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Evidence-Based Cervical Cancer Screening: The Modern Evolution of the Pap Smear

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1. Introduction

The Papanicolou screen ("Pap smear") was developed in 1928 by Dr. George Papanicolaou for the identification of cervical cancers. It became widely known after his publication in 1941 and widely used in clinical practice in the 1950s; it is now the most commonly performed cancer screening test world-wide (1). This has been one of the most successful cancer screening techniques in modern medicine, and in the United States rates of cervical cancer have decreased by almost 80% since the 1950s (2,3). Pap smear screening has been widely embraced by physicians and women alike, and is considered a critical part of the routine health care of women. However, up to 20% of American women do not receive regular Pap smears, and in developing countries without the complex resources required to process and read Pap specimens, screening remains a challenge (4). Among women with cervical cancer in the U.S., at least 60% did not have appropriate Pap surveillance prior to their diagnoses (5).

In the decades since the initial development of the Pap smear, our understanding of the pathophysiology of cervical cancer has evolved considerably. The occurrence of pre-malignant cervical lesions, now referred to as cervical dysplasia, was recognized as early at the 1940s (6). During the 1970s and 1980s, the human Papilloma virus (HPV) was identified within cervical lesions (7, 8). As early as 1976, Dr. Harald zur Hausen and colleagues postulated a role for the HPV in cervical oncogenesis, and his subsequent work isolating oncogenic HPV strains and elucidating the oncogenic process earned him the Nobel Prize in Medicine in 2008 (9-11).

The discoveries of premalignant cervical lesions and the role of HPV in cervical dysplasias and cancers have also enabled physicians to gradually refine the use of Pap smear screening. As a result, the number of women who need Pap smears, and the frequency at which they are recommended, has changed significantly over the last several years. However, dissemination of the newest guidelines has been met with some resistance both from women and their physicians.

In this article, we will review these advancements and the current evidence about the modern use of Pap smears and HPV screening, the evidence leading to the new recommendations and some barriers to their full implementation.

2. Fundamentals of screening for disease

Screening can be defined as the effort to identify asymptomatic disease or disease precursors through examinations or tests applied rapidly to an appropriate segment of the population. Screening tests delineate patients who appear well and have a disease from those who do not have a disease. Numerous examples of screening tests exist in clinical practice as a part of primary or secondary prevention, including blood pressure measurements, serum cholesterol measurements, pap tests, and colonoscopy. Importantly, screening tests are not intended to be diagnostic. A positive screening test requires follow-up and commitment to further investigation.

A successful and appropriate screening test depends on numerous criteria, which cluster in to three general categories delineated by Katz: disease-specific criteria, test-specific criteria, and society or system-criteria (Table 1) (12). All of the factors listed in Table 1 impact the potential benefits of screening programs both to individual patients and populations. Disease screening would be unjustified if the burden of disease is insignificant or if treatment outcomes are no different between asymptomatic cases diagnosed at an early stage and symptomatic cases diagnosed at later stage. If an effective treatment for a disease is not available, screening and early detection confers no benefit to patients. Disease prevalence, discussed in detail below, is integral to screening programs as screening for extremely rare conditions would not be cost-effective or accurate given that false-positive tests may outnumber true-positive results. The screening test itself must be convenient, acceptable, safe, and cost-effective for patients. An ideal screening test should take only a

Disease-specific
• Condition must have significant burden on health (morbidity, mortality, suffering) • Disease detectable in asymptomatic state • Natural history of disease modifiable with treatment • Early, effective treatment available • Appropriate prevalence: not too rare or too common
Test-specific
• Highly sensitive to reliably identify disease cases • Highly specific to minimize false positives • Cost-effective • Test is safe, convenient, and acceptable to patients
Society/System-specific
• Confirmatory, diagnostic testing readily available for screen positive • Effective treatment readily available for confirmed cases • Screening program cost-effective for population

Adapted from Katz DL, Fundamentals of screening: the art and science of looking for trouble, Sage Publications, London, 2001 (reference 12).

Table 1. Characteristics of an Appropriate Screening Test

few minutes to perform, require minimal preparation by the patient, and be inexpensive. Additionally, given that screening programs require a significant commitment of resources, they should be cost-effective and confer benefit on a population or societal level. As described further in this chapter, screening for cervical cancer exemplifies an ideal screening test by meeting all of the aforementioned criteria.

Importantly, a successful screening program is dependent upon the various characteristics of the screening test, and an understanding of these principals is fundamental to providers and public health officials. Sensitivity and specificity are characteristics inherent to a test and are independent of disease prevalence. Sensitivity is the probability that if the disease is present, the test is positive. Mathematically, the numerator is the number of subjects with a disease who have a positive test and the denominator is the total number of subjects with a disease. A test with high sensitivity effectively identifies subjects with disease and infrequently misses true cases (low false negative rate). Specificity is the probability that if a disease is absent, the test is negative. Mathematically, the numerator is the number of subjects without a disease who also have a negative test, and the denominator is the total number of subjects without disease. Tests with high specificity infrequently identify subjects as having disease when they do not (low false positive rate). Given that screening tests must identify disease in asymptomatic patients where the prevalence is usually low (even in high risk groups), a good screening test must have high sensitivity as to not miss the few cases of disease present. Additionally, the sensitivity must remain high in the early stages of disease. A test that demonstrates high sensitivity only in late-stage disease, where treatment may be less effective, will not provide clinical utility. Good screening tests should also have high specificity to reduce the number of false positive results which require follow-up evaluation or intervention.

