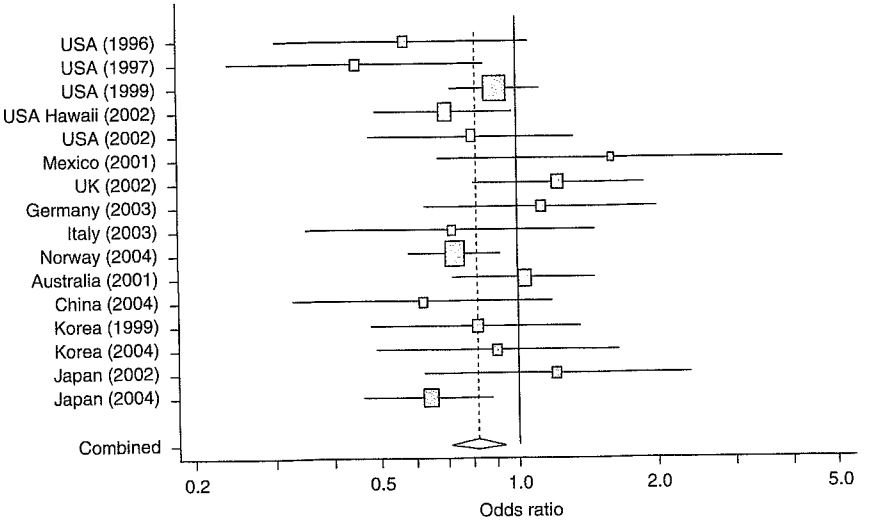

Fig. 2. Meta-analysis of 16 studies on the *MTHFR 677TT* genotype and colorectal cancer. The center of a box and the horizontal line indicate the odds ratio and the 95% confidence interval in each study, with the areas of the boxes representing the weight of each study. The summary odds ratio (random effect model) is represented by the middle of a diamond whose width indicates the 95% confidence interval. The summary odds ratio is also shown by the dotted vertical line.

In some of the studies, odds ratios were not adjusted for sex and age, and estimation of the combined odds ratio and 95% confidence interval (CI) relied upon crude odds ratios and their standard errors. The crude odds ratio would not differ much from that adjusted for sex, age, and lifestyle factors because the genotype of *C677T* is unlikely to vary according to these variables. The lack of adjustment for ethnicity may result in a biased estimate of odds ratios, however. In fact, adjusted odds ratios were not much different from crude odds ratios.

Whereas the first two studies demonstrated a large decrease in the risk of colorectal cancer associated with the *677TT* genotype, subsequent studies did not necessarily replicate the first observation (Table 1). Although individual results are seemingly variable (Fig. 2), the between-study heterogeneity is not statistically significant ($P = 0.16$). The combined odds ratio for the *677TT* versus *677CC* genotype is estimated to be 0.82 (95% CI 0.72–0.93). Overall, there is no decrease in the risk of colorectal cancer among individuals with the *677CT* genotype. Decreased risk associated with *677TT* was not observed in case-control studies in Mexico,[23] the United Kingdom,[24] Germany,[25] Australia,[28] or Japan.[32] Inconsistent findings in small studies can be ascribed to random variation, but such findings in large studies are difficult to interpret. Particularly notable is the lack of association reported in two large case-control studies in the United Kingdom[24] and Australia.[28]

Four studies have examined association with the *C677T* polymorphism by subsite of the colorectum. Two studies suggested a more marked decrease in the risk of proximal colon cancer associated with the *677TT* genotype,[20,26] but the other two found no difference in the frequency of *677TT* genotype between proximal and distal colon cancer.[28,33]

A1298C polymorphism

Few studies have examined the relationship between *MTHFR A1298C* polymorphism and colorectal cancer (Table 2).[21,22,25,29,32–35] A study reported by Chen *et al.*[34] was

Table 2. Summary of studies on *MTHFR A1298C* polymorphism and colorectal cancer

Study (year)	Country	No. of cases/ controls	Odds ratio (95% confidence interval)*		Frequency of *1298C* allele†	Adjusted factors other than sex and age
			1298AC	*1298CC*		
Chen *et al.* (2002)[34]	US	210/344	0.94 (0.64–1.39)	0.73 (0.37–1.43)	0.324	Multivitamin use and others
Le Marchand *et al.* (2002)[21]	US (Hawaii)	539/653	0.9 (0.7–1.1)	0.8 (0.5–1.4)	0.238	Racial background, BMI, PA, and others
Keku *et al.* (2002)[22]	US (white)	309/541	0.9 (0.6–1.1)	0.5 (0.3–0.8)	0.344	None
	US (black)	243/329	1.1 (0.8–1.6)	0.8 (0.3–2.1)	0.190	None
Curtin *et al.* (2004)[35]	US (men)	892/1039	1.0 (0.8–1.2)	1.0 (0.7–1.4)	0.307	BMI, PA, and others
	US (women)	703/925	1.0 (0.8–1.2)	0.6 (0.5–0.9)	0.333	BMI, PA, and others
Plaschke *et al.* (2003)[25]	Germany	287/346	1.08 (0.76–1.55)	1.42 (0.79–2.56)	0.337	None
Jiang *et al.* (2004)[29]	China	125/336	0.71 (0.44–1.14)	0.39 (0.05–3.34)	0.171	None
Matsuo *et al.* (2002)[32]	Japan	142/241	1.06 (0.76–1.67)	0.56 (0.15–2.13)	0.193	None
Yin *et al.* (2004)[33]	Japan	685/778	1.07 (0.85–1.34)	1.71 (0.93–3.14)	0.181	Alcohol and place
Combined estimate‡			0.98 (0.90–1.07)	0.83 (0.63–1.09)		
Heterogeneity			$P = 0.90$	$P = 0.02$		

BMI, body mass index; PA, physical activity. *Referent is the *1298CC* genotype. †Frequency among controls. Le Marchand *et al.* (2002)[21]: Japanese (0.210), whites (0.307), and Hawaiian (0.230). ‡Based on the random effect model.

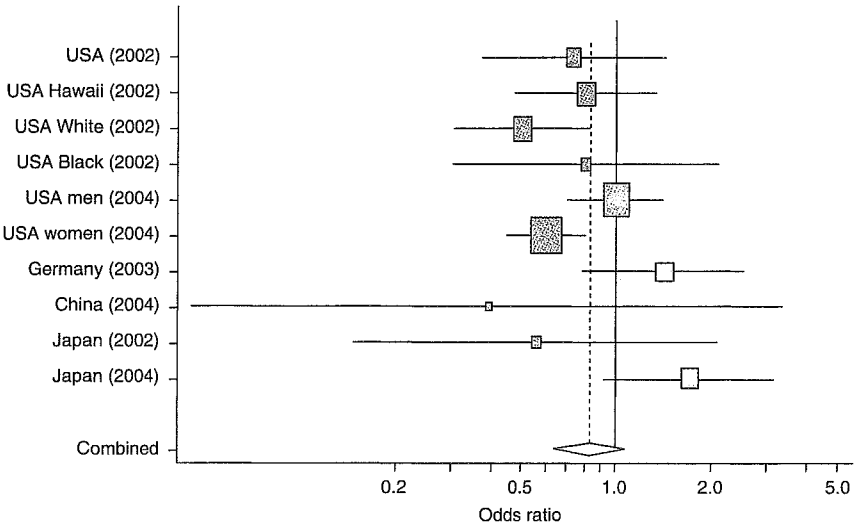

Fig. 3. Meta-analysis of eight studies on *MTHFR 1298CC* genotype and colorectal cancer. The center of a box and the horizontal line indicate the odds ratio and the 95% confidence interval in each study, with the areas of the boxes representing the weight of each study. The summary odds ratio (random effect model) is represented by the middle of a diamond whose width indicates the 95% confidence interval. The summary odds ratio is also shown by the dotted vertical line.

a case-control study in the Physicians' Health Study, and that by Curtin *et al.*[35] is the multicenter case-control study in the US that reported on MTHFR *C677T* as previously discussed.[20] All of the other studies reported the association with *A1298C* as well as with *C677T* polymorphism. The frequency of the variant *1298C* allele is much lower in Japanese and Chinese people (< 20%) than in Caucasians or populations consisting of predominantly Caucasians (30–35%). Again, none of the studies indicates a deviation of the genotype distribution from the Hardy–Weinberg equilibrium.

Although the heterozygous genotype (*1298AC*) is consistently unrelated to the risk of colorectal cancer, the association with the homozygous variant (*1298CC*) is quite variable (Fig. 3). The combined odds ratio for *1298CC* versus *1296AA* is 0.83 (95% CI 0.63–1.09). The overall decrease in the risk associated with *1298CC* is largely influenced by results from the subgroup analysis in two studies, that is, a decreased risk observed in white Americans in one study[22] and in women in another study.[35]

Combined genotype of *C677T* and *A1298C*

The *MTHFR C677T* and *A1298C* polymorphisms are in linkage disequilibrium, and combinations of *677CT* and *1298CC*, *677TT* and *1298AC*, and *677TT* and *1298CC* are null or almost null.[22,25,29,33–35] Thus an independent effect of *1298CC* (or *677TT*) is only examined in individuals with the *677CC* (or *1298AA*) genotype. Overall, the eight observations in six studies indicate that having one variant allele of either *677T* or *1298C* does not affect the risk of colorectal cancer (Table 3). The MTHFR activity of individuals with combined heterozygosity (*677CT* and *1298AC*) may be lowered to the extent that is observed among those with the *677TT* genotype,[17] but the combined heterozygosity does not seem to be functionally relevant to colorectal cancer risk.

