Prevention and Early Detection of Colorectal Cancer


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Abstract: Chemoprevention and early detection are key to reducing the mortality rates in patients with colorectal cancer. Epidemiological studies have demonstrated the major role of diet in the etiology of colorectal cancer. In the carcinogenesis of colorectal cancer, a high fat, low residue diet is causative, whilst a low-fat, high residue diet is protective. Epidemiological studies had documented a 40–50% reduction in the risk of developing colorectal cancer in individuals taking NSAIDs as aspirin, which are inhibitors of cyclooxygenase. These data strongly suggest that the inhibition of COX-2 is chemopreventive. However, epidemiological and experimental studies pertaining to vitamins, antioxidants, fiber, and calcium supplementation have led to some discrepancies. Randomized trials have revealed that screening with fecal occult blood tests facilitates a 15–25% reduction in the mortality from colorectal cancer. Whilst the National Polyp Study has reported that removal of colorectal adenomas (over 5mm in diameter) contributes to a 76–90% reduction in the mortality rates of the disease. These results also support the hypothesis of the adenoma-carcinoma sequence in the carcinogenesis of colorectal cancer.

Key words: Primary prevention; Secondary prevention; Early diagnosis; Early-stage colorectal cancer

Introduction

The control of factors involved in the occurrence and progression of colorectal cancer is important for the prevention (primary prevention) of the cancer, and for early diagnosis (secondary prevention), and mass screening has considerable significance. We report the currently available results of chemoprevention and data on the efficacy of colorectal cancer mass screening.

Primary Prevention

1. Initiation and promotion

It has been assumed that colorectal cancer is caused by the accumulation of multiple genetic alterations (multi-stage carcinogenesis). The details of the process have not been uncovered, however, it is known that the initiators (carcinogen and mutagens) change normal cells into mutant cells, and that the promoters (tumor promoting agent) induce the proliferation and
growth of the mutant cells (cancer cells) (Fig. 1).

2. Primary prevention of carcinogenesis

Primary prevention is defined as the attempt to decrease the incidence of colorectal cancer by removing the above factors (initiators and promoters), and is the most important strategy for cancer eradication.

The initiation of carcinogenesis (the stage at which genes in normal cells are damaged by chemical substances, etc.) is considered to occur in the age range from the twenties to the early thirties. Conversely, eliminating environmental factors that may contribute to genetic damage and the active consumption of foods containing antioxidative substances, which prevent genes from being damaged, are considered to be essential until this age. In order to prevent the initiation of carcinogenesis, i.e., to “prevent cancer from putting forth buds,” cancer prevention should be started in the teenage years.

Factors or substances affecting the initiation of carcinogenesis include lifestyle (smoking, excessive fat intake, obesity, lack of exercise, food additives, etc.), and living environments (various chemical substances, air pollution, endocrine disrupting substances, etc.).

Following the initiation of carcinogenesis, accumulated gene mutations cause carcinogenic promotion. At this stage, cancer can be prevented by “nipping cancer in the bud.” For example, green tea (catechin), red wine (polyphenol) and the pigment in oranges (β-cryptoxanthin) have been reported to decrease the incidence of cancer. These substances are thought to retard the progression of carcinogenesis instead of inhibiting the carcinogenesis itself.

Some foods promote carcinogenesis and others inhibit it. With regard to the carcinogenesis of colorectal cancer, it has long been understood that a high-fat, low-residue diet is causative, while a low-fat, high-residue diet is protective. In addition to the above-mentioned factors, it is known that bile acid, alcohol, and estrogen promote colorectal carcinogenesis, while dietary fiber, vegetables rich in beta-carotene, vitamins C, D, and E, beta-carotene as well as NSAIDs (nonsteroidal antiinflammatory drugs) inhibit it. Both the rectum and the colon are parts of the large intestine, but they are thought to differ in terms of the envi-

Fig. 1  Multistage carcinogenesis model with the initiation and promotion stages (Kinzer, K.W. and Vogelstein, B.: Cell 1996; 87: 159–170)
ronmental factors that contribute to their carcinogenesis. In the past, the region most prone to cancer in the large intestine in Japan was the rectum with few exceptions, but in recent years this region is increasingly located in the colon, especially in the sigmoid colon. Concerning the risk factors of rectal cancer, it has been reported that excessive alcohol intake and positive family history are associated with a 4-fold increase in risk, and that black tea, vegetables, and seaweed are linked to 50% decrease in the risk. On the other hand, with respect to the risk factors for colon cancer, it has been reported that excessive alcohol intake and positive family history are related to an increase of some 2–3 times, that black tea and fruits are associated with a 2–3 fold increase in the risk, and that coffee, smoking, and green tea are linked to decreased risk. Among the substances which have been reported to exert an effect on “primary prevention,” antioxidative substances, free radical scavengers, intestinal flora balancers, antiinflammatory substances, bile-acid toxicity inhibiting substances, substances involved in the arachidonate cascade, tumor immunity protectors, etc. are considered to exhibit efficacy (Table 1).

