Perspectives in Cancer Research

Natural History of Intraepithelial Neoplasia in Humans with Implications for Cancer Chemoprevention Strategy

Charles W. Boone,1 Gary J. Kelloff, and Vernon E. Steele

Chemoprevention Branch, Cancer Prevention Research Program, Division of Cancer Prevention and Control, National Cancer Institute, NIH, Bethesda, Maryland 20892

Abstract

Intraepithelial neoplasia is of critical importance to the cancer chemoprevention field because it is a target condition for which drugs must be sought that will prevent its development or stop its progression. The term “dysplasia” refers to the morphological alterations that characterize intraepithelial neoplasia and according to many authors consists of seven basic morphological changes that occur in the majority of human epithelia, as well as in the epithelium of mouse skin papillomas induced by 7,12-dimethylbenz[a]anthracene and 12-O-tetradecanoylphorbol-13-acetate: increased nuclear size; altered nuclear shape; increased nuclear stain uptake; nuclear pleomorphism (increased variation in nuclear size, shape, and stain uptake); increased mitoses; abnormal mitoses; and disordered or absent maturation. Clonal evolution appears to begin early in the neoplastic process during intraepithelial neoplasia. Aneuploidy has been found during intraepithelial neoplasia in many human epithelia, and, in association with other forms of genetic instability, may provide the increase in genetically variant cells required for clonal evolution to occur. It is postulated that two major factors affecting the rate of progression of intraepithelial neoplasia are the cellular mutation rate, which is enhanced by environmental carcinogens, and the cellular proliferation rate, which is enhanced by agents that include sex hormones, inducers of chronic inflammation, and irritant chemicals which stimulate reactive hyperproliferation. A preferred chemoprevention strategy should consist of the development of drugs and drug combinations which will block mutagenic carcinogens or prevent epithelial hyperproliferation or its causes. Two examples of the induction of regression of intraepithelial neoplasia by chemopreventive drugs are the regression of oral leukoplakia produced by β-carotene and the regression of colorectal polyps in patients with familial polyposis produced by sulindac. It is evident that there is a strong need for more research on the induction of regression of intraepithelial neoplasia with chemopreventive agents. There is also a critical need to identify and develop biomarkers that correlate with the appearance and regression of intraepithelial neoplasia.

Human epithelial neoplasia generally begins as a focal, clonal (1) overgrowth of morphologically altered stem cells near the basement membrane which expands upward and laterally within the confines of the epithelium. This intraepithelial stage of neoplastic development typically lasts for a number of years before invasion occurs (2). A better understanding of human intraepithelial neoplasia is of critical importance to investigators in the chemoprevention field; it can assist in the more rational design of drugs that will slow or stop the progression of intraepithelial neoplasia, and it will also assist in the development of early biomarkers that are modulated by chemopreventive drugs.

Morphological Characteristics of Intraepithelial Neoplasia

Fortunately, the early development and widespread use of tissue biopsies and cytological screening of exfoliated cells from the uterine cervix has produced a system of nomenclature and descriptive terminology that can be applied to other epithelia. In particular, the equivalence of the terms “dysplasia” and “intraepithelial neoplasia” is especially appropriate and is widely accepted by gynecological cytopathologists, who use the term “cervical intraepithelial neoplasia” (2). In recent years the term “dysplasia” has been used by six separate WHO committees to designate the collection of morphological changes characteristic of intraepithelial neoplasia (3–8). From a survey of the literature there appear to be seven irreducible defining morphological criteria of intraepithelial neoplasia: increased nuclear size, altered nuclear shape, increased nuclear stain uptake, nuclear pleomorphism (increased variation in size, shape, and stain uptake), increased mitoses, abnormal mitoses, and disordered or absent maturation. Each of these criteria has been specifically listed for the term “dysplasia” in articles on uterine cervix (2, 9–14), oral leukoplakia (15–18), larynx (19), lung (20), esophagus (21), colon (7, 22–25), urinary bladder (26–30), and skin (31).

Fig. 1 presents an example of dysplastic change in histological sections of human vocal cord.2 Each of the criteria of dysplasia, except increased mitoses, is shown in Fig. 1B and is contrasted with the normal tissue in Fig. 1A. The abnormal “3-group” mitosis in Fig. 1B is due to clustering of a few nondisjoined chromosomes at each pole of the metaphase spindle. After cytokinesis each daughter cell will be aneuploid for the chromosomes which did not make it to the metaphase plate. The normal maturational stratification of basal, intermediate, and superficial cells seen in the normal vocal cord is absent in the severely dysplastic vocal cord.