As mentioned earlier, the *1298CC* genotype was associated with a decreased risk of colorectal cancer in subgroups of the study subjects,[22,35] and the relative importance of *677TT* and *1298CC* genotypes may be of some interest. Overall, a decreased risk of colorectal cancer is greater for *677TT* than for *1298CC*, although the 95% CI of the two odds ratios overlap to a large extent. Furthermore, the results for the combination of *677TT* and *1298AA* are more consistent than those for the composite genotype of *677CC* and *1298CC*. The two studies reporting inconsistent results within each study suggest that *1298CC* rather than *677TT* may be more important in certain situations.[22,35] These results from the subgroup

Table 3. Colorectal cancer risk according to combined genotypes of *MTHFR C677T* and *A1298C* polymorphisms

Study	Country	No. of cases/ controls	Adjusted odds ration (95% confidence interval)*				
			677CC + 1298AC	*677CC + 1298CC*	*677CT + 1298AA*	*677CT + 1298AC*	*677TT + 1298AA*
Chen *et al.* (2002)[34]	US	201/325	0.98 (0.54–1.78)	0.78 (0.36–1.72)	1.16 (0.62–2.18)	1.04 (0.57–1.92)	0.52 (0.25–1.10)
Keku *et al.* (2002)[22]	US (white)	306/536	0.9 (0.6–1.4)	0.5 (0.2–0.8)	1.1 (0.7–1.7)	0.8 (0.5–1.3)	0.8 (0.4–1.4)
	US (black)	243/327	1.1 (0.8–1.7)	0.8 (0.3–2.1)	1.0 (0.6–1.7)	0.9 (0.4–2.0)	0.8 (0.2–3.2)
Curtin *et al.* (2001)[35]	US (men)	892/1039	0.9 (0.6–1.2)	1.0 (0.7–1.4)	1.0 (0.7–1.3)	1.0 (0.7–1.4)	0.7 (0.5–1.0)
	US (women)	705/925	1.0 (0.7–1.4)	0.6 (0.4–0.9)	0.9 (0.6–1.3)	0.9 (0.6–1.2)	0.8 (0.5–1.2)
Plaschke *et al.* (2003)[25]	Germany	287/346	1.12 (0.64–1.96)	1.41 (0.74–2.71)	1.29 (0.74–2.25)	1.41 (0.81–2.45)	1.18 (0.62–2.24)
Jiang *et al.* (2004)[29]	China	124/327	0.73 (0.37–1.45)	0.54 (0.06–5.06)	1.06 (0.62–1.82)	0.67 (0.32–1.40)	0.57 (0.28–1.17)
Yin *et al.* (2004)[33]	Japan	685/778	0.93 (0.65–1.32)	1.53 (0.80–2.95)	0.89 (0.66–1.22)	0.90 (0.62–1.31)	0.64 (0.44–0.94)
Combined estimate†			0.96 (0.83–1.12)	0.87 (0.65–1.16)	1.00 (0.86–1.16)	0.94 (0.80–1.11)	0.72 (0.60–0.86)
Heterogeneity			$P = 0.97$	$P = 0.12$	$P = 0.96$	$P = 0.82$	$P = 0.76$

*Referent is the *677CC* and *1298AA* genotypes. Adjusted factors are the same as described in Table 2. †Based on the random effect model.

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analysis need further confirmation, however. No plausible explanation has been given for the inconsistency within a study.[22,35]

Effect modification of folate

A decreased risk of colorectal cancer associated with *677TT* was more evident in health professionals with high folate intake (≥ 461 μg/day) and in physicians with high folate levels in plasma (≥ 3.0 ng/mL) in the US.[18,19] A suggested effect modification of dietary folate intake in the same direction was observed in two of the three subsequent studies in the US.[20,21] However, a decreased risk associated with *677TT* was seen in both white Americans and African Americans with low folate intake (< 400 μg/day) in the study reported by Keku *et al.*[22] In that study, there was virtually no difference in the risk according to *C677T* polymorphism in individuals with high folate intake (≥ 400 μg/day). Curtin *et al.* examined the effect modification of folate on the risk associated with the composite genotype of *C677T* and *A1298C*, and showed a decrease in the risk associated with *677TT* (compared with *677CC*) in women with the *1298AA* genotype who had low folate intake (≤ 273 μg/day), with no difference in the risk between *677TT* and *677CC* genotypes in women with the *1298AA* genotype who had intermediate and high (> 388 μg/day) folate intake.[35]

Importantly, these apparently inconsistent findings are not incompatible with the role of *MTHFR C677T* polymorphism in colorectal carcinogenesis with respect to the size of the thymidylate pool. Low activity of MTHFR or the *677TT* genotype is probably advantageous because it ensures an adequate thymidylate pool for DNA synthesis when folate supply is sufficient, as originally proposed by Chen *et al.*[18] In the folate-depleted situation, as suggested by Keku *et al.*,[22] high activity of the enzyme or the *677CC* genotype may be disadvantageous because 5,10-methylenetetrahydrofolate is converted and the thymidylate pool is depleted. Increased risk for *677TT* versus *677CC* would be seen in the folate-depleted situation if aberrant DNA methylation is a primary mechanism, but no such increase has been observed.

Two studies have examined the interaction between *A1298C* polymorphism and folate. The decreased risk associated with *1298CC* observed in white Americans in the study by Keku *et al.*[22] seemed more marked when folate intake was low, and that observed in women in the study by Curtin *et al.*[35] was more evident when folate intake was high.

Effect modification of vitamins B_6 and B_{12}

Vitamins B_6 and B_{12} are important cofactors in folate metabolism. Vitamin B_6 is required for recycling tetrahydrofolate (a product of 5-methyltrahydrofolate after methyl-transfer to homocysteine) to 5,10-methylenetetrahydrofolate. Vitamin B_{12} is a cofactor of methionine synthase, and converts homocysteine to methionine. The limited results available regarding the effect modification of vitamin B_6 and B_{12} were generally similar to those observed for folate,[20,21,35] with the exception of the lack of interaction with B_{12} in the study in Hawaii.[21] This similarity is not likely to be derived from intercorrelation between intakes of these vitamins. The major food sources of folate are vegetables and fruits, but vitamin B_{12} is present primarily in animal foods, and vitamin B_6 is present in diverse foods of both animal and plant origin, as illustrated by food sources of these vitamins in the Japanese diet (Table 4).[36] With regard to methionine, the study of health professionals showed a more marked decrease in the risk associated with *677TT* in those with high methionine intake,[18] but the decrease was more marked in those with low methionine intake in Hawaii[21] and did not differ by methionine intake in the multicenter study in the US.[20]

Table 4. Average per capita intake of vitamins B_6 and B_{12} and folate in Japan, 2001

Food group	Amount (g/day)	Vitamin B_6 (mg/day)	Vitamin B_{12} (μg/day)	Folate (μg/day)
Cereals	464	0.10 (8.5)	0.01 (0.1)	27.8 (8.9)
Legumes	57	0.05 (4.2)	–	15.6 (5.0)
Vegetables	279	0.21 (17.8)	–	115.4 (36.8)
Fruits	132	0.11 (9.3)	–	21.5 (6.9)
Fish and shellfish	94	0.22 (18.6)	5.64 (73.4)	11.6 (3.7)
Meat	76	0.17 (14.4)	0.82 (10.7)	11.5 (3.7)
Eggs	37	0.03 (2.5)	0.34 (4.4)	13.6 (4.3)
Dairy foods	170	0.04 (3.4)	0.44 (5.7)	6.4 (2.0)
Tea (fluid)	301	0.03 (2.5)	–	37.7 (12.0)
Others	432	0.22 (18.6)	0.43 (5.6)	52.2 (16.7)
Total	2042	1.18	7.68	313.3

Values in parentheses are percentage nutrient intake from individual food groups. Content of each nutrient per unit amount of each food group can be obtained by dividing nutrient intake by intake of food group. Source: National Nutrition Survey in Japan, 2001.[36]

Effect modification of alcohol

Excessive alcohol consumption causes folate deficiency, as exemplified by megaloblastic anemia among chronic alcoholic abusers. Alcohol consumption leads to folate depletion by decreasing intestinal absorption and hepatic uptake, increasing renal excretion, and cleaving folate.[37] Folate deficiency may explain part of the moderate increase in the risk of colorectal cancer associated with alcohol use.[38] Studies of health professionals and physicians in the US demonstrated that risk of colorectal cancer associated with the *677TT* genotype was more markedly decreased among those with low alcohol intake.[18,19] This observation was confirmed in a case-control study in Japan,[33] but not in other studies in the US.[20,35] Three case-control studies also examined the effect modification of alcohol use on the association with *C677T* or *A1298C* in the US,[22] China,[29] and Korea,[31] but the results from these studies are not informative because alcohol consumption was extremely low[22] or was not quantified,[29] and because the *677CT* and *677TT* genotypes were collapsed into one group.[31]

Interpretation

Decreased risk of colorectal cancer associated with the *677TT* genotype has been observed in different populations with few exceptions. This decrease was observable in either high or low folate status. The thymidylate pool associated with MTHFR activity is a probable mechanism underlying the decreased risk for the *677TT* versus *677CC* genotype. The effect modification of nutritional factors such as folate and alcohol remains possible, even when there is no overall

inverse association between *677TT* genotype and colorectal cancer. Inconsistently observed decreases in the risk associated with the *A1298C* polymorphism need to be corroborated in other large studies. The effect modification of nutritional factors other than alcohol has been examined exclusively in the US, and further studies in different countries will elucidate the role of folate metabolism in colorectal carcinogenesis from a global perspective.

