Research Article

Cancer Epidemiology, Biomarkers & Prevention

Prediagnostic Circulating Parathyroid Hormone Concentration and Colorectal Cancer in the European Prospective Investigation into Cancer and Nutrition Cohort

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Abstract

Background: Parathyroid hormone (PTH) has been proposed to play a promoting role in carcinogenesis. However, no epidemiologic studies have yet directly investigated its role in colorectal cancer (CRC).

Methods: A case-control study nested within the European Prospective Investigation into Cancer and Nutrition cohort was conducted with 1,214 incident, sporadic CRC cases matched to 1,214 controls. Circulating prediagnostic PTH and 25-hydroxy vitamin D [25(OH)D] concentrations were measured by enzyme-linked immunosorbent assays. Detailed dietary and lifestyle questionnaire data were collected at baseline. Multivariable conditional logistic regression was used to estimate the incidence rate ratio (RR) with 95% confidence intervals (95% CI) for the association between circulating PTH and CRC risk.

Results: In multivariate analyses [including adjustment for 25(OH)D concentration] with *a priori* defined cutoff points, high levels of serum PTH (≥65 ng/L) compared with medium PTH levels of 30–65 ng/L were associated with increased CRC risk (RR = 1.41, 95% CI: 1.03–1.93). In analyses by sex, the CRC risk was 1.77 (95% CI: 1.14–2.75) and 1.15 (95% CI: 0.73–1.84) in men and women, respectively ($P_{heterogeneity} = 0.01$). In subgroup analyses by anatomical subsite, the risk for colon cancer was RR = 1.56, 95% CI: 1.03–2.34, and for rectal cancer RR = 1.20, 95% CI: 0.72–2.01 ($P_{heterogeneity} = 0.21$). Effect modification by various risk factors was examined.

Conclusions: The results of this study suggest that high serum PTH levels may be associated with incident, sporadic CRC in Western European populations, and in particular among men.

Impact: To our knowledge, this is the first study on PTH and CRC. The role of PTH in carcinogenesis needs to be further investigated. *Cancer Epidemiol Biomarkers Prev; 20(5); 767–78. ©2011 AACR.*

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Introduction

It has been suggested that parathyroid hormone (PTH) may have carcinogenic and tumor promoting effects (1), and that higher concentrations may be associated with risk for colorectal cancer (CRC). The latter suggestion has been derived from observations reported in several case reports and one observational study that primary hyperparathyroidism, a medical condition that results in higher PTH concentration, is associated with colon cancer (2–5), and that both normal and malignant colonic cells express PTH receptors (6–9). It has been proposed that PTH may affect cancer risk directly via mitogenic and antiapoptotic effects (1, 10), or indirectly via a number of different mechanisms (1). For example, PTH may increase hepatic production of insulin growth factor-1 (IGF-1; refs. 11–14), a potential cancer promoter, which has been found to be modestly positively associated with CRC risk (15). PTH may also influence colon carcinogenesis by way of its intimate involvement in the homeostasis of serum calcium and phosphate, and close interrelation with the active form of circulating vitamin D, 1,25-dihydroxy vitamin D [1,25-$(OH)_2$-vitamin D]. In addition, elevated levels of PTH, through 1,25-$(OH)_2$-vitamin D activation, lead to enhanced intestinal calcium absorption and consequently to a potentially reduced concentration of calcium in the colon lumen (16). Calcium has been long known as a potential chemopreventive agent against colorectal neoplasms (17–19). Proposed anticarcinogenic mechanisms of calcium in the colon lumen include protection of colonocytes against cytotoxic effects of luminal cytotoxic surfactants (20, 21), regulation of cell cycle (22), and modulation of β-catenin and E-cadherin through the calcium-sensing receptor (CaSR) (22, 23). Therefore, a decreased dietary intake of calcium coupled with increased absorption of calcium from the intestine as a result of elevated PTH may promote colon carcinogenesis.

A role for PTH in carcinogenesis is also supported by some further indirect evidence. In men, a significant positive correlation has been observed between serum PTH and prostate specific antigen (PSA), a measure of prostate pathological changes and growth (24). Taken together, the experimental and human findings suggest a potential role of circulating PTH in carcinogenesis, yet to date no studies have directly investigated the association between blood levels of PTH with CRC risk. Therefore, we investigated the hypothesis that increased circulating levels of PTH are associated with incident, sporadic CRC risk in a case-control study nested within the European Prospective Investigation into Cancer and Nutrition (EPIC). We also investigated the potential effect modification of this association by various suspected modifying factors including circulating vitamin D, dietary calcium intake, obesity, and others.

Methods

Study population and collection of data

We used a case-control design nested within the EPIC cohort, a large prospective study with over 520,000 participants enrolled from 23 centers in 10 Western European countries (Denmark, France, Greece, Germany, Italy, the Netherlands, Norway, Spain, Sweden, and United Kingdom). The methods of EPIC have been detailed elsewhere (25). Between 1992 and 1998, standardized lifestyle and personal history information, validated dietary country-specific questionnaires, anthropometric data, and blood samples were collected from most participants at recruitment. Biological samples are stored at the International Agency for Research on Cancer in −196°C liquid nitrogen for all countries except Denmark (−150°C, nitrogen vapor) and Sweden (−80°C, freezers).

Follow-up for cancer incidence and vital status

Incident cancer cases were identified through record linkage with regional cancer registries in Denmark, Sweden, the Netherlands, the United Kingdom, Spain, and in most of the Italian centers. In Germany, France, Greece, and Naples (Italy), follow-up was based on a combination of methods, including health insurance records, cancer and pathology registries, and active follow-up through study subjects and their next-of-kin. For each EPIC study center, closure dates of the study period were defined as the latest dates of complete follow-up for both cancer incidence and vital status, and ranged from December 1999 to June 2003 for centers using registry data, and from June 2000 to December 2002 for centers using active follow-up procedures.

The study was approved by the IARC Ethics Committee as well as the Institutional Review Board of each participating EPIC center. Written consent was obtained from EPIC participants at enrolment into the study.

