

*Forum Minireview***Life Style-Related Diseases of the Digestive System:
Colorectal Cancer as a Life Style-Related Disease: from Carcinogenesis
to Medical Treatment**

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Received July 10, 2007; Accepted September 10, 2007

Abstract. Life style-related diseases are associated with an increased risk of colorectal cancer (CRC). Recently, an association has been demonstrated between obesity and CRC. CRC has been associated with markers of insulin or glucose control, and insulin resistance might be the unifying mechanism by which several risk factors affect colorectal carcinogenesis. We evaluated the association between the number of aberrant crypt foci (ACF) and obesity, insulin resistance, hyperlipidemia, and other factors of life style-related disease. As a result, age, body mass index (BMI), waist circumference, and visceral fat obesity were significantly associated with the number of ACF. These results suggest that visceral fat obesity is an important target for CRC prevention. Peroxisome proliferator-activated receptor gamma (PPAR γ) is a member of the nuclear receptor superfamily and is highly expressed in CRC. PPAR γ ligand administration for 1 to 8 months significantly reduced the number of ACF in human subjects. PPAR γ ligand is a promising candidate as a chemopreventive agent. Further investigation is needed to elucidate these mechanisms.

Keywords: life style-related disease, colorectal cancer, chemoprevention, aberrant crypt foci (ACF), peroxisome proliferator-activated receptor gamma (PPAR γ)

Introduction

A diet rich in fat and calories and low intake of vegetable, fruits, and fibers are referred to as a Western diet. Chronic conditions including obesity, diabetes, hyperlipidemia, hypertension, and cardiovascular disease have been shown to be associated with a Western diet, alcohol intake, and smoking. Indeed, obesity has been reported to be associated with an elevated risk of cardiovascular disease, diabetes, and mortality (1–4). Especially, visceral fat obesity is increasing and is becoming a significant social problem. Recently, these life styles have also been shown to be correlated with

increase in colorectal cancer (CRC) risk.

CRC is a disease with a high mortality and morbidity rate, and currently, its prevalence has been increasing worldwide. On the other hand, CRC is potentially one of the most preventable malignancies (5, 6). Correction of the life styles mentioned above may have a major potential for CRC prevention. On the other hand, early detection of CRC or CRC precursor lesions may be promoted by screening of the population at high risk. In addition, chemoprevention, the use of medications to prevent disease, has now been extensively explored in CRC. Some of these interventions, such as supplemental fibers, calcium supplementation, aspirin, nonsteroidal anti-inflammatory drugs (NSAIDs), and selective cyclooxygenase (COX)-2 inhibitors, have been shown to have a potential to reduce both CRC and colorectal adenomas. CRC is thought to progress through several morpho-

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Published online in J-STAGE: October 6, 2007

doi: 10.1254/jphs.FM0070022

logical stages, from the formation of adenomatous polyps to malignant conversion (7). Genetic alterations including mutations in the *APC*, *K-ras*, and *p53* genes have been reported to accompany the disease progression (8). The earliest identifiable lesion in this pathway may be the aberrant crypt foci (ACF). ACF are pre-polyp abnormalities identified in single crypts by magnifying colonoscopy after the administration of methylene blue dye. Therefore, ACF may be a surrogate marker of CRC, and analysis of the association between clinicopathological variables and ACF formation may be of great significance.

Diabetes, obesity, and CRC

Diabetes, obesity, hyperinsulinemia, and insulin resistance have been repeatedly shown to be associated with CRC (9–14). Diabetes was associated with an increased risk for CRC in cohort studies, in accordance with previous studies that demonstrated that diabetes is a moderate risk factor for CRC. Overweight, obesity, or high BMI has been consistently associated with increased risk for CRC incidence and mortality, at least in men and premenopausal women (15–18). The WHO definition of the life style-related disease allows the use of a body mass index (BMI) of at least 30 kg/m² instead of waist circumference or waist-to-hip ratio (19).

ACF as a biomarker of CRC

ACF, which represent clusters of aberrant colorectal crypts, were first discovered in mice treated with azoxymethane (20). ACF have been demonstrated to be precursor lesions of CRC, and with further investigations, ACF have been established as a biomarker of the risk of CRC in azoxymethane-treated mice and rats (21). In humans, the relationship between ACF and CRC is less clear. The number of ACF was measured using magnifying endoscopy, but the association between ACF and CRC was only partially evident. ACF, however, are also thought to be precursor lesions of colorectal adenoma and CRC in humans (22). Many factors are known to be associated with increased or decreased risk of CRC. Among them, only history of adenomas, age, and the use of NSAIDs have been examined in relation to the development of ACF. The relationships of other factors to the occurrence of ACF in the colon remain unknown.

