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The association between body mass index and molecular subtypes in endometrial carcinoma

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ABSTRACT

Objective: This study aims to investigate the relationship between body mass index (BMI) and molecular subtypes of endometrial carcinoma using an immunohistochemistry (IHC)-based classification approach.
Methods: We analyzed a consecutive series of endometrial cancer cases undergoing surgical staging in southern Alberta (2019–2021). Molecular classification was determined through IHC-based molecular typing, incorporating p53 and mismatch repair (MMR), and further characterized with the addition of ER and PR. BMI associations with molecular classification were assessed using t-tests. Hormone receptor status was further examined in a separate cohort of MMRd endometrial cancer patients undergoing surgical staging at Foothills Medical Centre (Alberta, Canada).
Results: Among 289 cases, comprising various histological subtypes, the pNSMP subtype exhibited the highest average BMI (33.93 kg/m^2) compared to the p53 abnormal subtype (30.40 kg/m^2, $p = 0.02$). The MMRd subtype had an average BMI of 33.22 kg/m^2. While there were no significant BMI differences between FIGO grade 1 and grade 2/3 tumours in the pNSMP or MMRd, a trend toward higher BMI in grade 1 tumours versus grade 2/3 tumours in the MMRd was observed ($p = 0.13$). A separate cohort of 53 MMRd endometrial carcinomas revealed that FIGO grade 1 tumours were associated with higher BMI ($p < 0.05$) and more frequent ER/PR expression compared to grade 2/3 tumours ($p < 0.05$).
Conclusions: This study suggests an association between obesity and NSMP endometrial carcinoma. The relationship between BMI and low-grade MMRd endometrial carcinomas with increased ER/PR expression warrants further exploration.

1. Introduction

Obesity is a significant risk factor for the development of endometrial cancer, with a relative risk of 1.59 per 5 kg/m^2 increase in body mass index (BMI) (Renehan et al., 2008 Feb). In recent years, there has also been a surge in the prevalence of obesity globally, which paralleled the rise in the incidence of endometrial cancer (Amant et al., 2005 Aug). Endometrial cancer is now the most common gynecologic malignancy in high income countries, with obesity also contributing to the development of various chronic illnesses, such as type 2 diabetes and cardiovascular disease (Guh et al., 2009 Dec).

In the traditional Bokhman classification, endometrial cancers were broadly classified into two groups based on tumour histotyping (Lax and Kurman, 1997). Type I tumours included endometrioid-type carcinomas, and were associated with excess or unopposed estrogenic stimulation and positive hormone receptor expression by tumour cells. Type II tumours included serous carcinoma and were regarded as estrogen-independent. It is well-established that obesity is a significant risk factor for Type I endometrial cancers due to its role in increasing estrogen levels through peripheral aromatization in adipose tissue. However, the influence of obesity on the four molecular classifications described by The Cancer Genome Atlas (TCGA) remains less understood, which forms the basis of our study.

In 2013, The Cancer Genome Atlas (TCGA) described four molecular

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subsets of endometrial cancer (Kandoth et al., 2013). The World Health Organization (WHO) has since then endorsed an integrated molecular classification system endometrial endometrioid carcinomas into Polymerase-epsilon (*POLE*)-mutated, mismatch repair (MMR) protein deficient (MMRd), p53-abnormal (p53abn), and no specific molecular profile (NSMP) (Kim et al., 2020). P53abn and MMRd molecular subtypes can be reliably identified by p53 and MMR immunohistochemistry respectively and both sets of immunohistochemistry markers are readily available in most clinical laboratories. *POLE* mutated group only accounts for about 5–10 % of endometrial cancer in population-based series (Kommoss et al., 2018 May 1) and the identification of pathogenic *POLE* exonuclease domain mutations require genetic analysis, which is not as widely available clinically across the world. Some centres perform *POLE* testing only in selected clinical scenarios in which *POLE* mutation status may impact management decision with regards to adjuvant therapy (Roque et al., 2016 Aug). Consequently, most clinical laboratories utilize an immunohistochemistry-based molecular classification system with p53 and MMR markers to separate endometrial cancer into p53abn, MMRd and a provisional NSMP (pNMSP) group with the understanding that the majority of *POLE*-mutated tumours reside in the provisional NSMP group. This modified immunohistochemistry-based molecular classification system was used for the current study, representing a real-world application of the molecular classification of endometrial cancer.

