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Association between Sex Hormones and Colorectal Cancer Risk in Men and Women

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Abstract

Background & Aims—There is observational and clinical evidence that indicate that sex hormones affect development of colorectal cancer (CRC) in men and women. However, the relationship between endogenous sex hormone levels and CRC is unclear.

Methods—We collected data on lifestyle, medical history, and diet etc. (through 2008), along with blood samples, from the Nurses' Health Study, the Women's Health Study, the Health Professional Follow-Up Study, and the Physicians' Health Study II. We measured plasma levels of estrone, estradiol, testosterone, sex hormone binding globulin (SHBG), and c-peptide among 730

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women (293 cases of CRC and 437 healthy individuals, as controls) and 1158 men (439 CRC cases and 719 controls), and used unconditional logistic regression to estimate relative risks (RRs) and 95% confidence intervals (CIs). All statistical tests were 2-sided.

Results—Total testosterone, SHBG, and the ratio of estradiol to testosterone were associated with CRC in men after adjustments for matching and risk factors for CRC, including BMI and plasma levels of C-peptide. The RRs in the highest relative to the lowest quartile were 0.62 for testosterone (95% CI, 0.40–0.96), 0.65 for SHBG (95% CI, 0.42–0.99), and 2.63 for the ratio (95% CI, 1.58–4.36) (*P*-values for trend = 0.02). However, in women, only the ratio of estradiol to testosterone was (inversely) associated with CRC after adjustments for all factors (RR, 0.43; 95% CI, 0.22–0.84; *P*-value for trend, .03).

Conclusions—Based on combined data from 4 population studies, there appears to be an association between levels of sex hormones and CRC risk in men. There also appears to be an inverse association between the ratio of estradiol to testosterone and CRC in postmenopausal women.

Keywords

estrogen; incidence; colorectal cancer; testosterone

INTRODUCTION

Men tend to have a higher incidence rate of colorectal cancer than women of similar age in the US.¹ In families with hereditary nonpolyposis colorectal cancer (HNPCC), the lifetime risk of developing colon cancer is much lower in females (30%) than in males (74%).² It has also recently been shown that female patients respond better than male patients to adjuvant chemotherapy.³ These observations suggest a potential sex-related difference in colorectal cancer development and prognosis.

Numerous observational studies have suggested that an increase in female hormones as a result of pregnancy and use of exogenous hormones such as oral contraceptives and postmenopausal hormone therapy (HT) are associated with a lower risk for developing colorectal cancer in women.^{4–6} In support of these findings, the Women's Health Initiative trial of the estrogen plus progestin arm reported a 40% lower risk for colorectal cancer in the treatment group as compared with the placebo group.^{7, 8} Similarly, in men, lower androgenicity due to longer CAG repeats of the androgen receptor (AR) or treatment with androgen deprivation therapy is associated with an increased risk for colorectal cancer.^{9, 10} There is, thus, a potential role of estrogens and/or progesterone in women and androgens in men in colorectal cancer prevention.

Current data on the association of endogenous levels of estrogens and androgens with colorectal cancer risk in men and women are very limited. Two prospective studies of postmenopausal women did not report a lower risk for colorectal cancer with higher estradiol or estrone levels.^{11, 12} In men, a small prospective study has reported that higher circulating levels of dehydroepiandrosterone sulfate (DHEAS), an androgen precursor, were associated with a lower risk for colon cancer.¹³ In this case-control study nested in 4 prospective study cohorts, we comprehensively evaluated plasma levels of sex steroids (estrone, estradiol, and testosterone) and sex hormone binding globulin (SHBG) in relation to colorectal cancer risk in both men and postmenopausal women not receiving HT.

METHODS

Study Population

The present study included 4 prospective female and male prospective study cohorts: the Nurses' Health Study (NHS), the Women's Health Study (WHS), the Health Professional Follow-Up Study (HPFS), and the Physicians' Health Study II (PHSII). Description of the 4 study cohorts and collection of blood samples is provided in Supplementary Methods. Informed consent was obtained from all participants in all 4 cohorts, and this study was approved by the institutional review board of the Brigham and Women's Hospital.

