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Risk of endometrial cancer in relation to medical conditions and medication use

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Abstract

We studied the relation of medical conditions related to obesity and medications used for these conditions with endometrial cancer. We also investigated the association of other medical conditions and medications with risk. This US population-based case-control study included 469 endometrial cancer cases and 467 controls. Information on putative risk factors for endometrial cancer was collected through personal interviews. We asked women about their medical history and medications used for six months or longer and the number of years each medication was taken. Risk was strongly associated with increasing obesity (p for trend <0.001). Among conditions related to obesity, and after adjustment for age, body mass index (BMI), and other risk factors and conditions, uterine fibroids were independently related to an increased cancer risk (adjusted OR= 1.8, 95%CI= 1.2–2.5). Although hypertension was not significantly related to endometrial cancer after adjustment for age and BMI, use of thiazide diuretics was independently associated with an increased risk (OR= 1.8, 95%CI= 1.1–3.0). Anemia was associated with decreased risk (OR= 0.6, 95%CI= 0.5–0.9). Use of non-steroidal anti-inflammatory drugs was related to a decreased risk (OR= 0.7, 95%CI= 0.5–0.97). To our knowledge, the observation about thiazide diuretics is novel and requires confirmation in other studies and populations.

Keywords

cancer; endometrial; risk; medications; conditions

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Introduction

Endometrial cancer is the fourth most common cancer among women of westernized countries and the most common malignancy of the female genital tract(1). Obesity is strongly related to endometrial cancer, probably through the increased production of unopposed endogenous estrogens. Type 2 diabetes mellitus (t2 DM) is also related to increased risk, although its independence from BMI remains somewhat unclear. Both obesity and t2DM facilitate a pro-inflammatory cellular milieu(2). Experimental evidence has shown that NF-kB, COX-2, and PGE2 are over-expressed in endometrial cancer cells, further suggesting an implication of inflammation in endometrial carcinogenesis(3–5). The relation of other obesity-related conditions such as hypertension and dyslipidemia with endometrial cancer is less clear and findings could be related to the uncontrolled effect of obesity(6–8). Consistent with the inflammatory theory, two epidemiological studies found that regular aspirin use –a common anti-inflammatory-was related to a decreased risk of endometrial cancer among obese women (9,10).

In a population-based case-control study among US women, we assessed the relation of medical conditions and their treatments with endometrial cancer.

Methods

Study population

The EDGE Study (Estrogen, Diet, Genetics, and Endometrial Cancer) is a population-based case-control study conducted in six counties in northern New Jersey. Cases were eligible if they were aged 21 and over, lived in one of the six counties (Bergen, Essex, Hudson, Middlesex, Morris, and Union) at the time of diagnosis, spoke English or Spanish, and were physically and cognitively able to take part. They were diagnosed with invasive epithelial endometrial cancer between July 1, 2001 and June 30, 2005. Cases were identified by the New Jersey Department of Health and Senior Services using rapid case ascertainment supplemented with review of state Cancer Registry data to identify cases diagnosed out of the area. Pathology reports and slides were obtained for cases who consented to be in the study and sent to the study pathologist for review. All epithelial histologic types are included in this analysis; 90% had tumors classified as endometrioid or predominantly endometrioid. During the four years of the study, 1559 eligible women were identified of whom 1108 could be contacted within one year of diagnosis. A total of 469 completed the interview. The major reason for not completing the interview was refusal. In comparison to all women diagnosed with endometrial cancer in these counties in this time period, the cases included were younger and more likely to have localized disease. The mean age of those included was 61.7 (median 61, range 33–88), compared to 63.6 in all women. Our case group included 11% who were aged ≥75, a smaller proportion than the 20% in all cases. Seventeen per cent of the women included in EDGE had SEER Stage classified as regional or distant, compared to 26% in all cases. These imbalances are likely to be due to refusal, language barriers, illness, or death among the older and more seriously ill women.

Controls had the same eligibility requirements as cases and, in addition, could not have had a hysterectomy. Three methods were used to locate controls. Women aged <65 were located through random digit dialing. Using names and phone numbers from a commercial research service that we contracted with, we reached 355 eligible women, of whom 175 (49%) completed the interview and the remainder declined. Initially, women aged ≥65 were identified through lists purchased from the Centers for Medicare and Medicaid (CMS); they were contacted by letter, followed by telephone calls when we were able to locate the numbers. We identified 316 women, of whom 68 (22%) completed the interview, while the remainder declined. Because many telephone numbers were not available from CMS, in August 2003 we

began using area sampling to reach older controls. Initially we sought women aged ≥65; later we included women aged ≥55. In randomly selected areas within the six counties, we identified 30 consecutive households according to postal route. Each selected household was sent a letter by mail introducing the study, then visited by interviewers to ascertain eligibility and interest in participating. We identified 524 eligible women, of whom 224 (43%) completed the interview. In total, 467 controls completed the interview, including 175 from RDD, 68 from CMS, and 224 from area sampling. The study was approved by the Institutional Review Boards at Memorial Sloan-Kettering Cancer Center and the New Jersey Department of Health and Senior Services.

For RDD and CMS controls, we frequency matched controls to the expected distribution of cases by 5-year age group; however, in area sampling this would have required a complex sampling scheme that would have been difficult to execute in the field. Instead, we included all age-eligible women who were willing to take part in the study. We were able to enroll more older controls, leading to an imbalance in age between the cases and controls. Area sampling has the potential to introduce bias because women living in the same neighborhoods are likely to have similar characteristics. The 224 women recruited through area sampling lived in 150 neighborhoods, with the number from any one neighborhood ranging from 1 (in 90 neighborhoods) to 7 (in one neighborhood).

