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Reappraisal of etiologic field effect in cancer predisposition and progression

The term field effect, which is also known as field defect, field cancerization, and field carcinogenesis, has been used to describe a field of cellular and molecular alteration that predisposes to the development of neoplasms within that territory. The authors explored an expanded, integrative concept, called etiologic field effect, which asserts that various etiologic factors—the exposome including dietary, lifestyle, environmental, microbial, hormonal, and genetic factors—and their interactions (the interactome) contribute to a tissue microenvironmental milieu that constitutes a "field of susceptibility" to neoplasia initiation, evolution, and progression. Importantly, etiological fields predate the acquisition of molecular aberrations commonly considered to indicate presence of field effect. Inspired by molecular pathological epidemiology (MPE) research, which examines the influence of etiologic factors on cellular and molecular alterations during disease course, an etiologically focused approach to field effect can broaden inquiries into cancer susceptibility and progression at molecular, cellular, and environmental levels during all stages of tumor evolution; embrace host-environment-tumor interactions, including gene-environment interactions, occurring in the tumor microenvironment; and help explain intriguing observations, such as shared molecular features between bilateral primary breast carcinomas and between synchronous colorectal cancers, where similar molecular changes are absent from intervening normal colon. MPE research has identified a number of endogenous and environmental exposures that can influence not only molecular signatures in the genome, epigenome, transcriptome, proteome, metabolome, and interactome, but also host immunity and tumor behavior. The authors anticipate that future technological advances will allow the development of in vivo biosensors for detecting and quantifying etiologic field effect as abnormal network pathology patterns of cellular and microenvironmental responses to endogenous and exogenous exposures. Through an etiologic field effect paradigm and holistic systems pathology approaches to cancer biology, personalized prevention and treatment strategies for precision medicine can be improved.

Lochhead P, Chan AT, Nishihara R, et al. Etiologic field effect: reappraisal of the field effect concept in cancer predisposition and progression. *Mod Pathol.* 2015;28:14–29.

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Relevance of expression levels of *SF3B3* in ER-positive breast cancer

De novo or acquired resistance to endocrine therapy limits the utility of such therapy in a significant number of estrogen receptor-positive breast cancers. It is crucial to identify novel targets for therapeutic intervention and improve the success of endocrine therapies. Splicing factor 3b subunit 1 (*SF3B1*) mutations are described in luminal breast cancer, albeit in low frequency. The authors conducted a study in which they evaluated the role of *SF3B1* and *SF3B3*, critical parts of the SF3b splicing complex, in estrogen receptor-positive endocrine resistance. To ascertain the role of *SF3B1*/*SF3B3* in endocrine resistance, their expression levels were evaluated in estrogen receptor-positive/endocrine-resistant cell lines (MCF-7/LCC2 and MCF-7/LCC9) using real-time quantitative reverse-transcription polymerase chain reaction (qRT-PCR). To further determine their clinical relevance, expression analysis was performed in a cohort of 60 paraffin-embedded estrogen receptor-positive, node-negative breast carcinomas with low, intermediate, and high Oncotype DX recurrence scores. Expression levels of *SF3B1* and *SF3B3* and their prognostic value were validated in large cohorts using publicly available gene-expression data sets, including The Cancer Genome Atlas. *SF3B1* and *SF3B3* levels were significantly increased in estrogen receptor α-positive cells with acquired tamoxifen (MCF-7/LCC2; both $P<0.0002$) and fulvestrant/tamoxifen resistance (MCF-7/LCC9; $P=0.008$ for *SF3B1* and $P=0.0006$ for *SF3B3*). Expression levels of MCF-7/LCC2 and MCF-7/LCC9 were not affected by additional treatments with estradiol or tamoxifen, or both. Furthermore, qRT-PCR analysis confirmed that *SF3B3* expression is significantly upregulated in Oncotype DX high-risk groups when compared with low-risk ($P=0.019$) groups. Similarly, in publicly available breast cancer gene-expression data sets, overexpression of *SF3B3*, but not *SF3B1*, was significantly correlated with overall survival. Furthermore, the correlation was significant in estrogen receptor-positive, but not estrogen receptor-negative, tumors. The authors concluded that potential strategies for therapeutic targeting of the splicing mechanisms need to be evaluated.

Gökmen-Polar Y, Neelamraju Y, Goswami CP, et al. Expression levels of *SF3B3* correlate with prognosis and endocrine resistance in estrogen receptor-positive breast cancer. *Mod Pathol.* 2015;28:677–685.

