HHS Public Access

Author manuscript

Cancer Epidemiol. Author manuscript; available in PMC 2016 August 01.

Published in final edited form as:

Cancer Epidemiol. 2015 August ; 39(4): 567–570. doi:10.1016/j.canep.2015.05.003.

Prospective Study of Body Fat Distribution and the Risk of Endometrial Cancer

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Abstract

Background—Epidemiologic studies have found that overall obesity is positively related to endometrial cancer (EC) risk. However, data assessing the association between body fat distribution and risk of EC are still limited.

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Contribution of authours: Woong Ju and Eunyoung Cho were responsible for the initial plan, study design, conducting the study. Hyunja Kim was responsible for statistical analysis. Woong Ju, Hyunja Kim, Eunyoung Cho were responsible for data collection, and data extraction, and data interpretation. Susan E Hankinson Sc.D.4),5),6), Immaculata De Vivo were responsible for data collection and data interpretation. Woong Ju was responsible for manuscript drafting. Eunyoung Cho is the guarantor for this paper and has full responsibility for this study.

Competing interest statement

All authors have no support from any organization for the submitted work; no financial relationships with any organizations that might have an interest in the submitted work, no other relationships or activities that could appear to have influenced the submitted work.

Data sharing: No additional data available.

Methods—We followed 51,948 women who first reported waist circumference (WC) and hip circumference in 1986 in the Nurses' Health Study. Waist-to-hip ratio (WHR) was calculated.

Results—During 24 years of follow-up, 449 incident invasive EC cases were diagnosed. In a multivariate analysis without adjusting for body mass index (BMI), the relative risks (RRs) for EC comparing extreme categories were 2.44 (95% confidence interval [CI] 1.72-3.45) for WC and 1.69 (1.20-2.40) for WHR. However, after adjustment of BMI, those positive associations were substantially attenuated and no longer significant; RR= 1.08 (0.69-1.67) for WC and 1.15 (0.81-1.64) for WHR, respectively.

Conclusion—In our prospective cohort study, we found no independent association between body fat distribution and the risk of EC after adjustment for BMI.

Keywords

Body fat distribution; Endometrial Cancer; Prospective Cohort Study

1. Introduction

Endometrial cancer (EC) was the fourth most common cancer in US women in 2013 [1]. Risk factors for EC include obesity, postmenopausal hormone replacement therapy, type II diabetes, tamoxifen use, and conditions related to unopposed estrogen such as chronic anovulation [2-4]. Among these factors, excessive body-mass index (BMI) has been well-established as a risk factor, and is present in about 50% of women with endometrial cancer [5]. According to an expert review panel organized by the World Cancer Research Fund (WCRF) and the American Institute for Cancer Research (AICR) [6], almost all cohort studies and case-control studies have found increased risk of EC with higher overall body fatness (as measured by BMI), which prompted the panel to judge obesity as a convincing risk factor of EC.

Body fatness may promote endometrial carcinogenesis by increasing hormones and growth factors [7], altering sex hormone binding globulin [8], and several pro-inflammatory cytokines [9, 10]. Abdominal fat is hypothesized to be biologically different from other fat in the body in characteristics favoring cell proliferation or vascularization [11, 12]. However, there has been limited evidence whether abdominal fatness is associated with EC independent of whole body fatness [13-16]. Several previous studies on abdominal fatness and EC risk have found inconsistent results [17-19]. The WCRF/AICR review panel judged abdominal fatness as a 'probable' risk factor for EC.[6]

Therefore, the purpose of this study was to prospectively investigate whether body fat distribution is associated with the risk of EC, independent of overall fatness.

2. Methods

2.1 Study population

The Nurses' Health Study cohort was established in 1976 and continues to be followed up by biennial questionnaires to update information on lifestyle factors and to identify cases of newly diagnosed diseases including cancers. This study was restricted to 51,948 women

who reported waist circumference (WC) and hip circumference (HC) in the 1986 questionnaire and also were free of prior history of cancer (except non-melanoma skin cancer), and hysterectomy.

2.2 Assessment of body fat distribution

In the 1986 questionnaire, participants were instructed to measure and report their WC (at the umbilicus) and HC (the largest circumference) to the nearest quarter-inch. WHR (waist-to-hip ratio) was calculated based on WC and HC reported at 1986, which were updated in 1996 and 2000. These measurements were validated by technicians who visited participants in their homes in a sample of 140 nurses. The correlations between self-reported measure and the average of two technician-measured values were 0.89 for WC and 0.84 for HC respectively [20].