Data collection

The interview covered established and possible risk factors for endometrial cancer. These included reproductive history, menstrual history, and oral contraceptive and hormone replacement therapy use. Body mass index ($wt(kg)/ht(m)^2$) was ascertained at the reference date (date of diagnosis for cases and six months before the interview for controls). Participants were specifically asked if they had ever been told by a health professional that they had a number of medical conditions, including those related to BMI (t2 DM, high cholesterol, hypertension, osteoporosis or thinning bones, and fibroids in the uterus) and other conditions (bladder or urinary infections, low blood count or anemia, depression, migraine headaches, ovarian cysts, endometriosis, rheumatoid arthritis, hyperthyroidism or Graves' disease, and Crohn's disease). Age at first diagnosis was recorded, as well as what medications, if any, were taken for the conditions reported. Participants were also asked about other medications they may have used continuously for at least 6 months. Total duration of use was recorded for each medication. We considered only conditions and medications used before the reference date.

The effect of duration of the disease was assessed by categorizing duration as shorter or longer than the median time since diagnosis for each particular disease among the controls.

Medications were categorized as follows. Type 2 DM related medications were biguanides (e.g., metformin), insulin, and sulphonylureas (e.g., glibenclamide, repaglinide). Hypercholesterolemia medications were statins (e.g., atorvastatin, simvastatin) and fibrates (e.g., bezafibrate). Hypertension medications were angiotensin converting enzyme inhibitors (ACEI, e.g., ramipril, captopril), angiotensin 2 receptor antagonists (e.g., candesartan, telmisartan), beta blockers (e.g., atenolol, bisoprolol), calcium channel antagonists (e.g., verapamil, nifedipine), thiazide diuretics (e.g., hydrochlorothiazide, indapamide), loop diuretics (e.g., furosemide, torasemide), and potassium sparing diuretics (e.g., spironolactone). Osteoporosis medications were biphosphonates (e.g., pamidronic acid, alendronic acid) and calcitonin. Pain and inflammation medications were non-steroidal anti-inflammatory drugs (NSAIDs, e.g., aspirin, ibuprofen, diclofenac), analgesics (e.g., paracetamol, phenacetin), and corticosteroids (e.g., cortisone, prednisone). Mood disorder medications were serotonin selective reuptake inhibitors (SSRIs, e.g., paroxetine, fluoxetine) and benzodiazepines (e.g., diazepam, lorazepam). Gastrointestinal medications were proton pump inhibitors (e.g., omeprazol, pantoprazole). Duration of medication use was categorized based on years of use

among the controls, using the median or tertiles, depending on the number of women who used each medication.

Statistical analysis

Unconditional logistic regression was used to estimate odds ratios (OR) and 95% confidence intervals (CI) as the measure of association between specific variables and the occurrence of endometrial cancer. In logistic regression, we used a spline technique that modeled the association between age and case-control status separately according to three age categories: <65; 65 to <80; and ≥80 (11). To investigate the possible effects of clustering by neighborhood in area sampling on the results, we compared results from the logistic models to those obtained by fitting generalized estimating equations(12), which account for the clustering of subjects. Since differences in parameter estimates and standard errors were trivial, indicating that the clustering did not affect the results, we used logistic models.

In the results, odds ratios adjusted for age and BMI are shown. In one analysis, we considered conditions related to obesity (t2 DM, hypercholesterolemia, hypertension, osteoporosis, and uterine fibroids) and medications used to treat them. For this analysis, we present results from a second model, adjusted for other factors that have been related to increased risk of endometrial cancer: age at menarche, parity, menopausal status at index date, oral contraceptive use, hormone replacement therapy use, and family history of endometrial cancer. This model (the "fully adjusted model") was also adjusted for the conditions and medications.

Whenever numbers allowed, confounding by indication was specifically addressed by restricting the analyses to individuals with the condition for which the drug is generally prescribed. Additionally, direct comparison of ORs found for different medications usually prescribed for the same indication (e.g., 2 different types of diuretics for hypertension) was also used to assess the possibility of confounding by indication. Stratification for BMI (<30 and ≥30) was conducted for obesity-related conditions and medications, and for NSAIDs, to assess possible effect modification by obesity. These models were also fully adjusted and included BMI as a continuous variable.

In analyses for other conditions and medications that are not strongly related to obesity, two models were used, one adjusting for age and BMI and another adjusting for these variables and other endometrial cancer risk factors as listed above.

Categories for variables included in logistic regression were as follows: race (white, black, Hispanic (any race), other); education (high school graduate or less, some college, graduate school); smoking (never smoked at least one cigarette per day for one year, past, current); BMI (<25, 25–<30, 30–<35, ≥35); age at menarche (<12 years of age vs ≥12); parity (0–1, 2, ≥3); menopausal status (premenopausal, early menopause (<50), late menopause (≥50), post menopause, age unknown); oral contraceptive use (ever, never); hormone replacement therapy use (never, unopposed estrogen only, ever combined therapy); and history of endometrial cancer in first degree relative (yes, no). Women were considered postmenopausal if their last menstrual period occurred more than one year before the reference date. Women who had a "natural" menstrual period (i.e., had not taken hormone or oral contraceptives) within the year were considered premenopausal, while others were considered premenopausal if aged <55 and postmenopausal if older.

The data were analyzed using SAS version 9.1 (SAS Institute, Cary NC). Due to the exploratory nature of the analysis, we did not adjust for multiple comparisons. The results were evaluated at a level of significance α=0.05.

Results

Table 1 shows the socio-demographic characteristics and endometrial cancer risk factors of the 469 cases and 467 controls. Several differences between cases and controls existed. For instance, cases were younger than controls. As expected, cases were also more obese, had had menarche earlier, and had fewer offspring after adjustment for age.

