Association of a Common Polymorphism in the Human GH1 Gene with Colorectal Neoplasia

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Background: Growth hormone (GH) may be associated with the development of colorectal tumors directly and/or indirectly via an increased plasma level of insulin-like growth factor-I (IGF-I), which has been associated with colorectal cancer risk. Because a T-to-A polymorphism in the human GH1 gene at position 1663 is putatively associated with lower levels of GH and IGF-I, we investigated the relationship of this polymorphism to the risk of colorectal neoplasia.

Methods: We analyzed data from two case–control studies conducted in Hawaii: a population-based study of 535 case patients with colorectal adenocarcinoma and 650 control subjects and a sigmoidoscopy screening-based study with 139 case patients with adenoma and 202 control subjects. All subjects were tested for the GH1 polymorphism. Logistic regression was used to adjust for known risk factors. Plasma IGF-I and IGF binding protein-3 (IGFBP-3) levels were measured in a subset of 293 subjects in the adenoma study (135 case patients and 158 control subjects). All statistical tests were two-sided. Results: Adjusted odds ratios (ORs) for colorectal cancer associated with T/T, T/A, and A/A genotypes were 1.00, 0.75 (95% confidence interval [CI] = 0.58 to 0.99), and 0.62 (95% CI = 0.43 to 0.90), respectively ($P_{\text{trend}} = .006$). Adjusted ORs for adenoma were 1.00, 0.76 (95% CI = 0.46 to 1.24), and 0.62 (95% CI = 0.31 to 1.22), respectively ($P_{\text{trend}} = .17$). Data from both studies consistently showed that the A allele was associated with a lower risk of colorectal neoplasia than the T allele, although the association with adenoma was not statistically significant. These associations were consistently suggested in Caucasians and Native Hawaiians but not in Japanese. The ratio of plasma IGF-I/IGFBP-3 was lower in individuals with the A allele than in individuals with the T allele ($P = .01$). Conclusion: The human T1663A GH1 gene polymorphism, which may confer lower levels of GH and IGF-I, appears to be associated with a decreased risk of colorectal cancer. [J Natl Cancer Inst 2002;94:454–60]
The subjects for the first study have been described in detail elsewhere (13). Patients with colorectal cancer were identified through the rapid reporting system of the Hawaii Surveillance, Epidemiology, and End Results (SEER)1 Program registry and consisted of all Japanese, Caucasian, and Native Hawaiian residents of Oahu who were newly diagnosed with an adenocarcinoma of the colon or rectum between January 1994 and August 1998. Control subjects were selected from participants in an ongoing population-based health survey conducted by the Hawaii State Department of Health and from Health Care Financing Administration participants. One control subject was matched to each case patient by sex, ethnicity, and age (±2 years). Personal interviews were obtained from 768 matched pairs, resulting in a participation rate of 58.2% for case patients (from a total of 1320 eligible case patients identified, including 770 Japanese, 343 Caucasians, and 207 Native Hawaiians) and 53.2% for control subjects (from a total of 1444 control subjects identified as eligible). If a control subject declined to participate, he or she was replaced. The reasons for nonparticipation were as follows: in case patients, refusal (22.5%), death before contact (10.9%), severe disease (6.7%), and inability to locate (1.7%); in control subjects, refusal (34.8%), inability to locate (9.2%), and major illness or death (2.8%). Compared with noninterviewed case patients, interviewed case patients had a similar ethnic distribution, were less likely to have a regional or distant metastasis (46% versus 55%), and were younger by an average of 1.8 years. A blood sample was obtained from 548 (71%) of interviewed case patients and 656 (85%) of interviewed control subjects. Case patients and control subjects who donated blood were similar to all interviewed subjects with regard to age, sex, and ethnicity, as well as the variables found to be associated with the risk of colorectal cancer in this study (see below). Stock of extracted DNA was depleted for 13 case patients and six control subjects. Consequently, 535 case patients with adenocarcinoma and 650 control subjects were studied.

