viewed that if a woman clears infection, no matter how long there has been a history of persistence, she is no longer at risk for the development of cancer. The duration of HPV infection before the development of precancerous lesions can be as short as months [5,6], whereas some women may never develop lesions while taking years to clear the virus [7].

The final mechanisms associated with the development of cervical cancer are not well understood. Invasive cervical cancers can occur without viral integration. The disruptions of cell cycle control and telomerase activity are likely the key factors in the development of cancer. The oncogenic properties of high-risk HPV types are the result of E6 and E7 proteins' disruption of cell cycle control through multiple mechanisms. E6 has the ability to enhance p53 degradation. E6 also activates telomerase, a telomere lengthening enzyme, resulting in prolonged cell life. By disrupting the E2F/pRb complex, E7 causes activation of an important cellular transcription factor, E2F. E7 is also involved in the blockade of cellular apoptosis [2]. Although the active expression of both E6 and E7 are important and may be synergistic,

the final mechanisms for cancer are likely due to multifactorial events, which is true of many cancers [8].

Manifestations of HPV Infections—Abnormal Cervical Cytologic and Histologic Findings

Both high-risk and low-risk HPV types can cause changes detected on Pap tests and colposcopy. The Bethesda System for cervical cytology is the standard classification system used for reporting Pap test results in the United States (US). This system classifies squamous cell changes caused by HPV as SIL or atypical squamous cells (ASC) [9], and has replaced the World Health Organization (WHO) cervical cytology categories of cervical intraepithelial neoplasia (CIN). Figure 3 describes the comparison of categories. The cytologic categories of SIL are used to triage women for further testing, as discussed later. The categories reflect the extent of molecular changes caused by HPV infection. Low-grade SIL (LSIL) results from early gene expression in HPV infection leading to mild basal cell proliferation and perinuclear halos. These changes are benign and reversible. High-grade SIL (HSIL), on the other hand, is not benign and is considered a precancerous lesion. HSIL describes cells with aneuploidy, altered chromatin texture, and increased nuclear volume. These changes occur with increased E6 and E7 production. Many believe that all active HPV infections result in some histologic change that may not be detected on cytology screening. ASC is used to describe cellular abnormalities that are suggestive of SIL but are not able to be definitively diagnosed as SIL. ASC of undetermined significance (ASCUS) is considered to harbor relatively benign lesions, whereas ASC cannot exclude HSIL (ASC-H) and is associated with an increasing predictive value for detecting a more serious lesion.

Treatment algorithms use the WHO categories CIN 1, 2, and 3 for histologic diagnoses of cervical biopsy samples obtained at colposcopy. In women of all ages, CIN 1 is considered benign, as the majority of lesions regress [10]. On the other hand, CIN 3 is considered truly precancerous, as 30–70% of CIN 3 lesions progress to cancer [11,12]. Determining the prognosis of CIN 2 is complicated by two problems. First, it is difficult for pathologists to reliably identify which lesions are CIN 2 [13]; second, there is the possibility that the natural history of CIN 2 lesions is different in older and younger women. Some older studies have shown that only 21% of CIN 2 lesions progress [11], as discussed later. Because of the difficulty of diagnosing CIN 2 and its potential to progress, some pathologists will group CIN 2 and CIN 3 (i.e., CIN 2/3), which is similar to the Bethesda System for grading cytology.

Epidemiology of HPV, SIL, and Cervical Cancer

HPV epidemiology

HPV is transmitted by skin-to-skin contact, thus genital HPV infections are transmitted by sexual contact. Vaginal and anal intercourse are likely the most efficient means of transmission of HPV to the cervix and anus, respectively. HPV can be detected in the cervix of women without a history of vaginal intercourse, as demonstrated by one study of female university students aged 18–20 years. Of 757 genital specimens taken from females reporting no history of vaginal intercourse, 13 specimens were positive for HPV-DNA [14]. HPV may also be detected in the anus in women without a history of anal intercourse [15], and in women who have sex with women only [16]. These findings may suggest that other means of sexual contact, such as finger sex, may be a mode of transmission. Although studies show that HPV can be detected on the hand, this finding alone does not confer transmission. Certainly, genital warts can be transmitted by skin-to-skin contact alone. There has also been recent data showing that oral sex is a risk factor for transmission to the oral cavity. There are few data to suggest that other modes of transmission (i.e., objects or hygiene) are important in transmission [17].