Case ascertainment and selection

Colorectal cancer cases were selected among participants (men and women) who developed colon (C18.0–C18.9, according to the 10th Revision of the International Statistical Classification of Diseases, Injury, and Causes of Death) and rectum (C19–C20) cancers. Cancers of the anus were excluded. CRC is defined as the combination of the colon and rectal cancers. Fifty-six cases were excluded due to missing information on fasting status, and 52 cases due to missing PTH and/or 25-(OH)-vitamin D measurements from either assay failure or insufficient serum volume in the sample. A total of 1,214 incident CRC cases (764 colon, 450 rectum) with measurements of blood PTH and 25-(OH)-vitamin D were included in the analyses (19). Cases from Norway were not included into this analysis because blood samples were only recently collected and very few CRC cases were diagnosed after blood donation. Also, cases were not selected from the Malmö center in Sweden (19).

Control selection

For each case, one control was selected by incidence density sampling from all cohort members alive and free of cancer (except nonmelanoma skin cancer) at the time of diagnosis of the cases, and matched by age at blood collection (±6 months at recruitment), sex, study center, time of the day at blood collection (±2–4 hours interval), fasting status at blood collection (<3 hours; 3–6 hours; and >6 hours); among women, additionally by menopausal status (premenopausal, perimenopausal, postmenopausal, and surgically postmenopausal), and among premenopausal women, by phase of menstrual cycle (early follicular, late follicular, ovulatory, early luteal, mid luteal, and late luteal) and hormone replacement therapy use at time of blood collection (yes/no). The latter matching criteria were of necessity to other studies that were being conducted using the same matched case-control sets.

Laboratory assays

All laboratory assays for blood PTH and 25-(OH)-vitamin D were conducted at the Laboratory for Health Protection Research, National Institute for Public Health and the Environment, the Netherlands, using commercially available enzyme immunoassay kits (DSL-10-8000 active I-PTH ELISA kit, DSLabs; OC-TEIA 25-(OH)-D kit, Immunodiagnostic Systems Inc.). For technical reasons, some case-control sets were not measured in the same analytical batch. However, PTH batch-to-batch differences are considered to be minor: the coefficient of variation (interassay) as determined with two kit control samples was minimal (7.6% at the level of 56 ng/L), no significant between-day drift, time shifts, or other trends were observed. Laboratory assays for markers in the insulin signaling pathway [IGF-1, IGFBP-3, glycosylated hemoglobin (HbA1c), and C-peptide] have been previously detailed (15, 26, 27), and were done only for a subsample of subjects ($N = 808$ for IGF-1 and IGFBP-3; $N = 784$ for C-peptide; and $N = 731$ for Hb1Ac) with PTH and 25-(OH)-vitamin D measurements. For all analyses, laboratory technicians were blinded to the case-control status of the samples.

Statistical Analysis

Differences between cases and controls with respect to important covariates were evaluated using conditional logistic regression (for categorical variables) and paired *t*-tests (for continuous variables). Among controls, age-, sex-, body mass index (BMI)-, and study center-adjusted Spearman partial correlation coefficients were calculated between blood PTH levels and other continuous variables.

Unadjusted (matching factors only) and multivariable (adjusted for potential confounders other than those controlled for by matching) conditional logistic regression models were used to assess the strengths of association (incidence rate ratio, RR; with 95% confidence intervals and tests for trend) within each strata of PTH. In a nested case-control study with controls being selected by incidence density sampling, the odds ratio from conditional logistic regression estimates the incidence RR (28). For the main exposure variable, serum PTH concentrations, quintile sex-specific cutoff points were calculated on the basis of distribution in control subjects, with the middle category chosen as the referent because it included the middle range of normal PTH values and allowed investigation of the cancer risk for both high and low PTH levels. Specific quintile cutoff point values are shown in Table 3. Additional analyses were also conducted using biologically meaningful cutoff points of serum PTH levels. The first cutoff point (30 ng/L) was chosen as the low plateau level of serum PTH among controls. This cutoff point was chosen because it is the value at which the serum PTH concentration among controls approaches a relatively stable plateau level as long as 25-(OH)-vitamin D concentrations are higher than 75 nmol/L [Figure 1, created using locally weighted scatterplot smoothing (LOESS) procedure implemented in SAS 9.2 software]. In addition, a 3-parameter exponential decay model (29) fitted to the serum PTH and 25-(OH)-vitamin D concentrations showed that serum PTH reached plateau level at 29.7 ng/L, with approximate 95%CI: 26.5–32.8. The resulting equation was: PTH (ng/L) = $30 + 54^{*}e^{[-0.06\times 25\text{-(OH)D (nmol/L)}]}$. The second cutoff point (65 ng/L) was chosen as the upper limit of normal PTH values on the basis of previously published literature (30–33). Thus, the resultant biologically meaningful categories for serum PTH levels used in this study were: <30, 30–65, and ≥65 ng/L. In this analysis, the middle category was also chosen as the reference category for the same reasons stated above.

The two conditional logistic models used in these analyses were as follows: (i) crude model based on matching factors only and (ii) multivariable adjusted model with

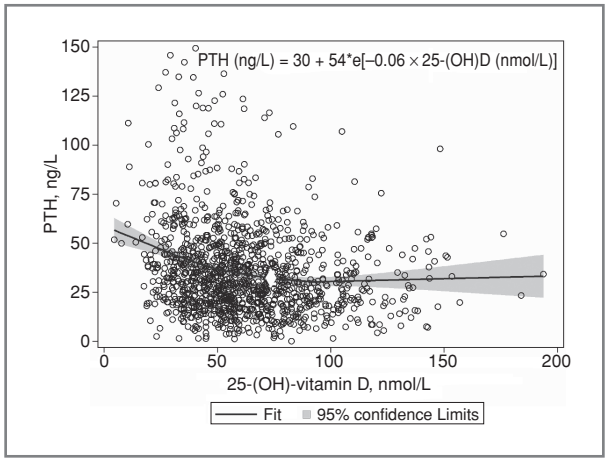

Figure 1. Serum PTH concentrations versus 25-(OH)-vitamin D concentrations among controls using LOESS model. Solid line represents LOESS plot, and shaded area represents 95% CI of the LOESS plot. The diamond indicates the point at which PTH concentrations attain the plateau value among controls, based on the exponential decay function.