The subjects for the second study were identified among individuals who underwent flexible sigmoidoscopy screening as part of the baseline examination for the Hawaii component of the Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial between July 1996 and February 2000 or in the Colorectal Screening Clinic of Kaiser Permanente, Hawaii, between December 1995 and April 2000. For all case patients, the first diagnosis of an adenomatous polyp was confirmed histologically. Control subjects had a normal sigmoidoscopy and were matched to case patients in a 2:1 ratio by age, sex, ethnicity, endoscopy date, and screening center. The participation rate was 70.3% for case patients (196 case patients were interviewed of 279 identified as eligible) and 70.8% for control subjects (303 control subjects interviewed of 428 identified as eligible). The reasons for nonparticipation among case patients were refusal (24.4%), physician refusal (3.2%), and inability to locate (2.1%). The reasons for nonparticipation among control subjects were refusal (22.9%), physician refusal (4.0%), and inability to locate (2.3%). A blood sample was obtained from 94.3% of interviewed case patients and 91.0% of interviewed control subjects. The present analysis was performed on the first 139 case patients and 202 control subjects genotyped for human GH1.

Interviews

For both studies, in-person interviews were conducted at the subject’s home by trained interviewers, using the same questionnaire. This questionnaire included detailed information on demographics; a quantitative food-frequency questionnaire; a lifetime history of the use of tobacco, alcohol, and nonsteroidal anti-inflammatory drugs; a history of recreational sports activities since age 18 years; a personal history of various relevant medical conditions; a family history of colorectal cancer in parents and siblings; information on height and weight at different ages; and for women, a history of reproductive events and hormone use. The diet questionnaire assessed the frequencies and amounts consumed during the year before the onset of symptoms for case patients with colorectal cancer or the year before interview for case patients with adenoma and all control subjects for 268 food items or categories. Participants also reported their intakes and dosages of vitamin and mineral supplements during the reference period.

Laboratory Assays

In the adenoma study, all subjects were asked to fast for 10 hours before blood was drawn. In both studies, the samples were processed within 4 hours of collection and kept frozen at –80 °C until analysis. All laboratory assays were performed blinded to the case–control status and ethnicity of the subjects. DNA was extracted from buffy coat cells. The polymerase chain reaction assay used to detect the T-to-A variant at position 1663 (T1663A) in intron 4 of the GH1 gene was a two-step method because of the close homologies that exist between GH1 and the other related genes in the GH cluster. The first amplification involved denaturation at 94 °C for 5 minutes, followed by 25 cycles of 94 °C for 30 seconds, 64 °C for 30 seconds, and 72 °C for 30 seconds.
for 1 minute 30 seconds, and a final extension at 72°C for 10 minutes, using the primers F4 (5'-GGCTGACCCAGGAGTCC-3') and R1 (5'-AGAAGAACCTAGTCAGACA-3') to produce a 2176-base-pair (bp) product. One microliter of this product was further amplified with the mutagenic forward primer GH1MF2 (5'-GAGAAACACTGCTGCCCTTTTAGAGCG-3', modified nucleotides are underlined) and GH1R2 (5'-AAGAGAGGGAGGCAA GC-3') to produce a 180-bp product. The T allele was digested with AarII to fragments of 149 bp and 31 bp, whereas the A allele was not digested with AarII (Fig. 1). The authenticity of this assay was confirmed by DNA sequencing.

For the first 293 subjects (135 case patients and 158 control subjects) interviewed for the adenoma study, plasma levels of IGF-I and IGFBP-3 were measured by enzyme-linked immunosorbent assays and levels of plasma IGFBP-1 were measured by a double-antibody, immunoradiometric assay with commercial kits (Diagnostic Systems Laboratories, Webster, TX). The IGF-I assay included an initial acid–ethanol extraction step to separate IGF-I from its binding proteins. Twenty-two samples were analyzed in duplicate to estimate intrabatch laboratory variation in hormone measurement, yielding intraclass correlation coefficients of 0.86 (95% confidence interval [CI] = 0.71 to 0.94), 0.74 (95% CI = 0.47 to 0.88), and 0.99 (95% CI = 0.98 to 1.00) for IGF-I, IGFBP-3, and IGFBP-1, respectively. The intraclass correlation was computed as the between-subject variation divided by total variation, where the variance components were computed by a random effects regression model.