Estimating the Severity of Intraepithelial Neoplasia

Fig. 2 illustrates how the severity of intraepithelial neoplasia is estimated from the extent of the lesion as well as on the degree of deviation from normal morphology. The initial clonal focus of proliferating neoplastic cells near the basement membrane enlarges by expanding upward and laterally within the epithelium, replacing normal epithelial cells as it does so. The lesion is called “mild dysplasia” when the neoplastic cells extend to the junction of the lower and middle thirds of the epithelium, “moderate dysplasia” when they extend to the junction of the middle and upper thirds, and “severe dysplasia” when they extend to the full thickness of the epithelium. In the case of cervical intraepithelial neoplasia grades 1, 2, and 3 are applied to mild, moderate, and severe dysplasia (2).

In severe dysplasia of cervical and other epithelia, where there is complete absence of normal epithelial cells in the topmost layers, the term “carcinoma in situ” is sometimes used. There is now much well reviewed evidence that “severe dyspla-

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1 To whom requests for reprints should be addressed.

2 Each histological section of human tissue in this paper is a drawing based on a selected photograph in the literature, with modifications to increase emphasis and eliminate artifact. The reference to the photograph is cited in the figure legend of each drawing.
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Fig. 1. Human vocal cord epithelium. Normal, showing squamous epithelium with basal, intermediate, and superficial regions of maturation. B, dysplastic, showing all the criteria of dysplasia except increased mitoses. Note abnormal, "3-group" mitosis.

Fig. 2. Estimating the severity of intraepithelial neoplasia (dysplasia). The extent of the lesion as well as the deviation from normal cellular morphology is used.

"Intraepithelial neoplasia" and "carcinoma in situ" are virtually identical and form one single spectrum of neoplastic disease (9, 10). Unfortunately, the term "carcinoma in situ" connotes the false concept of a disease entity that is separate and distinct from dysplasia; this term has misled some into assuming that the neoplastic process actually starts with carcinoma in situ and that the preceding morphological changes of dysplasia are to be considered "preneoplastic." On the contrary, the neoplastic process is a single indivisible continuum that begins within the epithelium as mild dysplasia and progresses through dysplasia of increasing extent and severity until finally invasion across the basement membrane occurs, at which time, by definition, the terms "malignant," "cancer," or "carcinoma" apply. [It is a curious convention of cancer nomenclature that the same morphological changes identified as "severe dysplasia" before invasion are called "anaplasia" after invasion (32)]. Thus, the neoplastic continuum of intraepithelial neoplasia may be called preinvasive, premalignant, or precancerous, but it is an error to call it preneoplastic. As an example of this statement, the thickened epithelium covering the head of an adenomatous polyp of the colon, an undoubted intraepithelial neoplasm, exhibits all degrees of dysplasia. With time, the polyp enlarges and the severity of the dysplasia increases until ultimately invasion into the stalk of the polyp occurs, at which point, by definition, the neoplasm has become a malignant cancer (25). Clearly, the dysplasia seen here characterizes a neoplastic, and not a preneoplastic, process. Foulds (33) had this opinion on the subject: "The most frustrating gap in the terminology of pathology of tumours in man is a lack of a satisfactory name for the so-called pre-cancerous lesions... "Preneoplastic"... can only mean that the lesions are not neoplastic whereas I maintain strongly that they are neoplastic and that this should be recognized in their designation." The name that Foulds might have accepted is "intraepithelial neoplasia."

Intraepithelial Neoplasia in Human Epithelia

The above seven morphological criteria of intraepithelial neoplasia are illustrated below in three representative epithelia, uterine cervix, lung, and colon.

Uterine Cervix. Fig. 3 illustrates the progression of intraepithelial neoplasia from mild (Fig. 3A) to severe (Fig. 3D) grade. Abnormal mitoses, a marker for aneuploidy (11), begin to become prominent at the stage of moderate dysplasia (13). Aneuploidy itself is found even in mild dysplasia (13). Any degree of dysplasia is expected to progress to severe dysplasia/carcinoma in situ in about 80% of cases during a 10-year period (34). Once the stage of severe dysplasia/carcinoma in situ is reached, further progression occurs in about 20% of cases within 5 years (35).

