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COMMENTARY

The impact of the patient macroenvironment on molecular subgroups in endometrial cancer

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Abstract

More than half of endometrial cancer diagnoses can be attributed to obesity. A purely molecular classification in endometrial cancer hampers further understanding of the impact of patient macroenvironment as a major risk factor. The relationship between patient factors, such as age, body mass index (BMI), comorbidity, and ethnicity, and molecular subgroups was studied in a publicly available data set (N = 225) and two multicenter European cohorts (N = 223; N = 946). Age at diagnosis was highest in the *TP53*-mutated subgroup, and differed significantly between molecular subgroups. Patients with obesity were younger at diagnosis compared to their lean counterparts across all molecular subgroups (61.9 vs. 66.2 years; $p < .01$). Survival was worst in the *TP53*-mutated subgroup but improved with increasing BMI, which resulted in nonsignificant differences from other subgroups when BMI was >35. These data underscore that patient factors remain important,

and their integration with molecular factors needs to be better understood to ultimately improve treatment and prevention strategies in endometrial cancer.

KEYWORDS
body mass index, comorbidity, endometrial neoplasm classification, ethnicity, health behavior, obesity, prognosis, risk factors

INTRODUCTION

Endometrial cancer (EC) is the most common type of gynecological cancer in Western countries, with steadily rising incidence.[1,2] EC is strongly associated with obesity, which is the most important risk factor, along with advancing age.[3,4] Since the early 1980s, known patient factors, including obesity, increased sex steroid hormone levels, and insulin resistance, have been strongly associated with EC pathogenesis.[5] Obesity promotes carcinogenesis via at least three mechanisms: increased sex steroid hormone production, hyperinsulinemia/insulin resistance, and chronic obesity-induced inflammation.[6–8] Each mechanism results in stimulation of mitosis, vessel formation, and inhibition of apoptosis. Ultimately, more than half of ECs can be attributed to obesity. EC molecular subgroups, introduced in 2013 by The Cancer Genome Atlas (TCGA), caused a conceptual change by classifying EC from its genetic tumor profile rather than by histological subtype.[9–11] The four molecular subtypes, polymerase ε (*POLE*) ultramutated, microsatellite instability (MSI) hypermutated, no specific molecular profile (NSMP), and tumor protein 53 (*TP53*)-mutated, show consistent differences in prognosis.[12,13] However, molecular tumor classification alone precludes further understanding of the impact of patient macroenvironment as a major factor in EC. Few studies have reported on existing differences in patient macrovariables, including body mass index (BMI) and age, between molecular subgroups, and questioned whether EC molecular tumor class is completely independent from the patient in which the tumor arises.[14–17] However, the aforementioned studies were often limited by small sample sizes, were single-institution cohorts or lacked comprehensive molecular tumor classification. We studied the relationship between patient macroenvironment and molecular tumor classification in large multicenter cohorts. We hypothesized that patient factors, including age, BMI, comorbidity, and ethnicity, affect molecular tumor subgroup adherence. This topic is extremely relevant to better cope with the rising incidence of EC to improve treatment and prevention strategies.

MATERIALS AND METHODS

A retrospective study was performed using large multicenter EC cohorts with extensive clinical annotation: the original publicly available American TCGA EC cohort (N = 225) and a previously published European Network for Individualised Treatment of Endometrial Cancer (ENITEC) cohort (N = 223); both had complete molecular classification, and were after initial comparison merged as a primary research cohort (N = 448; Table S1).[11,18,19] Patients were included if complete surgical staging, BMI, molecular classification, and age were known. Annotation on previous malignancies was available. The publicly available US cohort further provided specific annotation on ethnicity, whereas the ENITEC cohort offered detailed information on comorbidities. A second European cohort without molecular classification, although with available immunohistochemical p53 status, served as a validation cohort (N = 946; Table S2).[20]

For BMI and age, median and range were chosen as descriptive statistics in the presence of extreme outliers.