Given the known role of obesity in the development of endometrial cancer and the advent of an integrated molecular classification of endometrial cancer, recent studies have focused on evaluating the relationship between obesity as reflected by BMI status across the different molecular subtypes of endometrial cancer (Kommoss et al., 2018 May 1; Roque et al., 2016 Aug; Timmerman et al., 2020 Apr; Talhouk et al., 2017 Mar 1; Talhouk et al., 2015 Jul 14). BMI status is known to be associated with differential gene expression across different cancer types (Xiong et al., 2022). The objective of this study was to evaluate the association between BMI and the immunohistochemistry-based molecular subtypes of endometrial cancer in a real-world setting and population-based series.

2. Methods

In accordance with the journal's guidelines, we will provide our data for independent analysis by a selected team by the Editorial Team for the purposes of additional data analysis or for the reproducibility of this study in other centers if such is requested.

2.1. Study series

The primary study cohort included a consecutive series of patients who underwent surgical resection of their endometrial cancer at Foothills Medical Centre/Tom Baker Cancer Centre (Alberta, Canada) between November 2019 and February 2021 (Kang et al., 2022 Jan). Cases who received neoadjuvant chemotherapy were excluded. *POLE* testing was not universally available, and therefore, cases classified as *POLE* mutated were also excluded due to the small number of cases where it was performed. The exclusion of POLE-mutated cases (n = 3) is unlikely to have significantly influenced our results due to the very small sample size. Additionally, POLE-mutated endometrial cancers are typically associated with lower BMI and distinct molecular characteristics, which means their inclusion might have skewed the results towards a null effect or masked associations within the pNSMP and MMRd subtypes. However, given their unique profile, future studies with comprehensive POLE testing could provide further insights. Tumour histotyping and grading were assigned by subspeciality gynecologic pathologists. Demographics including age, body weight and height, clinical FIGO (International Federation of Gynaecology and Obstetrics) 2019 tumour stage were retrieved from the Alberta Cancer Registry. A separate cohort of 53 MMRd endometrial cancer from patients who underwent surgery at the same site represented on tissue microarrays published previously (Han et al., 2013) and from more recent cohorts (2021–22) with available materials for further immunohistochemistry analysis were used for hormone receptor study. The study was approved by the Health Research Ethics Board of Alberta (HREBA.CC-20-0400).

2.2. Immunohistochemistry-based molecular typing

P53 and MMR immunohistochemistry analysis were performed on representative whole-section tumour slides. For p53, ready-to-use (RTU) clone DO-7 (Catalogue # GA61661-2; Agilent Technologies, Santa Clara, CA, USA) was used with the following conditions – 30 min of heat-induced pretreatment using the high pH retrieval buffer and the DAKO Omnis protocol H30-10M-30. p53 immunostaining was interpreted as previously described (Köbel et al., 2016 Oct). For MMR, PMS2 and MSH6 immunohistochemistry was performed in the initial iteration with tumours showing intact expression of PMS2 and MSH6 being designated as MMR proficient. Either MLH1 or PMS2 was subsequently ordered in MMR-deficient tumours to further characterize the pattern of deficiency. The antibody clones, dilutions, and DAKO specific protocols were as follows: MLH1 (clone ES05, RTU, high pH, H30-10M-30), MSH2 (clone FE11, RTU, H30-10M-30M), MSH6 (clone EP49, RTU, *H*10-10R-10) and PMS2 (clone EP51, RTU, H20-10R-20) (Agilent Technologies, Santa Clara, CA, USA) (Rodriguez et al., 2021 Nov 1).

