Polyp-Cancer Sequence

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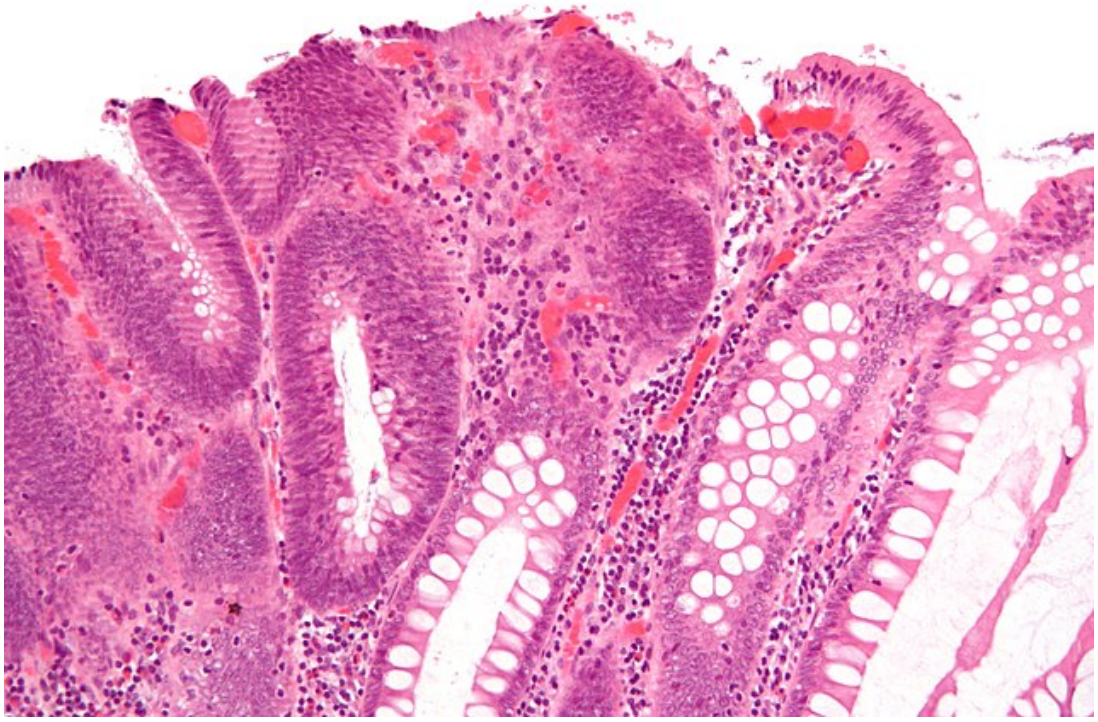
Colorectal cancer is the third most common variant of cancer and can be called a polyp-cancer sequence. Colorectal cancer is believed to occur secondary to the transformation of the mucosal epithelial cells and is characterized by rapid progression. The mucosal cells protrude into the lumen as polyps, which may transform into a dysplastic and invasive lesion. Adenomatous polyps are the most common colon polyps associated with malignant transformation. Herein, we discuss the different types of colon polyps, the genetic basis of colorectal cancer, and an overview of management strategies.



Introduction

Colorectal cancer is characterized by the development of polyps in the lumen that arise from the mucous layer of the colon. It begins with the formation of benign tumors known as polyps. Colorectal cancer can be sporadic, familial, or inherited. The inherited disease is associated with a **genetic mutation leading to either polyposis or nonpolyposis colorectal cancer**. Hereditary polyposis colorectal cancer includes familial adenomatous polyposis (FAP), juvenile polyposis syndrome, and Peutz-Jeghers syndrome, while hereditary nonpolyposis colorectal cancer includes Lynch syndrome.

Adenomatous polyps are most commonly associated with cellular dysplasia, which may lead to colorectal carcinoma. It takes 7–10 years for the carcinoma to develop. Mucosal epithelial cells are renewed continuously from the crypt cells towards the lumen owing to

continuous shedding and turnover of the epithelium into the lumen. Dysplastic cells acquire invasive potential and transform into malignant carcinoma.

Histological Types of Colonic Polyps

Colonic polyps are mucosal or sub-mucosal projections into the colonic lumen. They can manifest with bleeding, intestinal obstruction, and may sometimes transform into malignant tumors. Colonic polyps can be **classified as neoplastic, non-neoplastic, hamartomatous, serrated, or sub-mucosal variants**. Non-neoplastic polyps include hyperplastic, mucosal, sub-mucosal, inflammatory, and hamartomatous types. Neoplastic polyps are adenomas or adenomatous polyps.

