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Body mass index does not influence post-treatment survival in early stage endometrial cancer: Results from the MRC ASTEC trial

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ABSTRACT

Body mass index (BMI) is a major risk factor for endometrial cancer incidence but its impact on post-treatment survival is unclear. We investigated the relationships of BMI (categorised using the WHO definitions) with clinico-pathological characteristics and outcome in women treated within the MRC ASTEC randomised trial, which provides data from patients who received standardised allocated treatments and therefore reduces biases. The impact of BMI on both recurrence-free survival (RFS) and overall survival (OS) was analysed using the Cox regression models. An *a priori* framework of evaluating potential biases was explored. From 1408 participants, there were 1070 women with determinable BMI (median = 29.1 kg/m^2). Histological types were endometrioid (type 1) in 893 and non-endometrioid (type 2) in 146 women; the proportion of the latter decreasing with increasing BMI (8% versus 19% for obese III WHO category versus normal weight, $p_{trend} = 0.003$). For type 1 carcinomas, increasing BMI was associated with less aggressive histopathological features (depth of invasion, $p = 0.006$; tumour grade, $p = 0.015$). With a median follow-up of 34.3 months, there was no influence of BMI on RFS - adjusted HRs per 5 kg/m^2 were 0.98 (95% CI 0.86, 1.13) and 0.95 (0.74, 1.24), for type 1 and 2 carcinomas; and no influence on OS – adjusted HRs per 5 kg/m^2 were 0.96 (0.81, 1.14) and 0.92 (0.70, 1.23), respectively. These findings demonstrate an important principle: that an established link between an exposure (here, obesity) and increased incident cancer risk, does not necessarily translate into an inferior outcome following treatment for that cancer.

1. Introduction

Endometrial cancer is now the most common gynaecological malignancy in the developed world. In 2007, there were 6237 new cases in England.[1] The age-standardised incidence of corpus uteri cancer in England remained stable between 1975 and 1993, but increased by 40% between 1993 and 2007.[1] Hysterectomy and bilateral salpingo-oophorectomy

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(BSO) is the standard treatment for early stage disease with European 5-year survival rates of approximately 78%.[2]

Increased body fatness, commonly measured as body mass index (BMI), is a major risk factor for incident endometrial cancer.[3,4] Using a standardised meta-analysis approach, we recently quantified this risk as 1.59 (95% CIs: 1.50–1.68) per 5 kg/m^2 increase in BMI, ranking endometrial cancer as the highest risk per unit exposure among BMI-associated cancers in women.[3] With plausible biological explanations[5,6], consistency of association, and long durations between BMI measurement and cancer occurrence in the meta-analysed cohort studies,[3] these associations are probably causal.[4] Additionally, two large population-based cohort studies – one in the US[7]; one in the UK[8] – reported that increased BMI at cohort baseline is associated with an increased risk of endometrial cancer-related mortality – risk ratio = 6.25 (95% CIs: 3.75–10.42) for BMI $\geqslant$ 40 kg/m^2 versus normal weight; relative risk = 2.46 (95% CIs: 1.78–3.39) per 10 unit BMI increase, However, while these studies inform public health regarding attributable disease burden, they do not directly inform us of the effect of excess body weight (a modifiable factor) on treatment outcome. For instance, gross obesity could result in suboptimal treatment and reduced overall survival as a consequence of co-morbidity.

Several analyses in patients with other cancer types have noted that increased BMI at start of treatment impacts negatively on outcome in the following malignancies: breast (systematic reviews[9,10]; adjuvant endocrine-therapy studies,[11,12]) colorectal,[13–15] ovary[16,17] and prostate.[18] For women with endometrial cancer, a number of studies[19–21] have evaluated the same question but found that an elevated BMI was not an unfavourable prognosticator, and indeed, may be associated with slightly improved survival.[21] However, these studies were from retrospective series where there are substantial concerns of confounding by treatment indication. To reduce treatment selection bias, the Gynecologic Oncology Group retrospectively analysed data from their trial of surgery with or without adjuvant radiation therapy,[22] and found no effect of BMI on survival but the study size was small (380 patients). Furthermore, endometrial carcinomas are conventionally subdivided into two main histological subtypes, Bokhman types[23] – type 1 is associated with hyperoestrogenic states and obesity, while type 2 is not related to oestrogen status and has a more aggressive natural history. None of the reported studies to-date evaluated the impact of BMI on treatment outcome based on sub-categorisation into Bokhman types.

The aim of this study was to address these uncertainties – the first hypothesis is that excess body weight, a major risk factor for incident endometrial cancer, is an unfavourable prognostic factor for endometrial cancer; the alternate, second hypothesis is that obesity, a hyperoestrogenic state, is associated with an increased incident risk of the less aggressive type 1 endometrial cancer and thus predicts for a more favourable outcome after treatment. These hypotheses were tested using the data collected in the MRC ASTEC surgery trial, the largest randomised surgery trial in endometrial cancer. The whole MRC ASTEC study has two components: ASTEC surgery trial of lymphadenectomy and ASTEC radiotherapy trial of external beam radiotherapy. They showed no survival benefit from either lymphadenectomy[24] or external beam radiotherapy,[25] though the latter did result in a reduced rate of pelvic recurrence.

2. Methods

We investigated the relationships of BMI with clinic-pathological characteristics, treatment and survival using the data collected in the MRC ASTEC surgery trial.[24] In design, this represents an observational study within a randomised trial – thus STROBE[26] reporting guidelines were used and REMARK[27] guidelines used for reporting prognostic-related issues.