Tumours showing diffuse mutated p53 staining patterns and intact expression of MMR proteins were classified within p53abn molecular subtype. Tumours showing wild-type or subclonally abnormal p53 staining pattern and loss of expression of MMR protein(s) were classified as MMRd molecular subtype. None of the tumours evaluated exhibited concurrent loss of MMR protein expression and diffuse mutated p53 staining pattern. Tumours showing wild-type p53 staining pattern or subclonal mutated p53 staining pattern and intact expression of MMR proteins were classified as provisional non-specific molecular subtype (pNSMP).

2.3. Estrogen receptor and progesterone receptor immunohistochemistry analysis and interpretation

A separate cohort of 53 MMRd endometrial endometrioid-type carcinoma with available materials as described above were evaluated by estrogen receptor (ER) and progesterone receptor (PR) immunohistochemistry. For ER, ready-to-use Roche SP1 clone was used with 30 min of heat-induced pretreatment using the high pH retrieval buffer and the DAKO Omnis protocol H30-10R-10. For PR, mouse monoclonal DAKO PGR1294 clone was used with 20 min of heat-induced pretreatment using the high pH retrieval buffer and the DAKO Omnis protocol H20-X-20.

ER and PR expression were quantified into < 1 % (negative), <50 % (focal) or ≥ 50 % (diffuse).

2.4. Patient and public Involvement statement

Patients or the public were not involved in the design, conduct, reporting, or dissemination plans of our research.

2.5. Statistical analysis

Student's *t*-test was performed for comparisons between groups, specifically to compare the average BMI between different molecular subtypes and between tumor grades within each molecular subtype. For all t-tests, a two-tailed Type 2 (independent) *t*-test was used, with a p-value of < 0.05 considered to be significant. All statistical analyses were conducted using statistical software (e.g., SPSS, R, or Excel), and results were verified through multiple comparisons to ensure robustness.

3. Results

3.1. Clinicopathologic and molecular features

The cohort included a total of 306 cases, and after excluding 14 cases that received neoadjuvant chemotherapy, and 3 cases with pathogenic *POLE* mutations, a total of 289 cases of endometrial cancer were included in this study (Table 1). The age ranged from 35 to 90 with an average age of 65 years. Using immunohistochemistry-based molecular subtyping, 173 tumors (60 %) were pNSMP, 74 tumors (26 %) were MMRd while 42 tumors (14 %) were p53 abnormal. The p53ab molecular subtype was associated with older age at presentation compared to MMRd ($p < 0.01$) and pNSMP ($p < 0.01$). There were 24 tumours that had subclonal p53 loss (all endometrioid histology). Of these, 10 were MMRd and therefore classified as such, and 14 were MMRp.

In the MMRd molecular subtype, the majority of cases were grade 1 endometrioid carcinoma (EEC1) at 55.4 % followed by grade 2 endometrioid carcinoma (EEC2) at 27.0 %. Within the pNSMP molecular subtype, the majority also were EEC1 (78.6 %) followed by EEC2 (11.0 %). In the p53abn molecular subtype, the majority were endometrial serous carcinoma (ESC) at 35.7 %, followed by carcinosarcoma (CS) at 28.6 % and grade 3 endometrioid carcinoma (EEC3) at 17 %. Clinical staging (FIGO 2019) was available in 288 of 289 cases, and the majority were FIGO Stage I-II disease (n = 245, 85 %) while 43 patients (15 %) had FIGO stage III-IV disease.

Table 1
Clinicopathologic and molecular features of the study cohort: MMRd: mismatch repair.