Several studies have shown that cervical infections occur shortly after sexual debut, emphasizing the importance of sexual intercourse in transmission [14,18,19]. Approximately half of all new HPV infections in a cohort of American university students occurred within 3 years of sexual debut [14]. The risk for infection also increases with having a new sexual partner, underscoring the ease of transmission via sexual acts.

Paralleling sexual behavior, most studies show that younger women have much higher rates of cervical HPV infections than older women. This discrepancy is thought to be predominantly associated with the higher number of sexual partners in younger than older women. Worldwide, the peak prevalence of HPV occurs in women younger than 25 years, with a rate between 20% and 25% [17]. Prevalence rates start falling in women in their 30's, with a prevalence rate of around 10%; this rate remains relatively stable into their 60's. Although some populations have a rise in prevalence of HPV in women over 60 years of age, the rates continue to remain lower than in women under 25 years. A recent report of HPV prevalence in the US showed that almost half (49.3%) of sexually active women aged 20 to 24 years had HPV. Forty percent of women aged 14 to 19 years were infected with HPV; prevalence dropped in those over 24 years of age. Approximately 25% of older women were infected (27.8% of 25–29 year-olds; 27.3% of 30–39 year-olds; 23.9% of 40–49 year-olds; and 20.2% of 50–59 year-olds) [20]. However some countries show no second peak in the prevalence of HPV, with rates equal across all age groups [21]. This usually occurs in countries where the overall number of sexual partners is low among both men and women.

Among the HPV types that cause cervical infections, high-risk types, including HPV 16, are more common than low-risk types [22]. Regardless of cytology status (i.e., normal versus abnormal), HPV 16 is the most common type detected in women. Additionally, with increasing severity of cervical disease, HPV 16 makes up an increasing proportion of the types detected; women with normal cytology have the lowest proportion of HPV 16, and those with cervical cancer have the highest proportion [8,23].

Unlike other sexually transmitted viruses, such as herpes simplex virus and HIV, HPV is a transient infection for most women. The duration of most infections is generally 7–10 months [19]. Within 3 years of observation, 70–93% of infections become undetectable [24,25]. It is the women who do not clear the infection (show persistence) who remain at risk for the development of cancers.

SIL epidemiology

As mentioned, some believe that SIL develops in all women infected with HPV; however data show repeatedly that SIL is detected less commonly than HPV. Moscicki et al found that a quarter of women with HPV developed SIL, even with repeated cytology [18]. Cytology testing is a comparatively insensitive test, especially when cervical lesions are small, which may explain why the majority of women with cervical infections detected by HPV-DNA testing have normal cytology.

Knowing that SIL is a result of HPV replication, it would be expected that rates of SIL would parallel those of HPV, with the highest rates detected in adolescents. A higher rate of abnormal cytology in young women compared with older women was demonstrated by Mount et al, who reviewed more than 79,000 cytology slides. Overall, 3.9% of slides from women aged 15 to 19 years had SIL compared with 1.3% of women aged 30–39 years [26]. As expected, most SIL in adolescents was LSIL; the majority of adolescents (2.5%) were diagnosed with LSIL, much fewer (0.7%) with HSIL, and none with carcinoma in situ. The high rate of LSIL in adolescents with abnormal cytology was also emphasized in a large study that recruited women for cancer screening. Bjorge showed, in over 100,000 reviewed slides, that LSIL was twice as common as HSIL and carcinoma was not detected in females aged 15–19 years [27].

These studies illustrate the commonness of HPV-associated LSIL in young women. If the majority of LSIL in adolescents is truly benign; we would expect the LSIL to regress in parallel with the clearance of HPV. Studies have shown that 90% of LSIL in young women will regress within a 2–3-year period [6,10]. A study of women with LSIL, aged 13–22 years, showed the probability of regression of LSIL to normal cytology was 61% by 1 year and 91% by 3 years. The average time to clearance of LSIL, 8 months, was similar to estimates of time to HPV clearance [10].

