

# A Genetic Explanation of Slaughter's Concept of Field Cancerization: Evidence and Clinical Implications<sup>1</sup>

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## Abstract

The concept of "field cancerization" was first introduced by Slaughter *et al.* [D. P. Slaughter *et al.*, *Cancer (Phila.)*, 6: 963–968, 1953] in 1953 when studying the presence of histologically abnormal tissue surrounding oral squamous cell carcinoma. It was proposed to explain the development of multiple primary tumors and locally recurrent cancer. Organ systems in which field cancerization has been described since then are: head and neck (oral cavity, oropharynx, and larynx), lung, vulva, esophagus, cervix, breast, skin, colon, and bladder. Recent molecular findings support the carcinogenesis model in which the development of a field with genetically altered cells plays a central role. In the initial phase, a stem cell acquires genetic alterations and forms a "patch," a clonal unit of altered daughter cells. These patches can be recognized on the basis of mutations in *TP53*, and have been reported for head and neck, lung, skin, and breast cancer. The conversion of a patch into an expanding field is the next logical and critical step in epithelial carcinogenesis. Additional genetic alterations are required for this step, and by virtue of its growth advantage, a proliferating field gradually displaces the normal mucosa. In the mucosa of the head and neck, as well as the esophagus, such fields have been detected with dimensions of >7 cm in diameter, whereas they are usually not detected by routine diagnostic techniques. Ultimately, clonal divergence leads to the development of one or more tumors within a contiguous field of preneoplastic cells. An important clinical implication is that fields often remain after surgery of the primary tumor and may lead to new cancers, designated presently by clinicians as "a second primary tumor" or "local recurrence," depending on the exact site and time interval. In conclusion, the development of an expanding preneoplastic field appears to be a critical step in epithelial carcinogenesis with important clinical consequences. Diagnosis and treatment of epithelial cancers should not only be focused on the tumor but also on the field from which it developed.

## Introduction

In their classical paper of 1953, Slaughter *et al.* (1) used the term field cancerization for the first time, when studying oral cancer. The authors did not provide a clear definition, but by performing extensive histological examinations, a concept was proposed describing issues covered by the term field cancerization: (a) oral cancer develops in multifocal areas of precancerous change; (b) abnormal tissue surrounds the tumor; (c) oral cancer often consists of multiple independent lesions that sometimes coalesce; and (d) the persistence of abnormal tissue after surgery may explain SPTs<sup>3</sup> and local recurrences. Many investigators have cited this paper in connection with the development of SPTs. Field cancerization or the "field effect" was and

is used in the context of the existence of (pre-)neoplastic processes at multiple sites, often with the unproven assumption that these have developed independently. Organ systems in which field cancerization has been described are: HNSCC in oral cavity, oropharynx, and larynx (2); lung (3); esophagus (4); vulva (5); cervix (6); colon (7); breast (8); bladder (9); and skin (10).

Many recent studies have addressed the molecular basis of the process of cancer development, and genetic progression models have been proposed for various tumor types. It is now well established that an accumulation of genetic alterations forms the basis for the progression from a normal cell to a cancer cell, referred to as the process of multistep carcinogenesis (11). Until now, the number of genetic alterations is known to increase with the level of malignancy as judged by histopathological examination. The process of field cancerization can be defined in molecular terms, and its position in the process of multistep carcinogenesis can be delineated. Several lines of evidence, presented by us and other investigators, indicate that the presence of a field lesion with genetically altered cells is a distinct biological stage in epithelial carcinogenesis with important clinical implications. Because most studies on field cancerization have been performed on HNSCC, we will focus on this tumor type as a model.

## Characteristics of a Genetically Altered Field

Molecular analyses have been performed on tumor-adjacent "normal tissue" and surgical margins to assess the presence of a field lesion. Markers used are LOH, microsatellite alterations (12), chromosomal instability (13), and mutations in the *TP53* gene (14) detected by DNA amplification techniques, immunohistochemistry, and *in situ* hybridization. By measuring LOH, a quantitative analysis has been performed on HNSCC, and it was shown that at least one-third (10 of 28) of unselected tumors have tumor-associated genetic alterations in a biopsy taken from the macroscopically normal mucosa adjacent to the tumor (12). This frequency is based on the analysis of four biopsies that were taken in each quadrant surrounding the tumor, using 15 microsatellite markers on 6 different chromosomes. In the majority (7 of 10) of these cases the genetically altered cells could also be found in margins of a specimen that had been removed by the surgeon. These lesions were >4 mm in diameter and, as is inherent of LOH determinations, contained >50% aberrant cells. Histopathological analysis has failed to detect tumor cells in these margins. So, it appears that in at least a quarter of a group of unselected HNSCC patients cells with tumor-associated genetic alterations are left behind in the patient. Detailed analysis of the alterations between a mucosal lesion and the corresponding tumor revealed a genetic relationship for almost all of the cases (12). In this context it is important to discuss the study of Brennan *et al.* (14). These authors showed with a very sensitive *TP53* plaque assay that cells clonally related to the tumor could be detected in the surgical margins of more than half of all of the HNSCC patients; these margins were considered to be tumor-free using conventional histopathology. It is likely that in some cases relatively large groups of preneoplastic cells were detected by this

