Underwriting Implications of Premalignant Disease
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Abstract: The study of premalignant disease may hold the promise of cancer prevention and, in some cases, this potential is already being realized. In other instances, however, increased risk of mortality and morbidity has been identified without clear data to guide treatment. This series reviews the current state of information about premalignant disease from the perspective of diagnosis, treatment and underwriting risk. The first article will focus on prostatic intraepithelial neoplasia.

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This is the first of a series dealing with underwriting implications of premalignant lesions. This article will overview general concepts of premalignant lesions and discuss prostatic intraepithelial neoplasia. Subsequent installments will focus on premalignant lesions of the uterine cervix (cervical intraepithelial neoplasia), esophagus (Barrett’s esophagus), and premalignant breast disease.

Preventive medicine is an area which has progressed in leaps and bounds over the past decades. Infectious disease was the number one cause of death early in the century, but the emergence of the germ theory of disease allowed us to prevent many infectious diseases by improving public sanitation while developing vaccines and antibiotics. Coronary artery disease (CAD) then replaced infectious disease as the number one cause of death in the United States and much of the developed world. Over the past few decades, improvements in the treatment of CAD, as well as recognition and treatment of risk factors for CAD, have begun to lower the death rate from atherosclerotic diseases. As a result of this decrease, some researchers have predicted that the cancer death rate may soon surpass that of heart disease. The fact that cancer is already the number one killer of women in their middle years adds to the growing concern.

Most attempts to decrease cancer deaths have been based on the assumption that cancers detected and treated in the early stages will be curable. This approach has had widely varying success in different organs. Even with early detection, many people will still die of their cancer because small invasive cancers may have spread throughout the body by the time of diagnosis. In theory, if cellular abnormalities which lead to cancer could be treated before invasion occurs, cancer could be completely prevented. This is the rationale for research on premalignant disease, but one result of the development of this information is the creation of a variety of complex and actuarially uncertain levels of increased risk.
The concept of a premalignant lesion evolved from years of observation of tissue abnormalities which were not cancer but which shared some or many of the features of cancer, and from an observed increased cancer risk at a given site. The Pap smear was the original early detection screening program for cancer. Observations of cervical cytology and subsequent cancer risk led to the idea that we could possibly treat noncancerous but high-risk lesions to prevent cancer. In fact, in countries which use cervical cytology to screen women for cancer and premalignant changes, cervical cancer deaths dropped dramatically. In countries which do not screen a substantial proportion of women, cervical cancer remains the number one cause of cancer death in women.

Premalignant lesions have now been identified in many tissues including the prostate, breast, colon, skin, lung and esophagus. The problem of how to treat these lesions and whom to treat is compounded by the fact that not all premalignant lesions become invasive; the presence of a premalignant lesion identifies increased risk, but the degree of increased risk is variable from tissue to tissue. The decision about whom to treat is also made more difficult if the proposed treatment is disfiguring or involves loss of function.

How is a premalignant lesion defined? First, a definition of cancer is in order. Most cancers are carcinomas which means they arise in epithelial tissues. The epithelium is the layer of cells which lines virtually all our organs and glands. The limit of the epithelium is the basement membrane which underlies it and separates it from the rest of the organ. The outer layer of skin is an epithelium and so are the linings of our respiratory, biliary, reproductive, gastrointestinal and urinary tracts. Carcinomas arise in these epithelial tissues and are defined by their microscopic appearance (histology) and the way they invade into the tissue through the basement membrane.

The strictest definition of a premalignant lesion is a lesion which can be shown on serial biopsy to progress to carcinoma. If this definition can be met, there is usually little controversy about its significance, although precise risk assessments may remain arguable. This kind of serial biopsy has been done in certain organs such as the cervix because of its unique anatomic features. This standard cannot be applied in many other tissues because it is generally not technically possible to biopsy an exact location. In most organs it is necessary to rely on circumstantial evidence that a lesion is premalignant to justify the association of a particular histologic pattern with cancer risk. Some of these factors include the spatial relationship between a premalignant lesion and observed cancers, microscopic (pathologic/histologic) similarities to cancer, biochemical findings, neovascularity (formation of new blood vessels), genetic analysis and nuclear studies.

For example, biomarkers such as growth factors and tissue-specific enzymes can be measured and often confirm the similarities between premalignant lesions and cancer as distinct from other kinds of abnormal changes. Each tissue has individual properties which will over time probably lead to less and less dependence on purely histologic findings for the determination of risk.

However, the microscopic appearance of a lesion is still the primary method by which we diagnose a premalignant or malignant lesion. Because the field is relatively young and new information has been continually changing our understanding of the process by which a lesion becomes malignant, the terminology used to describe premalignant lesions has also been evolving. Unfortunately, one group of researchers may agree to a new terminology system, but pathologists and clinicians frequently go on using the terminology with which they are most comfortable. As a result, multiple overlapping terms remain in everyday use.