MTHFR polymorphisms and colorectal adenoma risk

C677T polymorphism

The association between the *MTHFR C677T* polymorphism and colorectal adenoma has been examined in eight studies in the US,[39–42] Mexico,[23] Japan,[43,44] and Norway.[45] A study of 257 adenoma cases and 713 controls in a cohort of female nurses in the US was the first to investigate the relationship between *MTHFR C677T* polymorphism and colorectal adenoma, and found no association.[39] In this study, the controls were women undergoing sigmoidoscopy who had not been diagnosed with colorectal adenoma. The lack of association between *C677T* polymorphism and colorectal adenoma was further noted in three studies of 527 cases and 645 controls, of 471 cases and 510 controls, and of 379 cases and 726 controls in the US[40–42] and in two studies of 205 cases and 220 controls and of 452 cases and 1050 controls in Japan.[43,44] All of these studies were on the basis of colonoscopy or sigmoidoscopy. In the above-mentioned Mexican study of colorectal cancer,[23] 31 cases of colorectal adenoma were included separately, and no clear association with *C677T* polymorphism was observed. On the basis of these seven studies, the pooled estimate of odds ratio for *677TT* versus *677CC* (or *677CC* and *677CT* combined) is 1.02 (95% CI 0.85–1.22). However, in a small study of 443 subjects undergoing colonoscopy in Norway,[45] the *677TT* genotype was associated with an increased risk of high-risk adenoma (defined as adenomas ≥ 10 mm in size or adenomas with villous components or severe dysplasia); there were 47 cases with high-risk adenoma, and the odds ratio for the *677TT* versus *677CC* genotype was 2.41 (95% CI 0.82–7.06) with adjustment for sex, age, erythrocyte folate, and others.

A1298C polymorphism

Only one study examined the association of this polymorphism with colorectal adenoma, and found no overall association.[42]

Effect modification of nutritional status

Despite the overall lack of association with *C677T* polymorphism, two studies in the US found a statistically significant increase in the risk of colorectal adenoma among those with the *677TT* genotype who had a high alcohol intake, which was defined as > 9.5 g/day in one study[41] and as > 30 g/day in the other.[42] A similar, but less evident, finding was also noted in a Japanese study.[43] Inconsistently, a statistically significant increase in risk was noted among those with the *677CC* genotype who had a high alcohol intake (> 7 g/day) in one study,[40] and among female nurses with the *677TT* genotype who had low alcohol intake in another study.[39] The latter finding was interpreted as being probably due to chance, but no clear explanation is evident for the former findings.

In the study reported by Ulrich *et al.*, low intake of folate, vitamin B_{12}, vitamin B_6, and methionine tended to be associated with an increased risk of colorectal adenoma among those with the *677TT* genotype, while high intakes of these nutrients tended to be associated with lower risk among those with the *677TT* genotype.[40] Those with the *677TT* genotype had somewhat elevated risk when plasma folate was low and decreased risk when plasma folate was high in the US[41] as well as in Japan.[46] A substantial increase in the risk of high-risk adenoma was reported among those with the *677TT* genotype with low folate status in erythrocytes in Norway.[45] There was no clear interaction between folate intake and 677TT genotype in studies of nurses and health professionals in the US,[39,42] but the combination of high alcohol and low folate intake was associated with an increased risk, while the opposite combination was related to a decreased risk in the latter study.[42]

Interpretation

The reported decrease in adenoma risk associated with high folate or low alcohol intake among those with the *677TT* genotype is small and no more than suggestive of an association. In contrast with the observation regarding colorectal cancer, the *677TT* genotype was associated with increased risk of colorectal adenoma under conditions of low folate or high alcohol intake. Folate depletion results in a decrease in *de novo* synthesis of methionine as well as an insufficient pool of thymidylate, but DNA hypomethylation associated with low folate status seems to be limited to individuals with the *677TT* genotype.[47] Thus the increased risk observed for the combination of poor folate status and *677TT* genotype could be interpreted as suggesting that reduced availability of methyl groups for DNA methylation might be more relevant to adenoma formation rather than the progression from adenoma to carcinoma.

Conclusion

Decreased risk of colorectal cancer associated with the *MTHFR 677TT* genotype has fairly consistently been observed in different populations, and the effect of *MTHFR C677T* polymorphism on colorectal cancer risk may differ in accordance with folate status. Without consideration of the interaction between *MTHFR* polymorphism and nutritional factors, it would be concluded that folate metabolism is unrelated to the occurrence of colorectal adenoma. However, the results from analysis of the interaction between *MTHFR* polymorphism and folate or alcohol intake suggest that folate metabolism is involved in an important way in the occurrence of colorectal adenoma as well. Different patterns in the effect of the interaction between *MTHFR C677T* polymorphism and folate or alcohol intake on risks of colorectal cancer and adenoma suggest that DNA synthesis and methylation may be differently relevant to early and late stages of colorectal tumorigenesis. Although the underlying mechanisms still remain to be clarified, epidemiological findings regarding *MTHFR C677T* polymorphism provide strong evidence that adequate folate status confers protection from colorectal cancer.

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Epidemiological studies of functional genetic polymorphisms are very useful for understanding the role of dietary factors in carcinogenesis with respect to both biological mechanisms and prevention. Measurement of food and nutrient intake is always prone to a sizable random variation, unintentionally adding to the degree of homogeneity in terms of a factor under study, which in turn causes difficulties in detecting an effect of the factor. It goes without saying that a study should be large enough to address a specific question it is purported to answer, as recognized in this review.

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COMMENTARY

Comparison of Japanese, American-Whites and African-Americans - Pointers to Risk Factors to Underlying Distribution of Tumours in the Colorectum

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Abstract

Relative incidence rates for colon and rectal cancer vary greatly between populations in the world. While Japanese have historically had low prevalence, immigration to the United States has now resulted in equal if not higher rates than in Caucasian- or African-Americans. Furthermore, recent data from some population-based registries in Japan itself are also pointing to particularly high susceptibility. Of particular interest is the fact that Japanese in both the home country and the US in fact have far higher rates for rectal cancer than the other two ethnic groups. An intriguing question is whether they might also demonstrate variation from Caucasian- and African-Americans in the raltive incidence rates for proximal and distal colon cancers, given the clear differences in risk factors like diabetes, physical exercise, smoking, alcohol consumption, meat and fish intake and calcium exposure which have been shown to operate in these two sites. A comprehensive epidemiological research exercise is here proposed to elucidate ethnic variation in colorectal cancer development, based on cross-cancer registry descriptive and case control approaches. It is envisaged that additional emphasis on screened populations should further provide important insights into causal factors and how primary and secondary prevention efforts can be optimized.

Key Words: Colon cancer - proximal - distal - rectal cancer - registry data - case-control - endoscopy screening

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Introduction

While colon and rectal cancer rates in Caucasian-American, African-American and to some extent, Japanese-American populations appear to be now decreasing, in Japan itself they continue to increase, albeit at remarkably different rates in different registries (see Figure 1). In fact Japanese in some registries, both in the US and in Japan itself, now demonstrate higher rates than either their White or Black counterparts. There is also considerable variation in the relative incidences of colon as opposed to rectal cancer, and a trend has been evident for the ratios of colon to rectal cancers to increase over the last 25 years (see Table 1), as already documented in Japan (Takada et al., 2002).

