Approaches to Prevention of Epithelial Cancer during the Preneoplastic Period

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Summary

The development of epithelial cancer is a disease process that takes many years to reach its final, invasive stage in humans. This disease process has the potential to be controlled by physiological or pharmacological means during its preneoplastic stages. Mechanisms whereby the progression of preneoplastic lesions can be stabilized, arrested, or reversed are discussed. Pharmacological enhancement of such mechanisms by synthetic vitamin A analogs (retinoids) offers a possible means for prevention of invasive epithelial cancer.

The death rates for several common forms of epithelial cancer either increased or showed no decrease during the 20-year period from 1950 to 1970 (47). These epithelial cancer sites included the lung and pancreas in both men and women, the colon and bladder in men, and the breast and ovary in women. If we include deaths from both sexes, the above 6 sites alone will account for over half of the total cancer deaths that are expected to occur in the United States in 1975 (47). It should be apparent that these statistics tell us that some new approaches are necessary if we intend to solve the problem of epithelial cancer in humans.

The conventional clinical approach that has been followed with most epithelial cancer has been to wait until the patient has invasive disease and then treat this disease with cytotoxic chemotherapy, surgery, or radiation. None of these modalities has been uniquely successful for the treatment of all types of epithelial cancer, in spite of some advances that have occurred. In the conventional approach to the disease, cancer is treated as if it were an entity that could be destroyed or removed. Ignoring the evidence that cancer is a diffuse, evolutionary, developmental process (18). What is called "cancer" in clinical incidence statistics is the process in its terminal stages; by this time many of the physiological controls that allow for orderly epithelial growth have been lost.

An alternative approach to the problem of epithelial cancer is to consider the disease as a process that takes many years to reach its final, invasive stage in humans. This disease process has the potential to be controlled by physiological or pharmacological mechanisms during its early stages, with the goal of prevention of end-stage, invasive, terminal disease. This alternative approach requires that we consider that cancer is a disease process that begins at the time of the original carcinogenic insult, not at the time when a patient is diagnosed as having invasive disease. This alternative approach leads us to consider 2 topics. (a) What fundamental, common properties are known to be shared by preneoplastic epithelial lesions? (b) What possible mechanisms are known whereby the progression of such lesions can be stabilized, arrested, or reversed? The remainder of this paper will be concerned with a discussion of the above 2 topics.

In considering common properties of preneoplastic lesions of epithelia from different organ sites, we may begin with the axiomatic proposition that these lesions all represent altered states of epithelial differentiation; that indeed is the criterion by which they are recognized as such. In addition to this self-evident proposition, experimental and clinical studies have elucidated several other important properties of preneoplastic lesions that are not quite so apparent. First of all, preneoplastic epithelial lesions are often diffuse and multifocal; i.e., an entire organ may have multiple foci or centers of preneoplastic disease. This has now been extensively documented for the breast, lung, bladder, and liver. The problem of bilateral primary breast cancer has long been recognized as an important clinical entity (38, 40). More recent studies have further confirmed the extent to which diffuse histological disease may occur in both breasts (21, 50); a single breast may have as many as 100 discrete preneoplastic lesions (50). Similarly, multiple primary cancers of the lung have been described (17, 31), and both autopsy and bronchoscopic studies have confirmed the extent to which diffuse preneoplastic disease of the tracheobronchial epithelium can occur (1, 5, 42). Histological study of bladders removed for carcinoma has shown that preneoplastic disease is often widespread throughout the entire bladder epithelium (28, 33, 45). It has long been known that the liver of the experimental animal fed chemical carcinogens shows a diffuse preneoplastic response and that multiple discrete primary hepatomas are a frequent result of such treatment (15).

