ARTICLE TITLE: Current Concepts in the Diagnosis and Pathobiology of Intraepithelial Neoplasia: A Review by Organ System

EDUCATIONAL OBJECTIVES:
1. Describe the terminology used in the diagnosis of intraepithelial neoplasia of several anatomic sites of interest to a diverse group of clinicians.
2. Review the key biological/molecular changes in this heterogeneous group of intraepithelial neoplasms.
3. Discuss the clinical significance of the intraepithelial neoplasms covered in this article.

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Current Concepts in the Diagnosis and Pathobiology of
Intraepithelial Neoplasia: A Review by Organ System

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Abstract: In this report, a team of surgical pathologists has provided a review of intraepithelial neoplasia in a host of (but not all) anatomic sites of interest to colleagues in various medical specialties, namely, uterine cervix, ovary, breast, lung, head and neck, skin, prostate, bladder, pancreas, and esophagus. There is more experience with more readily accessible sites (such as the uterine cervix and skin) than with other anatomic sites, and the lack of uniform terminology, together with divergent biology in various sites, makes it difficult to paint a unifying, relevant portrait. The authors' aim was to provide a framework from which to move forward as we care for patients with such precancerous lesions. CA Cancer J Clin 2016;66:408-436. © 2016 American Cancer Society.

Keywords: carcinoma in situ, dysplasia, intraepithelial neoplasia, precursor, preinvasive neoplasia

Introduction

The concept of precancerous lesions that can be detected and eradicated to prevent cancer is an old one. The prime example in the United States has been the recognition that uterine cervical cancer could be prevented by population-based screening for precursor lesions. As such, every physician hopes for the day when most invasive cancers in most anatomic sites might be prevented with similar interventions. This review, amassed with the collective expertise of pathology colleagues with experience in lesions from a host of anatomic sites, is an attempt to describe the present understanding of such precursor lesions. It is believed that lesions become carcinomas and thereby acquire the capacity to metastasize once they invade the epithelial basement membranes of the organ in question. Of course, in many anatomic sites, carcinomas that have invaded minimally beyond the basement membrane retain a low risk of metastasis and are usually amenable to local removal alone. However, there is international variation in diagnostic criteria (especially in the gastrointestinal tract) for early invasive carcinoma; in fact, there are data suggesting that early carcinomas can produce their own basement membranes, thereby masking their invasiveness under the microscope. Similarly, the terminology for in situ lesions remains inconsistent in various anatomic sites. For instance, the term “hyperplasia” is used at some sites to indicate a nonneoplastic cellular proliferation (eg, usual ductal hyperplasia in the breast) and at others to denote the earliest histologic form of neoplasia (eg, atypical adenomatous hyperplasia [AAH] in the lung). Although there are many issues that stand in the way of exploiting our knowledge of precursor lesions throughout the body, there is also great optimism that rapidly evolving data will allow us to better perform our role as physicians in reducing suffering by preventing cancer. We are unable to cover every anatomic site in this review, but we have attempted to include a sampling of those that are of greatest interest to oncologists, surgeons, primary care physicians, pathologists, and other clinicians and researchers. We have omitted colorectal lesions, as most colleagues have a working understanding of them based on...
large-scale public health efforts directed at removal of adenomatous precursors. Colorectal adenomas have been recently reviewed elsewhere. Overall, the prevention of colorectal carcinomas by endoscopic polypectomy has been a public health success in the United States, even if it remains a work in progress.

**Uterine Cervix**

**Introduction and Terminology**

For virtually all body sites discussed in this review, the term intraepithelial neoplasia is modeled after concepts developed for squamous precancer of the uterine cervix. This portion will be restricted to squamous neoplasia of the uterine cervix; whereas women with severe dysplasia or less were treated more conservatively by conization. In 1956, Koss and Durfee described cells with a cave-like vacuole around an enlarged nucleus, labeling them koilocytes (from the Greek word for cave), and noted the similarity to descriptions of Reagan et al’s mild dysplasia. It took another 20 years for Meisels and Fortin to link koilocytosis with human papillomavirus (HPV) infection. In 1969, Richart brought forth the concept that cervical cancer could arise from a morphologic continuum ranging from mild dysplasia to CIN. This morphologic spectrum led to the term cervical intraepithelial neoplasia (CIN). Mild dysplasia was equated to CIN1, moderate dysplasia was equated to CIN2, and severe dysplasia and CIS were combined into CIN3. Importantly, because all grades of CIN were thought to be on a continuum of risk for cancer, treatment became based on the size and location of the lesion regardless of grade, and hysterectomy was no longer advocated for any grade of CIN except in much rarer clinical circumstances, such as women who were no longer of childbearing age. Between 1980 and 2000, the advent of molecular biology refined our understanding of HPV and cervical carcinogenesis. CIN1/mild dysplasia/koilocytic atypia became defined as both the cytologic and histologic correlate of a productive HPV infection and were proven to be pathologically indistinguishable. These lesions were low grade or low risk for progression, because most regressed, and management was deemed to be observation. In contrast, CIN2/CIN3/CIS and their synonyms were proven to be the morphologic correlate of HPV oncogene-induced cell transformation. These lesions were more likely to persist, progress, and/or become invasive, so they were viewed as high grade or high risk. These biologic concepts greatly influenced the classification of cervical Papanicolaou (Pap) cytology, leading to the Bethesda System, which was introduced in 1988 and revised 3 times, most recently in 2014. Similarly, the massive improvements in our understanding of the biology, epidemiology, and pathologic variability of cervical biopsies led to the adoption of the same conceptual terminology in the 2012 Lower Anogenital Squamous Terminology project (LAST) and, subsequently, by the fourth edition of the World Health Organization (WHO) blue book on gynecologic neoplasia. Thus, low-grade squamous intraepithelial lesion (LSIL) and high-grade SIL (HSIL) are the recommended terminology not only for CIN but for all lower anogenital tract, HPV–associated intraepithelial neoplasias in both men and women.

**Diagnostic Criteria**

Conceptually, an LSIL is the morphologic manifestation of the differentiation-dependent expression of an HPV’s virion production program on host squamous cells. This is characterized by a proliferation of basal-like cells that extend no more than one-third of the way up the epithelial thickness. Mitotic activity is confined to this lower zone; and, for most LSILs, the mitoses are not abnormal. In the upper two-thirds of the epithelium, the cells differentiate and gain cytoplasm; however, nuclear enlargement also occurs, such that the nucleus to cytoplasmic (N:C) ratio remains increased. Nuclei are hyperchromatic, often have nuclear membrane irregularities, and cells frequently develop halo-like vacuoles around the nucleus, which, together with the nuclear abnormalities, is termed koilocytosis or HPV cytopathic effect (Fig. 1). Critically, all SILs have histocytic abnormalities in all layers of the epithelium, but the distinction of LSIL from HSIL is conceptually based on whether one thinks the lesion is the result of a transforming infection by the abnormal expression of the early region viral genes E6 and E7 or not. Morphologically, this translates into whether the pathologist thinks the
lesion is still under “control” of the viral production program as opposed to the proliferating compartment replicating in a less controlled manner and overgrowing the epithelium.

Hence, HSILs include CIN2 and CIN3/CIS. CIN2 has the poorest interobserver reproducibility of any cervical biopsy diagnosis. More than one-half of CIN2 biopsies on follow-up excision have CIN3 as a final diagnosis, in part because of sampling error and in part because of interpretive variability. Hence, CIN2-CIN3 is used by some as synonymous to HSIL rather than trying to split what may be biologically a single entity. No biomarker defines a distinct intermediate state of CIN2, and the current consensus is that CIN2 is a mix of biologic CIN1 (ie, productive infection) and CIN3 (ie, precancer), the true nature of which is confounded by issues of colposcopic biopsy sampling variability and pathologic interpretive variability. These concepts apply equally to both cytology and histology samples. However, in women who want to maintain their fertility, clinicians may request distinction of HSIL (CIN2) from HSIL (CIN3) to allow for the possibility of regression of HSIL (CIN2) under careful clinical follow-up, thereby potentially sparing women of childbearing age the potential complications of cervical excision.

The hallmark of HSIL is cell proliferation. The cells have abnormal nuclei with increased nuclear size, irregular nuclear membranes, and increased N:C ratios accompanied by mitotic figures. There is little or no cytoplasmic differentiation, as the proliferating cell compartment extends up into the middle one-third (HSIL [CIN2]) or the superficial one-third (HSIL [CIN3]) of the epithelium. Mitotic figures are more abundant in all levels of the epithelium (especially the upper layers) than in LSIL, and abnormal mitotic figures are commonly present (Fig. 2). In problematic cases, the careful application of p16 immunolabeling, as outlined by the LAST project, has become well established as an adjunct in distinguishing mimics from true HSIL and as an aid in separating LSIL from HSIL in borderline cases.

Risk Factors
Because >90% of cervical cancers are caused by HPV, it is only logical that >90% of SILs should be HPV associated. Indeed, studies that describe HPV-negative SIL either are descriptions of morphologically misclassified non-SILs or are limited by the technical sensitivity of the HPV testing methods. Greater than 40 HPV types infect the cervix, although from 13 to 15 high-risk (HR) types and from 4 to 6 low-risk (LR) types account for the majority of infections, and most clinically valid HPV tests only test for 13 or 14 HR types. Eighty-five percent of LSILs are caused by HR-HPVs. In HSILs there is a restriction in the spectrum of types, with 50% of HSILs caused by HPV-16 and HPV-18 alone. The detection of HSIL tends to occur up to 2 decades earlier than invasive carcinoma, but epidemiological risk factors are generally similar. Thus, older age, lengthier history of sexual activity, less frequent screening, and perhaps cigarette smoking are risk factors for cancer and HSIL/precancer. While HSIL occurs at an older age than LSIL, there is broad overlap, and it has been demonstrated that HSIL develops within a year or 2 of HPV infection. The cross-sectional prevalence of HSIL in Western screened populations is from 0.5% to 1%. The estimated risk of progression of untreated HSIL to cancer is from 0.5% to 1% per year. Estimates of HSIL regression vary from 30% to 50%, depending on age, lesion size, and HPV type, but are confounded by the potential impact of biopsy, which may be therapeutic in up to 30% of patients.

Molecular Underpinnings
Theoretically, to produce new virions, all HPVs make the histologic equivalent of an LSIL. An LSIL morphologically represents the coordinate expression of an HPV genome in a differentiating squamous epithelium. In contrast, an HSIL can be thought of as a clonal expansion of cells that are driven to proliferate by the abnormal
expression of HPV E6 and E7 in cells still capable of cell division. Most HSILs exhibit aneuploidy, a reflection of genetic instability. HPV DNA integration is more frequent in HSIL compared with LSIL. Chromosomal abnormalities shared more frequently with cancer are present to a greater extent in HSIL than in LSIL and include abnormalities of 1p and 3q. Similarly, methylation patterns vary between LSIL and HSIL/cancer.

