Colorectal cancer (CRC) is a malignant disease with an incidence of over 1.8 million new cases per year worldwide. CRC outcome is closely related to the respective stage of CRC and is more favorable at less advanced stages. Detection of early colorectal adenomas is the key to survival. In spite of implemented screening programs showing efficiency in the detection of early precancerous lesions and CRC in asymptomatic patients, a significant number of patients are still diagnosed in advanced stages. Research on CRC accomplished during the last decade has improved our understanding of the etiology and development of colorectal adenomas and revealed weaknesses in the general approach to their detection and elimination. Recent studies seek to find a reliable non-invasive biomarker detectable even in the blood.

Colon capsule endoscopy (CCE) is a non-invasive method suitable for individuals who are unwilling to undergo colonoscopy because of discomfort or any other obstacles. Meta-analysis showed that CCE for any polyp has a specificity of 89% and sensitivity of 73%. Though CCE is not as accurate as FIT are followed by endoscopic examination [11].

**Table 1.** Classification of non-neoplastic and neoplastic polyposis and polycolposis [18].

| Non-Neoplastic | Neoplastic |
|----------------|------------|
| Sporadic       | Hereditary |
| Sporadic       | Hereditary |

Benigns
adenomas: Tubular
Table 2. Current surveillance recommendation [20,30].

| Neoplasia Found                                      | Recommended Interval for Colonoscopy Examination | Comment                                                                                   |
|------------------------------------------------------|-------------------------------------------------|-------------------------------------------------------------------------------------------|
| Small rectal hyperplastic polyps                     | 10 years                                        | Exception are patients with hyperplastic polyposis syndrome, who need more intensive follow up. |
| One or two small (<1 cm) tubular adenomas with only low-grade dysplasia | 5–10 years                                      | The precise timing within this interval should be based on other clinical factors (such as prior colonoscopy findings, family history, and the preferences of the patient and judgment of the physician). |
| 3 to 10 adenomas, or any adenoma ≥ 1 cm, or any adenoma with villous features, or high-grade dysplasia | 3 years                                         | Adenomas must have been completely removed. If the follow up colonoscopy is normal or shows only 1 or 2 small, tubular adenomas with low-grade dysplasia, then the interval for the subsequent examination should be 5 years. |
| More than 10 adenomas at one examination             | < 3 years                                       | The interval should be based on the clinician judgement and consider the possibility of an underlying familial syndrome. |
| Sessile adenomas that are removed piecemeal          | 2 to 6 months                                   | Once complete removal has been established, subsequent surveillance needs to be individualized based on the endoscopist’s judgment. Completeness of removal should be based on both endoscopic and pathologic assessments. |

Around 5–10% of CRC cases are related to heredity including most common syndromes such as hereditary non-polyposis colorectal cancer (HNPCC), familial adenomatous polyposis (FAP) and attenuated familial adenomatous polyposis (aFAP), MUTYH-associated polyposis (MAP), Juvenile polyposis syndrome (JPS), Peutz-Jeghers syndrome (PJS), Polymerase proofreading-associated polyposis (PPAP), PTEN hamartoma tumors syndrome (PHTS), Cowden syndrome, and Familial colorectal cancer type X, while more than 90% of CRC cases are of sporadic origin [6,7]. Syndromes are usually detected at an early age. However, sporadic CRC correlates with increasing age due to the accumulation of mutations in intestine cells [23,24].

In the study by Brenner et al. [25], 10 years of cumulative risk of CRC among both sex with advanced adenomas increases from 25.4–25.2% at age 55 years to 42.9–39.7% at age 80 years. The development of carcinoma from adenoma tissue can last 5 to 20 years, and it is not influenced purely by one pathway [26,27]. This transition is a complex, multifactorial process that has been characterized by chromosomal instability (CIN), microsatellite instability (MSI), and DNA methylation in CpG islands areas (CIMP). All these pathways may overlap with each other and are responsible for genetic instability in adenoma that could undergo malignant transformation [28] (Figure 1). The events contributing to these processes are constantly subject to intensive investigations [27].
Considering the current knowledge about the CRC development and with an application of screening programs, we are still missing identification of patients with asymptomatic disease progression in early stages, where detection plays a key role in cancer survival. Recent studies seek to find new non-invasive biomarkers measurable even in early stages of CRC from an area of non-coding RNA, inflammatory biomarkers, or cell-free DNA [29].

**Transition of Adenoma to Carcinoma in Colon**

The colon epithelium is constantly and rapidly renewing tissue. Old cells on the top of the villus are released into the lumen and replaced with new cells raised from colonic crypts. On the bottom of colonic crypts are stem cells that proliferate and differentiate into the cellular compartment of colon epithelium [31]. Vogelstein et al. [32] proposed the classical model of tumor evolution in the large bowel (Figure 1). Cells with high WNT signaling activity arise from aberrant crypts and evolve into a tubular or tubule-villous polyp. The subsequent proliferation of polyp may lead to the development of early adenoma with a low grade of dysplasia. Early adenoma expands into advanced adenoma with a high grade of dysplasia and with increasing accumulation of mutations in daughter cells progressing ultimately further into carcinoma [2, 32, 33]. Each mutation that provides tumor cell-selective growth advantage is called driver mutation. This advantage slightly increases the growth rate of clonal expansion around 0.4% and is increasing with every new driving mutation [34]. Driver mutations enhance the accumulation of a large number of somatic mutations due to altering the cell condition and reduce the population fitness landscape. The predominant mutations, so-called passenger mutations, are mutations without selective growth advantage. With each clonal expansion of cancer cells, heterogeneous passenger mutations are generated that constitute the enormous variations of unique tumors [35].

Thanks to the next-generation sequencing (NGS) technique, thousands of mutations in the human genome were identified and some of them contribute to malignant evolution [36]. The driver mutations in the APC gene, predominantly frameshift at codon 1,554 [37], provide cell-selective growth advantage [32], and cause loss of cell ability to control the concentration level of protein β-catenin in the cytoplasm. β-catenin implements in the WNT signaling pathway and its concentration imbalances lead to uncontrolled growth and cell division [36]. Following mutations in TPS3 or SMAD4 genes induce transformation into a malignant tumor, which overgrows into basal tissue and has an ability to metastasize into lymph nodes and distant organs [27].

**Keywords**

colorectal adenoma; colorectal cancer; biomarkers; early detection

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