As mentioned earlier, HPV persistence is important for the development of cervical cancer; consequently it is known that not all HPV infections clear. This would then be expected of LSIL as well, raising a concern that low-grade lesions may progress. Furthermore, even though LSIL is considered a benign lesion and expected to regress, most CIN 2/3 lesions are detected in women who were triaged for having LSIL or ASCUS. This observation is likely due to the fact that CIN 2/3 lesions often have adjacent CIN 1 lesions. For reasons that are not clear, it is easier to “pick up” the cells on cytology that are associated with CIN 1 than with CIN 2/3. Studies have shown that 12–16% of women with LSIL will have CIN 2 or higher grade lesions after referral for colposcopy [28]. In contrast, one study in adolescents found that only 7% with LSIL had CIN 2/3 [29]. Thus, LSIL remains a threshold for referral for further testing of older women but not adolescents (see Overview of Guidelines).

HSIL describes cells consistent with CIN 2 or CIN 3 lesions. Both CIN 2 and CIN 3 are referred to as precancerous lesions. However CIN 3 is considered a truly precancerous lesion, whereas CIN 2 is a heterogeneous diagnosis. HSIL on cytology is less likely than LSIL to represent a lesion that will regress. The rate of regression of HSIL is difficult to determine because the diagnosis of HSIL has low reproducibility. Although the sensitivity to pick up CIN 3 is extremely low with HSIL, the specificity in adult women is quite high. This is in contrast to LSIL where the sensitivity is higher for CIN 3 but the specificity is quite low for CIN 3. In adolescents, HSIL appears to have even less specificity. This is because adolescents are more likely to have CIN 2 than CIN 3 lesions [30], and CIN 2 appears to have a higher rate of spontaneous regression than CIN 3. In a 10-year prospective study of 528 women with abnormal cytology, Syrjanen et al reported that 53% of CIN 2 lesions and only 14% of CIN 3 lesions regressed [11].

Understanding the progression of HSIL is based on studies of histology. It is estimated that 30–50% of HSIL will progress to invasive cancer [12]. However few studies have attempted to separate CIN 2 and CIN 3. Data from the Syrjanen et al prospective study showed that 69% of CIN 3 lesions progressed to cancer compared with 21% of CIN 2 [11]. It would be unethical to repeat these studies now that CIN 3 is a known precancerous lesion. The time for CIN 3 lesions to progress to invasive cancer most likely varies among women [31].

Clonal events

It is not clear whether low-grade lesions progress through a continuum of high-grade lesions and cancer or whether high-grade lesions develop independently from low-grade lesions. It may be that CIN 3 lesions develop directly as a result of a specific clonal event rather than a progressive event occurring within a CIN 1 lesion. The question then remains, why do studies show that HSIL will develop in women with LSIL? Studies have shown that around 20% of LSIL in women will progress to HSIL or cancer [7]. In contrast, Moscicki et al found that only 3% of women with LSIL developed HSIL [10]. The idea of progression may merely reflect the fact that cytology is insensitive and may have simply missed the cases of CIN 3 at entry. As lesions enlarge, they are easier to detect on repeated cytology.

Epidemiology of cervical cancer

From the perspective of adolescents and screening measures, cervical cancer is almost nonexistent in young women. According to US data, cervical cancer has been diagnosed in women less than 20 years old, but these data do not provide any information about factors (i.e., immune status) involved in these few reported cases. From 2000–2004, there were no cervical cancer cases reported in girls less than 14 years old. There were 0.1/100,000 cases reported in adolescents 15–19 years and 1.5/100,000 in women 20–24 years old. Interestingly, the peak age of incidence of cervical cancer occurs in women who have the lowest rates of HPV infection. The first peak seen for cervical cancer in women in the US is in those aged 40–44 years, with a rate of 15.8/100,000 [32]. Screening in adolescents is undertaken with the intent to detect and treat precancerous lesions in addition to the extremely rare cases of cancer.

Risks associated with the development of cervical cancer have been high parity, prolonged oral contraceptive use, smoking tobacco, and Chlamydia infection. The additional risk associated with these factors compared with persistent infection, however, is miniscule; persistent HPV infections are associated with a 400–800-fold increased risk of cancer compared with a 2–3-fold increased risk associated with these other factors [33]. On the other hand, general points around cancer prevention counseling should include avoidance of tobacco smoking and prevention of sexually transmitted infections. The risk associated with prolonged oral contraceptive use and high parity may reflect behavioral risks, not biologic risks [34]. Studies are still needed to determine associated pathways. Adolescence may reflect a unique biologic risk for acquisition and development of viral persistence. This risk is associated with the maturation process of the cervical epithelium that normally occurs during adolescence. The adolescent ecto-cervix is most often covered by the mono-layered columnar epithelium, which is more fragile than the multi-layered squamous epithelium of most mature cervixes and may be more vulnerable to HPV acquisition. Adolescence is also a time for a process of rapid changes to occur in the columnar epithelium, termed squamous metaplasia. During the differentiation of columnar to squamous epithelium occurring in the transformation zone, the rapid differentiation may increase this area's vulnerability to abnormal cytologic changes from HPV [35]. The transformation zone is the area where squamous cell cervical cancers are known to arise.