The calculation of sensitivity and specificity for screening tests are determined in a manner similar to that of diagnostic tests, however one major difference deserves mention. The sensitivity and specificity of diagnostic tests are based on comparisons between the test results and a different test (the reference or "gold standard"). For a screening test, the "gold standard" for detecting disease includes both another test and a period of follow-up. Additional testing is routinely administered to those who have positive screening tests for confirmation (differentiation of true and false-positive results). However, a period of follow-up is necessary for all negative results to differentiate subjects with true and false-negative tests. This characteristic is particularly important in cancer screening, where cancers discovered during the period of follow-up (interval cancers) occur. Choosing the appropriate duration of follow-up may impact the sensitivity and specificity of the test, which overestimates sensitivity if the follow-up period is too short and underestimates sensitivity if the follow-up period is too long. (13)

Positive and negative predictive values (PPV, NPV) also represent important characteristics of screening tests. PPV represents the probability that a subject with a positive test has a disease. The numerator is the number of subjects with disease who have a positive test and the denominator is the number of subjects with a positive test. Conversely, NPV represents the probability that subject with a negative test does not have disease. The numerator is the number of subjects without disease who have a negative test and the denominator is the number of subjects with a negative test. The predictive values depend on disease prevalence within a population. For a test with a given sensitivity and specificity, as prevalence rises

the PPV of a test increases and the NPV decreases. Conversely, as prevalence falls, the PPV decreases and the NPV increases. This observation has important implications for screening tests, where the disease prevalence is generally low. Therefore, most screening tests have low PPV and high NPV (despite high sensitivity and specificity). Clinically, this implies that providers offering screening tests to their patients must accept the fact that many patients will screen positive and not truly have disease; however, these patients still require follow-up evaluation and testing.

3. Biases and pitfalls of screening programs

Instinctively, screening for disease has apparent benefits. However, given that no test in medicine is perfect, widespread adoption of screening tests prior proving their benefit can become problematic. Therefore, prior to implementing population-wide screening programs, a test should be subject to careful study. Similar to any intervention in medicine, the most rigorous means of establishing the efficacy of a treatment or intervention is with a randomized controlled trial. However, many years and large numbers of patients are required to establish the efficacy of a preventative intervention or screening test. For example, a study demonstrating that early treatment of colorectal cancer detected by disease screening reduced cancer-related mortality by one-third required 45,000 subjects and 13 years of follow-up surveillance (14). Therefore, a case series describing screening programs or a "clinical impressions" of the impact of screening do not suffice to establish efficacy.

Rigorous study is necessary to avoid biases specific to the study of screening programs. One such bias, lead-time bias, occurs when discovering a disease in an early stage with screening does not impact mortality rates or outcomes relative to discovering the disease later when it would typically present with symptoms. Discovering the disease early may appear beneficial by increasing "survival time". However, in reality, early detection only serves to advance diagnosis, thereby increasing the duration of time a patient has a disease. A patient living with disease for a longer period of time may be subject to more frequent examinations and tests as well as increased anxiety from a longer time with knowledge of disease.

Another type of bias present in screening programs is length-time bias. Length-time bias is a type of selection bias that occurs when outcomes appear better in a screened population of subjects due to the fact that diseases with a favorable prognosis are more readily discovered with screening. This phenomenon is exemplified by cancer screening, where slow-growing lesions are diagnosed more readily than rapidly-growing lesions due to a longer pre-clinical, asymptomatic period. Given that slow-growing tumors generally have a better prognosis than rapidly-growing tumors, screening programs generally discover slow-growing tumors with inherently more favorable prognoses. Therefore, while mortality rates for cancers discovered through screening may be more favorable, screening is not truly protective in this setting.

Lastly, compliance bias can occur in studying the efficacy of screening programs. Compliance, the degree to which patients follow or adhere to medical advice, may impact studies of disease screening as compliant patients tend to have better prognoses independent of screening. For example, studies that compare disease outcomes between subjects who volunteer for screening and those that do not may demonstrate improved outcome, however this improvement may be secondary to higher compliance amongst

volunteers rather than any benefit conferred by the screening program. Therefore, to effectively evaluate the impact of any screening test or program, randomized trials with concurrent screening and control groups must be conducted to minimize the introduction of length-time and compliance bias. By following studied populations with mortality rates, rather than survival rates, lead-time bias can be avoided.

Screening programs also have the potential to produce significant adverse effects in a screened population, which highlights another critical reason to rigorously study screening tests prior to their widespread application. Adverse effects range from discomfort produced from the test itself to false-positive test results to overdiagnosis. In effective screening programs, false-positive results account for a minority of all test results. However, false-positive results can still have a substantial impact on a large number of patients by producing anxiety and the discomfort and cost of additional follow-up tests. Given that screening tests are often repeated in intervals, each repeat screen is subject to further false-positive results. Additionally, the negative impact of overdiagnosis cannot be overstated. While the underlying presumption in cancer screening is that earlier detection translates into improved outcomes, recent evidence has challenged this thesis. In a recent editorial, Welch reviewed the impact of a 10-year course of screening mammography on 2500 women in the US at age 50 (15). While one breast cancer-related death would be prevented by mammography, up to 1000 women will have at least one false-positive result and approximately half will undergo a breast biopsy. Additionally, breast cancer will be overdiagnosed in 5-15 women who will be treated "needlessly" with surgery, chemotherapy, radiation, or a combination thereof. Therefore, even excellent screening tests are not without pitfalls.