Premalignant lesions are usually described as having both increased numbers of cells
(hyperplasia) and findings generally referred to as atypia. Changes in the shape, orientation and size of cells as well as nuclear and nucleolar abnormalities are usually considered atypical changes. These findings have often been labeled as atypical hyperplasia (AH) or dysplasia depending on the terminology history of a particular tissue. Dysplasia is often further classified according to the depth of involved epithelium. Hence, mild dysplasia refers to changes involving only the basal layer and moderate and severe dysplasias refer to dysplasias involving increasing thickness of the epithelium. Carcinoma in situ (CIS) refers to a lesion which has all the cellular attributes of invasive cancer and replaces the full thickness of the epithelium, but has not yet become invasive (invasive cancers are those which extend beyond the basement membrane into other parts of the tissue). There appears to be a continuum of abnormality from AH to CIS, but, in theory, hyperplasias are considered less severe.

In hopes of clarifying some of the terminology issues, the term intraepithelial neoplasia (IN) was introduced with a grading system from I to III to indicate severity. This system eliminates the need to use terms that appear to imply more substantial differences in risk than really exist. In other words, pathologists were concerned that in some instances the term AH might not concern a treating physician even though it could be highly significant, while CIS might provoke an inappropriately aggressive approach in other instances. Since the IN terminology was introduced, consensus conferences of pathologists and clinicians have decided that in at least some tissues this grading system is untenable because there is no unanimity on the precise boundaries between the grades, and that the three part system implies a finer ability to determine risk than exists. As a result, the terms low-grade (LG) IN and high-grade (HG) IN have come about. HG generally includes everything from moderate dysplasia through CIS. The truly unfortunate aspect of all this naming and renaming is that rather than a new system replacing the old, all the terms continue to be used simultaneously.

There are additional issues which are closely related to the terminology issues and which add further to the confusion. For example, the pathology community often cannot agree on how to define a specific controversial lesion. There has also been concern about demonstrated interobserver discrepancies, especially in the low- and moderate-grade lesions. Sampling problems and even what constitutes an adequate sample are still being determined in most tissues. These discrepancies are some of the reasons consensus groups have decided to create broader categories.

The natural history of IN is incompletely understood. In many tissues, the increased cancer risk observed seems quite unequivocal, but assigning degree of risk to an individual patient has been elusive and studies frequently differ significantly. In general, AH and LG lesions are felt to often regress or remain stable. HG lesions, which include CIS, are felt to be very unlikely to regress but they do not always progress to invasive cancer either.

To make an underwriting assessment of risk of a premalignant lesion, we need to consider the following points:

- the organ of origin
- the risk of the invasive cancer itself
- the likely stage and grade of cancers found after surveillance versus those found after the development of symptoms related to cancer
- the range of risk reported for a given lesion
- any additional risk factors which may be helpful
- the general uncertainty of this immature area of medicine.

Here is an additional thought for underwriting this kind of risk: increased cancer risks reported in the 2-3 times normal range are rarely actuarially significant although they may be important on a population basis.
Despite this, vague but impressive reports of risk in this range do cause a great deal of concern in patients and physicians alike. We don't want to jump too quickly on the bandwagon of increased risk and penalize applicants who receive medical care before we have a reasonably well-substantiated level of actuarially significant risk to assess. Using CAD as a model, we can accept quite a bit of increased risk without penalty to the applicant in many instances. We should probably approach cancer risk in the same manner, keeping in mind the omnipresent problem of antiselection.

Prostatic Intraepithelial Neoplasia

Perhaps no premalignant lesion has received as much attention recently as prostatic intraepithelial neoplasia (PIN) found on biopsy. This interest has been fueled by the fact that prostate cancer is the most common cancer in men in some countries. In the United States, 10-15% of men will be diagnosed with prostate cancer during their lifetimes, and approximately 3% of all male deaths are caused by prostate cancer. Although there has been a tendency to blame increased detection rates for the rise in prostate cancer incidence, the actual total number of men dying annually from prostate cancer has risen in the last decade.

Early detection of prostate cancer has great potential to prevent death because prostate cancer is clearly much more curable if treated before it extends outside the prostate. One of the fascinating and confounding aspects of prostate cancer detection and treatment is the well-known, autopsy-established fact that more than 40% of men have prostate cancer by age 75, but only about 10% of men will develop clinically significant cancer. Researchers have been trying to find ways to determine which men with cancer have disease which is likely to be life-threatening if untreated.

To further confuse matters, PIN has now emerged as a risk factor for cancer. PIN is one of several pathologic entities which have been proposed as possible premalignant lesions of the prostate. In the last 10 years high-grade PIN has been fairly well accepted as the likely precursor to the clinically most important type of prostate cancer, adenocarcinoma of the peripheral zone of the prostate.