Identification of Case and Control Subjects

Colorectal cancer cases were ascertained through 2008. In the NHS and WHS, case and control subjects were selected from women who were postmenopausal and had not currently using hormone therapy at blood collection. One control in the WHS and PHSII and up to 2 controls in the HPFS were matched with one case by age (± 2 years), fasting status (≥ 8 or < 8 hours since last meal), time of day of blood draw (± 2 hours). Although cases in the NHS were not matched to controls, we controlled for the matching factors utilized by the other 3 cohorts in the regression models (see below in Statistical Analysis). As a result, 732 cases and 1156 controls were included in the present analysis.

Laboratory Methods

Estrone and estradiol in men and women, and testosterone in women were measured in the Molecular lab at the Mayo Clinic (Rochester, MN) using the turbulent flow liquid chromatography tandem mass spectrometry (LC-MS/MS). SHBG and albumin in men and women and testosterone in men only were assayed in Dr. Rifai's Lab at the Children's Hospital (Boston, MA) using a competitive electrochemiluminescence immunoassay (SHBG and testosterone) and a colorimetric assay (albumin). The c-peptide samples in the WHS and PHSII were also measured in Dr. Rifai's Lab using a competitive electrochemiluminescence immunoassay. In the NHS and HPFS, the c-peptide samples were assayed using ELISAs with reagents in Dr. Pollak's Lab. All case and control samples within each cohort were assayed together in random sample order. Laboratory technicians were blinded to case-control status.

The c-peptide samples in the NHS and HPFS were each assayed at 2 different batches using the same lab. The c-peptide samples in the WHS and PHSII and the rest plasma samples in all 4 cohorts were assayed in the same batch. The mean intra-assay coefficients of variation from our quality control samples were 4%–7% in men and 3%–7% in women for the 5 biomarkers. Free estradiol and free testosterone were calculated by the law of mass action as described by Sodergard et al¹⁴.

Statistical Analysis

We first identified statistical outliers using the generalized extreme studentized deviate many-outlier detection approach¹⁵, and removed eight testosterone, nine estradiol, and one c-peptide values in men as well as one testosterone, two estradiol, and one estrone values in women. We then categorized the plasma markers into quartiles within each cohort based on the distribution in the controls (Supplementary Table). For the c-peptide levels in the NHS and HPFS, the quartile categorization was performed in each batch within each cohort. Differences between case-control pairs in continuous and categorical variables were tested using a t-test and a χ^2 test, respectively.

We used unconditional logistic regression to estimate relative risks (RRs) and 95% confidence intervals (CIs) for colorectal cancer with adjustment for matching factors

including age at blood draw (in years), study cohort, fasting status (<8, ≥8 hours), time for the blood draw (am, pm), and for risk factors for colorectal cancer including status of physical activity (yes, no), family history of colorectal cancer in a first-degree relative (yes, no), history of colorectal polyps (yes, no), smoking status (never, past, current), current alcohol consumption (no, yes), and screening exam (yes, no). We additionally controlled for body mass index (BMI, continuous, kg/m²) and c-peptide levels (median levels of each quartile, ng/mL) in the models. We also conducted stratified analyses according to BMI (<25, ≥25 kg/m²). Tests for trend were performed by assigning the median (loge-transformed plasma levels) of each quartile for each marker as a continuous variable in the models. We used SAS statistical software (version 9.2; SAS Institute, Cary, NC) for all analyses. All p values were two sided.

RESULTS

Descriptive data analysis

In both female and male cohorts, colorectal cancer subjects were heavier and less likely to be physically active as compared with control subjects (Table 1). Male cases also had a higher prevalence of colorectal polyps. With respect to plasma markers, male cases, relative to controls, had lower plasma levels of total and free testosterone, and SHBG, but had higher c-peptide levels and the ratio of estradiol over testosterone. In women, only c-peptide levels were different between cases and controls with cases having higher c-peptide levels.

Correlation among loge-transformed plasma levels of sex steroids, SHBG, and c-peptide as well as BMI were estimated in male and female control subjects separately (Table 2). In men, testosterone, which was highly correlated with SHBG, was moderately inversely correlated with BMI and c-peptide levels. In women, estradiol and estrone were moderately correlated with BMI. SHBG was inversely correlated with BMI and c-peptide in women and, to a lesser extent, in men. In addition, the ratio of estradiol to testosterone was positively correlated with BMI and c-peptide in both men and women.