Management, Limitations, and Caveats
LSIL is managed conservatively, namely, by observation without treatment, based on an expectation of regression within 2 years. Persistence longer than 2 years is correlated with HSIL risk. HSIL, especially HSIL/CIN3, is treated with ablation, usually by electrosurgical excision that is both diagnostic as well as therapeutic. Currently, the concept of balancing the benefits of screening and treatment with the potential harms of over diagnosis and over treatment fills the literature on the management of CIN.21,22 The 60-year decline in cervical cancer incidence is completely due to the detection of precancer (HSIL) and eradicating it to prevent cancer. Yet, even with all our knowledge, we still treat hundreds of women to prevent one cancer. Thus, there is continued pressure to focus on treating only those women at highest risk. Perfection is not achievable, and balancing the risk of therapy with the risk of allowing invasive cancer to develop is a tension that will always remain while HPV infections plague women. Fortunately, today, we can discuss primary prevention of cervical precancer and cancer through HPV vaccination. A second-generation, 9-valent HPV vaccine capable of preventing greater than 90% of cervical HSIL and cancer was released in 2015.21 Thus, the diagnosis and management of CIN may now be viewed part of a secondary prevention program in populations that take advantage of primary prevention through vaccination.

Ovary
There are many histologic types of primary ovarian carcinomas, and each of these is biologically unique with respect to histologic, immunohistochemical, and molecular features and pathogenesis. High-grade serous carcinoma is the most common ovarian malignancy and thus will be the focus of discussion for this section. Recent research has identified the precursor for this tumor as serous tubal intraepithelial carcinoma (STIC), which originates in the mucosa of the distal (fimbriated) end of the fallopian tube.

Terminology
STIC is the standardized designation for this form of intraepithelial neoplasia.24,25 Lesions related to STIC are serous tubal intraepithelial lesions (STILs) and “p53 signatures” (described below; see Molecular Underpinnings). It should be noted that these latter 2 lesions are not synonymous with STIC, and they are thought to precede the development of STIC as part of its pathogenesis. STIL, which is an atypical mucosal lesion intermediate between p53 signature and STIC, has also been referred to by a variety of other descriptive terms.26 It also should be noted that the term p53 signature should be reserved only for research studies and should not be used in the pathology report.21,22

Diagnostic Criteria
STIC is histologically characterized by significant nuclear atypia (Fig. 3). Several studies; however, have used different criteria for distinguishing STIC, atypical intermediate lesions, p53 signatures, and normal mucosa from one another. Consequently, there are no standardized criteria for these lesions, and the establishment of exact histologic diagnostic criteria for STIC has been difficult, because the morphologic spectrum of STIC is wide, and no 2 STICs appear to be exactly the same because of various degrees of
histologic overlap between STICs. Variability of a diagnosis of STIC exists between pathologists, and several studies have shown that the interobserver agreement among pathologists based only on histologic features is inadequate.

For these reasons and to establish working criteria for standardization between pathologists for routine diagnosis and research, a diagnostic algorithm was developed that combines histologic features with coordinate immunohistochemical expression of p53 and Ki-67 (these markers are used to assess mutant tumor protein 53 [p53] and the proliferation index, respectively). Accordingly, STIC is diagnosed when significant atypia is present in combination with abnormal p53 expression and a high Ki-67 index. Interobserver reproducibility studies using this algorithmic approach have demonstrated that the agreement for STIC between pathologists was improved to a substantial level (from $\kappa = 0.50$ to $\kappa = 0.67$) compared with using only morphologic assessment and that this algorithm can be reproducibly applied.

**Molecular Underpinnings**

Abundant histologic and molecular evidence that has emerged over roughly the last 8 years strongly supports findings that the vast majority of ovarian and peritoneal high-grade serous carcinomas originate in the fallopian tube, specifically from an STIC, and thus implies that these ovarian/peritoneal tumors are metastases. It has been proposed that the p53 signature is the earliest step in the pathogenesis of STIC. The p53 signature consists of short stretches of tubal epithelium composed of cytologically benign, nonciliated (secretory) cells with overexpression of p53 and a low Ki-67 labeling index. However, the exact relation between p53 signatures and STIC is unclear (for additional information regarding the potential relation between the p53 signature and STIC/invasive high-grade serous carcinoma, see Vang et al.).

**Management, Limitations, and Caveats**

STIC may be recognized as an isolated finding in either 1) prophylactic specimens from women with an increased risk of ovarian/tubal carcinoma (ie, BRCA mutation carriers) or 2) routine specimens as part of a gynecologic surgical procedure performed for benign indications in women without a known history of breast/ovarian carcinoma or those not known to be BRCA mutation carriers (ie, sporadic cases). For such patients, the extent to which further clinical evaluation is needed is unclear. Using chemotherapy in this situation has not been preferred, but some patients in the literature have been treated in this fashion. Also, a proportion of patients with STIC as an isolated finding have had positive peritoneal cytology.

A significant limitation to the complete understanding of the natural history of STIC as an isolated finding is the availability of only a few studies with limited numbers of cases and short follow-up. While one study of isolated STIC observed no recurrences (median follow-up, 2.3 years), a subset of patients in other studies subsequently developed recurrences as carcinoma from 3.6 to 4.0 years later. Furthermore, the outcome data on isolated STICs are based on BRCA germline mutation-associated cases. Because BRCA germline mutation-associated ovarian high-grade serous carcinomas have better survival than sporadic cases, it is possible that isolated sporadic STICs may have a greater propensity for progression compared with BRCA germline mutation-associated cases.
Therefore, because 1) STIC is the histologic and immu-
nohistochemical counterpart to endometrial serous intrae-
pithelial carcinoma, 2) the latter can have extrauterine
disease in the absence of myometrial invasion, and
3) STIC is typically located in the fimbriated end of the
fallopian tube with direct access to the peritoneal cavity,
the prognosis for patients with isolated sporadic STIC
should be considered uncertain.

The opportunistic salpingectomy has been recognized as a
potential means of preventing extrauterine high-grade serous
carcinoma for women at average risk in whom the fallopian
tubes have been removed before STIC can develop.32 Thus,
the entire fallopian tubes are removed in women undergoing
pelvic surgery in instances in which an oophorectomy would
not have been performed (eg, tubal ligation and hysterectomy
in premenopausal women). Given that the ideal surgical can-
didate would be relatively young and that the mean age of
women with sporadic STIC is the early 60s, it will likely be
decades before future studies show the actual impact of the
opportunistic salpingectomy on the general population. How-
ever, recent evidence suggests that this surgical procedure will
be beneficial. In a Swedish population-based study in which
women underwent bilateral salpingectomy, the risk for ovar-
ian carcinoma was decreased by 65% (P = .004).33 If addi-
tional large studies with lengthy follow-up can confirm these
findings in women who undergo opportunistic salpingectomy,
then this form of prevention will be of enormous value to
women, because current screening modalities for detecting
ovarian high-grade serous carcinoma have been unsuccessful.

Breast
Introduction and Terminology
Atypical lobular and ductal intraepithelial proliferations of
the breast encompass various morphologic lesions arising in
the breast terminal duct lobular unit that impart an
increased relative risk of developing invasive carcinoma.
Atypical hyperplasia and CIS exist on a morphologic con-
tinuum. The term “lobular neoplasia” (LN) encompasses
atypical lobular hyperplasia (ALH) and lobular CIS
(LCIS), and LCIS is further subdivided into a classical
type or pleomorphic LCIS (PLCIS). Atypical intraductal
proliferations include atypical ductal hyperplasia (ADH)
and ductal CIS (DCIS), and DCIS is further subclassified
by nuclear grade into low grade (LG) (nuclear grade 1),
intermediate grade (IG) (nuclear grade 2), and high grade
(HG) (nuclear grade 3). DCIS was historically classified by
architectural patterns; however, in general, the architectural
pattern is of secondary importance to nuclear grade.

Diagnostic Criteria
LN consists of loosely cohesive cells that involve the breast
lobular acini and terminal ducts by undermining the normal
epithelium by pagetoid spread (Fig. 4),34 a term denoting
spread of individual neoplastic cells within otherwise nor-
mal epithelium without invasion of the basement mem-
brane. ALH and LCIS differ in the extent to which the
atypical cells fill, distend, and distort the breast terminal
duct lobular unit (Fig. 4A and 4B), with LCIS distending
more than one-half of the lobular unit. The cells of ALH
and classical LCIS are morphologically identical and are
typically small with eccentrically located, normochromatic
nuclei, pale cytoplasm, and occasional intracytoplasmic
vacuoles. The cells of PLCIS are dyscohesive but display
nuclear pleomorphism, including increased nuclear size,
hyperchromasia, and prominent nucleoli similar to that
seen in nuclear grade 3 DCIS (Fig. 4C). Necrosis can be
seen in either classical LCIS or PLCIS. The cells of LN
typically display loss of membranous E-cadherin labeling
by immunohistochemistry (Fig. 4D).

LG DCIS consists of a monotonous intraductal epithe-
"lial proliferation of small uniform cells and atypical archi-
tectural patterns, including solid sheets, rigid arcades,
round cribriform spaces, and bulbous micropapillary projec-
tions (Fig. 5).35 The cells and architectural patterns of
ADH are identical to those of LG DCIS, but ADH is dis-
tinguished by smaller size (≤2 mm span) or <2 duct spaces
and an absence of involvement of larger ducts (Fig. 5).35
HG DCIS consists of an intraductal epithelial proliferation
of cytologically malignant cells exhibiting hyperchromatic
nuclei, prominent nucleoli, and abundant mitotic figures
(Fig. 5C). There is no minimum size criterion for defining
HG DCIS. Comedo pattern DCIS is defined by high
nuclear grade, solid architecture, and extensive central
necrosis. IG DCIS contains cells of moderate nuclear
atypia intermediate between LG and HG DCIS, frequently
associated with focal central necrosis. In some cases, IG
DCIS coexists with focal LG DCIS or focal HG DCIS,
suggesting that IG DCIS may be a more “heterogeneous”
entity.

Risk Factors
LN is typically an incidentally discovered lesion at the time of
core-needle biopsy (CNB) performed for a separate clinici-
ally or radiographically detected abnormality, with an
estimated prevalence in otherwise benign biopsies of up to
4%.34 The incidence of ADH and DCIS has increased tre-
mendously in the mammographic era, as they are frequently
associated with calcifications, and DCIS now comprises
approximately 20% of all newly discovered breast carcino-
mas36 (see also cancer.org/acs/groups/content/@editorial/
documents/document/acspc-044552.pdf). The risk factors
for developing DCIS are similar to those for developing
invasive breast carcinoma and include family history as well
as factors related to increased estrogen exposure, such as
high body mass index, nulliparity, late age of first birth, and late menopause.

