TESTING FOR CERVICAL CANCER – AN UPDATE

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Executive Summary *Screening for cervical cancer consists of sampling cervical cytology and/or testing for oncogenic human papilloma virus (HPV). Over time results can be complex due to the clearing of disease, treatment and/or reinfection. The 5-year risk can be predicted based on cytology findings and HPV testing. Most cervical cancers develop in women who have never been screened or who have not been screened in the 5 years before diagnosis.*

A 44-year-old female applied for life insurance. Four years prior to the application, she had a Pap test that showed atypical squamous cells of undetermined significance (ASC-US). Colposcopy and biopsies were done and were negative for premalignant or malignant cells.

She also tested positive for human papilloma virus (HPV). Three years prior to the application, her Pap test was negative. Two years prior to the application, the Pap test showed low-grade squamous intraepithelial lesion (LSIL) on cytology. Just under 1 year prior to application, her Pap test was again negative, and testing for HPV was negative for types 16 and 18, but positive for HPV mRNA (messenger RNA). Yearly follow-up was planned but not completed at the time of application.

What is the significance of abnormal cervical cytology and a positive test for human papilloma virus (HPV)?

In 2015, 12,845 women were diagnosed with cervical cancer in the US with 4,175 reported deaths. The lifetime risk of being diagnosed with cervical cancer was 0.62 %, and the number of deaths was 2.3 per 100,000 women per year.[1,2]

There has been a dramatic decrease in risk (up to 75%) over the past 50 years, primarily due to improved screening and earlier treatment. The annual age-adjusted death rate due to cervical cancer has fallen more than 50% from 1975 to 2014 in the US. Future expectations are that HPV vaccination programs will further reduce the incidence of disease. Australia has high rates of HPV vaccination and has already seen an approximately 40% reduction in the incidence of high-grade dysplasia on Pap tests.

From HPV infection to cervical cancer

The natural history of HPV leading to cervical cancer starts when a woman becomes infected with oncogenic HPV. In the US this often happens between ages 20 and 30. Most young women will clear the HPV infection in 8 to 24 months. However, if the infection with oncogenic strains becomes chronic, there is typically a lag time of 10-15 years before cervical cancer develops.

Cervical cancer is often preceded by the development of premalignant squamous lesions called cervical intraepithelial neoplasia (CIN). Previous terminology had used CIN to describe findings in cytology, but currently CIN refers to histologic (from a biopsy) findings. CIN 1 is considered low risk and often regresses spontaneously. High-grade CIN (CIN 2 or 3) typically precedes invasive cervical cancer by 8-13 years if cancer is going to develop.

Screening for cervical cancer consists of Pap tests and testing for oncogenic types of HPV.

Pap testing

Dr. George Papanicolaou is credited with developing the Pap test. His initial publication was in 1928, but his landmark book, *Diagnosis of Uterine Cancer by the Vaginal Smear*, was published in 1943.[3] In the Pap test, direct collection of cells from the cervix is done in one of two ways. Samples are transferred from a

spatula or brush to a slide and fixed, or after collection, they are suspended in a liquid transfer medium. Some liquid Pap test systems also allow for testing for HPV and sexually transmitted disease.

In the US the American College of Obstetrics and Gynecology suggests screening of asymptomatic, immunocompetent women beginning at age 21 with a Pap test. If testing remains normal, then between ages 21 and 30 they can be screened with a Pap test every 3 years.

Screening for pathologic strains of human papilloma virus (HPV) (also called high-risk strains or hrHPV) can also be considered starting at age 25 (since most young women clear the virus, other screening guidelines do not recommend starting HPV testing until age 30). For ages 30 to 65, either co-testing with Pap and HPV every 5 years, testing for hrHPV alone every 5 years, or Pap testing every 3 years can be considered.

If testing has been negative, depending on risk factors, consideration can be given to discontinue screening at age 65. There are also recommendations to discontinue screening in women who have had hysterectomy or removal of the cervix and did not have a history of cervical cancer or high-grade precancerous cervical lesions.