Screening for cervical cancer exemplifies a good screening test by satisfying the aforementioned criteria described by Katz (Table 1). Cervical cancer is appropriately prevalent and has a significant disease-related morbidity and mortality. The natural history of the disease, from HPV infection to carcinoma, has been clearly established. A premalignant window for intervention exists such that treatment significantly decreases disease burden. Follow-up testing with colposcopy is generally available and effective at detecting premaligant lesions. Excision procedures reliably treat premalignant lesions and prevent progression to cancer. When utilized for screening, Pap smears have acceptable test characteristics. While reports of sensitivity and specificity vary significantly between studies, a meta-analysis demonstrated sensitivity as high as 86% and specificity as high as 100% (16). Additionally, negative predictive values have been demonstrated to be higher than 95% (17). As such, Pap screening remains one of the most significant and successful screening tests in the history of modern medicine. The remainder of this chapter provides and evidence-based assessment of Pap and HPV screening with a discussion current recommendations and controversies.

4. History of Pap screening and impact of screening on cervical cancer incidence and mortality

Dr. George Papanicolaou, a physician and scientist trained in Greece in the early 1900s, immigrated to the United States in 1913 seeking greater opportunities in medicine and research (Figure 1). He became acquainted with T.H. Morgan, a well-known zoologist who had already read and cited Papanicolaou's doctoral thesis in a publication. Mr. Morgan

Adapted from Vilos G. Dr. George Papanicolaou and the Birth of the Pap Test. Obstetrical & Gynecological Survey. 54(8):481-483, August 1999.

Fig. 1. Dr. George Papanicolaou

recommended Papanicolaou for a part time position as a technician in the pathology department at New York Hospital. His scientific mind impressed the department and shortly thereafter he was appointed as an assistant professor in the anatomy department at Cornell Medical School. His research on the chromosomal basis of gender differentiation in guinea pigs led to the discovery that exfoliated cells from the vagina could predict the timing of ovulation. In his initial experiments, he used a small nasal speculum to obtain the sample and then plated slides for microscopy, noting "an impressive wealth of diverse cell forms and a sequence of distinctive cytologic pattern" (21). With this observation, he

hypothesized that an analogous pattern could be appreciated in humans. Concomitantly, he began to obtain samples from his wife for further study, which represented the birth of the Pap smear. Shortly thereafter, he initiated the systematic study of exfoliated vaginal cells in women working at New York Hospital. In February 1295, he encountered a woman with an undiagnosed carcinoma of the cervix. The slide produced from her sample was recognized as cancer, and he then understood the implications of his methods on the diagnosis of cervical cancer. He confirmed his findings by recruiting other women with known cervical cancers and characterizing their cervicovaginal samples. He presented his test and findings at the Third Race Betterment Conference in Battle Creek, Michigan in January of 1928 (22).

Papanicolaou's 1928 presentation was greeted with skepticism by pathologists at the time as they felt biopsy should remain the gold standard diagnostic modality. Unfortunately, ten additional years of research was required before the Pap test was evaluated rigorously as a potential diagnostic tool. Finally, in 1939, at the urging of his department chair, Papanicolaou and fellow gynecologic pathologist Herbert F. Traut initiated a clinical trial of the Pap test. Vaginal samples were collected from all women admitted to the obstetric and gynecologic services at New York Hospital. They published their findings in the *American Journal of Obstetrics and Gynecology* in 1941, which detailed the differences between normal and malignant cells of the cervix. In this landmark publication, Papanicolaou proposed his technique as a simple, inexpensive means to test large numbers of women and diagnose cancer at an earlier stage which would be more amenable to treatment (1).