additional adjustments for potential confounding variables (19, 34), including circulating 25-(OH)-vitamin D (continuous), years of education (none/primary, technical/professional, secondary, university or higher, and missing/unspecified), physical activity [metabolic equivalent hours (METS) per week of combined recreational and household activity, continuous], smoking status (never smokers, former smokers who smoked for <10 years, former smokers who smoked for ≥10 years, current smokers who smoke <15 cigarettes/day, current smokers who smoke 15–25 cigarettes/day, current smokers who smoke ≥25 cigarettes/day, and missing), BMI, total energy intake, and total daily intakes of calcium, alcohol, fruits, vegetables, and red/processed meats (all continuous). Other potential confounders including waist to hip ratio (WHR), total daily intakes of fish, retinol, and fiber were examined but were not included in the final multivariate model as they did not change substantially risk estimates (by >10%). In general, three criteria were used to assess confounding factors: (i) biological plausibility; (ii) whether the variable of interest was associated with the outcome and exposure; and (iii) whether the logistic regression coefficient of the primary exposure variable substantially changed (by >10%) after adding the potential confounding variable in the model. For all models, tests for linear trend were carried out using category-specific mean values of serum PTH levels. All analyses were run separately for men and women combined and separate, as well as for CRC anatomical subsites (colon and rectum; distal and proximal colon). Heterogeneity of effects by sex and CRC anatomical subsites were assessed by χ^2 statistic.

In analysis of biologically meaningful categories, several potential interaction variables were considered: sex, predefined cutoff points of circulating 25-(OH)-vitamin D based on the proposed levels of vitamin D deficiency/sufficiency (<50, 50–75, and ≥75 nmol/L), tertiles of total calcium intake (<812, 812–1,129, ≥1,129 mg/day; based on the distribution in control subjects), BMI categories (<25, 25–30, ≥30 kg/m^2), tertiles of markers related to the insulin signaling pathway (IGF-1, IGFBP-3, C-peptide, and HbA1c; based on the distribution in control subjects), tertiles of C-reactive protein (CRP; <1.45, 1.45–3.54, ≥3.54 mg/L; based on the distribution in control subjects), age at blood collection (<56, 56–61, ≥61 years; based on the distribution in control subjects), genetic polymorphisms in the *VDR* and *CASR* genes (*BsmI,* rs1544410; *Fok1*, rs2228570, and rs1801725; ref. 35), and for women, menopausal status and hormone replacement therapy. A potential multiplicative interaction of the effects of serum PTH levels with these variables on CRC risk was tested by including interaction terms formed by the product of interaction variable categories and the value of biologically meaningful categories of PTH concentration. As 25-(OH)-vitamin D, dietary calcium intake, and BMI play a key role in PTH regulation, we *a priori* decided to present the results of interaction analyses for these variables even if the statistical significance was not reached.

The effect of the season or month of blood collection on 25-(OH)-vitamin D levels have been previously investigated (19). There was no substantial effect of the season or month of blood collection on PTH levels. In sensitivity analyses, matched case-control pairs were excluded where the case was diagnosed within 2 years after enrolling into the study to exclude reverse causation. Also, the heterogeneity in effect estimates by county/center/geographical regions was investigated.

All statistical tests were two-sided, and P values of less than 0.05 were considered statistically significant. All statistical analyses were conducted using SAS version 9.2 (SAS Institute, Inc.).

Results

Baseline characteristics of cases and controls

Selected baseline characteristics of the CRC cases and matched controls are shown in Table 1. The mean age at blood donation of colon cancer cases and controls was 58.7 years, and of rectal cancer cases and controls, 58.1 years. On an average, colon and rectal cancer cases had 4 years between blood donation and the time of diagnosis. Colon cancer cases were more likely to have higher BMI and lower levels of 25-(OH)-vitamin D compared with the matched controls. Cases of rectal cancer tended to have lower intakes of dietary calcium and higher intakes of alcohol and red and processed meats. The data set included 450 rectum cancer cases and 764 colon cancer cases, among which there were 311 distal colon cancer cases, 359 proximal colon cancer cases, 73 unspecified or overlapping colon cancer cases, and 21 colon cancer cases with missing data on anatomical subsite localization within the colon.

Correlation analyses

Spearman's partial correlation coefficients by sex between PTH and 25-(OH)-vitamin D, dietary calcium intake, and BMI are shown in Table 2. Among controls, serum PTH concentration was negatively correlated with 25-(OH)-vitamin D ($\rho = -0.16$, $P<0.001$), and dietary calcium intake ($\rho = -0.07$, $P = 0.02$). A positive correlation was found between serum PTH and BMI ($\rho = 0.19$, $P<0.001$), and WHR ($\rho = 0.16$, $P<0.001$). No strong associations were found between serum PTH and IGF-1 ($\rho = -0.05$, $P = 0.18$), and other markers in the insulin signaling pathway, namely IGFBP-3 ($\rho = -0.01$, $P = 0.80$), C-peptide ($\rho = -0.04$, $P = 0.38$), and Hb1Ac ($\rho = -0.07$, $P = 0.06$).

Analyses by quintile of PTH

In multivariate adjusted analyses by quintile, using the middle category as a referent, both the highest and the lowest quintiles of serum PTH level were associated with a nonsignificant increased risk for CRC (Q_1: RR = 1.19, 95% CI: 0.90–1.57; Q_5: RR = 1.09, 95% CI: 0.82–1.44; P_{trend}

Table 1. Selected baseline characteristics of incident colon and rectal cancer cases and matched controls[a] in the nested case-control study within the EPIC cohort