**Molecular Underpinnings**

There are separate molecular pathways that give rise to LG neoplasia and HG neoplasia in the breast. ALH, classical LCIS, ADH, LG DCIS, and LG invasive carcinomas are parts of the LG neoplastic pathway that display recurrent genomic aberrations, including loss of heterozygosity (LOH) of chromosomes 11q, 16q, and 17 with recurrent gains at 1q. \(^{37}\) LN, like invasive lobular carcinomas, is also molecularly defined by the loss of function in the E-cadherin cell-cell adhesion protein, either by LOH of 16q or mutations in the cadherin 1 type 1 (CDH1) gene located on 16q. This corresponds to the loss of membranous E-cadherin labeling by immunohistochemistry and poor cohesion by histology seen in the majority of LN (Fig. 4D). Lesions in the LG neoplastic pathway are typically estrogen receptor (ER)-positive. This family of lesions often arises in the setting of columnar cell change or multiple micropapillomas. Usual duct hyperplasia is not thought to be part of this pathway.

In contrast, HG DCIS and HG invasive carcinomas are part of the HG neoplastic pathway and rarely show loss of 16q but, instead, show complex karyotypes with aneuploidy and multiple amplifications. \(^{37}\) Interestingly, PLCIS shows loss of 16q and gain of 1q like classical LCIS but also displays increased genomic instability, with the copy number alterations and amplifications more commonly seen in HG DCIS. HG DCIS and PLCIS are more likely to be ER-negative and to overexpress human epidermal growth factor receptor 2 (HER2).

**Management**

Although molecular evidence supports the classification of LN as a nonobligate precursor to invasive carcinoma, LN is managed as a global relative risk factor, as it is frequently multifocal and bilateral. \(^{34}\) Treatment considerations include excisional biopsy, hormone therapy prophylaxis, and rarely bilateral mastectomy. Clinical surveillance, such as yearly mammography and breast examinations, is recommended for women with LN (please see cancer.org/acs/groups/content/@editorial/documents/document/acspc-044552.pdf). LN is most commonly diagnosed as an incidental finding on
breast CNB performed for another reason (eg, palpable mass or radiographic microcalcifications), and the management of patients with classical LN alone on CNB is controversial. PLCIS or LCIS growing in large ducts associated with central necrosis is best managed as per DCIS: ie, with conservative excision.

ADH carries a 4-fold to 5-fold increased risk of developing invasive breast carcinoma, and ADH on CNB is managed by conservative excision. LG and IG DCIS, if left untreated, carry an approximately 25% to 30% risk of developing invasive carcinoma in the ipsilateral breast within 15 years. The risk of recurrence or progression of LG and IG DCIS persists even after 30 years of follow-up, but the risk of recurrence or progression in HG DCIS is highest within 5 years. DCIS on CNB is traditionally managed by lumpectomy with radiation therapy or by mastectomy (please see cancer.org/acs/groups/content/@editorial/documents/document/acspc-044552.pdf). A subset of women with small LG DCIS may be candidates for excision alone without radiation therapy. Sentinel lymph node sampling should be considered in women who have extensive, mass-forming DCIS or DCIS with suspected microinvasive carcinoma on CNB. Immunohistochemical testing for ER may be performed on DCIS after excision, because adjuvant antihormonal therapy like tamoxifen may diminish recurrence.

**Limitations and Caveats**

The distinction between ADH and LG DCIS is made on the basis of size and extent of ductal involvement, which at times can be difficult to assess on CNB because of tissue fragmentation. A conservative approach is recommended on CNB to avoid overdiagnosis of small, limited lesions as DCIS. Although concern for interobserver variability and reproducibility in the classification of intraductal and intralobular proliferations of the breast has received recent press, interobserver concordance can be readily reached with the application of standardized criteria in most cases on excision.

**Lung**

**Introduction and Terminology**

Lung cancer is the leading cause of cancer death in the industrialized world. A dismally low cure rate largely reflects the propensity of lung cancer to present as clinically advanced tumors, when options for effective therapeutic intervention are limited. There is clearly a need to recognize the early changes of lung tumorigenesis in a way that would promote timely and effective therapy. However, unlike the upper respiratory tract, the lower respiratory tract is not readily accessible to visual inspection. Accordingly, epithelial precursor lesions have been recalcitrant to detection and to comprehensive descriptions of their clinical and pathologic features. Recent advances in early stage lung cancer detection strategies now permit better access to these elusive lung epithelial precursor lesions. Low-dose computed tomography for the screening of high-risk patients has improved the discovery of small parenchymal lung lesions in a way that is facilitating a better understanding of early glandular neoplasia of the lung. At the same time, the development of autofluorescence bronchoscopy has improved the sensitivity for detecting squamous epithelial precursor lesions taking origin from the mucosa of the central airways.

**Squamous Dysplasia and Squamous Cell CIS**

Preinvasive squamous bronchial lesions are strongly associated with tobacco exposure. Before the onset of invasion, these premalignant lesions are entirely asymptomatic. The only noninvasive test that enables detection is sputum cytology. The cytologic manifestations of dysplasia occur along a gradation that parallels histologic progression and include increasing variation in nuclear size and shape, nuclear hyperchromasia with nuclear membrane contour irregularities, coarsely granular and irregularly distributed...
chromatin granules, and cytoplasmic keratinization seen as dense cytoplasmic eosinophilia. But even vigilant screening of sputum samples for morphologic evidence of early squamous neoplasia is not effective in curbing mortality rates in at-risk individuals, pointing to the need for more invasive detection methods. The development of bronchoscopic imaging techniques, such as autofluorescence bronchoscopy, has greatly improved the detection of preinvasive central airway lesions over white-light bronchoscopy alone. As the bronchial epithelium progresses from low-grade to high-grade dysplasia, there is a progressive decrease in green autofluorescence relative to red fluorescence, resulting in brown-to-red discolorations of the airway epithelium that signal the presence of premalignant changes.

The histologic changes culminating in invasive squamous cell carcinoma (SCC) occur along a continuum that encompasses basal cell hyperplasia, immature squamous metaplasia, mature squamous metaplasia, dysplasia, and CIS (Fig. 6). Of these, only squamous dysplasia and CIS are recognized in the current classification by the WHO as precursors of SCC. Like squamous precursor lesions of the head and neck, categorical grading is based on the severity of the cytologic and architectural disturbances and on the level at which these alterations extend from the basal cell layer into the upper portions of the epithelium, features similar to those observed in the uterine cervix. In mild dysplasia, for example, the degree of cytologic atypia is mild, and the architectural disarray is confined to the lower one-third of the epithelium. In CIS, the cytologic atypia is severe, and the basilar zone is expanded throughout the epithelium without maturation at the surface. Milder forms of dysplasia must be distinguished from basilar hyperplasia and squamous metaplasia-reactive changes of the airway epithelium in response to chronic irritation. As for high-grade squamous dysplasia and CIS, downward extension within bronchial gland ducts may cause confusion with true stromal invasion (Fig. 7). The distinction between noninvasive and invasive growth may be further confounded in small superficial biopsies when the epithelial-subepithelial interface is not well represented for the histologic evaluation of infiltration.

Although studies attempting to follow the natural history of squamous precursor lesions have tended to be limited by suboptimal access, short follow-up times, and therapeutic intervention, they have suggested the following: 1) most dysplasias, even severe dysplasias, regress spontaneously; 2) the risk of progression to CIS or invasive cancer is higher for severe dysplasia than for metaplasia or mild dysplasia; 3) most CIS progresses to invasive carcinoma; 4) high-grade dysplasia and CIS are markers of cancer development for the entire lung; and 5) most of those lung cancers are SCCs.

Molecular Underpinnings of Squamous Dysplasia and SCC CIS

The histologic progression of SCC of the lung is driven by the sequential accumulation of epigenetic and genetic alterations in the bronchial epithelial cells. When these genetic alterations are because of the effects of tobacco exposure, they tend to be widely distributed throughout the bronchial tree. Some of these alterations, such as LOH at chromosomal loci 3p and 9p21, consistently occur early during the molecular multistage pathogenesis of squamous cell lung carcinoma, even before changes can be appreciated at the light microscopic level. A growing understanding of the nature and timing of these molecular changes may be helpful in developing novel strategies for detecting premalignancy and predicting the likelihood of progression to invasive SCC.
Early Glandular Neoplasia of the Lung

Adenocarcinoma now comprises the most common subtype of lung cancer. It is particularly notorious for eluding early detection by sputum cytology. Adenocarcinomas of the lung tend to arise peripherally, and malignant cells are not shed into the sputum until these tumors have developed into sizeable and frankly invasive cancers. Radiological detection of the earliest stages of glandular neoplasia of the lung requires high-resolution computed tomography scanning. In this context, noninvasive forms of adenocarcinoma are generally seen as small localized areas of pure ground-glass opacity.

Recent refinements in the histologic classification of lung adenocarcinomas now provide greater resolution of the sequential steps of glandular neoplasia of the lung. Several lines of evidence now implicate AAH as an initial morphologic stage in multistep lung tumorigenesis. AAH is a localized (usually 0.5 cm or less) proliferation of mildly to moderately atypical pneumocytes lining the alveolar walls and is usually an incidental histologic finding in lung tissue resected for adenocarcinoma. It is characterized by the proliferation of cuboidal-to-columnar epithelial cells with various degrees of cytologic atypia (Fig. 8A and 8B). These cells line the intact, albeit thickened, alveolar septa. The range of cytologic and architectural atypia falls along a spectrum of increasing severity. Low-grade lesions are characterized by a single layer of round-to-cuboidal cells with low cellular density, small cell size, and minimal variation in nuclear size, shape, and chromaticity. In low-grade lesions, there is minimal thickening of the alveolar septum. With progressive atypia, AAH demonstrates higher cellular density with stratification of the epithelial cells, more significant cytologic atypia, and more extensive fibrosis and thickening of the alveolar septa (Fig. 8C). Because of problems with reproducibility, grading of AAH is not routinely used.

Adenocarcinoma in situ (AIS) (formerly known as bronchioloalveolar carcinoma) is a small (≤3 cm) and localized form of adenocarcinoma in which the neoplastic cells populate preexisting alveolar structures (ie, “lepidic” growth) without microscopic evidence of stromal, vascular, or pleural invasion (Fig. 8D). Like AAH, it is recognized as a noninvasive form of glandular neoplasia but one that exhibits increased size, cellular atypia, and cellularity with more pronounced cellular crowding and even mild stratification. In effect, AIS represents the next step in the continuum toward invasive adenocarcinoma. The precise threshold at which AAH transitions into AIS in not well defined, but
0.5 cm is often used as a size criterion in separating the 2 lesions. Virtually all cases of AIS are of the nonmucinous type, in which the atypical cells represent type II pneumocytes or Clara cells.

