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Increasing BMI is associated with both endometrioid and serous histotypes among endometrial rather than ovarian cancers: a case-to-case study

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HIGHLIGHTS

- Obesity is independently linked to endometrial carcinogenesis, for both type I and type II tumors.
- Serous tumors at endometrial level may be estrogen dependent.
- This effect in endometrium is much more evident than in the ovary.
- Obesity seems to be not very linked to ovarian carcinogenesis.

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ABSTRACT

Aim. Although obesity has been associated with endometrioid (type I) and, to a lesser extent, with serous (type II) endometrial cancer (EC), the association with the same histotypes of ovarian cancer (OC) remains unclear. Therefore, we intended to compare the role of BMI in carcinogenesis of endometrioid and the serous malignancies, at both ovarian and endometrial level.

Methods. A retrospective case-to-case study was performed in the University Hospital of Bologna (Italy), through the review of primary EC matched with the corresponding OC cases in the same period (1988–2017).

Results. We included 1052 women diagnosed with EC ($n = 897$ endometrioid, $n = 52$ serous) and 955 women affected by OC ($n = 132$ endometrioid, $n = 627$ serous). EC patients had higher median BMI than women diagnosed with OC (27.3 [23.4–31.9] vs 24.9 [21.7–27.5], $p < 0.01$). After controlling for confounding, 1 unit increase in BMI was associated with a 5% higher odds of endometrial as opposed to ovarian cancer (OR for ovarian as opposed to endometrial cancer 0.95; 95% CI 0.91–0.98, $p = 0.004$).

Conclusions. Increasing BMI is associated with endometrial rather than ovarian cancer, among both serous and endometrioid histotypes.

1. Introduction

Ovarian cancer remains the leading cause of death from gynecological tumors, while endometrial cancers are more common but with better survival rates [1].

A number of studies have found an association between obesity and hormone-dependent cancers, such as endometrial cancer and postmenopausal breast cancer [2–4]. In particular, endometrial cancers have long been divided into two types: type I (endometrioid), associated with unopposed estrogen stimulation, and type II (serous, previously known as papillary), commonly described as estrogen independent, arising in atrophic endometrium [5]. Although obesity has been strongly associated with type I endometrial cancer, risk factors for type II tumors are still largely unknown, mainly because most epidemiologic studies have lacked enough cases to study this histotype separately. However,

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recent data from a large pooled analysis [6] demonstrated that increasing BMI was similarly associated with both endometrioid and serous endometrial cancers, though the odds ratio (OR) was weaker for type II than that for type I tumors.

The role played by obesity as a risk factor for ovarian cancer remains unclear [7,8], even among histotypes such as endometrioid, clearly associated with higher BMIs among endometrial malignancies.

As both the ovary and the endometrium share the same histotypes of malignancies, that may present with indistinguishable morphology, clinical similarities, and common genetic abnormalities [9,10] (Fig. 1), we have conducted a case-to-case study to investigate the differences between ovarian and endometrial cancer, according to their histotypes, with a special focus on BMI.

2. Materials and methods

2.1. Data source and process of collection

A retrospective case-to-case study was performed at the University Hospital Sant'Orsola-Malpighi of Bologna (Italy) through the review of the medical records of 2075 consecutive women that were diagnosed with primary malignant ovarian or endometrial cancers between 1988 and 2017 (see the flow diagram in Fig. 2).

Baseline patients' characteristics (age and BMI), cancer histotype, grade and stage were evaluated at the time of the initial diagnosis. Only primitive epithelial ovarian or endometrial cancers were considered. Ovarian metastases (such as stomach or breast), germline or theca-granulosa (sex-cord stromal) tumors and synchronous carcinomas (ovarian and endometrial) were excluded.

A delegated specific data manager (S.F.) has continuously updated a specific database collecting relevant patients' data in the last 10 years (**G**ynecolog**I**c **O**ncology **T**rea**T**ment and **O**utcome - **GIOTTO**).