Risk Factors

There are clear differences in risk and beneficial factors for the two body sites (Table 2). Colon cancer appears more closely associated than rectal cancer with environmental factors leading to obesity, and this association is more pronounced in men than in women (Nakaji et al., 2003). Rectal lesions, in contrast, appearmore linked to alcohol consumption and tobacco smoking (World Cancer Research Fund, 1997; Toyomura et al., 2004), although both alcohol consumption and smoking have been found to be clearly associated with colorectal cancer overall in men (Otani et al., 2003). In one study, age, gender, family history of colon or rectal cancer, height, body mass index, physical activity, folate, intake of beef, pork or lamb as a main dish, intake of processed meat and alcohol were all found to be significantly associated with colon cancer risk, while only age and sex were associated with rectal cancer (Wei et al., 2004)

Division is not only necessary for colon and rectal cancers, but also for subsites within the colon. For all age groups in the US, a proximal migration of colon tumors over time was identified by Mostafa and coworkers (2004), although this might partly be attributable to decrease in the

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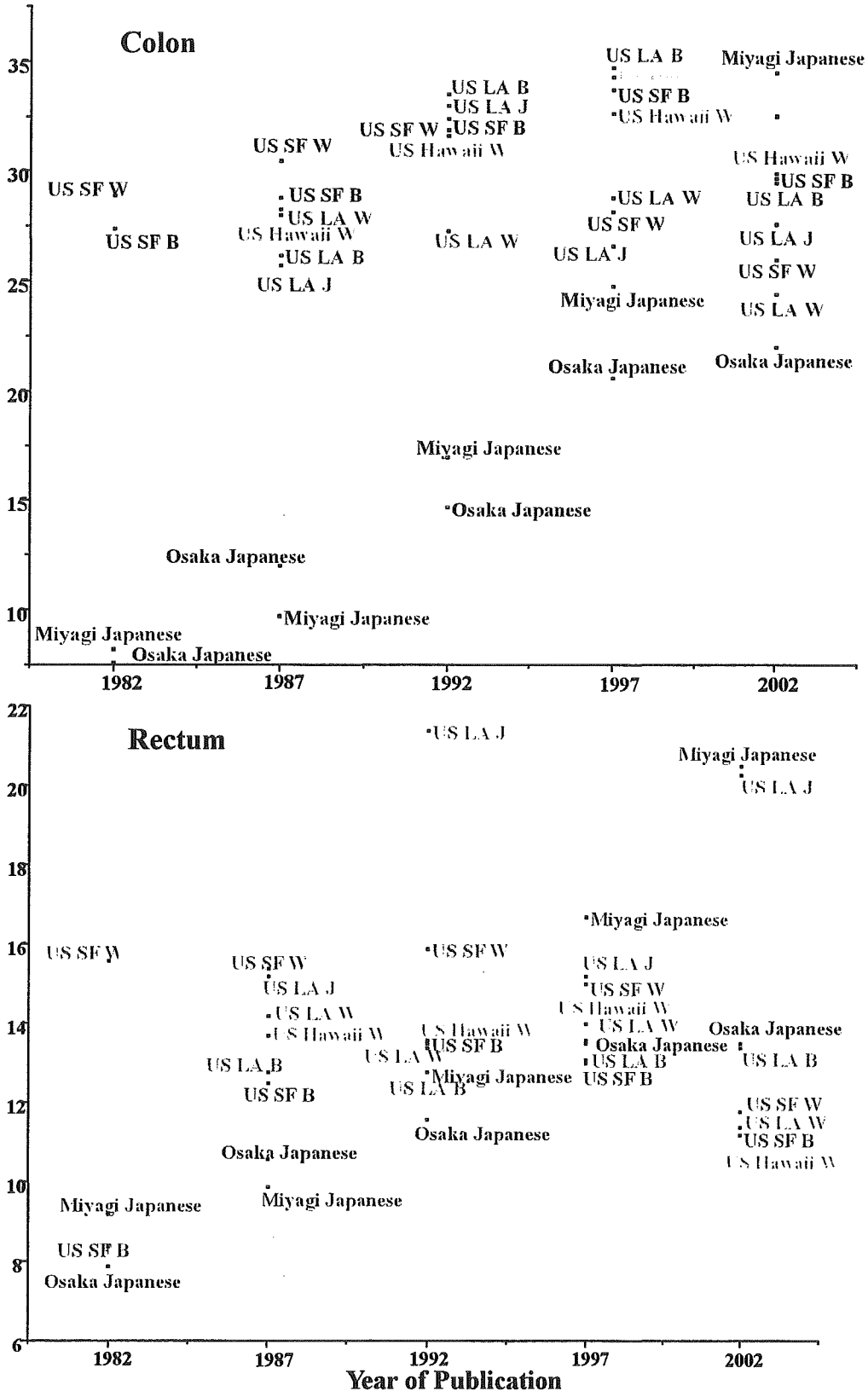


Text-Figure 1. Trends in Colon and Rectal Cancer Incidence Rates for Japanese, Blacks and Whites (Data from Cancer Incidence in Five Continents (Vols IV-VIII)

Table 1. Colon/Rectal Cancer Incidence Ratios for Selected Cancer Registries*

Asian Registry	1982	2002	Change	Western Registry	1982	2002	Change
China Hong Kong	1.3:1	1.6:1	++	Australia, NSW	1.7:1	1.6:1	-
China, Shanghai	0.7:1	1.3:1	+++	Colombia, Cali	1.3:1	1.6:1	++
Hawaii, Hawaiians	1.2:1	1.5:1	++	Slovakia	0.7:1	1.1:1	++
India, Bombay	0.8:1	1.2:1	++	Spain Zaragoza	1.1:1	1.4:1	++
Singapore, Chinese	1.0:1	1.3:1	++	Sweden	1.5:1	1.5:1	+/-
Singapore Indian	1.3:1	1.2:1	-	UK S Thames	1.3:1	1.5:1	+
Singapore, Malay	0.7:1	0.9:1	+	UK Scotland	1.6:1	1.7:1	+
Japan, Miyagi	0.9:1	1.7:1	++++	US SF White	1.9:1	2.2:1	++
Japan, Osaka	1.0:1	1.6:1	+++	US SF Black	3.3:1	2.7:1	---

*Values calculated from data in Cancer Incidences in Five Continents 1982 and 2002

incidence of distal cancers coupled with aging of the population (Rabeneck et al., 2003). Among non-Hispanic whites a decline in all sites and stages has been documented, but the decrease was most pronounced for rates of *in situ* and regional/distant tumors in the rectum and sigmoid (Cress et al., 2000). However, in African-Americans proximal cancer rates do appear to be increasing (Troisi et al., 1999). Asians and Pacific Islanders in the US, contrasting with their white and black counterparts, have approximately equal numbers of proximal and distal cancers (Wu et al., 2004). Division of the colorectum anatomically at the junction of the descending and sigmoid colon, and including the rectum above the anal canal with "distal" colorectal cancers demonstrated a predominance of African Americans among those at risk of proximal and a predominance of white males among those at risk of distal lesions (Nelson et al., 1997). In Canada, decreasing rates for colorectal cancer appear limited to tumours located in the distal colon and rectum; the incidence of cancers of the proximal colon has not changed over time (Gibbons et al., 2001). French results also confirm the existence of different trends in colorectal cancer incidence between subsites and sexes (Mitry et al., 2002). In Korea changes in the colon-to-rectal ratio appear mainly be due to an increase in left-sided colon cancer (Kim et al., 2002). It remains to be determined which site is now predominating in different Japanese populations but an earlier study suggested that distal cancer might be most affected by the change in diet in Japan (Tajima et al., 1985)..

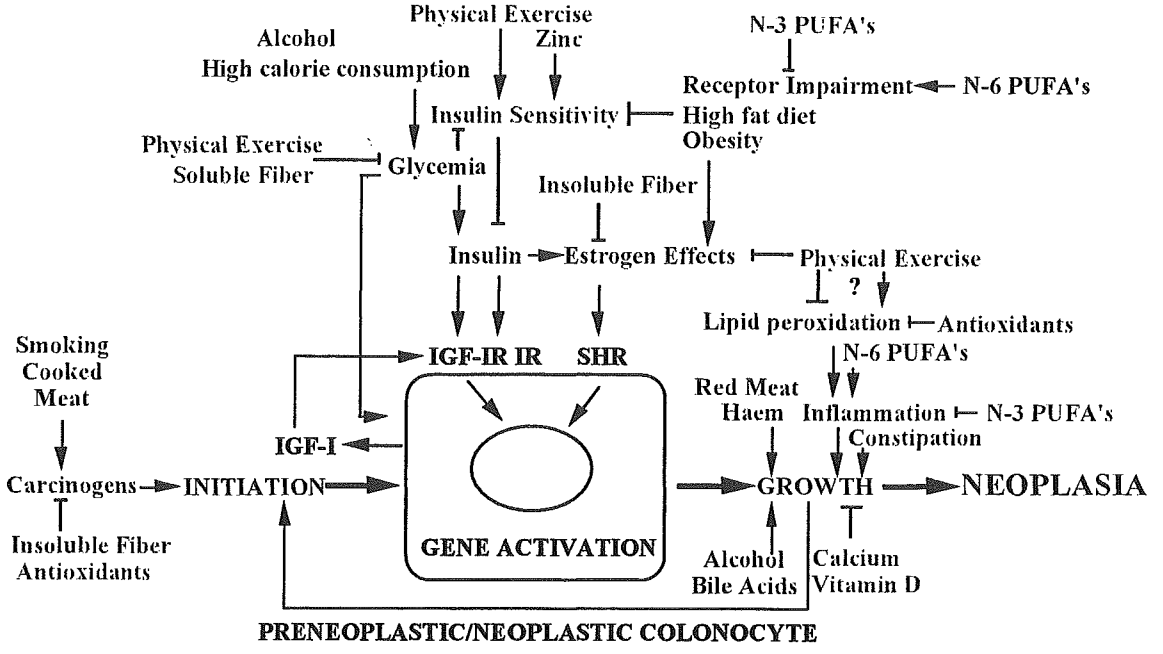
Table 2. Possible Risk and Protective Factors for Cancer of the Proximal and Distal Colon and Rectum

Factor	Proximal	Distal	Rectum
Risk			
Smoking	?	+	++
Alcohol	?	+	+
Western Diet	+	++	?
Asian Diet	+?	--	?
Red Meat	?	+	+
NIDDM	++	+	+
Constipation	+	++	?
Cholecystectomy	++	?	?
Protective			
Physical Activity	-	-	-?
Fibre Intake	-	-	?
Calcium	?	--	--
Vitamin D	?	--	--
Fish	-	-	-

+, ++ promotion -,-- inhibition +?/-? possible effect, ? unclear

A summary of data regarding separation of the different sites within the colorectum for risk factors is also provided in Table 2 and possible modes of action are illustrated in Figure 2. Cigarette smoking may be significantly associated with an increased risk of adenomas, regardless of the location, but most pronouncedly for rectal lesions in one study (Toyomura et al., 2004). In another in China, increasing tertiles of smoking duration in ever smokers was also associated with increased rectal cancer risk (Ho et al., 2004). 'Irritable bowel' (soft or loose feces) might be associated with distal subsites of colorectal cancer, independently or combined with habitual smoking (Inoue et al., 1995). Regarding the impact of alcohol, an increased risk of colorectal cancer was found in current drinkers (Ho et al., 2004), and daily consumption of any type was associated with increased risks of cancer of the distal colon and the rectum but not the proximal colon (Sharpe et al., 2002). Similar findings have been documented for adenomas in Japan (Toyomura et al., 2004). However, in 8 cohort studies a positive alcohol association was evident for cancer of the proximal colon, distal colon and rectum (Cho et al., 2004).