Minimally invasive adenocarcinoma is likewise defined as a small (≤3 cm) and localized adenocarcinoma with a predominantly lepidic pattern but one that demonstrates limited areas of invasive growth. Specifically, the extent of invasion does not exceed 0.5 cm in any one focus. Invasion is recognized as infiltration of a myofibroblastic stroma and/or the presence of any architectural growth pattern other than the lepidic pattern (eg, acinar, papillary, or solid). Invasive growth is present, albeit so limited that these carcinomas have been associated with 100% disease-free survival. Currently, there is insufficient evidence in the literature to confirm similar survival rates for AIS and minimally invasive adenocarcinomas that are larger than 3 cm. The term lepidic-predominant adenocarcinoma has been proposed for those adenocarcinomas larger than 3 cm that fall into this ambiguous group.

Molecular Underpinnings of Early Glandular Neoplasia of the Lung

The link between AAH, AIS, and microinvasive adenocarcinoma is strong and compelling: from 5% to 20% of lungs resected for primary adenocarcinomas also harbor AAH, and AAH harbors some of the same genetic and epigenetic alterations found in adenocarcinomas, including Kirsten rat sarcoma viral oncogene homolog (KRAS) mutations, epidermal growth factor receptor (EGFR) mutations, LOH at 9q and 16p, p53 mutations, and epigenetic alterations in the WNT pathway. Certain molecular alterations, such as mutations KRAS, TP53, and EGFR, may be particularly important in triggering malignant transition. The presence of these same mutations in paired sputum and circulating DNA samples opens the door to novel strategies for detecting and tracking the early stages of glandular neoplasia of the lung.

Head and Neck

Introduction and Terminology

Greater than 90% of head and neck cancers are SCCs that arise from the mucosa lining the oral cavity, larynx, pharynx, and sinonasal tract. In the oral cavity and larynx, invasive growth is generally preceded by an asymptomatic but clinically visible phase characterized by white and red patches of the mucosa designated as leukoplakia and erythroplakia, respectively. These terms are purely clinical descriptors, they are not to be used to confer a histologic diagnosis, and their association with true neoplastic changes of the lining epithelium is inconstant. In the oral cavity, the frequency of premalignant or malignant changes in leukoplakia ranges from 15% to 40%. This association is much stronger for erythroplakia, in which the vast majority harbor some degree of dysplasia, and over one-half are associated with an invasive component. An association with premalignant and malignant changes is also strongly influenced by anatomic subsite. Leukoplakia and erythroplakia involving the floor of mouth have the highest risk of harboring epithelial dysplasia, CIS, and even unsuspected invasive SCCs. Assisted visualization of oral dysplasia is being developed along several lines, including toluidine blue staining and autofluorescence, but accurate determination of the presence, severity, and distribution of squamous dysplasia still requires tissue biopsy with histopathologic evaluation.

Epithelial precursor lesions of the head and neck are regarded as genetically altered cells with an increased likelihood of progression to invasive SCC. These genetic alterations are reflected, to various degrees, at the microscopic level. Taken together, the morphologic alterations are encompassed under the traditional term squamous dysplasia. More contemporary terms like squamous intraepithelial neoplasia embrace the concept of sequential histologic progression before invasive tumor growth. In the head and neck, progression through the histologic stages of dysplasia culminating in invasive carcinoma is neither constant nor inevitable. Although the presence of dysplasia indicates increased risk for the development of SCC, only 7% to 36% of oral dysplasias and 8% to 29% of laryngeal dysplasias progress to invasive carcinomas. Generally, the more advanced the degree of dysplasia, the higher the likelihood of developing SCC. Importantly, at least some dysplasias are reversible. For patients who smoke, the potential revocability of premalignancy strongly argues for smoking cessation.

Diagnostic Criteria

The microscopic changes of squamous dysplasia include both architectural and cellular alterations of the surface epithelium. Various systems have been advocated for grading the degree of dysplasia. Three-tiered systems generally recognize mild, moderate, and severe stages of dysplasia. In 4-tiered systems, an effort is often made to separate severe dysplasia from CIS. The same paradigm for grading dysplasias of the female cervix is often used for grading dysplasia in the head and neck, but 3 tiers are often retained. For mild dysplasia, the atypia is confined to the lower one-third of the epithelium (Fig. 9A). In moderate dysplasia, the disturbances extend into the middle one-third of the epithelium (Fig. 9B). In severe dysplasia, the atypia occupies more than two-thirds of the epithelium. CIS is reserved for those lesions that show full-thickness involvement of the surface epithelium without any surface maturation. This distinction between severe dysplasia and CIS may be of no
real consequence, as the presence of surface maturation in the form of keratinization does not appear to lessen the risk of progression to invasive carcinoma. The cellular and architectural changes of dysplasia are not specific and can be encountered as reactive changes related to various stimuli, including irritation and infection (eg, Candida mucositis). Particularly in mild forms of dysplasia in which the atypical features of dysplasia are not fully developed, distinction from a reactive atypia is not very reliable. Although the value of grading squamous dysplasias as a means of predicting subsequent invasion is well recognized, sequential histologic progression through the various stages is less consistent in the head and neck than in the cervix. Indeed, carcinomas can arise from the basal cell layer of a surface epithelium, showing complete maturation with minimal cellular and architectural disturbances.

**Risk Factors**

Tobacco is a primary etiologic agent in head and neck SCC (HNSCC), but growing numbers of head and neck carcinomas are caused by HPV. HPV-related carcinogenesis preferentially targets the specialized lymphoepithelium lining the crypts of the lingual and palatine tonsils. Histologic parameters used to recognize and grade conventional squamous dysplasias are not readily applicable to HPV-related neoplasia of the oropharynx. Indeed, small carcinomas with full malignant potential may arise in small patches of the tonsillar epithelium in the absence of premalignant alterations that characterize smoking-related cancers. Much less commonly, HPV-associated carcinomas may arise in the oral cavity proper. Unlike their counterparts in the oropharynx, these HPV-related oral SCCs are associated with premalignant surface alterations, including a bright eosinophilic parakeratin layer, full-thickness dysplasia, prominent apoptosis, and a distinctive form of nuclear fragmentation resembling mitotic figures (ie, “mitosoid bodies”) (Fig. 10). When these histologic features are well developed, the likelihood of finding high-risk HPV using p16 immunohistochemistry or DNA in situ hybridization is very high.

**Molecular Underpinnings**

At the genetic level, progression through the sequential stages of dysplasia and culminating in invasive carcinoma is driven by the accumulation of genetic alterations. According to the current model of head and neck tumorigenesis, some genetic alterations occur early, even preceding histologic evidence of dysplasia. Indeed, the ability of genetically damaged cells to populate tracts of histologically normal epithelium may account for certain distressing clinical phenomena, such as “field cancerization” (multifocal carcinomas arising in a “condemned mucosa”) and local tumor recurrence after seemingly complete surgical resection with histologically negative margins. These alterations tend to accumulate with histologic progression such that advanced stages of dysplasia harbor a spectrum of alterations that is qualitatively and quantitatively similar to invasive carcinoma. The alterations involve the activation of oncogenes and the inactivation of tumor-suppressor genes in a way that disrupts key signaling pathways regulating DNA stability, cell growth, motility, and stromal interactions. The TP53 and retinoblastoma (Rb) pathways are almost universally disrupted in HNSCCs, indicating the importance of these pathways in head and neck tumorigenesis. Potentially, the presence of specific genetic alterations may be of value in predicting those premalignant lesions that are most likely to progress to invasive carcinoma. LOH of chromosomes 3p, 9p, and 17q3, for example, has been reported to confer significant risk of malignant...
progression of squamous dysplasia and even squamous hyperplasia with dysplastic changes.\textsuperscript{61,62}

In HPV-related HNSCC, abrogation of p53 function is mediated by degradation of the p53 protein by the viral oncoprotein E6. Accordingly, HPV-positive HNSCCs are much less likely to harbor a mutation of the $\text{TP53}$ gene. In a similar manner, the protein encoded by the viral oncoprotein E7 binds and degrades wild-type Rb protein, rendering upstream inactivation of p16$^{\text{INK4A}}$ (Cyclin-Dependent Kinase Inhibitor 2A) unnecessary in HPV-positive HNSCCs. Indeed, intact p16 protein is overexpressed in HPV-related cancers.

Management, Limitations, and Caveats
At this point, close follow-up with biopsies can be offered to patients in whom precursor lesions are detected. However, although immunohistochemical detection of p16 protein can be used to detect these HPV-related cancers, there is currently no equivalent of the cervical Pap test to detect premalignant lesions or assess cancer risk for the oral cavity and oropharynx.

Skin
Introduction and Terminology
Current estimates indicate that up to 20\% of Americans will develop skin cancer, which is the most common type of cancer in the United States.\textsuperscript{63-65} Most cases will be nonmelanoma skin cancers, although the incidence of melanoma is rising. About 2\% of Americans will develop melanoma in their lifetime, resulting in 65\% of all skin cancer deaths.\textsuperscript{66} Preventive measures and early detection of cutaneous neoplasia are the key factors in decreasing the morbidity, mortality, and public health burden of skin cancer.

Cutaneous intraepithelial neoplasia can be divided into 2 main forms—squamous cell CIS (SCCIS) and melanoma in situ (MIS). “ Bowen disease” is a clinical term often used synonymously with SCCIS. Although several histologic variants of SCCIS exist, most are not routinely subclassified in daily practice. The exception is SILs on sun-protected sites of the vulva and penis. These are subtyped based on histologic and clinical features, which correlate with the presence or absence of HPV integration. These will not be further addressed for the purposes of this discussion. MIS is subclassified into 3 main subtypes: superficial spreading, lentigo maligna, and acral lentiginous.

Diagnostic Criteria
SCCIS typically presents on sun-exposed skin of middle-aged and elderly adults as a scaly, erythematous plaque. Microscopically, the epidermis shows full-thickness atypia of keratinocytes and disordered maturation. Other common features include parakeratosis, mitotic figures above the basal cell layer, necrotic keratinocytes at various epidermal levels, and solar elastosis (Fig. 11).