This study was exempt from institutional review board (IRB) approval because its design was observational (i.e., without any modification of the routine clinical practice), and all data were obtained from the institutional electronic database and anonymized before analysis. All patients included in the study gave their written consent for the anonymous use of their clinical data for research purposes.

2.2. Staging used for malignant cancers

Ovarian cancers were classified according to the FIGO stage revised in 1988 in Rio de Janeiro [11], while the revised 2009 FIGO staging system for endometrial cancer was used [12].

2.3. Primary outcome

Our primary outcome was to understand the specific role of BMI as a risk factor for endometrioid and serous malignancies, the 2 most common histotypes of ovarian and endometrial cancers.

2.4. Statistical analysis

The characteristics of women with ovarian cancers and endometrial neoplasms were analyzed and compared. Categorical variables were tested with Chi square, while non-normally distributed continuous variables were compared with Rank Sum test. A level of statistical significance of $P \leq 0.05$ was considered. Multivariate logistic regression analysis was used to investigate risk factors associated with the

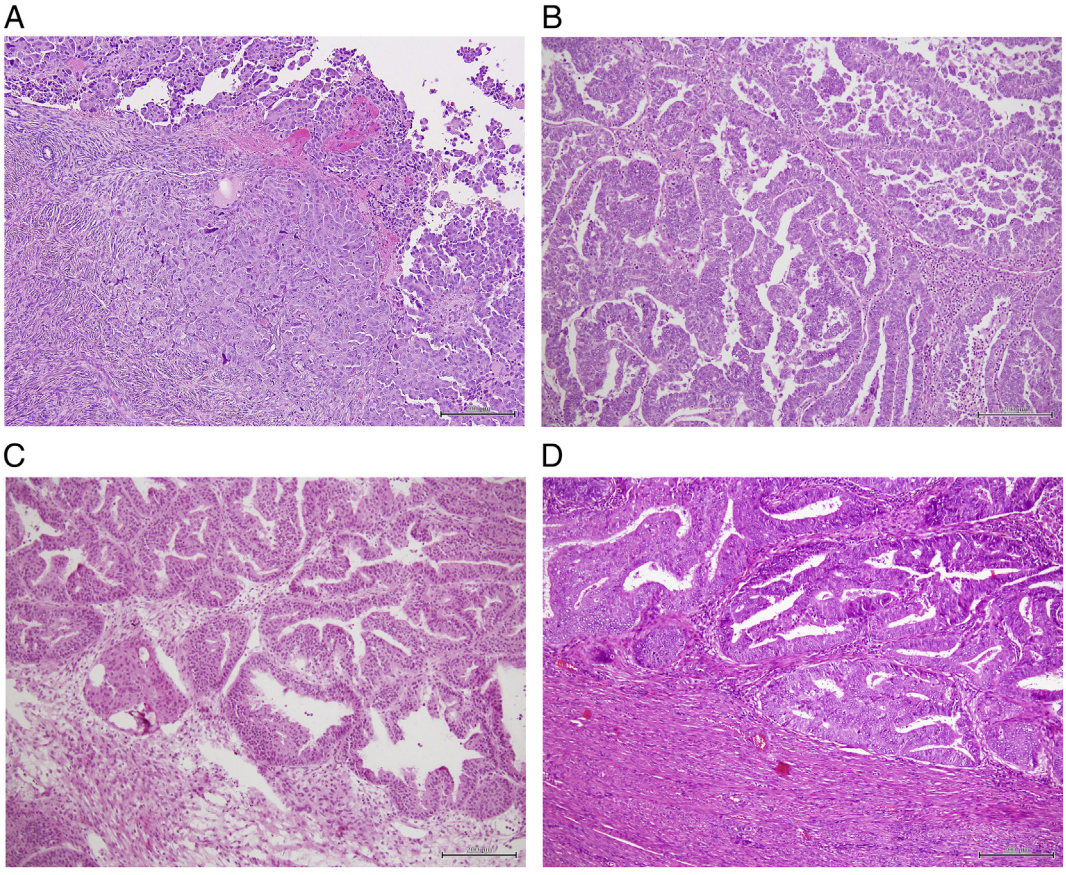

Fig. 1. Indistinguishable pathologic morphology between serous ovarian (1A) and endometrial (1B) cancers and between endometrioid ovarian (1C) and endometrial (1D) cancers. Ematoxilin-Eosin 10×. (Courtesy of Laura Botticelli M.D.).