Clearly there must be effects of nutrition and in Korea, a Western dietary pattern was found to be associated with colon cancer risk, especially in females with distal colon cancer, while a traditional diet appeared linked to proximal lesions (Kim et al., 2005). Similarly, Japanese-style foods may decrease the risk of distal colon cancer, but increase the likelihood of proximal tumour development (Inoue et al., 1995). A moderately positive association between higher western pattern scores and risk of colon or distal colon adenomas has also been documented (Wu et al., 2004). One important component of the Western diet is red meat intake and there is evidence that this is an important determinant of colon cancer risk (Kono, 2004; Norat et al., 2005). In one study, highest versus lowest tertile meat consumption appeared significantly linked with both colon and rectal



Influences of major risk and beneficial factors on preneoplastic and neoplastic cells. PUFAs, polyunsaturated fatty acids; IGF-IR, insulin like growth factor I receptor; IR, insulin receptor; SHR, steroid hormone receptor; NSAIDs, non-steroid anti-inflammatory drugs; ⟶, enhancing stimulus; ⟞, inhibitory effect.

Figure 2. Mechanisms Whereby Risk and Protective Factors Could Impact on Colon and Rectal Cancer Development

cancer, independent of the sex (Ye et al., 2003), but in another substantial increase was only apparent for distal colon cancer (Chao et al., 2005; Larsson et al., 2005). Increased risk may be related to the cooking temperature and close contact of the food to the heating source, higher risks being observed for heavily browned surfaces when meats were barbecued or iron-pan cooked (Navarro et al., 2004). Dietary haem iron that is present in red meat is associated with an increased risk of proximal colon cancer, especially among women who drink alcohol (Lee et al., 2004), and it has been argued that the association between consumption of red meat and the risk of colon cancer is mainly due to its haem content, and is largely independent of any included dietary fat (Sesink et al., 2000).

Given the conclusion of protective effects of fruit and vegetables in the World Cancer Research Fund publication of 1997, recent cohort data offering little support for associations between intakes and colorectal cancer risk are surprising, although legume fiber did appear to have benefit (Lin et al., 2005). One problem is the considerable confounding by other dietary and lifestyle factors (Michels et al., 2005). With high intake of nuts and seeds a significant inverse association was observed in subgroup analyses for colon cancer in women (Jenab et al., 2004). In an earlier survey of 13 colon and rectum case-control studies (Howe et al.,1992), twelve demonstrated an inverse association with fiber, similar for both left and right sides of the colon. An international comparison of starch consumption similarly revealed a strong inverse link with colorectal cancer incidence (Cassidy et al., 1986). The drop in consumption of fiber by Japanese in the post-war period has in fact been found to be followed after a time-lag by increase in colon cancer (Tsuji et al., 1996).

Another protective factor may be consumption of raw or cooked fish, primarily in the colon but also to some extent in the female rectum (Yang et al., 2003). This was recently extended to total omega-3 polyunsaturated fatty acids (Kojima et al., 2005). A focus on distal adenomas, however, did not provide support for the hypothesis that a higher intake of marine n-3 fatty acids or a higher n-3/n-6 ratio reduces the risk (Oh et al., 2005).

Although one major study did not generate evidence in favour of an association of calcium and vitamin D intake and colorectal cancer risk (Lin et al., 2005), 800 mg of calcium per day confered an approximately 25% reduction in another (Flood et al., 2005). High levels of calcium intake were found to reduce risk of rectal cancer in women but not men (Slattery et al., 2004). In the same study, similar reduction in rectal cancer risk among women was observed for vitamin D, low-fat dairy products and sunshine exposure. An inverse association for milk has also been documented, but limited to cancers of the distal colon and rectum (Cho et al., 2004a). Furthermore, benefit from higher 25-hydroxyvitamin D 25(OH)D concentrations was observed for cancers of the distal colon and rectum, but not the proximal colon (Feskanich et al., 2004). Regarding mechanisms of action, reports of increased apoptosis (Miller et al., 2005) and reduced proliferation (Kallay et al., 2005) are of obvious relevance.

There have been a number of reports of increased risk

of proximal colonic cancer after cholecystectomy (Vernick et al., 1980; Alley and lee, 1983; Paul et al., 1993) and recently a decrease linked to a CYP7A1 polymorphism rendering less activity of the enzyme converting cholesterol to bile acids has provided compelling evidence (Hagiwara et al., 2005), in line with the proposed promoting role of bile acids and metabolic activity of colonic bacteria (Zuccato et al., 1993). Some data have been documented supporting the hypothesis that cholecystectomy may be a risk factor for right-sided colon cancer, but indicating that it may exert a protective influence against rectal cancer (Caprilli et al., 1989).

A great deal of interest has been concentrated on possible links between type II diabetes and associated obesity on the one hand and colorectal cancer on the other (see Moore et al., 1998 for review) and in Japan the time trends for the two diseases are in line with an important contribution (Kuriki et al., 2004). Waist circumference has been found to be a stronger predictor of colon cancer risk than BMI, central obesity being linked to an increased risk of cancer of both the proximal and distal colon (Moore et al., 2004). While NIDDM was associated with modestly increased risk of sigmoid colon adenomas in Japan (Kono et al., 1998), statistically significant elevation in relative risk was limited to the proximal colon in the US (Limburg et al., 2005). Of interest in this context is the finding that dietary zinc, protective against diabetes, is linked with a decreased risk in both proximal and distal colon sites (Lee et al., 2004). Diet with a high dietary glycemic load may increase the risk of colorectal cancer in women (Higginbotham et al., 2004) but this could not be confirmed for distal adenomas (Oh et al., 2004).

There may be a role for estrogen and reproductive factors like age at menarche, particularly in distal colon cancer (Yoo et al., 1999). An inverse association was detected between the number of full-term pregnancies and the risk of colon cancer in female subjects, as well as the age at menarche (Ghadirian et al., 1998). In this context, the possibility of protective effects of phytoestrogens, possibly due to competitive binding to estrogen receptors needs to be taken into account (Lechner et al., 2005).

There is considerable evidence in the literature that physical activity is associated with reduced risk of colon but not rectal cancer in both males and females (for review see Moore et al., 1998). The same conclusion was drawn from a major meta-analysis (Samad et al., 2005). However, a significant inverse association has been reported for moderate/heavy occupational activity in the distal colon and rectum but not in the proximal colon (Colbert et al., 2001). One possible mechanism whereby physical exercise might be protective is through effects on insulin actions (Moore et al., 1998a; 1998b). Another is on constipation, which has been shown to have a positive association with risk of colon cancer (Ghadirian et al., 1998), especially in the distal region in black women (Roberts et al., 2003). However, a meta-analysis (Sonnenberg and Muller, 1993), as well as a case control study focused on middle-aged adults (Jacobs and White, 1998), suggested the colon rather than the rectum to be the site of greatest impact of this factor.

Pointers for Future Research

Clearly there are a number of different factors which are active in different sites within the colorectum and presumably these reflect physiological variation. The major difference between the proximal and distal colon is that the former is far more active in absorbing water from the feces, while the latter has a greater role for storage before defecation through the rectum. Why should there be the observed variation in sub-site dependence of cancer development? Can we find plausible explanations as to the underlying mechanisms? One approach might be to take advantage in racial and geographical variation in incidence rates. For example the available data for colon and rectal cancers in Japan and the different racial groups in the US suggest that cancer registries are in a good position to clarify the situation regarding sub-site distributions of colorectal cancers in Japanese in Japan, Hawaii and the West Coast, as well as both Caucasian- and African-Americans. There is considerable variation between incidence rates among the racial groupings (see Figure 3), with striking separation on a racial basis, Japanese in the US continuing to group together with their counterparts in Japan itself. Elucidation of what might be the responsible factors is necessary for generation of effective programs for primary and secondary prevention and for this purpose cross-registry collaboration is essential. A number of concrete approaches can be envisaged marrying descriptive with analytical epidemiology.

1) Determination of Change in Sub-Site and Stage Distribution, as well as Age at Diagnosis and Size, of Colon and Rectal Cancers Over Time.