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<sup>3</sup> The abbreviations used are: SPT, second primary tumor; HNSCC, head and neck squamous cell carcinoma; LOH, loss of heterozygosity; SFT, second field tumor.

method, as was indeed shown later by van Houten *et al.* (15). Taken together, we interpret in these data that HNSCC can arise in a contiguous field of preneoplastic cells, which is principally of monoclonal origin (12–16). This presumed monoclonality is supported by the notion that multiple biopsies share “early markers of carcinogenesis” (15–17). Heterogeneity with respect to the “late” markers point to the development of multiple subclones, known as the process of clonal divergence (18).

On the basis of recent molecular findings, we propose the following definition of field cancerization: “the presence of one or more areas consisting of epithelial cells that have genetic alterations. A field lesion (or shortly ‘field’) has a monoclonal origin, and does not show invasive growth and metastatic behavior, the hallmark criteria of cancer.” A field lesion is preneoplastic by our definition; it may have histological aberrations characteristic for dysplasia. A detailed comparison between histology (dysplasia grading) and molecular pathology in oral fields shows (19): (a) a relatively large interobserver variability of histopathological grading; (b) a genetically altered field can occur with normal histology; and (c) all moderately and severely dysplastic lesions, and about two-thirds of the mildly dysplastic lesions show genetic alterations. It was additionally shown that genetically altered cells in a field show a high proliferative capacity, as determined with KI-67 staining (19).

### Field Precursor Lesions: Patches

In various epithelia, clusters of cells with cancer-associated genetic alterations can be found that are much smaller than the fields described above. With respect to tumor-adjacent oral mucosa, clusters (<200 cells diameter) can be observed with a TP53 immunostaining (15). Sequence analysis showed that the type of mutation in *TP53* in these clusters always differed from that in the tumor (15). Following the criteria of Garcia *et al.* (20), we refer to these clusters as “patches,” defined as a group of cells that share a common genotype, contiguous at the moment of consideration (20). Waridel *et al.* (21) found that clusters of cells with *TP53* mutations are present in biopsies of the normal mucosa of HNSCC patients, and particularly frequent in patients with multiple primary head and neck tumors. Clusters of *TP53*-mutated keratinocytes have been observed in normal human skin (22). In sun-exposed skin these clusters were more frequent and larger than in sun-shielded skin. Park *et al.* (23) showed by LOH analysis in the normal bronchial epithelium of lung cancer patients small patches with genetic alterations different from the primary tumor. Analogously, patches with genetic alterations were also found in histologically normal breast tissue (24).

These mutated TP53-positive patches can be considered equivalent to a “clone” or “clonal unit,” defined as a family of cells from a common progenitor (20, 22). These units with a stem cell, transit-amplifying and differentiated cells make up the squamous epithelium (25). When the stem cell acquires a genetic alteration, its derived clonal patch will contain the same change, explaining the cluster of TP53-immunopositive cells. There are few data concerning the patch size in human tissues, based on the analysis of the pattern of X inactivation (20). For bladder (26) and gastric (27) epithelium a size of 1 cm<sup>2</sup> has been reported. For skin, the organ system most comparable with the head and neck mucosa, a size of 2 mm in diameter has been estimated (28). This dimension corresponds to the patch size in the oral epithelium we have derived from a maximum diameter of 200 TP53 immunopositive cells and a cell diameter of 10 μm (15).

### Field and Second Primary Cancer

The phenomenon of field cancerization has often been brought up to explain the occurrence of SPTs. A number of recent studies have

looked into this in more detail, and have addressed the genetic relation between multiple neoplastic and preneoplastic lesions within one organ system. For a rather high proportion of cases in oral cavity (Ref. 29 and references therein), bladder (Ref. 30 and references therein), and esophagus (4), it was shown conclusively that there was a common clonal origin, even if the lesions were >7 cm apart. The decision that the lesions are genetically related is based on the similarity of genetic changes. A more detailed description of the method that can be used, and the problems involved when determining the genetic relationship between multiple lesions in the head and neck area has been published recently (31). Because the techniques have limitations, uncertainty may remain for the apparently unrelated lesions; they have truly independently evolved or no sufficient data are available yet to prove a common origin.