Prevention Measures for Cervical Cancer

Prevention of HPV infection

Preventing HPV infection is presumably the most efficient way to prevent cervical cancer. Abstinence and condom use can reduce the risk of HPV infection [36] but are not practical over a woman's lifespan. Vaccination against HPV infection is now an important, additional measure in cervical cancer prevention [37].

Cervical cancer screening and treatment of abnormal cytology

Screening for cervical cancer precursors continues to be the mainstay of cervical cancer prevention. The introduction of prophylactic HPV vaccination may create confusion regarding the role of screening as a preventive measure against cervical cancer. Until the full impact of HPV vaccination on cervical cancer and its precursors can be realized, examined, and incorporated into guidelines, all women should continue to be screened regardless of vaccination status. Vaccinated women remain at risk for HPV infection with other high-risk types. The duration of protection provided by the vaccine is not yet known.

Separate from the development of HPV vaccines, current cervical cancer prevention guidelines have shifted towards identifying adolescent and young women as a unique population. Recent changes resulted from the recognition that HPV is most commonly a transient infection in

adolescents; most abnormal cytology is benign in this age group, and the development of cervical cancer takes years. Screening, monitoring, and treatment guidelines have attempted to balance the benefits of preventing cervical cancer with the risks of unnecessary screening and treatment.

Current Methods for Cervical Cancer Screening Cytology

The conventional Pap test involves the collection of exfoliated cervical cells, smearing of cervical cells onto a slide by the clinician, as well as staining, interpreting, and reporting results by laboratory personnel. Conventional Pap tests generally have a high detection rate of abnormal and precancerous cell changes. However the collection method and slide preparation can limit its sensitivity. Collection can be limited by small or inaccessible lesions. Slide preparation can be limited by overlapping cells, inadequate number of cells, or background artifact from inflammatory or blood cells [38].

Liquid-based Pap (LBP) involves the clinician placing the cervical sample directly into a liquid fixative; slide preparation occurs in the laboratory. LBP tests can potentially improve the quality of the sample reviewed by the laboratory staff by immediate fixation of the cells. Improved slide preparation can allow for a more even distribution of cells and decreased background artifact and overlapping of cells. In most studies, LBP has been shown to have a lower false-negative rate compared with conventional Pap tests. It is believed that LBP yields a comparable or increased rate of false-positives to conventional Pap tests [38]. Current screening guidelines address the use of this test in addition to conventional Pap tests. Using either method, the sensitivity of cytology to detect CIN 2/3 lesions is around 20% if HSIL is used as the threshold for referral, and ranges from 40–70% if ASCUS is used as the threshold.

Role of HPV-DNA Testing in Cervical Cancer Screening and Management of Abnormal Cytology

HPV testing involves obtaining a sample of exfoliated cervical cells and testing for the presence of HPV-DNA. Current testing methods can be performed on an LBP sample after it has been used to prepare the cytology slide. One HPV-DNA test is currently licensed for clinical use by the Food and Drug Administration. This test, the Hybrid Capture II (HC2), detects 13 high-risk HPV types. Results are reported for all types as a group and not for individual types [38].

Current guidelines address the use of this test in cervical cancer screening and management of abnormal cytology in older women. HPV testing does not detect precancerous lesions, per se. When used in conjunction with Pap testing, the intended goal of viral DNA detection is to identify women with the necessary combination of persistent infection with a high-risk HPV type and abnormal cytology. It is women with these two findings who are at risk to develop cervical cancer. As previously discussed, an infection with a high-risk HPV type that clears does not lead to cervical cancer. Based on prevalence rates of HPV and longitudinal studies of HPV clearance, it is well known that young women have a high rate of HPV infection and a high rate of clearance. Therefore, a positive HPV test in an adolescent will not assist clinicians in assessing the patient's risk of cervical cancer. However the likelihood that a high-risk HPV result represents a persistent infection increases as a woman's age increases. Thus, a high-risk HPV type detected in an older woman is more likely to represent a persistent infection than a high-risk HPV type detected in a younger woman. Unfortunately, there is no discrete age at which this transition occurs. Current guidelines for primary cervical cancer screening [39,40] discuss preliminary recommendations for the use of HPV-DNA testing in women over 30 years, as a means to increase the interval between cytology screening. It should be emphasized that HPV DNA testing should not be used in primary cervical cancer screening in women under 30 years of age.

