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Clinical Study

Adult BMI Change and Risk of Colon Cancer in Postmenopausal Women

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Purpose. We recently reported an association of adult BMI change with colon cancer risk. Here, we sought to further explore this association with respect to postmenopausal HRT use in a larger study population. *Methods*. We included 1,457 postmenopausal women participating in an ongoing population-based case-control study of colon cancer. *Results*. We confirmed a previously reported association of adulthood weight gain and increased risk of colon cancer: compared to those with <5 kg/m^2 change of BMI, women who reported moderate (5–10 kg/m^2) and large (>10 kg/m^2) BMI changes since their 20s had OR estimates of 1.54 (95% CI = 1.09–2.19) and 1.45 (95% CI = 0.90–2.33), respectively (P for trend = 0.05). Stratified analyses showed that this association was limited to HRT nonusers: ORs were 1.77 (95% CI = 1.02–3.05) and 2.21 (95% CI = 1.09–4.45), respectively (P for trend = 0.03), for BMI changes occurring between the 20s decade and time of recruitment among non-users. Similar associations were observed for BMI changes since the 30s decade. There was no association among HRT users. *Conclusion*. Our results suggest early adulthood weight gain increases colon cancer risk in postmenopausal women who do not use HRT.

1. Introduction

Obesity and central adiposity, in particular, are now a well-recognized risk factor for several malignancies including colon cancer in both men and women [1–3]. Body mass index (BMI) is commonly used to assess obesity (BMI ≥ 30 kg/m^2), and a large number of epidemiological studies support a BMI-colon cancer risk association. This association is generally stronger for men than that for women [4–6], possibly due to sex differences in fat distribution and/or hormonal milieus. Possible putative pathophysiologic mechanisms for the positive association of obesity with colon cancer include higher levels of circulating peptide hormones such as insulin and insulin-like growth factor-1 (IGF-1), adipose and gut hormones, inflammatory cytokines, free radicals, fatty acid metabolites, and sex steroid hormones in the obese [7, 8].

Both animal and human studies have demonstrated modulatory effects of reproductive hormones on tumor cell growth and proliferation [9–12] and estrogen, either endogenously produced in premenopausal females or administered exogenously in the form of hormone replacement therapy (HRT), has been consistently shown to exert a protective effect against colorectal cancer in women [4, 13, 14]. A number of epidemiological studies have shown that the obesity-colon cancer risk association is stronger in pre-menopausal women as compared to postmenopausal women [1, 15, 16], suggesting an interactive effect of obesity and estrogen in the development of colon cancer.

We have previously demonstrated increased colon cancer risk for men and women with BMIs over ≥30 kg/m^2 at time of recruitment as well as for large BMI changes (≥10 kg/m^2) during the 30s or 20s decades in women [17]. These results

further strengthened the evidence for the role of obesity in increasing colon cancer risk, and suggest that adulthood BMI changes may be a sensible measure of obesity-related colon cancer risk in women. However, no studies have examined how *changes* in BMI over time might be affected by HRT use among postmenopausal women in colon cancer development. Therefore, we evaluated potential associations between BMI and changes in adult BMI over time (since 20s, 30s, 40s, 50s, and 2 years before study recruitment ("current")) and colon cancer risk in 1,457 postmenopausal women participating in a population-based case-control study. We hypothesize that HRT use may offset the risk effect of adult weight gain to the extent that the risk associated with large adult BMI change and colon cancer will be diminished in postmenopausal women taking HRT, as compared to those not taking HRT.

2. Methods and Procedures

2.1. Study Population. The Kentucky colon cancer genetic epidemiology study has been described previously [17]. The present analysis is based on patients recruited through May 2011. Briefly, patients with newly diagnosed colon cancer (rectal cancer excluded) were identified from the Kentucky Cancer Registry, a participant in the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) Program as well as the Centers for Disease Control and Prevention's National Program of Cancer Registries. The registry database was reviewed quarterly and all primary incident colon cancer cases were identified and invited to participate in the study via mailed letter. They were then called approximately 3 weeks later and interviewed to determine eligibility. We excluded patients with known history of inflammatory bowel disease (IBD), family history of familial adenomatous polyposis (FAP), and hereditary nonpolyposis colorectal cancer (HNPCC).