The cells captured during the Pap test are examined for changes of precancerous or cancerous lesions. An adequate specimen will have 8,000-12,000 squamous cells, while a liquid preparation must have 5,000 or more. When a specimen is determined to be inadequate for a variety of reasons, but negative for an intraepithelial lesion or malignancy, follow-up is often determined by positivity for oncogenic HPV types. If oncogenic HPV types are present, earlier repeat testing is pursued but, if absent, routine schedule screening is often resumed.

Approximately one-half of women diagnosed with invasive cervical cancer have never had a Pap test. An additional 10% have not had a Pap test within 5 years prior to the diagnosis.

The Pap test report should indicate if the specimen is adequate among other things. If adequate, it should also indicate if there are squamous cell abnormalities. There could be non-neoplastic changes, such as squamous metaplasia, keratotic changes, tubal metaplasia, atrophy or pregnancy-associated changes.

One large study in the US found 96% of Pap tests to be negative. Significant epithelial cell abnormalities found on Pap tests are noted in Table 1. By far the most common abnormality is ASC-US.

Glandular cell abnormalities are found more commonly in women age 40 and older. Due to the higher likelihood of premalignant or malignant neoplasia, recommendations are that they be evaluated with tissue sampling. Detailed discussion of glandular cell abnormalities is beyond the scope of this case review.

Table 1: Significant epithelial cell abnormalities

Squamous cell		
Terminology	**Description**	**Frequency**
ASC-US	Atypical squamous cells of undetermined significance	2.8%
ASC-H	Atypical squamous cells, cannot exclude HSIL	0.17%
LSIL	Low-grade squamous intraepithelial lesion	0.97%
HSIL	High-grade squamous intraepithelial lesion	0.21%
Squamous Cell carcinoma	Squamous cell carcinoma	0.0045%
Glandular cell		
AGC	Atypical Glandular Cells	0.21%
	Atypical Glandular Cells – favor neoplastic	
AIS	Endocervical adenocarcinoma in situ	
	Adenocarcinoma	

HPV, Pap and cervical cancer

While squamous cell abnormalities found on Pap tests can be considered alone, the risk can also be based on the combination of cytology and HPV status.

Currently, about 15 types of HPV are thought to be carcinogenic or high risk for causing cervical cancer (Table 2). HPV can be detected in 99.7% of cervical cancers.

Many clinics find the most effective method of screening for cervical cancer is a protocol called reflex HPV testing. A specimen is collected, and if there is abnormal cytology, then HPV testing is performed on the specimen.

Studies on very large groups of women have provided statistics relating cervical cytology and HPV results to the 5-year risk of developing premalignant or malignant disease (Table 3).[4,5,6,7]

Table 2: HPV types and incidence of cervical cancer[8]

HPV Type	Percentage of Cervical Cancer Caused
16	50%
18	20%
31, 33, 45, 52, 58	19%
35, 39, 51, 56, 59, 68, 69, 73, 82	also classified as high risk

Table 3: 5-year risk of premalignant (CIN 3+) or malignant cervical disease

Age 21-24			
Cytology Result	**Oncogenic HPV**	**CIN 3+**	**Cervical Cancer**
ASC-US	Not Done	3.0%	0.032%
	Positive	4.4%	0.055%
	Negative	0.57%	No cases identified
LSIL	Not Done	3.0%	No cases Identified
ASC-H	Not Done	16%	No cases identified
Age 25-29			
Cytology Result	**Oncogenic HPV**	**CIN 3+**	**Cervical Cancer**
ASC-US	Not Done	3.9%	0.12%
	Positive	7.1%	0.16%
	Negative	0.59%	0.018%
LSIL	Not Done	5.0%	No cases identified
ASC-H	Not Done	24%	1.5%
Age 30-64			
Cytology Result	**Oncogenic HPV**	**CIN 3+**	**Cervical Cancer**
Negative		0.26%	0.025%
ASC-US	Not Done	2.6%	0.18%
	Positive	6.8%	0.41%
	Negative	0.43%	
LSIL	Not Done	5.2%	0.16%
	Positive	6.1%	
	Negative	2.0%	
ASC-H	Not Done	18%	2.6%
HSIL	Not Done	47%	7.3%
Atypical Glandular Cells	Not Done	8.5%	2.7%
Squamous Cell Cancer	Not Done	84%	68%