Three theories have been proposed to explain the common clonal origin of multiple primary tumors: first, single cells or small clusters of cells migrate through the submucosa or, secondly, are shed in the lumen of an organ (*e.g.*, the oral cavity or the bladder) at one place and regrow at another (16, 32). However, recent findings in the head and neck, esophagus, and bladder are in strong support of a third theory: a large contiguous genetically altered field exists in the epithelium in which multiple clonally related neoplastic lesions develop (4, 29, 30). The results indicate that a large proportion of multiple primary tumors in the same or adjacent anatomical area have developed within a single preneoplastic field. It should be noted that the decision of whether the tumors and the intervening mucosa of the field were of common clonal origin was based on rather strict criteria. There is a possibility that in reality the percentage of clonally related tumors is even higher.

### A Model of Biological Multistep Carcinogenesis

The results available previously support the following progression model for cancer in the head and neck mucosa, esophagus, and bladder (see Fig. 1). A stem cell acquires one (or more) genetic alterations and forms a patch with genetically altered daughter cells. As a result of subsequent genetic alterations the stem cell escapes normal growth control, gains growth advantage, and develops into an expanding clone. The lesion, gradually becoming a field, laterally displaces the normal epithelium. The enhanced proliferative capacity of a genetically altered clonal unit is the driving force of the process. As the lesion becomes larger, additional genetic hits give rise to various subclones within the field. Different clones diverge at a certain time point with respect to genetic alterations but do share a common clonal origin (12). The presence of a relatively large number of genetically altered stem cells in a field is a ticking time bomb, and as a result of the process of clonal divergence and selection, eventually a subclone evolves into invasive cancer. For this part of the process the alterations in the cyclin D1 gene, located at 11q13 appears to be important (33). The chance of the ultimate transforming event to happen in a patient will be proportional to the number of affected stem cells and additional hits. So this proposed biological carcinogenesis model has a monoclonal origin as a firm basis. Two critical steps in this model can be discriminated: (a) the conversion of a patch stem cell into a group of stem cells without proper growth control; and (b) the eventual transforming event, turning a field into an overt carcinoma showing invasive growth and metastasis.

### Clinical Consequences

The concept of the expanding field in carcinogenesis has important clinical consequences. It is a well-known clinical experience that after surgical removal of a tumor, there is still a high risk for another tumor in the same anatomical area. For some cases the new tumor is