Population controls were recruited via random digit dialing throughout the state of Kentucky. Area codes and exchanges of cases were utilized with random digit generation of the remaining four digits. Among those reached, telephone screening was employed to determine eligibility. The controls were at least 40 years of age and could not have had any personal history of nonskin cancer. Additional exclusion criteria included history of IBD, FAP, and HNPCC. Of those who answered the phone and allowed eligibility determination, 70.8% of cases and 66.7% of controls agreed to participate in the study. The Institutional Review Boards of the University of Kentucky, Lexington and University Hospitals Case Medical Center approved the study and all participants provided written informed consent. For this analysis, we included postmenopausal women only (516 cases, and 941 controls), excluding 190 women who were premenopausal at the time of recruitment and all 1,125 male participants from the dataset.

2.2. Data Collection. Eligible cases and controls were sent a lifestyle risk factor questionnaire developed by the National Cancer Institute Colon Cancer Familial Cancer Registry https://bioinformatics.dartmouth.edu/ccfrc/Downloads/RFQ.pdf. This survey includes questions on height and weight throughout the 20s, 30s, 40s, since the age of 50, and 2 years prior to diagnosis for cases and the previous 2 years for controls ("current"). BMI categories were calculated based on World Health Organization definition as follows: normal (BMI $\geq$ 18.5 to $<25\,kg/m^2$); overweight (BMI $\geq$ 25 to $<30\,kg/m^2$); obese BMI $\geq$ 30) [18]. Changes in BMI were categorized as "Small" $<5\,kg/m^2$ (weight gain of approximately <25 lbs); "Moderate" 5–10 kg/m^2 (approximate weight gain of 25–50 lbs), and "Large" $>10\,kg/m^2$ (weight gain exceeding 50 lbs).

Menopausal status was defined as cessation of menses for 12 months or longer prior to the recruitment. Bleeding resulting from HRT, progestin, or withdrawal from such, was not considered menstrual bleeding. Seven women who temporarily stopped menstruating or who ceased bleeding due to hysterectomy (without concomitant oophorectomy), radiation, and/or chemotherapy were excluded from the analysis.

Family history of colorectal cancer was defined as any history in a first degree relative of colorectal cancer. Smoking was classified as "ever" versus "never" based on cigarette smoking of at least one cigarette per day for 3 months or longer. Alcohol use was based on patient response ("yes" versus "no") to history of consumption of any alcoholic beverage at least once a week for 6 months or longer. Nonsteroidal anti-inflammatory drug (NSAID) use was defined as use of medications, such as aspirin or ibuprofen (brand or generic) at least twice weekly for 6 months or more. Physical activity (PA) was assessed using intensity because information on frequency and duration across the decades was not sufficiently available. We assigned metabolic equivalent values (metabolic activity of task or METs) to the activity and categorized intensity into Light (1 to <3 METs), moderate (3×6 METs), or vigorous (>6 METs) [19, 20].

2.3. Statistical Analysis. We first examined all variables of interest univariately for association with colon cancer risk in our sample. Continuous variables were evaluated using a standard student's t-test; categorical variables were evaluated using a chi-square test.

We then used unconditional logistic regression modeling to evaluate the potential associations between overweight and obesity compared to normal body size and colon cancer risk in each decade (20s, 30s, 40s, 50s, and current). All analyses were adjusted for potential confounding by other known colon cancer risk factors including age, race, education, income, physical activity, family history of colon cancer, smoking, alcohol, nonsteroidal anti-inflammatory drug use, age at menarche, and parity.

Changes in BMI over time were calculated for each individual for different age decades through the time of recruitment. These were categorized into "Small, Moderate, and Large" changes as described in the data collection section. Those with "Small" BMI changes were used as the referent group. In logistic regressions, we adjusted for all variables included in the logistic regression models for BMI, and additionally adjusted for current BMI. These logistic

regressions were then stratified by HRT use to evaluate differential association of BMI changes by HRT use. We examined the interaction of HRT use and weight change by adding into the full regression model a cross-product term of HRT and weight change during various age decades. Significance testing was based on likelihood ratio tests with one degree of freedom.

All P values are from two-sided tests and P values < 0.05 were considered statistically significant. All analyses were undertaken using SAS (Version 8.2, SAS Institute, Cary, NC, USA).