Risk of colorectal cancer in men

Higher levels of total testosterone and SHBG were associated with a lower risk for colorectal cancer in men with multivariate adjustment (Table 3). Men in the highest quartile group relative to those in the lowest group had a RR of 0.56 for testosterone and 0.55 for SHBG (p-values for trend = 0.001). The associations remained after additional adjustment with BMI and c-peptide (p-values for trend=0.02). Similar risk reduction patterns were also seen for free testosterone levels (data not shown). In contrast, higher c-peptide levels were associated with an increased risk for colorectal cancer (p-value for trend=0.01), and the association was no longer statistically significant after additional adjustment for BMI and c-peptide (p for trend=0.27). In addition, the ratio of estradiol to testosterone was positively associated with colorectal cancer even after controlling for BMI and c-peptide (p for trend=0.001). When we combined testosterone, SHBG, and c-peptide levels as a composite score by assigning testosterone and SHBG in reverse order and summing their quartile coding, we found the positive association with colorectal cancer risk became slightly stronger (p for trend=0.003). When we modeled both testosterone and SHBG in the analysis, the risk estimates were no longer statistically significant (p values = 0.13). Moreover, there was no interaction between sex steroid levels and BMI in relation to colorectal cancer risk (p-values for interaction = 0.46).

Risk of colorectal cancer in postmenopausal women not taking HT

The association between levels of total estrone, estradiol, and testosterone and colorectal cancer risk in women was not statistically significant (Table 4). There was also no

association with free estradiol and testosterone levels (data not shown). However, a positive association was observed between c-peptide levels and colorectal cancer risk (p-value for trend=0.02), which was attenuated after additional adjustment for BMI and estradiol (p-value for trend=0.09). Interestingly, there was an inverse association of the ratio of estradiol to testosterone with colorectal cancer after additional adjustment for BMI and c-peptide (p-value for trend=0.03). When stratified by BMI, the inverse association was observed among normal weight women (p value for interaction=0.07); the RRs in the higher quartile groups were 0.71, 0.72, and 0.26 (p for trend=0.03). In contrast, there was no association in overweight and obese women (the range of RRs=1.15–1.26, p for trend=0.89). Stratifying analysis for other sex steroids according to BMI did not change the overall association (p-values for interaction 0.25). The association with sex hormone levels was also largely similar in the analysis with only never users of HT (data not shown). Finally, the association between sex steroid levels and colorectal cancer risk was not modified by tumor locations in men and women (data not shown).

DISCUSSION

In this prospective analysis of circulating sex hormones and colorectal cancer risk, we found that, in men, higher levels of testosterone and SHBG as well as a lower ratio of estradiol over testosterone were associated with a decrease in risk for developing colorectal cancer even after additionally controlling for BMI and c-peptide levels. In contrast, in postmenopausal women not taking hormone therapy, sex steroids and SHBG were not significantly associated with colorectal cancer risk, although an inverse association was present between the ratio of estradiol to testosterone and colorectal cancer risk after additional adjustment for BMI and c-peptide. Specifically, the inverse association between the ratio and colorectal cancer risk was present only among normal weight women.

Our findings of the inverse association of circulating testosterone levels with colorectal cancer risk in men are in line with the previous studies^{9, 13} suggesting that men with lower androgenicity as a result of reduced AR activity or lower circulating DHEAS are at a greater risk for colorectal cancer. Men treated with androgen deprivation therapy are also more likely than non-therapy users to develop colorectal cancer¹⁰. In addition, our observation of the inverse association between circulating SHBG and colorectal cancer risk also agree with a recent study¹⁶ showing an association between the SHBG gene variation (ie, rs6259) and colorectal cancer in men. Possible mechanisms by which testosterone and SHBG may prevent colorectal cancer are linked to their role in preventing obesity-induced adverse effects^{17–19}, which have been consistently shown to be associated with increased colorectal cancer risk²⁰. Nevertheless, the association of circulating testosterone and SHBG with colorectal cancer was reduced but not eliminated after adjustment for BMI and c-peptide, suggesting an independent role of testosterone and/or SHBG in colorectal cancer development.

In our male population, estrone and estradiol levels were not associated with colorectal cancer risk. However, a higher ratio of estradiol over testosterone, reflecting elevated aromatase activity, was associated with an increased risk for colorectal cancer. The increased production of estradiol from aromatase conversion sends the negative feedback response which prohibits the secretion of gonadotropin proteins such as luteinizing hormone (LH) and subsequent decrease in testosterone secretion.²¹ Thus, our observations suggest that estradiol affects colorectal cancer risk in men through the indirect effects on testosterone levels.