2.3 Ascertainment of covariates

On the baseline questionnaire in 1976, participants were asked for information about age, weight and height, menopausal status, oral contraceptive use, parity, age at first birth, age at menarche, age at menopause, and smoking status. Information on type of postmenopausal hormone use (i.e., estrogen alone or estrogen with progesterone) was obtained from 1978. Information on duration of oral contraceptive use was asked on each questionnaire through 1984, while other covariate data (except height) have been updated on all subsequent biennial questionnaires. In this analysis, we used the updated data as time varying covariates. If the updated covariate data were not available for any cycle, those women were assigned to a missing category for that period. Weight from the previous questionnaire cycle was carried forward if missing. If weight was not reported for two consecutive time periods, women were excluded from follow-up until an updated weight was reported. Participants were classified to postmenopausal women from the time women returned a questionnaire reporting natural menopause. Pack-years of smoking were calculated by multiplying the duration and dose of smoking; one pack-year is equivalent to having smoked one pack/day for one year. BMI (kg/m^2) was calculated using the reported height and weight.

2.4 End points

Participants have been asked on each biennial questionnaire whether they had been diagnosed with EC during the previous two years. For a woman who reported a diagnosis of EC, the relevant medical records and pathology reports were reviewed by study physicians blinded to questionnaire information. Cases confirmed as invasive endometrial adenocarcinoma were included in this study because other histologic types such as endometrial carcinosarcoma or mixed Müllerian tumor are not only rare but also very heterogeneous in composition.

2.5 Statistical analysis

Women were grouped into five categories of WC, HC, or WHR using pre-specified cutoffs. Participants contributed person-time from the date of return of the 1986 questionnaire to the date of diagnosis of EC, the date of death, the date of report of other cancer except non

melanoma skin cancer, hysterectomy (with or without oophorectomy), or the end of follow-up (June 1, 2010) whichever occurred first.

Relative risk (RR) was calculated as the incidence rate for a given category of the measurements compared with the lowest category. Cox proportional hazard regression models were used to estimate RR and 95% confidence intervals (CI) of EC. To control as finely as possible for confounding by age, calendar time, and any possible two-way interactions between these two time scales, we stratified the analysis jointly by age in months at start of follow-up and calendar year of the current questionnaire cycle. In multivariate analysis, we also adjusted for the following covariates: smoking pack-years, age at menarche, duration of oral contraceptive use, menopausal status, postmenopausal hormone use, parity, and BMI, age at last birth. To calculate the *P* value for the test for trend, participants were assigned the median value of category of WC, HC, WHR, and this variable was used as a continuous variable in the study-specific regression models. All statistical analyses were conducted with SAS version 9.1 (SAS Institute Inc, Cary, NC). $P<0.05$ were considered significant.

Results

During 24 years of follow-up of 51,948 women (671,781 person-years), we identified a total of 449 cases of endometrial cancers. Table 1 presents the distribution of risk factors for EC by categories of WC, HC and WHR in 1986. Age of menarche, smoking, oral contraceptive use, menopause status, and postmenopausal hormone use were not different across the categories of WC, HC and WHR. In addition the types of postmenopausal hormone replacement were similar across the categories. On the other hand age, BMI, and parity increased with higher WC, HC, or WHR.

In the age-adjusted model, higher categories of WC were associated with an increased risk of EC (P_{trend} <0.001); the association became slightly stronger after adjusting for confounding variables except BMI, with RR of 2.44 (95% CI=1.72-3.45) for the fifth category of WC compared with the first category (Table 2). However, the association became substantially attenuated and non-significant when BMI was additionally adjusted for; the RR for the extreme category was attenuated to 1.08 (95% CI = 0.69-1.67; P_{trend} =0.23).

Similar patterns of associations were observed between HC and WHR and the incidence of EC; the strong positive association in age-adjusted and multivariate analysis (not adjusting for BMI) was substantially attenuated and no longer significant when BMI was additionally adjusted for. The fully adjusted RRs for extreme categories were 1.06 (95% CI = 0.66-1.69; P_{trend} =0.78) for HC and 1.15 (95% CI = 0.81-1.64; P_{trend} =0.37) for WHR.

We also conducted a stratified analysis of these measures of body fat distribution by BMI (<25, 25−<30, 30+ kg/m^2). There was no significant association between these measures and EC across the BMI categories. For example, the multivariate RRs for extreme categories of WHR were 0.85 (95% CI 0.59-1.24) in BMI <25 kg/m^2, 1.21 (95% CI 0.78-1.89) in BMI 25−<30 kg/m^2, and 1.29 (95% CI 0.74-2.26) in BMI 30+ kg/m^2.