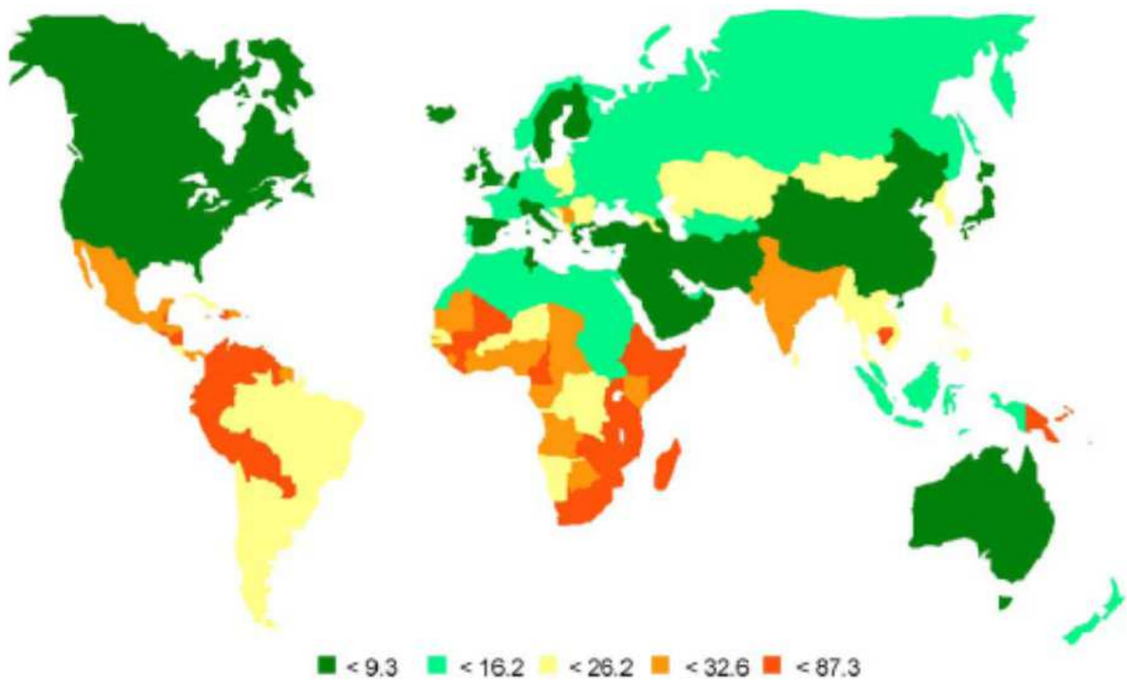
Shortly after the publication of this manuscript, his technique started to gain more widespread acceptance including the support of the National Cancer Institute and the American Cancer Society (ACS). In 1948, the ACS held the first interdisciplinary conference to promote the "Pap" test (23). In the late 1940s and early 1950s, community-based projects were undertaken to explore the feasibility and acceptance of screening large proportions of the population as well as to evaluate the impact of screening on cancer incidence and mortality. Screening programs in Ohio, Tennessee, and Kentucky all demonstrated increases in the detection of carcinoma in situ and decreases in the incidence of invasive carcinoma. For example, in the study from Kentucky, over 90% of the female population in the greater Louisville area was screened at least once during an 11 year period and the rate of cervical cancer declined by 32% (24-26).

With local and regional programs demonstrating benefit, the ACS promoted a national effort and campaign for screening. In 1957, the ACS initiated a campaign for annual, universal screening called the "Uterine Cancer Year". The American College of Obstetricians and Gynecologists followed with recommendations for cervical cytologic screening in their first and second editions of the Manual of Standards in Obstetric-Gynecologic Practice, published in 1959 and 1965 respectively (27). At that point, the framework was in place for the incorporation of Pap screening into standard gynecologic practice.

The aforementioned community-based evaluations established that cervical cytologic screening was acceptable to large populations of women. Importantly, these evaluations also demonstrated a consistent decrease in cervical cancer incidence and mortality in each community where screening was introduced. Interestingly, however, no randomized clinical trials of cervical cytology assessment with Pap screening have been performed to date.

Therefore, while a true causal relationship may never be formally established, a consistent association of screening with a reduction in cervical cancer burden provides convincing evidence of the impact of the Pap test.

The international epidemiology of cervical cancer further supports a direct correlation between screening programs and decreased cancer incidence and mortality. Prior to the widespread adoption of screening programs in developed countries, incidence rates of cervical cancer were similar to those found in developing countries today (28). Currently, however, marked disparities exist between the incidence of cervical cancer as well as cervical cancer-related mortality between the developed and developing world (Figure 2). Due to widespread implementation of cervical cancer screening programs in the developed world, cervical cancer has become one of the least common malignancies impacting women. In the United States in 2007, approximately 12,000 women were diagnosed with cervical cancer and 4000 died from the disease. Additionally, as noted by the NCI Surveillance Epidemiology and End Results (SEER) data, the incidence and mortality rate for cervical cancer continues to decline at 2.6% per year and 0.6% per year respectively (data available through 2008) (29, 30). Worldwide, however, the incidence of cervical cancer is approximately 500,000 cases per year with over 250,000 cancer-related deaths (31). According to the World Health Organization, over 80% of cervical cancer-related deaths occur in the developing world, and the lack of access to screening and prevention programs represents the primary reason for the enormous disparity between resource-rich and resource-poor nations (32). Additionally, even in countries with adequate screening programs, poor women suffer a disproportionate share of the burden of disease, with incidence rates



Adapted from: Sankaranarayanan R, Ferlay J. Worldwide burden of gyaecological cancer: the size of the problem. Best Pract Res Clinc Obstet Gynaecol. 2006;20:207-225.

Fig. 2. Age-standardized incidence rates of cervical cancer per 100,000 women

approximately two-fold higher than more affluent women (28). Cervical cancer does not make the list of the ten most incident or lethal cancers in the United States. However, cervical cancer remains the second leading cause of cancer-related female mortality worldwide (29, 32). It is therefore a substantial public health challenge despite the presence of an effective screening test. Moving forward, resources must be allocated for the development of comprehensive screening programs as well as HPV vaccination programs in the developing world.

5. HPV as the causative agent for cervical cancer

Human Papilloma viruses (HPV) were first identified in cervical cancer cells in 1947 by Pund et al, who noted "koilocytic changes" in cervical tissues (6). Subsequently, multiple investigators have elucidated that infection with HPV is the critical factor in cervical oncogenesis (7-11). There are over 120 strains of HPV, and approximately 30 strains affect the anogenital region (33). These are classified as either "low risk" or "high risk" HPV subtypes. Low risk HPV subtypes include 6, 11, 40, 42 and 43 and are associated with genital warts, but not significantly associated with cervical cancer. High risk HPV subtypes include 16, 18, 31, 33, 35, 39, 45, 51, 52, 56 and 58; these are associated with cervical dysplasia and cancer. HPV 16 accounts for approximately half of squamous cervical cancers, HPV 18 for another 10-15%, and 31, 33, 35, 52 and 58 about 2-5% each. Overall, between 95-100% of squamous cervical cancers are HPV-related (34, 35).