Non-neoplastic polyps are of the following types:

1. Serrated polyps can be hyperplastic polyps, which are the most common non-neoplastic colonic polyps. A heterogeneous group of polyps constitutes sessile serrated adenomas. They develop in the ascending colon, are more common in women than men, and show characteristic flat and irregular growths that extend toward the crypt base. Serrated polyposis syndrome is **characterized by large polyps > 10 mm** that are usually located proximal to the sigmoid colon.
2. Juvenile polyps or hamartomatous polyps consist mainly of connective tissue covered by epithelium. They appear as pedunculated, cherry-red smooth polyps. These polyps are seen in about 75% of children < 10 years of age and are, therefore, termed as juvenile polyps. They are highly vascular and tend to cause bleeding. Intussusception and obstruction are complications that may occur due to polyps.

Juvenile polyps and juvenile polyposis coli (JPC) are hamartomas that could potentially develop into colorectal and gastric cancer. JPC refers to the presence of ten or more juvenile polyps along the GI tract and is usually associated with the *SMAD4* mutation. Mutation of *SK11* is also associated with hamartomatous polyps in Peutz-Jeghers syndrome. The risk of a polyp transforming into colon cancer is high and could also result in other malignancies, including those of the pancreas, stomach, and breast.

1. Inflammatory polyps are pseudo polyps and are common in patients with inflammatory bowel disease and ulcerative colitis. The polyps are formed as a result of the accumulation of inflammatory infiltrates in the damaged mucosa.
2. Submucosal colorectal polyps are not truly colorectal polyps. They are lesions within the submucosal layer of the colon and could either be benign or malignant.

Neoplastic polyps

Adenomatous polyps are the most common neoplastic polyps in the colon. Most colon cancers arise from adenomatous polyps within a span of 7–10 years.

Morphologically, **adenomas can be sessile, pedunculated, or non-polypoid flat or depressed lesions**. Pathologically, they can be classified as villous, tubular, and tubulovillous adenomas.

Tubular adenomas are the most common and show branching epithelium, while the villous variant is less common with straight adenomatous glands. Advanced adenomas are large adenomas measuring > 10 mm with high-grade dysplasia. Synchronous adenomas are colorectal adenomas that are discovered simultaneously during the diagnosis of primary adenomas. A metachronous adenoma is one that is diagnosed six months after the diagnosis of an existing adenoma.

Risk Factors

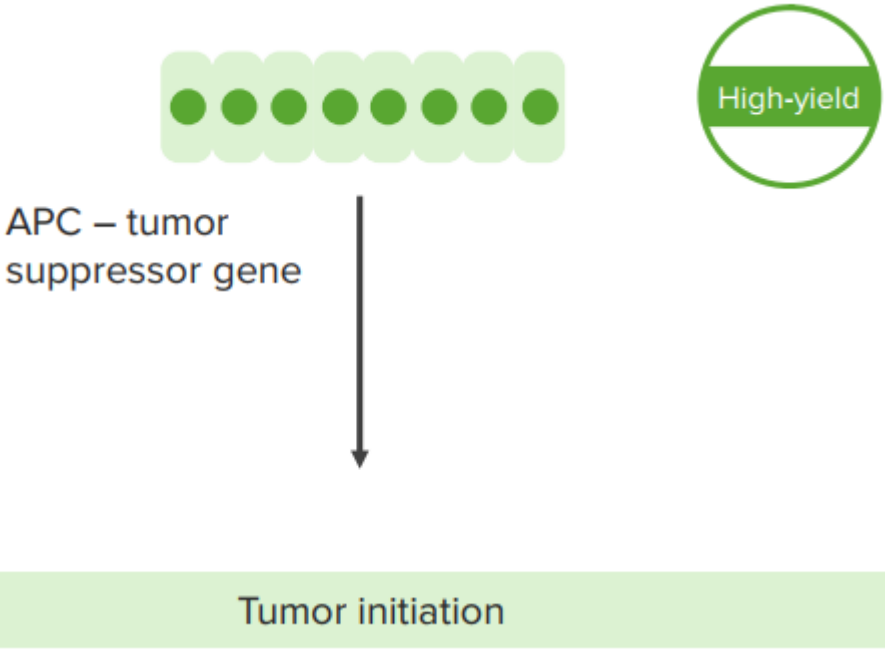
Risk factors for adenoma transformation are villous histology, high-grade dysplasia, and adenoma size. Adenomas measuring > 10 mm are more susceptible to develop carcinoma. High-grade dysplasia is often associated with invasive and metachronous carcinomas, especially with large polyps.