Access data from Japanese and American (Hawaii, California) Registries for the period 1976 to the present and make comparisons, taking into minor variation in diagnostic criteria.

2) Determination of the Sub-Site and Stage Distribution, as well as Age of Diagnosis and Size, of Lesions Detected by Colonoscopy Following a Positive ImmunoFOBT Test or Other Screening Result.

Access data from screening centers in Japan and where possible in the US to ascertain the influence of different screening modalities and diagnostic procedures.

3) Develop Consistent Food Frequency/Lifestyle Questionnaires for Use in Japan and the United States to Determine Risk and Beneficial Factors.

In order to allow full comparability of case-control studies between registries and countries, questionnaires need to be collated for consistency, as for example with the South-East Asia-Japan Project being conducted by Tokudome et al (2004).

4) Using Physician-Diagnosed or Screened Cases, Conduct Case-Control Studies of Risk Factors for Separate Colorectal Subsites as well as ChemopreventionTrials, feo example with NSAIDs.

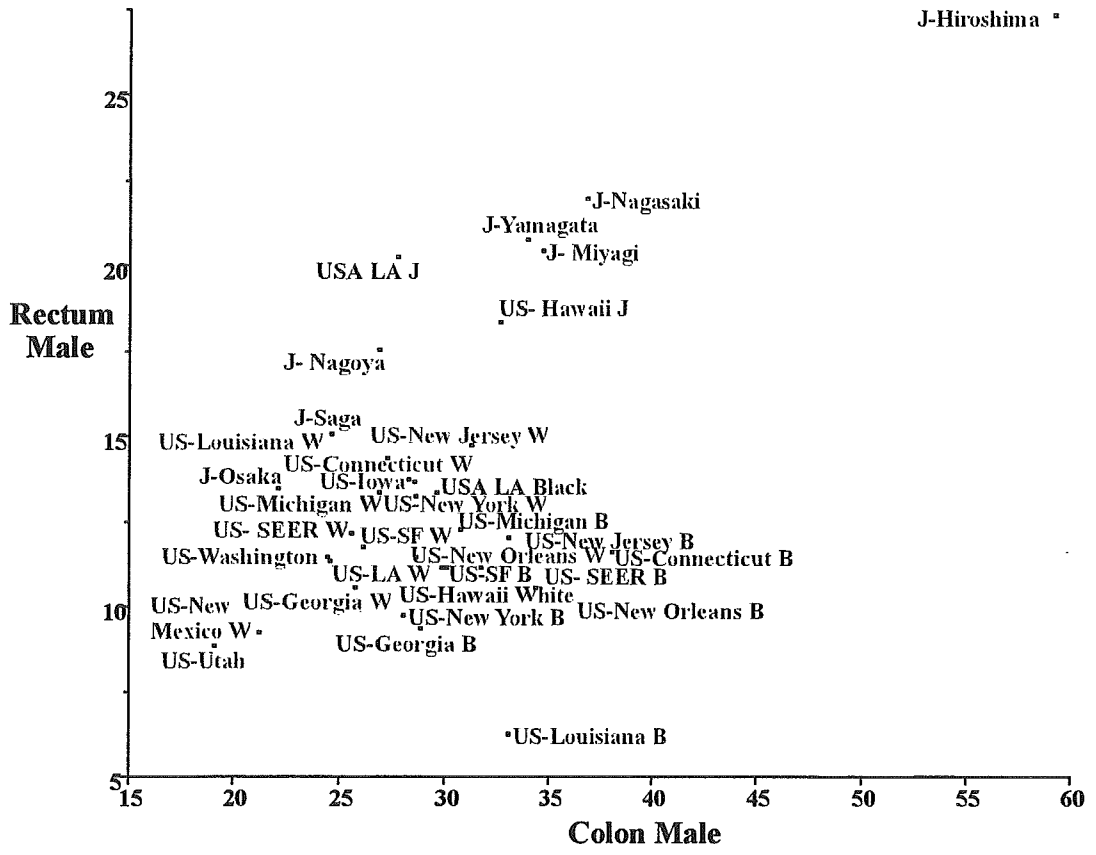


Figure 3. Colon-Rectal Cancer Ratios for Male Japanese, Blacks and Whites (Data from Parkin et al., 2002).

As collaborative efforts, comprehensive case-control studies focusing on colorectal physiology, diet, fecal characteristics, anthropomorphic parameters, diabetes, physical exercise, smoking and alcohol consumption as risk factor for separate subsites within the colon and rectum might be conducted in tandem by scientists in the US and Japan. On the Japanese side the HERPACC program of Aichi Cancer Center (Tajima, 2000) and the Fukuoka Colorectal Cancer Study (Kono et al., 2004) are concrete examples of research projects already underway which might be persuaded to participate in collaborative exercises.

While organization of cross-registry and cross-country research presents ergonomic problems because of distant locations, these are no more unsurmountable that the difficulties involved in setting up major cohort-based projects. Benefits might include the ability to effectively focus on ethnic variation in gene polymorphisms which could be participating in genetic-environmental interactions. Elucidation of what determines risk is essential to provide the basis for mechanism-based cancer prevention - international cooperation among scientists is a core tool for this purpose.

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RESEARCH COMMUNICATION

The Metabolic Syndrome is Associated with Increased Risk of Colorectal Adenoma Development: The Self-Defense Forces Health Study

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Abstract

The metabolic syndrome, a cluster of metabolic abnormalities linked to insulin resistance, has attracted much interest as a risk factor for cardiovascular disease and type 2 diabetes. Hyperinsulinemia is also a postulated biological risk factor for colorectal carcinogenesis. We therefore here examined the relation between the metabolic syndrome and colorectal adenoma development. The study subjects were 756 cases of colorectal adenoma and 1751 controls with no polyps who underwent total colonoscopy during the period January 1995 to March 2002 at two Self Defense Forces (SDF) hospitals in Japan. The metabolic syndrome was defined with reference to abdominal obesity in combination with any two of the following conditions: elevated triglycerides (≥150 mg/dL); lowered HDL cholesterol (<40 mg/dL); elevated blood pressure (systolic blood pressure ≥130 mmHg and/or diastolic blood pressure ≥ 85 mmHg); and raised fasting glucose (≥110 mg/dL). Abdominal obesity was defined as a waist circumference of 85cm or more(Japanese criterion) or ≥90cm (Asian criterion). Statistical adjustment was made for age, hospital, and rank in the SDF. The metabolic syndrome was found to be associated with a moderately increased risk of colorectal adenomas whether either of the Japanese and Asian criteria was used; adjusted odds ratios with the Japanese and Asian criteria were 1.38 (95% confidence interval [CI] 1.13-1.69) and 1.48 (95% CI 1.13-1.93), respectively. Increased risk was more evident for proximal than distal colon or rectal adenomas, and was almost exclusively observed for large lesions (≥ 5mm in diameter). Thus the metabolic syndrome appears to be an important entity with regard to the prevention of colorectal cancer, as well as cardiovascular disease and type 2 diabetes.

Key Words: Abdominal obesity – metabolic syndrome – colorectal adenoma – Japanese men

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Introduction

The metabolic syndrome has recently drawn much attention in connection with the emerging global epidemic of obesity and type 2 diabetes mellitus (Haslam and James, 2005; King et al., 1998). The syndrome is a constellation of metabolic abnormalities including glucose intolerance, hypertriglyceridemia, and hypertension which increases the risk of cardiovascular disease as well as type 2 diabetes mellitus (Eckel et al., 2005). The pathophysiology of the metabolic syndrome is considered to be primarily attributable to insulin resistance associated with obesity and physical inactivity. In this context, abdominal rather than subcutaneous fat appears of particular concern because visceral fat leads to high influx of abundant free fatty acids and proinflammatory cytokines into the liver, thereby accentuating insulin resistance and a local and systematic proinflammatory state (Eckel et al., 2005; Haslam and James, 2005). Thus abdominal obesity is currently considered as a core component of metabolic syndrome, with two or more comorbid conditions of abnormalities of serum triglycerides, serum HDL cholesterol, fasting blood glucose, and blood pressure as criteria for diagnosis (Alberti et al., 2005).

Obesity and physical inactivity are also consistently related to an increased risk of colon cancer (IARC, 2002), with hyperinsulinemia associated with insulin resistance as one of the postulated underlying mechanisms (McKeown-Eyssen, 1994; Giovannucci, 1995; Moore et al., 1998a).

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Insulin has been shown to promote colorectal carcinogenesis (Corpet et al., 1997; Tran et al., 1996) and several studies have shown an increased risk of colon or colorectal cancer with diabetes (Weiderpass et al., 1997; Wideroff et al., 1997; Hu et al., 1999). Diabetes mellitus has also been shown to be associated with an increased risk of colon adenoma development (Kono et al., 1998; Nishii et al., 2001; Marugame et al., 2002). It is thus naturally of interest whether the metabolic syndrome is related to colorectal carcinogenesis. In this paper, we therefore examined links between the metabolic syndrome and colorectal adenoma, a well-established precursor lesion for colorectal cancer (O'Brien et al., 1990), in a population of middle-aged Japanese men.