MIS typically presents as a pigmented patch with color variegation, asymmetry, border irregularity, and a diameter greater than 6 mm. Lesions less than 6 mm and amelanotic variants also occur. Superficial spreading MIS is the most common subtype. It shows a propensity to develop on the trunk of males and the lower extremities of females. A precursor nevus is sometimes present. Microscopically, it is characterized by a poorly circumscribed and confluent intraepithelial proliferation of atypical melanocytes with prominent pagetoid growth (proliferation of malignant cells in the intraepithelial compartment without invasion beyond the basement membrane) (Fig. 12).

The lentigo maligna variant of MIS presents on chronically sun-exposed skin with a predilection for the face of middle-aged and elderly adults. Microscopically, it is characterized by an ill-defined and confluent
proliferation of atypical melanocytes arranged along the basal cell layer. Unlike the superficial spreading subtype, there is only limited (if any) pagetoid spread, and it may display less cytologic atypia. There is also more conspicuous intraepithelial extension of atypical melanocytes along adnexal structures, including hair follicle epithelium and eccrine sweat ducts.

Acral lentiginous MIS is the least common of the 3 subtypes. It presents on palmo-plantar surfaces and nail epithelium of middle-aged and elderly adults. A large proportion of melanomas diagnosed in patients with darker skin types are of the acral lentiginous subtype. Like lentigo maligna, it is characterized by a confluent lentiginous and focally nested proliferation of atypical melanocytes along the basal cell layer; the pathologic changes may be subtle in early lesions. Pagetoid growth is seen but may not be prominent, and melanocytes sometimes display dendritic processes.

Risk Factors

Long-term, cumulative ultraviolet (UV) light exposure is the most important risk factor for squamous neoplasia. Other risk factors include exposure to ionizing radiation, chemical carcinogens, immunosuppression, organ transplantation, and genetic predispositions.67

UV exposure also plays a role in melanoma development, with intermittent and intense exposure most strongly associated with the superficial spreading subtype and long-term, chronic UV exposure contributing to lentigo maligna. UV exposure is less significant in the development of acral lentiginous melanoma. These differences may be partially explained by different molecular alterations involved in the tumorigenesis of each subtype (see below). Other risk factors for MIS include fair skin, presence of numerous nevi or freckles, history of dysplastic nevi, and personal or family history of melanoma.68

Molecular Underpinnings

An early event in cutaneous squamous neoplasia is point mutation of the tumor suppressor gene \( TP53 \). Clonal expansion of stem cells containing a mutant \( TP53 \) allele with a UV signature has been demonstrated in histologically normal sun-exposed skin.69 These cells show increased resistance to UV-induced apoptosis, resulting in selection advantage. Over time, continued UV damage results in mutation of the second \( TP53 \) allele and additional genetic alterations, which correlate with greater degrees of squamous dysplasia and potential for tumor invasion.67,69

Most molecular studies on melanoma have been performed on invasive rather than in situ disease. However, a recent study focused on sequencing cancer-relevant genes in invasive melanomas as well as their precursor lesions, including MIS.70 This study showed that precursor lesions undergo a series of genetic alterations leading up to invasive melanoma, including initiating mutations known to activate the mitogen-activated protein kinase (MAPK) pathway and telomerase reverse transcriptase (TERT) promoter mutations. Biallelic inactivation of cyclin-dependent kinase inhibitor 2A (\( CDKN2A \)) on chromosome 9p21 occurred only in invasive disease. Their findings also indicated that UV radiation plays a major role in the development of precursor lesions and in the progression from in situ to invasive melanoma. Interestingly, other studies of invasive melanoma have demonstrated that \( BRAF \) (v-Raf murine sarcoma viral oncogene homolog B) and \( NRAS \) (neuroblastoma RAS viral oncogene homolog) mutations are more frequent in melanomas at sites with intermittent sun exposure compared with chronically sun-exposed and sun-protected acral surfaces.71,72 This suggests that different clinical subtypes of melanoma show reproducible genetic differences that significantly correlate with different patterns of UV light exposure.

Management

Management of SCCIS includes simple excision with histologically clear margins. Lesions may also be treated by a variety of other means, including curettage with electrosiccation and nonsurgical options such as topical 5-fluorouracil.73 Management of MIS is achieved by wide local excision with at least 5 mm surgical margins.74

Limitations and Caveats

Occasionally, there are diagnostically borderline lesions. Atypical squamous proliferation is a term used for a small percentage of cases in which partial sampling may preclude definitive diagnosis. For example, the pathologist may find it challenging to discern reactive from neoplastic atypia of epidermal keratinocytes in a superficially sampled lesion that is broadly transected at the biopsy base. Simple excision or
additional sampling is often recommended to exclude an underlying, more aggressive lesion.

Atypical intraepidermal (or lentiginous) melanocytic proliferation is a term used for a small percentage of cases in which intraepidermal melanocytes are poorly nested and show cytologic atypia but lack confluence and well-developed pagetoid growth. Partial sampling may also impede diagnostic certainty. These lesions may represent either atypical nevi or evolving MIS. They should be managed by complete excision, with adequacy of margin clearance depending upon the degree of pathologic and clinical concern.

**Prostate**

**Terminology**

There are 2 preneoplastic lesions in the prostate: prostatic intraepithelial neoplasia (PIN) and intraductal carcinoma of the prostate (IDC-P). PIN is subdivided into low grade and high grade.

**Diagnostic Criteria**

PIN consists of architecturally benign prostatic acini or ducts lined by cytologically atypical cells, yet it lacks the more advanced features of IDC-P. The distinction between low-grade and high-grade PIN (HGPIN) is the finding of prominent nucleoli in HGPIN (Fig. 13).

IDC-P (Fig. 14) has morphologic criteria that either architecturally or cytologically clearly exceed those seen in HGPIN. There are several similar definitions, with the most common being malignant epithelium filling large acini or ducts with preservation of basal cells, which is similar to PIN. However, there is either a solid or dense cribriform pattern (which is absent in PIN) or a loose cribriform or micropapillary pattern, as can be seen with PIN, yet with either 1) marked nuclear atypia or 2) necrosis, features that are not observed in PIN.75

**Risk Factors**

There have been limited data on risk factors for precursor lesions, and none are well established.

**Molecular Underpinnings**

PIN shares certain molecular features with adenocarcinoma of the prostate, in that the expression of various biomarkers in HGPIN is either 1) the same in HGPIN and carcinoma as opposed to benign prostate tissue, or 2) intermediate between benign prostate tissue and carcinoma.76

IDC-P has more advanced molecular abnormalities compared with HGPIN. For example, 29% of Gleason pattern 4 cancers and 60% of IDC-Ps demonstrated LOH of certain microsatellite markers, while LOH was rarely observed in PIN and Gleason pattern 3 adenocarcinoma.77 Several studies have found a higher incidence of ETS-related gene (ERG) immunohistochemical expression in IDC-P compared with HGPIN.78 More discriminating is that cytoplasmic phosphatase and tensin homolog (PTEN) loss was frequently identified in IDC-P but was not observed in HGPIN. PTEN genomic and PTEN protein losses in prostate cancer have been associated with more aggressive disease, and it is possible that PTEN loss may be a key underlying molecular aberration driving poor prognosis in IDC-P.

**Management**

PIN that is low grade should not be documented as a finding in pathology reports for several reasons. First, there is a lack of reproducibility in its diagnosis even by uropathologists. More importantly, there does not appear to be a higher risk of cancer after a diagnosis of low-grade PIN on a biopsy as compared with that after a benign diagnosis on a biopsy.79 The median risk of cancer after a diagnosis of HGPIN on biopsy at 1 year follow-up is only 21%.
compared with 19% after a benign diagnosis.79 There does not appear to be any clinical parameter that helps to identify men with HGPIN on a needle biopsy who are more likely to have cancer on rebiopsy. A recent molecular test has documented that, in the setting of HGPIN on biopsy, the absence of methylation of glutathione S-transferase π 1 (GSTP1), adenomatous polyposis coli (APC), and Ras association domain family 1 isoform A (RASSF1) can provide reassurance of a low risk of cancer on repeat biopsy.80 Men do not need a routine repeat needle biopsy within the first year after the diagnosis of a single core with HGPIN in the absence of other clinical indicators of cancer.79 If there are 2 or more cores with HGPIN, the risk of cancer is sufficiently high (range, 30%-40%), justifying rebiopsy within 6 months.81 If rebiopsy is performed for HGPIN, sampling should be proportionally more in the region of the original HGPIN site and in adjacent sites, although the entire prostate should be sampled. Men who have HGPIN identified on needle biopsy and cancer identified on a rebiopsy and subsequently undergo radical prostatectomy have a more favorable pathologic stage than those who have cancer diagnosed on the first biopsy.

IDC-P has very different management implications compared with HGPIN. Earlier studies documented that spread of adenocarcinoma within prostatic ducts was associated with higher grade cancer and was considered to be progression of an established invasive cancer rather than a precursor to it. More recently, it has been shown that IDC-P does not always represent intraductal spread of preexisting, high-grade, invasive carcinoma, and at least a subset of IDC-P could be a precursor lesion of invasive carcinoma, because it can be seen distant from invasive carcinoma and in a minority of prostate glands in the absence of infiltrating carcinoma.82 In a prospective study of 1176 needle biopsies in which 33 patients (2.8%) had IDC-P and carcinoma, the invasive cancer was typically high grade (Gleason score 7 [53.3%], 8 [13.3%], and 9 [33.3%]).83 When IDC-P on prostate biopsy is associated with invasive high-grade cancer, its diagnosis is not critical for management, although it may have some prognostic implications, as discussed below. In the uncommon setting (approximately 0.26% of needle biopsies) when IDC-P is found on biopsy alone in the absence of invasive cancer and a radical prostatectomy is performed, over 50% of prostate will be associated with extraprostatic extension, and there is high-grade, aggressive cancer (median Gleason score, 8).84 On the basis of this and other studies, definitive therapy (ie, surgery or radiation therapy) is recommended for men who have IDC-P identified on needle biopsy, even in the absence of invasive prostate cancer on the biopsy. It must be recognized that, in about 10% of these cases, only IDC-P will be found in the corresponding radical prostatectomy specimen; however, because IDC-P is considered a precursor lesion to mostly aggressive cancer, the surgery can still be justified.84 Even in the setting of metastatic prostate cancer, IDC-P on biopsy was predictive of decreased cancer-free survival even in a subset of men with Gleason score ≥8 cancer.82 IDC-P has also been shown to be an independent prognosticator of early biochemical relapse and metastatic failure after radiation therapy.82 When IDC-P is seen associated with lower grade cancer on biopsy, it is important to notify the clinician that these cases typically are associated with higher grade, more aggressive cancer that was not sampled on biopsy. For example, active surveillance would not be appropriate for a man who had IDC-P and limited Gleason score 6 cancer on biopsy. There have also been studies evaluating the significance of IDC-P at radical prostatectomy when associated with invasive prostatic adenocarcinoma. In multivariate analysis, IDC-P has been significantly associated with reduced biochemical recurrence–free survival and cancer–specific survival and, in another study, was identified as an independent predictor for biochemical recurrence.82 In summary, IDC-P appears to be a distinct precursor of and is more likely to be associated with aggressive prostate cancer than HGPIN.