HPV is a family of double-stranded, circular DNA viruses. The genome codes for two oncogenic proteins, E6 and E7, that interfere with control of host cell replication. The E6 protein binds to the tumor suppressor gene, p53, and inactivates it. The E7 protein binds to the Rb tumor suppressor gene which results in loss of apoptosis and cell-cycle control. This leads to unchecked replication of infected cells, and shedding of the virus which can be passed on to new hosts. Episomal replication can lead to destabilization of host genome and aneuploidy, which in turn may promote integration of the HPV genome in fragile areas of the host DNA. Integration of HPV DNA into the host cell DNA is associated with cervical dysplasias and cancer.

HPV is transmitted by sexual contact, and in fact is the most common sexually transmitted infection in the world. Population-based studies have found that the lifetime prevalence of HPV infection is 50-80% (35). The estimated attack rate after contact with an HPV-infected partner is 66% (34). However, over 75% of HPV infections are asymptomatic, and are cleared by the host immune system within 6-24 months without clinical sequelae (34, 36-39). Most of these infections are not evident to the patient and are never detected before they are cleared. For patients with HPV that is clinically detected, approximately 70% will demonstrate viral clearance within one year, and 90% within two years. Importantly, it is *persistent* infection with high risk HPV that is associated with progressive cervical dysplasias and cervical cancer.

Screening for cervical cancer consists of cytologic screening—the Pap smear—either alone or in conjunction with HPV testing. In the following sections we will review screening strategies and the current recommendations for the use of both Pap smears and the available HPV tests.

6. Pap smear screening strategies

Pap smear screening has been considered an integral part of well-woman care for over 50 years, and both physicians and women have incorporated it into their annual routines. Because of the recognition that sexual debut put women at risk for HPV, older guidelines recommended starting Pap smear screening at coitarche, or by age 18 if coitarche had not occurred. Pap smears were performed annually throughout a woman's life, without a recommended terminus. A better understanding of the epidemiology and time course of HPV infection has allowed these long-standing recommendations to be gradually modified, in order to minimize unnecessary testing.

6.1 Adolescents and young women

When considering younger women, two points are important to bear in mind. The first is that the interval between HPV infection and a clinically detectable cervical dysplasia is months to several years. The second is that HPV is highly prevalent (up to 80%) and usually transient (without clinical sequelae) (34, 36, 39, 40). Understanding the time course initially led to an updated recommendation that women should start Pap smear screening three years after coitarche or by age 21. However, a finer understanding of both points together implies that detection of minor abnormalities in very young women is probably clinically irrelevant, because they nearly always resolve. Only 1 of 1000 women diagnosed with cervical cancer in the United States are under the age of 21, or approximately 10-12 women per year nationwide (41). Thus, current guidelines from the multiple American College of Obstetrics and Gynecology (ACOG) have been simplified to recommend initiation of Pap smear screening at age 21, regardless of the timing of sexual debut (40).

Between the ages of 21 and 29, two different possible screening strategies are recommended. Currently, ACOG recommend biennial screening for these women. The American Society for Colposcopy and Cervical Pathology (ASCCP), ACS and the United States Preventative Services Task Force (USPSTF) have recently released draft consensus guidelines which recommend Pap smear screening every 3 years in this age group (40, 42, 43).

6.2 Adult women

Starting at age 30, the recommended interval for Pap smear screening can be extended, assuming several criteria are met. First, healthy women who have reached age 30 and have had three prior consecutive normal Pap smears can then extend their Pap screening interval to every three years. Second, women who have a normal Pap smear *and* a negative high risk HPV test can then be screened every three years (see additional information in "HPV Screening Strategies", below). Women in either group are unlikely to develop a clinically significant dysplasia during the two unscreened years, and the resultant decrease in unnecessary Pap smears should translate into a significant savings to the health care system (40, 42).

There are several important caveats to extended interval screening. First, it is key that women are educated about the rationale for extended interval screening, and that they understand that their "annual exam" consists of more than their Pap smear. Women should be encouraged to have a regular physical examination even in the years when a Pap is not

indicated. Second, there are a number of exclusion criteria for extended interval screening. Women with a history of moderate to severe cervical dysplasia (grades 2 or 3) are not eligible for this extended interval; they should continue annual Pap smears for at least twenty years after treatment. Other women who should continue to have annual screening include women exposed to diethylstilbesterol (DES), women on immunosuppressant medication, and women living with HIV/AIDS. Women who have a history of cervical cancer must continue to be screened with Pap smears indefinitely. In contrast, women who have undergone hysterectomy (with removal of the cervix) for reasons other than cervical dysplasia or cervical cancer do not need any further Pap smears postoperatively.

Pap smear screening can be stopped between the ages of 65 or 70, depending on the source of the guidelines: ACOG recommends cessation between 65 and 70, and the ASCCP/ACS/USPSTF draft guidelines recommend cessation of Pap testing by age 70. Termination of Pap smear screening also requires that women meet the exclusion criteria noted above—that at least 20 years have passed since a moderate or severe cervical dysplasia, and no significant immunosuppression. Importantly, while the peak incidence of cervical cancer among Caucasian women is in the 40s, it is in the 70s for Hispanic and Asian women, and increases throughout the lifespan for African American women. Therefore, it is important that prior history and screening be taken into account prior to discontinuing Pap smears (40).