A 2nd important property of preneoplastic epithelial lesions is the statistical or probabilistic nature of their progression toward malignancy. In other words, once an individual early lesion has been initiated, it is not inevitable that it will progress toward malignancy; one can only state the statistical probability that a population of preneoplastic lesions will develop into a focus of invasive carcinoma (3, 14, 15). Although this phenomenon may be intuitively apparent to the practicing cytopathologist, who sees many more epithelial specimens with minimal histological abnormality.
than specimens with severe histological abnormality, it has not always been recognized. With the development of models for induction of epithelial cancer in the experimental animal, it is now possible to analyze the biological basis for this phenomenon. It is now clear that preneoplastic lesions, once initiated, can be arrested, stabilized, or even made to disappear. In many types of epithelia, in order for end-stage carcinomatous disease to result, it would appear that a prolonged period of exposure to carcinogenic, cocarcinogenic, or promoting agents is required. In the absence of such chronic exposure, the epithelium may repair the original carcinogenic insult and revert to a more normal differentiated state. For example, a redifferentiation of cells in a liver hyperplastic nodule can occur to yield cells that resemble normal liver cells (15). Still another example of this phenomenon in humans is the repair of preneoplastic damage in tracheobronchial epithelium which has been shown to occur upon cessation of smoking (2).

A 3rd fundamental property of many preneoplastic epithelial lesions is that they appear to be associated with enhanced DNA synthetic activity, either in the original development of lesions (20) or during the subsequent progression of lesions toward a more neoplastic state (4, 16, 22, 39, 49). This enhanced DNA-synthetic activity may simply be reflected in what is seen as basal cell hyperplasia, or it may be measured in a more sophisticated way by evaluation of an elevated mitotic index or an elevated thymidine-labeling index. Although correlations are not perfect, in many cases there is a good correspondence between the severity of a preneoplastic or neoplastic lesion and the intensity and extent of DNA synthesis within the lesion (4, 22, 39). Moreover, it appears that an important role of cocarcinogens or promoting agents, which cause preneoplastic lesions to progress, is to enhance DNA synthesis. This appears to be well established for croton oil (and its active constituents, phorbol esters) in skin carcinogenesis (10, 24); recent studies on the role of asbestos in respiratory carcinogenesis suggest a similar enhancement of DNA synthesis (19).

Whether there is any functional mechanistic connection between the enhanced DNA-synthetic activity in a preneoplastic lesion and the altered state of differentiation in that particular lesion remains a matter of conjecture.

I would now like to turn to the 2nd topic of our discussion, namely, consideration of possible mechanisms whereby the progression of preneoplastic epithelial lesions can be stabilized, arrested, or reversed. We have already mentioned that the progression of lesions to a more malignant state is a statistical process and that progression is not inevitable. This in itself suggests that there must be mechanisms whereby the organism protects itself from the development of potentially dangerous aberrant clones of invasive epithelial cells. In an important recent review, Cairns (11) has discussed 3 such possible epithelial mechanisms: (a) minimizing the number of “immortal” stem cells in the basal layer of epithelia, thus minimizing the opportunity for accumulation of dangerous mutations; (b) segregation of replicating DNA strands, so that “immortal” daughter cells receive DNA molecules that have the older of the 2 parental DNA strands, while the “mortal” daughter cells receive DNA molecules that have the younger parental strand. By means of this mechanism, permanent accumulation of dangerous mutations is lessened, since the defective DNA strands are given to cells that will be discarded from the epithelium; and (c) restricting stem cells to limited territories, so that they cannot compete with each other. Such a mechanism isolates potentially dangerous stem cells and assures that their defective progeny are discarded from the epithelium, rather than allowing them to form expanding clones of replicating cells.

There are other innate protective mechanisms that are known to exist, such as endocrine and immunological responses that can suppress the development of invasive cancer. The suppression of breast cancer in the experimental animal by pregnancy was described many years ago (25), and endocrine influences that suppress the development of human breast cancer are well established (26, 32). The important role of the immune system as an innate protective mechanism against carcinogenesis has been discussed at length by others (29, 34) and will not be considered here.

Important as all innate protective mechanisms may be for suppression of potentially carcinogenic lesions, they are not adequate in themselves for elimination of the epithelial cancer problem in humans. The carcinogenic burden in our external environment or internal milieu is too great, and if we are to achieve the goal of prevention of invasive cancer during its preneoplastic period some type of exogenous nutritional, hormonal, immunological, or pharmacological enhancement of innate protective mechanisms will be required.