2.1. *Exposure measurement*

Height and weight were measured at the time of recruitment using local protocols and BMI calculated using the formula of weight in kilograms divided by the square of the height in metres (kg/m^2). BMI was then categorised using WHO definitions as follows: underweight as BMI < 18.5 kg/m^2; normal weight as BMI from 18.5 to 24.9 kg/m^2; overweight as BMI from 25.0 to 29.9 kg/m^2; obese I as BMI from 30.0 to 34.9 kg/m^2; obese II as BMI from 35.0 to 39.9 kg/m^2; and obese III as BMI $\geqslant$ 40.0 kg/m^2.

2.2. *Outcome measures*

Trial randomisation, data collection and monitoring were through the MRC Clinical Trials Unit, London. Details on WHO performance status (0–4), time since diagnosis, and planned surgical approach (open versus laparoscopic) were collected on all recruited women as these were included in the stratified randomisation. Surgical and pathology details (based on local reporting) were collected after surgery. The minimum dataset of the Royal College of Pathologists as the standard for pathology reporting was used.[28] Tumour stage was classified using the FIGO system[29] and risk stratified for subsequent adjuvant therapy into low-risk early; intermediate and high-risk early; and advanced, as previously described.[24]

After randomisation women were clinically assessed every 3 months in the first year, every 6 months in years 2 and 3, and every year thereafter. Follow-up data collected included details of endometrial cancer recurrence and radiotherapy received, vital status, and early and late (after 3 months) toxicity related to adjuvant radiotherapy treatment.

For this analysis, the primary outcome measures were recurrence-free survival (RFS) and overall survival (OS); the secondary outcome measures were adverse effects from treatment.

2.3. *Framework for evaluating potential biases*

As per protocol for this analysis, we specifically developed an *a priori* framework of evaluating key areas for potential confounding of the influence of BMI on post-treatment survival in women with endometrial cancer. We identified eight steps on the patient pathway – step 1, delayed diagnosis (higher

stage and/or more aggressive histopathology as best available surrogates); step 2, selection for initial treatment (surgery); step 3, 30-day mortality; step 4, selection for adjuvant therapy (namely, external beam radiotherapy, EBRT); step 5, early toxicity; step 6, altered treatment efficacy; step 7, late toxicity; and step 8, competing risks for death. We rationalised that in the setting of the two randomisations,[24,25] biases at steps 2 and 4 would be considerably reduced, yet we tested for each of these and the other six steps throughout our analyses.

2.4. *Statistical analysis*

Differences in baseline characteristics across the BMI categories were explored using standard approaches for continuous (1-ANOVA) and categorical (chi-squared test for multiple categories) variables as appropriate. We used Cuzick's non-parametric test and the Cochran–Armitage test for trends ($2 \times n$ tables) as appropriate. Deaths were classified as disease-related and non-disease related, and differences compared across BMI categories. We constructed Kaplan–Meier curves for all time-to-event outcome measures and compared across groups with the standard log-rank test. We defined RFS as the time from randomisation to first reappearance of endometrial cancer or death from any cause. We defined OS as the time from randomisation to death from any cause. For all time-to-event analyses, women who were known to be alive at the time of the analysis were censored at the time of their last follow-up.

Cox models were applied to assess whether BMI is an independent prognostic factor on RFS and OS. We used a seven step approach advocated by Hosmer and colleagues[30] forcing the BMI categories into the final model (Supplemental material p1). Models were also constructed with BMI as a continuous variable and results expressed as per 5 kg/m^2 increment. We tested predictive accuracy and calibration of the models using a concordance index (C-statistic; values ranging from 0.5 to 1.0) and the calibration statistic, analogous to the Hosmer-Lemeshow goodness-of-fit test (with a value $\leqslant 20$ indicating good agreement).[31] All statistical analyses were performed using STATA version 11.1 (College Station, Tx, USA).

3. Results

From an initial trial of 1408 women randomised to standard surgery versus standard surgery plus pelvic lymphadenectomy[24], 1070 women had determinable BMI (Fig. 1). We explored for factors associated with missing BMI data in 338 (24%) cases and found no differences by surgical allocation ($p = 0.318$), age groups ($p = 0.240$), performance status ($p = 0.282$) or main histological types ($p = 0.523$).

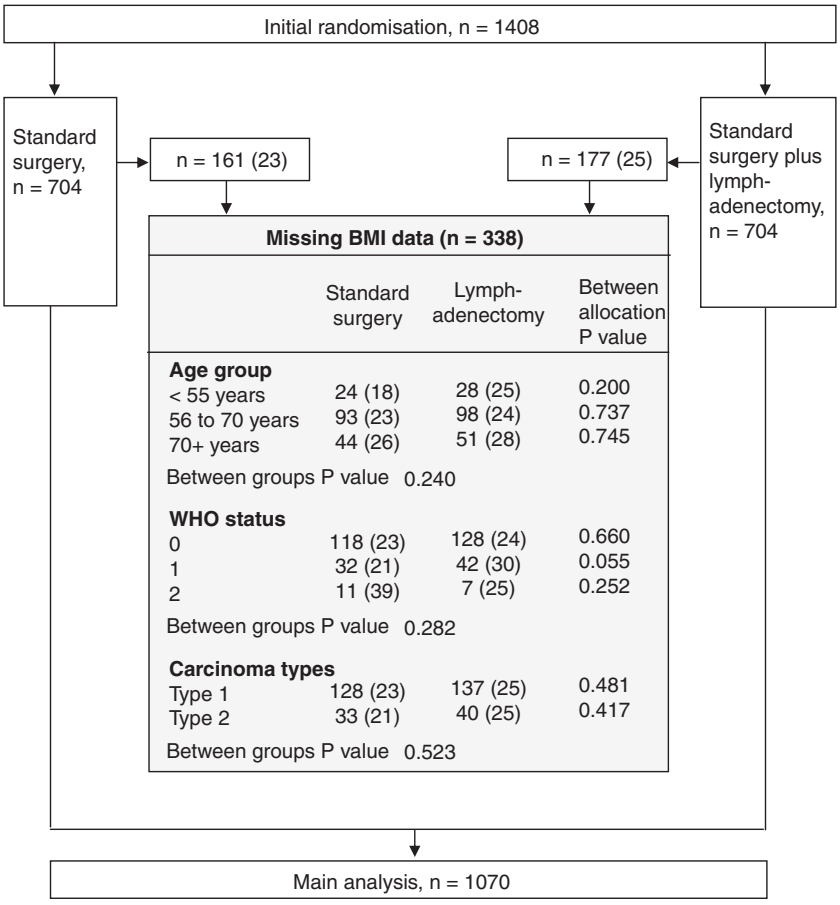

Fig. 1 – Flow diagram from initial randomisation of 1408 women to 1070 cases with determinable BMI data. BMI: body mass index. Values in parentheses are percentages.