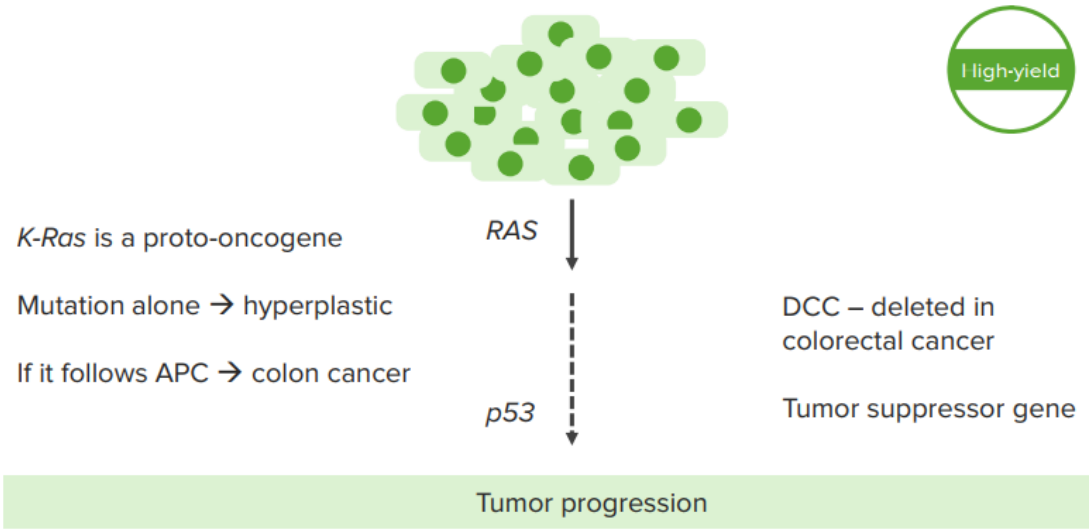
Transformation of the epithelium into adenoma and then carcinoma can be explained by the following pieces of evidence:

- The simultaneous presence of adenoma and carcinoma
- Metachronous adenoma after resection of the carcinoma in about 30% of cases
- Synchronous adenoma in about 30% of patients with carcinoma
- Large adenomas (high risk of dysplasia)

Several theories have been proposed to explain the molecular basis for a polyp-cancer sequence, including hypermethylation, activation of oncogenes, and deactivation of the tumor suppressor genes. The first step in epithelial transformation is the **hyperproliferation of the epithelium to form aberrant crypt foci and low-grade dysplasia,** which is followed by high-grade dysplasia and eventually carcinoma.

Chromosomal instability is the gain or loss of chromosomal segments due to the over-activation of oncogenes or de-activation of tumor suppressor genes leading to uncontrolled cellular growth. Chromosomal instability can lead to an alteration in the chromosomal number, molecular changes in **chromosome 5q, 18q, and 17p, and mutations in *APC* and *K-RAS***.





Microsatellite instability or the mutator phenotype/mismatch repair pathway: Mutations in the DNA mismatch repair enzymes lead to the transformation of polyps into carcinoma, especially in Lynch syndrome and sporadic cases. The mismatch repair mutation leads to an accumulation of microsatellites within the DNA. Hereditary non-polyposis colorectal cancer is a result of a germline mutation in the mismatch repair genes, while methylation of the *hMLH1* mismatch repair gene leads to sporadic disease.

Hypermethylation phenotype pathway: Hypermethylation of certain genes leads to the silencing of their expression.

Oncogenes are normal cellular genes that promote cellular growth. Gain-of-function mutations lead to uncontrolled cellular growth and multiplication. ***RAS, SRC, MYC,*** and ***HER2*** are examples of cellular oncogenes.

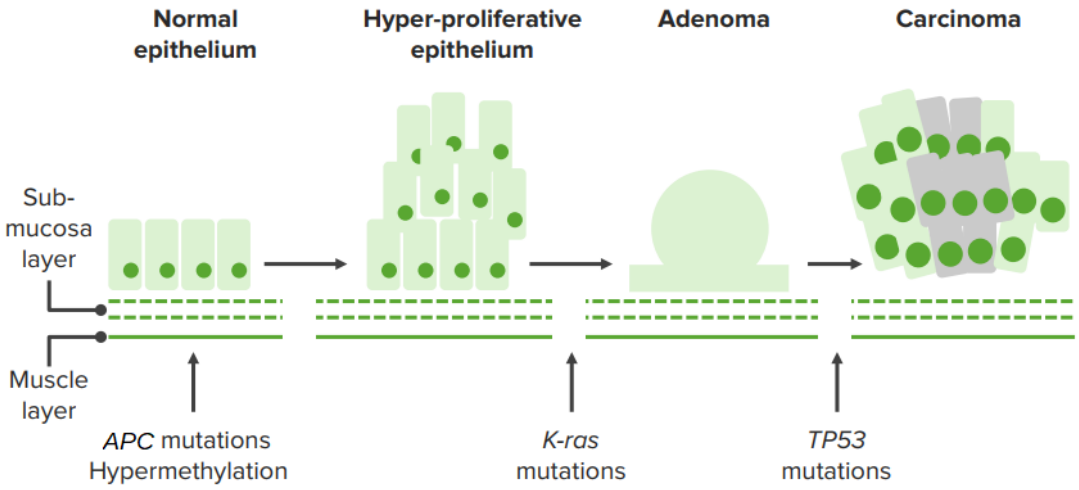
G-protein coupled receptors activate *RAS* oncogenes, which transmit growth factor signals to the nucleus. *RAS* mutation prevents lysis of the activated GTP with continuous signaling and proliferation. *RAS* mutation is associated with resistance to treatment against growth factors receptors, e.g., anti-epidermal growth factor receptor (EGFR) chemotherapy.