3. Results

Characteristics of the participants included in the present analysis are summarized in Table 1. Mean age for the cases (63.8 years) was similar to controls (63.4 years) ($P = 0.38$). There were significant differences with respect to education and income, with controls tending toward both higher educational attainment and higher incomes (Table 1). Controls were also significantly more likely to drink alcohol and to smoke than were cases. Cases, however, were more likely to have a family history of colorectal cancer ($P = 0.004$) and less likely to use NSAIDs than controls ($P = 0.003$). Use of HRT was significantly lower in cases ($P < 0.001$). The two groups did not differ significantly with respect to race or physical activity levels during the 20s, 30s, or 50s decades ($P > 0.05$).

Table 2 summarizes the results of the logistic regression models to evaluate the association of BMI at different ages on colon cancer risk. In the overall sample, there were no statistically significant associations for BMI reported at different age decades or up to 2 years prior to recruitment. Stratified analyses by HRT use only revealed a statistically significant increase of risk of colon cancer in obese postmenopausal women who used HRT (OR = 1.74; 95% CI = 1.08–2.80). Table 3 summarizes the association of changes in BMI over age decades and colon cancer risk with and without stratification by HRT use. Among all women, weight gain or BMI changes taking place during the 20s and 30s decades moderately, but statistically significantly, increased risk for colon cancer (P for trend = 0.05 and = 0.02, resp.). Stratified analyses revealed that the increase of risk for weight gain or BMI changes taking place during both age decades was limited to postmenopausal women not using HRT, with a greater than 2 fold increase of colon cancer risk for large BMI change ($>10\,kg/m^2$) in the 20s age decade (OR = 2.21; 95% CI = 1.09–4.45; P for trend = 0.02). There was no evidence for statistically significant association among postmenopausal women reporting HRT use. HRT use itself was statistically significantly associated with a decreased risk of colon cancer in both univariate and fully adjusted analyses (data not shown).

4. Discussion

We have previously shown that large adult weight gain or BMI changes taking place in the 20s or 30s age decade significantly increased the risk of colon cancer independent of current BMI (within 2 years prior to recruitment), particularly among women [17]. Our previous report was based on 438 cases (212 women) and 491 controls (380 women). In the current study, based on a much larger sample size of postmenopausal women (516 cases and 941 controls), we confirmed our previous results. Taken together, these results suggest that weight gain occurring since early adulthood may be a rational indicator of visceral adiposity accumulation and an important phenotypic marker for assessing obesity-related colon cancer risk in women.

BMI is commonly used in epidemiological studies to assess degree of obesity, and the BMI-colon cancer association has consistently been found to be stronger in men than in women [1, 21–24]. In the current study, we found that overall there is no colon cancer risk association for BMI reported for most of the age decades or 2 years prior to recruitment. The statistically significant association for obesity ($BMI \geq 30\,kg/m^2$) reported for the 50s age decade among HRT users is somewhat unexpected. Given that there is no consistent pattern of risk increase (OR = 0.95 for overweight ($BMI \geq 25$ to $< 30\,kg/m^2$)) in this nor in any other age decade, we believe this is likely due to chance.

It is speculated that central adiposity is the major driver for increased circulating levels of insulin, IGFs, and inflammatory cytokines, as well as decreased levels of IGF binding proteins—all of which have been implicated as tumor-promoting [8, 25–29]. As a result, some have advocated that alternative methods for body size characterization such as waist-hip ratio (WHR) and waist circumference may more accurately reflect abdominal obesity [30]. Other studies have failed to demonstrate any increased association of WHR or waist circumference, as compared to BMI, with colorectal cancer in women [31] thereby arguing against body fat distribution as the sole determinant of gender-based differences in CRC risk.

Consistent with our hypothesis of opposing effects of adult weight gain and HRT use, we have found that the increased risk of colon cancer associated with weight gain since early adulthood was largely limited to postmenopausal women reporting no prior use of HRT. Although testing for multiplicative interaction between BMI change and HRT use was not statistically significant, this was likely due to limited power in our study. HRT non-users with "Large" BMI changes during their 20s were more than twice as likely to develop colon cancer. Similarly, this same group of women had a 77% increased risk of colon cancer if they experienced even "Moderate" changes in BMI beginning in their 20s. Likewise, both "Moderate" and "Large" BMI change between the 30s decade and recruitment was associated with a higher risk of colon cancer, though this association was only statistically significant for those reporting "Moderate" changes (P for trend 0.05). Smaller numbers in the "Large" BMI change category for this age decade may have resulted in the nonsignificant finding.