Guidelines addressing appropriate management of women with abnormal cytology have incorporated HPV-DNA testing as a management option in women 21 years and older in certain circumstances, such as ASCUS. However HPV testing is not appropriate under any circumstance for female adolescents (defined as 20 years and younger), including the management of ASCUS. HPV-DNA testing should only be used in conjunction with the evaluation of abnormal cytology. Additional management recommendations for older women are available from the American Society for Colposcopy and Cervical Pathology (www.asccp.org).

A review of recent research indicates a potential to further incorporate HPV testing into screening programs for cervical cancer. Two published studies have compared the use of HPV testing with conventional cytology triage for screening within large cohorts of women over 30 years of age [41,42]. Although these studies add important information to our body of knowledge about cervical cancer prevention, they do not offer sufficient information to replace consensus driven guidelines [43]. Therefore, to incorporate these findings into clinical practice, further studies comparing HPV testing with the conventional Pap test or the more commonly used LBP test are needed. The impact of new algorithms for rates of colposcopy and cervical cancer prevention has yet to occur.

Overview of Guidelines for Cervical Cancer Screening and for Follow-Up and Treatment of Abnormal Cytologic Findings

To prevent cervical cancer by detecting and treating lesions destined to become cancerous, consensus guidelines have been developed to recommend the most effective use of Pap tests, HPV testing, and colposcopy. The goal of the guidelines is to evaluate the available evidence and to form expert opinion when evidence is not adequate. Guidelines are developed by incorporating considerations of the risks and benefits of the recommendations on both the individual and the community. Individual risks include the psychologic and health consequences related to treatment of a false-positive result, as well as the risk of cancer due to false-negatives or not detecting lesions before they progress to cancer. A community risk includes the inefficient use of health care resources, both financial and personnel. Because of this, guidelines based on the same evidence will differ in countries with different health care delivery systems. In the US, cytology screening guidelines have been published by the American Cancer Society (ACS), the American College of Obstetricians and Gynecologists (ACOG), and the US Preventative Services Task [39,40,44]. The ACS screening guidelines were most recently updated in 2002. The ASCCP has recently published two sets of guidelines (available at www.asccp.org), one for the management of women with abnormal Pap test results [45,46] and one for the management of women with abnormal histology (CIN and adenocarcinoma in situ) [28,47]. Each set of guidelines recognizes adolescent and young women as a distinct group with unique recommendations for this age group.

Cervical cancer prevention screening guidelines

Recommendations applicable to adolescent and young women for cervical cancer screening include when to start and how often to screen women [39,40]. Screening should be initiated approximately 3 years after the onset of vaginal intercourse. In order to accommodate for potential situations in which patients do not reveal vaginal intercourse, clinicians are guided to initiate screening by the age of 21 years, despite the patient's reported sexual history. However if a woman older than 21 years has undoubtedly never had vaginal intercourse and has no history of sexual abuse, the clinician and woman may discuss when screening should begin. This discussion should consider the epidemiologic finding of HPV in women who report no history of vaginal intercourse. It is presumed, although not proved, that sexual behaviors such as finger-vaginal sexual activity or masturbation could account for these findings. As

guidelines cannot be developed for each patient's circumstance or lifestyle, the initiation of screening in these situations may rely upon the clinician's judgment.

As discussed in the guidelines, insufficient evidence exists to form general recommendations for when to start screening in women who have a history of penetrative sexual abuse before the onset of puberty [39]. Also, current guidelines do not contain recommendations specific to women who have sex only with women. The majority of evidence informing the guidelines has not focused on women who have sex with women as a separate group.