Table 1 – Baseline characteristics by WHO BMI categories.

	Total	WHO BMI categories						
		Under-weight	Normal weight	Over-weight	Obese I	Obese II	Obese III	*P* value
No. of patients (%)	1070	8	228 (21)	347 (32)	245 (23)	150 (14)	92 (9)	
Cut-off points (kg/m^2)		<18.5	18.5–24.9	25.0–29.9	30.0–34.9	35.0–39.9	⩾40.0	
Median (IQR)	29.1 (25.4–34.3)	17.9	22.8	27.3	32.0	37.1	43.4	
Mean age (sd)	63.4 (9.4)	64.8 (15.9)	62.7 (9.9)	64.5 (9.3)	63.7 (9.1)	62.7 (8.9)	61.6 (9.1)	0.043[a]
WHO performance status (%)								
0	811	5	190 (82)	275 (80)	177 (72)	106 (71)	58 (63)	
1	221	3	37 (16)	59 (17)	61 (25)	33 (22)	28 (30)	<0.0001[b]
2–4	38	0	5 (2)	9 (3)	7 (3)	11 (7)	6 (7)	
Surgical allocation (%)								
Standard surgery	543	2	123 (53)	163 (48)	134 (55)	72 (48)	49 (53)	
Lymphadenectomy	527	6	109 (47)	180 (52)	111 (45)	78 (52)	43 (47)	0.352[c]
Surgery received (%)								
Total abdominal hysterectomy	1052	6	231 (99)	339 (98)	242 (99)	146 (97)	88 (99)	
Subtotal hysterectomy	7	1	0	1	2	2	1	0.390[c]
Unknown	11	1	1	3	1	2	3	
Surgical technique used (%)								
Laparoscopic	66	1	16 (7)	22 (6)	10 (4)	9 (6)	8 (9)	
Open	994	7	216 (93)	318 (93)	234 (96)	138 (92)	81 (88)	0.503[c]
Vertical incision	541	4	109 (50)	174 (55)	134 (58)	73 (53)	47 (58)	
Pfannenstiel	384	2	92 (43)	122 (38)	87 (37)	55 (40)	26 (32)	
Other transverse	60	1	14 (6)	20 (6)	10 (4)	8 (6)	7 (9)	0.781[c]
Unknown	9	0	1	2	3	2	1	
Unknown	10	0	0	3	1	3	3	
Blood transfusion								
Yes	56	3	10 (4)	20 (6)	11 (4)	8 (5)	4 (4)	
No	998	5	220 (95)	320 (94)	232 (95)	139 (93)	82 (91)	0.937[c]
Unknown	12	0	2	2	2	2	4	
Median (range) units		3 (3–4)	2.5 (2–4)	2 (1–4)	2 (2–5)	3 (1–4)	4 (2–7)	0.134[d]
Length of operation								
Median (range) minutes		77.5 (35–150)	75 (25–245)	80 (13–319)	80 (10–210)	90 (30–390)	90 (30–200)	0.001[d]
Post-operative days in hospital								
Median (range)	6 (2–71)	6 (3–12)	6 (2–34)	6 (2–40)	6 (2–35)	6 (2–71)	7 (2–25)	0.278[d]
Unknown	27	0	4	8	7	4	4	
Nodes harvested (%)								
Yes	499	4	111 (48)	172 (50)	108 (44)	72 (48)	32 (35)	
No	547	3	112 (48)	165 (48)	134 (55)	76 (51)	57 (62)	0.039[b]
Unknown	24	1	9	6	3	2	3	
Numbers of nodes harvested (%)								
1–4	61	0	14 (13)	21 (12)	10 (9)	10 (14)	6 (19)	
5–9	107	1	24 (22)	34 (20)	24 (22)	17 (24)	7 (22)	
10–14	112	1	28 (25)	39 (23)	22 (20)	15 (21)	7 (22)	
> 14	202	2	42 (38)	74 (43)	46 (43)	26 (36)	12 (38)	0.986[b]
Unknown	17	0	3	4	6	4	0	
Median (range)	13 (1–59)	14.5 (6–23)	12 (1–51)	12 (1–51)	14 (1–41)	11.5 (1–43)	11.5 (1–43)	0.645[d]
Lymph node ratio[e]								
Median (range)	0.18 (0.04–1)		0.40 (0.05–1)	0.18 (0.06–1)	0.18 (0.07–0.32)	0.07 (0.04–1)	0.43 (0.04–1)	0.342[d]

Table 1 – (*continued*)

	Total	WHO BMI categories						
		Under-weight	Normal weight	Over-weight	Obese I	Obese II	Obese III	*P* value
Adjuvant radiotherapy (%)								
No radiotherapy	697	5	147 (64)	219 (63)	157 (64)	103 (69)	66 (72)	
Any radiotherapy	351	3	78 (34)	122 (35)	84 (34)	42 (28)	22 (24)	0.060[b]
External beam ± brachytherapy	262	1	59 (76)	95 (78)	60 (71)	31 (74)	16 (73)	
Brachytherapy only	89	2	19 (24)	27 (22)	24 (29)	11 (26)	6 (27)	0.517[b]
Unknown	22	0	3	6	4	5	4	
Total radiation dose								
Median (range) Gy	45 (4–60)	45 (45–45)	45 (28–60)	45 (22–50)	45 (40–50)	45 (30–50)	45 (4–54)	0.145[d]
Unknown	97	2	20	27	24	11	8	
Other therapies (%)								
Any other therapy	65	3	19 (8)	24 (7)	7 (3)	6 (4)	6 (7)	
No other therapy	977	5	209 (90)	312 (91)	233 (95)	137 (91)	81 (88)	0.094[b]
Unknown	28	0	4	7	5	7	5	