Discussion

In this large prospective cohort study, we found that abdominal fatness assessed by WC, HC, and WHR did not have a significant association with the risk of EC after adjustment for BMI.

Our findings are in accordance with some of the previous epidemiologic studies which found a similar attenuation of association between abdominal fatness and EC risk after adjusting for BMI [14, 16, 17]. However, other case-control studies [13-15] and two cohort studies [18][19] found a positive association between abdominal fatness and EC risk, even after adjusting for BMI. Case-control studies measured body size of subjects at the time of interview just after enrollment of participants, while cohort studies, including this study, ascertained anthropometry data at the baseline of cohort follow-up. Anthropometry which was performed after diagnosis rather than prior to diagnosis cannot rule out an effect of reverse causation on the relation between abdominal adiposity and EC. Although body size may not change acutely over weeks or months, the difference in reference year of exposure might contribute to the inconsistent findings between several case-control studies and cohort studies including ours.

Body fatness is known to promote endometrial carcinogenesis by increasing estrogens and growth factors [7], altering sex hormone binding globulin levels [8], and increasing insulin and several pro-inflammatory cytokine levels [9, 10]. Abdominal fat is hypothesized to be biologically different from other fat in the body with characteristics favoring cell proliferation or vascularization [11, 12]. The biologic effect of adipose tissue may vary depending on its location in terms of functional activity to store and release fatty acids and to synthesize and secrete adipokines [21], which subsequently can discriminate the carcinogenic potential of fat tissue. Another hypothesis suggesting the role of abdominal fatness in carcinogenesis is that the abdominal adiposity is mainly composed of white adipose tissue with little brown adipose tissue. White adipose tissue is responsible for increased insulin resistance, and inflammatory cytokines whereas brown adipose tissue is not [22].

Our study had several strengths. First, self-reported data on anthropometry were validated, with high correlations between self-reported and technician assessed measurements [20]. Second, anthropometric information was collected multiple times during follow-up and updated in the statistical analysis, reducing the potential for misclassification of anthropometric measures. Third, since all the participants of the cohort were medical professionals who were fully aware of the importance of body size measurement as well as life style exposures in a medical field, technical errors in ascertainment of exposure might be less than other studies composed with lay people.

The current study also has limitations. We did not differentiate the pathology of endometrial cancer. It has been known that endometrioid histology is more strongly linked with estrogen stimulation and obesity than other subtypes such as papillary serous type or clear cell type. However, the main result would not likely to change even if we performed a subgroup

analysis based on its histology because the incidence of non-endometrioid endometrial cancer is far lower than that of endometrioid type.

In summary this prospective cohort study found no independent association between body fat distribution and the risk of EC after adjusting for BMI.

Acknowledgments

Funding info: This study was supported by research grant CA87969 from the National Institutes of Health.

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Measures of body fat distribution were prospectively evaluated in relation to endometrial cancer risk in women.

Higher body fat distribution was associated with endometrial cancer risk without adjusting for body mass index.

No association was found between body fat distribution and endometrial cancer after adjustment for body mass index.

Table 1

Age-standardized Characteristics According to Measures of Baseline Body Fat Distribution* in 1986 in the Nurses' Health Study