Characteristic[b]	Colon Cases (*N* = 764)	Matched controls (*N* = 764)	P_{diff}[c]	Cases (*N* = 450)	Rectum Matched controls (*N* = 450)	P_{diff}[c]
Total no. of women, *n* (%)	406 (53.1)	406 (53.1)	–	206 (45.8)	206 (45.8)	–
Age at blood collection, *y* mean (SD)	58.7 (7.2)	58.7 (7.2)	0.55	58.1 (6.8)	58.1 (6.8)	0.20
Years of follow-up, mean (SD)	3.8 (2.2)	–	–	3.9 (2.2)	–	–
Smoking status/duration/intensity, *n* (%)						
Never smokers	323 (42.3)	349 (45.7)	0.36	173 (38.4)	177 (39.3)	0.45
Former, duration of smoking < 10y	42 (5.5)	34 (4.5)		17 (3.8)	21 (4.7)	
Former, duration of smoking ≥ 10y	193 (25.3)	199 (26.1)		125 (27.8)	108 (24.0)	
Former, missing duration of smoking	18 (2.4)	13 (1.7)		4 (0.9)	8 (1.2)	
Smokers, <15 cigarettes/day	64 (8.4)	71 (9.3)		54 (12.0)	48 (10.7)	
Smokers, ≥15 to <25 cigarettes/day	65 (8.5)	53 (6.9)		35 (7.8)	51 (11.3)	
Smokers, ≥25 cigarettes/day	15 (2.0)	16 (2.1)		13 (2.9)	12 (2.7)	
Missing smoking status	44 (5.8)	29 (3.8)		29 (6.4)	25 (5.6)	
Education level, *n* (%)						
None/primary	287 (37.9)	301 (39.7)	0.69	157 (35.4)	172 (38.6)	0.41
Technical/professional	181 (23.9)	183 (24.1)		125 (28.2)	125 (28.0)	
Secondary	144 (19.0)	126 (16.6)		65 (14.6)	61 (13.7)	
University or higher	127 (16.8)	132 (17.4)		87 (19.6)	83 (18.6)	
Missing/unspecified	18 (2.4)	16 (2.1)		10 (2.3)	5 (1.1)	
Body mass index (BMI), kg/m^2 (SD)	26.9 (4.5)	26.3 (3.9)	0.01	26.6 (4.1)	26.4 (3.9)	0.50
Physical activity, METS/week (SD)	84.4 (54.2)	86.0 (51.4)	0.58	86.6 (51.2)	85.7 (50.0)	0.77
Dietary variables, mean (SD)						
Total energy, kcal/day	2141.7 (747.9)	2114.3 (646.4)	0.38	2,197.2 (693.9)	2,153.0 (628.7)	0.25
Calcium intake, mg/day	1,008.7 (434.8)	1014.9 (405.9)	0.77	996.3 (425.6)	1,047.4 (439.6)	0.09
Dietary vitamin D, μg/day	4.0 (2.6)	4.0 (2.4)	0.98	4.1 (2.5)	4.2 (2.6)	0.30
Retinol, μg/day	911.5 (834.7)	894.1 (823.0)	0.66	999.6 (840.1)	970.2 (928.5)	0.61
Alcohol, g/day	15.7 (21.6)	14.8 (19.4)	0.30	19.8 (23.8)	16.8 (21.4)	0.03
Total vegetables, g/day	182.6 (120.4)	189.5 (123.0)	0.19	184.5 (163.1)	183.0 (124.4)	0.86
Total fruits, g/day	230.6 (185.9)	241.4 (184.9)	0.21	218.4 (168.8)	222.8 (169.6)	0.65
Red and processed meats, g/day	112.5 (78.6)	109.4 (57.3)	0.31	124.0 (65.9)	116.5 (64.5)	0.04
Circulating biomarkers, geometric mean (5th–95th percentile)						
25-(OH)-vitamin D, nmol/L[d]	52.9 (24.1–102.0)	57.6 (27.5–116.0)	<0.001	56.4 (26.1–110.8)	57.3 (24.2–116.5)	0.72
Parathyroid hormone (PTH), ng/L[d]	30.9 (7.3–81.0)	30.5 (9.1–79.9)	0.67	31.1 (8.2–82.9)	32.9 (8.4–85.2)	0.10

[a]The distribution of cases (colon/rectum) by country was: Denmark = 183/165, France = 26/6, Germany = 89/55, Greece = 11/13, Italy = 101/41, the Netherlands = 92/43, Spain = 77/41, Sweden = 41/24, and United Kingdom = 144/62.
[b]Data are presented as means (SD) unless otherwise specified.
[c]By paired t-test for continuous variables, or conditional logistic regression for categorical variables.
[d] Paired *t*-test was done on natural log transformed variable.

= 0.97; Table 3); whereas the fourth quintile of serum PTH level was associated with a statistically significant decreased risk for CRC (Q_4: RR = 0.69, 95% CI: 0.52–0.91). No statistically significant associations were observed for colon and rectum anatomical subsites analyzed separately ($P_{heterogeneity\ by\ colon\ site}$ = 0.10), nor for proximal and distal colon ($P_{heterogeneity\ by\ anatomical\ sub\text{-}site}$ = 0.06). There was no evidence of multiplicative interaction by sex for CRC ($P_{interaction\ by\ sex}$ = 0.24), and its anatomical subsites, colon ($P_{interaction\ by\ sex}$ = 0.35) and rectal ($P_{interaction\ by\ sex}$ = 0.65) cancers.

Analyses by *a priori* defined cutoff points of PTH

Results for analyses by the *a priori* defined cutoff points are shown in Table 4. In all participants, only the highest category of serum PTH (≥65 ng/L) was statistically significantly associated with increased risk for CRC and colon cancer (RR = 1.41, 95% CI: 1.03–1.93; and RR =

Table 2. Spearman's partial correlation coefficients among controls between serum PTH levels and 25-(OH)-vitamin D, dietary calcium, markers in the insulin signaling pathway, BMI, and WHR stratified by sex

Risk factor	All			Male			Female		
	N	ρ[a]	P[b]	N	ρ[a]	P[b]	N	ρ[a]	P[b]
25-(OH)-vitamin D	1,214	−0.16	<0.001	602	−0.17	<0.001	612	−0.15	<0.001
Dietary calcium	1,214	−0.07	0.023	602	−0.06	0.128	612	−0.07	0.094
IGF-1[c]	808	−0.05	0.180	443	−0.04	0.421	365	−0.05	0.309
IGFBP-3[c]	808	−0.01	0.800	443	0.04	0.389	365	−0.06	0.225
C-peptide[c]	784	−0.04	0.380	439	−0.05	0.277	345	−0.04	0.512
Hb1Ac[c]	731	−0.07	0.062	408	−0.07	0.140	323	−0.06	0.273
BMI[d]	1,214	0.19	<0.001	602	0.17	<0.001	612	0.24	<0.001
WHR[e]	1,149	0.16	<0.001	565	0.11	0.01	584	0.19	<0.001

[a]Spearman's partial correlation coefficient adjusted for study center, age, sex, and body mass index (BMI) (if appropriate).
[b]*P* value.
[c]Insulin growth factor 1 (IGF-1); insulin growth factor binding protein 3 (IGFBP-3); C-peptide, a **marker** of the endogenous insulin production; glycosylated hemoglobin (HbA1c), a marker for average glucose level in blood.
[d]BMI, body mass index.
[e]WHR, waist to hip ratio.