IQR: interquartile range. sd: standard deviation.
Adjuvant radiotherapy defined as within 3 months post surgery.
All tests across BMI groups excluded 'underweight' category due to small sample sizes.
[a] One-way analysis of variance.
[b] Cochran-Armitage test for trends across ordered groups. For performance status, this is PS 0 versus others.
[c] Chi-squared test across multiple groups excluding unknown categories where applicable.
[d] Cuzick's non-parametric test for trends across ordered groups.
[e] Lymph node ratio is based on 49 cases i.e. excluded zero values.

3.1. *Baseline characteristics*

For the 1070 women, the median BMI was 29.1 (inter-quartile range, IQR: 25.4–34.3) kg/m^2 with a mean age of 63.4 (standard deviation: 9.4) years (Table 1). Women in the overweight and obese I categories were older than those in the normal weight and obese II and III categories ($p = 0.043$). Not unexpectedly, increasing BMI categories were associated with worsening performance scores ($p_{trend} < 0.0001$). Across the BMI categories, there were no differences in surgery allocation, type of surgery received, surgical technique used, and blood transfusion utilisation, although median length of operations were longer with increasing BMI ($p_{trend} = 0.001$). Lymph nodes were harvested in 499 (47%) patients with some evidence that harvesting was done less frequently with increasing BMI category ($p_{trend} = 0.039$). However, in women where nodes were harvested, BMI did not appear to influence the number of nodes harvested or the proportion of positive nodes. Following initial treatment, the use of EBRT was determined by randomisation[25] – nonetheless, there was some evidence that increasing BMI category was associated with decreased use of any radiotherapy ($p_{trend} = 0.060$), but not in total radiation dose received.

3.2. *BMI and histological types*

There were 893 women with type 1 (endometrioid) carcinomas; 146 with type 2 (non-endometrioid) carcinomas (Table 2). The proportion of type 2 carcinomas reduced with increasing BMI category ($p_{trend} = 0.003$) and the odds of the histological type being type 1 increased with increasing BMI category ($p_{trend} < 0.001$). Because of this significant difference in relationships with BMI categories, subsequent analyses were stratified by histological types.

3.3. *BMI and pathological characteristics*

For type 1 carcinomas, we explored several histopathological parameters and staging by BMI category (Table 3). There was evidence that increasing BMI was associated with less aggressive histopathological features – the proportions with endometrial only invasion increased with increasing BMI ($p = 0.006$) – for example, depth of endometrium invasion only, 21% in obese III versus 12% in normal weight; and the proportion of low grade features increased with increasing BMI ($p = 0.015$) – for example, well differentiated carcinoma, 50% in obese III versus 36% in normal weight. The proportion of tumours with lymphovascular permeation decreased with increasing BMI ($p_{trend} = 0.052$). As composite classifications of the above features, there was evidence that the proportions with FIGO low stage ($p < 0.001$) and low risk early disease ($p = 0.018$) increased with increasing BMI. By contrast, there were no patterns of associations between BMI categories and pathological characteristics among type 2 carcinomas.

3.4. *BMI and deaths*

For type 1 and 2 carcinoma patients combined, there were 139 any cause deaths – 93 in women with type 1 (10%); 46 in women with type 2 (32%, $p < 0.0001$). The majority of deaths (93/139, 68%) were disease-related, but this proportion was higher in type 2 compared with type 1 carcinoma patients (83% versus 60%, $p = 0.009$). However, across BMI categories,

Table 2 – BMI categories and main histological types

	Total	WHO BMI categories						P value
		Under-weight	Normal weight	Over-weight	Obese I	Obese II	Obese III	
Type 1 (Endometrioid)	893	7 (88)	177 (76)	289 (84)	206 (84)	132 (88)	82 (89)	
Type 2 (Non-endometrioid)	146	1	45 (19)	46 (13)	30 (12)	16 (11)	8 (8)	0.003[a]
Odds ratio for type 1 (95% CIs)[b]		Not included	1.00 (referent)	1.69 (1.07–2.65)	1.81 (1.09–3.00)	2.15 (1.16–3.97)	2.65 (1.19–5.87)	<0.001[c]

Non-carcinoma cases excluded.
[a] Cochran-Armitage test for trends across ordered groups.
[b] Adjusted for age in a logistic regression model.
[c] Post-estimation test for trends.

there were no differences by disease-related versus non-disease related deaths for type 1 and 2 carcinomas, combined or separately (Supplemental material p2).

3.5. BMI and survival

With a median follow-up of 34.3 (IQR: 21.7–51.6) months, 188 women had died or had recurrence of disease. For all 1070 cases, the 5-year RFS was 75% but there was no influence by BMI categories (Supplemental material p3 & 4). As expected, patients with type 1 carcinomas had a better 5-year RFS compared with that for type 2 carcinomas (79% versus 58%, logrank test: $p < 0.001$) (Supplemental material p5). We tested the effect of BMI on 5-year RFS separately by the main histological types – there was no influence by BMI categories in type 1 ($p = 0.871$) (Fig. 2A) or type 2 ($p = 0.674$) (Fig. 2B) carcinomas.