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Management of flat epithelial atypia on breast core biopsy based on clinical and radiographic findings

Flat epithelial atypia of the breast commonly co-exists with atypical ductal hyperplasia, lobular neoplasia, and indolent forms of invasive carcinomas, such as tubular carcinoma. Most patients with pure flat epithelial atypia on core biopsy undergo surgical excision to evaluate for carcinoma in the adjacent breast tissue. Studies have reported varying upgrade rates, with most recommending follow-up excision. These studies have often lacked detailed radiographic correlation, central review by breast pathologists, and information regarding the biology of the carcinomas identified on excision. The authors conducted a study in which they reported the frequency of upgrade to invasive carcinoma or ductal carcinoma in situ in excision specimens following a diagnosis of pure flat epithelial atypia on core biopsy. Radiographic correlation was performed for each case, and grade/receptor status of detected carcinomas was reported. Seventy-three core biopsies containing pure flat epithelial atypia were identified from the authors' files, meeting inclusion criteria for the study. In the subsequent excision biopsies, five (seven percent) cases contained invasive carcinoma or ductal carcinoma in situ and 17 (23 percent) contained atypical ductal hyperplasia or lobular neoplasia. All of the ductal carcinoma in situ cases with estrogen receptor results were estrogen receptor positive and intermediate grade. The invasive tumors were small (pT1a) hormone receptor-positive, HER2-negative, low-grade invasive ductal or tubular carcinomas with negative sentinel lymph-node biopsies. No upgrades were identified in the 14 patients who had all of their calcifications removed by stereotactic core biopsy. The rate of upgrade to carcinoma, once cases with discordant imaging were excluded, was at the lower end of the range reported in the literature. The authors concluded that given the low upgrade rate and indolent nature of the carcinomas associated with flat epithelial atypia, case management may be individualized based on clinical and radiographic findings. Excision may not be necessary for patients with no

calcifications remaining after core biopsy.

Calhoun BC, Sobel A, White RL, et al. Management of flat epithelial atypia on breast core biopsy may be individualized based on correlation with imaging studies. *Mod Pathol.* 2015;28:670–676.

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Differentiating primary and extragenital metastatic mucinous ovarian tumors

The authors analyzed the utility of the algorithm combining PAX8 with clinicopathological characteristics—tumor size, laterality, and patient age—for differentiating primary ovarian mucinous tumors (POMTs) from extragenital metastatic mucinous carcinomas involving the ovary (EMOMCs). Immunohistochemical staining for PAX8 was performed on formalin-fixed, paraffin-embedded tissues from 47 POMTs, 18 EMOMCs, and 70 extragenital primary mucinous carcinomas (EPMCs) using anti-PAX8 rabbit polyclonal antibody (pAb) and anti-PAX8 rabbit monoclonal antibody (mAb). PAX8 (pAb) positive signals were found in three of 18 EMOMCs and 32 of 70 EPMCs. PAX8 (mAb) demonstrated superior specificity, with zero positivity in EMOMCs and EPMCs, but unfavorable sensitivity, with 60.9 percent in ovarian mucinous borderline tumors and 45.8 percent in POMCs. Although PAX8 (mAb) immunostaining status (66.2 percent), tumor size (75.4 percent), and laterality (84.6 percent) demonstrated unsatisfactory accuracy when evaluated individually for differentiating POMTs from EMOMCs, a combination of PAX8 (mAb) immunostaining status, tumor size, and laterality markedly increased accuracy (86.2 percent), with a satisfactory Youden Index (63.7 percent). The authors concluded that PAX8 (mAb) was a specific marker in differentiating POMTs from EMOMCs. As a simple, convenient, and high performance-to-price ratio algorithm, a combination of PAX8 (mAb) immunostaining with tumor size and laterality will improve the diagnostic criteria of ovarian mucinous metastasis.

Hu A, Li H, Zhang L, et al. Differentiating primary and extragenital metastatic mucinous ovarian tumours: an algorithm combining PAX8 with tumour size and laterality. *J Clin Pathol.* 2015;68:522–528.

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Role of spatial heterogeneity in ER-negative breast cancer

The abundance of tumor-infiltrating lymphocytes has been associated with a favorable prognosis in estrogen receptor-negative breast cancer. However, a high degree of spatial heterogeneity in lymphocytic infiltration is often observed, and its clinical implication remains unclear. The authors conducted a study in which they combined automated histological image processing with methods of spatial statistics used in ecological data analysis to quantify spatial heterogeneity in the distribution patterns of tumor-infiltrating lymphocytes. Hematoxylin-and-eosin–stained sections from two cohorts of estrogen receptor-negative breast cancer patients (discovery: n=120; validation: n=125) were processed with the authors' automated cell-classification algorithm to identify the location of lymphocytes and cancer cells. Subsequently, hot-spot analysis (Getis–Ord Gi*) was applied to identify statistically significant hot spots of cancer and immune cells, defined as tumor regions with a significantly high number of cancer cells or immune cells, respectively. The authors found that the amount of colocalized cancer and immune hot spots weighted by tumor area, rather than the number of cancer or immune hot spots, correlates with a better prognosis in estrogen receptor-negative breast cancer in univariate and multivariate analysis. Moreover, colocalization of cancer and immune hot spots further stratifies patients with immune cell-rich tumors. The authors concluded that their study demonstrates the importance of quantifying not only the abundance of lymphocytes, but also their spatial variation in the tumor specimen, for which methods from other disciplines, such as spatial statistics, can be successfully applied.

Nawaz S, Heindl A, Koelble K, et al. Beyond immune density: critical role of spatial heterogeneity in estrogen receptor-negative breast cancer. *Mod Pathol.* 2015;28:766–777.

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