1.56, 95% CI: 1.03–2.34, respectively). Further adjustment for IGF-1 levels did not substantially change the effect estimates (PTH ≥ 65 vs. <30 ng/L: RR = 1.50, 95% CI: 1.05–2.14 for CRC, and RR = 1.59, 95% CI: 1.00–2.54 for colon cancer); however, the number of participants included in this analysis was smaller because IGF-1 levels were measured only for a subsample of study subjects (808 out of 1,214). No statistically significant associations were observed for colon and rectum anatomical subsites analyzed separately ($P_{\text{heterogeneity by colon site}} = 0.21$), nor for proximal and distal colon ($P_{\text{heterogeneity by anatomical subsite}} = 0.74$).

In men, high levels (≥ 65 ng/L) and low levels (<30 ng/L) of serum PTH were positively and statistically significantly associated with CRC risk (Table 4). The associations were stronger although statistically non-significantly for rectal cancer compared with colon cancer, and particularly for the lowest PTH category ($P_{\text{heterogeneity by colorectal site}} = 0.19$). In women, no statistically significant associations were observed between biologically meaningful categories of serum PTH and risk of CRC ($P_{\text{interaction by sex}} = 0.01$), colon ($P_{\text{interaction by sex}} = 0.15$), or rectal cancer ($P_{\text{interaction by sex}} = 0.004$).

Interaction analyses by *a priori* defined cutoff points of PTH

In interaction analyses, the association between serum PTH and CRC risk varied by levels of circulating 25-(OH)-vitamin D, but the interaction was not statistically significant ($P_{\text{interaction}} = 0.57$; Table 5). Subjects with the highest levels of 25-(OH)-vitamin D and serum PTH showed a strong positive but not statistically significant association between PTH and CRC (RR = 2.16, 95% CI 0.92–5.06). When considered by anatomical subsite, the association was statistically significant for colon (RR = 3.25, 95% CI: 1.11–9.52; Table 5) but not for rectal cancer (RR = 1.38, 95% CI = 0.29–6.53). In those with the 25-(OH)-vitamin D levels less than 75 nmol/L, higher levels of serum PTH were associated with statistically significant increase in CRC and colon cancer risks.

Interaction analyses with dietary calcium showed that among those who have the highest serum PTH levels, the lowest intake of calcium is positively associated with CRC (RR = 2.49, 95% CI: 1.38–4.50; $P_{\text{interaction}} = 0.64$), colon cancer (RR = 2.59, 95% CI 1.22–5.47; $P_{\text{interaction}} = 0.38$), and rectal cancer (RR = 2.61, 95% CI 0.92–7.40; $P_{\text{interaction}} = 0.49$).

Interaction analyses for BMI showed that among those with BMI 25–30 kg/m^2, the highest serum PTH levels (≥65 ng/L) were associated with the highest colon cancer risk (RR = 1.93, 95% CI: 1.06–3.51; $P_{\text{interaction}} = 0.28$) when compared with those whose BMI is less than 25 kg/m^2. Similar results were observed for CRC and rectal cancer; however, effect estimates and the tests for interaction were not statistically significant (Table 5).

IGF-1, IGFBP-3, C-peptide, HbA1c, CRP, age at blood collection, genetic polymorphisms in the *VDR* and *CASR* genes (*BsmI*, rs1544410; *Fok1*, rs2228570, and rs1801725), and menopausal status and hormone replacement therapy in women did not modify the association between PTH and CRC.

Sensitivity analyses

For quintile and by *a priori* defined cutoff points of PTH analyses, the exclusion of cases with less than 2 years of follow-up did not substantially change any of the results. Furthermore, limiting our analyses to cases with stage I and/or stage II CRC (data were available only for a

Table 3. Crude and multivariable-adjusted rate ratios (RRs) and 95% confidence intervals (CIs) of CRC and its subsites by sex-specific quintile of serum parathyroid hormone (PTH) concentrations.