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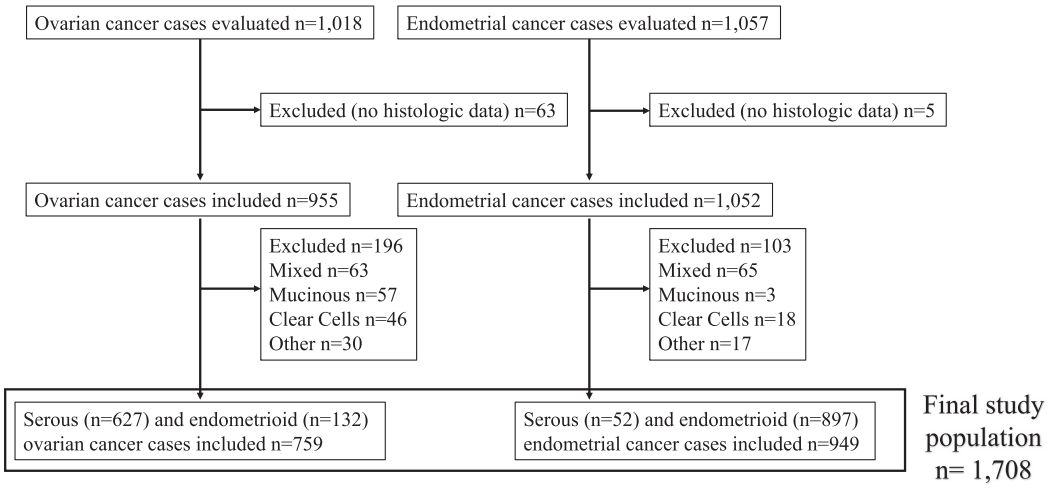

Fig. 2. Flow chart of the study.

diagnosis of ovarian as opposed to endometrial cancer, adjusting for confounding: candidate variables were included if significant on univariate analysis or clinically relevant.

The study of the interaction between patients' BMI and cancer histotype, as well as grade and stage was planned prior to the analyses. The strength of the association between the covariates and the dependent variable was estimated as area under the curve of a receiver operating characteristic (ROC) curve plotted with the true-positive rate compared with the false positive rate. Statistical analyses were performed using Stata 15 (StataCorp, College Station, TX).

3. Results

3.1. Features of ovarian and corresponding endometrial cancers

Fig. 2 shows how we identified our final population consisting in 2007 cancer patients (955 ovarian (48.6%) and 1052 cases of endometrial malignancies (52.4%)).

All histological examinations were performed by the same group of trained gynecological pathologists; reports are presented in Table 1. Serous, clear cells and mucinous histotypes more commonly encountered among ovarian malignancies ($p < 0.0001$), while endometrioid was more common among endometrial cancers ($p < 0.0001$) (Table 1).

3.2. Stages of cancer at diagnosis

3.2.1. Ovarian cancer

Stage FIGO 1988 at histological diagnosis were respectively: 101/955 (10.6%) stage IA, 18/955 (1.9%) stage IB, 75/955 (7.9%) stage IC (total stage I: 194, 20.4%), 20/955 (2.1%) stage IIA, 27/955 (2.8%) stage IIB, 29/955 (3.0%) stage IIC (total stage II: 76, 7.9%), 27/955 (2.8%) stage IIIA, 43/955 (4.5%) stage IIIB, 486/955 (50.9%) stage IIIC (total stage III: 556, 58.2%), 129/955 (13.5%) stage IV (Table 1).

3.2.2. Endometrial cancer

The revised 2009 FIGO Stage for corresponding endometrial cancers at histological diagnosis were respectively: Stage I ($n = 800$, 76.0%) [IA $n = 597$ (56.7%), IB $n = 203$ (19.3%)], Stage II ($n = 92$, 8.7%), Stage III ($n = 127$, 12.1%) [IIIA $n = 32$ (3.0%), IIIB $n = 7$ (0.7%), IIIC 88 (8.4%)], Stage IV only $n = 33$ (3.1%) [IVA n = 9 (0.08%), IVB $n = 24$ (2.3%)] (Table 1).

