

Research Article

Body Mass Index, Hormone Replacement Therapy,
and Endometrial Cancer Risk: A Meta-AnalysisEmma J. Crosbie¹, Marcel Zwahlen², Henry C. Kitchener¹, Matthias Egger², and Andrew G. Renehan³

Abstract

Background: Body mass index (BMI) is a risk factor for endometrial cancer. We quantified the risk and investigated whether the association differed by use of hormone replacement therapy (HRT), menopausal status, and histologic type.

Methods: We searched MEDLINE and EMBASE (1966 to December 2009) to identify prospective studies of BMI and incident endometrial cancer. We did random-effects meta-analyses, meta-regressions, and generalized least square regressions for trend estimations assuming linear, and piecewise linear, relationships.

Results: Twenty-four studies (17,710 cases) were analyzed; 9 studies contributed to analyses by HRT, menopausal status, or histologic type, all published since 2003. In the linear model, the overall risk ratio (RR) per 5 kg/m² increase in BMI was 1.60 (95% CI, 1.52–1.68), $P < 0.0001$. In the piecewise model, RRs compared with a normal BMI were 1.22 (1.19–1.24), 2.09 (1.94–2.26), 4.36 (3.75–5.10), and 9.11 (7.26–11.51) for BMIs of 27, 32, 37, and 42 kg/m², respectively. The association was stronger in never HRT users than in ever users: RRs were 1.90 (1.57–2.31) and 1.18 (95% CI, 1.06–1.31) with P for interaction = 0.003. In the piecewise model, the RR in never users was 20.70 (8.28–51.84) at BMI 42 kg/m², compared with never users at normal BMI. The association was not affected by menopausal status ($P = 0.34$) or histologic type ($P = 0.26$).

Conclusions: HRT use modifies the BMI-endometrial cancer risk association.

Impact: These findings support the hypothesis that hyperestrogenia is an important mechanism underlying the BMI-endometrial cancer association, whilst the presence of residual risk in HRT users points to the role of additional systems. *Cancer Epidemiol Biomarkers Prev*; 19(12); 3119–30. ©2010 AACR.

Introduction

Endometrial cancer is the commonest gynecologic malignancy in many countries with incidences increasing in these populations over the past 2 decades (1). Body mass index (BMI) is an established risk factor for endometrial cancer (2). In a recent standardized meta-analysis of 20 cancer types, we found that the association of BMI with cancer risk ranked highest for endometrial cancer,

with a relative risk of 1.59 per 5 kg/m² incremental increase (3).

Alterations in endogenous sex hormone metabolism might mediate the effect of BMI on endometrial cancer risk (4, 5). Specifically, in postmenopausal women, the increased risk might be explained by higher rates of conversion of androgenic precursors to estradiol through increased aromatase enzyme activity ("aromatization") in adipose tissue, thus leading to a hyperestrogenic state. In premenopausal cases, chronic obesity-related ovarian hypogonadism, with a concomitant relative or absolute progesterone deficiency, may create a cellular environment favoring tumorigenesis.

Sex hormone-related states might therefore influence the association between BMI and endometrial cancer (6, 7). For example, associations might be attenuated in postmenopausal women on estrogen-containing hormonal replacement therapy (HRT), who are in an excess estrogen state. Furthermore, associations might differ according to Bokhman histologic subtype (8): a stronger association would be expected with Type I (conventionally considered to arise in hyperestrogenic states and associated with endometrial hyperplasia) than in Type II (unrelated to hyperestrogenic conditions, arising in atrophic endometrium; ref. 7).

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The aim of the present meta-analysis was to investigate the influences of sex hormone-related states—with a focus on HRT, menopausal status, and of histologic subtypes—on the strength of the association between BMI and endometrial cancer risk.

Methods

Search strategy and selection criteria

We updated our previous systematic review to end of December 2009. The search strategy has been described in detail elsewhere (3). Briefly, we searched MEDLINE and EMBASE, with no language restrictions, for human studies reporting the association between body weight and endometrial cancer incidence, using terms related to bodyweight ("body mass index," "body size," "body fatness," "obesity," and "adiposity") and combined this with site-specific terms ("endometrium," "corpus uteri," and "uterine corpus"). Reference lists from reviews (4, 5, 9, 10), and reports (2, 11) were also scrutinized.

We included cohort studies (or case-control studies nested within cohorts) that determined BMI at baseline (either self-reported or directly measured), recorded incident cancer cases during follow-up and reported risk estimates (relative risk, odds ratio, or hazard ratio) across at least 3 BMI categories. Eligibility was assessed independently by 2 investigators (A.G.R., E.J.C.).

Data extraction

Data were extracted by 1 investigator (A.G.R.) and checked by a second (E.J.C.), including information on: study design and patient characteristics, risk ratio estimates, and their 95% confidence intervals (CI). Where available, data were collected for minimally and maximally adjusted estimates. Geographic populations were categorized into North American, European, and Asia-Pacific origin. One study (12) recruited a multiethnic population from the United States of America and this study was considered separately. We extracted the mean BMI and its standard deviation for each study to estimate median BMI values for open-ended BMI categories.