The beneficial role of exogenous estrogen and/or progestin use against colorectal cancer development has been consistently shown among postmenopausal women.^{5, 6, 22, 23}

However, data are limited on the association between endogenous estrogen levels and colorectal cancer in postmenopausal women not taking HT. The WHI observational study (WHI-OS) reported a positive association between estradiol levels and colorectal cancer risk.¹¹ However, our study and the New York Women's Health Study (NYWHS)¹² found no association between circulating estradiol and/or estrone and colorectal cancer risk. It is noted that >60% of the WHI-OS women¹¹ were either overweight or obese, as compared to <40% of women in our study and the NYWHS¹². Alternatively, there may be a threshold for estrogens to exert meaningful effects on colorectal cancer prevention, as HT use in women results in estrogen levels several times higher than the levels in women not taking HT.

We also found no association between SHBG levels and colorectal cancer risk, which is consistent with the NYWHS¹² showing no association between SHBG and colorectal cancer after adjustment for BMI. However, a higher ratio of estradiol to testosterone levels, reflecting higher aromatase activity and thus increased estradiol production, were associated with a lower risk for colorectal cancer in our female population after adjustment for BMI and c-peptide levels. Specifically, the inverse association between the ratio and colorectal cancer risk was primarily seen among women with normal weight, suggesting a potential benefit of aromatase activity, which not only elevates estradiol levels but also controls testosterone secretion, in preventing colorectal cancer in postmenopausal women. In contrast, no beneficial effect of aromatase activity in obese women was evident, perhaps due to close association with adiposity.

Limitations of this study include having only a one-time blood measure, which reduced our ability to evaluate associations between long-term circulating levels of these exposures and risk. However, previous studies of our female and male cohorts have reported the stability of several sex hormone levels over time, with the within-person correlation coefficients ranging in values from 0.55 for estradiol in men to 0.92 for SHBG in postmenopausal women,^{24, 25} suggesting that a single measure captures long term exposure well. In addition, we did not prospectively measure, in all 4 cohorts, waist circumference which may be a better indicator for central obesity. We also had no information on other obesity-associated phenotypes (eg, lipid profile) to additionally control for other obesity-induced effects on colorectal cancer.

In conclusion, this prospective study offers supportive evidence of a role of sex steroid hormones in colorectal cancer development in men, and, perhaps, in postmenopausal women. Validation of our results in other studies will help elucidate the effects attributable to sex steroids on colorectal cancer and refine risk profiles of colorectal cancer development in both men and women. It will also be important to determine the molecular link (eg, cell-cycle gene expression)²⁶ underlying sex hormones and colorectal cancer development.

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Table 1
Baseline characteristics (mean±standard deviation or %) among colorectal cancer cases and controls.*

Characteristics	Men		Women	
	Case	Control	Case	Control
N participants	439	719	293	437
Age, yr	67.2(8.6)	66.7(8.6)	62.7(5.8)	62.2(5.5)
BMI, kg/m ²	26.2(3.4)	25.5(3.0)	26.6(5.5)	25.8(4.9)
Current smoking, %	4.8	4.9	10.5	15.6
Current alcohol consumption, %	67.4	73.1	56.6	55.0
Physically inactive [†] , %	16.3	8.2	22.7	15.8
Family history of colon cancer, %	13.4	12.3	15.9	14.8
History of colon polyps, %	15.9	8.6	2.7	1.6
Sigmoidoscopy exam during the past 2 years, %	29.4	32.1	25.4	28.3
Estrone(pg/mL) [‡]	38(24–57)	37(23–55)	28(12–44)	28(13–44)
Estradiol(pg/mL) [‡]	27(18–39)	27(18–37)	7(3–13)	7(3–12)
Testosterone(ng/dL) [‡]	450(256–684)	489(287–712)	24(10–41)	23(10–39)
Sex-hormone binding protein(nmol/L) [‡]	25(14–37)	27(16–40)	51(18–98)	54(19–93)
Free estradiol(pg/mL) [‡]	0.5(0.3–0.7)	0.5(0.3–0.6)	0.1(0.03–0.2)	0.1(0.03–0.2)
Free testosterone (ng/dL) [‡]	8.3(5.2–11)	8.6(5.5–12)	0.2(0.1–0.5)	0.3(0.1–0.5)
Estradiol (pg/mL)/Testosterone(pg/mL) [‡]	0.007(0.004–0.01)	0.006(0.004–0.009)	0.04(0.01–0.07)	0.03(0.01–0.06)
C-peptide(ng/mL) [‡]	3.1(1.3–5.9)	2.6(1.1–4.9)	2.6(1.1–4.6)	2.4(1.1–4.2)

* Male cohorts include Health Professional Follow-up Study and Physicians' Health Study II; female cohorts include Nurses' Health Study and Women's Health Study.