Limitations and Caveats

HGPIN is distinguished from low-grade PIN based on “prominent nucleoli,” although the definition of how many and how prominent the nucleoli should be is subjective and the source of a considerable lack of interobserver reproducibility.

IDC-P has criteria that are more objective, but there are still cases in which it can be difficult to distinguish HGPIN from IDC-P, and an equivocal diagnosis is rendered stating the differential diagnosis and typically requesting repeat biopsy to clarify the diagnosis. It can also be difficult to distinguish IDC-P from infiltrating prostate cancer without special stains documenting the presence of a basal cell layer around the malignant epithelium, such that IDC-P is often diagnosed as infiltrating, high-grade cancer. Typically, this misdiagnosis lacks major significance, because IDC-P is usually associated with invasive high-grade cancer; and, even in the uncommon cases in which there is only IDC-P on biopsy, definitive therapy is still recommended.

Bladder

Background and Terminology

In 2015, over 74,000 new cases of bladder cancer will be diagnosed in the United States, leading to over 16,000 deaths.85 Most (approximately 75%) newly diagnosed bladder cancer cases belong to the nonmuscle-invasive bladder cancer (NMIBC) group, which encompasses noninvasive papillary precursor lesions. The majority of muscle-invasive bladder cancers (MIBC) are thought to originate through
progression from dysplasia to flat CIS and noninvasive papillary high-grade lesions, whereas low-grade noninvasive papillary lesions appear to originate from benign urothelium through a process of urothelial hyperplasia. Progression from nonmuscle-invasive to muscle-invasive disease accounts for only a small percentage (range, 10%-20%) of the entire pool of noninvasive papillary precursor lesions.

**Diagnostic Criteria**

In 2004, the WHO adopted a 1998 consensus classification for noninvasive urothelial neoplasms, as described below. The classification remained largely unaltered in the most recent classification from 2016.

**Urothelial proliferation of uncertain malignant potential**

Urothelial proliferation of uncertain malignant potential is a new term that was introduced in the 2016 WHO classification of urothelial lesions. It encompasses lesions that have a potential to be precursors for which there is limited proof and subsumes so-called “papillary urothelial hyperplasia” and flat thickening of the urothelium with minimal cytologic atypia that falls short of dysplasia. These lesions are generally considered as precursors to low-grade papillary urothelial neoplasms. The often thickened, undulating urothelium lacks cytologic atypia and is arranged into nonbranching papillary folds, at times acquiring a tent-like shape. Given the existence of some molecular evidence linking such lesions to the subsequent development of papillary bladder cancer, some have suggested that patients with these proliferations may merit closer clinical follow-up than the normal population.

**Urothelial dysplasia**

The term “urothelial dysplasia” defines the earliest morphologically recognizable abnormalities among “flat” precursors of urothelial neoplasms. Unlike terminology for other organs, no additional qualifier of the degree of dysplasia is used. Urothelial dysplasia is usually detected in bladders that have already developed carcinomas.

Histologically, urothelial dysplasia is characterized by loss of normal, orderly architecture and by mild disorganization and clustering of cells with moderately enlarged nuclei and nuclear membrane irregularity. The distinction between dysplasia and reparative epithelial changes is sometimes a challenge. The presence of dysplasia in association with urothelial neoplasms has been suggested to increase their risk of recurrence and progression. In patients with a prior history of CIS, dysplasia in a biopsy could indicate disease recurrence.

**Urothelial CIS**

Urothelial CIS is defined as a flat (high grade by definition), noninvasive urothelial carcinoma. By convention, the term CIS is reserved to this category of noninvasive urothelial carcinoma and is not applied to noninvasive carcinoma precursors of papillary architecture. Unlike other organ sites, the presence of cytologically malignant cells in a flat lesion, regardless of their quantity, qualifies it for the diagnosis of CIS, and full-thickness mucosal involvement is not a prerequisite. The nuclear enlargement and hyperchromasia in CIS is appreciable on low-power microscopic examination. Cellular dyscohesiveness, at times leading to extensive sloughing with only an incomplete basal layer of neoplastic cells retained, nuclear pleomorphism, and atypical mitotic figures are helpful diagnostic features. Because of this prominent dyscohesiveness, urine cytology is an important diagnostic tool.

Lesions with cytologic feature of CIS that acquire an early papillary architectural profile have been referred to by some as “CIS with early papillary formations” and are thought to represent a morphologic transition into noninvasive high-grade papillary urothelial carcinoma and should be managed as CIS.

The presence of CIS in association with a papillary noninvasive precursor lesion significantly increases the overall risk for recurrence and progression. As such, it is prudent for the cystoscopist to take biopsies from both papillary lesions and flat urothelial mucosa. Multifocality is associated with a worse outcome. Furthermore, CIS that is refractory to 2 or more courses of intravesical bacillus Calmette-Guerin/chemotherapy carries a significantly high risk for developing muscle-invasive disease, leading to the consideration of radical cystectomy as a preemptive treatment option for such patients.

**Noninvasive papillary urothelial neoplasms**

The WHO/International Society of Urologic Pathology (ISUP) classification of noninvasive papillary urothelial neoplasms has gained wide acceptance in the United States. In addition to its superior reproducibility rate, the WHO/ISUP classification allows for separation of these lesions into histologic entities with distinct risks of recurrence and progression to higher stage disease. As such, the urothelial papilloma category carries the lowest risk of recurrence, with practically no risk of stage progression. Increasing biologic virulence is mounted by 1) papillary urothelial neoplasm of low malignant potential (PUNLMP) (25%-47% risk of recurrence, 4%-29% risk of progression, and less than 1% mortality), followed by 2) noninvasive low-grade urothelial carcinoma (30%-76% recurrence, 10% progression, and less than 5% mortality), and finally 3) noninvasive high-grade urothelial carcinoma. The latter category is associated with the highest rates of recurrence (range, 36%-69%), progression (range, 25%-65%), and mortality (15%).
Urothelial papilloma

As defined in the WHO/ISUP classification, urothelial papilloma is a rare benign neoplasm that comprise less than 1% of all urothelial tumors.96,94 Papilloma typically occurs in younger patients, but cases in older adults are on record. Histologically, the exophytic papillary proliferation maintains delicate fibrovascular cores lined by architecturally and cytologically normal urothelium. Several studies have addressed outcomes in patients with urothelial papilloma, and the largest study was by Magi-Galluzzi and Epstein, who assessed 34 de novo papillomas.95 In their study, the mean patient age was 58 years, and the male-to-female ratio was 2.4:1. None of the patients in that study progressed to invasive disease: 8.8% developed noninvasive low-grade papillary urothelial carcinoma or PUNLMP, and an additional 8.8% developed recurrent urothelial papilloma.

PUNLUMP

The difficulty in pronouncing the somewhat awkward term PUNLMP is outweighed by its advantageous implication in avoiding the word “carcinoma” from the nomenclature of a lesion that carries a very low if any likelihood of stage progression or mortality. This is especially poignant given the relatively increased incidence of such lesions in children and young adults.96 PUNLMP papillae are lined by urothelium that has almost normal architecture with the slightest nuclear atypia. The usually thickened urothelium displays only rare mitotic figures that are restricted to the basal layer. Rarely, PUNLMP can display an inverted architectural pattern. This should not be misinterpreted as invasion into lamina propria and does not affect outcome.97 Patients presenting with PUNLMP have a less than 10% chance of progression and a less than 1% chance of dying from bladder cancer. The prognosis of PUNLMP lesions diagnosed during surveillance for a prior higher grade urothelial neoplasm is dictated by the higher grade tumor.93

Noninvasive papillary urothelial carcinoma, low grade

At low scanning magnification, low-grade papillary urothelial carcinoma exhibits an overall orderly appearance. On higher magnification, mild variations in nuclear size, shape, and chromatin texture are discernible. Most notable is the presence of scattered, dark, enlarged nuclei in a background of more uniform nuclear morphology features. The N:C ratio in noninvasive low-grade papillary carcinoma is lower than that in high-grade papillary carcinoma. Mitotic figures can be seen away from the basal layer but usually are limited to the lower one-half.86,97

Noninvasive papillary urothelial carcinoma, high grade

Noninvasive high-grade urothelial carcinomas are aggressive malignant neoplasms of either papillary or nodular architecture. A high degree of cytologic and architectural disorder is the hallmark of high-grade papillary urothelial carcinomas on both low-power and high-power magnification. On scanning view, the papillary fronds have an overall basophilic with variable degrees of dyscohesion and denudation. Moderate-to-marked cellular pleomorphism, clumped chromatin, and prominent nucleoli are appreciated. Mitotic figures are easily identifiable throughout the height of the lining epithelium and may include atypical forms.86,97

Molecular Underpinnings

Molecular genetic studies predating the current genomic era deciphered 2 distinct pathogenetic pathways for bladder cancer development that seem to parallel the contrasting dual clinical phenotypes of the “superficial” NMI-BC and the significantly more lethal MI-BC (Fig. 15).98,99

Three primary genetic alterations have consistently been shown to drive the pathogenesis pathway of papillary precursor lesions and NMI-BC. These include alterations in tyrosine kinase receptor fibroblast growth factor receptor 3 (FGFR-3), the Harvey rat sarcoma viral oncogene homolog (H-RAS), and phosphatidylinositol-4, 5-bisphosphate 3-kinase, catalytic subunit α (PIK3CA),100 which are responsible for activating the mitogen-activated protein/extracellular signal-regulated kinase/c-Myc (MAP-ERK-MYC) axis of cell proliferation and activating the mammalian target of rapamycin (mTOR) pathway. In contrast, alterations in tumor-suppressor genes involved in cell-cycle control, including TP53, p16, and Rb,99 are the engine of oncogenesis in “flat” neoplastic precursors of MI-BC: namely, CIS and urothelial dysplasia. In fact, progression of the subset of papillary NMI-BC into higher grade muscle-invasive disease is similarly dependent on inactivation of the TP53 and Rb tumor-suppressor genes.

