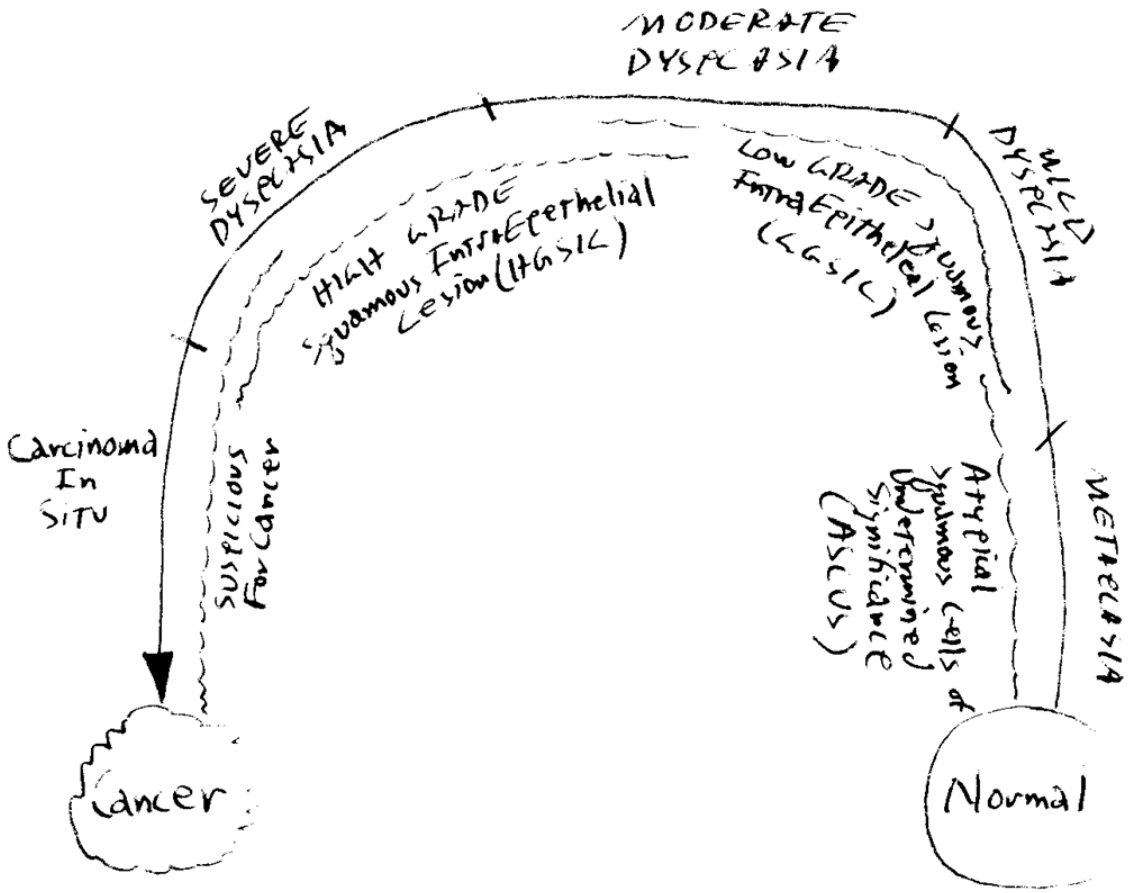
ABNORMAL PAP

Abnormalities of exfoliative cervical cytology are discussed here. The Bethesda Classification System, developed in 2002, is used commonly to classify abnormal Pap smears. Both epithelial and glandular cells can be seen on Pap Smears. Most abnormalities relate to epithelial cells.

Epithelial Cells

Transit time from a normal epithelial cell to a cancer cell is often described as five to seven years. A normal cell goes through various changes on the way to cancer. These stages include metaplasia, dysplasia, and carcinoma in situ followed by invasive cancer. There are three stages of dysplasia; mild, moderate, and severe.

Pap smears are read as within normal limits or abnormal. If abnormalities are noted they are often classified as follows: chronic inflammatory changes, ASCUS (atypical squamous cells of undetermined significance), low-grade squamous intraepithelial lesion (LGSIL), high-grade squamous intraepithelial lesion (HGSIL), or cancer. The diagram below illustrates these progressive changes.