[†] Lack of regular exercise or with a MET (per week) score of 0.

[‡] Median (10th – 90th range).

Partial correlation among BMI and loge-transformed plasma biomarkers among controls from male (the white area) and female cohorts (the gray area)^{*,†,‡}

Table 2

	BMI	C-peptide	E1	E2	T	SHBG	Free T	Free E2	E2/T
BMI		0.36***	0.27*	0.48***	-0.14	-0.54***	0.21**	0.59**	0.58***
C-peptide	0.39***		0.02	0.17*	-0.15	-0.47***	0.17*	0.31***	0.30***
E1	0.13*	0.06		0.87***	0.41***	-0.01	0.41***	0.77***	0.47***
E2	0.18**	0.03	0.70***		0.40***	-0.23**	0.54***	0.95***	0.60***
T	-0.26***	-0.19***	0.22***	0.47***		0.33***	0.78***	0.25**	-0.50***
SHBG	-0.26***	-0.20***	0.09	0.25***	0.71**		-0.32**	-0.52***	-0.51***
Free T	-0.15**	-0.12**	0.22***	0.46***	0.85***	0.26***		0.59***	-0.17*
Free E2	0.30**	0.11	0.66***	0.91**	0.19***	-0.14**	0.39***		0.68***
E2/T	0.43***	0.22***	0.37***	0.36***	-0.66***	-0.54***	-0.51***	0.57***	

* See Table 1.

† E1=total estrone, E2=total estradiol, T= total testosterone, SHBG=sex hormone binding globulin, E2/T=total estradiol over total testosterone.

‡ * <0.05;

** <0.001;

*** <0.0001.

Table 3
Association of circulating levels of sex hormones and binding protein with colorectal cancer in the male cohorts*.

	Q [‡] /1 (lowest)	2	3	4 (Highest)	P _{trend}
T [‡] (ng/dL)					
N case/control	141/175	114/176	98/177	77/174	
Model 1 [‡]	1.00	0.81 (0.57–1.15)	0.65 (0.45–0.95)	0.56 (0.38–0.82)	0.001
Model 1+BMI+C-peptide [‡]	1.00	0.77 (0.52–1.13)	0.67 (0.45–1.01)	0.62 (0.40–0.96)	0.02
E2 [‡] (pg/mL)					
N case/control	105/112	122/121	84/100	117/102	
Model 1 [‡]	1.00	1.08 (0.73–1.61)	0.87 (0.57–1.32)	1.12 (0.74–1.68)	0.73
Model 1+BMI+C-peptide [‡]	1.00	1.09 (0.70–1.69)	0.86 (0.54–1.37)	1.15 (0.73–1.81)	0.67
E1 [‡] (pg/mL)					
N case/control	110/114	120/117	91/98	115/107	
Model 1 [‡]	1.00	1.23 (0.82–1.83)	0.98 (0.64–1.50)	1.14 (0.76–1.71)	0.70
Model 1+BMI+C-peptide [‡]	1.00	1.16 (0.75–1.79)	1.04 (0.65–1.65)	1.04 (0.68–1.62)	0.96
SHBG [‡] (nmol/L)					
N case/control	147/177	117/176	85/176	87/176	
Model 1 [‡]	1.00	0.73 (0.51–1.03)	0.55 (0.38–0.79)	0.55 (0.38–0.80)	<.001
Model 1+BMI+C-peptide [‡]	1.00	0.78 (0.53–1.14)	0.62 (0.42–0.92)	0.65 (0.42–0.99)	0.02
C-peptide (ng/mL)					
N case/control	67/158	85/156	123/157	120/156	
Model 1 [‡]	1.00	1.21 (0.79–1.85)	1.84 (1.22–2.78)	1.69 (1.09–2.61)	0.01
Model 1+BMI+T [‡]	1.00	1.13 (0.73–1.75)	1.59 (1.03–2.46)	1.29 (0.80–2.08)	0.27
E2 (pg/mL)/T (pg/mL) [‡]					
N case/control	59/107	105/107	109/107	155/107	
Model 1 [‡]	1.00	1.94 (1.23–3.05)	1.85 (1.17–2.87)	2.68 (1.72–4.16)	<.001
Model 1+BMI+C-peptide [‡]	1.00	1.85 (1.15–2.99)	1.87 (1.15–3.04)	2.63 (1.58–4.36)	0.001
T+SHBG+c-peptide [§]					