Lung. Fig. 4 shows the changes typically induced in human bronchial epithelium by smoking. The respiratory epithelium first undergoes replacement by squamous epithelium, a process termed "squamous metaplasia," which progresses from an immature, newly formed state to a mature state resembling epidermis (Fig. 4, A-D). The mature squamous epithelium is then at risk for subsequently developing dysplastic changes characteristic of intraepithelial neoplasia (Fig. 4E).

Colon. Fig. 5 shows that in contrast to the mucus-secreting epithelium of the respiratory tract, the mucus-secreting columnar epithelium of the colonic crypts does not undergo squamous metaplasia prior to the development of intraepithelial neoplasia. Instead, the crypt epithelium first becomes directly hyperplastic and then develops the dysplastic changes of intraepithelial neoplasia. The foci of dysplasia seen in the flat mucosa of ulcerative colitis, a chronic proliferative disease of unknown etiology, are morphologically identical to the dysplasia seen in the epithelium covering adenomatous polyps. Fig. 5D demonstrates a characteristic "snowplow" effect of a laterally spreading proliferative focus of intraepithelial neoplasia. The dysplastic cells literally shave off the adjacent hyperplastic normal epithelium from the basement membrane.
Intraepithelial Neoplasia in the DMBA\(^3\)/TPA Mouse Skin Model

The progression of the dysplastic morphological changes of intraepithelial neoplasia in the epithelium of skin papillomas of mice, induced by skin painting once with DMBA and twice weekly with TPA, appears to be virtually identical to the analogous changes seen in human epithelia that characterize intraepithelial neoplasia (38). The photographs in Fig. 6, A-D, show the sequence of morphological changes of intraepithelial neoplasia in the SENCAR mouse model.\(^4\) The conditions of DMBA and TPA application are given in the Legend to Fig. 6. An initial period of hyperplasia is followed by dysplasia of increasing severity. The characteristics of progressive dysplasia seen in human epithelia are recapitulated with remarkable similarity. The data in Table 1 show that as promotion proceeds, the epithelium of the papillomas becomes progressively more aneuploid, reaching 100% aneuploidy after 30 weeks (39). As will be discussed below, aneuploidy is also commonly seen in human intraepithelial neoplasia.

Suitability of the Mouse Skin Model for Experimental Studies in Chemoprevention. The mouse skin model appears to lend itself very well to a study of the effects of chemopreventive agents on the histomorphological progression of intraepithelial neoplasia. Each papilloma is typically monoclonal, being derived from a single stem cell of the so-called epidermal proliferative unit (40). A papilloma on the skin of a treated mouse represents a convenient visual marker for a focus of developing intraepithelial neoplasia that can be observed, treated, and biopsied, analogous to the human case where an adenomatous polyp of the colon represents a visual marker for a focus of progressing intraepithelial neoplasia (25).

More importantly, the mouse skin model provides an opportunity to study mechanisms of regression of intraepithelial neoplasia at the histological and biochemical levels, both spontaneous regression and regression modulated by chemopreventive drugs. There appear to be no reported histological studies specifically directed at documenting the mechanisms of mouse skin papilloma regression.

Human “Field Cancerization” Studied in the Mouse Skin Model. Frequently large areas of an epithelial cell sheet, or “field,” are exposed to a uniform flux of carcinogen delivered from the environment. Ready examples are solar UV irradiation to the skin or the carcinogens in tobacco smoke delivered to large areas of respiratory epithelium and ultimately to bladder epithelium. The phenomenon in humans of multiple epithelial foci of intraepithelial neoplasia progressing concurrently to form multiple primary cancers, usually at different times, has been called “field cancerization” by Slaughter et al. (41). An example of the magnitude of this problem is shown by a reported 10–40% incidence of later second primary tumors somewhere in the aerodigestive tract in patients with squamous carcinoma of the head and neck (42). The mouse skin model is an excellent system in which to study field cancerization since, as stated above, each papilloma is a visual marker for a separate clonal focus of intraepithelial neoplasia that can be observed.