Obesity and conditions related to obesity

Table 2 shows the associations of endometrial cancer with BMI, conditions related to obesity (t2 DM, hypercholesterolemia, hypertension, osteoporosis, and fibroids) and their treatments. For these conditions and medications, results of two models are shown: ORs adjusted for age and BMI; and ORs adjusted for age, BMI, risk factors shown in Table 1, and other conditions and drugs shown in Table 2 (fully-adjusted model). Obesity was strongly related to increased risk of endometrial cancer in both models (p for trend <0.001). The age and BMI adjusted risks for t2 DM and hypertension were only marginally significant (OR t2 DM= 1.4, 95%CI= 0.9–2.3; OR hypertension= 1.2, 95%CI= 0.9–1.6). After full adjustment, no association was seen for hypertension (fully adjusted OR=0.9, 95%CI= 0.6 – 1.5) but a marginally significant relationship still existed for t2 DM (fully adjusted OR=1.9, 95%CI= 0.9 – 4.1). Hypercholesterolemia was also associated with a marginally significant decreased risk of endometrial cancer (OR= 0.7, 95%CI= 0.4–1.0). Osteoporosis was related to a significantly lower risk of endometrial cancer in the age and BMI adjusted models, and to a somewhat lower risk in the fully adjusted models (OR=0.7, 95%CI= 0.4–1.2). Analysis of t2 DM stratified by BMI (<30 and ≥30) was carried out to assess the possibility of effect modification by obesity. Although no statistically significant interaction with BMI was seen, a previous history of diabetes was associated with a somewhat larger risk of endometrial cancer among women with a BMI ≥30 (OR= 2.2, 95%CI= 0.7–7.2) than among women with a BMI< 30 (OR= 1.8, 95% CI= 0.6–5.6) (data not shown).

Endometrial fibroids were significantly associated with an increased risk of endometrial cancer in all models (fully adjusted OR= 1.8, 95%CI=1.2 – 2.5). Women who had been diagnosed more than 15 years ago showed a significantly increased endometrial cancer risk in the fully adjusted model (OR= 2.0, 95%CI= 1.2–3.2) (data not shown).

Medications for conditions related to obesity

Two medications used for hypertension, angiotensin 2 converting enzyme (ACEI) and thiazide diuretics, were related to endometrial cancer after adjustment for age and BMI (OR= 1.6, 95% CI= 1.1–2.5 and OR= 1.7, 95%CI= 1.2–2.5 respectively) (Table 2). After full adjustment, only use of thiazides remained a statistically significant risk factor (OR = 1.8, 95%CI= 1.1–3.0). Duration of thiazide use was also assessed: only the longest duration of use (i.e., >6 years) was significantly related to an increased risk of endometrial cancer (fully adjusted OR= 2.4, 95% CI= 1.2–4.8). Long term use of ACEI (i.e., >5 years) was not significantly associated with risk (data not shown). An alternative analysis restricted to subjects with hypertension (221 cases, 173 controls) –the condition for which thiazides are primarily used- consistently showed a significantly increased risk among users of thiazides (fully adjusted model, OR= 1.7, 95%CI= 1.0–3.0) (data not shown). The other medications used to treat hypertension (i.e., ACEI, Beta blockers, calcium channel blockers, angiotensin 2 receptor antagonists, loop diuretics, and K sparing diuretics) were not associated with an increased risk of cancer in this restricted analysis. In analysis stratified by BMI (<30 and ≥30), thiazide diuretic use appeared to be more strongly related to increased risk of endometrial cancer among those with lower BMI (OR= 2.2, 95% CI= 1.1–4.5 and OR= 1.2, 95%CI= 0.5–2.9, for those with lower and higher BMI, respectively), although differences were not statistically significant (data not shown).

Use of biphosphonates or calcitonin was related to somewhat lower risk of endometrial cancer: OR=0.7 (95%CI= 0.4–1.2) for each medication (fully adjusted model). Longer duration of use of biphosphonates (i.e., >2 years) was related to a somewhat lower risk of endometrial cancer than shorter use: OR>2yrs= 0.6, 95%CI= 0.3–1.1 and OR≤2yrs= 0.9, 95%CI= 0.4–2.1 (fully adjusted models, data not shown). Duration of use of calcitonin was not related to a lower risk of cancer (OR≤5yrs= 0.7, 95%CI= 0.4–1.5 and OR>5yrs= 0.6, 95%CI= 0.3–1.3) (data not shown). An alternative, fully adjusted analysis restricted to subjects with osteoporosis (51 cases and 102 controls) –the condition for which biphosphonates and calcitonin are used- showed no modification of risk for calcitonin (OR= 0.9, 95%CI= 0.3–2.7) or biphosphonates (OR= 0.8, 95%= 0.3–2.2), but numbers of exposed subjects were low. In an analysis stratified by BMI, calcitonin use was significantly associated with a decreased risk of endometrial cancer among subjects with a BMI ≥30 (OR= 0.2, 95%CI= 0.1–0.7) but not among those with a BMI< 30 (OR= 1.0, 95%CI= 0.5–1.8) (data not shown).

Other medical conditions

Table 3 shows the risks of endometrial cancer associated with several other medical conditions. Anemia was significantly associated with a decreased risk of endometrial cancer in the BMI and age adjusted model (OR= 0.6, 95%CI= 0.5–0.9). Further adjustment for risk factors did not significantly modify this association (data not shown). Reduced risk associated with anemia was the same for those diagnosed ≤34 years ago and those diagnosed more recently (data not shown).