Quality assessment

We assessed 3 characteristics of studies that might affect the strength of the BMI cancer risk association: whether BMI was measured or self-reported, the extent to which studies adjusted for potential confounding variables, and the mean length of study follow-up.

Statistical analysis

We transformed category-specific risk estimates into estimates of the risk ratio (RR) associated with every 5 kg/m² increase in BMI, for 2 reasons: i) this increase approximates the difference between the mid-points of BMI categories defined by World Health Organization (normal, overweight, obese) (13); ii) it approximates the standard deviation for BMI distributions in many populations (14). We used the method of generalized least

squares for trend estimation (GLST) described by Orsini and colleagues (15). Risk estimates were calculated based on the assumption of a linear relationship of the natural logarithm of RR with increasing BMI. We assigned a single value to each BMI category: for closed categories, the mid-point was assigned; for open categories, the median BMI value was calculated assuming a normal distribution.

We combined RRs per 5 kg/m² increase in BMI in random-effects meta-analysis using the most adjusted risk estimate from each study. We explored possible sources of heterogeneity using meta-regression analyses (16). We had previously observed that the association of BMI with risk of several cancer types was log-linear in general, but that it might not be log-linear for endometrial cancer (3). We therefore also modeled BMI associations with endometrial cancer using piecewise linear regression. The inflection point and slopes were taken from the model with the best goodness-of-fit (ref. 15; Supplementary material p. 1).

For both linear and piecewise models, we calculated separate risk estimates per 5 kg/m² increase in BMI by use of HRT, menopausal status, and Bokhman's histologic type, and where possible, associations with use of oral contraceptives and tamoxifen. We then compared estimates in meta-regression analyses. As the number of studies per subgroup were too small to robustly fit separate piecewise linear models to each subgroup, we extrapolated estimates from the linear models using the equation underpinning the piecewise linear model for all studies, relative to the linear model (supplemental material p. 2).

Between study heterogeneity was evaluated using the I² statistic (17): values of 25%, 50%, and 75% correspond to low, moderate, and high degrees of heterogeneity. Sensitivity analyses included repeating analyses using a fixed-effects model, using minimally compared with maximally adjusted RRs, and influence analyses to assess the effect of a single study on the summary risk estimates (18). Publication bias was examined in funnel plots and using a regression asymmetry test (19). All statistical analyses were performed using STATA version 9.2 (College Station, TX, USA).

Results

Figure 1 shows the search and selection process: we identified at total of 24 eligible studies (12, 20–42), adding 5 studies (38–42) since our earlier analysis (3). Nineteen (79%) of the 24 eligible studies were published since 2003. Ten articles did not meet criteria: 2 included fatal cases only (43, 44); 3 were duplicates (45–47); 2 reported fewer than 3 BMI categories (48, 49); and 2 did not provide data on BMI (50, 51). The Million Women Study (52) did not report the association between BMI and endometrial cancer risk overall but allowed calculations of RRs in HRT users. The HUNT II study published its main results on the associations between BMI and endometrial cancer