Recent genomic studies, including a recent comprehensive molecular characterization of MI-BC by The Cancer Genome Atlas project,101 have validated and expanded upon the above-described genetic pathways, promising to better define clinically relevant molecular subtypes of bladder cancer.102,103

Management

Currently, surveillance and ablation of precursors is the primary management strategy. Surveillance strategies revolve around regular cystoscopy and/or urine cytologic examinations at increasing intervals over time. Multitarget fluorescent in situ hybridization urine analysis and other urine biomarkers can be exploited with varying success.104

Limitations and Caveats

Prognostic parameters that can accurately predict progression in patients with NMI-BC precursors are actively sought to further facilitate identification of those in need of vigilant surveillance and intervention. The latter is especially pertinent in a disease in which the financial and quality-of-life burdens for patients under surveillance are significant. The fact remains that, per patient, bladder cancer is the most costly...
solid tumor type, with a staggering 3 billion dollar annual cost to health care resources. Established clinicopathologic prognostic parameters for NMI-BC include: 1) pathologic tumor (pT) classification (the presence or absence of lamina propria invasion); and 2) grade, size, and multifocality of noninvasive papillary precursor and the presence of an accompanying “flat” precursor lesion, ie, CIS.105

Pancreas
Terminology
Three major forms of intraepithelial neoplasia, defined by their gross and microscopic appearances, are recognized in the pancreas. Pancreatic intraepithelial neoplasia (PanIN) is a microscopic lesion, whereas intraductal papillary mucinous neoplasm (IPMN) and mucinous cystic neoplasm (MCN) are both macroscopic lesions (Fig. 16).

Diagnostic Criteria
PanIN is defined as a microscopic, flat or papillary, noninvasive epithelial neoplasm characterized by various amounts of mucin and degrees of cytologic and architectural atypia (Fig. 16B).106 IPMN is defined as a grossly visible, predominantly papillary or rarely flat, noninvasive, mucin-producing epithelial neoplasm arising in the main pancreatic duct or branch ducts (Fig. 16C).106 IPMNs can be characterized into intestinal, pancreatobiliary, oncocytic, and gastrofoveolar subtypes based on the types of mucin expressed by the neoplastic cells.107 MCN is a cyst-forming epithelial neoplasm that usually does not communicate with the pancreatic duct system and is composed of columnar, mucin-producing epithelium associated with ovarian-type stroma (Fig. 16D).106 PanINs, IPMNs, and MCNs can each be further categorized based on the microscopic degree of architectural and cytologic dysplasia, into low-grade, intermediate-grade, and high-grade lesions.106 It has recently been proposed that lesions with low-grade or intermediate-grade dysplasia should be lumped under the designation “low-grade dysplasia,” creating a simplified and more clinically relevant 2-tier system composed of only low-grade and high-grade dysplasia.108 While PanINs, IPMNs, and MCNs are all noninvasive lesions, microscopic and genetic studies have demonstrated that those lesions with high-grade dysplasia are most likely to progress to invasive carcinoma.

Risk Factors
The risk factors for developing intraepithelial neoplasia in the pancreas are not well defined, but the risk factors for PanINs are presumed to be similar to those for invasive ductal adenocarcinoma of the pancreas.106 As such, they would include older age, cigarette smoking, obesity, long-standing diabetes mellitus, and chronic pancreatitis.106 MCNs are remarkable in that they are much more common in women than in men, with a female-to-male ratio of 20 to 1.106 The risk factors for IPMNs are not well defined.

Molecular Underpinnings
PanINs, IPMNs, and MCNs arise through the accumulation of genetic alterations in key oncogenes and tumor-suppressor genes. The accumulation of these genetic alterations is associated with increasing degrees of dysplasia. Telomere shortening and activating point mutations in the KRAS2 oncogene appear to be among the earliest
genetic alterations in PanIN lesions, as these genetic changes are present in the majority of PanINs with low-grade dysplasia. Inactivating mutations in the p16/CDKN2A gene start to appear in PanINs with low-grade to intermediate-grade dysplasia, whereas inactivating mutations in the SMAD family member 4 (SMAD4) and TP53 tumor-suppressor genes appear to be “late” events, as they are seen essentially only in PanINs with high-grade dysplasia. There are several implications of this genetic progression. First, the genes mutated in PanIN lesions are exactly the same genes that are altered in invasive ductal adenocarcinomas of the pancreas (pancreatic cancer), helping to establish that PanINs can indeed progress to invasive cancer. Second, the order in which these alterations occur has clinical implications. Mutations in KRAS2 are early and common events, suggesting that KRAS2 alterations may be a good marker for precursor lesions, but that alterations in this gene will not provide information about the grade of the lesion. By contrast, TP53 and SMAD4 alterations are late events, suggesting that alterations in one of these genes indicates a clinically significant lesion. For completeness, it should be noted that aberrant methylation of genes, including p16/CDKN2A, has been reported in PanIN lesions, as have alterations in gene and microRNA expression patterns. For example, compared with the normal ductal cells of the pancreas, PanINs overexpress the microRNAs miR-21 and miR-155.

The genetic alterations observed in IPMNs include some of the same genes altered in PanINs (KRAS, p16/CDKN2A, TP53, and SMAD4). As observed with PanINs, KRAS and p16/CDKN2A mutations are early events (seen in IPMNs with low-grade to intermediate-grade dysplasia), whereas TP53 and SMAD4 alterations are late events, occurring in IPMNs with high-grade dysplasia and IPMNs with an associated invasive carcinoma. In addition, 2 genes not typically targeted in PanINs, ring finger protein 43 (RNF43) and guanine nucleotide–binding protein, α stimulating (GNAS), are frequently altered in IPMNs. Aberrant methylation of the promoters of several genes has been reported in IPMNs, as has differential microRNA expression.

The genetic alterations in MCN are almost identical to those found in IPMNs, except GNAS mutations appear to be more common in IPMNs than in MCNs. As discussed in greater detail below, the molecular alterations present in PanINs, IPMNs, and MCNs may form the basis for clinical tests for PanIN, and some may be therapeutically targetable.
Management

In general, PanINs do not present a clinical management problem. Most PanIN lesions are simply too small to be detected using current imaging technologies. Furthermore, there is no concrete evidence that treating a PanIN lesion improves patient outcome. By contrast, IPMNs can be detected using currently available imaging techniques, and a growing body of clinical evidence supports the resection of IPMNs with high-grade dysplasia. Many IPMNs are now being detected in patients undergoing abdominal imaging for another indication. These lesions present a significant and growing clinical challenge. On one hand, their diagnosis represents a chance to remove a precursor lesion and prevent a cancer; on the other, there is a real risk of overtreating patients for lesions that would never have caused harm to the patient. In 2012, a group of international experts proposed guidelines for the management of patients with IPMN, and these guidelines (called the “Sendai guidelines”) have been validated in several follow-up studies. A “hands-off” approach has recently been advocated in the American Gastroenterology Association Institute guidelines, but those guidelines are very controversial, because some have argued that they were derived using flawed methodologies.

Most MCNs are surgically resected, because invasive cancer can arise focally in these lesions, and the cysts of MCNs have thick walls, making it hard to identify focal invasion on imaging. As suggested above, molecular analyses hold great promise for the management of intraepithelial precursor lesions in the pancreas. As clinical tests are developed to detect genetic alterations and changes in gene expression, they can be used to detect the presence of an intraepithelial lesion, and these tests may ultimately provide information on the type of lesion and its histologic grade.

Limitations and Caveats

Intraepithelial neoplasia presents a real conundrum in the pancreas. The detection and treatment of these lesions has the potential to prevent the development of a deadly invasive carcinoma. Conversely, these lesions are common, and the over treatment of lesions that ultimately would not have harmed the patient (progressed) is a real risk. New molecular-based approaches, when integrated in together with clinical findings and state-of-the-art imaging, have the real potential to make a difference.

Esophagus

Introduction and Terminology

Esophageal intraepithelial neoplasia (IEN) may be squamous or glandular/columnar (in the setting of Barrett esophagus [BE]). For the purposes of this discussion, we will focus on columnar IEN, because it comprises the vast majority of esophageal preinvasive lesions in the United States. The American Gastroenterological Association requires the presence of goblet cells (equivalent to intestinal differentiation) to define Barrett mucosa, but this is the subject of debate. For example, in Japan and the United Kingdom, the presence of columnar epithelium with or without goblet cells in the tubular esophagus is definitional for BE, but all observers acknowledge that the presence of goblet cells conveys a higher risk for progression to adenocarcinoma.

The term dysplasia is used by both gastrointestinal (GI) and general surgical pathologists when evaluating specimens from patients with BE. Although the GI section of the WHO makes a distinction between “dysplasia” and “intraepithelial neoplasia” (it defines the former as “presence of morphological features of neoplasia” and the latter as “lesions with cytological or architectural alterations perceived to reflect underlying molecular abnormalities that may lead to invasive carcinoma”), for practical purposes, they are considered synonymous by most pathologists. Gastroenterologists in the United States are familiar with the term “dysplasia,” and use of the term “intraepithelial neoplasia” in this setting would probably cause a great deal of confusion among clinical colleagues. Furthermore, most GI pathologists are familiar with and use the Vienna system, published in 2000, which proposed the following categories for the classification of GI IEN:

1. Negative for neoplasia/dysplasia (normal, reactive, hyperplastic, etc)
2. Indefinite for neoplasia/dysplasia (the changes are not equivocally reactive or neoplastic)
3. Noninvasive low-grade neoplasia (low-grade adenoma/dysplasia)
4. Noninvasive high-grade neoplasia
   a. High-grade adenoma/dysplasia
   b. Noninvasive carcinoma (CIS)
   c. Suspicion of invasive carcinoma
5. Invasive neoplasia
   a. Intramuscosal carcinoma (invasion into the lamina propria or muscularis mucosae)
   b. Carcinoma in the submucosa or beyond.

This classification system is useful because it allows for stratification and management of patients according to the likelihood of progression of neoplasia.

Cancer risk in patients with nondysplastic BE has been regarded as low (annual cancer incidence for patients without dysplasia is approximately 0.5%) using pooled data, but other data suggest minimal risk (0.1% annual risk). However, still others have suggested that the risk is extremely low in the first 5 years of follow-up but then climbs to about 9% or 10% cumulative incidence after...
20 years, which has implications for intensified screening as time passes. Patients with high-grade dysplasia (HGD) in BE have an estimated risk of progression to adenocarcinoma of 55.7 to 65.8 per 1000 person-years (about 6% per person per year), whereas a diagnosis of low-grade dysplasia (LGD) confers a lower risk of progression to either HGD or carcinoma, with up to 20% to 28% progression within 5 years (about 4%-5% progression per person per year to either HGD or carcinoma). Interobserver variability is lower at the ends of the diagnostic spectrum (“negative” and “HGD”) but increases for a diagnosis of “indefinite for dysplasia.” For this reason, establishing the risk of cancer in patients whose biopsies are indefinite for dysplasia is difficult. This risk of progression to cancer has been estimated at 14% at 5 years in one study. A more recent study with a greater number of patients indicated that 12.9% of patients diagnosed as “indefinite for dysplasia” had prevalent neoplasia (LGD, HGD, or carcinoma) when biopsied within 1 year of the “indefinite” diagnosis (estimated risk for HGD and carcinoma, 1.68 cases per 100 patient-years).