	Q [‡] 1 (lowest)	2	3	4 (Highest)	P _{trend}
N case/control	67/160	74/148	113/164	132/145	
Model 1 [‡]	1.00	1.15 (0.74–1.77)	1.46 (0.97–2.20)	2.17 (1.44–3.28)	<.001
Model 1+BMI [‡]	1.00	1.14 (0.74–1.78)	1.32 (0.87–2.02)	1.92 (1.24–2.98)	0.003

^{*} See Table 1.

[‡] Q=quartile.

[‡]Model 1 was adjusted for age at blood draw, fasting status, hour at blood draw, smoking, current alcohol intake, family history, physical activity, history of polyps, screening exam; BMI, c-peptide.

[§]It was estimated by summing the quartile coding (1–4, where 4=highest quartile) of c-peptide, T,and SHBG. The coding of both T and SHBG were reversed.

Table 4

Association of circulating levels of sex hormones and binding protein with colorectal cancer in the female cohorts^{*}.

	Q [†] 1 (lowest)	2	3	4 (highest)	P _{trend}
T [‡] (ng/dL)					
N case/control	58/69	86/74	62/65	66/62	
Model 1 [‡]	1.00	1.45 (0.89–2.36)	1.15 (0.67–1.92)	1.41 (0.85–2.36)	0.30
Model 1+BMI+C-peptide [‡]	1.00	1.36 (0.80–2.31)	1.18 (0.68–2.07)	1.43 (0.82–2.50)	0.26
E2 [‡] (pg/mL)					
N case/control	67/71	67/67	57/64	79/65	
Model 1 [‡]	1.00	1.12 (0.69–1.82)	0.97 (0.59–1.59)	1.38 (0.86–2.24)	0.36
Model 1+BMI+C-peptide [‡]	1.00	1.03 (0.60–1.77)	0.88 (0.51–1.53)	1.12 (0.62–2.03)	0.93
E1 [‡] (pg/mL)					
N case/control	70/78	70/60	57/65	73/63	
Model 1 [‡]	1.00	1.40 (0.86–2.28)	0.95 (0.58–1.55)	1.44 (0.89–2.33)	0.31
Model 1+BMI+C-peptide [‡]	1.00	1.28 (0.76–2.17)	0.95 (0.55–1.62)	1.30 (0.74–2.26)	0.55
SHBG [‡] (nmol/L)					
N case/control	79/73	74/64	62/63	55/60	
Model 1 [‡]	1.00	1.04 (0.64–1.69)	0.93 (0.57–1.54)	0.83 (0.50–1.38)	0.43
Model 1+BMI+C-peptide [‡]	1.00	1.21 (0.70–2.07)	1.17 (0.64–2.13)	1.17 (0.63–2.20)	0.68
C-peptide(ng/mL)					
N case/control	54/55	48/54	62/61	82/52	
Model 1 [‡]	1.00	0.92 (0.52–1.60)	1.09 (0.64–1.87)	2.00 (1.14–3.52)	0.02
Model 1+BMI+E2 [‡]	1.00	0.86 (0.49–1.51)	0.98 (0.56–1.73)	1.73 (0.94–3.18)	0.09
E2(pg/mL)/T(pg/mL) [‡]					
N case/control	66/54	55/58	69/54	56/56	
Model 1 [‡]	1.00	0.76 (0.45–1.30)	0.96 (0.57–1.63)	0.84 (0.49–1.44)	0.73
Model 1+BMI+C-peptide [‡]	1.00	0.60 (0.35–1.05)	0.64 (0.36–1.15)	0.43 (0.22–0.84)	0.03

^{*} See Table 1.

[†]See Table 3.

[‡]See Table 3.