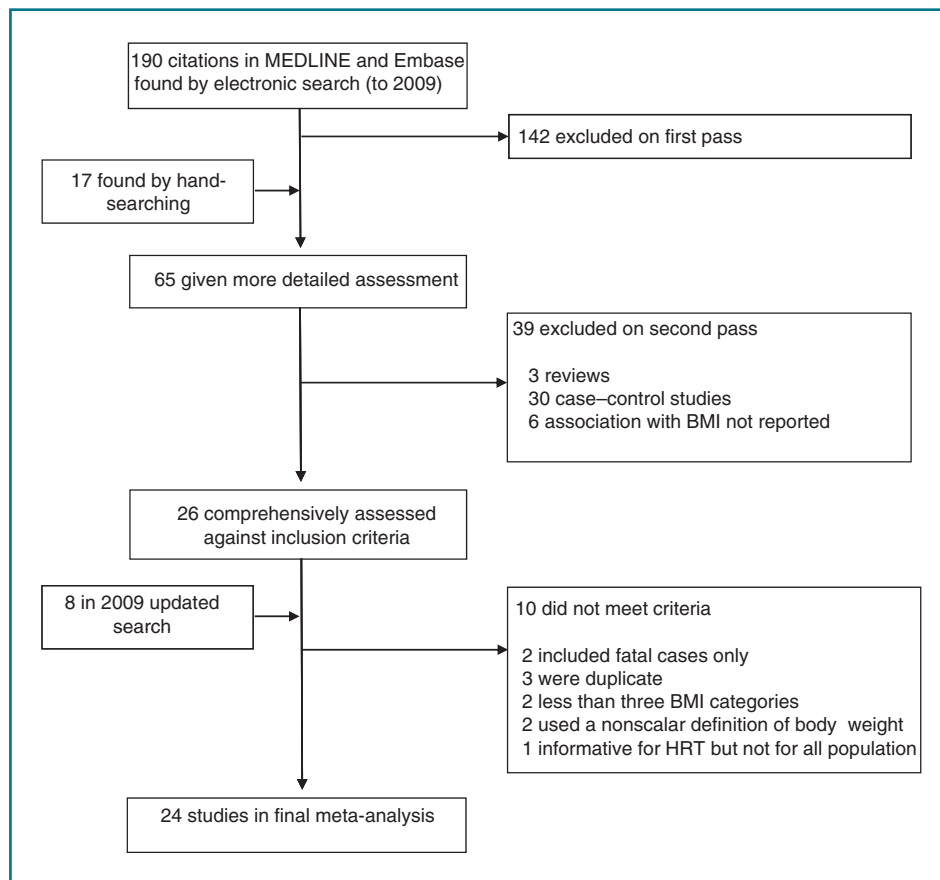


Figure 1. Flow diagram of literature search.

risk in one paper (42), and associations by histologic subtype in a separate paper (53). Data from both papers were used. After the closure of our literature search, the Me-Can project (54) published a pooled analysis of data from 7 European cohorts, including 3 studies already identified in our search (25, 29, 31). As individually reported studies were more informative for baseline characteristics, they were used in the main analysis, subgroup analyses, and meta-regression—while data from the Me-Can project (54) was not included in the main analysis, it was included in sensitivity analyses to assess study influence.

Study characteristics

The characteristics of included studies are summarized in Table 1. In total, there were 18,234 incident endometrial cancers with a geometric mean follow-up of 10.5 (95% CI, 8.5–12.8) years. Eleven studies (46%) measured BMI, the remaining used self-reported BMI. The number of potential confounders included in adjusted analyses varied (median = 5; range 1–11 variables).

Overall analyses

Figure 2 shows the results of the random-effects meta-analyses for all 24 studies. The number of cases included

in the main analysis was 17,710, as in the derivation of study-specific slopes (15), categories with BMI values less than the referent BMI category were dropped in the modeling (no. of cases: 524 or 2.8%; Supplementary material p. 3). For the linear model, the combined RR per 5 kg/m² was 1.60 (95% CI, 1.52–1.68). RRs for geographic populations were similar ($P = 0.46$ from global F test). However, there were moderate-to-high degrees of heterogeneity between all studies, and between studies within geographic regions. In piecewise regression analysis, the best fit was obtained with an inflection point at 27 kg/m² (P for difference in slopes < 0.0001, see supplemental material p1). In the piecewise model, RRs were smaller than those for the linear model up to BMI 30 kg/m² but larger thereafter (referent categories for both was 22 kg/m²): RRs at 27, 32, 37, and 42 kg/m² compared with women with a normal BMI were 1.22 (1.19–1.24), 2.09 (1.94–2.26), 4.36 (3.75–5.10), and 9.11 (7.26–11.51), respectively (Table 2).

Sources of heterogeneity

There was some evidence that studies with self-reported height and weight produced stronger associations: the RR per 5 kg/m² was 1.67 (95% CI, 1.55–1.81) compared with 1.49 (95% CI, 1.42–1.57) in studies

Table 1. Baseline characteristics of studies included in meta-analysis

First author (year) (ref.)	Country, study name	Study participants & age range	No. of BMI cases determination	Recruitment period(FU) year	Adjustments
Nested case-cohorts					
Bernstein et al. (1999) (23)	USA, SEER 4 region database	671 women with breast cancer Age range not stated	From medical records	1978–1992 (not stated)	Age, smoking, OC use, HRT use, tamoxifen & breast cancer chemotherapy
Schouten et al. (2004) (26)	Netherlands, Netherlands Cohort Study	1,636 55–69 y	Baseline questionnaire	1986–1994 (9.3)	Age, smoking, physical activity, age at menarche, OC use, parity, menopausal status
Twin Study					
Lundqvist et al. (2007) (36)	Sweden, Swedish Twin Registry	14,058 43–89 y	Self administered questionnaire	1961–1975 (22)	Age, smoking, education, physical activity, birth country, diabetes
Cohorts					
Baanders-van Halewijn et al. (1985) (20)	The Netherlands, the DOM project	14,000 50–65 y	Questionnaire	1974–1980 (7.5)	Age
Tornberg & Carstensen (1994) (21)	Sweden, Two Countries Screening Programme	47,003 Age range not stated	Weight & height " were measured"	1963–1965 (20.3)	Age, period of follow-up
Tulinius et al. (1997) (22)	Iceland, Icelandic Cardiovascular Risk Factor Study	11,580 Age range not stated	"Anthropometric measurements"	1967–1969 (not stated)	Age
Olson et al. (1999) (24)	USA, Iowa Women Study	24,848 55–69 y	Multi-phase questionnaire	1986–1987 (10)	Age
Furberg & Thune (2003) (25)	Norway, Norwegian Cohort Study	24,460 20–49 y	Weight & height "were measured"	1974–1981 (15.7)	Age, smoking, birth country, physical activity, hypertension & serum glucose
Kuriyama et al. (2005) (27)	Japan, Miyagi Prefecture Study	13,747 over 40 y	Self reported	1984–1992 (9)	Age, smoking, alcohol, dietary factors, parity, menopausal status, health insurance type
Lacey et al. (2005) (28)	USA, Breast Cancer Detection Demonstration Project	30,379 Age range not stated	Questionnaire	1979–1998 (13)	Age, HRT use, type of HRT