These findings confirm earlier studies showing that HRT use may modify the effects of obesity in postmenopausal women [16] possibly by counteracting the known risks of weight gain during the early premenopausal years [2]. Modification of weight gain-associated CRC risk by use of

Table 1: Characteristics of the Kentucky colon cancer genetic epidemiology study postmenopausal females.

Characteristic		Cases ($N = 516$)	Controls ($N = 941$)	P value[a]
Age (years)		63.8 (8.9)[b]	63.4 (9.4)[b]	0.38
Race				
Caucasian		483 (93.6%)	878 (93.3%)	0.43
African American		24 (4.7%)	54 (5.7%)	—
Other		8 (1.6%)	7 (0.7%)	—
Unknown		1 (0.2%)	2 (0.2%)	
Education				
<8 years		16 (3.1%)	8 (0.9%)	<0.001
8–11 years		62 (12.0%)	78 (8.3%)	—
High school (HS) diploma		165 (32.0%)	260 (27.6%)	—
Some post-HS training		165 (32.0%)	318 (33.8%)	—
Bachelor's degree		43 (8.3%)	114 (12.1%)	—
Graduate degree		65 (12.6%)	163 (17.3%)	—
Income				
<$15,000		89 (17.2%)	118 (12.5%)	<0.001
$15,000–$29,000		122 (23.6%)	174 (18.5%)	—
$30,000–$44,000		93 (18.0%)	182 (19.3%)	—
$45,000–$69,000		96 (18.6%)	164 (17.4%)	—
≥$70,000		83 (16.1%)	229 (24.3%)	—
Refused		33 (6.4%)	74 (7.8%)	—
Cigarette smoker				
Ever		244 (47.2%)	460 (48.9%)	0.04
Never		262 (50.8%)	476 (50.6%)	
Unknown		10 (1.9%)	5 (0.5%)	
Alcohol drinker				
Yes		147 (28.5%)	353 (37.5%)	<0.001
No		354 (68.6%)	550 (58.4%)	
Unknown		15 (2.9%)	38 (4.0%)	
Family history of colorectal cancer				
Yes		192 (37.2%)	276 (29.3%)	0.004
No		295 (57.2%)	588 (62.5%)	
Unknown		29 (5.6%)	77 (8.2%)	
NSAIDs use				
Yes		189 (36.6%)	420 (44.6%)	0.003
No		327 (63.4%)	521 (55.4%)	
HRT				
Yes		222 (43.0%)	573 (60.9%)	<0.001
No		290 (56.2%)	356 (37.8%)	
Unknown		4 (0.8%)	12 (1.3%)	
Physical activity				
20s	Light intensity[c]	76 (14.7%)	133 (14.1%)	0.80
	Moderate intensity[c]	391 (75.8%)	709 (75.3%)	—
	Vigorous intensity[c]	49 (9.5%)	99 (10.5%)	—
30s	Light intensity[c]	72 (14.0%)	120 (12.8%)	0.20
	Moderate intensity[c]	411 (79.7%)	737 (78.3%)	—
	Vigorous intensity[c]	33 (6.4%)	84 (8.9%)	—
50s	Light intensity[c]	96 (18.6%)	208 (22.1%)	0.19
	Moderate intensity[c]	398 (77.1%)	685 (72.8%)	—
	Vigorous intensity[c]	22 (4.3%)	48 (5.1%)	—

[a]P value for t-test or χ^2-test with k (number of groups)—1 degrees of freedom. [b]Mean and SD of the mean in parentheses. [c]Light intensity: 1 to <3.0 metabolic equivalents (METs); moderate intensity: ≥3.0 to ≤6.0 METs; vigorous intensity: >6.0 METs.