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\(^3\) The abbreviations used are: DMBA, 7,12-dimethylbenz(a)anthracene; TPA, 12-O-tetradecanoylphorbol-13-acetate.

\(^4\) Photographs are of histological sections prepared from paraffin blocks provided by A. J. P. Klein-Szanto (38).
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Fig. 4. Human bronchial epithelium. The respiratory epithelium is first replaced by squamous epithelium, a process termed "squamous metaplasia," in which dysplasia then may develop. A, normal bronchial respiratory epithelium with goblet cells and ciliated cells (20). B, beginning replacement of respiratory epithelium by immature squamous epithelium pushing up from below. The large vacuoles in the respiratory epithelium represent beginning degeneration (36). C, complete replacement of the respiratory epithelium by immature squamous cells (36). D, later maturing of the squamous cells (20). E, Severe dysplasia developing in the mature squamous cells (37).

for the growth suppressive or regressive effects of various chemo-preventive agents.

Clonal Evolution during the Progression of Intraepithelial Neoplasia

Clonal evolution was first documented in hematopoietic and lymphopoietic neoplasms by Nowell (43, 44) and is generally considered to occur in solid neoplasms as well. Clonal evolution is the process occurring within tumor cell populations of the continuous production of genetically variant cells, with selection and clonal expansion of those variants that have an additional growth advantage under the prevailing set of selection pressures. The sequential emergence of multiple competing subclones within the tumor forms the basis for the continuing
changes in various “unit characters” of the neoplastic phenotype described as “tumor progression” by Foulds (45).

It is now apparent that clonal evolution within epithelial neoplasms begins early in the neoplastic process during intraepithelial neoplasia. A clear example, as described by Vogelstein et al. (46), is the sequence of gene mutations, each followed by clonal expansion, that occurs during the progression of intraepithelial neoplasia in adenomatous polyps of the human colon.

Genetic instability, as manifested by gene mutations, gene amplifications, chromosomal structural rearrangements and defects, and aneuploidy, is characteristic of practically all cancers and is postulated to be the basis for the increased production of genetically variant cells associated with clonal evolution (47, 48). Of the four types of genetic change mentioned, aneuploidy is technically the easiest to determine because of recent advances in quantitative flow and image cytospectrophotometry (49). These techniques and karyotypic analysis have revealed that aneuploidy is present in a large percentage of cases of intraepithelial neoplasia exhibiting moderate or severe dysplasia, as described for the cervix (13, 50), skin (51), oral leukoplakia (52), larynx (53, 54), lung (55), esophagus (56), stomach (57), and colorectum (58, 59).

Considering that in an aneuploid cell population there is variation not only in the total number of chromosomes per cell but also in the number of copies of each chromosome per cell, the number of karyotypically variant cells in the population becomes considerable, and conditions are established for the development of clonal evolution. If one adds one or more of the other forms of genetic instability that may be occurring concurrently with aneuploidy, i.e., chromosome structural changes, gene amplifications, and gene mutations, the likelihood of the presence of clonal evolution is increased even more. Foulds, in his description of “intermediate phase B" intraepithelial neoplastic lesions, which include mild, moderate, and severe dysplasia, discusses their progression in terms of the stepwise acquisition of permanent new “unit” changes in morphology and function (33). These changes appears to be the phenotypic expression of the intraepithelial clonal evolution discussed above.

Since during clonal evolution each sequentially expanding clone possesses an additional growth advantage, the repeated cycles of genetic variation and clonal expansion should be associated with an increase in mitotic frequency of the intraepithelial neoplastic cell population. This was confirmed by Richart (60), who showed that during the progression of cervical intraepithelial neoplasia, the tritiated thymidine labeling index rose from a normal value of 4.6% to 10.3% during mild dysplasia to 46.5% during “carcinoma in situ.”

The overall picture emerges of epithelial neoplasia as a continuum of clonal evolution, starting with the first mutation and clonal expansion that initiates intraepithelial neoplasia and progressing through successive cycles of genetic variation and clonal expansion, first within the epithelium and later during invasion and metastasis.