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Table 1. Baseline characteristics of studies included in meta-analysis (Cont'd)

First author (year) (ref.)	Country, study name	Study participants & age range	No. of BMI cases determination	Recruitment period(FU) year	Adjustments
Rapp et al. (2005) (29)	Austria, Vorarlberg Health Monitoring and the Promotion Program (VHM & PP) Study	78,484 19–94 y	175 Weight & height "were measured by trained staff"	1985–2001 (9.9)	Age, smoking, occupational group
Silvera et al. (2005) (30)	Canada, Canadian National Breast Screening Study	49,613 40–59 y	426 Questionnaire	1980–1985 (16.4)	Age, smoking, alcohol, diet, physical activity, age at menarche, OC use, parity, menopausal status, HRT use
Bjorge et al. (2006) (31)	Norway, Cancer Registry of Norway	1,038,018 20–74 y	9,227 Weight & height "were measured by trained staff"	1963–1965 (25)	Age, birth cohort
Lukanova et al. (2006) (32)	Sweden, Northern Sweden Health & Disease Cohort	35,362 29–61 y	118 Weight & height "were measured"	1985–1996 (8.3)	Age, smoking, calendar year
Chang et al. (2007) (33)	USA, NIH-AARP Diet and Health Study Cohort	103,882 50–71 y	677 Questionnaire	1995–1996 (4.6)	Age, race, smoking, physical activity, diabetes, age at menarche, parity, OC use, HRT use, age at menopause
Friedenreich et al. (2007) (34)	Europe, European Prospective Investigation into Cancer and Nutrition	223,008 35–70 y	567 Measured anthropometric factors except centers in France and from the Oxford 'health conscious' cohort	1992–2000 (6.4)	Age, smoking, dietary factors, alcohol, physical exercise, birth country, education, OC use, menopausal status, HRT use
Larsson et al. (2007) (35)	Sweden, Swedish Mammography Cohort	61,226 49–83 y	608 Self administered questionnaire, including height & weight	1987–1990 (15.6)	Age
Reeves et al. (2007) (37)	UK, Million Women Study	1,222,630 50–64 y	2,657 Questionnaire	1996–2001 (5.4)	Age, smoking, alcohol, physical activity, parity, menopausal status, HRT, geographic region, socioeconomic status

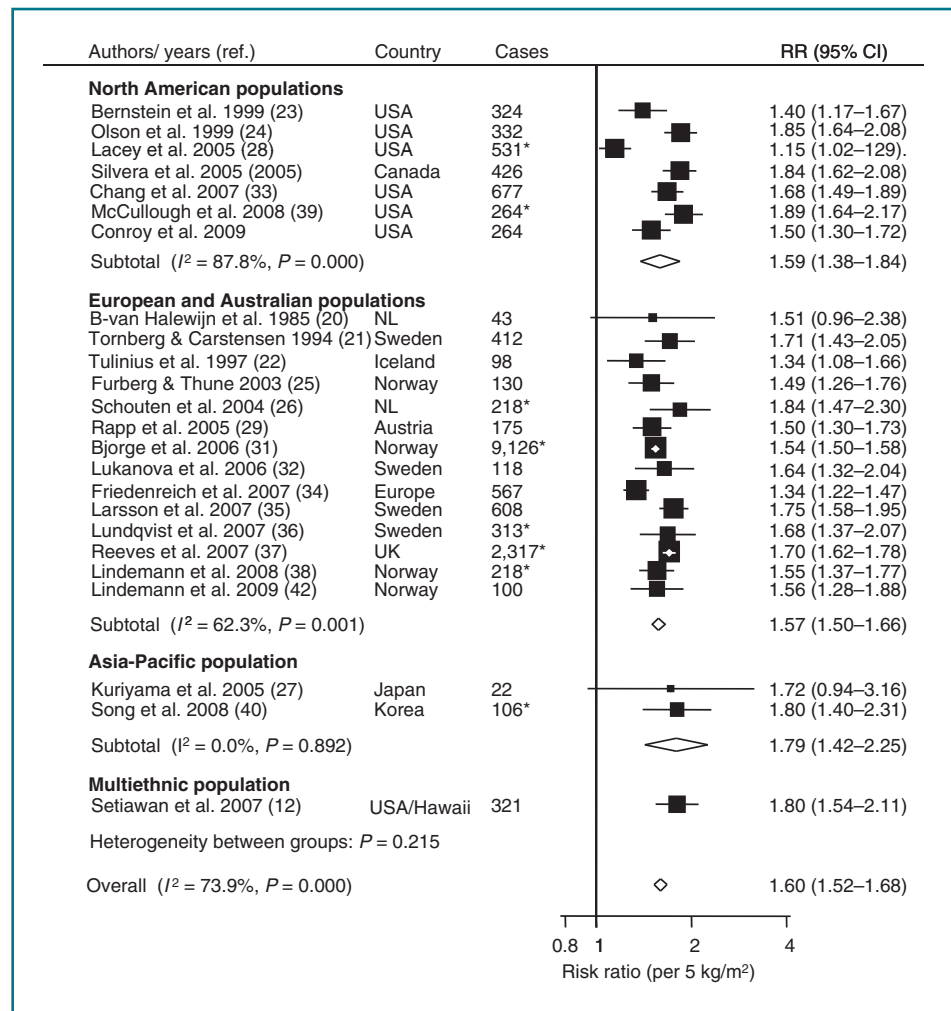
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Table 1. Baseline characteristics of studies included in meta-analysis (Cont'd)