Molecular subtype	MMRd	pNSMP	p53abn	Total study series	p Value
Sample size (% of the series)	74 (25.6 %)	173 (59.9 %)	42 (14.5 %)	289 (100 %)	
Age					
Average (years)	64.73	63.98	69.33	65	p < 0.01
Range (years)	41–83	35–90	38–84	35–90	
Tumor type					p < 0.01
Grade 1 endometrioid carcinoma	41 (55.41 %)	136 (78.61 %)	1 (2.38 %)	178 (61.59 %)	
Grade 2 endometrioid carcinoma	20 (27.03 %)	19 (10.98 %)	0 (0.0 %)	40 (13.84 %)	
Grade 3 endometrioid carcinoma	7 (9.46 %)	12 (6.94 %)	8 (19.05 %)	26 (9.00 %)	
Endometrial serous carcinoma	0 (0.00 %)	0 (0.00 %)	15 (35.71 %)	15 (5.19 %)	
Carcinosarcoma	0 (0.00 %)	0 (0.00 %)	12 (28.57 %)	12 (4.15 %)	
Endometrial clear cell carcinoma	0 (0.00 %)	5 (2.89 %)	4 (9.52 %)	9 (3.11 %)	
Dedifferentiated endometrial carcinoma	6 (8.11 %)	1 (0.58 %)	2 (4.76 %)	9 (3.11 %)	
Clinical stage (FIGO)					p > 0.05
IA	46 (62.16 %)	117 (67.63 %)	19 (45.24 %)	182 (62.98 %)	
IB	14 (18.92 %)	31 (17.92 %)	9 (21.43 %)	54 (18.69 %)	
II	2 (2.70 %)	5 (2.89 %)	2 (4.76 %)	9 (3.11 %)	
IIIA	2 (2.70 %)	5 (2.89 %)	2 (4.76 %)	9 (3.11 %)	
IIIC1	5 (6.76 %)	10 (5.78 %)	7 (16.67 %)	22 (7.61 %)	
IIIC2	3 (4.05 %)	2 (1.16 %)	2 (4.76 %)	7 (2.42 %)	
IVB	1 (1.35 %)	3 (1.73 %)	1 (2.38 %)	5 (1.73 %)	

deficient; pNSMP: provisional no specific molecular profile; p53 abn: p53 abnormal; EEC1: grade 1.
endometrioid carcinoma; EEC2: grade 2 endometrioid carcinoma; EEC3: grade 3 endometrioid.
carcinoma; ESC: endometrial serous carcinoma; CS: carcinosarcoma; ECCC: endometrial clear cell.
carcinoma; DDC: dedifferentiated endometrial carcinoma.

3.2. BMI across histotypes and molecular subtypes

BMI information was available for 281 of 289 patients, and the average BMI was 33.2 kg/m^2 where over half of the population had a BMI of > 30 kg/m^2 and 18.7 % had a BMI > 40 kg/m^2. With respect to molecular subtype (Fig. 1A), the pNSMP molecular subtype was associated with the highest average BMI of 33.93 kg/m^2, which was significantly higher than the p53abn molecular subtype that was associated with the lowest average BMI at 30.40 kg/m^2 ($p = 0.02$) (Fig. 1A). The MMRd molecular subtype had an average BMI of 33.22 kg/m^2, which was not statistically significant when compared to the p53abn group ($p = 0.07$). With regards to the pNSMP tumours showing subclonal mutated p53 staining pattern (which may encompass some *POLE*-mutated tumors given this testing was not routinely available), the average BMI in these 14 cases was 29.9 kg/m^2, which was lower than the average BMI for the pNSMP molecular group and similar to the average BMI of the p53abn molecular subgroup. Table 2 summarizes the of BMI findings across the molecular categories of endometrial carcinomas in the present study as well as five earlier studies (Kommoss et al., 2018 May 1; Roque et al., 2016 Aug; Timmerman et al., 2020 Apr; Talhouk et al., 2017 Mar 1; Talhouk et al., 2015 Jul 14).

With respect to tumour histotype (Fig. 1B), EEC1, EEC2 and EEC3 displayed the highest average BMIs, at 34.24 kg/m^2 and 32.78 kg/m^2 respectively, while the ECCC and carcinosarcoma (CS) had the lowest average BMI, at 28.49 kg/m^2 and 29.26 kg/m^2, respectively.

Given that the majority of EEC1 were distributed across pNSMP and MMRd molecular subtypes, we further evaluated the relationship between BMI and FIGO tumour grade within each of these two molecular subtypes. The average BMI for EEC1 and EEC2/EEC3 tumours in the MMRd and pNSMP molecular subtypes are depicted in Fig. 2. We used a Two-Tailed Independent Samples t-Test (assuming equal variances) to determine the significance of the differences in average BMI between tumor grades within each molecular subtype. Within the MMRd molecular subtype, EEC1 (n = 39) had a higher average BMI (34.8 kg/m^2) compared to EEC2/EEC3 (n = 27) with an average BMI of 31.53 kg/m^2 but the difference was not statistically significant ($p = 0.13$). Within the pNSMP molecular subtype, EEC1 (n = 131) had an average BMI (34.2 kg/m^2) that was comparable to the EEC2/EEC3 group (n = 30) with an average BMI of 33.9 kg/m^2 ($p = 0.89$).