Materials and Methods

Subjects

Study subjects were male officials in the Self-Defense Forces (SDF) who received a preretirement health examination at the SDF Fukuoka Hospital from January 1995 to March 2002 or at the SDF Kumamoto Hospital from May 1996 to March 2002. The preretirement health examination is a nationwide program offering a comprehensive medical examination to those retiring from the SDF, details of which have been described elsewhere (Kono et al., 1999; Toyomura et al., 2004). Colonoscopy was a routine procedure among others during a 5-day admission. The study was approved by the ethical committee of Kyushu University.

The present investigation included 756 cases of histologically confirmed colorectal adenomas and 1751 controls with no polyps among 3552 men who underwent total colonoscopy successfully. In a consecutive series of 4219 men during the above-mentioned period, 8 refused to participate in the survey, and 659 did not undergo successful total colonoscopy (no colonoscopy, 126; poor results, 11; and partial colonoscopy, 522). Of the 3552 undergoing total colonoscopy, 324 were excluded because of a history of colectomy (n = 20), colorectal polypectomy (n = 283), malignant neoplasms (n = 36), or inflammatory bowel disease (n = 3). In the remaining 3228 men, colonoscopic findings were classified as colorectal cancer (n = 2), polyp (n = 1471), non-polyp benign lesions such as diverticula (n = 207), and normal (n = 1548). Of the 1755 controls with normal or non-polyp benign lesions, 1751 were used as controls after exclusion of 4 men for whom the waist was not measured. Of the 1471 men with colorectal polyps, 756 were found to have adenomas without in situ or invasive carcinoma, and they were used as cases for the present study.

Numbers of cases having adenomas of the proximal colon alone, distal colon alone, and rectum alone were 258, 294, and 79, respectively. Proximal colon included cecum, ascending colon and transverse colon. A total of 125 cases had adenomas at multiple sites. Cases with adenomas sized of <5, 5–9, and ≥10 mm (the largest size for multiple adenomas) numbered 460, 243, and 49, respectively. Size of adenoma was not recorded with 4 cases. In the present study, adenomas of 5 mm or greater diameter was classified as large, while lesions measuring less than 5 mm in diameter were defined as small adenomas.

Clinical and Laboratory Data

Venous blood was drawn after an overnight fast for the determination of serum lipids and other biochemical measurements. Serum triglycerides and HDL-cholesterol were assayed enzymatically at each hospital laboratory using reagents from different sources. Plasma glucose levels were assayed by the glucose oxidase method using a commercial kit (Shino Test, Co. Ltd., Tokyo) at each hospital laboratory. A single blood pressure reading on the first day of admission was used for the present study. Waist and hip circumferences were measured in the horizontal plane at the level of the umbilicus and at the largest circumference around the buttocks, respectively. Medical history and current medication were ascertained by ward nurses and physicians.

Definition of the Metabolic Syndrome

In accordance with the diagnostic criteria proposed by the Japanese Committee of the Metabolic Syndrome Diagnostic Criteria (2005) and the International Diabetes Federation (Alberti et al., 2005), the metabolic syndrome was defined as the combination of abdominal obesity with any two of the following conditions: elevated triglycerides (≥150 mg/dL); lowered HDL cholesterol (<40 mg/dL); elevated blood pressure (systolic blood pressure ≥130 mmHg and/or diastolic blood pressure ≥85 mmHg); and raised fasting glucose (≥110 mg/dL). Medication for hypertension and treatment for diabetes mellitus were taken as evidence of raised blood pressure and fasting glucose, respectively. Of the cases and controls combined, 300 (12.0%) were under antihypertensive medication, 109 (4.3%) were under dietary or drug treatment for diabetes mellitus. It has been recommended by the International Diabetes Federation (Alberti et al., 2005) that cutoff points for abdominal obesity take account of the ethnicity and sex, and a waist circumference of ≥ 85cm has been adopted as the definition for abdominal obesity for Japanese men (≥ 90cm for Japanese women). However, cutoffs of 90 cm for men and 80 cm for women have already been specified for Chinese and South Asians (Alberti et al., 2005). The clinical significance of the different cutoffs remains uncertain at the present, and therefore we applied both 85 cm and 90 cm (for men), as the Japanese and Asian definitions, respectively, for the present analysis.

Statistical Analysis

Odds ratios (ORs) and 95% confidence intervals (CIs) were obtained by logistic regression analysis; the 95% CI was derived from the standard error for the logistic regression coefficient. Statistical adjustment was made for age (continuous variable), hospital, and rank in the SDF. Two-sided P values less than 0.05 were regarded as statistically significant. All computations were performed using SAS version 8.2 (SAS Institute Inc., Cary, NC).

Table 1. Relation of Each Component of the Metabolic Syndrome to Colorectal Adenomas

Variable/category	Number (%)		OR (95% CI) [a]
	Cases	Controls	
Waist circumference (cm)			
<85	377 (50)	1034 (59)	1.00 (referent)
85-89	199 (26)	417 (24)	1.31 (1.06-1.61)
≥90	180 (24)	300 (17)	1.66 (1.33-2.06)
Triglycerides (mg/dL)			
<150	491 (65)	1201 (69)	1.00 (referent)
≥150	265 (35)	550 (31)	1.18 (0.98-1.41)
HDL (mg/dL)			
≥40	702 (93)	1605 (92)	1.00 (referent)
<40	54 (7)	146 (8)	0.85 (0.61-1.18)
Elevated blood pressure [b]			
(–)	287 (38)	729 (42)	1.00 (referent)
(+)	469 (62)	1022 (58)	1.16 (0.98-1.39)
Raised fasting glucose [c]			
(–)	613 (81)	1435 (82)	1.00 (referent)
(+)	143 (19)	316 (18)	1.06 (0.85-1.32)

OR, odds ratio; CI, confidence interval.
[a] Adjusted for age, hospital, and rank in the Self Defense Forces.
[b] Either systolic blood pressure ≥130 mmHg and/or diastolic blood pressure ≥85 mmHg or medication for hypertension.
[c] Either fasting plasma glucose ≥110 mg/dL or treatment for diabetes mellitus.

Results

Ages ranged 49-57 years for the cases and 44-59 years for the controls, with 99% in the range of 50-55 years in both groups. Abdominal obesity defined by the Japanese criterion (≥85cm in waist circumference) was observed with 50% of of the cases and 41% of the controls. Abdominal obesity based on the Asian criterion (≥90 cm) was much less frequent, but was also more prevalent in the cases (Table 1). Prevalent odds of colorectal adenoma progressively increased with higher values for waist circumference. Adjusted ORs for colorectal adenoma with abdominal obesity as classified by the Japanese (≥85 cm versus <85 cm) and Asian (≥90 versus < 90 cm) criteria were 1.45 (95% CI 1.22-1.73) and 1.52 (95% CI 1.23-1.87), respectively. Hypertriglyceridemia, lowered HDL cholesterol, raised blood pressure, and raised fasting glucose were evident in 31%, 8%, 58%, and 18%, respectively, for the control group. None of these four components of the metabolic syndrome was measurably associated with colorectal adenoma.

Table 2. Risk of Colorectal Adenomas in Relation to the Metabolic Syndrome

Metabolic syndrome	Number (%)		OR (95% CI) [a]
	Cases	Controls	
Japanese criteria			
(–)	563 (74)	1403 (80)	1.00 (referent)
(+)	193 (26)	348 (20)	1.38 (1.13-1.69)
Asian criteria			
(–)	657 (87)	1588 (91)	1.00 (referent)
(+)	99 (13)	163 (9)	1.48 (1.13-1.93)

OR, odds ratio; CI, confidence interval.
[a] Adjusted for age, hospital, and rank in the Self Defense Forces.

The prevalence rates for the metabolic syndrome as defined by the Japanese criteria were 26% in the cases and 20% in the controls. The corresponding values on the basis of the Asian criteria were 13% and 9% (Table 2). The adjusted OR for colorectal adenomas was moderately but statistically significantly increased in individuals with the metabolic syndrome, independent of the criteria applied. When the analysis was conducted by tissue site (Table 3), the ORs associated with metabolic syndrome were consistently increased for proximal colon adenomas. A less evident increase in the OR of distal colon adenoma associated with metabolic syndrome was statistically significant only when the Japanese definition was used, while a statistically non-significant increase in the OR of rectal adenoma was more pronounced with the Asian definition.

A positive association with metabolic syndrome was observed almost exclusively for large adenomas (Table 4). Of the cases with proximal colon adenoma alone (n = 258), 85 cases were classified as having large adenomas, and adenomas of the remaining 173 cases were classified as small. Cases of large proximal colon adenoma with the metabolic syndrome defined by the Japanese and Asian criteria numbered 27 and 12, respectively, resulting in an OR of 1.90 (95% CI 1.18-3.04) for the Japanese definition and an OR of 1.70 (95% CI 0.90-3.20) for the Asian definition. The ORs for small proximal adenomas were 1.42 (95% CI 0.99-2.03) and 1.61 (95% CI 1.02-2.55), respectively.