Other medications

Table 4 shows the associations of endometrial cancer with the reported use of other commonly used medications. Only non-steroidal anti-inflammatory drugs (NSAIDs) (OR= 0.7, 95%CI= 0.5–0.97, adjusted for age and BMI) were significantly associated with a decreased risk of endometrial cancer. However, no indication of a duration-response trend was observed after adjustment for age and BMI (p= 0.12) (data not shown). When we separately assessed aspirin and non-aspirin NSAIDs, a similar effect on endometrial cancer risk was observed for both types of drugs in the age and BMI adjusted model although neither was statistically significant (OR aspirin= 0.7, 95%CI=0.4–1.0; OR non-aspirin NSAIDs= 0.8, 95%CI= 0.5–1.3). In analyses stratified by BMI, risk associated with use of any NSAIDs or aspirin was similarly reduced in each stratum. For non-aspirin NSAIDs, reduced risk was somewhat more apparent in women with lower BMI (OR=0.7, 95% CI 0.4–1.4) than in those with higher BMI (OR=0.9, 95% CI 0.4–1.9), after adjustment for age and BMI (data not shown).

Discussion

We found a strong association between obesity and an increased risk of endometrial cancer, consistent with the conclusion of the recent review by WCRF/AICR that body fatness is a convincing cause of this disease. In that meta-analysis, obesity was shown to increase the risk of endometrial cancer by about 50% per 5 units of BMI (i.e., kg/m2) in both cohort and case-control studies, with a good deal of heterogeneity in the size of the effect(13). On this scale, our results were a 66% increase in risk per 5 units of BMI, higher than reported in most other studies. Our results showed that some other conditions related to obesity also were associated with risk. As in other studies (summarized in Saltzman(14), reviewed in Friberg (15)), risk estimates for t2 DM were above unity, although non-significantly. The association of hypertension with risk is less consistent and, in our study and others, not independent of obesity (6–8). In our study osteoporosis was related to a somewhat lower risk of endometrial cancer (fully adjusted OR=0.7, 95% CI= 0.4–1.2), similar to what others have observed(16–18). A previous diagnosis of endometrial fibroid tumors was related to an increased risk of endometrial cancer. A recent paper(19) found increased risk for endometrial cancer in women with fibroid

tumors using record linkage methods, although in that study the risk was not significantly increased among women with follow-up of ≥5 years. Since women with hysterectomy were ineligible for our study, and fibroids are the major reason for hysterectomy(20), women in our study were likely to have relatively small or less symptomatic fibroids. There is likely to be confounding by estrogen levels in our study, since both osteoporosis(21) and fibroids(22) are related to estrogen levels. BMI and other variables included in our models do not completely control for estrogen level(23).

The other condition found to be significantly related to risk was anemia, with controls more likely to report this condition than cases. To our knowledge this has not been reported before. In this study we have not been able to rule out the possibility of anemia acting as a marker of irregular menstruation or menorrhagia that could be related to a modified risk of endometrial cancer mediated by alterations in estrogen exposure. Confirmation of this finding in further studies is needed before a relationship can be established.

In studying medications, we found an elevated risk of endometrial cancer for thiazide use after adjustment for age, BMI, risk factors, and other conditions and treatments related to obesity (i.e., in the fully adjusted model). To our knowledge, this association has not been previously reported. An analysis restricted to hypertensive subjects eliminated to a large extent the concern about confounding by indication for thiazides. Also, the fact that other medications used to treat hypertension (i.e., other diuretics, calcium channel blockers, etc) were not related to endometrial cancer –in the overall and the restricted analyses-suggests a causal relationship for thiazides. Risk increased with longer duration of use. Studies of the prototypic thiazide hydrochlorothiazide in rats showed no carcinogenic effects(24). Some studies have suggested that thiazides could increase the risk of t2 DM by increasing insulin resistance (reviewed in Sowers (25)), possibly explaining the elevated risk for endometrial cancer, although other, well designed studies, have not confirmed this association(26,27). Several studies have found chronic use of thiazides to be related to a decreased risk of hip fractures(28) and to a reduced risk of radial bone loss (i.e., osteoporosis)(29). Hip fractures are related to osteoporosis, a hormone-dependent condition caused by a reduction in estrogen levels. In postmenopausal women, administration of estrogens prevents osteoporosis and fractures (30). An elevated risk of endometrial cancer could be explained if thiazides had an estrogen-like activity. Further research is needed to confirm this hypothesis. Thiazides are usually selected as the initial treatment for hypertension, especially among subjects without other risk factors, such as diabetes or previous cardiovascular events(31). Therefore, since we only found an increased risk of endometrial cancer for thiazide diuretics, and not for other anti-hypertensive drugs, it is unlikely that the results observed in our study could be explained by residual confounding from diabetes or other cardiovascular-related pro-inflammatory conditions.

The protective effect of osteoporosis was not modified by the medication used to treat it (i.e., calcitonin or biphosphonates), suggesting that the relationship between the condition and the risk of cancer is independent of the treatment used. The effect of potential residual confounding by obesity or estrogen levels remains to be elucidated.