The relationship between high risk human papillomavirus (HPV) and the development of cervical cancer has become clear over the last decade. Relationship between number of sexual partners and the likelihood of cervical cancer has always historically suggested a potential infective agent in the pathogenesis of cervical cancer. The high-risk HPV subtypes are now well known to be associated with the development of cervical cancer.

The carriage rate for HPV in the young sexually active female population in most publications is stated to be between 20% and 30%.

Abnormal Pap requires further evaluation of the cervix through colposcopy and pathologic scrutiny of colposcopically directed biopsies.

Recognizing this new information ACOG developed new guidelines largely encompassed in Practice Bulletin Number 99, from 2008 and reaffirmed in 2010. Since 2006 ACOG has recognized differences in management of abnormal cervical cytology in women based on three age ranges: adolescents (less than 21 years of age), young women (less than 30) and older women (greater than 30).

First, there is a very high prevalence of HPV infection / carriage in young women. Seventy-four percent (74%) of the estimated six million new cases of HPV every year occur in women 15 – 24 years of age. HPV positivity is much more prevalent in women aged 18 -22 years (71%0 versus those older than 29 years (31%). According to ACOG, "it is important to avoid aggressive management of benign lesions in adolescents because most CIN I (70%) and CIN II (50%) regress."

Colposcopy and directed biopsy remains the mainstay of initial evaluation of abnormal PAP smears. In young women benign biopsies with Positive High Risk HPV, CIN I and CIN II are followed with PAP at six and twelve months or with High Risk HPV DNA testing at twelve months with repeat colposcopy and biopsy as indicated by results. CIN III and Carcinoma In Situ (CIS) require ablative or excisional therapy. In older women CIN II and CIN III mandate ablative or excisional therapy.

The likelihood of re-infection is discussed particularly in this light, because approximately 20% to 30% of young woman are known to have HPV it is theorized that at least the same percentage of men harbor the HPV infection. Further, because men do not present to a physician on an annual basis for STD testing and penile cytology, it is unclear what the true carriage rate in the young male population is. But, because the carriage rate is expected to be at least as high as it is in the young female population the likelihood of a woman being re-infected with HPV after previous treatment is between one in three and one in five per new sexual partner. This exceedingly high likelihood of re-infection also speaks against repetitive treatment of the cervix through surgical means.

Immunization against HPV is now possible—Gardasil from Merk is a Quadravalent vaccine for HPV subtypes 6, 11, 16 and 18. Types 16 and 18 together are responsible for 70% of invasive cases of cervical cancer. Types 6 and 11 account for 90% of cases of genital warts. Gardasil is indicated for women from 9 – 26 years of age. Total of three doses are required: initial, two months after first dose and six months after first dose. Just because a woman has a single positive HPV subtype does not disqualify her from Gardasil candidacy. Merk provides brochures and other information on Gardasil. On the Internet, go to www.Gardasil.com to learn more.

Recent multi-center, multi-national studies including Future I and Future II published in NEJM in 2007 confirmed efficacy of vaccine in preventing high grade SIL associated with viral subtypes targeted by Gardasil with 98 to 100% prevented.

Compliance is the key ingredient in expectant management protocols. It is the patient's responsibility to assure that she presents for scheduled, interval, Pap smears and colposcopies. Just because expectant management has become the principal follow-up plan for young women with HPV positivity and dysplastic changes it does not mean that the situation should be ignored and that the patient should not continue follow-up. The patients who do not comply with care and have regular screening examinations continue to be at risk for progression to severe dysplasia and possibly to carcinoma in situ or even invasive cervical cancer.

It is also essential to screen women with HPV infections for other sexually transmitted diseases and follow up those results as indicated.

Table 1.

Management of cervical abnormalities by 5-year risk of CIN 3+

Column 3 orders risks from all cytologies and column 6 orders risks for each cotest. Column 7 gives the current ASCCP management guideline. Managing cotest results by these benchmarked implicit risk thresholds ensures equal management for equal risks.