**Data Analysis**

The statistical analysis used unconditional logistic regression (14) to adjust odds ratios (ORs) for the matching variables (age, sex, and ethnicity), as well as for the variables found to be associated with risk (see Table 2), entered as continuous variables. Nutrient intakes were adjusted for total calories by the subject's number of variant A alleles (zero, one, and two variant alleles, respectively). The χ² test was used to compare the observed genotype distributions with those expected by the Hardy-Weinberg equilibrium. Multiple covariance analysis was used to compute adjusted means for plasma hormones. All statistical tests are two-sided.

**RESULTS**

Table 1 shows relevant characteristics of the subjects by case-control status. Case patients with colorectal cancer were less educated, less likely to have used aspirin regularly, had smoked more cigarettes, exercised less during their adult life, were heavier, and consumed more calories, less calcium, less non-starch polysaccharides from vegetables, and less folate than control subjects. Case patients with adenoma had smoked more, used nonsteroidal anti-inflammatory drugs for a shorter period (18 versus 26 months, on average) during their life, and consumed more calories and less calcium and folate from foods and supplements than did control subjects.

Based on the population control subjects of the adenocarcinoma study, the frequency of the A variant of the GH1 allele in our population was estimated to be 42.2% for Japanese, 42.1% for Caucasians, and 56.3% for Native Hawaiians. The overall and ethnic-specific distributions of the genotypes were consistent with the Hardy-Weinberg equilibrium. All individuals with T/T, T/A, and A/A genotypes had adjusted ORs for colorectal cancer of 1.00, 0.75 (95% CI = 0.58 to 0.99), and 0.62 (95% CI = 0.43 to 0.90) (P trend = .006) (Table 2). Similar risk estimates were found in stratified analyses for males and females and for colon and rectal cancer (data not shown). The adjusted ORs for adenoma for all individuals with T/T, T/A, and A/A genotypes were 1.00, 0.76 (95% CI = 0.46 to 1.24), and 0.62 (95% CI = 0.31 to 1.22) (P trend = .17) (Table 2). These ORs were consistent with those obtained from the adenocarcinoma study, because their point estimates were similar. It should be noted that, for adenoma, the size of our sample was small and our study had a statistical power of less than 50% to detect any of the observed ORs or slopes as statistically significantly different from the null value.

Ethnic-specific analyses suggested differences in the strength of the association of the GH1 A allele with adenocarcinoma among ethnic groups. The association was strong in Caucasians and Native Hawaiians but was not observed in Japanese (Table 2). Caucasians with T/T, T/A, and A/A genotypes had adjusted ORs for colorectal cancer of 1.00, 0.85 (95% CI = 0.50 to 1.43), and 0.44 (95% CI = 0.21 to 0.93) (P trend = .05). The corresponding ORs for Hawaiians were 1.00, 0.39 (95% CI = 0.16 to 0.94), and 0.20 (95% CI = 0.07 to 0.59) (P trend = .003). In contrast, those for Japanese were 1.00, 0.79 (95% CI = 0.56 to 1.12), and 0.85 (95% CI = 0.53 to 1.36) (P trend = .34). The results for adenoma were consistent with those ethnic patterns (Table 2).

The association of the A allele with a lower risk of colorectal cancer was found to be stronger for subjects aged 66 years or younger (median). In this group of individuals with T/T, A/T,
Adenoma detected. investigated in both studies. No suggestions of interaction were
limited by the small sample size of these subset analyses. Inter-
actions of the GH1 genotype with height, body mass index, total
and higher level of IGFBP-1 was associated with the A/A ge-
notype. This pattern was consistent across ethnic groups and was
particularly strong in Native Hawaiians. The mean IGF-I/
IGFBP-3 ratio for the T/T, T/A, and A/A genotypes (and the
IGF-I/IGFBP-3 ratio were lower for the A/A genotype than for
both, \( P_{\text{trend}} = .01 \). The mean level of plasma
IGF-I was higher for individuals with the A/A genotype than for
those with the T/T genotype (\( P = .03 \)). Although limited by
the small number of subjects examined, an ethnic-specific com-
parison found that the pattern of a lower ratio of IGF-I/IGFBP-3
and higher level of IGFBP-1 was associated with the A/A ge-
notype. This pattern was consistent across ethnic groups and was
particularly strong in Native Hawaiians. The mean IGF-I/
IGFBP-3 ratio for the T/T, T/A, and A/A genotypes (and the
P value for differences between T/T and A/A genotypes) were