	WC Categories (in)			HC Categories (in)			WHR Categories		
Category cutoff	≤27	30–32	≥38	≤36	39-40	≥45	≤0.73	0.77–<0.81	≥0.88
Number of subjects	7612	9101	2667	6890	7542	3050	8298	7312	2431
Age, yr	50.3 (7.0)	53.4 (7.1)	54.5 (7.0)	51.6 (7.4)	52.9 (7.3)	53.4 (7.0)	50.4 (7.0)	53.2 (7.1)	55.2 (7.1)
BMI, kg/m^2	20.9 (1.9)	24.4 (2.6)	33.5 (5.2)	21.0 (2.2)	24.1 (2.4)	33.2 (4.9)	22.7 (3.3)	24.9 (4.4)	28.3 (5.3)
Smoking									
Never, %	43	44	44	39	45	47	48	43	40
Past, %	33	35	38	31	36	38	34	34	34
Current, %	24	21	18	30	19	15	18	23	25
Pack years	12.0 (17.2)	12.4 (17.9)	13.9 (19.7)	14.8 (19.2)	11.7 (17.2)	11.7 (17.6)	9.7 (15.2)	12.9 (18.0)	15.9 (20.6)
Age at menarche, yr	12.7 (1.4)	12.6 (1.4)	12.3 (1.5)	12.7 (1.5)	12.6 (1.4)	12.3 (1.4)	12.6 (1.4)	12.6 (1.4)	12.5 (1.5)
Parity (no. of children)	2.7 (1.5)	3.0 (1.6)	3.1 (1.7)	2.8 (1.6)	3.0 (1.6)	3.1 (1.7)	2.8 (1.5)	3.0 (1.6)	3.1 (1.7)
Oral contraceptive use, %	49	47	43	48	48	44	49	47	45
Postmenopausal, %	55	55	57	56	55	56	55	56	56
Postmenopausal hormone use, % (among postmenopausal women only)									
No use	57	64	76	62	64	76	60	65	73
Oral conjugated estrogen	15	12	8	14	12	8	14	12	9
Oral estrogen & progesterone	11	9	4	9	9	4	10	8	4
Others	17	15	12	16	15	11	16	15	14

*WC, waist circumference; HC, hip circumference; WHR, waist-to-hip ratio. All data are presented as mean (standard deviation) unless otherwise specified. With the exception of age, all data shown are standardized to the age distributions of the cohort.

Table 2

Multivariable relative risks (RRs) of incident endometrial cancer (EC) according to categories of Waist Circumference (WC), Hip Circumference (HC) and Waist to Hip Ratio (WHR) in the Nurses' Health Study

		Median	Number of cases	Age-adjusted RR*	Multivariable RR1†	Multivariable RR2‡
WC (inch)	≤27	26	47	1.0 (Ref)	1.0 (Ref)	1.0 (Ref)
	28-29	28	47	0.82 (0.54-1.23)	0.83 (0.55-1.25)	0.75 (0.50-1.13)
	30-32	31	81	0.95 (0.66-1.37)	0.98 (0.68-1.41)	0.77 (0.53-1.12)
	33-37	35	129	1.31 (0.93-1.85)	1.38 (0.97-1.95)	0.88 (0.61-1.28)
	≥38	40	145	2.30 (1.63-3.24)	2.44 (1.72-3.45)	1.08 (0.69-1.67)
		p for trend		<0.001	<0.001	0.23
HC (inch)	≤38	35	49	1.0 (Ref)	1.0 (Ref)	1.0 (Ref)
	37-38	38	67	1.09 (0.75-1.57)	1.07 (0.74-1.56)	0.96 (0.66-1.39)
	39-40	39	86	1.39 (0.98- 1.98)	1.37 (0.96-1.96)	1.06 (0.73-1.52)
	41-44	42	136	1.71 (1.23-2.38)	1.69 (1.21- 2.36)	1.04 (0.73-1.50)
	≥45	47	111	2.82 (2.00-3.97)	2.85 (2.01-4.02)	1.06 (0.66-1.69)
		p for trend		<0.001	<0.001	0.78
WHR	<0.73	0.71	52	1.0 (Ref)	1.0 (Ref)	1.0 (Ref)
	0.73-<0.77	0.75	73	1.08 (0.75-1.54)	1.11 (0.77-1.59)	1.05 (0.73-1.51)
	0.77-<0.81	0.79	83	1.13 (0.79-1.60)	1.19 (0.83-1.69)	0.98 (0.69-1.40)
	0.81-<0.88	0.84	121	1.29 (0.92-1.80)	1.38 (0.98-1.92)	1.04 (0.74-1.46)
	≥0.88	0.93	120	1.56 (1.11-2.20)	1.69 (1.20-2.40)	1.15 (0.81-1.64)
		p for trend		0.002	<0.001	0.37

*Model was stratified by age in months at start of follow-up and calendar year of the current questionnaire cycle.

†Model was stratified by age in months at start of follow up and calendar year of the current questionnaire cycle and was simultaneously adjusted for pack-years of smoking (0, 0.1-20, 20.1-40, >40 pack-years), race (White, Black, others), age at menarche (7-11, 12, 13, 14-18 years), oral contraceptive use (no use, <1, 1-3, 36, >6 years), menopausal status (premenopausal, postmenopausal), postmenopausal hormone use (no use, oral conjugated estrogen, oral estrogen and progesterone, others), and parity (0, 1, 2, 3, >3).

‡Model was adjusted for variables in multivariable model 1 and BMI (kg/m^2, continuous).