χ^2 tests, one-way analysis of variance tests, and Kaplan–Meier analyses were applied to test associations between categorical and continuous variables and molecular classification, as well as the effect of BMI on survival within molecular groups. The Charlson Comorbidity Index, classified into low (0–2) or high (≥3) comorbidity burden, was calculated to reflect patient comorbidity.[21] Significance level (p value) was set at .05. Analyses were performed with SPSS, version 28.

Ethical approval and consent to participate

Informed consent was obtained from all participants, and institutional review board approval was in place for all original studies. For the European cohorts; ethical approval was given at Radboud University Medical Centre, Nijmegen, the Netherlands (institutional study protocol 2015-2101) and by University Hospital Brno, Czech Republic (approval number 06-151221/EK). The study was performed in accordance with the Declaration of Helsinki.

RESULTS

The public TCGA data set comprised patients who were overall more obese (BMI, 33.6 vs. 29.0; $p < .001$), and included more high-grade ECs (grade 3, 39.1% vs. 22.5%; $p < .001$; 18.7% vs. 6.3% non-endometrioid histology; $p < .001$) and more *TP53*-mutated cases (25.3% vs. 10.3%; $p < .001$), compared to patients included in the ENITEC data set (Table S1). After being merged, the primary research cohort was balanced with a median age of 63.5 years, 11.9% non-endometrioid histology, 30.9% grade 3 ECs, and 17.9% *TP53*-mutated cases (Table S1).

Table 1 shows the associations between important patient factors and molecular subgroups. Patients with *TP53* mutations were

TABLE 1 Relationship between patient factors and molecular subgroups: Merged cohort.

	Molecular subgroup				
	POLE-mutated (n = 36)	MSI (n = 114)	*TP53*-mutated (n = 80)	NSMP (n = 218)	p
Age, median, years	57.50	64.00	67.00	62.00	<.001
BMI, median, kg/m^2	29.53	31.00	30.67	30.00	.753
BMI, No. (%), kg/m^2					.639
<25	9 (25)	23 (20)	20 (25)	42 (19)	
25–29.9	10 (28)	28 (25)	17 (21)	66 (30)	
≥30	17 (47)	63 (55)	43 (54)	110 (50)	
Previous malignancy, No. (%)					.002
Yes	0 (0)	3 (3)	12 (15)	14 (6)	
No	36 (100)	111 (97)	68 (85)	204 (94)	
Ethnicity,[a] No. (%)					.006
White	11 (69)	51 (82)	42 (76)	74 (86)	
Black	1 (6)	3 (5)	11 (20)	4 (5)	
Other	4 (25)	8 (13)	2 (4)	8 (9)	
Comorbidity[b]					
T2DM	1 (5)	5 (10)	6 (26)	16 (12)	.165
CVZ with AHT[c]	4 (21)	16 (31)	8 (35)	50 (39)	.438

Abbreviations: BMI, body mass index; CVZ with AHT, cardiovascular disease including hypertension with antihypertensive treatment; MSI, microsatellite instability; NSMP, no specific molecular profile; *POLE*-mutated, polymerase ε; T2DM, type 2 diabetes mellitus; *TP53*-mutated, tumor protein 53.

[a]European Network for Individualised Treatment of Endometrial Cancer cohort missing; n = 223 missing.

[b]The Cancer Genome Atlas cohort missing; n = 225 missing.

[c]n = 1 missing.

eldest, and with *POLE*-mutated tumors were youngest, at diagnosis (median age, 67.0 vs. 57.5 years; $p < .001$). This association remained in a grade 3–only subset (data not shown). Black American women more frequently demonstrated *TP53* mutations (57.9% vs. 22%; $p = .006$), and more often had tumors with serous histology (47.4% vs. 15.5%; $p < .001$; data not shown) compared to other ethnicities. Overall, 6.5% of patients had a history of previous cancer, as demonstrated in Table S1. This was specified for the EU cohort; detailed diagnostic information was missing in the American cohort. Interestingly, patients with a history of cancer were classified as *TP53*-mutated or NSMP significantly more often (89.3%) compared to those without a history of cancer.