Finally, in our study, NSAID use was related to a marginally significant decreased risk of endometrial cancer (after adjustment for age and BMI, OR= 0.7, 95%CI= 0.5–0.97) whereas other analgesics (i.e., paracetamol and phenacetin), which are prescribed for similar indications as NSAIDs but lack their anti-inflammatory capacity, were not related to a decreased risk of endometrial cancer. Also, the fact that conditions for which NSAIDs are frequently used, such as migraine or rheumatoid arthritis, were not related to a decreased risk of endometrial cancer, argues against confounding by indication. No overall differences were seen between aspirin and non-aspirin NSAIDs. One previous case-control study found that regular use of aspirin was related to a significantly decreased risk of endometrial cancer, although only among obese

women (OR= 0.50, 95%CI= 0.27–0.92)(9); other NSAIDs were not studied. A recent cohort study has reported a decreased risk of endometrial cancer among current users of aspirin who were obese or postmenopausal and had not taken postmenopausal hormones, but no risk modification among other NSAID users (10). In contrast, the effect we noted in our study was similar in obese and non-obese women. Interestingly, one recent study has reported that use of NSAIDs is related to lower levels of circulating estrogens, offering a mechanistic hypothesis by which anti-inflammatories could reduce the risk of endometrial cancer(32). Also, factors related to an increased risk of endometrial cancer, such as obesity, insulin resistance, aging or menorrhagia have been linked to higher inflammation levels, whereas protective factors such as pregnancy or regular menses have been related to lower inflammation levels(2).

In our study no evidence was found for a significant interaction between BMI and the conditions and medications assessed. Nevertheless, we found a suggestion of a greater risk of endometrial cancer among obese diabetics than among non-obese diabetics, something that others have also observed (33,34).

The EDGE Study has several strengths: a population-based design, relatively large sample size, high quality exposure and pathology assessment, and expert evaluation and classification of drug use. Use of population controls is especially important for studies assessing conditions and medications to limit selection bias. However, to further assess the possibility of selection bias, we compared the characteristics of our controls with other available data. In our study, 55% of control women were overweight, obese, or very obese at the interview date (i.e., BMI of 25–<30, 30–<35, or ≥35 respectively). This finding is similar to the 59.3% estimation of overweight or obesity prevalence among women aged more than 45 in the US in 2005(35). Type 2 DM and hypertension were reported respectively by 8% and 37% of our controls, somewhat lower than the estimated values of 12.5% and 43.5% among women older than 45 years old in the US in 2005 in the Behavioral Risk Factor Surveillance Survey(35). In our study, 13% of the control women reported having used thiazides for at least 6 months. In the US Nurses' Health Study, regular use of thiazides among participants in 1980 was 8%(36) and in a 2004 Danish study, 22% of the controls reported having ever used a thiazidic diuretic (28). Since differences in the definition of user exist across studies, we consider the prevalence of thiazide use in our study to be in general agreement with the published data. Finally, in our controls we found a prevalence of NSAID use for at least 6 months of 24%, consistent with the 26% prevalence of daily use for at least 2 months in a recent breast cancer study in a population similar to ours(37). We therefore consider control subjects included in our study to be representative of the similarly aged, general US female population in terms of the studied conditions and medications.

On the other hand, our analysis may suffer from some potential shortcomings. The novel findings of associations with thiazide diuretics and anemia may be due to chance, since we examined a large number of conditions and medications in this study. However, given the exploratory nature of this analysis -designed to reveal potential new associations- we consider that all the signals from our data were important to capture. As in most interview-based case-control studies, information on study subjects is based on self-report. Therefore, recall bias is a potential threat to the validity of the study results. In our study, however, we do not expect recall bias to be an issue, as patients are unlikely to relate most of the conditions and medications assessed to a modified risk of endometrial cancer. Also, the fact that we have focused on medications chronically used (i.e., for at least 6 months) should help to enhance general recall of use, regardless of disease status. Recall bias is probably lower for drugs used on a daily basis (i.e., hydrochlorothiazides) than for drugs used sporadically (i.e., NSAIDs) or drugs whose use was suspended by the subject a long time ago. However, a residual degree of misclassification for medication use and presence of medical conditions cannot be completely ruled out. Bias due to an increased probability of diagnosis of the conditions assessed or treatments prescribed

because of medical consultation due to an undiagnosed endometrial cancer is possible in this kind of study. However, we think it is unlikely that this bias would differentially affect drugs used to treat the same condition (i.e., thiazide diuretics and loop diuretics for hypertension), which, in our opinion, argues against a strong effect of a diagnostic bias on our data. We did not ask specifically about time since last use of medications, so could not account for recency in our analyses. In addition, we did not ask about some conditions associated with use of NSAIDs, such as osteoarthritis. Larger numbers of cases and controls are needed to further investigate interactions of conditions and medications with BMI.

In conclusion, obesity, history of fibroids, and thiazide diuretic use were associated with an increased risk of endometrial cancer. A diagnosis of anemia and use of NSAIDs were related to decreased risk of endometrial cancer. The novel findings related to thiazide diuretics and anemia need to be confirmed in other studies.