Quintiles of serum PTH concentration[a]	All participants			Men			Women		
	N (cases/controls)	Crude RR[b] (95% CI)	Multivariable RR[c] (95% CI)	*N* (cases/controls)	Crude RR[b] (95% CI)	Multivariable RR[c] (95% CI)	*N* (cases/controls)	Crude RR[b] (95% CI)	Multivariable RR[c] (95% CI)
Colorectum									
1	277/243	1.11 (0.86–1.45)	1.19 (0.90–1.57)	136/122	1.20 (0.82–1.75)	1.14 (0.75–1.74)	141/121	1.06 (0.74–1.52)	1.20 (0.82–1.77)
2	213/239	0.87 (0.67–1.13)	0.87 (0.66–1.15)	132/120	1.17 (0.81–1.69)	1.19 (0.79–1.77)	81/119	0.60 (0.40–0.89)	0.59 (0.39–0.90)
3 (reference)	248/242	1.00	1.00	117/119	1.00	1.00	131/123	1.00	1.00
4	183/245	0.73 (0.56–0.96)	0.69 (0.52–0.91)	78/121	0.64 (0.44–0.95)	0.56 (0.36–0.87)	105/124	0.80 (0.56–1.15)	0.77 (0.52–1.15)
5	293/245	1.17 (0.91–1.52)	1.09 (0.82–1.44)	139/120	1.20 (0.82–1.75)	1.04 (0.69–1.59)	154/125	1.15 (0.81–1.65)	1.16 (0.79–1.71)
P_{trend}		0.37	0.97		0.79	0.41		0.14	0.36
Colon									
1	173/154	1.07 (0.77–1.49)	1.17 (0.82–1.66)	82/75	1.16 (0.72–1.88)	1.13 (0.65–1.97)	91/79	1.03 (0.66–1.61)	1.23 (0.76–1.98)
2	131/161	0.78 (0.56–1.10)	0.80 (0.56–1.14)	80/81	1.07 (0.66–1.73)	1.07 (0.63–1.81)	51/80	0.54 (0.33–0.89)	0.54 (0.32–0.92)
3 (reference)	152/149	1.00	1.00	64/66	1.00	1.00	88/83	1.00	1.00
4	111/153	0.73 (0.53–1.02)	0.70 (0.49–1.00)	43/65	0.67 (0.39–1.14)	0.58 (0.32–1.06)	68/88	0.75 (0.49–1.16)	0.73 (0.46–1.17)
5	197/147	1.35 (0.98–1.88)	1.24 (0.86–1.77)	89/71	1.37 (0.83–2.29)	1.15 (0.65–2.06)	108/76	1.36 (0.88–2.09)	1.36 (0.84–2.20)
P_{trend}		0.04	0.32		0.52	0.93		0.03	0.16
Rectum									
1	104/89	1.18 (0.76–1.84)	1.07 (0.66–1.74)	54/47	1.25 (0.67–2.34)	0.99 (0.48–2.07)	50/42	1.12 (0.60–2.09)	1.25 (0.61–2.56)
2	82/78	1.03 (0.67–1.59)	0.99 (0.62–1.60)	52/39	1.37 (0.77–2.44)	1.52 (0.76–3.02)	30/39	0.69 (0.35–1.36)	0.71 (0.33–1.51)
3 (reference)	96/93	1.00	1.00	53/53	1.00	1.00	43/40	1.00	1.00
4	72/92	0.74 (0.48–1.15)	0.62 (0.38–1.02)	35/56	0.63 (0.36–1.12)	0.55 (0.28–1.08)	37/36	0.94 (0.47–1.90)	0.87 (0.40–1.88)
5	96/98	0.92 (0.60–1.39)	0.84 (0.52–1.34)	50/49	0.99 (0.56–1.75)	0.90 (0.46–1.76)	46/49	0.83 (0.44–1.58)	0.83 (0.41–1.71)
P_{trend}		0.24	0.25		0.23	0.36		0.64	0.59

[a]Quintile sex-specific cutoff points based on the distribution in control subjects: Men: Q_1, <19.35; Q_2, ≥19.35–29.45; Q_3, ≥29.45–38.75; Q_4, ≥38.75–53.05; Q_5, ≥53.05 ng/L; Women: Q_1, <16.85; Q_2, ≥16.85–24.2; Q_3, ≥24.2–34.1; Q_4, ≥34.1–46.1; Q_5, ≥46.1 ng/L. Mean (SD) serum PTH concentrations in control subjects: Men: Q_1, 12.61(4.93); Q_2, 24.19 (3.20); Q3, 33.86 (2.66); Q4, 45.59 (4.41); Q5, 73.17 (22.44); Women: Q_1, 11.48 (4.18); Q_2, 20.67 (2.02); Q3, 28.46 (2.57); Q4, 39.34 (3.41); Q5, 71.60 (27.90).

[b] Rate ratio (RR) with corresponding 95% confidence interval (CI) from conditional logistic regression model. Matching variables are sex, age, study center, fasting status, time of blood collection, and in women, menopausal status, day of menstrual cycle, and postmenopausal hormone therapy use.

[c]Multivariable models were conditional logistic regression models additionally adjusted for 25-(OH)-vitamin D (continuous), education (none/primary, technical/professional, secondary, university or higher, and missing/unspecified), physical activity (continuous), smoking status (never smokers, former smokers who smoked for <10 years, former smokers who smoked for ≥10 years, current smokers who smoke <15 cigarettes/day, current smokers who smoke 15–25 cigarettes/day, current smokers who smoke ≥25 cigarettes/day, and missing), body mass index (BMI), total energy intake, total daily intakes of calcium, alcohol, fruits, vegetables, red and processed meats (all continuous).

Table 4. Crude and multivariable-adjusted RRs and 95% CIs of CRC and its subsites by categories of serum parathyroid hormone (PTH) concentrations, stratified by sex

Category of serum PTH concentration[a], ng/L	All Participants			Men			Women		
	N (cases/controls)	Crude RR[b] (95% CI)	Multivariable RR[c] (95% CI)	*N* (cases/controls)	Crude RR[b] (95% CI)	Multivariable RR[c] (95% CI)	*N* (cases/controls)	Crude RR[b] (95% CI)	Multivariable RR[c] (95% CI)
Colorectum									
1–30	574/573	1.06 (0.88–1.28)	1.15 (0.94–1.41)	277/245	1.48 (1.13–1.95)	1.66 (1.22–2.25)	298/329	0.78 (0.60–1.01)	0.85 (0.64–1.12)
30–65	501/532	1.00	1.00	246/302	1.00	1.00	255/230	1.00	1.00
≥65	138/108	1.37 (1.03–1.83)	1.41 (1.03–1.93)	79/55	1.77 (1.19–2.62)	1.77 (1.14–2.75)	59/53	1.01 (0.66–1.54)	1.15 (0.73–1.84)
Colon									
1–30	361/374	1.00 (0.79–1.27)	1.08 (0.84–1.40)	164/158	1.26 (0.88–1.82)	1.32 (0.88–1.98)	198/217	0.83 (0.61–1.14)	0.92 (0.65–1.30)
30–65	308/325	1.00	1.00	143/167	1.00	1.00	165/158	1.00	1.00
≥65	94/64	1.58 (1.10–2.27)	1.56 (1.03–2.34)	51/33	1.82 (1.11–3.00)	1.71 (0.95–3.06)	43/31	1.36 (0.80–2.30)	1.58 (0.87–2.89)
Rectum									
1–30	213/199	1.18 (0.87–1.60)	1.31 (0.93–1.84)	113/87	1.86 (1.21–2.85)	2.35 (1.41–3.90)	100/112	0.68 (0.43–1.07)	0.76 (0.45–1.28)
30–65	193/207	1.00	1.00	103/135	1.00	1.00	90/72	1.00	1.00
≥65	44/44	1.06 (0.66–1.70)	1.20 (0.72–2.01)	28/22	1.59 (0.83–3.01)	2.00 (0.96–4.17)	16/22	0.57 (0.27–1.19)	0.58 (0.25–1.34)

