

C-peptide and colorectal cancer in a nested case-control study of US women enrolled at a New York City mammography screening center. One possible explanation is that small or large variations of C-peptide concentrations may determine whether a statistically significant association is found between plasma C-peptide and the risk of colorectal cancer. A population showing a statistically significant association covered a wider range, 1.48–6.01 ng/ml (serum, unknown percentage of fasting subjects),¹⁰ than others showing a nonstatistically significant association, 0.9–3.6 ng/ml for the US Nurses' cohort (plasma, 60–70% of subjects were fasting),¹² and 1.1–4.8 ng/ml for ours (plasma, 57% of subjects were fasting). The difference between serum and plasma samples is not a focus of argument, because plasma measurements highly correlate with serum ones, and there is no substantial difference between absolute values of plasma and serum measurements.²⁶ Another possible reason may be the different characteristics of study populations as to whether obesity is detectable as a risk factor of colorectal cancer. The Nurses' Health Study²⁷ and our cohort²⁸ reported that a high body mass index was either weakly or not at all associated with the risk of colorectal cancer. In contrast, New York City women showed a strong association between body mass index and colorectal cancer.¹⁰ Moreover, we might interpret the factor of sex difference in the association between plasma C-peptide and colorectal cancer as follows: Considering findings that postmenopausal women may be protected from colorectal cancer by hormone replacement therapy,²⁹ and that the body mass of postmenopausal women correlates with blood estrogen levels,³⁰ women's adiposity might influence the risk of colorectal cancer differently when compared with men's adiposity in terms of increasing the risk.²⁸ As another explanation, we expected to observe a statistical interaction between smoking or alcohol consumption and plasma C-peptide. In our cohort, male colorectal cancers were largely attributable to smoking and alcohol consumption, compared to female colorectal cancers.³¹ However, an additional analysis did not show such statistical interaction among them: Ps for interaction were 0.61 in men and 0.65 in women between smoking and C-peptide; and 0.52 in men and 0.64 in women between alcohol consumption and C-peptide.

IGFBP-1 was not associated with the risk of colorectal cancer. An elevated insulin level suppresses the production of this peptide,³ which also inhibits the IGF-I effect.⁶ Therefore, we hypothesized that IGFBP-1 is a protective marker against colorectal cancer. Some other studies showed an inverse association,^{10,12} while another study did not.⁹ Since the evidence on this peptide has not yet been completely accumulated, further studies will be needed to confirm such an association.

IGF-I is consistently associated with the risk of colorectal cancer, especially in all but one¹⁵ previous studies.^{10,12–14,16} Our results were at odds with those reports. This discrepancy may be due to the difference in target populations. One previous study in Chinese men by Probst-Hensch *et al.*¹⁵ showed no association of IGF-I such as ours, both of which studies targeted Asian populations. Other studies showing a positive association were derived from Western populations. Still another explanation may be whether body height can be determined as a risk factor of colorectal cancer in a study population. From the viewpoint of the growth hormone-IGF-I axis, a tall body height resulting from a high secretion level of growth hormone has been associated with IGF-I exposure³² and the risk of colorectal cancer. Two studies from Western populations showed a positive association with the body height,^{33,34} while our previous study did not, possibly because of a

low percentage of taller adults.²⁸ The growth hormone gene has a genetic polymorphism associated with a reduced secretion of growth hormone and IGF-I,³² and a reduced risk of colorectal neoplasms.³⁵ However, the Japanese population did not seem to be associated with such a reduced risk in spite of a reduced secretion of IGF-I.³⁵ IGF-I levels in our study covered a range similar to that of other Western^{10,12–14,16} and Asian populations.¹⁵ The association between the IGF-I level and the risk of colorectal cancer may differ among target populations, a difference that may be explained by the gene expression of IGF-I receptor making IGF-I effective. An animal study showed that colonocytic IGF-I receptor expression increased with an increased dietary lipid intake.³⁶ A difference in dietary habits may lead to disparate levels of IGF-I receptor expression, resulting in different effects arising from the same blood IGF-I level.

IGFBP-3 is supposed to bind IGF-I and inhibit the IGF-I mediated-effect.³ In addition, anti-proliferative pathways involved in IGFBP-3 have been proposed.⁶ Although any actions of IGFBP-3 can be expected to reduce the risk of colorectal cancer, epidemiologic findings are not always consistent.¹⁷ Although US health professional cohorts have consistently found an inverse association between IGFBP-3 and colorectal cancer,^{12–14} other studies, including ours, reported that IGFBP-3 is not inversely associated with that risk.^{10,15,16} As Palmqvist *et al.*¹⁶ pointed out that it may be due to the fact that assay methods adopted differed between studies showing or not showing the inverse association. The US health professional studies used enzyme-linked immunosorbent assay (ELISA),^{12–14} while other studies used immunoradiometric assay^{10,15,16}; however, Palmqvist *et al.*¹⁶ also reported that repeatedly assaying those same samples using ELISA did not substantially change the results, *i.e.*, no inverse association of IGFBP-3.

We collected blood samples before cancer diagnosis, supporting the idea that plasma peptides indicated a cancer-free status and may predict a subsequent risk of colorectal cancer incidence. Plasma peptides were measured only once. Since plasma C-peptide is especially affected by time elapsed since the last meal, we matched that time interval between cases and controls to minimize the attenuation of risk estimates derived from measurement errors. Half-life of C-peptide in blood is very brief,³⁷ while IGF-I and IGFBP blood levels are relatively stable.^{38,39} We cannot entirely rule out a random misclassification of blood measurements as part of the reason for finding no association with the risk of colorectal cancer. Additionally, more outcomes may have been needed to exclude the risk of nonassociation by random variation or chance, especially when data stratified by sex or tumor site were analyzed.

In conclusion, a higher plasma C-peptide may indicate a subsequent risk of colorectal cancer in men. Our results did not support the existing hypotheses that IGF-I may increase and IGFBPs may decrease the risk of colorectal cancer.

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