and A/A genotypes, the adjusted ORs for colorectal cancer were
1.0, 0.74 (95% CI = 0.52 to 1.07), and 0.48 (95% CI = 0.29
to 0.81), respectively (\( P_{\text{trend}} = .005 \)). The corresponding ORs
for subjects older than 66 years were 1.00, 0.79 (95% CI = 0.52
to 1.20), and 0.79 (95% CI = 0.47 to 1.34) (\( P_{\text{trend}} = .32 \)).
However, the test for interaction was not statistically significant
(\( P = .54 \)). This modifying effect of age for colorectal cancer
was observed in Caucasians and Native Hawaiians but not in
Native Hawaiians. No clear modifying effect of age was observed for
adenoma, although the statistical power to detect differences was
limited by the small sample size of these subset analyses. Inter-
actions of the GH1 genotype with height, body mass index, total
calories, total fat, saturated fat, and polyunsaturated fat were also
investigated in both studies. No suggestions of interaction were
detected.

Plasma levels of IGF-I and IGFBP-3 were also explored
across GH1 genotypes among 293 subjects (135 case patients
and 158 control subjects) in the adenoma study (Table 3).
The adjusted means for the level of plasma IGF-I and the
IGF-I/IGFBP-3 ratio were lower for the A/A genotype than for
the T/T genotype (for both, \( P = .01 \)). The mean level of plasma
IGFBP-1 was higher for individuals with the A/A genotype than
for those with the T/T genotype (\( P = .03 \)). Although limited by
the small number of subjects examined, an ethnic-specific com-
parison found that the pattern of a lower ratio of IGF-I/IGFBP-3
and higher level of IGFBP-1 was associated with the A/A ge-
notype. This pattern was consistent across ethnic groups and was
particularly strong in Native Hawaiians. The mean IGF-I/
IGFBP-3 ratio for the T/T, T/A, and A/A genotypes (and the
P value for differences between T/T and A/A genotypes) were

Table 1. Characteristics of adenocarcinoma and adenoma case patients and control subjects*

| Characteristic | Adenocarcinoma | | Adenoma | |
|---------------|---------------|----------------|---------|
| | Case patients (\( n = 535 \)) | Control subjects (\( n = 650 \)) | Case patients (\( n = 139 \)) | Control subjects (\( n = 202 \)) |
| Males, % | 60.8 | 57.9 | 71.2 | 70.3 |
| Japanese, % | 58.5 | 60.3 | 45.3 | 44.1 |
| Caucasian, % | 27.3 | 26.3 | 32.4 | 36.1 |
| Native Hawaiian, % | 14.2 | 13.4 | 22.3 | 19.8 |
| Age, y | 66 | 67 | 64 | 65 |
| Education, y | 12 | 14 | 14 | 14 |
| Pack-years, No.† | 8 | 1 | 13 | 2 |
| BMI, kg/m²‡ | 25 | 24 | 26 | 25 |
| Lifetime recreational physical activity, h | 3072 | 4344 | 7552 | 6580 |
| Ever use of aspirin, %§ | 19.8 | 28.6 | 23.1 | 23.1 |
| Total calories, kcal/day | 2008 | 2166 | 2166 | 2006 |
| Total fat, g/day¶ | 2008 | 2166 | 2166 | 2006 |
| Saturated fat, g/day | 2008 | 2166 | 2166 | 2006 |
| Polyunsaturated fat, g/day | 2008 | 2166 | 2166 | 2006 |
| Total calcium, mg/day¶ | 808 | 955 | 931 | 1040 |
| Total folate, mg/day¶ | 366 | 442 | 463 | 520 |

*Data are the median, except for percentages as indicated.
†Pack-years = number of cigarettes smoked per day/20 x duration in years.
‡Body mass index (BMI) 5 years before diagnosis or interview for adenocarcinoma case patients and control subjects, respectively. Current BMI for adenoma case patients and control subjects.
§Ever use = twice a week for three consecutive months or more.
¶From foods and supplements (adjusted for total calories).