exogenous HRT may be partly explained by the opposing effects of HRT and adiposity on circulating levels of insulin and IGF-1, and endogenous sex hormones such as estrogen. Higher levels of insulin and bioactive IGF-1 are both established risk factors for colon cancer and are believed to at least partially account for the obesity-associated increased risk of colon cancer [32]. HRT use decreases hepatic synthesis of insulin-IGF-1 axis factors [33, 34], thus offsetting the insulin-IGF-1 mediated colon carcinogenic effect of adiposity. HRT use also increases the synthesis of sex hormone binding globulin, leading to reduced circulating levels of bioavailable endogenous estrogen [35]. In postmenopausal women, adipose tissue is the main source of endogenous estrogen production. Accumulating evidence suggests that in contrast to the well established protective effects of HRT use against colon carcinogenesis, increased lifetime exposure to and high circulating levels of endogenous estrogen promote the development of colon cancer [32, 36–38]. It is thus plausible that HRT use may offset obesity-associated risk of colon cancer by reducing the circulating levels of bioavailable endogenous estrogen in postmenopausal women.

Study limitations include the possibility for information bias from our case-control study design as well as potential recall bias inherent in the use of self-reported height and weight to calculate BMI. However, correlations between self-reported and actual measured weight are generally quite high [39, 40]. Additionally, in elderly patients, accurate recall of self-reported weight has been demonstrated for as long as 28 years prior [41]. The modest participation of controls recruited through random digit dialing was another study limitation. Random digit dialing, although still prone to selection bias, because of preference toward individuals with landlines, was the most feasible method through which recruitment of a sample most representative of our case source population (State of Kentucky) could be achieved. All analyses were adjusted, however, for well established risk factors including education and income using very finely defined categories.

In summary, our results confirm earlier findings of the protective role of HRT in CRC and suggest that, in postmenopausal women, HRT may ameliorate the negative effects of early pre-menopausal weight gain to some extent. This finding is of paramount clinical importance, especially

Table 2: Odds ratios (ORs) of colon cancer for BMI by age, decades[a].

		All postmenopausal women				Postmenopausal women with no HRT				Postmenopausal women with HRT			
		Case/control	OR	*P*	*P**	Case/control	OR	*P*	*P**	Case/control	OR	*P*	*P**
	Normal[c] (ref)	147/315	1.00	—		72/105	1.00	—		75/210	1.00	—	
BMI 2 yrs[b]	Overweight	159/302	0.98 (0.73–1.32)	0.88		87/117	0.95 (0.60–1.49)	0.82		72/185	1.01 (0.67–1.52)	0.96	
	Obese	188/279	1.25 (0.92–1.69)	0.16	0.19	120/123	1.39 (0.89–2.17)	0.15	0.11	68/156	1.21 (0.78–1.87)	0.39	0.57
	Normal (ref)	192/410	1.00	—		101/145	1.00	—		91/265	1.00	—	
BMI 50s	Overweight	125/242	0.96 (0.74–1.32)	0.77		73/91	1.06 (0.68–1.65)	0.79		52/151	0.95 (0.58–1.40)	0.66	
	Obese	126/163	1.27 (0.97–1.92)	0.07	0.19	70/79	1.18 (0.72–1.93)	0.50	0.64	56/84	1.74 (1.08–2.80)	0.02	0.08
	Normal (ref)	250/529	1.00	—		127/192	1.00	—		123/337	1.00	—	
BMI 40s	Overweight	101/176	1.07 (0.78–1.47)	0.66		57/64	1.29 (0.80–2.07)	0.30		44/112	1.01 (0.65–1.59)	0.93	
	Obese	71/114	1.25 (0.85–1.82)	0.26	0.43	43/59	1.18 (0.69–2.00)	0.54	0.81	28/55	1.45 (0.82–2.57)	0.20	0.25
	Normal (ref)	306/629	1.00	—		159/227	1.00	—		147/402	1.00	—	
BMI 30s	Overweight	66/115	1.06 (0.74–1.52)	0.76		37/52	1.02 (0.60–1.72)	0.95		29/63	1.11 (0.65–1.87)	0.71	
	Obese	42/56	1.42 (0.90–2.27)	0.13	0.90	27/27	1.50 (0.80–2.83)	0.21	0.47	15/29	1.38 (0.68–2.83)	0.38	0.76
	Normal (ref)	333/650	1.00	—		178/250	1.00	—		153/400	1.00	—	
BMI 20s	Overweight	48/74	1.15 (0.76–1.75)	0.50		29/30	1.32 (0.73–2.40)	0.35		19/44	1.10 (0.60–2.02)	0.77	
	Obese	18/36	0.87 (0.47–1.63)	0.67	0.50	13/20	0.85 (0.38–1.87)	0.68	0.20	5/16	0.91 (0.31–2.65)	0.86	0.93