First author (year) (ref.)	Country, study name	Study participants & age range	No. of BMI cases determination	Recruitment period(FU) year	Adjustments
Setiawan et al. (2007) (12)	Multiethnic, Multiethnic Cohort Study	49,933 Age range not stated	321 Questionnaire	1993–1996 (7.3)	Age, family history, smoking, parity, menopausal status, HRT use, birth country, OC use, diabetes
Lindemann et al. (2008) (38)	Norway, HUNT I study	36,761 20–101 y	222 Weight & height "were measured"	1984–1986 (15.7)	Age, diabetes, smoking, physical activity, hypertension, alcohol
McCullough et al. (2008) (39)	USA, Cancer Prevention Study II Nutrition Cohort	33,436 55–70 y	318 Questionnaire	1992–1993 (8.9)	Age, smoking, age at menarche, OC use, parity, physical activity, age at menopause, HRT use
Song et al. (2008) (40)	Korea, Korean National Health and Nutrition Survey	170,481 40–64 y	112 Weight & height "were measured using standardized stadiometers and scales"	1994–2003 (8.75)	Age, height, smoking, alcohol, physical exercise, salary level
Conroy et al. (2009) (41)	USA, Women's Health Study	32,642 ≥ 45 y	264 Self reported, questionnaire	1992–1995 (8.8)	Age, smoking, alcohol, saturated fat intake, fiber intake, fruit/vegetable intake, parity, menopausal status, HRT use, HRT type
Lindemann et al. (2009a) (42)	Norway, HUNT II study	31,473 20 yr and older	100 Weight & height "were measured"	1995–1997 (9.0)	Age, lipids, diabetes, hypertension, smoking, parity

BMI: body mass index. FU: follow-up. OC: oral contraceptive use. HRT: hormonal replacement therapy.

Figure 2. Forest plot of the associations between 5 kg/m² BMI increase (linear model) and endometrial cancer risk stratified by main geographic populations. *Number of cases included in the analysis after excluding cases with lesser BMI values than the referent BMI category.



measuring height and weight (P for interaction = 0.055, see supplemental material p. 4). There was little evidence for differences in associations according to the degree of adjustment for potential confounding factors (<5 variables versus ≥ 5 variables), adjustment for family history of endometrial cancer, physical activity, smoking, alcohol consumption, menopausal status, use of HRT, parity, and oral contraceptive use. Mean age at baseline, mid-enrollment year (as an approximation of study period), mean BMI at baseline and the mean duration of follow-up also had little effect on the BMI-cancer associations (supplemental material p5).

Associations in studies stratified by sex hormone-related states

A total of 9 studies (36–39, 52) contributed to these analyses, all published since 2003 (supplemental material p6).

Three studies (33, 34, 39) stratified analyses according to never versus ever HRT use and the Million Women Study (52) reported the number of cases in women on combined

HRT across BMI categories giving an analyzed total cases of 2,253. Associations were stronger for never users compared with ever users of any HRT preparation (Fig. 3): the RRs per 5 kg/m² were 1.90 (95% CI, 1.57–2.31) and 1.18 (95% CI, 1.06–1.31), respectively (P for interaction = 0.003). The difference remained when restricting the analysis to studies of combined HRT preparations ($P = 0.032$). The piecewise linear model estimated that, in never HRT users, the risk was substantially increased in obese women compared with women at normal BMI: the RR at 42 kg/m² was 20.70 (95% CI, 8.28–51.84).