### Secondary Prevention

#### 1. Significance of mass screening

Although all cancers including colorectal cancer become difficult to eradicate once they have invaded deeper tissues or have metastasized, most early-stage cancers can be cured completely, and it is possible to eradicate 98%

<table>
<thead>
<tr>
<th>Table 1 Effective Substances for Primary Prevention</th>
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<td><strong>Mechanism of action</strong></td>
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<tr>
<td>Antioxidative activity</td>
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<tr>
<td>Free radical scavenging</td>
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<tr>
<td>Intestinal flora balancing</td>
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<td>Antiinflammatory effect</td>
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<td>Bile-acid toxicity inhibition</td>
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<tr>
<td>Polyamine synthesis</td>
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<td>Carcinogen metabolism</td>
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![Fig. 2](image-url) Progression from carcinogenesis to early-stage cancer and to advanced cancer.
of early-stage colorectal cancers. In addition, unlike gastric cancers, which are linked to poor prognosis if they have already progressed to the later stages, about 80% of colorectal cancers, even when advanced, can be surgically resected and cured completely if they have not metastasized.

Cancers detected through mass screening examinations are often in the earlier stages, and are curable even if they are relatively advanced. It takes considerable time for tumors to grow into visible masses (with diameters of 1 cm), and the growth rate is not steady (Fig. 2). In order to detect smaller tumors (early-stage cancers), advances in diagnostic techniques by imaging or endoscopy are crucial. Whilst visible tumors were previously thought to be about 1 cm in diameter, it is currently possible to detect colorectal cancers measuring about 3–5 mm in diameter.

2. Methods and efficacy of mass screening for colorectal cancer

Currently, various immunological fecal occult blood tests utilizing human hemoglobin-specific antibodies (including reversed passive hemagglutination [RPHA] technique) are used as the mass screening methods of colorectal cancer. In a case-control study, it was reported that when compared with groups of subjects who did not undergo mass screening, the relative risk for mortality due to colorectal cancer in the group of subjects who underwent mass screening was 0.36. Therefore since 1992, mass screening using 2-day immunological fecal occult blood testing has been incorporated into the third program of health care services for the elderly in Japan. However, in 1998, since mass cancer screening services were considered to be well established in this country, the screening was subsequently excluded from health care services for the elderly.

The rate of positive results (rate of identification of individuals who need to undergo detailed examination) in the 2-day immunological fecal occult blood testing is about 5–6%, and among individuals who get positive results in mass screening, about 70–80% undergo a detailed examination (currently, total colonoscopy is adopted), although this rate varies regionally. The incidence of detection of colorectal cancer is 0.1–0.3%, and 60–70% of the detected cancers are in the earlier stages.

3. Lowering effects of colonoscopic polypectomy on the incidence of colorectal cancer

In the National Polyp Study conducted by Winawer et al., it was reported that the relative risks of colorectal cancer in patients who underwent colonoscopic polypectomy, as compared to comparators, were 0.10 (0.03–0.24) in the cases at the Mayo Clinic, 0.12 (0.04–0.27) in the cases at St. Mark’s Hospital, and 0.24 (0.08–0.56) in the cases in the SEER Program (Surveillance, Epidemiology, and End Results). Given the rate of risk decrease in subjects who underwent colonoscopic polypectomy, it can be said that at least 50% or more (possibly 76–90%) of colorectal cancers originally develop as adenomatous polyps and undergo malignant transformation.

In a multicenter study conducted by Saito’s team (belonging to the team council of the Ministry of Health, Labor and Welfare), the incidence of colorectal cancer in the groups of subjects who underwent colonoscopic polypectomy was compared with that in the subjects who did not undergo this examination. The incidence rates in the former group and the latter group were 0.7% and 1.0%, respectively, at 5 years after the polypectomy, and 2.2% and 5.2%, respectively, at 10 years, suggesting that the incidence of colorectal cancer is significantly decreased in subjects who undergo polypectomy.

Further, in a multicenter study performed by Murakami et al., the risk of colorectal cancer in subjects with colorectal polyps and the decreasing effects of colonoscopic polypectomy on the incidence of colorectal cancer were also evaluated, demonstrating that during the
observation period of 9.8–11.8 years on average, 5-year cumulative incidence rates of colorectal cancer were 0.3% in Group N (the group of subjects who did not develop colon polyp), 1.1% in the group of subjects who underwent polypectomy, and 2.3% in the group of subjects who did not undergo polypectomy. This suggested that the incidence of colorectal cancer was significantly higher in the subjects with colorectal polyps and in those subjects who did not undergo polypectomy as compared with that in those subjects undergoing polypectomy. In this study, Murakami et al. also assessed the 5-year cumulative incidence rates of colorectal cancer by stratifying the subjects by polyp size (length of major axis), thereby ascertaining that the incidence rates were 0.4% in the ≤5-mm stratum, 1.7% in the 5–9-mm stratum, and 12.9% in the ≥10-mm stratum, leading to the conclusion that polypectomy is not indicated for patients with polyps with diameters of 5 mm or less because the 5-year cumulative incidence rate of colorectal cancer in such patients is low.

Conclusion

Colonoscopic polypectomy has been shown to inhibit the occurrence of colorectal cancer and to lower the mortality rate due to the cancer. In other words, the “malignant transformation of adenomas” has been indirectly proven and the prevention of adenomas is therefore considered to be significant for the prevention of colorectal cancer; progress in studies on NSAIDs, COX-2, etc. is expected. In addition, early detection, diagnosis, and treatment of colorectal adenomas and cancers should be conducted through mass screening utilizing the immunological fecal occult blood test. At present, however, it is considered that only adenomas with a diameter of 6 mm or more should be resected.

REFERENCES