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Reference List

1. Ferlay; Bray, F.; Pisani, P.; Parkin, D. GLOBOCAN 2000: Cancer Incidence, Mortality and Prevalence Worldwide. Vol. 5. IARC Press; 2001.
2. Modugno F, Ness RB, Chen C, Weiss NS. Inflammation and endometrial cancer. Cancer Epidemiol Biomarkers Prev 2005;14:2840–7. [PubMed: 16364998]
3. Vaskivuo TE, Stenback F, Tapanainen JS. Apoptosis and apoptosis related factors Bcl-2, Bax, tumor necrosis factor-α, and NF-κβ in human endometrial hyperplasia and carcinoma. Cancer 2002;95:1463–71. [PubMed: 12237915]
4. Cao QJ, Einstein MH, Anderson PS, Runowicz CD, Balan R, Jones JG. The expression of cyclooxigenase-1 and -2 in proliferative endometruim and endometrial carcinoma. Int J Gynecol Pathol 2002;21:147–54. [PubMed: 11917224]
5. Jeon YT, Kang S, Kang DH. Cyclooxygenase-2 and p53 expressions in endometrial cancer. Cancer Epidemiol Biomarkers Prev 2004;13:1538–42. [PubMed: 15342458]
6. Furberg AS, Thune I. Metabolic abnormalities (hypertension, hyperglycemia and overweight), lifestyle (high energy intake and physical inactivity) and endometrial cancer risk in a Norwegian cohort. Int J Cancer 2003;104:669–76. [PubMed: 12640672]
7. Weiderpass E, Persson I, Adami HO, Magnusson C. Body size in different periods of life, diabetes mellitus, hypertension, and risk of postmenopausal endometrial cancer (Sweden). Cancer Causes and Control 2000;11:185–92. [PubMed: 10710204]
8. Soler M, Chatenoud L, Negri E, Parazzini F, Franceschi S, La Vecchia C. Hypertension and hormone-related neoplasms in women. Hypertension 1999;34:320–5. [PubMed: 10454461]
9. Moysich KB, Baker JA, Rodabaugh KJ, Villella JA. Regular analgesic use and risk of endometrial cancer. Cancer Epidemiol Biomarkers Prev 2005;14:2923–8. [PubMed: 16365011]
10. Viswanathan AN, Feskanich D, Schernhammer ES, Hankinson SE. Aspirin, NSAID, and acetaminophen use and the risk of endometrial cancer. Cancer Res 2008;68:2507–13. [PubMed: 18381460]
11. Harrell, FE. Regression Modeling Strategies with Applications to Linear Models, Logistic Regression, and Survival Analysis. New York: Springer; 2001.
12. Liang KY, Zeger SL. Longitudinal data analysis using generalized linear models. Biometrika 1986;73:13–22.
13. World Cancer Research Fund/American Institute for Cancer Research. Food, Nutrition, Physical Activity, and the Prevention of Cancer: a Global Perspective. 2007Report No.: 2

14. Saltzman BS, Doherty JA, Hill DA, et al. Diabetes and Endometrial Cancer: An Evaluation of the Modifying Effects of Other Known Risk Factors. Am J Epidemiol 2007;167:607–14. [PubMed: 18071194]
15. Friberg E, Orsini N, Mantzoros CS, Wolk A. Diabetes mellitus and risk of endometrial cancer: a meta-analysis. Diabetologia 2007;50:1365–74. [PubMed: 17476474]
16. Persson I, Naessén T, Adami HO, et al. Reduced risk of hip fracture in women with endometrial cancer. Int J Epidemiol 1992;21:636–42. [PubMed: 1521965]
17. Persson I, Adami HO, McLaughlin JK, Naessén T, Fraumeni JF Jr. Reduced risk of breast and endometrial cancer among women with hip fractures (Sweden). Cancer Causes and Control 1994;5:523–8. [PubMed: 7827239]
18. Newcomb PA, Trentham-Dietz A, Egan KM, et al. Fracture history and risk of breast and endometrial cancer. Am J Epidemiol 2001;153:1071–8. [PubMed: 11390325]
19. Brinton LA, Sakoda LC, Frederiksen K, et al. Relationships of uterine and ovarian tumors to pre-existing chronic conditions. Gynecologic Oncology 2007;107:487–94. [PubMed: 17825884]
20. Cramer SF, Patel A. The frequency of uterine leiomyomas. Am J Clin Pathol 1990;94:435–8. [PubMed: 2220671]
21. Weitzmann MN, Pacifici R. Estrogen deficiency and bone loss: an inflammatory tale. J Clin Invest 2006;116:1186–94. [PubMed: 16670759]
22. Ross RK, Pike MC, Vessey MP, Bull D, Yeates D, Casagrande JT. Risk factors for uterine fibroids: reduced risk associated with oral contraceptives. British Med J 1986;293:359–62.
23. Potischman N, Hoover RB, Brinton LA, et al. Case-control study of endogenous steroid hormones and endometrial cancer. J Natl Cancer Inst 1996;88:1127–35. [PubMed: 8757192]
24. Bucher JR, Huff J, Haseman SL, et al. Toxicology and carcinogenicity studies of diuretics in F344 rats and B6C3F1 mice. 1. Hydrochlorothiazide. J Applied Toxicol 1990;10:359–67. [PubMed: 2254588]
25. Sowers JR, Bakris GL. Antihypertensive therapy and the risk of type 2 diabetes mellitus. N Eng J Med 2000;342:969–70.
26. Gress TW, Nieto J, Shahar E, Wofford MR, Brancati FL. Hypertension and antihypertensive therapy as risk factors for type 2 diabetes mellitus. N Eng J Med 2000;342:905–12.
27. Padwal R, Mamdani M, Alter DA, et al. Antihypertensive therapy and incidence of type 2 diabetes in an elderly cohort. Diabetes Care 2004;27:2458–63. [PubMed: 15451916]
28. Rejnmark L, Vestergaard P, Mosekilde L. Reduced fracture risk in users of thiazide diuretics. Calcif Tissue Int 2005;76:167–75. [PubMed: 15719207]
29. Sowers MR, Clark MK, Jannausch ML, Wallace RB. Body size, estrogen use and thiazide diuretic use affect 5-year radial bone loss in postmenopausal women. Osteoporosis Int 1993;3:314–21.
30. Lekander I, Borgström F, Tröm O, Ethraeus N, Kanis JA. Cost effectiveness of hormone therapy in women at high risks of fracture in Sweden, the US and the UK--results based on the Women's Health Initiative randomised controlled trial. Bone 2008;42:294–306. [PubMed: 18053789]
31. August P. Initial treatment of hypertension. N Eng J Med 2003;348:610–7.
32. Hudson AG, Gierach GL, Modugno F, et al. Nonsteroidal anti-inflammatory drug use and serum total estradiol in postmenopausal women. Cancer Epidemiol Biomarkers Prev 2008;17:680–7. [PubMed: 18349287]
33. Schoff SM, Newcomb PA. Diabetes, body size, and risk of endometrial cancer. Am J Epi 1998;148:234–40.
34. Anderson KE, Anderson E, Mink PJ, et al. Diabetes and endometrial cancer in the Iowa Health Study. Cancer Epidemiol Biomarkers Prev 2001;10:611–6. [PubMed: 11401910]
35. Global Behavioural Risk Factor Surveillance. New York: Kluwer Academic/Plenum Publishers; 2005.
36. Leitzmann MF, Tsai CJ, Stampfer MJ, Willett WC, Giovannucci E. Thiazide diuretics and the risk of gallbladder disease requiring surgery in women. Arch Intern Med 2005;165:567–73. [PubMed: 15767534]
37. Kirsh VA, Kreiger N, Cotterchio M, Sloan M, Theis B. Nonsteroidal antiinflammatory drug use and breast cancer risk: subgroup findings. Am J Epidemiol 2007;166:709–16. [PubMed: 17660454]