3.3. Univariate analysis

As we decided to focus on the most prevalent histotypes, we included 759 cases of ovarian cancer ($n = 627$ serous, $n = 132$ endometrioid) and 949 cases of endometrial malignancies ($n = 52$ serous, $n = 897$ endometrioid) (Fig. 2). Table 2 presents the characteristics of the final study population. Ovarian cancer patients were more likely to be younger and leaner than women diagnosed with

Table 1
Features about cancer histotypes, stage and grade at ovarian and endometrial level.

	Ovarian ($n = 955$)	Endometrial ($n = 1052$)	p
Histotype			
Endometrioid	132 (13.8%)	897 (85.3%)	<0.0001
Serous	627 (65.6%)	52 (4.9%)	<0.0001
Clear Cells	46 (4.8%)	18 (1.7%)	<0.0001
Mucinous	57 (6.0%)	3 (0.2%)	<0.0001
Mixed	63 (6.6%)	65 (6.2%)	0.71
Other	30 (3.2%)	17 (1.7%)	0.024
Stage			
I	194 (20.3%)	800 (76%)	<0.0001
II	76 (8.0%)	92 (8.7%)	0.525
III	556 (58.2%)	127 (12.1%)	<0.0001
IV	129 (13.5%)	33 (3.1%)	<0.0001
Grade			
1	75 (7.9%)	447 (42.5%)	<0.0001
2	113 (11.8%)	400 (38.0%)	<0.0001
3	767 (80.3%)	205 (19.5%)	<0.0001

Table 2
Univariate analysis. *Rank Sum test § chi square. Data are presented as median (IQR) or absolute values (%).

	Endometrial	Ovarian	P
Age (years)	63 [55–71]	61 [52–69]	<0.01*
BMI (kg/m^2)	27.3 [23.4–31.9]	24.9 [21.7–27.5]	<0.01*
Histotype			<0.01§
- Endometrioid	897 (92.4%)	132 (18.9%)	
- Serous	52 (7.6%)	627 (81.1%)	
Grade			<0.01§
- 1	414 (44.6%)	34 (4.6%)	
- 2	366 (39.4%)	71 (9.6%)	
- 3	148 (16%)	635 (85.8%)	
Stage			<0.01§
- I	717 (78.8%)	148 (20.2%)	
- II	78 (8.6%)	56 (7.6%)	
- III	94 (10.3%)	434 (59.1%)	
- IV	21 (2.3%)	96 (13.1%)	

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endometrial malignancies ($p < 0.01$); they more frequently presented with serous, less differentiated histotypes, diagnosed at higher stages ($p < 0.01$).

3.4. Multivariate analysis

Multivariate analysis confirmed findings on the univariate approach, as shown in Table 3. The odds of having ovarian as opposed to endometrial cancer were higher in case of serous histotypes, higher grades, and more advanced stages ($p \leq 0.01$). A positive interaction was detected between stage and histotype: the odds of stage II or III serous malignancies were higher than the odds of stage I endometrioid variants among women affected by ovarian as opposed to endometrial neoplasms ($p < 0.05$). Instead, age and BMI had a negative correlation with ovarian when compared to endometrial malignancies ($p < 0.01$). Specifically, 1 unit increase in BMI was associated with a 5% higher odds of having endometrial rather than ovarian cancer (OR 0.95; 95%CI 0.91–0.98, $p = 0.004$) (Table 3, Fig. 3).