3.3. Estrogen receptor (ER) and progesterone receptor (PR) expression in MMRd endometrioid carcinoma of the endometrium

Within the MMRd EEC1, a trend to higher BMI was seen compared to MMRd EEC2/3. The expression of ER and PR was evaluated in separate series of 53 MMRd endometrial endometrioid-type carcinomas (22 FIGO grade 1 and 31 FIGO grade 2 or 3). The results are summarized in Table 3. In EEC1,91 % and 86 % of the tumours show diffuse and strong ER and PR expression respectively, but only 55 % and 33 % of EEC2/3 tumours showed diffuse and strong ER and PR expression respectively ($p = 0.003$ for ER and $p = 0.0001$ for PR). Furthermore, in this cohort, the average BMI for EEC1 was 33.2 kg/m^2, which was significantly higher than the average BMI for EEC2/3 at 27.5 kg/m^2 ($p = 0.002$).

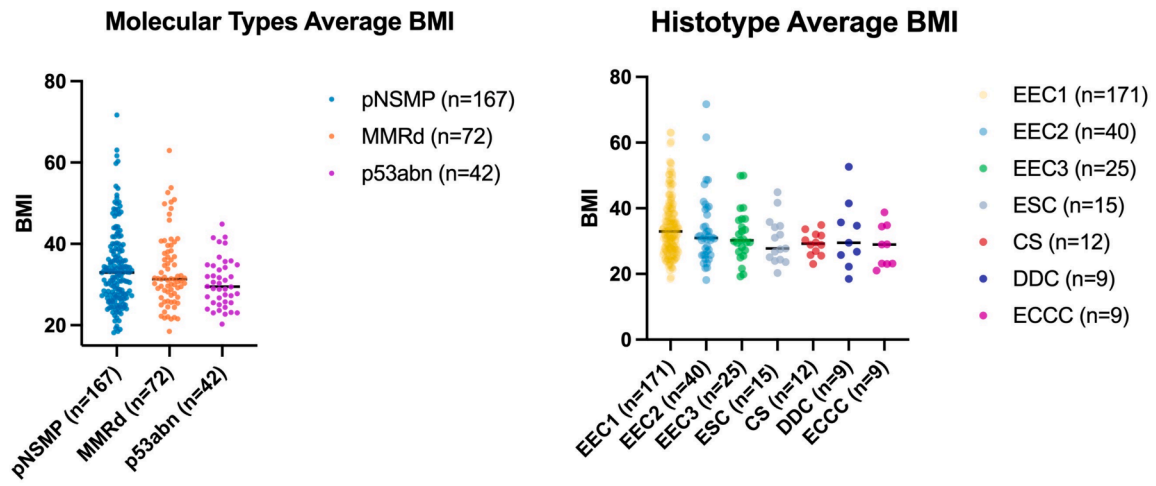

Fig. 1. Scatter plots showing body mass index (BMI) across different molecular subtypes (A) and histotypes (B) of endometrial carcinomas, with the average indicated by a horizontal bar. MMRd: mismatch repair deficient; pNSMP: provisional no specific molecular profile; p53 abn: p53 abnormal; EEC1: grade 1 endometrioid carcinoma; EEC2: grade 2 endometrioid carcinoma; EEC3: grade 3 endometrioid carcinoma; ESC: endometrial serous carcinoma; CS: carcinosarcoma; ECCC: endometrial clear cell carcinoma; DDC: dedifferentiated endometrial carcinoma.