Table 4: 5-year risk of developing cervical lesion of CIN 3 or worse

Five-year risk of developing CIN 3 or worse	Evaluation suggested*
>5%	Colposcopy
2-5%	Repeat Test 6-12 months
0.1-2%	Repeat Test 3 years
<0.1%	Return to routine screening

**Individual actions can be altered by symptoms, pregnancy, reproductive and other considerations.*

Subsequent evaluations are based on the 5-year risk of developing cervical lesions of CIN 3 or worse (Table 4).

Evaluation and follow-up strategies can then be broadly defined based on age, Pap and HPV findings (as illustrated in Table 4). These strategies can become very complex due to serial testing with variation in findings. Symptoms and other risk factors may also influence the choice of evaluation. Other risk factors for invasive cervical cancer reflect an increased likelihood of high-risk HPV infection or, in the case of immunosuppression, difficulty in clearing the virus.[9]

Returning to the case

The dynamic nature of serial Pap testing makes assessing the risk challenging. HPV infection is thought to affect up to three-quarters of sexually active adults in the US by age 50.

Given the relatively low percentage that ultimately develop invasive cervical cancer, the odds of doing so are small. Individuals usually clear the HPV infection, it can become dormant for long periods, and individuals may be infected or re-infected by different types of HPV. One may question if a normal Pap test following an abnormal one is due to regression or variation in sampling.

The history of abnormal cytology and the evidence of ongoing HPV infection put this case at slightly higher risk, which is mitigated by the conscientious follow-up for this treatable condition. Overall there would appear to be minimal excess mortality risk.

Notes

1. https://nccd.cdc.gov/uscs/. United States Cancer Statistics, last accessed August 2018.
2. https://seer.cancer.gov/statistics/summaries.html. National Cancer Institute Surveillance, Epidemiology, and End Results (SEER) Program, last accessed August 2018.
3. Yong S, et al. "George Papanicolaou (1883–1962): Discoverer of the Pap smear." *Singapore Med J*. 2015 Oct; 56(10): 586–587.
4. Katki H, et al. "Benchmarking CIN 3+ risk as the basis for incorporating HPV and Pap cotesting into cervical screening and management guidelines." *J Low Genit Tract Dis*. 2013;17(5 Suppl 1):S28.
5. Katki HA, et al. "Five-year risks of CIN 3+ and cervical cancer among women with HPV testing of ASC-US Pap results." *J Low Genit Tract Dis* 2013; 17:S36.
6. Katki HA, et al. "Five-year risks of CIN 2+ and CIN 3+ among women with HPV-positive and HPV-negative LSIL Pap results." *J Low Genit Tract Dis* 2013; 17:S43.
7. Katki HA, et al. "Five-year risks of CIN 3+ and cervical cancer among women with HPV-positive and HPV-negative high-grade Pap results." *J Low Genit Tract Dis* 2013; 17:S50.
8. UpToDate, last accessed August 2018.
9. "Screening for Cervical Cancer: US Preventative Services Task Force Recommendation Statement." *JAMA*. 2018;320(7):674-686.

About the Author

Richard Braun, MD, has been in the industry for over 30 years, starting at Life of Virginia and later moving to Lincoln Re. He was Medical Director for ExamOne before joining Generali USA Life Re, which was acquired by SCOR Global Life. He is a past President of the American Academy of Insurance Medicine and a past Chair of the ACLI Medical Section. He has written and spoken on mortality and underwriting topics on numerous occasions. He is board-certified in Internal Medicine and Insurance Medicine, and he currently serves as Vice President and Chief Medical Officer for SCOR Global Life Americas.