PIN was initially categorized by the original IN system into PIN I, II and III. Since a 1989 consensus conference, however, PIN is now grouped as low-grade PIN (LGPIN; formerly PIN I) and high-grade PIN (HGPIN; formerly PIN II and III). HGPIN is essentially a diagnosis of carcinoma in situ of the prostate.

LGPIN can be found in men as young as 20, but most authorities in the field are now convinced that the evidence linking LGPIN to cancer is very weak. There are many morphologic mimics of LGPIN, e.g., inflammation, and there is very little or no circumstantial evidence, such as biomarkers, linking LGPIN with cancer. For example, ploidy studies indicate that LGPIN is primarily diploid or tetraploid like benign prostatic hypertrophy (BPH). The incidence of cancer in follow-up of men with LGPIN on biopsy seems to be essentially the same as the risk of finding cancer in men who had only BPH on their first biopsy. The question of how frequently LGPIN evolves into HGPIN is unanswered, but the rate seems to be low enough to produce a negligible increase in risk when LGPIN is the only risk factor.

If LGPIN and an elevated PSA (prostate specific antigen) are both present, the risk of subsequent cancer is the same as the risk associated with the degree of PSA elevation alone. PIN does not seem to contribute appreciably to PSA elevations, so a finding of LGPIN does not explain the PSA elevation. Other diagnoses, such as the possibility that a cancer was missed on biopsy, may have to be considered. Therefore, if a biopsy shows only LGPIN, but the PSA is very high, one should proceed on the basis of whether the PSA alone would justify further investigation for cancer.

HGPIN is quite a different story. HGPIN is found in 5 to 16% of men who undergo needle
The relative risk for the development of prostate cancer in men who have HGPIN on biopsy is 15, making it the single greatest risk factor for prostate cancer.

It is not possible to do serial biopsies of the same group of cells in the prostate, but there are many pieces of evidence which link HGPIN to prostate cancer. Like most clinically significant prostate cancers, HGPIN is usually multifocal and located in the peripheral zone of the prostate. It is found in close spatial association to over 85% of prostate cancers. Many pathologists feel that its absence in some cancerous prostate specimens may be due to overgrowth of the HGPIN by the cancer which arose in it.

Numerous biomarkers for cancer are similar in HGPIN and studies also show similarities of neovascularity. HGPIN is more closely related by biomarkers and ploidy studies to high-grade than to low-grade prostate cancers. This is an important consideration because low-grade prostate cancers have much lower mortality than high-grade. Therefore, HGPIN may be a marker not only for risk of prostate cancer but for cancers of the greatest clinical significance.

Perhaps the most compelling evidence demonstrating the clinical importance of HGPIN is that 39%-100% of men with HGPIN will be found to have prostate cancer on a subsequent biopsy. A very significant proportion of them will have prostate cancer diagnosed within 6 months, indicating that the cancer was already present in many at the time of the initial biopsy. These studies suffer from the fact that they do not contain large numbers of men. In this situation, results can be expected to vary more than if very large numbers of men were followed. If all the studies are examined together, none report less than about a 35% risk of subsequent cancer. Thus, the significance of HGPIN seems unquestionable even if a precise risk cannot yet be assigned.

HGPIN in men with a normal PSA (<4ng/ml) is still associated with a very high risk of cancer and as the PSA rises, the risk becomes even greater. In Zlotta’s series, 33% of men with PSA values less than 4 ng/ml and HGPIN had invasive cancer on repeat biopsy. In the same study, men with HGPIN, PSAs greater than 12 ng/ml, and abnormal findings on digital rectal exam had a greater than 90% risk of developing invasive cancer during follow-up.

Currently there is no treatment recommended for HGPIN other than close follow-up and rebiopsy every 3-6 months for at least the first few years after the diagnosis. Chemoprevention using anti-androgens has shown promise, but there has not been enough time to prove any mortality benefit.

There is no simple answer at this time to the problem of HGPIN from an underwriting standpoint. The information available justifies serious concern but there is much uncertainty and even missing information. For instance, none of the reports indicated the nature of cancers detected in men with PIN. It would be extremely useful from a mortality standpoint to have a sense of the likely stage and grade distribution of prostate cancers found after a diagnosis of HGPIN. One researcher stated to this author that he was considering publication of a small series containing this kind of data in the near future.

For now, all relevant information including age, exam findings, PSA values, and overall health should be taken into account in the decision-making process. In some instances it might be best to postpone insuring men with HGPIN and only one set of biopsies, especially if they are relatively young (<60 years) or have an elevated PSA. In elderly men (>70 years) with similar findings, the additional mortality risk of HGPIN may add little to the overall risk if the PSA is less than 10 ng/ml.

At this time, data do not exist to allow precise mortality estimates for HGPIN and LGPIN. This forces us to make reasoned underwriting
decisions based on preliminary information. The challenge is to make these judgments without overreacting in situations complicated by both medical uncertainty and the potential for antiselection.

References