Table 2
The association between BMI and molecular subtypes of endometrial cancer within the published literature. MMRd: mismatch repair deficient; MSI-H: microsatellite instability high; POLE-mutated: polymerase epsilon mutated; NSMP: no specific molecular profile; CNL: copy number-low; p53 abn: p53 abnormal; CNH: copy number-high.

Reported BMI means in molecular subtypes (kg/m^2)						
	Study Population	**NSMP/CNL**	**MMRd/MSI-H**	**P53 abn/CNH**	**POLE-mutated**	**p value**
Roque *et. al*	United States Cohort, n = 290	35.8	33	32.2	29.8	
Kommoss *et. al*	German Cohort, n = 452	29.8	28.8	27.4	28.2	$p > 0.05$
Timmerman *et. al*	Belgian Cohort, n = 108	30.4	27.3	29.8	28	
Talhouk *et. al* 2017	Canadian Cohort, n = 319	32.2	33.9	29.7	25.9	$p < 0.01$
Talhouk *et. al 2015*	Canadian Cohort, n = 143	36	32	29	28	$p < 0.05$
Present Cohort	Canadian Cohort, n = 289	33.9	33.2	30.4		

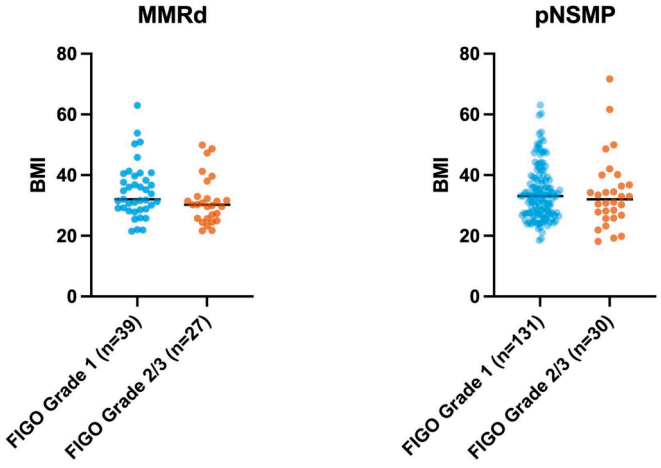

Fig. 2. Scatter plots showing body mass index (BMI) in low-grade (FIGO grade 1) and high-grade (FIGO grade 2–3) tumors among pNSMP molecular subtype (A) and MMRd molecular subtype (B) with the average indicated by a horizontal bar. MMRd: mismatch repair deficient; pNSMP: provisional no specific molecular profile; EEC1: grade 1 endometrioid carcinoma; EEC2: grade 2 endometrioid carcinoma; EEC3: grade 3 endometrioid carcinoma; ESC: endometrial serous carcinoma; CS: carcinosarcoma; ECCC: endometrial clear cell carcinoma; DDC: dedifferentiated endometrial carcinoma.

Table 3
Estrogen receptor (ER) and progesterone receptor (PR) expression in MMRd endometrial endometrioid carcinomas. EEC1: FIGO grade 1 endometrial endometrioid carcinoma; EEC2/3: FIGO grade 2/3 endometrial endometrioid carcinoma.

	ER staining			**PR staining**		
	0	<50 %	≥50 %	0	<50 %	≥50 %
EEC1 MMRd (n = 22)	1 (4.5 %)	1 (4.5 %)	20 (91 %)	1 (5 %)	2 (9 %)	19 (86 %)
EEC2/3 MMRd (n = 31)	7 (22.5 %)	7 (22.5 %)	17 (55 %)	15 (50 %)	5 (17 %)	10 (33 %)

4. Discussion

4.1. Summary of main results

Using an immunohistochemistry-based molecular classification approach including pNSMP, MMRd and p53abn groups, we evaluated the relationship between BMI and molecular subtypes on a consecutive population-based cohort of 289 endometrial cancer patients who underwent surgical staging. Results suggest an association between higher BMI and the pNSMP subtype, which showed a higher average BMI compared to the p53abn molecular subtype. Within the MMRd subtype, FIGO grade 1 tumors were associated with higher BMI and more frequent estrogen receptor (ER) and progesterone receptor (PR) expression.

