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The Precancers: Waiting for a Classification

Precancers are the morphologically identifiable lesions that precede invasive cancers. In theory, the identification and elimination of cancer precursors would lead to the eradication of most human cancers, justifying an assertion that precancers are the most important lesions in modern man.[1]

Pathologists and cytologists have leveraged the pathology of precancer to achieve the most dramatic reduction in cancer deaths attributable to medical intervention. Americans often forget that cancer of the uterine cervix is the leading cause of cancer deaths in women in many developing countries.[2,3] The relatively low number of cervical cancer deaths in the United States is the result of a 70% reduction in age-adjusted mortality after the introduction of organized Pap smear screening.[4-6] No effort aimed at treating invasive cancers has provided an equivalent reduction in cancer deaths.

Recently, precancer has enjoyed renewed attention from the American Association for Cancer Research (AACR), which created a multidisciplinary task force on the treatment and prevention of intraepithelial neoplasia (IEN). In February 2002, the task force published its recommendations, which included "focusing on established precancers as the target for new agent development because of the close association between dysplasia and invasive cancer and because a convincing reduction in IEN burden provides patient benefit by reducing cancer risk and/or by decreasing the need for invasive interventions."[7]

Precancers have been a subject of research interest for decades. Many will remember the enthusiasm in the 1960s and 1970s for experimental precancer models. A classical description of the progression of precancer to cancer was described by the late Leslie Foulds, who died while nearing completion of his multivolume work on neoplastic progression.[8] Given the decades-long history of precancer research, why is there renewed interest in precancers at this moment?

A major stimulus for precancer research has come from the Food and Drug Administration's Modernization Act of 1997 (FDAMA).[9] The FDAMA contains provisions for "surrogate endpoints" in drug evaluation when the endpoints seem clinically useful. This opens the door to using precancers in several surrogate roles. Foods or drugs that cause precancers to regress are likely to reduce the incidence of cancer, whereas substances that increase the incidence of precancers are likely to increase the incidence of cancers that develop from those precancers.

The FDAMA seems to provide some relief from the creeping fear that neither the drug companies nor the National Cancer Institute (NCI) nor society has the resources or the patience to conduct randomized clinical trials for all of the promising new anticancer drugs, particularly if the endpoints are remote (eg, incidence or survival).[10] One of the most interesting biological features of precancers is regression.[11] The prevalence of precancers in the population is much higher than the incidence of cancers that arise from these lesions (eg, colon adenomas, actinic keratoses, squamous intraepithelial lesions of the cervix). Precancers may be amenable to treatment with agents that enhance the natural tendency of regression. It may take less time to determine whether a COX-2 inhibitor reduces the number of colon adenomas than to determine whether the same inhibitor reduces the number of colon cancer deaths.

Clinically, the different precancers have a broad range of importance. Some, such as colon adenomas and atypical nevi, can be effectively excised. Others, such as multifocal oral dysplastic leukoplakia, markedly dysplastic Barrett's esophagus, and refractory anemia with excess blasts, may pose frightening clinical dilemmas. Cancer drug trials for the more serious precancers are just as important for the affected patients as clinical trials are for invasive cancers.

Another reason for the renewed focus on precancers is the new imaging technology that has the potential to reach the cellular level. Recent advances in endoscope-coupled microscopy may allow identification of precancers in deep-seated viscera.[12]

A third stimulus for renewed interest comes from the bioinformatics community. Various high-through-

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put methods are now available for characterizing normal tissues, precancers, and cancers by their molecular profiles. This is the major goal of the NCI's Cancer Genome Anatomy Project.[13] These studies require well-designed protocols using pathology-annotated lesions logically integrated into vast data libraries. For this to occur, the scientific community is waiting for a classification of precancerous lesions that can be used consistently by the pathology community.

In 2001, an NCI-sponsored workshop urged the development of a well-characterized and practical classification for the precancers.[14] Subsequently, we published a comprehensive listing and draft classification of the precancers.[15] The draft precancer classification contains 4700 precancer terms, with 568 distinct precancer concepts and 6 precancer classes: (1) acquired microscopic precancers, (2) acquired large lesions with microscopic atypia, (3) precursor lesions occurring with inherited hyperplastic syndromes that progress to cancer, (4) acquired diffuse hyperplasias and diffuse metaplasias, (5) currently unclassified entities, and (6) superclass and modifiers. The precancer list contains both epithelial and nonepithelial precancerous lesions.

Modern classifications serve as informatics devices capable of linking, integrating, and retrieving information contained in diverse biological datasets.[16] We used a novel approach to disease classification, annotating precancer terms and classes with metadata (ie, data that describe the data). Metadata annotations are a critical part of the data, because the annotations can link data from different databases, aiding the discovery of new knowledge relevant to precancers.[17]

We anticipate that the first-draft classification of the precancers will serve as a scaffold for molecular annotation. Over the past decade, pathologists may have noticed an increase in the number and variety of biopsy specimens submitted to rule out precancerous lesions. These small specimens will have enormous importance to the practice of pathology and to cancer research. Pathologists should be actively engaged in efforts to describe and understand these lesions, and are invited to offer modifications or contributions to the draft precancer classification.

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