Obesity prevalence was comparable in all molecular subgroups (median BMI overall, 32; lowest in *POLE*-mutated; highest in MSI; $p = .753$); similar findings were observed in a subset of grade 3–only patients. Comorbidity prevalence, including type 2 diabetes mellitus (T2DM), varied among molecular subgroups and remained similar with a higher BMI cutoff at 35, although with small group sizes.

In classifying patients as obese (BMI, ≥30) and nonobese (BMI, <30), those with obesity were significantly younger at diagnosis compared to their lean counterparts in all molecular subgroups ($p < .001$). In both lean patients and patients with obesity, those with *TP53*-mutated tumors were eldest, and those with *POLE*-mutated tumors were youngest (Figure 1A). This trend of younger age at diagnosis was even stronger when BMI cutoffs of 35 or 40 were applied (Table S2). Although very small numbers of Black women were available for analysis, the association between Black American women and the *TP53*-mutated subgroup appeared only relevant in the obese group ($p = .002$); the nonobese *TP53*-mutated group showed a more heterogeneous ethnic representation ($p = .48$) (Figure 1B).

Overall survival curves generated for the molecular subgroups showed the worst survival for the *TP53*-mutated group in lean patients (BMI, 18–25), compared to all other subgroups. However, with increasing BMI (BMI cutoffs of 25, 30, or 35), survival of *TP53*-mutated patients clearly improved, and starting BMI >35 differences were no longer significant despite equal International Federation of Gynecology and Obstetrics stage distribution (Figure 1C–E).

In the European validation cohort, findings were confirmed. Age at diagnosis was highest in patients with abnormal p53 (p53abn) tumors. Starting at a BMI of 35, median age at diagnosis was significantly lower in both p53abn and wild-type p53 patients (69.5 vs. 65.9 and 64.8 vs. 63.8 years, respectively; $p < .001$; data not shown). Patients with p53abn tumors had more comorbidity (63.8% vs. 52.9%; $p = .021$) but less T2DM (13.1% vs. 20.9%; $p = .021$) (Table S3). Finally, patients in the p53abn group showed a trend