Implications of Intraepithelial Neoplasia for Cancer Chemoprevention Strategy

Chemoprevention was originally defined by Sporn et al. (61) in 1976 as the use of drugs to prevent cancer, i.e., to prevent...
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Fig. 6. SENCAR mice were skin-painted once with 10 nmol of DMBA and twice weekly with 2 μg of TPA for 40 weeks. A, normal Sencar mouse skin. B, Hyperplasia (10 weeks). C, mild dysplasia in a papilloma (20 weeks). D, E, severe dysplasia in a papilloma showing abnormal mitoses (30-40 weeks).

invasive neoplasia. Sporn’s (62) definition included the use of drugs to eliminate or reduce what was then described as preinvasive intraepithelial precursor lesions which progress to invasive cancer and what is now identified as intraepithelial neoplasia. Although the elimination of intraepithelial neoplasia with drugs could be considered as the “therapy” of neoplasia, as shown by Sporn’s definition it is customarily viewed as the prevention of invasive neoplasia, or cancer. The concept of chemoprevention obviously also includes the use of drugs that act earlier to prevent the onset of intraepithelial neoplasia.

Chemoprevention by Blocking the Effect of Chronic Exposure to Mutagenic Carcinogens with Antimutagenic Agents. Experimentally, Druckrey (63) has shown, for a number of carcinogens, cancer types, and animal species, that when animals are given a daily dose of carcinogen over a prolonged period, the length of time before the appearance of cancer (when intraepithelial neoplasia is progressing) becomes shorter as the daily dose of carcinogen is increased, over a wide range of doses. An equivalent statement of this relationship is: the higher the level of exposure to a carcinogen, the faster is the rate of progression of intraepithelial neoplasia. We postulate a mechanism for this effect as follows. Increased exposure of the intraepithelial neoplastic cells to a carcinogen increases their mutation rate, which speeds clonal evolution because it leads to the more rapid production of genetically variant cells and to a corresponding increase in the probability that variants with a growth advantage will arise and undergo selective clonal expansion.

It therefore appears that the long-term administration of an
antimitogenic drug should be considered in cases in which prolonged exposure to a mutagenic carcinogen is likely. Humans may be chronically exposed to carcinogens in the diet, atmosphere, and workplace and also in their life-style habits, particularly the use of tobacco. Wattenberg (64) has reviewed the various mechanisms by which chemopreventive agents can block mutagenic carcinogens. Wattenberg’s type A blocking compounds, which induce phase II conjugating enzymes, such as N-acetylcysteine (65) and oltipraz (66), are especially desirable because they do not carry the risk, however small, of modulating the phase I cytochrome P-450 mixed function oxidases in a way that causes them to activate, rather than detoxify, ingested procarcinogens. Oltipraz is strongly cancer preventive in a number of animal model systems (67).

Chemoprevention by the Prevention of Hyperproliferation. We postulate that exposure of ongoing intraepithelial neoplasia to environmental or endogenous factors which stimulate epithelial proliferation will increase the cellular mutation rate in the neoplastic cell population and therefore will speed the rate of neoplastic progression for the reasons given above. The cellular mutation rate is increased in two different ways when proliferation is increased: (a) the selective clonal expansions during clonal evolution occur more rapidly, and the resulting greater population size per given time interval increases the probability of subsequent mutational events, either spontaneous (68) or carcinogen-induced; (b) the susceptibility of the neoplastic population to mutations, or to spontaneous mutations, increases because a larger fraction of the cells are in the S phase of the cell cycle, when there is greater exposure of mutagen-vulnerable single-stranded DNA and also less time for DNA repair enzymes to act (68, 69). Direct experimental evidence in support of the concept that epithelial hyperproliferation speeds the rate of intraepithelial neoplastic progression is found in the mouse DMBA/TPA model of skin carcinogenesis. By increasing the dose of TPA, which stimulates the rate of mouse epidermal proliferation in a dose dependent fashion (70), the time period before appearance of squamous cell carcinomas is shortened (71), i.e., the rate of progression of intraepithelial neoplasia during this period (38) is sped up.

Preston-Martin et al. (72) has reviewed in detail the numerous factors which produce a sustained increase in epithelial cell proliferation and which are associated with an increased risk of cancer. Examples include the hormones estrogen and testosterone, infectious agents causing chronic inflammation such as the hepatitis B virus, and irritant chemical agents which stimulate reactive hyperproliferation, e.g., alcohol and components in tobacco smoke. One would expect these factors to operate not only prior to the onset of intraepithelial neoplasia but also during its progression.