Discussion

The present study revealed a statistically significant

Table 3. Risk of Adenomas of the Proximal Colon, Distal Colon and Rectum in Relation to the Metabolic Syndrome

Metabolic syndrome	Proximal colon		Distal colon		Rectum	
	No [a]	OR (95% CI) [b]	No [a]	OR (95% CI) [b]	No [a]	OR (95% CI) [b]
Japanese criteria						
(–)	186	1.00 (referent)	218	1.00 (referent)	60	1.00 (referent)
(+)	72	1.56 (1.16-2.10)	76	1.41 (1.06-1.88)	19	1.27 (0.75-2.16)
Asian criteria						
(–)	221	1.00 (referent)	259	1.00 (referent)	67	1.00 (referent)
(+)	37	1.64 (1.11-2.40)	35	1.33 (0.90-1.96)	12	1.75 (0.92-3.31)

OR, odds ratio; CI, confidence interval. [a] Number of adenoma cases. [b] Adjusted for age, hospital, and rank in the Self Defense Forces.

Table 4. Risks of Colorectal Adenoma in Relation to the Metabolic Syndrome by Size of Adenoma

Metabolic syndrome	Small adenomas		Large adenomas	
	No[a]	OR (95% CI)[b]	No[a]	OR (95% CI)[b]
Japanese criteria				
(–)	352	1.00 (referent)	209	1.00 (referent)
(+)	108	1.24 (0.97-1.59)	83	1.60 (1.21-2.12)
Asian criteria				
(–)	407	1.00 (referent)	247	1.00 (referent)
(+)	53	1.26 (0.90-1.75)	45	1.83 (1.28-2.62)

OR, odds ratio; CI, confidence interval.
[a] Number of adenoma cases.
[b] Adjusted for age, hospital, and rank in the Self Defense Forces.

increase in the risk of colorectal adenoma associated with the metabolic syndrome, most prevalent for the proximal colon rather than the distal colon or rectum, and particularly for large adenomas. We were unable to rule out a small increase in the risk of distal colon or rectal adenoma associated with metabolic syndrome, however. It should be noted that the findings were consistent with both the Japanese and Asian criteria for abdominal obesity.

Previously, to our knowledge, only one study has examined the relation between a cluster of metabolic abnormalities and colorectal cancer (Trevisan et al., 2001). The focus was on abnormal values for triglycerides, HDL cholesterol, and fasting glucose (each defined by the highest or lowest quartile) and hypertension (systolic pressure ≥140 mmHg and/or ≥90 mmHg). Abdominal obesity was not taken into account, but the cluster of metabolic abnormalities was associated with a statistically significant 3-fold increase in mortality from colorectal cancer (Trevisan et al., 2001).

The present findings are in agreement with the previous observations regarding diabetes mellitus and colon adenomas in the SDF Health Study. In earlier analyses (Nishii et al., 2001; Marugame et al., 2002), based on some of the subjects included in the present analysis, diabetes mellitus was associated with increased risks of both proximal and distal colon adenomas, but was more strongly associated with proximal colon adenoma and with large adenomas (≥5 mm in diameter). The finding that the metabolic syndrome might also be more strongly associated with large adenomas indicates that hyperinsulinemic status may be responsible for growth of adenomas. Insulin may exert a proliferative effect on colonic tumor cells directly (Corpet et al., 1997; Tran et al., 1996) or via the insulin-like growth factor pathway indirectly (Yu and Rohan, 2000). Furthermore, increased production of proinflammatory cytokines and decreased production of an anti-inflammatory adiponectin in adipocytes may be relevant to the growth of adenomas (Eckel et al., 2005). Recently, high plasma levels of adiponectin were shown to be inversely related to the risk of colon cancer (Wu et al., 2005). However, it is not clear why the metabolic syndrome or diabetes mellitus should be most strongly associated with proximal colon adenoma. Subsite differences in the association with diabetes mellitus has also been observed as regards colorectal cancer. At least three studies have examined the relation of diabetes mellitus to subsite-specific colorectal cancer risk. One of these studies showed an increased risk associated with diabetes mellitus for proximal colon cancer exclusively (Limburg et al., 2005), and the other two found a more evident increase in the risk of proximal colon cancer (Weiderpass et al., 1997; Hu et al., 1999). However, central obesity has been reported to increase the risk in both proximal and distal sites (Moore et al., 2004) and dietary zinc, protective against diabetes, has been linked with reduction in both sites (Lee et al., 2004).

The present study features methodological advantages in that total colonoscopy was performed almost non-selectively in a defined population and that the absence of polyp lesions could thereby be confirmed in the controls. However, the study subjects were not representative of Japanese men in the general population. Thus the present findings may not be generalized. Another important aspect is that a fairly large number of the subjects (n = 283) had previously undergone colorectal polypectomy, and consequently cases with small adenoma accounted for a large proportion of the total adenoma cases. If the metabolic syndrome is most relevant to the growth of adenomas, the observed association may have been underestimated.

In the present study, physical activity and other factors associated with colorectal adenoma and cancer were not taken into consideration. Physical inactivity is one of the most important lifestyle factors related to the metabolic syndrome, as well as to colon cancer development (Moore et al., 1998b). In addition, moderate alcohol use is related to increased insulin-sensitivity (Facchini et al., 1994; Davies et al., 2002) while smoking exerts an opposite effect (Facchini et al., 1992). Both alcohol use and cigarette smoking are associated with increased risk of colorectal adenoma (Giovannucci et al., 1993; Giovannucci and Martinez 1996; Toyomura et al., 2000). Adjustment for these factors (except alcohol) probably causes overadjustment which necessarily tends to mask any association between the metabolic syndrome and colorectal adenoma. In fact, analysis allowing for physical activity, alcohol use, and cigarette smoking only attenuated the association to a limited extent with our subjects; ORs for adenomas at the colorectum, proximal colon, distal colon, and rectum with the Japanese definition were thus 1.31 (95% CI 1.07-1.61), 1.47 (95% CI 1.09-1.99), 1.34 (95% CI 1.00-1.79), and 1.16 (0.68-1.99), respectively. It could be argued that controlling for such factors is not appropriate when the aim is to address the role of the metabolic syndrome per se in the occurrence of colorectal adenomad.

In summary, the present reasonably large cross-sectional study in a population of middle-aged Japanese men showed an increased risk of colorectal adenomas, particularly of proximal colon adenomas and of large adenomas, associated with the metabolic syndrome. Thus the metabolic syndrome can be considered an important entity with regard to prevention of colorectal cancer as well as circulatory disease and type 2 diabetes.

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Helper T cell cytokine response to ribavirin priming before combined treatment with interferon alpha and ribavirin for patients with chronic hepatitis C

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Abstract

The viral genotype and serum viral level influence the response to interferon (IFN) treatment in patients with chronic hepatitis C virus (HCV) viremia. The aim of this study was to investigate a possible relationship between early virological response and helper T (Th) cell cytokine expansion by 4 weeks of ribavirin (RIB) alone followed by IFN and RIB combined in patients with genotype 1b and a high HCV RNA level, patients reported not to respond well to IFN treatment. Eighty-one patients with genotype 1b and a high HCV RNA level, over 100 international unit per milliliter (KIU/mL) (by Amplicor HCV Monitor), were assigned to two groups: Group A ($N=40$) with a 4-week RIB administration followed by a 24-week combination treatment, and Group B ($N=41$) with a 24-week combination treatment only. Blood was obtained from each patient on the following schedule: at Baseline (4 weeks before day 0), on day 0 (initiation day of the RIB and IFN combination treatment), weeks 4 (4 weeks after the start of the combination treatment), and at the end of the combination treatment. Flow cytometry was used to investigate sequential changes of IFN-γ producing (Th1) and interleukin-4 producing (Th2) cells from whole blood samples after stimulation with PMA and ionomycin. Serum HCV RNA clearances were 32.5% at week 4, 43.2% at week 8, 85.7% at the end of the combination treatment, and 22.9% within the 24-week follow-up in Group A; and 17.1%, 27.0%, 66.7% and 19.4% in Group B, respectively. The mean Th1/Th2 ratio significantly increased from 15.9 at baseline to 17.6 at day 0 with a decrease of Th2 cells, and then significantly decreased from 17.6 at day 0 to 15.5 at week 4 in Group A, while there was no significant change in Group B between baseline and day 0. In Group A, 13 patients with HCV RNA clearance within 4 weeks had a significantly increased Th1/Th2 ratio, from 14.0 at baseline to 22.1 at day 0, and then a significantly decreased ratio, from 22.1 at day 0 to 15.0 at week 4, while the others had no significant change in the ratio. RIB administration preceding combined treatment of RIB with IFN was more effective in Th2 cell expansion than the usual combined treatment of IFN with RIB and led to a relatively early virological clearance in chronic hepatitis C patients with genotype 1b and a high HCV RNA level.

Keywords: Interferon-α (IFN-α); Ribavirin (RIB); Hepatitis C virus (HCV); Interferon-γ (IFN-γ); Interleukin-4 (Il-4)

1. Introduction

Chronic hepatitis C virus (HCV) infection is alarmingly prevalent, 2–15%, throughout the world. Of Japanese patients with HCV, 30% have a consistently abnormal alanine aminotransferase (ALT) level and develop hepatocellular carcinoma (HCC) (Hayashi et al., 1997, 2000), with the incidence of HCC rising in recent years (Taylor-Robinson et al., 1997; El-Serag and Mason, 1999). Sustained virological response (SVR) rate is 20–30% in chronic hepatitis C patients following interferon (IFN) monotherapy, but only 5% in patients with both HCV genotype 1b and a high HCV RNA level (Di Bisceglie et al., 1989; Furusyo et al., 1997, 2002; Hayashi

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