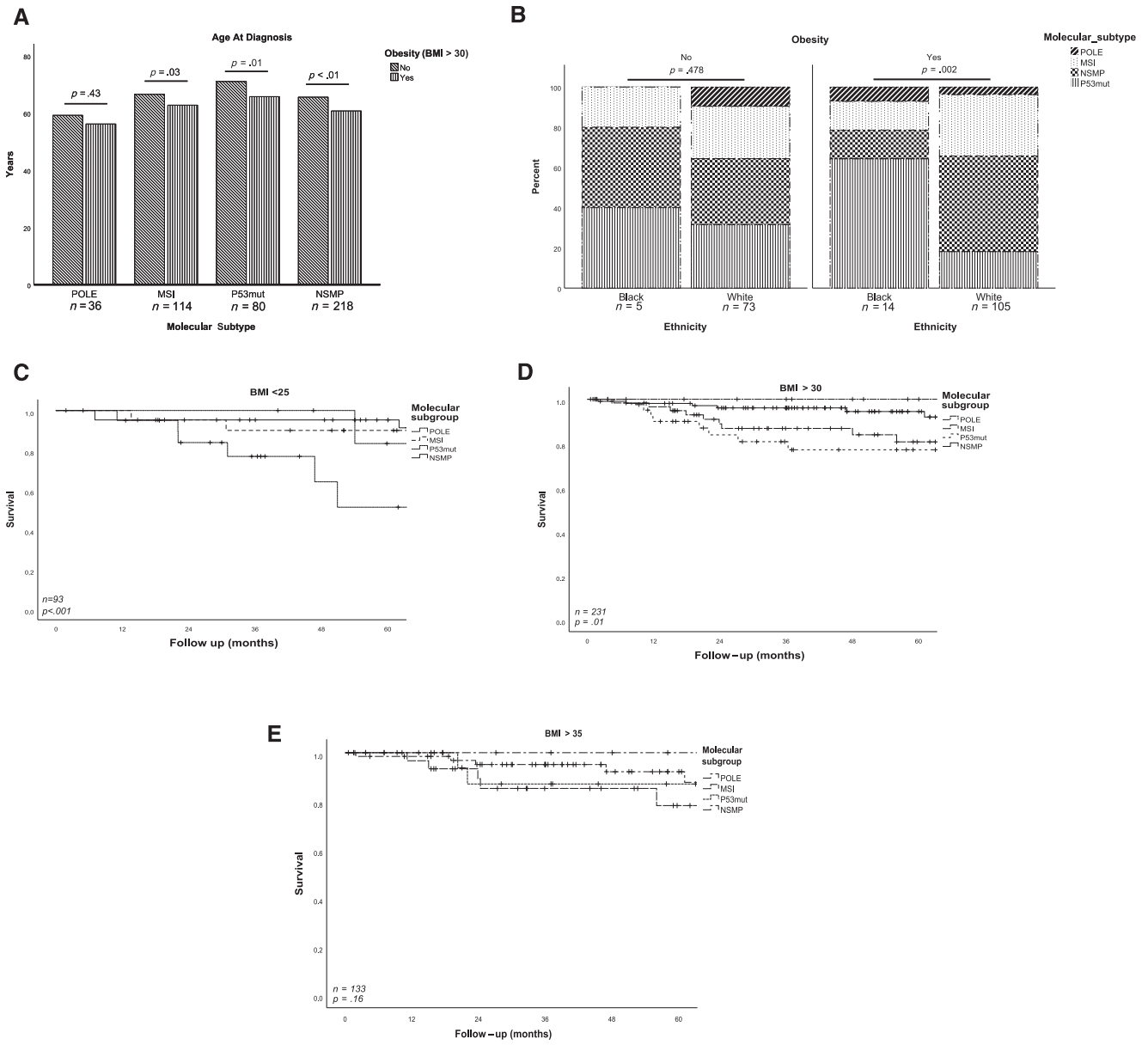

FIGURE 1 (A) Patients with obesity were significantly younger at diagnosis compared to their lean counterparts in all molecular subgroups. (B) Molecular subgroups are not uniformly distributed among ethnicities, and are further affected by BMI. (C–E) Overall survival curves (Kaplan–Meier) according to molecular subgroup and stratified according to BMI. (C) Patients with a BMI of 18–25. (D) Patients with a BMI of >30. (E) Patients with a BMI of >35. BMI indicates body mass index; MSI, microsatellite instability; *TP53*-mutated, protein 53 mutated; *POLE*-mutated, polymerase ε.

toward improved survival with higher BMI cutoffs (3-year survival: BMI, <25, 70.7%; BMI, >35, 85.2%; data not shown).

DISCUSSION

This study demonstrates that patient-related factors are of undiminished importance and their integration with molecular factors is essential.

The most important findings in this study, and confirmed in the validation cohort, include BMI-related age differences at diagnosis; a younger age at diagnosis was noted in women with obesity in all molecular subtypes; an improved prognosis was observed in women with obesity with *TP53*-mutated tumors; as well as noticeable associations between *TP53*-mutated tumors, ethnicity, and previous malignancy. The association between obesity and younger age at EC diagnosis has been previously described in general EC populations lacking molecular classification.[22,23] However, our observation that women with obesity are diagnosed at a younger age than women without obesity across all EC molecular subtypes is novel. The mechanisms via which obesity drives EC have been well documented, and show that obesity-driven hormonal imbalance, inflammation, and metabolic changes are likely intertwined in this disease, and possibly mutually stimulate each other.[7,24] Better understanding of the

dynamics between tumor, host, and molecular pathways will give us tools for better recognition of the population at risk and (secondary) prevention strategies.