Six studies (no. of analyzed cases: 16,056) (25, 31, 34, 36–38) reported analyses stratified by menopausal status, but with varying definitions of menopausal status. The combined RR was somewhat higher for postmenopausal women (1.60, 95% CI, 1.40–1.83) than for premenopausal women (1.49, 95% CI, 1.39–1.61) but the difference was not statistically significant ($P = 0.34$, see supplemental material p7). Three studies (no. of analyzed cases: 8,184; ref. 31, 39, 53) presented analyses stratified by histologic type. The combined RR was

Table 2. BMI-endometrial cancer risk associations stratified by population type and HRT use using the piecewise model

	No. of studies	Risk ratio (95% CIs)				
		22 kg/m ²	27 kg/m ²	32 kg/m ²	37 kg/m ²	42 kg/m ²
Total	24	1.00	1.22 (1.19, 1.24)	2.09 (1.94, 2.26)	4.36 (3.75, 5.10)	9.11 (7.26, 11.51)
Population type						
North American	8	1.00	1.21 (1.14, 1.29)	2.08 (1.66, 2.60)	4.33 (2.77, 6.78)	9.01 (4.61, 17.65)
European	13	1.00	1.21 (1.18, 1.23)	2.04 (1.89, 2.21)	4.18 (3.56, 4.90)	8.54 (6.72, 10.85)
Asia-Pacific	2	1.00	1.27 (1.16, 1.40)	2.49 (1.74, 3.58)	6.23 (3.02, 12.83)	15.53 (5.25, 45.97)
Multiethnic	1	1.00	1.28 (1.20, 1.36)	2.52 (1.99, 2.54)	6.35 (3.87, 10.45)	15.99 (7.61, 33.79)
HRT use						
Never	3	1.00	1.31 (1.20, 1.42)	2.74 (2.02, 3.73)	7.54 (4.09, 13.90)	20.70 (8.28, 51.84)
Combined HRT	3	1.00	1.08 (1.02, 1.14)	1.34 (1.08, 1.65)	1.78 (1.17, 2.72)	2.38 (1.26, 4.50)
Any HRT	5	1.00	1.07 (1.03, 1.12)	1.30 (1.10, 1.53)	1.68 (1.21, 2.33)	2.18 (1.33, 3.55)

CI; confidence interval., HRT: hormonal replacement therapy.

higher for type I (1.74, 95% CI, 1.50–2.02) compared with type II (1.51, 95% CI, 1.29–1.78), but this difference was not statistically significant ($P = 0.26$; see Supplementary material p. 8).

A possible effect modification of oral contraceptive use was examined only in the European Prospective Investigation into Cancer (EPIC) (34), and no difference was noted. We found no study that stratified analyses by tamoxifen use.

Sensitivity analyses and publication bias tests

Results were generally consistent when repeating analyses using a fixed-effects model (supplemental material p. 9). Repeating analyses using minimally adjusted rather than maximally adjusted estimates produced similar results (supplemental material p9). Influence analyses showed that exclusion of one study at a time did not influence the summary risk estimate (supplemental material p. 10). We added the risk estimates from the Me-Can

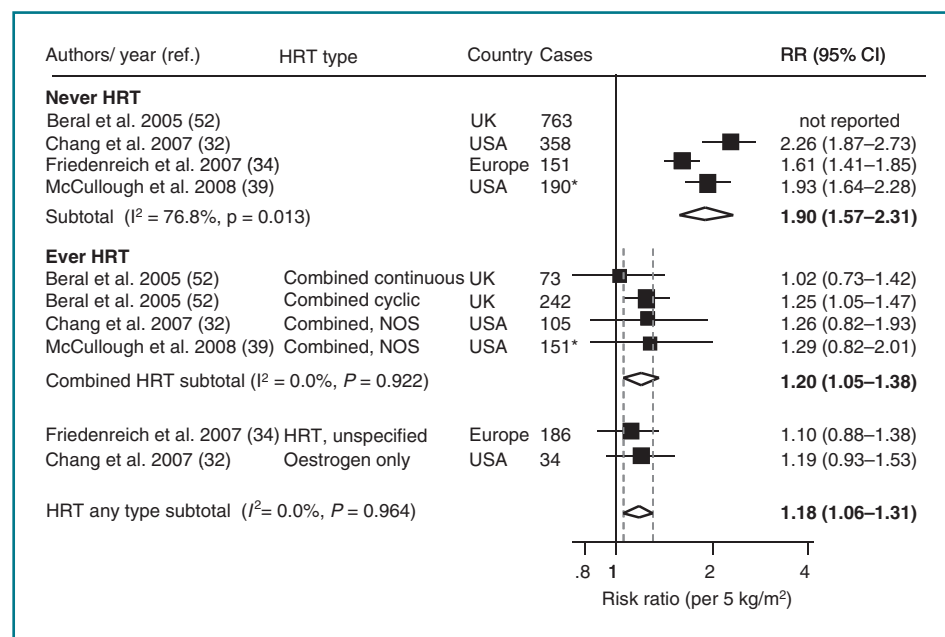


Figure 3. Forest plot of the associations between 5 kg/m² BMI increase (linear model) and endometrial cancer risk by studies, which reported results stratified by hormonal replacement therapy (HRT) use. Dotted vertical lines represent 95% CIs of combined risk estimate of any HRT user. NOS: not otherwise specified. *Number of cases included in the analysis after excluding cases with lesser BMI values than the referent BMI category.

pooled analysis of 7 cohorts (54), while excluding the 3 studies (25, 29, 31) mutual to that project and our main analysis — this made no material difference to the summary estimate (supplemental material p.11). Finally, there was little evidence for funnel plot asymmetry and tests for publication bias were not statistically significant (supplemental material p. 12).