Table 1

Sociodemographic characteristics and estrogen exposure related variables for cases and controls

	Cases n (%)	Controls n (%)	Age adjusted OR (95%CI)
Age			
<55	103 (22)	85 (18)	
55–64	205 (44)	159 (34)	
65–74	108 (23)	127 (27)	
≥75	53 (11)	96 (21)	
Race			
White	399(85)	408(87)	1 (ref)
Black	38(8)	23(5)	1.6 (1.0 – 2.8)
Hispanic	23(5)	23(5)	0.9 (0.5 – 1.7)
Other	9(2)	13(3)	0.6 (0.3 – 1.4)
Educational level			
High school	169(36)	155(33)	1 (ref)
College	207(44)	193(41)	0.9 (0.7 – 1.2)
Graduate school	93(20)	119(26)	0.6 (0.5 – 0.9)
Smoking			
Never	263(56)	238(51)	1 (ref)
Former	173(37)	178(38)	0.9 (0.7 – 1.2)
Current	33(7)	51(11)	0.5 (0.3 – 0.8)
BMI			
<25	118(25)	212(45)	1 (ref)
25–<30	127(27)	152(33)	1.6 (1.1 – 2.2)
30–<35	80(17)	71(15)	2.0 (1.4 – 3.0)
≥35	142(30)	32(7)	7.6 (4.8 – 11.8)
Early menarche (<12 years)			
No	202(43)	232(50)	1 (ref)
Yes	267(57)	235(50)	1.2 (1.0 – 1.6)
Parity			
0–1	171(37)	114(24)	1 (ref)
2	157(34)	167(36)	0.6 (0.5 – 0.9)
≥3	141(30)	186(40)	0.6 (0.4 – 0.8)
Menopausal status at index date			
Premenopausal	78(17)	66(14)	0.9 (0.6 –1.5)
Early menopause (<50)	122(26)	142(30)	1 (ref)
Late menopause(≥50)	216(46)	199(43)	1.3 (1.0 – 1.8)
Post menopause, age unknown	53(11)	59(13)	1.1 (0.7 – 1.7)
Oral contraceptive use			
No	268(57)	241(52)	1 (ref)
Yes	201(43)	226(48)	0.7 (0.5 – 0.9)
Hormone replacement therapy use			

	Cases n (%)	Controls n (%)	Age adjusted OR (95%CI)
Never	376(80)	345(74)	1 (ref)
Unopposed estrogen replacement therapy only	37(8)	39(8)	0.9 (0.5 – 1.4)
Ever combined replacement therapy	56(12)	83(18)	0.6 (0.4 – 0.8)
Family history of endometrial cancer			
No	444(95)	451(97)	1 (ref)
Yes	25(5)	16(3)	1.6 (0.9 – 3.1)

Table 2

Obesity and obesity-related conditions, their treatments and risk of endometrial cancer

	N cases	N controls	Age and BMI adjusted OR* (95%CI)	Fully and mutually adjusted OR** (95% CI)
BMI				
<25	118	212	1.0 (ref)	1.0 (ref)
25–<30	127	152	1.6 (1.1 – 2.2)	1.6 (1.1 – 2.3)
30–<35	80	71	2.0 (1.4 – 3.0)	1.6 (1.0 – 2.5)
>35	142	32	7.6 (4.8 – 11.8)	5.9 (3.6 – 9.9)
			P (trend test) < 0.001	P (trend test) < 0.001
Type 2 Diabetes Mellitus				
No	393	429	1.0 (ref.)	1.0 (ref)
Yes	76	38	1.4 (0.9–2.3)	1.9 (0.9 – 4.1)
Biguanides				
No	440	451	1.0 (ref.)	1.0 (ref)
Yes	29	16	1.1 (0.6–2.2)	0.6 (0.2 – 1.5)
Insulin				
No	455	462	1.0 (ref.)	1.0 (ref)
Yes	14	5	2.0 (0.7–6.1)	0.9 (0.2 – 3.4)
Sulphonylureas				
No	453	456	1.0 (ref.)	1.0 (ref)
Yes	16	11	1.0 (0.4–2.4)	0.6 (0.2 – 1.9)
Hypercholesterolemia				
No	286	281	1.0 (ref.)	1.0 (ref)
Yes	179	184	0.9 (0.7–1.2)	0.7 (0.4 – 1.0)
Statins				
No	355	360	1.0 (ref.)	1.0 (ref)
Yes	114	107	1.1 (0.8–1.5)	1.3 (0.8 – 2.1)
Fibrates				
No	460	460	1.0 (ref.)	1.0 (ref)
Yes	9	7	1.3 (0.4–3.6)	1.1 (0.4 – 3.6)
Hypertension				
No	248	294	1.0 (ref.)	1.0 (ref)
Yes	221	173	1.2 (0.9–1.6)	0.9 (0.6 – 1.5)
ACEI				
No	393	425	1.0 (ref.)	1.0 (ref)
Yes	76	42	1.6 (1.1–2.5)	1.4 (0.8 – 2.4)
Beta Blockers				
No	389	392	1.0 (ref.)	1.0 (ref)
Yes	80	75	1.0 (0.7–1.4)	1.0 (0.6 – 1.6)
Calcium channel blockers				
No	396	403	1.0 (ref.)	1.0 (ref)
Yes	73	64	1.0 (0.7–1.5)	0.9 (0.6 – 1.5)