4.2. Results in the context of published literature

Within this cohort, the highest average BMI was in the pNSMP molecular subtype. These findings are concordant with the observation made by Roque et al, who analysed published TCGA data and found that copy-number low molecular subtype that corresponded to the WHO NSMP molecular subtype, was associated with highest average BMI level, while microsatellite instability-high (MSI-H) molecular subtype was associated an intermediate BMI, and copy number high molecular subtype was associated with the lowest average BMI level among the molecular subtypes (Roque et al., 2016 Aug). As shown in Table 2. *POLE*-mutated tumours and copy-number high/p53abn tumours were both consistently associated the lower average BMI levels compared to copy number low/NSMP tumours among the 4 molecular subtypes (Kommoss et al., 2018 May 1; Roque et al., 2016 Aug; Timmerman et al., 2020 Apr; Talhouk et al., 2017 Mar 1; Talhouk et al., 2015 Jul 14). The average BMI of MSI-H/MMRd tumours were in contrast more variable, being either greater than or similar to copy number low/NSMP tumours in two of the six studies (both being Canadian cohorts) but lower than copy number low/NSMP tumours in the remaining four studies (Kommoss et al., 2018 May 1; Roque et al., 2016 Aug; Timmerman et al., 2020 Apr; Talhouk et al., 2017 Mar 1; Talhouk et al., 2015 Jul 14). This suggests that there may exist variation across different populations regarding the contribution of obesity and BMI in the development of MMRd tumours (Janssen et al., 2020).

4.3. Implications for practice and future research

We found the highest mean BMI within the pNSMP molecular subtype. Within the pNSMP group, there was no significant BMI difference between FIGO grade 1 and grade 2–3 tumors. However, in the MMRd molecular subtype, the well-differentiated tumours exhibited higher BMI levels compared to their poorly differentiated counterparts. These findings raise the hypothesis of how obesity influences the tumorigenesis of low grade MMRd tumours. The recently published CYCLE-P study showed that sustained aerobic exercise in individuals with Lynch syndrome lead to a significant reduction in colonic tissue inflammation, specifically through the decrease in mucosal PGE2 levels (Deng et al., 2023). In this study, aerobic exercise induced favourable changes in immune cell populations, notably increasing the activation and recruitment of NK cells and CD8+ T cells, crucial for immune surveillance against cancer cells (Deng et al., 2023). Further investigation is required to demonstrate if low grade MMRd endometrial cancer could be related to obesity-associated inflammatory pathways.

4.4. Mechanisms linking obesity and endometrial cancer

Obesity is known to create a pro-inflammatory state characterized by increased levels of circulating adipokines, insulin resistance, and chronic low-grade inflammation (Mair et al., 2020). These conditions can lead to enhanced estrogen production through aromatization in adipose tissue, contributing to endometrial proliferation and cancer development (Mair et al., 2020). Inflammatory pathways, such as those involving cytokines (e.g., IL-6, TNF-α) and prostaglandins (e.g., PGE2), can promote tumorigenesis by enhancing cellular proliferation, inhibiting apoptosis, and facilitating angiogenesis (Zhao et al., 2021 Jul 12). Our findings suggest that these mechanisms might be particularly relevant in the pNSMP and low-grade MMRd molecular subtypes, where higher BMI is associated with tumor characteristics.

4.5. Clinical implications

Our findings suggest that patients with a higher BMI, particularly within the pNSMP and MMRd molecular subtypes, may benefit from targeted lifestyle interventions aimed at reducing obesity and related inflammatory pathways. For instance, implementing regular aerobic exercise could potentially mitigate the risk or progression of these specific subtypes of endometrial cancer by decreasing systemic inflammation and improving immune function. These interventions could be integrated into survivorship care plans and preoperative counseling for endometrial cancer patients with a higher BMI. These interventions could be integrated into survivorship care plans and preoperative counseling for endometrial cancer patients with a higher BMI. Furthermore, public health interventions focusing on obesity reduction could be particularly effective in populations at risk for endometrial cancer.