Discussion

Summary of principal findings

This study confirms that BMI is strongly associated with an increased risk of incident endometrial cancer (2, 3). It extends our previous meta-analysis (3) demonstrating that the association becomes stronger above BMI 27 kg/m², and that the association is particularly strong in women who have never been exposed to HRT. Finally, it shows that menopausal status and histologic subtype did not significantly impact upon these associations.

Confounding and bias

Meta-analyses of observational studies are vulnerable to the biases and confounding inherent in the original studies (55). To minimize such biases, we restricted our analyses to cohort studies and case-control studies nested within cohort studies, excluding traditional case-control studies that are prone to recall bias (56). There was substantial heterogeneity between study results, with the method by which BMI was determined explaining some of the heterogeneity. This is not surprising as self-reported body weight underestimates true body weight, with the degree of misclassification increasing with age and weight (57). However, BMI measurement determination method does not explain all the between-study heterogeneity. Differences in the BMI distribution across studies are a potential source of heterogeneity when expressing results on a linear scale, as it ignores that the true relationship between the logarithm of the relative risk and BMI is probably not linear. Smoking may be an additional confounder as it is antiestrogenic (58) and there is evidence that the risk of endometrial cancer is attenuated for a given BMI category in smokers compared with nonsmokers (59, 60). However, the present analysis was not designed to assess the complex triangulated relationship of BMI, HRT, and smoking, and indeed our search failed to identify a study that assessed all three risk factors interactively. A collaborative reanalysis of the individual participant data (IPD) from the different studies would better allow examination of different forms of risk relationships and generally to explore sources of heterogeneity (61, 62). In the absence of IPD, we reported linear and piecewise linear models to give an appreciation of the magnitude of risk in the extreme ranges of the right-side of the BMI distribution. Interestingly, estimates from maximally adjusted analyses were similar to those for minimally adjusted analyses, suggesting that the association between BMI and endo-

metrial incident cancer is not confounded by other factors such as, use of oral contraceptives, alcohol, or other lifestyle factors. Finally, there was no evidence that results had been distorted by publication bias.

Findings in context with other studies

The results of the present analysis are consistent with our previous study (3), and an older meta-analysis (9) of 4 nested case-control studies, which found a risk increase per 5 kg/m² in BMI of 1.50. A comprehensive narrative review (4) and the International Agency for Research on Cancer 2002 report (11) cited a 2 to 5-fold increase in endometrial cancer risk associated with obesity, but these estimates were not modeled against a specific BMI incremental increase. The meta-analysis by the World Cancer Research Fund (WCRF), reported similar risk estimates per 5 kg/m²: 1.52 for cohort studies and 1.56 for case-control studies (2).

Several case-control studies have determined associations between BMI and endometrial cancer risk—for example, there were 28 studies of this type included in the WCRF report (2). However, only a small number of these reported BMI-cancer associations stratified by HRT status (63, 64), and due to small numbers, BMI categories were simply dichotomized. The WCRF report (2), which only included studies only to 2006, concluded that "there was no evidence of effect modification by . . . oestrogen-use status," whereas our updated analysis identified that there is an effect modification.

The inclusion of several recently published studies, the investigation of the shape of the dose-response relationship, and the study of sex hormone-related states, are strengths of the present meta-analysis. The meta-regression analyses showed that the association between BMI and endometrial cancer is much stronger in never-users of HRT, while the ever use of any type of HRT attenuated the association but importantly there was residual risk. The possible exception is the use of continuous combined HRT, where the association appears to be null, but this was based on one study only (52).

The HRT effect partly explains between study heterogeneity, for example, for populations where HRT prevalence use is low such as Asian-Pacific, risk estimates are elevated. However, it is important to emphasize that this does not imply that increasing BMI protects against the adverse effects of HRT on endometrial cancer risk. Rather, unopposed estrogen HRT use is associated with a 2- to 3-fold increased risk of incident endometrial cancer compared with nonusers (65, 66). Associations were somewhat stronger for postmenopausal cancers and Type-I histologies, and with more standardized definitions of these subgroups, these differences might be significant. Data were too scarce to allow separate estimates for use of estrogen-containing oral contraceptives, known to protect against endometrial cancer (67), or use of tamoxifen for breast cancer, a partial estrogen agonist that increases the risk of endometrial cancer (68).

Plausible mechanisms

Most major risk factors for endometrial cancer (e.g. early menarche, late menopause) probably act through pathways reflecting greater life-time exposure to estrogens. Pooled data from studies determining concentrations of sex steroids show that higher levels of plasma estrone and estradiol are associated with increased endometrial cancer risk in postmenopausal women (69) and administration of unopposed estrogen results in endometrial hyperplasia, a precursor of endometrial cancer (70). At a molecular level, estrogens increase transcription and enhance growth factor signaling pathways, favoring tumorigenesis (71). Obesity is a hyperestrogenic state through the increased aromatization of estrogen precursors in adipose tissues, and this is likely to be the main mechanism linking obesity with endometrial cancer risk.