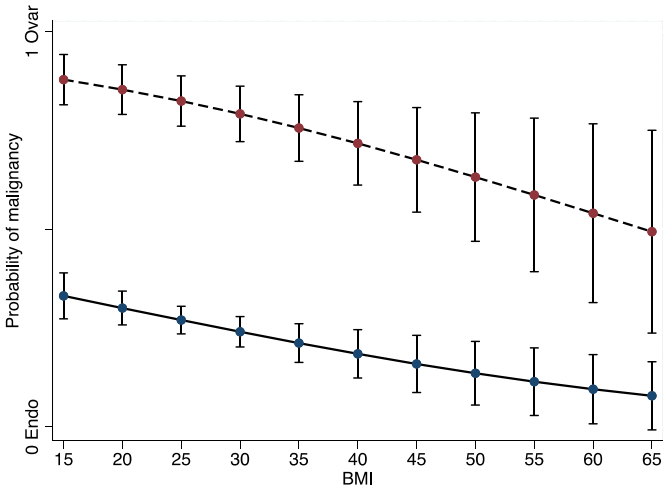

Fig. 3. Probability of ovarian (Ovar) as opposed to endometrial (Endo) cancer according to histotype and patients' BMI. Continuous line: endometrioid histotype; dashed line: serous histotype.

4. Discussion

4.1. Main findings

Increasing BMI is independently associated with both endometrioid (type I) and serous (type II) endometrial adenocarcinoma, when compared to the same histotypes of ovarian malignancies. Endometrium more than ovary presents in itself an environment susceptible to obesity as a carcinogenic risk. Endometrial endometrioid and serous cancers share some common etiologic pathways: the etiology of serous tumors at endometrial level may, therefore, not be completely estrogen independent, as previously believed.

4.2. Interpretation

Obesity represents an established risk factor for endometrial endometrioid cancer. In particular, obesity is associated with higher levels of circulating estrogens in postmenopausal women combined with lower progesterone levels in premenopausal women. Furthermore, in obese subjects levels of sex hormone binding globulin (SHBG), a protein that binds and modulates the biologic activity of estrogens [6], are lower.

The results of our large study confirm findings of other large epidemiologic studies that have evaluated the BMI, examining the possible risk factors also for type II serous endometrial tumors. In particular, a recent large pooled analysis has established that risk factor patterns, in particular BMI, for endometrioid and serous tumors were similar, though BMI had a greater effect on type I tumors than on type II tumors [6]. Similarly, stronger relations for type I versus type II tumors were seen for BMI of ≥30 vs. <30 kg/m^2 from a prospectively evaluated risk factors for incident endometrial cancers among 114,409 women [13]. Another previous large study found that BMI was associated with type II tumors as well as with type I tumors with a magnitude of risk was somewhat stronger for type I than type II tumors [14]. The other study that evaluated the impact of BMI on endometrial cancer type also found BMI to be associated also with type II tumors [15]. This is in agreement with the studies showing that postmenopausal hormone replacement therapies (in particular transdermal and oral cyclic combined estroprogestins, tibolone and vaginal estrogens) appeared weakly associated also with type II endometrial tumors [13,16], suggesting that the etiology of serous tumors at endometrial level may not be completely estrogen independent.

Our study showed the impact of BMI on the same histotypes is not the same at ovarian level. Few studies have provided information on BMI and risk of the most common histotypes of ovarian cancer. Only one study [15] and the pooled analysis by Kurian et al. [18] found a significant increased risk with increasing BMI for the endometrioid ovarian cancer, while 3 other studies [8,19–21] found no association between high BMI and risk of the endometrioid histotype. Three studies reported significantly increased risks associated with the highest category of BMI for the serous subtype [17,19,22]. On the other hand, other studies [8,18,20,21,23–25] found no association between obesity and the serous subtype. Our study did not quantify the absolute risk of ovarian cancer according to patient's BMI, showing that, in comparison to endometrial cancer, increasing BMI is less prevalent among ovarian malignancies. This may indicate that endogenous estrogen levels are unlikely to account for the increased risk of ovarian cancer, as it they do among endometrial malignancies. Instead, other hormonal stimuli may play an active role in ovarian carcinogenesis, such as testosterone, progesterone, leptin, insulin and the associated insulin-like growth factor-1 (IGF-1) [26]. Lukanova et al. [27] found a strong direct relationship between circulating IGF-1 levels and risk of developing ovarian cancer, suggesting that IGF-1 may increase ovarian cancer risk by increasing cell proliferation and inhibiting apoptosis, and/or by modulating the synthesis and bioavailability of sex steroid hormones.