Once screening is initiated, the recommended interval between Pap tests depends on the screening technology used and the age of the patient. Intervals for screening with conventional Pap tests, LBP tests, and, in women more than 30 years old, HPV-DNA testing combined with cytology are addressed. Conventional Pap tests alone should occur every year for women under 30 years, regardless of the number of previous negative cytology tests [39,40]. When LBP tests are used in women under 30 years, screening should occur every 2 years (ACS recommendation) or every year (ACOG recommendation) after three annual consecutive benign tests. Performing LBP at less frequent intervals is thought to compensate for the increased false-positive rate [39]. Cytology combined with HPV-DNA testing shows promise to allow an increase in the screening interval for women 30 and older, but has not been fully recommended by current guidelines. HPV testing in primary cervical cancer screening is not appropriate for female adolescents or women under 30 years of age.

Guidelines for management of abnormal cytologic findings

Detection of abnormal cytologic findings (SIL or ASC) on screening cytology triggers clinicians to refer women to colposcopy for diagnostic testing, monitoring with repeated cytology, or a combination of colposcopy and cytology [45,46].

Adolescents (women 20 years and younger) are considered separately from women 21 and older in guidelines for the management of abnormal cytology (Figure 4). The same finding on a Pap test indicates very different risks for invasive cancer for adults than adolescents. In adolescents, women 20 years and younger, LSIL or ASCUS detected by screening should be monitored with repeated cytology every 12 months. These two diagnoses have been combined since their natural histories are similar, if not identical. If, at the first 12-month follow-up, HSIL or ASC-H is detected, the patient should be referred to colposcopy for biopsy. If, at the first 12-month follow-up, the cytology is normal or if LSIL or ASCUS is detected, continued monitoring is recommended. Routine screening should resume if cytology is normal at the second 12-month follow-up (at 24 months). If cytology shows LSIL, ASCUS, ASC-H, or HSIL, referral for colposcopy is warranted.

This management recommendation is in contrast to adult women who should be referred to colposcopy when the first LSIL is detected on routine screening. Management of ASCUS in women 21 years and older includes three acceptable follow-up approaches, including monitoring every 6 months for a year, referral to immediate colposcopy, and testing for HPV-DNA. None of these follow-up approaches are appropriate in adolescents, 20 years and younger, including HPV testing. The high rate of HPV in adolescents and young women does not make HPV triage efficient in these young patients with ASCUS. In addition, if HPV results are inadvertently obtained for an adolescent with ASCUS, it is recommended that the results not be considered in the management of the cytology results.

Regardless of age, ASC-H and HSIL should prompt a referral to colposcopy. Unlike older women, immediate loop electrosurgical excision is unacceptable in adolescents with HSIL. Many CIN 2/3 lesions in adolescents will regress. Therefore, the detection of HSIL without

confirming the histologic diagnosis does not warrant the risk of a treatment that increases a woman's future risk of preterm labor, low birth weight infant, and cesarean section [28].

Guidelines for treatment of SIL/CIN in adolescents

After women with abnormal cytologic findings have been triaged to colposcopy and found to have CIN on histology, consensus guidelines that recommend appropriate treatment have been published [28,47]. Because of the differences in prevalence and the natural history of CIN in adolescents and older adults, recommendations differ for these two groups (Figure 5).

Adolescents with a histologic diagnosis of CIN 1 are monitored with cytology every 12 months for 2 years. Adult women with CIN 1 are managed with consideration of the cytology result that prompted the colposcopy referral (reviewed at www.asccp.org). This is not the case for adolescents. The management of CIN 1, regardless of the referral cytology, is observation at 12-month intervals. If HSIL or ASC-H is detected at the 12-month cytology, colposcopy referral is recommended. If LSIL, ASCUS, or normal cytology is reported at 12 months, repeat cytology is recommended at 24 months. If the result is normal, routine screening can resume. If LSIL, ASCUS, ASC-H, or HSIL is detected at 24 months, referral to colposcopy is recommended. CIN 1 in adolescents and adults indicates a benign lesion, and treatment, even if colposcopy is unsatisfactory, is not recommended. If the lesion remains CIN 1, the option to continue follow-up by cytology remains the preferable management.