Table 2. Odds ratios for colorectal adenocarcinoma and adenoma by GH1 genotype*

<table>
<thead>
<tr>
<th>GH1 Genotype</th>
<th>All</th>
<th>Japanese</th>
<th>Caucasian</th>
<th>Native Hawaiian</th>
</tr>
</thead>
<tbody>
<tr>
<td>T/T</td>
<td>1.0 (referent)</td>
<td>109/123</td>
<td>59/59</td>
<td>27/14</td>
</tr>
<tr>
<td>T/A</td>
<td>0.79 (0.58 to 0.99)</td>
<td>152/207</td>
<td>70/80</td>
<td>39/48</td>
</tr>
<tr>
<td>A/A</td>
<td>0.62 (0.43 to 0.90)</td>
<td>52/62</td>
<td>17/32</td>
<td>10/25</td>
</tr>
<tr>
<td>P_{trend} = .006‡</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>GH1 Genotype</th>
<th>All</th>
<th>Japanese</th>
<th>Caucasian</th>
<th>Native Hawaiian</th>
</tr>
</thead>
<tbody>
<tr>
<td>T/T</td>
<td>1.0 (referent)</td>
<td>27/33</td>
<td>15/17</td>
<td>12/13</td>
</tr>
<tr>
<td>T/A</td>
<td>0.76 (0.46 to 1.24)</td>
<td>27/46</td>
<td>24/36</td>
<td>14/18</td>
</tr>
<tr>
<td>A/A</td>
<td>0.62 (0.31 to 1.22)</td>
<td>9/10</td>
<td>6/20</td>
<td>5/9</td>
</tr>
<tr>
<td>P_{trend} = .55</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*OR = odds ratio; n = No. of case patients/No. of control subjects; 95% CI = 95% confidence interval.
†ORs for adenocarcinoma were adjusted for age, sex, ethnicity (when appropriate), pack-years of cigarette smoking, lifetime recreational physical activity, lifetime aspirin use, body mass index 5 years ago, years of schooling, and intakes of nonstarch polysaccharides from vegetables and calcium from food and supplements. ORs for adenoma were adjusted for age, sex, ethnicity (when appropriate), pack-years of cigarette smoking, lifetime use of nonsteroidal anti-inflammatory drugs (in months), and intake of calories and folate from foods and supplements. The nutrients were adjusted for calories by the method of residuals.
‡P_{trend} = P for the genotype variable assigned the values 1, 2, or 3, according to the subject’s number of A alleles (0, 1, and 2, respectively). All statistical tests are two-sided.
as follows: for Japanese, 0.21, 0.21, and 0.19 \((P = .14)\); for Caucasians, 0.22, 0.22, and 0.21 \((P = .57)\); and for Hawaiians, 0.28, 0.21, and 0.21 \((P = .02)\). Similarly, an analysis stratified on age (less than or equal to the median age of 70 years or greater than the median age) suggested that the differences in IGF-I/IGFBP-3 ratios between the GH1 genotypes were not limited to younger subjects. No differences were found among GH1 genotypes for height, body mass index, or caloric intake (Table 3).

**DISCUSSION**

In a population-based case–control study of colorectal cancer, we found that a polymorphism in the human GH1 gene was inversely associated with risk of adenocarcinoma of the large bowel with a gene–dosage effect. This association was consistent between sexes and subsites (colon and rectum) and was observed in Caucasians \((P_{\text{trend}} = .05)\) and Native Hawaiians \((P_{\text{trend}} = .003)\) but not in Japanese \((P_{\text{trend}} = .34)\). A preliminary analysis of an ongoing case–control study of adenoma revealed very similar overall and ethnic-specific risk estimates, arguing against a chance finding. In the subset of subjects whose IGF values had been determined, the AA genotype was found to be associated with a lower ratio of plasma IGF-I/IGFBP-3 and higher level of IGFBP-1, which are consistent with a lower GH secretion.