In the rat model, the formation of ACF was enhanced by cancer promoters and suppressed by chemopreventive agents (23). ACF has also been reported in colonic mucosa in humans (24, 25). Patients with CRC had more ACF with *K-ras* mutations than those without

Table 1. Relationships between selected risk factors for colorectal cancer and the number of ACF in the colorectum

| Risk factors | Correlation coefficient | P-value |
|------------------------|-------------------------|----------|
| Age (years) | 0.256 | 0.0121* |
| BMI | 0.263 | 0.0044* |
| Waist (cm) | 0.370 | 0.0003* |
| Fasting blood sugar | 0.021 | 0.7575 |
| HOMA-IR | 0.263 | 0.6174 |
| Total cholesterol | 0.263 | 0.4771 |
| Triglyceride | 0.263 | 0.2049 |
| VFA (cm ²) | 0.512 | <0.0001* |
| SFA (cm ²) | 0.108 | 0.2091 |

*P-values <0.05 were considered to denote statistical significance. HOMA-IR: homeostasis model assessment of insulin resistance.

CRC. These results suggest that ACF are not only morphologically but also genetically distinct lesions and are precursors of adenoma and CRC.

ACF and visceral fat obesity

The association between the number of ACF and age, BMI, waist circumference, diabetes, serum lipid, visceral fat area (VFA), and subcutaneous fat area (SFA) were evaluated (Table 1). Our findings indicate that age, BMI, waist circumference, and VFA were significantly associated with the number of ACF. Especially, VFA was strongly associated with the number of ACF. Visceral fat tissue is known as an endocrine organ that secretes adipocytokines such as TNF- α , leptin, and adiponectin. These adipocytokines and/or the visceral fat itself may play an important role in colon carcinogenesis. The number of ACF increased with age. Genetic and epigenetic alterations accumulate with advancing of age; therefore, the increased risk of ACF formation with age may be mainly influenced by these genetic alterations.

Chemoprevention for CRC

Chemoprevention, the use of medications to prevent disease, has now been extensively explored in CRC. Supplemental fibers, calcium supplementation, aspirin, NSAIDs, and selective COX-2 inhibitors have a potential to reduce both CRC and colorectal adenomas. Higher doses and longer durations of use of NSAIDs and COX-2 inhibitors seem to be associated with greater protection from CRC and adenoma. However, these agents are associated with significant cardiovascular events and/or gastrointestinal damage. The balance of benefits to risk does not favor chemoprevention by these

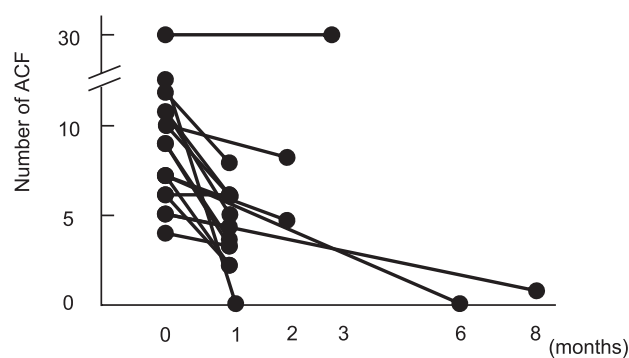


Fig. 1. The numbers of ACF were prospectively examined in 14 subjects before and after 1–8 months of pioglitazone treatment. After PPAR γ ligand treatment, the number of ACF significantly decreased.

agents in average-risk individuals.

ACF and PPAR γ

PPAR γ is mainly expressed in adipose tissue and plays a central role in adipocyte differentiation and insulin sensitivity. Activating synthetic ligands for PPAR γ , such as pioglitazone, are commonly used to treat diabetes. PPAR γ is also overexpressed in many tumors. This suggests that modulation of PPAR γ expression or function might have impact on tumor cell survival. Chemopreventive effects of PPAR γ ligand on the formation of the human ACF were evaluated. Fourteen patients were examined for ACF by magnifying colonoscopy before and after 1 to 8 months of pioglitazone treatment (Fig. 1). After PPAR γ ligand treatment, the number of ACF was significantly decreased. These results suggest that a PPAR γ ligand is a promising candidate as a chemopreventive agent for CRC.

Conclusions

Our results suggest that visceral fat obesity may be a risk factor for CRC and visceral fat may play an important role in colorectal carcinogenesis at an earlier stage in the adenoma-carcinoma sequence (25). Adipocytokines secreted by visceral fat tissue and/or the visceral fat itself may play an important role in colon carcinogenesis. PPAR γ ligand is a promising candidate for CRC chemoprevention.

Acknowledgments

We thank Masako Ochiai and Machiko Hiraga for their technical assistance. This work was supported in part by a Grant-in-Aid for research on the Third Term

Comprehensive Control Research for Cancer from the Ministry of Health, Labour, and Welfare, Japan to A.N.; a grant from the National Institute of Biomedical Innovation (NBIO) to A.N.; a grant from the Ministry of Education, Culture, Sports, Science, and Technology, Japan (KIBAN-B) to A.N.; a grant from the Ministry of Education, Culture, Sports, Science, and Technology, Japan (WAKATE-B) to H.T.; a research grant of the Princess Takamatsu Cancer Research Fund to A.N.; and a grant for 2007 Strategic Research Project (No. K19041) of Yokohama City University, Japan to H.T. and A.N.

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