4.6. Potential for targeted therapies

Moreover, understanding the distinct molecular profiles associated with higher BMI could pave the way for personalized treatment strategies. For example, the observed relationship between higher BMI and increased ER and PR expression in MMRd tumors suggests that hormonal therapies might be more effective in this subset of patients. Tailoring treatment based on BMI and molecular subtype could optimize therapeutic outcomes and reduce the risk of recurrence. Personalized approaches could include the use of anti-inflammatory agents or immunotherapies tailored to the patient's obesity status and tumor characteristics.

4.7. Research directions

Future research should focus on large-scale, prospective studies to validate these observations and explore the mechanistic links between obesity, inflammation, and molecular subtypes of endometrial cancer. Investigating the impact of weight loss interventions, such as diet and exercise programs, on tumor progression and patient outcomes in these specific subtypes would be particularly valuable. Additionally, exploring the potential benefits of anti-inflammatory agents or immunotherapies in obese patients with endometrial cancer could provide new avenues for treatment.

4.8. Strengths and weaknesses

A limitation of our study is the lack of universal access in our clinical setting to POLE testing. We anticipate that the majority of the *POLE* mutated endometrial cancer present (estimated to be about 15–30 cases given the size of the cohort) would be in the pNSMP molecular subtype group. Interestingly, there were 14 pNSMP tumours that showed subclonal mutated p53 staining pattern, a finding that is strongly suggestive of the presence of *POLE* mutation in the MMRp setting and 3 of these pNSMP tumours with subclonal mutated p53 staining did undergo *POLE* mutation analysis, and were found to harbour pathogenic *POLE* mutations. However, this limitation would skew the results to the null, as these tumors are included in the pNSMP group in the current analysis and POLE-mutated endometrial cancers are consistently found to be associated with low average BMI. Other limitations include inclusion of only patients who underwent surgical management for their endometrial cancer, excluding patients who presented with advanced stage disease. Furthermore, we were not able to address the prognostic association as the clinical follow-up in our more recent study cohort was limited.

Additionally, this is a retrospective, single-institution study, and the sample size was small, particularly within the MMRd cohort. This limitation necessitated examining ER/PR findings in a separate cohort, hindering comprehensive conclusions within the MMRd subgroup. Larger, prospective studies are crucial to validate and expand our observations, especially within the MMRd cohort.

5. Conclusion

These findings provide further support for the role of obesity in the

development of the NSMP molecular subtype of endometrial cancer. The role of obesity within low grade MMRd tumors requires further investigation. Our study highlights the potential benefits of integrating lifestyle interventions, such as aerobic exercise, into the clinical management of patients with a higher BMI to reduce inflammation and improve immune surveillance. Personalized treatment strategies that consider BMI and molecular subtype may enhance therapeutic outcomes and improve patient care. Further research is needed to validate these findings and explore effective interventions to mitigate the impact of obesity on endometrial cancer progression and patient outcomes.

6. Key points

6.1. What is already known on this topic

The link between obesity and type I endometrioid histotype endometrial cancer is well established. Within the molecular based classification system of endometrial cancer, the role of obesity is less defined.

6.2. What this study adds

Our results demonstrates the NSMP molecular subtype is associated with a higher average BMI compared to the p53 abnormal molecular subtype. Additionally, a trend to higher BMI was seen in grade 1 MMRd tumors compared to high-grade MMRd tumors.

6.3. How this study might affect research, practice, or policy

These findings suggest that obesity is an important risk factor in the development of NSMP and a grade-1 MMRd endometrial carcinomas, which suggests future studies are needed to further characterize these associations and mechanisms to guide prevention and treatment strategies.

CRediT authorship contribution statement

DuPreez Smith: . **Eun Young Kang:** Writing – review & editing, Data curation. **Gregg S. Nelson:** Writing – review & editing, Conceptualization. **Cheng-Han Lee:** Writing – review & editing, Supervision, Conceptualization. **Martin Köbel:** Writing – review & editing, Data curation, Conceptualization. **Christa Aubrey:** Writing – review & editing, Supervision, Data curation, Conceptualization.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: [Dr. Martin Koebel is a consultant for Helix Biopharma. No other competing interests to disclose].

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