Chemopreventive drugs that prevent epithelial hyperproliferation may act either by blocking a specific stimulant of proliferation or by suppressing the process of proliferation itself. Calcium blocks the proliferative effect of bile acids on colon epithelial cells by combining with them to form insoluble complexes and has been given to patients with familial polyposis with the aim of reducing the rate of adenomatous polyp development, and therefore the risk of cancer (73). α-Difluoromethylornithine suppresses cell proliferation by blocking the polyamine pathway required for cell growth. α-Difluoromethylornithine is markedly effective in preventing cancer development in animal models (67) and is now being tested for safety as a chemopreventive agent in humans (74). In experimental animals, retinoids inhibit cell proliferation induced by exposure to carcinogens or promoters (75). It has been hypothesized that retinoids suppress proliferation by enhancing the normal process of differentiation which is blocked or altered by the action of carcinogens (76). The retinoid, 4-hydroxyxenylretinamide, is now being evaluated for the prevention of primary lesions of the contralateral breast in women who had breast cancer (74).

Induction of Regression of Intraepithelial Neoplasia with Chemopreventive Agents. The most desirable effect of a chemopreventive agent would be to produce regression of intraepithelial neoplasia, even when aneuploidy or some other form of genetic instability is present. The disappearance of aneuploid cells during the spontaneous regression of intraepithelial neoplasia has been documented for human bronchial and cervical epithelium (77, 78). Possible mechanisms to explain the disappearance of aneuploid cells must involve supracellular events, since it would be unlikely that aneuploid cells could revert back to the euploid state. One reported mechanism involving the regression of cervical intraepithelial neoplasia is the undergrowth of dysplastic epithelium by adjacent normal epithelium, with uplifting and exfoliation of the dysplastic cells, a phenomenon that was seen in 9 cases of 1755 cervical biopsies screened (79).

There are two published examples of a chemopreventive agent causing regression of intraepithelial neoplasia. One is by Garewall (80), who presents photographs of biopsies of a large oral leukoplakic lesion before and after a 3-month course of oral β-carotene. The initial biopsy exhibited moderate dysplasia with multiple abnormal mitoses. The presence of abnormal mitoses makes it strongly probable that aneuploidy was present. After the patient had received oral β-carotene, the lesion appeared to regress macroscopically, and the second biopsy revealed only normal oral mucosa. The other example, reported by several authors (81, 82), is the regression of colorectal adenomatous polyps induced by sulindac, a nonsteroidal antiinflammatory agent, in patients with familial polyposis and Gardner’s syndrome. The most recent report (83) describes a randomized, placebo controlled, double blind crossover study in 10 patients with familial polyposis who had residual rectal

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* SCC, squamous cell carcinoma.
adematous polyps after colectomy. Sulindac p.o. induced complete regression of the polyps in 6 patients and almost complete regression in 3 patients. After the sulindac was discontinued, recurrence of polyps occurred in some, but not all, patients within 3–4 months. A second course of sulindac produced complete regression of the recurrent polyps.

Need for Biomarkers That Correlate with Intraepithelial Neoplasia. The development of intraepithelial neoplasia is associated with the appearance of a number of individual biomarkers that have been categorized as genomic (oncogene activation, gene amplification, aneuploidy), proliferative [thymidine labeling index, nuclear antigens such as Ki-67 and proliferating cell nuclear antigen (PCNA)], and differentiation related (abnormal glycoconjugate antigens, loss of cytoskeleton antigens) (84, 85, 86). Since the diagnosis of intraepithelial neoplasia requires the evaluation of dysplasia by trained specialists, it would be highly desirable if a group of biomarkers could be developed which correlate closely with the presence of intraepithelial neoplasia and which could be determined in an objective and quantitative manner by nonexperts. Some biomarkers would be expected to disappear concurrently with the regression of intraepithelial neoplasia produced by a chemopreventive agent. Others, such as a differentiation antigen not normally found in dysplastic epithelium, would reappear with the return to normal morphology. In addition to the use of biomarkers as a diagnostic tool, a goal of highest priority in chemoprevention research is the development of regression correlated biomarkers which can be used as modulatable intermediate end points in clinical trials of chemopreventive agents (87). Such intermediate end point biomarkers are needed to supplement the presently used end point of cancer incidence reduction, which requires large study populations, long observation periods, and great expense (74).

References
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