In the remainder of this paper I will discuss 1 possible approach to the problem of enhancement of protective mechanisms. This approach involves the use of vitamin A and its synthetic analogs (which, taken together, we shall call retinoids) for modulation of preneoplastic epithelial lesions. This topic has been reviewed recently (48) and only a brief summary will be given. I would like to emphasize that this is not a nutritional fad. There is a definite rational basis for considering retinoids as agents to modify preneoplasia, since retinoids are essential for the normal cellular differentiation of epithelia that account for more than one-half of the total primary cancer in both men and women. These epithelia include those of the bronchi and trachea, stomach, intestine, uterus, kidney and bladder, testis, prostate, pancreatic ducts, and skin. In the absence of retinoids in the diet, normal cellular differentiation does not occur in these epithelia. In many ways, the mode of action of retinoids resembles that of androgenic or estrogenic steroids which act on specific prostatic or uterine target sites.

Many years ago, Wolbach and Howe (51) noted that there was an increase in mitotic activity in certain epithelia of vitamin A-deficient animals, and they suggested that the dedifferentiated metaplastic epithelial lesions of vitamin A deficiency had features in common with those of neoplastic lesions. It is presently known that there is very little DNA synthesis under normal conditions in some epithelia, such as those of the trachea or bladder, that depend on retinoids for maintenance of normal differentiation. Under normal conditions, the basal cells of these epithelia are minimally labeled by thymidine; cell cycle times have been estimated to be as long as 2 weeks for tracheal epithelium and up to 6
Prevention of Epithelial Cancer

In summary, we have discussed some of the fundamental properties of preneoplastic epithelial lesions which suggest that there may be alternative ways to approach the entire problem of epithelial cancer in humans, other than to destroy invasive cancer cells with cytotoxic agents, radiation, or surgery. Basic to this approach is the concept that we must begin to think about cancer as a disease process that in humans begins many years before we record "cancer" as such in our disease prevalence statistics. Thus, there is an excellent likelihood that significant preneoplastic lesions are to be found in tremendous numbers of our population whom we do not presently consider to have cancer. Until we overcome this fundamental semantic problem and begin to realize that the proper time to control the disease is while it is "preneoplastic," before it is diagnosed as "invasive cancer" and thus often likely to kill its host within less than 5 years, we will have to depend on the rather unsatisfactory modalities of cytotoxic chemotherapy, radiation, and surgery.

This Conference has presented an outstanding summary of our current knowledge about preneoplasia in epithelia. It should be apparent that our understanding of this entire problem is still in a very primitive state and that an immense amount of basic research remains to be done in this area. Preneoplasia has not been a very popular area for research. The methodology has been difficult, and end points and markers to quantitate results have been few. In spite of these difficulties, I believe that there is a growing realization that we must solve the problem of epithelial preneoplasia if we are ever to control invasive epithelial cancer. Although this is not a very prevalent viewpoint in cancer research as a whole, I am sure that there are many investigators here today who would agree. As a closing statement, I cannot possibly do better than to repeat the conclusion of Wellings, Jensen, and Marcum (50) in their recent review of preneoplastic lesions of the breast:

A new and productive approach to the problem of human breast cancer would be the focus of more attention on the transformation from normal to preneoplastic lesions and from preneoplastic lesions to carcinoma in situ rather than the more traditional emphasis on the progression of carcinoma in situ to invasive cancer and metastasis. Certainly, great expenditure of resources for the improved outlook of the woman after she has developed the disease has resulted in little improvement in patient salvage. More emphasis might be shifted now to elucidation of the remote and early conditions that precede human breast cancer. This is perhaps the best approach to prevention, early diagnosis and cure.

In this one statement (Ref. 50, p. 242) the authors have given us a challenge to develop an entire new field of investigation for all epithelial cancer. I believe that many of us who have attended this stimulating meeting share a common belief that it is a challenge well worth undertaking.

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