GH1 is located in the human GH gene cluster on chromosome 17q and is expressed only in the anterior pituitary gland. GH secretion and mean diurnal levels of plasma GH peak around puberty and decline progressively with age. Although the T1663A substitution studied herein is located in a nontranscribed region, it has been shown by Hasegawa et al. \((12)\) to be in close linkage disequilibrium with two GH1 promoter variants (G218T and G439T). The 1663A allele might also be in linkage disequilibrium with two GH1 promoter variants described region, it has been shown by Hasegawa et al. \((12)\) to be in close linkage disequilibrium with two GH1 promoter variants (G218T and G439T). The 1663A allele might also be in linkage disequilibrium with a mutation in one of the intronic splice enhancers identified in GH1 \((16)\). Thus, this polymorphism may be related to gene expression or protein dysfunction. Indeed, in the same Japanese study, the 1663A allele was associated with decreased levels of plasma GH and IGF-I and height among prepubertal short children with mild or no GH insufficiency

**Table 3. Mean plasma IGF-I, IGFBP-3, and IGFBP-1 levels, height, BMI, and total caloric intake by GH1 genotype among subjects in the adenoma study**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>GH1 genotype</th>
<th>Overall</th>
<th>(P^*)</th>
<th>(P^\dagger)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>TT (n = 101)</td>
<td>TA (n = 140)</td>
<td>AA (n = 52)</td>
<td></td>
</tr>
<tr>
<td>IGF-I, ng/mL</td>
<td>172.3</td>
<td>175.0</td>
<td>152.3</td>
<td>.05</td>
</tr>
<tr>
<td>IGFBP-3, ng/mL</td>
<td>2859</td>
<td>3070</td>
<td>2792</td>
<td>.05</td>
</tr>
<tr>
<td>IGFBP-1, ng/mL</td>
<td>36.5</td>
<td>37.4</td>
<td>44.7</td>
<td>.18</td>
</tr>
<tr>
<td>Height, cm</td>
<td>170.0</td>
<td>169.5</td>
<td>170.0</td>
<td>.78</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>26.6</td>
<td>26.0</td>
<td>25.3</td>
<td>.21</td>
</tr>
<tr>
<td>Calories, kcal/day</td>
<td>2302</td>
<td>2307</td>
<td>2186</td>
<td>.69</td>
</tr>
</tbody>
</table>

*First 293 cases and controls interviewed. Data are mean levels adjusted for age, sex, ethnicity, and case–control status by multiple covariance analysis. All statistical tests are two-sided. IGF-I = insulin-like growth factor-I; IGFBP-3 = IGF binding protein-3; IGFBP-1 = IGF binding protein-1; BMI = body mass index.

‡\(P\) for differences among the three genotypes.

\(P\) for pairwise differences between the AA and TT genotypes.

§Molar ratio.
observed in Native Hawaiians are of interest because this group, like other Polynesians, has unexpectedly low rates of colon cancer (31). It is unclear why the association with colorectal cancer was not observed in Japanese because the A allele seems to affect circulating levels of IGF-I in this ethnic group as well. However, animal studies have shown that nutritional factors influence synthesis and action of various growth hormones. For example, fasting decreases GH binding in the liver, and IGF-I receptor expression in colonocytes is reduced in rats receiving a low-fat diet (32,33). Thus, the lack of association between GH1 and colorectal cancer in Japanese may be due to their low-fat diet (34) or other luminal or circulating factors. Nevertheless, in our data, there was no suggestion of an interaction between GH1 and recent caloric and fat intakes. Alternatively, other downstream, unidentified genetic risk factors over-represented in Japanese could also explain the lack of association in this group.

Our data indicate that further examination of the associations of genetic polymorphisms, growth hormones, and the risk of colorectal cancer is warranted. If the relationships observed in this study are confirmed, they should justify the investigation of approaches to reduce the bioactivity of growth hormones in groups at high risk for colorectal cancer.

REFERENCES


NOTES

1Editor’s note: SEER is a set of geographically defined, population-based, central cancer registries in the United States, operated by local nonprofit organizations under contract to the National Cancer Institute (NCI). Registry data are
submitted electronically without personal identifiers to the NCI on a biannual basis, and the NCI makes the data available to the public for scientific research.

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