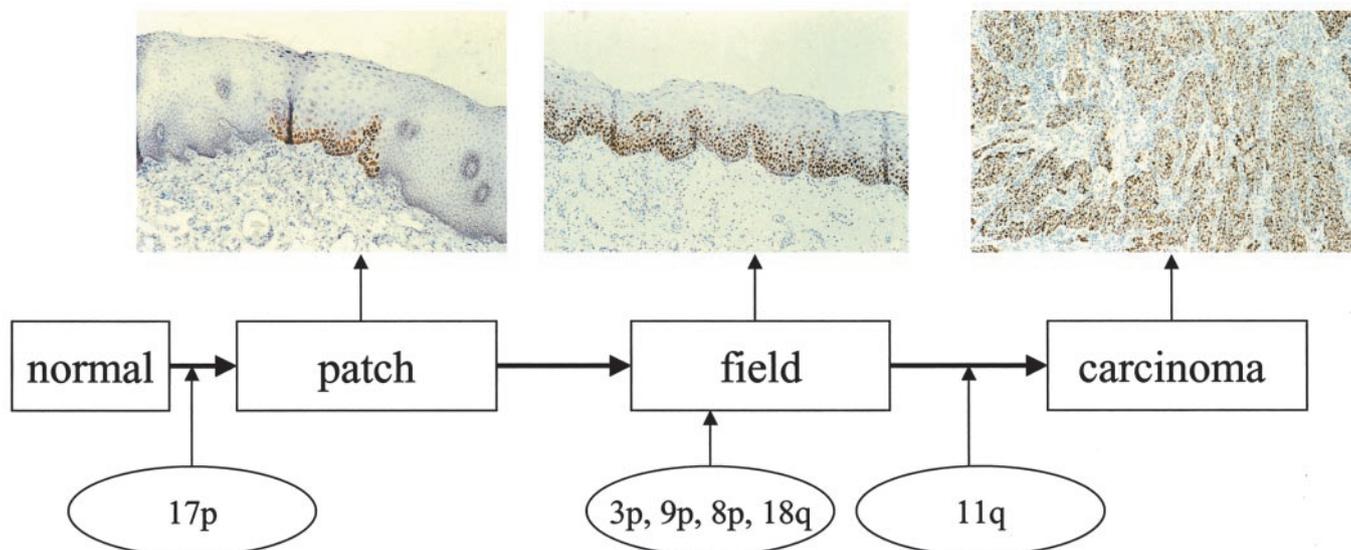


Fig. 1. Proposed model of HNSCC carcinogenesis. First a patch develops, consisting of a clonal unit of *TP53*-mutated cells (a stem cell and daughter cells) as has been described for breast, lung, skin, and HNSCC. The next step is the conversion from patch to a field, an epithelial lesion consisting of cells with cancer-related genetic alterations, which expands at the expense of normal tissue. At this moment, it is not known which genetic alterations are involved in the conversion of patch into field. During field progression a number of genetic alterations take place; indicated in the figure are the chromosomal locations for which LOH has been described. For the progression from field to cancer the amplification of 11q13 was shown to be important (33). This model is based on the genetic alterations as described for HNSCC. For other tumor types for which field cancerization has been described (lung, skin, esophagus, cervix, vulva, breast, bladder, and colon) analogous models can be proposed.

explained by the growth of incompletely resected carcinoma. However, for the cases where the tumor had radically been removed it seems logical to assume that a genetically altered field is the cause of new cancer. The presence of a field with genetically altered cells appears to be a continuous risk factor for cancer. Data are available that cancer can develop from genetically altered cells in a field that was left behind in the patient after surgery of the initial carcinoma (12, 34).

Clinical investigations are hampered by the fact that a field needs to be detected with molecular biological techniques or nonroutine visualization techniques, like fluorescence *in situ* hybridization (13, 35). However, leukoplakia is one exception: a proportion of the lesions can be considered field. Leukoplakia is defined as a “predominantly white lesion of the oral mucosa that cannot be characterized as any other definable lesion; some oral leukoplakias will transform into cancer” (36). The prevalence of leukoplakia is 0.1–0.2% in the normal population. Importantly, a proportion of these lesions develop into carcinoma with a constant rate of 2–3% per year (37). Some leukoplakia lesions do contain cancer-associated genetic alterations and are field by definition (38–40). Because only a part of the fields are clinically recognizable, there is an urgent need to improve the clinical detection of field. Diagnostic procedures, like the staining with toluidine blue (41) and fluorescence imaging (42), might provide improved detection possibilities.

The realization of a genetically altered field as a cancer risk factor provide a new paradigm, the definitions of “local recurrence” and SPT need a molecular addendum (31). The term “SPT” was proposed to be allocated for the second tumor that has developed independently from the first tumor. When a second tumor arises from the same field in which a first tumor has developed, it was preferred to designate it as a “second field tumor” (SFT). It is important to make this discrimination, because a different etiology may have clinical consequences. SFTs will be followed relatively easily by third and fourth field tumors. Therefore, SFT patients may need a different follow-up, characterized by more frequent and more focused screening.

Likewise, the clinical definition of “local recurrence” needs to be reconsidered in molecular terms. This type of lesion can be the result

of remaining tumor cells, but also the local remnants of a field may develop into cancer. So, in fact a local recurrence can be a SFT as well. In this case, the knowledge of whether there is a field at risk may have the same consequences.

The clinical implications of the presence of field depends not only on its size but also on how organ-sparing a surgeon has to be. In some organ systems extensive resection of the tumor including field is simply not possible because of anatomical constraints. Therefore, field-related problems will expectantly be higher in head and neck, vulva, or bladder than in the colon.

Additional research is needed to identify the fields that carry the highest risk for cancer. Besides host factors, like the amount of cigarettes smoked (43), the biological characteristics of the field itself might be of importance for HNSCC development. With respect to molecular markers, preliminary investigations with oral leukoplakia show encouraging results. It appeared that the presence of allelic loss at 3p and 9p is associated with an increased cancer risk (38–40). Additional losses at 17p increased cancer risk dramatically (39). Patients who have been surgically treated for HNSCC and are at risk for SFT can be enrolled to study the risk profile of a genetically altered field. A clinical trial of this type has an obvious advantage: it is known approximately where the lesion will develop (where the tumor has been), and it is possible to monitor the disease process (for instance by brushing cells). Furthermore, knowledge of the genetic alterations that precede the development to cancer will provide a basis for a rational therapy (*e.g.*, a gene-therapy based approach) of these preneoplastic lesions.

## Conclusions

The presence of a field with genetically altered cells is a risk factor for cancer. The large number of preneoplastic cells in the proliferating fields is likely to increase cancer risk dramatically. This also explains the high incidence of secondary cancers after surgery of the initial carcinoma. A biological progression model can be postulated in which field development plays a central role. Detection and monitoring of field may have profound implications for cancer prevention.

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