[a]Mean (SD) of serum PTH concentrations by predefined categories of PTH in all control subjects: PTH <30 ng/L, 18.86 (7.04); 30–65 ng/L, 43.39 (9.53); ≥65 ng/L, 92.83 (25.89).
[b] Rate ratio (RR) with corresponding 95% confidence interval (CI) from conditional logistic regression model. Matching variables are sex, age, study center, fasting status, time of blood collection, and in women, menopausal status, day of menstrual cycle, and postmenopausal hormone therapy use.
[c]Multivariable models were conditional logistic regression models additionally adjusted for 25-(OH)-vitamin D (continuous), education (none/primary, technical/professional, secondary, university or higher, and missing/unspecified), physical activity (continuous), smoking status (never smokers, former smokers who smoked for <10 years, former smokers who smoked for ≥10 years, current smokers who smoke <15 cigarettes/day, current smokers who smoke 15–25 cigarettes/day, current smokers who smoke ≥25 cigarettes/day, and missing), BMI, total energy intake, total daily intakes of calcium, alcohol, fruits, vegetables, red and processed meats (all continuous).

Table 5. Multivariable-adjusted RRs[a] and 95% CIs of CRC and its subsites by categories of serum parathyroid hormone (PTH) concentrations and categories of circulating 25-(OH)-vitamin D, BMI, and dietary calcium intake

Categories of risk factor variable	Categories of serum PTH, ng/L			$P_{interaction}$
	<30	30–65	≥65	
Colorectum				
Circulating 25-(OH)-vitamin D, nmol/L				
<50	1.74 (1.27–2.38)	1.47 (1.07–2.02)	1.71 (1.09–2.69)	
50–75 (reference)	1.34 (0.99–1.82)	1.16 (0.83–1.62)	1.76 (1.00–3.08)	
≥75	1.00	0.95 (0.64–1.39)	2.16 (0.92–5.06)	0.57
Dietary calcium intake, mg/day				
<812	1.28 (0.90–1.82)	1.09 (0.77–1.54)	2.49 (1.38–4.50)	
812–1,129	1.17 (0.86–1.60)	1.11 (0.79–1.56)	1.06 (0.63–1.77)	
≥1,129	1.00	0.84 (0.60–1.16)	1.08 (0.63–1.86)	0.64
Body mass index (BMI), kg/m^2				
<25	1.00	0.96 (0.70–1.31)	1.28 (0.71–2.29)	
25–30	1.01 (0.77–1.33)	0.87 (0.64–1.18)	1.44 (0.90–2.30)	
≥30	1.54 (1.02–2.35)	1.15 (0.78–1.71)	1.22 (0.68–2.19)	0.61
Colon				
Circulating 25-(OH)-vitamin D, nmol/L				
<50	1.88 (1.26–2.82)	1.72 (1.15–2.57)	2.26 (1.28–4.01)	
50–75 (reference)	1.46 (1.00–2.13)	1.34 (0.87–2.05)	1.82 (0.87–3.78)	
≥75	1.00	1.00 (0.60–1.64)	3.25 (1.11–9.52)	0.58
Dietary calcium intake, mg/day				
<812	1.04 (0.66–1.62)	1.08 (0.69–1.70)	2.59 (1.22–5.47)	
812–1,129	1.02 (0.68–1.51)	0.97 (0.62–1.50)	1.08 (0.57–2.03)	
≥1,129	1.00	0.80 (0.53–1.22)	1.15 (0.55–1.40)	*0.38*
Body mass index (BMI), kg/m^2				
<25	1.00	1.06 (0.72–1.58)	1.89 (0.86–4.16)	
25–30	1.08 (0.76–1.54)	0.96 (0.65–1.42)	1.93 (1.06–3.51)	
≥30	1.74 (1.04–2.91)	1.41 (0.85–2.36)	1.19 (0.58–2.44)	0.28
Rectum				
Circulating 25-(OH)-vitamin D, nmol/L				
<50	1.54 (0.90–2.63)	1.11 (0.63–1.96)	1.07 (0.47–2.43)	
50–75 (reference)	1.12 (0.64–1.96)	0.94 (0.53–1.64)	1.88 (0.75–4.74)	
≥75	1.00	0.95 (0.50–1.81)	1.38 (0.29–6.53)	0.65
Dietary calcium intake, mg/day				
<812	1.86 (1.01–3.41)	1.21 (0.67–2.17)	2.61 (0.92–7.40)	
812–1,129	1.54 (0.90–2.64)	1.49 (0.85–2.60)	1.04 (0.41–2.67)	
≥1,129	1.00	0.93 (0.53–1.63)	1.26 (0.53–3.01)	0.49
Body mass index (BMI), kg/m^2				
<25	1.00	0.83 (0.49–1.41)	0.81 (0.31–2.10)	
25–30	0.92 (0.59–1.43)	0.76 (0.46–1.25)	1.13 (0.50–2.56)	
≥30	1.54 (0.71–3.35)	0.87 (0.46–1.66)	1.41 (0.48–4.16)	0.90

[a]From multivariable conditional logistic regression models additionally adjusted (where appropriate) for 25-(OH)-vitamin D (continuous), education (none/primary, technical/professional, secondary, university or higher, and missing/unspecified), physical activity (continuous), smoking status (never smokers, former smokers who smoked for <10 years, former smokers who smoked for ≥10 years, current smokers who smoke <15 cigarettes/day, current smokers who smoke 15–25 cigarettes/day, current smokers who smoke ≥25 cigarettes/day, and missing), BMI, total energy intake, total daily intakes of calcium, alcohol, fruits, vegetables, red and processed meats (all continuous).

subsample of all CRC cases, $N = 457$) did not materially alter any of the reported results. In analyses excluding 1 country/center at a time, no substantial changes in risk estimates were observed. There was no significant heterogeneity in effect estimates by 3 geographical regions (South: Italy, Greece, and Spain; Central: France, Germany, the Netherlands, and UK; and North: Sweden, Denmark, and Norway; data not shown).