Adolescents, 20 years and younger, and young women with CIN 2 or CIN 2/3 (but not CIN 3) and satisfactory colposcopy can be observed by repeating both colposcopy and cytology at 6-month intervals for 2 years after discussing the risks with the patient. Routine screening can resume after two negative cytology and two normal colposcopy exams. Repeat biopsy is recommended if colposcopy or cytology worsens while the patient is being observed. Biopsy is also recommended if HSIL or CIN 2/3 persist for 1 year. Treatment is recommended if CIN 2/3 or HSIL persist for 2 years after initial diagnosis. If CIN 3 or carcinoma in situ is detected at any time, treatment is recommended.

"Young women" were not defined in the new ASCCP guidelines. The general rationale behind conservative treatment in young women is weighing the risk of cervical cancer, which is extremely low in young women (under 25 years of age), against the benefit of preserving fertility if treatment is deferred. "Young" may also refer to sexual experience. A 24-year-old who has been sexually active for 2 years likely reflects a very different risk factor than a 24-year-old who has been sexually active for 10 years.

Conclusion

Current guidelines for the management and treatment of abnormal cytology and histology are a timely and central addition to public health efforts to prevent cervical cancer. They reflect the discovery made in recent decades that the epidemiology and biology of HPV infection differs in adolescent and adult women. Guidelines also incorporate the addition of HPV-DNA testing in determining the prognosis of cervical lesions in older women. These tests have the possibility to become more integrated into future guidelines for older women, but the usefulness for screening in adolescents is not immediately apparent.

A new era of combined primary and secondary approaches to the prevention of cervical cancer and its precursors has begun, along with the recent availability of HPV vaccines. Over the coming years, as vaccines are introduced into countries and accepted into populations, careful attention to the epidemiology and natural history of HPV infection and cervical cytology in women of all ages must continue. Understanding vaccines' impact on HPV epidemiology will inform future revisions to screening, management, and treatment guidelines.

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Figure 1.

Life cycle of the human papillomavirus (HPV). HPV requires direct access to basal cells through a wound or inflammation. HPV then requires cell differentiation for its own transcription and replication process. As cells mature and move through the epithelium, the early protein, E6 and E7, are expressed while the infected cell is present in the basal cell layers. As the infected cell matures, other proteins are expressed, including E4, which is known to induce the cytopathic effect referred to as koilocytosis. The late proteins, L1 and L2, which are responsible for the outer capsid, are not expressed until the cells are fully mature. At the time, the infectious viral capsid is released as the anucleated cells are desquamated. (Reprinted from von Knebel Doeberitz M. New markers for cervical dysplasia to visualise the genomic chaos created by aberrant oncogenic papillomavirus infections. *Eur J Cancer* 2002;38:2292–42, with permission from Elsevier.)

Figure 2.

Role of persistent HPV infection in cervical cancer. CIN 3 = cervical intraepithelial neoplasia grade 3. (Reprinted from Moscicki AB. Updating the natural history of HPV and anogenital cancer. *Vaccine* 2006;24(Suppl 3):42–51, with permission from Elsevier.)

Figure 3. Comparison of cervical cytology descriptive systems. CIN = cervical intraepithelial neoplasia; WHO = World Health Organization. (Based on Solomon D, et al. The 2001 Bethesda System: Terminology for reporting results of cervical cytology. JAMA 2002 287:2114–9.)

Figure 4.

Algorithms for Management of Adolescent Women with Abnormal Cytology. Reprinted from *The Journal of Lower Genital Tract Disease* Vol. 11 Issue 4, with the permission of ASCCP © American Society for Colposcopy and Cervical Pathology 2007. No copies of the algorithms may be made without the prior consent of ASCCP. (A) Management of adolescent women with either atypical squamous cells of undetermined origin (ASC-US) or low-grade squamous intraepithelial lesion (LSIL). (B) Management of women with atypical squamous cells cannot exclude high-grade SIL (ASC-H). (C) Management of adolescent women (20 years or younger) with high-grade squamous intraepithelial lesion (HSIL).

Figure 5. Algorithms for Management of Adolescent Women with CIN. Reprinted from *The Journal of Lower Genital Tract Disease* Vol. 11 Issue 4, with the permission of ASCCP © American Society for Colposcopy and Cervical Pathology 2007. No copies of the algorithms may be made without the prior consent of ASCCP. (A) Management of adolescent women (20 years or younger) with a histologic diagnosis of cervical intraepithelial neoplasia grade 1 (CIN 1). (B) Management of adolescent and young women with a histological diagnosis of cervical intraepithelial neoplasia grade 2,3 (CIN 2,3).