Women often have some anxiety about stopping Pap smears, as they may fear that a cancer will be missed, or that their physicians are "abandoning" important screening practices simply because they are "too old." It is helpful to explain that the Pap smear screens only for cervical cancer, and that they will still have annual gynecologic exams to screen for ovarian cancer and other pathology.

7. HPV screening strategies

Screening tests for HPV have been available since 1999. Tests exist for both low risk and high risk HPV; however, since low risk HPV is not associated with carciongenesis, there are currently no clinical indications for low risk HPV testing. Some authors have even called for the low risk test to be removed from the market, as it does not appear to add any clinically useful information, and may contribute to confusion among clinicians about how and when to screen for HPV (44, 45). For high risk HPV subtypes, there are three currently available and FDA-approved tests; the best studied of these is Hybrid Capture, and further data are needed to assess the reliability of newer tests (46).

7.1 Reflex HPV testing for ASC-US Paps

Clinically, several strategies for using HPV tests have been employed. The first and most prevalent use of the HPV test is for the evaluation of a non-diagnostic Pap smear. Approximately 4% of Pap smears will result in a reading of "atypical squamous cells of undetermined significance," or ASC-US (47). These Paps may represent a wide spectrum of problems: non-specific inflammation, dysplasia of any severity, cervical cancer, or simply artifact. Further evaluation is therefore warranted; in 20-60% of women with an ASC-US Pap smear, dysplasia is present. The American Society for Colposcopy and Cervical Pathology (ASCCP) offers three management strategies: a repeat Pap smear in six months,

an immediate colposcopic examination of the cervix, or HPV testing. If an HPV test is performed and is negative, the Pap is considered normal, and the woman can simply have a Pap in one year. If HPV testing is positive, then the suspicion for dysplasia is higher and colposcopy is recommended (48). Thus in the setting of ASC-US, a negative HPV test will reassure those women at low risk for dysplasia and allow them to avoid unnecessary procedures, and a positive HPV test will ensure that women at higher risk for dysplasia are rapidly evaluated. For clinicians using liquid-based cytology, the HPV test can be done on the same sample as the Pap smear, thus obviating the need for the patient to return for a second exam if ASC-US is found.

7.2 Automatic HPV testing

The other testing strategy is "automatic" HPV testing (rather than reflexively in response to the cytologic result), and is appropriate for women over the age of 30. It is important that women under 30 years of age not undergo routine or automatic HPV screening, as the prevalence of HPV among younger women is very high, and most of these infections are transient and without consequence. Among women over 30, however, transient HPV infections are less common, and the HPV test has a higher positive predictive value for cervical dysplasia (48).

When a woman over 30 has a cytologically normal Pap smear and a negative high risk HPV test, she is considered very low risk for cervical dysplasia and cancer, and should thereafter receive Pap smears *only every three years* (40, 48). Even if a woman acquires an HPV infection during that three year interval, the long incubation time between HPV acquisition and development of significant dysplasia means that her next Pap smear should still detect any new dysplasia in its early stages.

When a woman over 30 has a cytologically normal Pap smear and a positive high risk HPV test, current guidelines recommend repeating both tests in 12 months, as it is only *persistent* HPV infection that leads to dysplasia. If at 12 months the HPV test is persistently positive, or if a cytologic abnormality has developed in that interval, then colposcopy is recommended (48).

8. HPV vaccination

There are currently two commercially available prophylactic vaccines against HPV: a quadrivalent vaccine against strains 6, 11, 16, and 18, and a bivalent vaccine against 16 and 18. Neither vaccine has been studied long enough nor in a large enough number of women to demonstrate a reduction in cervical cancer among vaccines. However, both vaccines have demonstrated excellent immunogenicity against the targeted HPV strains, and have shown efficacy at reducing the surrogate endpoints of grade 2 and grade 3 cervical dysplasia (49-51). It is anticipated that high uptake of the vaccine will reduce the number of women requiring colposcopy and subsequent extirpative procedures, and ultimately reduce cervical cancer rates. However, several caveats must be added.

First, as vaccination protects against only two oncogenic strains, women remain vulnerable to other (non-vaccine) HPV strains, and therefore remain at some risk for cervical dysplasia and cancer. Both vaccines induce some cross-protection against non-vaccine strains, though this is far from perfect. Therefore, vaccinated women should continue to undergo Pap

smears at the interval appropriate for their age and health status—the vaccine does not abrogate the need for Pap smears (40).

Second, availability and uptake of the vaccine has thus far been low for a variety of reasons. At present, approximately 37% of eligible girls in the United States have been vaccinated against HPV (52). There have been multiple barriers to its widespread adoption. These include parental uncertainty about the importance and timing of vaccinating young girls for a sexually transmitted disease, expense of the vaccine series, and even political posturing over the vaccine, to name a few. With widespread adoption, vaccination against HPV 16 and 18 has the potential to eliminate up to two thirds of cervical cancer worldwide (53). The highest burden of HPV disease and cervical cancer clearly lies in developing nations without easy access to cervical cancer screening. At present, the cost of the vaccine is such that it is not available to the populations most in need.