Discussion

The results of this nested case-control study suggest that the levels of serum PTH above the upper limits of normal may be independently associated with the increased risk for incident, sporadic CRC among Western European men. Although the tested interactions were not all statistically significant, the present findings indicate that the PTH–CRC association may differ by colon subsites, circulating levels of 25-(OH)-vitamin D, dietary intake of calcium, and BMI.

Parathyroid hormone may modulate CRC risk because of its role in the homeostasis of normal serum concentrations of calcium and phosphate, and interrelation with vitamin D (36). Some proposed mechanisms for PTH's potential promoting effects in colorectal carcinogenesis include increased hepatic production of IGF-1, modulation of the response to other growth factors, antiapoptotic actions, and a possible decrease in intracolonic calcium concentration (1). However, with the exception of the present study, to date there are no other reported human studies directly investigating the association between blood levels of PTH with colorectal neoplasms. Indirect evidence for a role of PTH in CRC comes from observations that patients with primary hyperparathyroidism are more likely to be diagnosed with a colon tumor (2–5). Consistent with these limited data, we found that prediagnostic serum PTH levels above high normal (as in hyperparathyroidism) may increase CRC or colon cancer risk, even after controlling for 25-(OH)-vitamin D concentration and other potential confounders.

One of the proposed carcinogenic mechanisms of PTH is increased hepatic production of IGF-1 (11–14). In our study, there was no statistically significant correlation between serum concentrations of IGF-1 (and other markers in the insulin signaling pathway) and PTH. Moreover, additional adjustment for IGF-1 levels in the multivariable models did not change substantially the estimates of the PTH–CRC association. Therefore, our data do not support IGF-1 as a potential mediator of the PTH–CRC association; however, further research is needed to confirm this finding.

Our results also indicated that the positive PTH–CRC association may be stronger among men than women, although this observation requires further validation. One possible explanation for a sex-specific difference may be related to sex hormone exposure. Estrogens have been shown to influence vitamin D and calcium metabolism (37), and to modulate expression of the vitamin D receptor and other vitamin D-related proteins in the colon epithelium (38), and may therefore modify the PTH–CRC association in women. However, we did not observe a statistically significant interaction by hormone replacement therapy or menopausal status.

As PTH is highly physiologically interrelated with serum calcium and circulating vitamin D, we investigated the potential interaction of the PTH–CRC association by 25-(OH)-vitamin D and dietary calcium intake, both of which have been previously associated with decreased CRC risk in this data set (20). In the present analyses, a statistically significant negative correlation was found between PTH and 25-(OH)-vitamin D, consistent with the systematic review of the literature (39). The observed positive association between PTH and CRC seemed to be the strongest among the participants with high PTH and 25-(OH)-vitamin D above 50 nmol/L. The PTH–CRC association was also the strongest among participants who had low dietary calcium intake, supporting the hypothesis that increased PTH may stimulate the absorption of calcium from the colon lumen thus lowering the calcium concentration in the colonic milieu and potentially interfering with the calcium binding of bile acids, which renders them inert (21) and may thereby reduce their damaging effect on cell membranes (40). Other proposed mechanisms for the anticarcinogenic effects of calcium include direct effects on cell cycle regulation (22), promotion of colonocyte differentiation (41, 42), and modulation of E-cadherin and β-catenin expression via the CaSR (22, 23, 43). Although a statistically significant statistical interaction was not observed, it does not discount a plausible biological interaction between PTH and 25-(OH)-vitamin D and calcium intake. Further studies are needed to confirm our results.

Obesity is associated with high serum PTH levels (30, 33, 44–51), and this is reflected here with an observed positive correlation between BMI and PTH concentration. This may be due to the decreased bioavailability of vitamin D in obese individuals (52). It has also been speculated that PTH may inhibit catecholamine-induced lipolysis, enhance *de novo* lipogenesis, and modulate 25-(OH)-vitamin D_3-1α-hydroxylase activity in adipose tissue (51, 53). Our results for colon cancer showed that high PTH levels were statistically significantly associated with almost doubling in colon cancer risk among overweight participants only. These results suggest a potential interaction between being overweight and PTH. However, given that that the P value for multiplicative interaction was not significant, this observation may be due to chance and requires further investigation with larger data sets.

This study had several limitations. CRC cases were identified within a relatively short period of time after enrollment into the study. Therefore, the presence of preneoplastic or neoplastic changes in the colon could have influenced the levels of PTH in serum. However, exclusion of cases with less than two years of follow-up and analyses by tumor stage did not substantially change any of the

results. Another potential limitation of this study is that levels of serum total and/or ionized calcium were not measured. Thus, it is unclear whether the observed positive association between PTH and CRC related directly to PTH, indirectly to serum calcium, or both. Also, data on primary or secondary hyperparathyroidism were not collected at baseline, so there is a possibility that some participants have been diagnosed and treated for these conditions. Furthermore, the PTH assay that was used in this study detected the intact form of PTH and did not differentiate between its 2 major metabolic fragments, carboxyl-terminal (C-PTH) and amino-terminal (N-PTH). Some evidence exists that these fragments may be regulated differently and able to exert opposite biological effects through 2 different PTH receptors in bone (54), but it is unclear whether they may have opposite effects in the colon. As with any epidemiologic study, residual confounding cannot be discarded despite the fact that this study utilized detailed and validated dietary and lifestyle questionnaires. It is also important to note that though this study is the largest case-control study of CRC based on geographically diverse Western European populations, the sample size for some subgroup analyses was nevertheless somewhat limited. Strengths of this study include its detailed data collection, prospective design, and the use of prediagnostic measurements of circulating PTH and other biomarkers, thereby minimizing the outcome and exposure misclassifications.

In conclusion, our findings suggest that higher PTH levels in serum may be associated with increased risk of incident, sporadic CRC risk among men in Western Europe. Although there were no other statistically significant interactions, our results suggested a potential biological interaction of the PTH–CRC association by colon subsites, circulating 25-(OH)-vitamin D concentration, dietary calcium intake, and obesity.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed

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