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ABSTRACTS**

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Inherited Syndromes in Gastrointestinal Cancers

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Hereditary factors have been frequently described in concert with associated cancer-causing germline mutations, involving multiple organ sites throughout the entire gastrointestinal tract and even outside it. Certain patterns of such integrally associated cancers are frequently encountered and, consequently, in each hereditary cancer-prone disorder it is mandatory that one consider cancers of diverse anatomic sites for each hereditary organ site under evaluation in the respective gastrointestinal cancer syndrome. A rather complex example is the Lynch syndrome (LS), which predominately involves cancer of the colon, often followed in frequency by carcinoma of the endometrium. Other cancers include gastric cancer (particularly in LS families in Korea and Japan), carcinoma of the pancreas, small bowel, upper uroepithelial tract, sebaceous adenomas and carcinomas and keratoacanthomas in the Muir-Torre LS variant, and brain tumors, predominantly glioblastomas, in the LS Turcot syndrome variant. While the list of extracolonic cancer sites appears to be extensive in the Lynch syndrome, we are still encountering putative integral LS cancer sites of the breast and prostate which we predict will ultimately be considered as integral lesions in LS.¹⁻³

As we cover the gastrointestinal tract in this brief lecture, we note the key familial/hereditary features in Barrett's esophagus, where a cancer-causing mutation(s) has not been found to date;

hereditary diffuse gastric carcinoma with the *CDH1* mutation; LS, the most common hereditary GI tract cancer syndrome, with its several mismatch repair germline mutations, namely *MLH1*, *MSH2*, *MSH6*, and *PMS2*; small bowel cancer in FAP, LS, and Peutz-Jeghers syndrome; and pancreatic carcinoma, particularly its association with malignant melanoma in the familial atypical multiple mole melanoma (FAMMM) syndrome, a subset of which is due to the *CDKN2A (p16)* germline mutation.

The familial polyposis syndromes require special attention, given the variable excess of colonic adenomas as in familial adenomatous polyposis (FAP) and their paucity in the attenuated FAP variant, both due to the *APC* mutation, the recent MAT syndrome due to *MUTYH* mutation, and the large number of hamartomatous polyposis syndromes. Important preventive colonoscopic surveillance and, when indicated, prophylactic colectomy, must constantly be considered, since there is such a strong cancer control benefit. This benefit is based on a detailed family history coupled with the physician's knowledge of how an excess of colonic polyps, as well as additional polyps such as involvement of the stomach and small bowel in FAP and AFAP, desmoid tumors, and additional cancer sites such as carcinoma of the pancreas, among others, must always be of concern to the physician. In the past (and, unfortunately, currently), many patients have been unnecessarily dying of metastatic CRC. While there has been progress in this area we realize that such high-risk hereditary polyposis patients are still in dire need of attention to otherwise preventable morbidity and mortality.

Identification of these syndromes requires that the proband provide a comprehensive family history that includes meticulous attention to cancer of all anatomic sites, and that the astute physician recognize its significance. This effort is essential for hereditary cancer syndrome diagnosis but, unfortunately, it is all too often neglected in the clinical practice setting. The patient needs to provide informed signed consent prior to genetic counseling and, when indicated, must be given an opportunity for DNA testing once they are fully aware of its pros and cons. Finally, we must consider who needs DNA testing.⁴

References

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