9. Barriers to adoption of evidence-based Pap smear screening

While the current Pap smear screening guidelines have been widely publicized and received considerable attention in the lay press when released, there remains ongoing evidence of Pap smear over-use by clinicians (44, 45, 54). There are a number of barriers to physician compliance with evidence-based treatment protocols. These include lack of awareness of the guidelines, lack of "buy-in" to the new recommendations, and inertia. In addition, patient expectations for an annual Pap smear may drive some Pap overuse, as it may be easier to accede to the patient's request than to spend limited visit time explaining HPV and the rationale for the new screening intervals. However, Pap smears performed too frequently or too early and HPV tests performed at inappropriate ages or intervals represent a significant cost to the health care system. Furthermore, there is the potential for patient harm when Pap smears are not performed according to current standards. For example, the diagnosis of HPV or a low grade dysplasia in an 18 year old woman may cause her real emotional distress, may result in her subjection to additional procedures such as colposcopies and biopsies, and possibly extirpative procedures. However, the 18 year old is likely to simply clear her HPV infection without intervention. By age 21, when her first Pap smear is due, one of two things will occur—she will have cleared her HPV, and her Pap smear will be normal, or she will have persistent dysplasia, in which case she merits further evaluation. The probability that she will have a cervical cancer is, as noted above, vanishingly small (41).

10. Areas of controversy and uncertainty

10.1 HPV triage: molecular screening for cervical cancer

As demonstrated in a large international study, the prevalence of HPV among documented cervical cancers was over 99%, which represents the largest attributable fraction ever identified for a cause of cancer (55). Therefore, significant interest exists in utilizing HPV testing as a primary screening modality. Several large clinical studies have been conducted to evaluate the efficacy of primary HPV screening and/or cotesting with conventional cytology. The Canadian Cervical Cancer Screening Trial evaluated the test characteristics of HPV testing with conventional cytology in 10, 154 women aged 30-69 who underwent both tests. Consistent with prior studies, the sensitivity of HPV testing for the detection of CIN 2

or greater was significantly higher than that of conventional cytology (96.4% versus 55.4%) and the specificity was lower (94.1% versus 96.8%) (27, 56, 57).

A population-based screening study in Amsterdam randomly assigned approximately 17,000 women to either cytology/HPV co-testing or cytology alone at an initial screen. These women were then followed with cytology/HPV co-testing at 5 years (the standard screening interval in the Netherlands). Results of CIN 3 or worse were detected in 70% more women in the group undergoing cytology/HPV co-testing at initial screening, and women in this group were less likely to have CIN3 or worse detected at the five year follow-up screening test. Overall, the number of cases of CIN3 lesions or cancers did not differ between trial arms, suggesting that initial co-testing may detect significant lesions earlier but not any more effectively than conventional cytologic screening (58). Similar results were obtained in a large study conducted in England (59).

A recent randomized controlled trial from Italy that evaluated conventional cytology compared with HPV DNA testing in over 47,000 women provides additional information regarding the efficacy of HPV screening as a primary modality (60). In this study, initial screening with HPV DNA testing reduced the number of invasive cervical cancers discovered at a second round of screening (0 cases with HPV screening, 9 cases with conventional cytology). Additionally, women screened with HPV testing were noted to have an excess number of cases of CIN 2 or greater over the two rounds of screening. Therefore, this study represents the first evidence that primary screening with HPV testing decreases the incidence of cervical cancer with earlier detection. However, HPV testing also leads to the overdiagnosis of women with CIN 2 or worse lesions that would have spontaneously regressed without treatment.

Lastly, a long-term prospective cohort study of over 330,000 women in a Northern California health-maintenance organization has provided interesting new data on the safety and efficacy of cytology/HPV cotesting. This study demonstrated that patients with an initial negative HPV test demonstrated an extremely low risk of CIN3 or worse over the subsequent 5 years. The risk was practically equal for those with negative and ASCUS cytologies and a negative initial HPV test. Notably, the cumulative 5-year risk of cancer was lower in those with negative HPV tests compared with negative cytology at the initial screen (3.8 per 100,000 compared with 7.5 per 100,000). The authors concluded that a single negative HPV test is sufficiently reassuring against a 5-year risk of cancer. They also advocated for a triage strategy of primary HPV testing with positive results undergoing triage by cytology (54).

While findings from these (and many other) studies vary in magnitude, consistent observations are noteworthy. Compared with cytology, HPV testing offers a highly reproducible, objective outcome that is easily monitored. Compared with cytology alone, HPV testing is more sensitive, less specific, and has a higher negative predictive value (27, 56, 57). The lower sensitivity relative to conventional cytology is significant in that with primary HPV screening, significantly more women would be recommended for unnecessary colposcopies for transient HPV infections, which would consume substantial health care resources. This phenomenon is particularly true for women under age 30, who have the highest incidence of HPV infection and the lowest rates of cervical cancer. The addition of HPV testing to conventional cytology may result in the earlier diagnosis of high grade lesions or cancer and may reduce the incidence of caner (evidence from one clinical trial),

however a mortality benefit has not been demonstrated to date. Thus, additional study regarding the optimal screening strategy is required.