For endometrial cancer arising in premenopausal women, chronic obesity-related anovulation is associated with relative or absolute progesterone deficiency, decreasing local uterine insulin-like growth factor binding protein (IGFBP)-1 synthesis, which in turn increases bio-availability of IGF-I and favors tumor formation (4, 5). Hyperestrogenia may also be relevant as obesity-related ovarian hyperandrogenism increases androgen precursors for aromatization by the peripheral adipose tissues.

The potential role of obesity-associated chronic hyperinsulinemia is supported by observations that high insulin levels are associated with increased endometrial cancer risk (72, 73). Chronic hyperinsulinemia also increases synthesis of androgen precursors peripherally, and as elevated plasma androstenedione and testosterone concentrations increase endometrial cancer risk in pre and postmenopausal women (69), hyperinsulinemia may be relevant in this cancer independent of menopausal status.

Adiponectin and leptin are the 2 most abundant adipokines and best studied in terms of endometrial cancer risk. Adiponectin is inversely proportional to BMI, acts as an insulin-sensitizer, a negative regulator of angiogenesis, and inhibits cell proliferation *in vitro* (74)—consistent with these attributes, several studies report an inverse association between circulating concentrations and endometrial cancer risk (75, 76). By contrast, leptin is mitogenic, antiapoptotic, proangiogenic, and proinflammatory, and high circulating concentrations are associated with endometrial cancer (77, 78).

How do we interpret our findings in light of the possible mechanisms summarized above? First, summaries of observational studies (65, 66) estimate that exogenous unopposed estrogen use is associated with a 2-to 3-fold increased risk of postmenopausal endometrial cancer, which is reduced towards that of nonusers in women who use combined estrogen-progesterone preparations. The difference in mean concentrations of estrogen-related hormones between obesity and

normal weight is approximately 2-fold (79), whereas mean concentrations are typically 6- to 10-fold greater after HRT administration [e.g., mean serum concentrations for estradiol and estrone in general population cohorts are in the order of 40 and 80 pmol/L, respectively (79); whereas in users of estrogen-progesterone preparations, the mean concentrations are approximately 250 pmol/L and 1,000 pmol/L, respectively (80)]. This "excess" estrogen environment may hide the association with BMI that is seen in women not using HRT. Second, the protective effects of progesterone in combined HRT may cancel out the carcinogenic effects of endogenous estrogen in the obese woman. The effect of progesterone may be dependent on the level of exposure (numbers of days per cycle) (81): consistent with this, there was no increase in risk with increasing BMI for continuous combined HRT whereas estimates for cyclical combined HRT were similar to those for estrogen alone (52). Third, obesity may be a risk factor for Type I endometrioid tumors, as the latter are linked with hyperestrogenic states (8). We observed a somewhat stronger association for Type I histologies; however, analyses were limited to three studies, with different definitions of histologic subtypes, and our study could not confirm or exclude a difference in the BMI-cancer risk association according to histology.

The residual risk associated with higher BMI among HRT users (with the possible exception of continuous combined) point to mechanisms additional to a hyperestrogenic state. These may include chronic hyperandrogenisms in premenopausal women, chronic hyperinsulinemia, and alterations of adipokine metabolism. Furthermore, the stronger associations in the higher BMI range (in the piecewise model) are compatible with several mechanisms. For example, increased insulin in the cellular environment of obese women may prime endometrial epithelium to the enhanced effects of IGF-I, leptin, or estrogens.

Implications and future research

With a global obesity epidemic, the attribution of excess weight to endometrial cancer risk across populations may be considerable: we recently estimated that in Europe, excess weight might account for 60% of new endometrial cancer cases each year (14). Sustained weight loss in morbidly obese patients (BMI >40 kg/m²) undergoing bariatric surgery reverses type 2 diabetes and reduces cardiovascular risk, but also is associated with reduced cancer incidence (82). This effect appears to be limited to women and includes reductions in endometrial cancer risk. For the wider overweight population, lifestyle, and dietary interventions aimed at weight reduction are often hampered by poor adherence and lack of sustained effects, and have yet to demonstrate reductions in cancer risk. Accordingly, there is a need to explore alternative approaches, based on the likely mechanisms mediating the link between body adiposity and endometrial cancer.

Contributors

A.G. Renehan and E.J. Crosbie contributed to protocol design, data extraction, quality assessment, statistical analysis, and writing of the report. M. Zwahlen contributed to statistical analysis, and writing the report. M. Egger and H. Kitchener contributed to interpretation of data and revision of the manuscript.

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Body Mass Index, Hormone Replacement Therapy, and Endometrial Cancer Risk: A Meta-Analysis

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