We think that our results may be particularly important for the populations at risk of hereditary both ovarian and endometrial cancers, sometimes concomitant and/or consecutive, such as women with Lynch syndrome (hereditary nonpolyposis colorectal cancer, HNPCC) [28] at highest risk of endometrioid histotype and BRCA mutation carriers [29] at higher risk for serous variants.

Table 3
Multivariate logistic regression. Area under receiver operating characteristic (ROC) curve 0.96.

	OR of having ovarian as opposed to endometrial cancer	P
Age (years)	0.95 [0.94–0.97]	<0.001
BMI (kg/m^2)	0.95 [0.91–0.98]	0.004
Serous histotype	93.2 [43.7–198.7]	<0.001
Grade		
- 2	1.7 [08–3.2]	0.1
- 3	4.9 [2.6–9.2]	<0.001
Stage		
- II	4.5 [1.8–10.6]	0.01
- III	19.1 [10.5–34.7]	<0.001
- IV	15 [5.8–38.8]	<0.001
Histotype/stage		
- Serous/II	0.2 [0.06–0.9]	0.046
- Serous/III	0.2 [0.06–0.4]	<0.001
- Serous/IV	0.2 [0.04–1.1]	0.06

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In our population women diagnosed with ovarian cancer were significantly younger than endometrial cancer patients. As BMI increases with age, and obesity is a strong risk factor for type II endometrial malignancies, we found that women with endometrial cancer were older than ovarian cancer patients. In general, in our sample ovarian cancers were diagnosed at a significant earlier age. Between endometrial cancers, endometrioid histotype is the one diagnosed early in life. It was suggested that as obesity becomes more severe, the underlying carcinogenic mechanisms cause endometrioid endometrial cancers earlier in women's lives [30], while the same association was not confirmed for type II endometrial tumors. BMI tends to naturally increase with age: for this reason, our results were confirmed in multivariate analysis models.

4.3. Limitations

Several limitations to the interpretation of the data in this study deserve mention. These data may not be generalizable to other populations because they were collected from a single Institution and in an Italian population.

We did not have any data on other risk factors of gynecological malignancies such as smoking, diabetes, or metabolic syndrome. Although the impact of smoking on gynecological malignancies has been debated, tobacco was shown to lower age at menopause, alter estrogen their metabolism, cause hyperinsulinemia, and increase levels of bioactive estrogens through a drop in SHBG [31]. Moreover, our study involved a retrospective cohort design and we could not directly assess hormone levels. Conversely, the relationship between BMI and endometrial cancer in comparison to ovarian cancer was very strong and showed a clear biologic gradient, making it unlikely that it could be readily explained by confounding with other variables.

5. Conclusions

Obesity is independently linked to endometrial carcinogenesis for both endometrioid and serous histotypes. Results from this study stimulate the next research into understanding why endometrium more than ovary presents in itself an environment susceptible to the action of obesity as carcinogenic risk.

Conflicts of interest

Sources of financial support for the research: nothing to declare.

Disclosure statement of any potential of interest for each author: nothing to declare.

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Contribution to authorship

Giovanni Grandi: concept and design, data analysis, interpretation, manuscript draft, final approval.

Anna Myriam Perrone: study execution, interpretation, manuscript revise, final approval.

Giuseppe Chiossi: data analysis, interpretation, manuscript draft, final approval.

Stefano Friso: study execution, manuscript revise, final approval.

Angela Toss: interpretation, manuscript revise, final approval.

Margaret Sammarini: interpretation, manuscript revise, final approval.

Fabio Facchinetti: interpretation, manuscript revise, final approval.

Laura Botticelli: manuscript revise, final approval.

Federica Palma: manuscript revise, final approval.

Pierandrea De Iaco: concept and design, study execution, manuscript draft, final approval.

Details of ethics approval

No ethical approval was requested by our institution for a simple review of the medical records, since the collection of these data was performed during clinical practice.

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