For all 1070 cases, the 5-year OS was 80% with no influence of BMI category (Supplemental material p6 & 7). By the main histological types, the 5-year OS was 84% for type 1 and 60% for type 2 carcinomas ($p < 0.001$) (Supplemental material p8). We tested the effect of BMI on 5-year OS – here again, there was no influence by BMI categories in type 1 ($p = 0.704$) (Fig. 2C) and type 2 ($p = 0.824$) (Fig. 2D) carcinomas.

We assessed the potential independent impact of BMI and other factors within Cox models with RFS as the dependent variable. For type 1 carcinomas, increasing age and risk groups, intermediate and high risk early disease, and advanced disease were independently prognostic, but not BMI (Table 4). Similar patterns were noted for type 2 carcinomas. The hazard ratios per 5 kg/m^2 increase in BMI were 0.98 (95% CI 0.86, 1.13) and 0.95 (0.74, 1.24), respectively, for type 1 and 2 carcinomas. As sensitivity analyses, we estimated risks per unit increase in BMI after log and square root transformation, but found no evidence of effect on RFS (0.89, 95% CI 0.39, 2.07 and 0.96, 95% CI 0.71, 1.30, respectively) in patients with type 1 carcinoma.

Similarly, we assessed the impact of BMI and other factors within Cox models with OS as the dependent variable (Table 4). Here again, no influence of BMI was observed – the hazard ratios per 5 kg/m^2 increase in BMI were 0.96 (0.81, 1.14) and 0.92 (0.70, 1.23), respectively, for type 1 and 2 carcinomas.

Finally, we tested for interactions between BMI and histological types and found no evidence of such in RFS ($p = 0.538$) and OS ($p = 0.465$) models.

3.6. BMI and adjuvant radiotherapy-related toxicity

Overall, early toxicity (fatigue and tiredness; diarrhoea; nausea and vomiting; urinary tract infection) was reported in 46% of women who underwent adjuvant radiotherapy but there were no differences in proportions of grades of early toxicity across the BMI categories (Supplemental material p9). Overall, late toxicity was reported in 2% of women. Here again, there were no differences in proportions of late toxicity across the BMI categories.

3.7. Framework for the evaluation of biases

We evaluated our findings against eight criteria of potential biases and concluded that there was minimal risk of bias in 7 steps; and modest risk at step 4. Taking the whole adjuvant therapy group, there was some evidence ($p_{trend} = 0.059$) that excess BMI was associated with a reduced use (Supplemental material p10). We tested these relationships further and showed (Supplemental material p11–13): (i) the decreased use of adjuvant radiotherapy in obese individuals was probably by chance as there were no associations with BMI for use of off-trial brachytherapy; (ii) increasing BMI was not associated with a delay in starting adjuvant radiotherapy; and (iii) competing risk survival analysis[32] (against non-cancer deaths) revealed no influence by BMI category.

4. Discussion

4.1. Summary of main findings

The findings of this study did not support our initial hypothesis that increased BMI is associated with a reduced post-treatment survival. All women received standardised allocated treatments, thereby reducing biases, yet there was no effect of BMI on either recurrence-free or overall survival following surgical treatment for endometrial cancer. Indeed, in women with type 1 carcinoma, increasing BMI was associated with a less aggressive histological phenotype, thus supporting our alternative second hypothesis.

4.2. Strengths and limitations

The present study has several strengths. First, this was a large trial with sufficient sample sizes to undertake analyses

Table 3 – Histological characteristics by BMI categories.

	Totals	WHO BMI categories						
		Under-weight	Normal weight	Over-weight	Obese I	Obese II	Obese III	*P* value
Type 1 (Endometrioid)								
Extent of tumour (%)								
Confined to corpus uteri	730	5	151 (87)	235 (80)	165 (80)	109 (83)	65 (79)	
Spread beyond corpus uteri	162	2	22 (14)	58 (20)	41 (20)	23 (17)	16 (20)	0.269[a]
Unknown	1	0	0	0	0	0	1	
Depth of invasion (%)								
Endometrium only	102	0	21 (12)	31 (11)	23 (11)	10 (8)	17 (21)	
Inner half myometrium	463	1	92 (53)	139 (48)	106 (51)	82 (62)	43 (52)	
Outer half myometrium	322	6	59 (34)	123 (42)	77 (37)	39 (30)	18 (22)	0.006[b]
Unknown	6	0	1	0	0	1	4	
Differentiation or grade (%)								
Well (G1)	324	1	62 (36)	84 (29)	82 (40)	54 (41)	41 (50)	
Moderate (G2)	442	1	86 (50)	161 (55)	95 (46)	66 (50)	33 (40)	
Poor (G3)	123	5	25 (15)	47 (16)	27 (13)	12 (9)	7 (9)	0.015[b]
Unknown	4	0	0	1	2	0	1	
Lymphovascular permeation (%)								
Present	160	2	32 (19)	60 (20)	38 (18)	19 (14)	9 (11)	
Not present	535	4	98 (57)	167 (57)	132 (64)	86 (65)	48 (59)	0.052[a]
Unknown	198	1	43	66	36	27	25	
Nodal involvement (if nodes harvested) (%) n = 409								
Yes	34	1	8 (10)	9 (6)	7 (8)	5 (8)	4 (13)	
No	375	3	73 (90)	134 (94)	78 (92)	60 (92)	27 (87)	0.703[a]
Number of involved nodes								
Median (range)	1 (1-6)	1 (1-1)	2 (1-5)	1 (1-6)	2 (1-5)	1 (1-3)	1 (1-3)	0.661[c]
FIGO stage (%)								
IA	96	0	20 (12)	29 (10)	21 (10)	10 (8)	16 (20)	
IB	398	1	83 (47)	113 (39)	92 (45)	71 (54)	38 (46)	
IC	234	4	47 (27)	93 (32)	52 (25)	28 (21)	10 (12)	
IIA	44	1	6 (4)	11 (4)	13 (6)	3 (2)	10 (12)	
IIB	74	0	9 (5)	29 (10)	17 (8)	15 (11)	4 (5)	< 0.001[d]
III/IV	41	0	7	17	10	5	1	
Unknown	6	0	1	1	1	0	3	
Risk groups[e]								
Low risk early disease	448	1	91 (53)	130 (44)	99 (48)	77 (58)	50 (61)	
Intermediate and high risk early disease	321	5	65 (38)	115 (39)	77 (37)	35 (27)	24 (29)	
Advanced disease	115	1	16 (9)	46 (16)	27 (13)	20 (15)	5 (6)	0.018[b]
Unknown	9	0	1	2	3	0	3	