Tumor suppressor genes control cell division and proliferation. Loss-of-function mutations in both alleles lead to the loss of inhibition control over cell division and proliferation. The retinoblastoma tumor suppressor gene has either two somatic mutations in both alleles or one somatic mutation in a single cell with an inherited mutation of the other allele. Examples of tumor suppressor gene mutations include *APC*, *P53, DCC, SMAD2,* and *SMAD4*. *P53* mutation on chromosome 17p is common in colorectal cancer. The P53 gene is responsible for cell cycle arrest during times of stress via activation of several genes and proteins which promote and apoptosis.

APC mutation is present in most cases of sporadic colorectal cancer and cases of FAP. The APC gene can be silenced via the Wnt pathway by phosphorylation and degradation of beta-catenin in the nucleus. **Mutations of *APC* lead to the loss of the regulatory effect and accumulation of beta-catenin** which, in turn, activates transcription factor Tcf-4. Activation of this pathway prevents the arrest of cell division, differentiation, and apoptosis. This further leads to the activation of the gastrin/cholecystokinin receptors, which in turn leads to inhibition of apoptosis and increase in cellular proliferation. SMAD4 mutation is associated with juvenile polyposis and sporadic cases of colorectal cancer as it acts as the central mediator in the TGF-β pathway.

Germline mutation in the base excision repair gene mutY homolog, MUTYH, is also associated with FAP and known as MUTYH-associated polyposis.

Cyclooxygenase inhibitors, including aspirin and sulindac, **exert protective effects and prevent the progression of adenomatous polyps to colorectal cancer**. Sulindac is helpful in patients with FAP and known to cause regression of colorectal polyps.



Management of Colonic Polyps

Colonoscopy remains the screening modality of choice for the detection of colonic polyps. This procedure is more suitable for the detection of polyps > 5 mm, especially in the descending colon. It is preferred over CT colonography for polyp removal and biopsy.

Excision of adenomatous tissue is the treatment of choice unless the polyps are present in large numbers. Tissues from multiple lesions should be collected for biopsy to exclude metaplasia. Adenomas > 2 cm are excised during follow-up colonoscopy after three months to ensure the removal of residual lesions or metachronous adenomas. Follow-up colonoscopy after resection varies depending on the size of the adenoma. Follow-up colonoscopy should be performed after ten years if no adenomatous polyps were detected during the first colonoscopy.

If one or two small tubular adenomas measuring < 10 mm are detected, a colonoscopy should be repeated after five years. Patients with more than three adenomas or those with advanced adenomas that are villous and large with high-grade metaplasia should be followed up after three years. Patients with small serrated polyps without dysplasia should undergo colonoscopy after five years. If the polyps are > 10 mm and show signs of dysplasia, a colonoscopy should be advised after three years.

Prevention of Colonic Polyps and Colorectal Cancer

A high-fiber diet rich in fresh fruits and vegetables, and abstinence from alcohol and smoking may prevent colorectal cancer. Aspirin has a proven protective role in preventing metachronous adenomas and colon cancer. **COX-2 inhibitors, such as celecoxib, have been used with success in the prevention** of colorectal cancer; however, they are associated with an increased risk of cerebrovascular incidents and heart attacks, which limit their use in high doses.

References

G. Busuttil, Colorectal Pathology Masterclass, Department of Surgery, Mater Dei Hospital, ; Adenoma-Carcinoma Sequence via maltime.com

Approach to the patient with colonic polyps via uptodate.com

Molecular genetics of colorectal cancer via uptodate.com

Adenoma-carcinoma sequence of colon via pathologyoutlines.com

Notes