[a]Adjusted for age, race, gender, education, income, physical activity, smoking, alcohol, nonsteroidal anti-inflammatory drugs use, family history of colorectal cancer, age at menarche, and parity. [b]2 years before recruitment/interview. [c]Normal: ≥18.5 to <25 kg/m^2; overweight: ≥25 to <30 kg/m^2; obese: ≥30 kg/m^2. **P* value for trend.

Table 3: Odds ratios (ORs) of colon cancer for changes in BMI over time by age, decades[a].

		All postmenopausal women				Postmenopausal women with no HRT				Postmenopausal women with HRT			
	kg/m^2	Case/control	OR	P	P*	Case/control	OR	P	P*	Case/control	OR	P	P*
	<5 (ref)[c]	366/691	1.00	—	—	189/259	1.00	—	—	177/432	1.00	—	—
Change in BMI in 50s	5–10	57/91	0.92 (0.61–1.40)	0.71	—	42/42	1.15 (0.66–1.99)	0.62	—	15/49	0.67 (0.17–2.65)	0.42	—
	>10	12/23	0.62 (0.27–1.43)	0.26	0.47	9/11	0.72 (0.24–2.16)	0.56	0.90	3/12	1.02 (0.66–1.58)	0.57	0.47
	<5 (ref)	286/587	1.00	—	—	142/208	1.00	—	—	144/379	1.00	—	—
Change in BMI in 40s	5–10	105/192	0.90 (0.64–1.26)	0.55	—	63/85	0.86 (0.53–1.40)	0.54	—	42/107	0.93 (0.56–1.52)	0.76	—
	>10	35/51	0.98 (0.57–1.69)	0.95	0.88	23/28	0.82 (0.39–1.70)	0.59	0.59	12/23	1.24 (0.54–2.86)	0.62	0.65
	<5 (ref)	197/473	1.00	—	—	94/171	1.00	—	—	103/302	1.00	—	—
Change in BMI in 30s	5–10	158/256	1.48 (1.06–2.07)	0.02	—	94/98	1.91 (1.16–3.17)	0.01	—	64/158	1.22 (0.76–1.95)	0.41	—
	>10	72/109	1.51 (0.94–2.43)	0.09	0.02	44/50	1.79 (0.90–3.55)	0.10	0.0498	28/59	1.57 (0.79–3.12)	0.20	0.10
	<5 (ref)	152/368	1.00	—	—	77/138	1.00	—	—	75/230	1.00	—	—
Change in BMI in 20s	5–10	182/313	1.54 (1.09–2.19)	0.02	—	91/110	1.77 (1.02–3.05)	0.04	—	91/203	1.41 (0.88–2.27)	0.16	—
	>10	122/185	1.45 (0.90–2.33)	0.12	0.049	83/81	2.21 (1.09–4.45)	0.03	0.02	39/104	1.11 (0.56–2.19)	0.76	0.38

[a]Adjusted for age, race, gender, education, income, physical activity, smoking, alcohol, nonsteroidal anti-inflammatory drugs use, family history of colorectal cancer, age at menarche, and parity. Analysis additionally adjusted for baseline BMI (BMI in the "recruitment period," 2 years before recruitment). [c]<5 kg/m^2 (weight gain of approximately <25 lbs); 5–10 kg/m^2 (weight gain of ~25–50 lbs) and >10 kg/m^2 (weight gain exceeding 50 lbs). *P value for trend.

in light of the fact that the use of hormone replacement has declined significantly since the Women's Health Initiative study findings were published in 2002 [42, 43]. Further study is warranted to evaluate why earlier versus later weight gain is so strongly associated with increased CRC risk. Furthermore, a deeper understanding of the exact biological mechanisms via which HRT may modify CRC risk due to obesity throughout adult life is necessary. Prospective studies in both pre- and postmenopausal women of various body sizes, and with varying types of fat distribution patterns, employing serum biomarkers such as insulin, IGF-1, estrogen, and how they change over time will be most instructive.

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