Diagnostic Criteria

Negative for dysplasia
Mild cytologic atypia is inherent to nondysplastic Barrett epithelium. Biopsies free of dysplasia typically display surface maturation with basal crypt nuclei that are larger, more hyperchromatic, and more stratified compared with more mature superficial cells, which display smaller, basally located, nonstratified nuclei. Glands should be round with ample intervening lamina propria. Nuclear and nucleolar contours from both surface epithelium and basal pits should be free of irregularities. Mitotic figures, if present, should be restricted to the basal compartment (Fig. 17A).

Indefinite for dysplasia
This diagnostic term applies to cases in which it is difficult to state with certainty whether cytologic and/or architectural changes are definitively neoplastic or reactive. Included are cases that have a mild degree of glandular crowding or cytologic features that are suggestive of dysplasia (nucleolar or nuclear contour irregularities, increased number of mitoses, some surface stratification) but that fall short of a definitive diagnosis because of a prominent inflammatory component or because, qualitatively, the changes are not robust enough to justify a diagnosis of dysplasia. Cases regarded as indefinite for dysplasia often show nuclear stratification extending to the surface with abundant acute inflammation.

LGD
Superficially located nuclei are irregular, hyperchromatic, mildly enlarged, and may show some degree of stratification.
### TABLE 1. Summary of Precursors to Carcinoma in Various Anatomic Sites

| ANATOMIC SITE | PRINCIPAL PRECURSOR LESION(S) | ASSOCIATIONS/RISK FACTORS | HOW ASSESSED | IS SCREENING CURRENTLY POSSIBLE? | DOES SCREENING PREVENT CANCERS? | PREVENTION AND/OR TREATMENT OF PRECURSORS |
|---------------|--------------------------------|---------------------------|--------------|----------------------------------|---------------------------------|------------------------------------------|
| Uterine cervix | LSIL, HSIL HPV                 | Cervical cytology with HPV testing | Yes          | Yes                              | HPV vaccination/eradication of HSIL, follow-up of LSIL |
| Ovary         | STIC                           | BRCA germline mutations, low parity | In resected fallopian tubes | No                               | Not currently except in BRCA mutation carriers | Elective salpingectomy in known BRCA mutation carriers and opportunistic salpingectomy in patients undergoing pelvic surgery for any reason |
| Breast        | LN, including ALH and LCIS, ADH, DCIS | Positive family history, high body mass index, nulliparity, late age of first birth, late menopause | Radiography (mammography, ultrasound, MRI) | Yes                              | Controversial | Surgical excision for DCIS; consider prophylactic hormonal therapy for ALH, LCIS, ADH, and ER-positive DCIS |
| Lung          | Squamous dysplasia and squamous cell carcinoma in situ, AAH, AIS | Smoking | Assessment limited, but radiologic assessment has been studied | Of limited value | Not currently | Smoking cessation |
| Head and neck | Squamous dysplasia (graded as mild, moderate, and severe) | Tobacco (most cases), HPV in a subset | Direct visualization and biopsies | Yes                              | Controversial | Tobacco cessation, HPV vaccination in a subset/mucosal ablation |
| Skin          | SCCIS/Bowen disease, MIS       | SCCIS: Long-term cumulative UV exposure, ionizing radiation, chemical carcinogens, immunosuppression, organ transplantation, genetic predispositions; MIS: UV exposure, pale skin, numerous nevi or freckles, dysplastic nevi, family history | Direct visual examination and biopsies | Yes | Yes | Prevention of sun exposure/ablation of lesions |
| Prostate      | PIN, IDC-P                     | Not established | Needle biopsies performed for elevated serum PSA | No                       | No               | None available |
| Bladder       | Urothelial dysplasia, urothelial carcinoma in situ, noninvasive papillary urothelial neoplasia | Smoking | Cytologic samples and mucosal biopsies | Yes | Yes | Smoking cessation, exposures/mucosal ablation |
| Pancreas      | PanIN, IPMN, MCN               | Older age, cigarette smoking, obesity, pancreatic for PanIN, female sex for MCN, unknown for IPMN | Currently not assessed-promising results using pancreatic fluid obtained from ampulla of Vater at endoscopy | Research only | Not currently | Smoking cessation |
| Esophagus     | Low-grade dysplasia, high-grade dysplasia | Male sex, gastroesophageal reflux disease, smoking, central obesity | Mucosal biopsies at time of upper endoscopy | Yes | Controversial | Weight reduction, smoking cessation, measures to reduce reflux/mucosal ablation |

AAH indicates atypical adenomatous hyperplasia; ADH, atypical ductal hyperplasia; ALH, atypical lobular hyperplasia; AIS, adenocarcinoma in situ; BRCA, breast cancer gene; DCIS, ductal carcinoma in situ; ER, estrogen receptor; HPV, human papillomavirus; HSIL, high-grade squamous intraepithelial lesion; IDC-P, intraductal carcinoma of the prostate; IPMN, intraductal papillary mucinous neoplasm; LCN, lobular carcinoma in situ; LN, lobular neoplasia; LSIL, low-grade squamous intraepithelial lesion; MCN, mucinous cystic neoplasm; MIS, melanoma in situ; MRI, magnetic resonance imaging; PanIN, pancreatic intraepithelial neoplasia; PIN, prostatic intraepithelial neoplasia; PSA, prostate-specific antigen; SCCIS, squamous cell carcinoma in situ; STIC, serous tubal intraepithelial cancer; UV, ultraviolet.
and mucin loss. Mitotic figures may be seen at or close to the surface. Nucleoli are not a feature typically encountered in dysplastic epithelium; instead, they are more common in reactive processes and in the setting of invasive carcinoma. Glandular crowding may be present, but intervening lamina propria must still be observed. Nuclei are oriented perpendicular to the basement membrane. Loss of nuclear polarity should not be observed (Fig. 17B).

HGD
These biopsies show superficial mucin loss with lack of surface maturation and minimal inflammation. Mitoses are common, and nuclei are large and irregular with a dark, smudged nuclear chromatin pattern. Nucleoli are typically not prominent. Glandular crowding is more striking, and glands may exhibit irregular shapes and budding. The most important feature to note is the lack of nuclear polarity, with nuclei arranged haphazardly in relation to the basement membrane (Fig. 17C).

Risk Factors
Long duration of reflux symptoms, large hiatal hernia, long-segment Barrett, the absence of Helicobacter pylori infection, and the presence of dysplasia at index diagnosis have been associated with an increased risk of developing HGD or carcinoma in patients with BE. The risk for Barrett-associated neoplasia (and Barrett mucosa itself) revolves around male sex, long segments of Barrett mucosa, and central obesity.

Molecular Underpinnings
Molecular mechanisms involved in the development and progression of BE are largely unknown. Aneuploidy, decreased E-cadherin expression, increased Ki-67 proliferation rate, and p53 immunostaining are observed in a subset of Barrett-associated dysplasias and invasive adenocarcinomas and have been advocated as markers of neoplastic progression. Mutations in the tumor-suppressor gene AT-rich interactive domain 1A (ARID1A) have recently been reported in 4.9%, 14.3%, 16%, and 12.2% of patients with nondysplastic BE, LGD, HGD, and carcinoma, respectively, and this loss is inversely proportional to the accumulation of nuclear p53. Although promising, these markers have limited utility in daily practice, and the risk stratification of patients is still based on evaluation of dysplasia on hematoxylin and eosin-stained slides. The American Gastroenterological Association recommends against the use of biomarkers to confirm a diagnosis of Barrett dysplasia, because it has not been demonstrated that they can robustly predict which patients are likely to progress.

Management
Patients with LGD may be treated with radiofrequency ablation (RFA), which leads to the reversion of dysplastic foci to normal squamous epithelium and a significantly lower risk of progression to HGD or carcinoma compared with patients who undergo surveillance. Patients with HGD may be treated with RFA if the focus is flat or with endoscopic mucosal resection (EMR) if the dysplasia is associated with a discrete, endoscopically visible lesion. Endoscopic ultrasound may oversize or undersize neoplasia such that performing EMR can sometimes refine staging, and concerning findings on endoscopic ultrasound should not preclude an attempt at EMR. Esophagectomy, although still a management option, is associated with increased morbidity compared with endoscopic therapies (RFA, EMR). Patients diagnosed as “indefinite for dysplasia” are followed with endoscopy and repeat biopsies.

Limitations and Caveats
Interobserver variation in diagnosis is a known issue, such that societies and expert opinion consensus suggest peer review in diagnosing dysplasia. The superficial nature of endoscopic biopsies can pose a challenge when confronted with some cases of HGD that in fact harbor foci of adenocarcinoma with lamina propria invasion that are not present in the biopsy sample. A definite diagnosis is sometimes not possible, and pathologists often use the term “HGD, cannot exclude invasion” to describe these cases. Thankfully, as in cases of HGD, cases of intramucosal carcinoma may be managed with EMR. Choosing the best patients to enter into surveillance protocols is not optimized, and compliance with screening guidelines, similarly, is suboptimal. However, men over 60 with reflux symptoms form the key pool of patients for screening and surveillance. The incidence of both BE and neoplasia is far less in women than in men, such that men are the key target population for screening.

Conclusion
Intraepithelial neoplasia in various anatomic sites is associated with wildly diverse risk factors and pathobiology (see Table 1). Furthermore, because some organs are more readily accessible for the detection of precursor lesions (skin, cervix, esophagus, colon), it should be easy for us to exploit this accessibility and prevent carcinomas in these locations. However, whereas there is widespread screening for colorectal carcinomas and cervical carcinomas, the cost effectiveness of esophageal mass screening in the United States is questionable. Furthermore, there is not widespread screening for skin lesions, which should be the easiest to detect. In contrast, the pancreatobiliary tree can only be screened with

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invasive procedures. In addition, the terminology across organ systems has not been unified, which in part is a result of divergent biology and risk factors in various anatomic locations, although specialized experts are generally familiar with the vagaries in the organ sites with which they deal. As molecular techniques become more sophisticated, they might be better exploited for screening and detection of precursors in anatomic sites that cannot be practically screened; however, at this time, serum tests are unlikely to detect most precursor lesions. Importantly, vaccines can now be administered to prevent both anogenital SCCs and a subset of HNSCCs, and mucosal ablation techniques have reduced morbidity for patients with esophageal precursor lesions. The challenge we will all face in the coming years is choosing the appropriate patients to screen aggressively based on the risk factors most relevant to various organs.

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