10.2 Visual inspection with acetic acid and "Screen and Treat" programs

Historically, visual inspection of the cervix without magnification was the initial screening test for cervical cancer. Introduced by Schiller in the 1930s, the test was initially performed by applying Lugol's iodine to the cervix (61). The test was rapidly replaced by Pap testing, which demonstrated improved specificity. However, visual inspection of the cervix, after the application of either acetic acid or Lugol's solution, remains a mainstay of cervical cancer screening in resource-poor settings given that the technique requires little equipment, provides rapid results, and is economical.

A substantial body of literature exists supporting the efficacy of visual inspection techniques and "screen and treat" protocols. Regarding test characteristics, observational studies have evaluated the sensitivity and specificity of visual inspection, which were noted to be 79% and 85% respectively in a meta-analysis of 11 of the higher quality studies (62). The efficacy of visual inspection as a part of "screen and treat" programs has also been evaluated in a number of studies. A large randomized controlled trial in India that evaluated over 80,000 women assigned to either triage with visual inspection followed by cryotherapy or excision versus standard therapy (health education). The visual inspection protocol decreased cervical cancer incidence and mortality (63). Additionally, a large randomized trial from South Africa evaluated the efficacy of two distinct screen and treat protocols in 6500 previously unscreened women. All women in the trial were screened with visual inspection, HPV testing, and cytology and were then randomized to one of three treatment arms: cryotherapy for positive HPV test, cryotherapy for positive visual inspection, or delayed evaluation (follow-up at 6 months). At the 6 and 12 month follow-up colposcopic evaluations, significantly fewer women were noted to have CIN 2 or worse in the HPV and visual inspections groups compared with conventional cytology (64).

Therefore, while conventional screening programs remain the backbone of cervical cancer prevention, visual inspection and screen and treat protocols provide options for women in low-resource settings where screening programs remain unavailable. These protocols provide opportunities for efficient, safe, and effective treatment of women and eliminate any potential problems related to communication barriers and non-compliance with follow-up. Additional research and resources must be directed toward the evaluation and implementation of effective screening and treatment protocols in low-resource settings.

10.3 Conventional Pap screening versus liquid-based cytology

With "conventional" Pap screening, cells obtained from the cervix are transferred directly to a glass slide with fixation by either ethyl alcohol or other spray fixative. Liquid-based cytology refers to the technology whereby cervical cells are suspended in a liquid transport medium and then displayed on a glass slide in the laboratory. Liquid-based cytology improves specimen adequacy by minimizing artifact, such as inflammation, non-cellular debris, and epithelial cell clumping, which may obscure interpretation of the smear. However, while the uniform cell layer from liquid-based cytology allows for easier interpretation, pathologists and cytotechnologists cannot use the additional information

provided by background inflammation as clues facilitating diagnosis. In addition, large systematic review challenged the clinical relevance of this difference in adequacy by failing to discover a difference in the number of unsatisfactory slides (65). One significant advantage conferred by liquid-based cytology is the ability to collect reflex HPV testing, which otherwise must be obtained by a separate sample in systems using conventional cytology.

At the time liquid-based cytology was developed, the test was marketed as a more sensitive screening test than conventional cytology which was supported by early studies with clear methodological inadequacies (66-69). Recent studies have challenged this notion, and to date, the question remains largely unanswered (20, 70, 71). A systematic review of 56 published studies that included over 1 million slides recently addressed the current literature on this subject (19). Regarding study design, no studies were noted to be "ideal" but five were considered to be of high-quality. The authors concluded that liquid-based cytology offered no improvement over conventional cytology for the detection of high-grade lesions. Other systematic and independent reviews have reported similar findings (18, 72). Observational data suggest that liquid-based samples may improve the detection of glandular lesions (73-75).

Arguably, the liquid-based Pap screening test is not a "better" test than conventional cytology. However, despite the increased cost, the liquid-based screen offers advantages that will maintain its use in developed countries, particularly the United States. In the 2006 screening guidelines, the American Society for Colposcopy and Cervical Pathology endorses reflex HPV testing as the preferred triage strategy for an ASCUS Pap result, which is supported by data from a large, well-designed clinical trial (37, 76). Therefore, given the ease of HPV testing with liquid-based samples and the current available infrastructure, the return of conventional cytology to the US is unlikely. However, should primary HPV screening with reflex cytology for positive results be adopted in the future, liquid based screening may become a less cost effective strategy given that the number of samples will decline. Importantly, the aforementioned studies support the use of conventional cytology as a safe, effective, and cost-effective screening strategy in settings with limited resources.

11. Conclusions

- The Pap smear is the single most successful cancer screening tool in modern medicine.
- Cervical cancer is due to persistent infection with high-risk, oncogenic HPV strains.
- Even in women with documented high-grade dysplasia (CIN 2 or greater), a long premalignant window exists which allows for purposeful intervention and prevention of progression to malignancy.
- As a result, newer screening recommendations have decreased screening intervals to maximize the benefit of screening and decrease unnecessary interventions
- As our understanding of HPV increases, Pap smear screening intervals continue to decline and triage strategies may change. It is imperative that practitioners remain informed of evidence-based guidelines.
- Despite the availability of screening and preventative strategies, the majority of the cervical cancer disease burden is in the developing world. Inequalities in the availability of screening are a substantial public health challenge.

- Universal vaccination against HPV has the potential to substantially reduce the cervical cancer disease burden worldwide, however cost and other barrier currently limited the widespread adoption of this strategy.

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Evidence Based Medicine - Closer to Patients or Scientists?

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