		Normal weight	Over-weight	Obese I	Obese II and III	
Type 2 (Non-endometrioid)						
Extent of tumour (%)						
Confined to corpus uteri	103	30 (67)	29 (63)	25 (83)	19 (79)	
Spread beyond corpus uteri	43	15 (33)	17 (37)	5 (17)	5 (21)	0.099[a]
Depth of invasion (%)						
Endometrium only	27	10 (22)	7 (15)	4 (13)	6 (25)	
Inner half myometrium	60	17 (38)	18 (39)	14 (47)	11 (46)	
Outer half myometrium	54	16 (36)	21 (46)	11 (37)	6 (25)	0.688[b]
Unknown	5	2	0	1	1	
Differentiation or grade (%)						
Well (G1)	8	3 (7)	2 (4)	3 (10)	0	
Moderate (G2)	16	4 (9)	5 (11)	3 (10)	4 (17)	
Poor (G3)	91	29 (64)	26 (57)	20 (67)	15 (63)	0.773[b]
Not applicable	28	9	11	3	5	
Unknown	3	0	2	1	0	

(*continued on next page*)

Table 3 – (*continued*)

		Normal weight	Over-weight	Obese I	Obese II and III	
Lymphovascular permeation (%)						
Present	39	10 (22)	15 (33)	9 (30)	5 (21)	
Not present	68	22 (49)	23 (50)	12 (40)	11 (46)	0.792[a]
Unknown	39	13	8	9	8	
Nodal involvement (if nodes harvested) (%) n = 76						
Yes	18	6 (27)	7 (24)	4 (24)	1	
No	58	16 (73)	22 (76)	13 (76)	7 (88)	0.462[a]
Number of involved nodes						
Median (range)	1 (1–6)	2 (1–5)	1 (1–4)	2 (1–6)	1 (1–1)	0.804[c]
FIGO stage (%)						
IA	22	8 (18)	5 (11)	3 (10)	6 (25)	
IB	45	12 (27)	13 (28)	12 (40)	8 (33)	
IC	34	9 (20)	11 (24)	9 (30)	5 (21)	
IIA	8	2 (4)	6 (13)	0	0	
IIB	10	5 (11)	5 (11)	0	0	0.103[d]
III/IV	22	7 (16)	5 (11)	5 (17)	4 (17)	
Unknown	5	2	1	1	1	
Risk groups[e]						
Low risk early disease	12	3	1	5	3	
Intermediate & high risk early disease	71	21 (47)	23 (50)	15 (50)	12 (50)	
Advanced disease	54	19 (42)	19 (41)	8 (27)	8 (33)	0.331[b]
Unknown	8	2	3	2	1	

NOS: not otherwise specified.

In the non-endometrioid cancer group, as there was one 'underweight' case, these were excluded from analysis.

The histological subtypes in the non-endometrioid group were as follows: clear cell, 21; papillary serous, 31; squamous cell, 9; mucinous adenocarcinoma, 5; mixed epithelial stromal, 12; sarcoma, 16; other epithelial, 8; mixed epithelial, 42; unknown, 1.

[a] Cochran-Armitage test for trends across ordered groups.

[b] Chi-squared test across multiple groups excluding unknown categories where applicable.

[c] Cuzick's non-parametric test for trends across ordered groups.

[d] Chi-squared test for multiple categories excluding FIGO III/IV; 'underweight' category and 'unknowns' due to small sample sizes.

[e] Risk was classified in three categories: low-risk, early-stage disease (FIGO IA or IB and low grade pathology [G1, G2]); intermediate-risk and high-risk, early-stage disease (FIGO IA or IB with high grade pathology [G3, papillary serous or clear cell], FIGO IC or IIA); and advanced disease – i.e. spread beyond the uterine corpus (FIGO stage IIB, IIIA, IIIB, and IV). Pelvic lymph-node status was not taken into account; thus no FIGO stage IIIC category was included.

stratified into the two main histological types of endometrial carcinoma. Second, height and weight (to determine BMI) were measured rather than self-reported; the latter associated with under-estimation of weight particularly heavier individuals.[33] Third, there were detailed data for clinical, surgical and pathological covariates allowing exploration for confounding and modification effects. Fourth, the cohort has a high median BMI such that there were sufficient numbers of cases in obese categories I, II and III, for purposes of analyses. Finally, we developed a framework for evaluating eight pre-identified steps on the patient pathway between diagnosis and death and examined the data for evidence of bias at each of these steps. As all patients received standardised allocated treatments, we were confident that in seven out of eight of these steps, there was minimal risk of bias.

This study has potential limitations. First, data were missing for BMI determination in almost quarter of participants, although testing against age, performance status, histological subtype, and trial allocation, suggested that these were data missing at random. Second, the study was restricted to early-stage endometrial cancer so we do not know whether our results extrapolate to patients with advanced or recurrent disease. Third, BMI may not be the most appropriate measure of body fatness – approximations of central adiposity such as waist circumference and waist-to-hip ratio may provide more accurate predictions of cancer-related and all-cause mortality.[34] In this clinical trial, there could have been recruitment bias and study participants may be relatively leaner and fitter than their 'real life' counterparts, though this is somewhat refuted by the fact that 46% of our patients were WHO obese, compared with, for example, 35% of endometrial cancer patients in the British-based Million Women study.[8] Additionally, 24% patients had a WHO performance status of one or more, suggesting that a representative range of women were recruited into this study.