	N cases	N controls	Age and BMI adjusted OR* (95%CI)	Fully and mutually adjusted OR** (95% CI)
Angiotensin 2 receptor antagonists				
No	410	422	1.0 (ref.)	1.0 (ref)
Yes	59	45	1.2 (0.8–1.9)	1.0 (0.6 – 1.8)
Thiazide diuretics				
No	369	408	1.0 (ref.)	1.0 (ref)
Yes	100	59	1.7 (1.2–2.5)	1.8 (1.1 – 3.0)
Duration of use 3 years	*28*	*19*	*1.4 (0.8 – 2.7)*	*1.6 (0.8 – 3.5)*
-	*23*	*18*	*1.3 (0.6 – 2.6)*	*1.2 (0.6 – 2.8)*
Duration of use >6 years	*48*	*22*	*2.3 (1.3 – 4.0)*	*2.4 (1.2 – 4.8)*
			P (trend test) =0.003	*P (trend test) = 0.39*
Loop diuretics				
No	454	455	1.0 (ref.)	1.0 (ref)
Yes	15	12	0.8 (0.3–2.0)	0.7 (0.3 – 1.8)
K sparing diuretics				
No	458	459	1.0 (ref.)	1.0 (ref)
Yes	11	8	1.1 (0.4–3.1)	0.7 (0.2 – 2.4)
Osteoporosis				
No	416	362	1.0 (ref.)	1.0 (ref)
Yes	51	102	0.6 (0.4–0.9)	0.7 (0.4 – 1.2)
Biphosphonates				
No	429	387	1.0 (ref.)	1.0 (ref)
Yes	40	80	0.6 (0.4–1.0)	0.7 (0.4 – 1.2)
Calcitonin				
No	440	405	1.0 (ref.)	1.0 (ref)
Yes	29	62	0.6 (0.3–0.9)	0.7 (0.4 – 1.2)
Endometrial fibroids				
No	331	372	1.0 (ref.)	1.0 (ref)
Yes	135	93	1.6 (1.2–2.2)	1.8 (1.2 – 2.5)

*adjusted for age (linear spline) and BMI (4 categories)

**adjusted for age (linear spline), BMI (4 categories), demographic factors (education, race) other estrogen related variables (menarche, HRT use, oral contraceptives use, age at menopause, parity), smoking, family history of endometrial cancer, plus all other variables included in the table

Table 3

Risk of endometrial cancer in relation to other medical conditions

	N cases	N controls	Age and BMI adjusted OR* (95%CI)
Bladder or urinary infections			
No	221	203	1.0 (ref.)
Yes	247	263	0.8 (0.6–1.1)
Anemia			
No	350	315	1.0 (ref.)
Yes	116	148	0.6 (0.5 – 0.9)
Depression			
No	380	379	1.0 (ref.)
Yes	86	84	0.8 (0.6 – 1.2)
Migraine headaches			
No	386	380	1.0 (ref.)
Yes	80	85	0.9 (0.7 – 1.3)
Ovarian cysts			
No	397	408	1.0 (ref.)
Yes	70	56	1.3 (0.9 – 1.9)
Endometriosis			
No	431	440	1.0 (ref.)
Yes	36	23	1.5 (0.8 – 2.6)
Rheumatoid arthritis			
No	441	425	1.0 (ref.)
Yes	27	35	0.7 (0.4 – 1.2)
Hyperthyroidism or Grave's disease			
No	436	439	1.0 (ref.)
Yes	27	26	1.2 (0.7 – 2.1)
Crohn's disease			
No	444	445	1.0 (ref.)
Yes	22	18	1.1 (0.6 – 2.3)

* adjusted for age (linear spline) and BMI (4 categories)

Table 4

Risk of endometrial cancer in relation to the use of other medications

	N cases	N controls	Age and BMI adjusted OR* (95%CI)
Pain and inflammation			
NSAIDs			P(trend duration) = 0.12
No	373	353	1.0 (ref.)
Yes	96	114	0.7 (0.5–0.97)
Aspirin			
No	413	391	1.0 (ref.)
Yes	56	76	0.7 (0.4–1.0)
Non-aspirin NSAIDs			
No	429	429	1.0 (ref.)
Yes	40	38	0.8 (0.5–1.3)
Analgesics			
No	451	455	1.0 (ref.)
Yes	18	12	1.2 (0.5–2.7)
Corticosteroids			
No	447	450	1.0 (ref.)
Yes	22	17	1.1 (0.5–2.1)
Mood disorders			
Serotonin selective reuptake inhibitors			
No	421	423	1.0 (ref.)
Yes	48	44	0.9 (0.6–1.4)
Benzodiazepines			
No	445	441	1.0 (ref.)
Yes	24	26	0.9 (0.5–1.7)
Gastrointestinal			
Proton pump inhibitors			
No	442	436	1.0 (ref.)
Yes	27	31	0.7 (0.4–1.2)

* adjusted for age (linear spline) and BMI in 4 categories