Cytology result			Cotesting result			Current management based on cytology only (7)
Cytologic finding (1)	Frequency (2)	5-year risk of CIN 3+ (3)	HPV/Cytology (4)	Frequency (5)	5-year risk of CIN 3+ (6)	
SCC	0.01%	83%	HPV+/HSIL	0.20%	50%	Immediate colposcopy
HSIL	0.20%	48%	HPV+/AGC	0.05%	34%	
			HPV–/HSIL	0.01%	29%	
			HPV+/ASC-H	0.12%	25%	
ASC-H	0.17%	18%	HPV–/ASC-H	0.05%	3.8%	
AGC	0.21%	8.7%	HPV–/AGC	0.16%	1.1%	
LSIL	0.92%	5.3%	HPV+/ASC-US	1.10%	6.8%	
			HPV+/LSIL	0.77%	6.2%	
ASC-US	2.70%	2.6%	HPV+/Pap–	3.50%	4.5%	Return in 1 year
			HPV–/LSIL	0.18%	2.1%	
Pap–	95.80%	0.26%	HPV–/ASC-US	1.80%	0.45%	Return in 3 years
N/A	N/A	N/A	HPV–/Pap–	92.1%	0.08%	Return in 5 years

Source: Katki HA, 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–S35.

AGC = atypical glandular cells; ASC-H = atypical squamous cells with a likelihood of high-grade cytology; ASC-US = atypical squamous cells of undetermined significance; CIN 3+ = cervical intraepithelial neoplasia grade 3 or higher; HPV = human papillomavirus; HSIL = high-grade squamous intraepithelial lesion; LSIL = low-grade squamous intraepithelial lesion; N/A = not applicable; Pap– = negative Pap test; SCC = squamous cell carcinoma.

Abnormal epithelial cells on the cervix are a reason for concern but not invariably related to development of cancer. Table 1 relates the Pap smear finding with five year development of CIN 3; the risk of progression with most low-grade lesions is low but compliance with follow-up is essential.

Glandular Cells

The second type of cells seen on Pap Smears are glandular cells. Abnormalities of these cells are far less frequently encountered. Divisions include normal and abnormal glandular cells (AGC). Abnormal classifications include atypical glandular cells and adenocarcinoma in situ. AGC can be associated with reactive inflammation or polyps, but can also be related to underlying neoplastic conditions including adenocarcinomas of the cervix, endometrium, ovary and fallopian tube. Studies indicate 9 – 38% of women with AGC have significant abnormalities and 3 – 17% have invasive cancer. [1]

The mere presence of normal glandular cells or endometrial cells on the Pap Smear report suggests abnormalities in postmenopausal women. In these women endometrial evaluation and sampling are required even in the presence of normal epithelial cells. Women over thirty-five or younger women who have abnormal bleeding or other risk factor for neoplastic endometrial lesion also require thorough evaluation.

Workup of abnormal glandular cells involves high-risk HPV assay, colposcopy, endometrial and endocervical samplings, endometrial biopsy in addition to any follow-up for abnormal epithelial cells. [2] Management is based on results.

Cheng reported on population-wide screening data in Taiwan for AGC. [3] In women with AGC their study confirmed a Relative Risk (RR) of 17.85 for cervical cancer, a RR of 5.68 for endometrial cancer and a RR of 2.04 for ovarian cancer. Additionally, at DWC we perform pelvic ultrasound in women at high risk for ovarian cancer.

If glandular cells are reported and the patient is status post hysterectomy (with removal of cervix) or premenopausal no special follow-up is mandated.

References

1. Wright TC, Massad LS, Dunton CJ, Spitzer M, Wilkinson EJ, Solomon D. 2006 American Society for colposcopy and cervical pathology-sponsored consensus conference. 2006 consensus guidelines for the management of women with abnormal cervical cancer screening tests. Am J Obstet Gynecol. 2007;197(4):346-355.
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3. Cheng WF, Chen YL, You SL, et al. Risk of gynecological malignancies in cytologically atypical glandular cells: follow-up study of a nationwide screening population. BJOG. 2011;118(1):34-41.