4.3. *Findings in the context of other studies*

Analyses in patients with cancer types other than endometrial cancer note that increased BMI at start of treatment impacts negatively on outcome – examples include cancers of the breast (systematic reviews[9,10]; adjuvant endocrine-therapy studies[11,12]), colon and rectum,[13–15] ovary[16,17] and prostate.[18] Increased BMI is also associated with increased

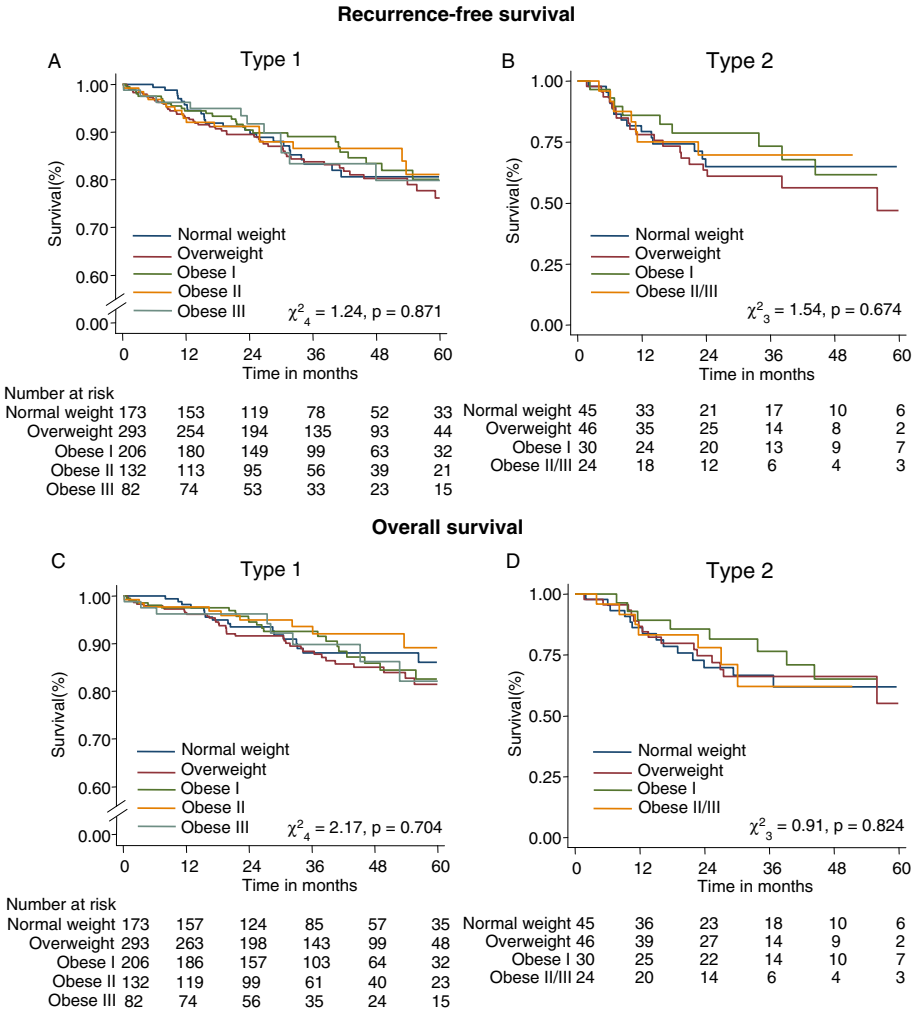

Fig. 2 – Kaplan–Meier curves for recurrence-free and overall survivals by BMI categories in types 1 and 2 endometrial carcinomas. Underweight BMI category is not shown due to small sample sizes. Note: abridged y-axis for Type 1 carcinoma plots.

incident risk for: post-menopausal breast cancer,[3] colon and rectum,[3] advanced prostate,[35] – while surrogates of central adiposity are associated with increased risk of ovarian cancer in never-users of hormonal replacement therapy.[36] Thus, it is conceivable that the biological mechanisms underpinning tumour development in these cancer types.[6] may also contribute to more aggressive tumour phenotypes, treatment resistance, and ultimately, poorer outcome.

Increased BMI is undoubtedly a major risk factor for incident endometrial cancer – our previous systematic review ranked endometrial cancer as the highest risk per unit exposure among BMI-associated cancers in women.[3] However, the findings of the present study indicate that BMI does not impact upon recurrence-free survival or overall survival. Indeed, increased BMI may be associated with less aggressive disease, at least for the most common type 1 endometrial carcinoma. These findings, from a prospective trial, are consistent with several retrospective studies. Thus, Everett et al.[19] and Martra et al.[20] found no influence of BMI on cancer-specific survival in 396 and 766 surgically-treated endometrial cancer patients, respectively, but the latter study did find evidence of treatment allocation bias, with obese patients less likely to receive adjuvant radiotherapy. Temkin and colleagues[37] ($n = 442$) speculated that BMI may be associated with a favourable survival, but this was not upheld after adjustment for potential confounders. In two recent studies, Munstedt and colleagues ($n = 1180$)[21] and Mauland and colleagues ($n = 1129$),[38] suggested that overweight may be associated with improved survival, but these survival rates were compared with underweight patients, where the prognosis is generally poor (an example of reverse causality). None of these studies analysed data separately by the histological types.

One other analysis from a prospective trial has addressed this question – the Gynecologic Oncology Group(GOG)[22] reported on 380 patients with early endometrial carcinoma who participated in a randomised trial of surgery with or without adjuvant radiation therapy and reported that increased BMI was associated with increased overall mortality (Hazard ratio = 2.76, 95% CIs: 1.20–6.33 for BMI $\geqslant$ 40 kg/m^2), but not disease recurrence.