The observed trend for improved survival in *TP53*-mutated EC in patients with obesity is clinically very relevant, and warrants further prospective and mechanistic investigation. Although some prior studies have hinted at a potential obesity paradox in EC (simultaneous increased risk of and improved survival in EC), those findings were mainly focused on the entire population or endometrioid subtypes.[25,26] Few studies have observed improved survival in patients with obesity with nonendometrioid histology, and have not specifically focused on *TP53*-mutated tumors.[23] The impact and interaction of inflammatory and hormone-related pathways, insulin resistance, and altered tumor microenvironments in patients with obesity with EC require further study in this context.[27,28] Related to this, recent evidence by Gómez-Banoy et al. showed that patients with obesity receiving immune checkpoint inhibitors experienced improved progression-free and overall survival, especially in the *TP53*-mutated group, associated with high IFN-γ signaling, which is suggestive that immune modulation mediates this survival benefit.[29]

Low numbers in other subtypes, such as clear cell tumors, hampered their in-depth analysis, although clear cell tumors were shown to be widely variable in molecular subtype. Interestingly, when molecular analyses in clear cell EC with "pure" and "mixed" histology have been compared, it has been shown that *POLE* mutations and/or MSI were mainly present in mixed clear cell tumors, with subsequent significant improved outcome, compared to pure clear cell tumors. Moreover, clear cell tumors allocated to the NSMP group often show loss of estrogen receptor and worse outcomes.[30] This is supported by the recently updated European Society of Gynaecological Oncology guidelines, which integrate estrogen receptor expression into the risk classification groups.[31]

We confirm that Black women, especially those with obesity, are more likely to suffer from *TP53*-mutated EC, as also indicated by others.[32–34] Weigelt and coworkers additionally showed important differences in driver mutations between Black and White women, including higher levels of chromosomal instability and lower tumor mutation burden even within subtypes, with implications for possible therapeutic targets.[35] This underscores the importance of attention to ethnicity and racial disparities for clinical perspectives in EC, and further of the impact on risk stratification and prevention.

A major strength of this study is the large multicentric cohorts of both European and US centers.

EC is increasingly becoming a disease that is molecularly approached in terms of classification, treatment, and prognosis. We argue that patient-related factors are of undiminished importance, and that integration with molecular factors may allow further treatment personalization. Even more important is the relevance of patient-related factors for primary and secondary prevention. We need to further unravel the impact of obesity on EC development by benefiting from the knowledge of subtype-specific tumor drivers that molecular classification has given us. Prospective studies in EC focusing on the interplay between raised hormone levels, inflammation, and metabolic health are needed.[36]

AUTHOR CONTRIBUTIONS

Henrica M. J. Werner: Conceptualization, writing–review and editing, writing–original draft, methodology, formal analysis, supervision, and visualization. **Frederiek A. H. van Dijk:** Data curation, formal analysis, methodology, and writing–original draft. **Stephanie W. Vrede:** Data curation, writing–review and editing, and investigation. **Anouk A. S. van den Bosch:** Visualization and writing–review and editing. **Marike S. Lombaers:** Methodology and writing–review and editing. **Jasmin Asberger:** Investigation and writing–review and editing. **Jutta Huvila:** Investigation and writing–review and editing. **Marc Snijders:** Investigation and writing–review and editing. **Valeria Tubita:** Investigation and writing–review and editing. **Gemma Mancebo Moreno:** Investigation and writing–review and editing. **Xavier Matias-Guiu:** Investigation and writing–review and editing. **Petra Bretová:** Investigation and writing–review and editing. **Vit Weinberger:** Investigation and writing–review and editing. **Johanna M. A. Pijnenborg:** Methodology, investigation, conceptualization, supervision, visualization, and writing–review and editing.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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