Beyond early endometrial carcinoma, a retrospective analysis of 949 patients pooled from five GOG trials for advanced

Table 4 – Multivariate Cox models for recurrence-free and overall survival.

	Categories	Type 1 carcinomas		Type 2 carcinomas	
		Hazard ratio (95% CIs)	p_{trends}	Hazard ratio (95% CIs)	p_{trends}
Recurrence-free survival[a]					
Main model					
BMI (categorical)	Underweight (<18.5 kg/m^2)	1.68(0.39, 7.13)		Not included	
	Normal weight (referent)	1.00		1.00	
	Overweight (25.0–29.9 kg/m^2)	0.97 (0.59, 1.57)		1.14 (0.57, 2.27)	
	Obese I (30.0–34.9 kg/m^2)	0.81 (0.47, 1.39)		0.93 (0.41, 2.16)	
	Obese II (35.0–39.9 kg/m^2) or obese II/III	0.94 (0.51, 1.75)		0.82 (0.33, 2.04)	0.805
	Obese III ($\geqslant$40.0 kg/m^2)	1.17 (0.57, 2.39)	0.957		
Risk group[b]	Low-risk early disease	1.00		1.00	
	Intermediate/high-risk early disease	2.28 (1.49, 3.48)		4.00 (0.53, 30.39)	
	Advanced disease	3.48 (2.12, 5.72)	<0.001	11.53 (1.55, 85.81)	0.047
Age (continuous)	Per year	1.04 (1.02, 1.06)	<0.001	1.07 (1.04, 1.11)	<0.001
Second model					
BMI (continuous) per 5 kg/m^2	In full model with risk group and age	0.98 (0.86, 1.13)	0.809	0.95 (0.74, 1.24)	0.723
		Test for interaction between BMI and carcinoma types, $p = 0.538$			
Overall survival[a]					
Main model					
BMI (categorical)	Underweight (<18.5 kg/m^2)	1.01 (0.13, 7.76)		Not included	
	Normal weight (referent)	1.00		1.00	
	Overweight (25.0–29.9 kg/m^2)	1.00 (0.56, 1.79)		0.96 (0.46, 2.02)	
	Obese I (30.0–34.9 kg/m^2)	0.84 (0.44, 1.61)		0.76 (0.31, 1.87)	
	Obese II (35.0–39.9 kg/m^2) or obese II/III	0.62 (0.27, 1.42)		0.88 (0.33, 2.35)	0.664
	Obese III ($\geqslant$40.0 kg/m^2)	1.17 (0.49, 2.76)	0.378		
WHO performance status	0	1.00		1.00	
	1	1.29 (0.77, 2.15)		0.88 (0.42, 1.85)	
	2, 3 and 4	2.69 (0.30, 5.58)	0.009	5.30 (1.51, 18.61)	0.021
Risk group[b]	Low-risk early disease	1.00		Not included	
	Intermediate/high-risk early disease	3.14 (1.83, 5.40)		Not included	
	Advanced disease	5.15 (2.80, 9.49)	<0.001	Not included	
Age (continuous)	Per year	1.03 (1.01, 1.06)	0.011	1.08 (1.05, 1.12)	<0.001
Second model					
BMI (continuous) per 5 kg/m^2	In full model with risk group and age	0.96 (0.81, 1.14)	0.635	0.92 (0.70, 1.23)	0.584
		Test for interaction between BMI and carcinoma types, $p = 0.465$			

CI: confidence interval. The second model included the same variables as in the main model but BMI entered as a continuous variable.

[a] For RFS full model in type 1 carcinomas, Harrell's C-statistic = 0.682 and likelihood ratio for goodness of fit = 22.431; for type 2 carcinomas, C = 0.754 and likelihood ratio for goodness of fit = 18.678. For OS full model in type 1 carcinomas, Harrell's C-statistic = 0.742 and likelihood ratio for goodness of fit = 28.778; for type 2 carcinomas, C = 0.737 and likelihood ratio for goodness of fit = 19.493

[b] Risk group was classified in three categories as in footnote to Table 2.

or recurrent endometrial cancer, found that BMI was associated with poorer survival in advanced stage but not recurrent endometrial cancer patients.[39] That analysis additionally found evidence for suboptimal chemotherapy dosing in obese patients – a process known as 'capping', where oncologists empirically dose-reduce obese patients.[40]

Interestingly, increasing numbers of studies in other cancer types have evaluated the associations between BMI and treatment outcome, and found increased BMI is not an unfavourable prognosticator. Examples include cervical carcinoma (after excluding underweight, which is a poor prognosticator)[41] and thyroid carcinoma.[42] Indeed, a number of analyses from patients with early renal cell carcinoma report that being overweight is associated with either no adverse effect[43] or a more favourable outcome[44–47] compared with normal weight.

The present study's findings should be contrasted with the observations in two large population-based prospective studies showing clear associations between cohort baseline BMI determination and endometrial cancer-related mortality.[7,8] However, the increased risk of cancer-mortality in these studies is partly conditional on the fact that BMI increases predisposition to incident endometrial cancer i.e. cancer-related mortality is an approximation of incident risk. Without

access to medical records, these studies are unable to control for confounding factors such as stage and treatment allocation bias, and thus, are unable to directly inform us regarding modifiable post-treatment effects.

4.4. *Conclusions and future*

The failure to support the first hypothesis demonstrates an important principle: that an established link between an exposure (here, obesity) and increased incident cancer risk, does not necessarily translate into an inferior outcome following treatment for that cancer. Nonetheless, we should still pursue strategies of long term weight reduction that might improve life expectancy in this predominantly obese patient population, with a generally good cancer prognosis.

5. Conflict of interest statement

None declared.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.ejca.2011.10.003.

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