Research Paper

Body Mass Index is Negatively Associated with Endometrial Cancer Stage, Regardless of Subtype and Menopausal Status

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Abstract

Objective: Obesity is one of the common risk factors for developing of endometrial cancer and is negatively associated with its survival, although this result is controversial. Endometrial cancer stages range from stage I, which has better clinical outcomes to stage IV, which has poorer clinical outcomes. Endometrial cancer traditionally divides into type 1 and type 2 dependent on histology which has different clinical outcomes. In this study we investigated whether obesity is associated with the stages of endometrial cancer taking into account subtypes of cancer and menopausal status.

Methods: Data on 1,104 women with endometrial cancer were retrospectively collected from the largest women's hospital in China and analysed. Data included age at diagnosis, body mass index (BMI), histology of cancer and menopausal status.

Results: The BMI in patients with stage I endometrial cancer was significantly higher than that in patients with stage II or III or IV (p=0.0001). However, there was no statistical difference in BMI between patients with stage II, and stage III endometrial cancer. This negative association was persisted with type 1 and type 2 endometrial cancer (p=0.1989) and premenopausal and post-menopausal status (p=0.4342). In addition, the proportion of over-weight or obese women in type1 endometrial cancer with stage I was not different to type 2 endometrial cancer with stage I.

Conclusion: Our data demonstrate that BMI is negatively associated with endometrial cancer in early stage regardless of subtypes of cancer, menopausal status and obesity may be also a potential risk factor for developing type 2 endometrial cancer.

Key words: endometrial cancer, BMI, subtype, menopause

Introduction

Endometrial cancer is the most common gynaecological cancer in developed countries, and the fourth most common cancer among women in the United States [1]. In 2014, it occurred in 320,000 women and caused 76,000 deaths worldwide [2]. Over time, there has been a significant increase in the number of Chinese women diagnosed with endometrial cancer [3]. Parity, body mass index (BMI), physical activity and diet may explain up to 80% of the risk of endometrial cancer [4].

Endometrial cancer survival is strongly associated with stage, myometrial invasion and histological type, including cancer cell differentiation [5]. Endometrial cancer stages range from stage I, which the cancer cells have not invaded beyond the lining of the uterus to stage IV, which the cancer cells have spread to distant organs, such as the liver. In general, lower stage cancers are less aggressive and require

less treatment than do higher stage cancers and have better clinical outcomes. Studies have suggested that BMI is negatively associated with endometrial cancer survival [6, 7], although the profiling of these results in this association is controversial [7, 8]. Other study also reported that BMI has no independent prognostic impact on survival [9]. This could be because the effect of BMI, including the weight changes during adulthood on the risk factors of developing endometrial cancer and clinical outcomes across different ethnic groups [10]. In addition, the World Health Organisation (WHO) classification of BMI for Asians is different from that for Caucasians, as is the proportion of population in each category [11].

Endometrial cancer is traditionally divided into type 1 and type 2. The majority of endometrial cancer (80-85%) is type 1, which traditionally is hormone sensitive, occurs at early stage and has better clinical outcomes. Type 2, on the other hand, is thought to be estrogen independent, tends to be higher grade and has poorer clinical outcomes.

Studies have suggested that over 70% women with type 1 endometrial cancer are obese [12, 13], and that 90% of Caucasian women with endometrial cancer are over 50 years of age, with a median age of 63 years (Endometrial cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up; European Society for Medical Oncology, 2013). These studies suggest that the association of BMI and survival may also depend on the subtypes of cancer and/or menopausal status. However, a number of recent studies indicated that type 2 endometrial cancer may not be completely estrogen-independent and has similar pathogenesis with type 1 [14-16]. Moreover, 42% of Chinese women with endometrial cancer in our recent study were pre-menopausal, regardless of subtype [17]. This prompted us to question whether the association of obesity and survival is in fact same in the different types of endometrial cancer as well.

BMI is positively correlated with the incidence of endometrial cancer and negatively associated with survival of endometrial cancer. Whether the negative association of BMI and survival of endometrial cancer is because of the association of BMI and the stages of endometrial cancer has not been investigated yet. Therefore the objective of this retrospective study was to investigate the association between BMI and endometrial cancer stages in Chinese women, taking into account histologic type and menopausal status.

Materials and Methods

This study was approved by the Ethics Committee of The Hospital of Obstetrics & Gynaecology, Fudan University, China.

Study participants

This was a retrospective cohort study of 1,104 women with endometrial cancer admitted to The Hospital of Obstetrics and Gynaecology, Fudan University, China from January 1, 2011 to December 31, 2014. This is the largest Obstetrics & Gynaecology university teaching hospital, serving a diverse urban and rural population in Shanghai, the largest city in China with a population of 20 million. Data on all patients with a primary diagnosis of endometrial cancer were collected from electronic medical records. Clinical data included age at diagnosis, self-reported age at menopause, BMI, and subtypes and stages of cancer.

Weight and height at time of diagnosis were measured and BMI calculated and classified according to the ethnicity-specific WHO classification for Asian/Indian women: underweight (under 18.4 kg/m^2), normal weight (18.5-22.99 kg/m^2), overweight (23–27.49 kg/m^2), and obese (over 27.50 kg/m^2) [11]. The classification of type 1 and type 2 endometrial cancer was determined by pathological examination of biopsies, including cancer histologic subtype and grade. We classified endometrioid and adenosquamous carcinoma with grade 1 and 2 as type 1 endometrial cancer. Clear-cell, serous, mucinous carcinoma and grade 3 endometrioid carcinoma were classified as type 2 endometrial cancers, according to the classification of the International Federation of Gynaecology and Obstetrics (FIGO)[18]. The stage of endometrial cancer was also classified by FIGO guideline [19].

Statistical analysis

The association between BMI and stages of endometrial cancer, adjusting for age, menopausal status and the subtypes of endometrial cancer, was analysed using multiple linear regression using SAS software version 9.4 (SAS Institute Inc., Cary, NC, USA). The statistical difference in the proportion of overweight or obese between type 1 and type 2 endometrial cancer was assessed by Fisher's exact test using Prison software version 7. Two side P value of less than 0.05 was considered statistically significant.

Result

Clinical characteristics of the study population

The clinical characteristics of study participants are summarised in Table 1. The median age of patients at diagnosis was 54 (range 26-88) years old. Of 1,104 patients, 483 (43.7%) patients were diagnosed before menopause and 713 (65%) patients were overweight or obese. Of 1,104 patients, 872 (79%) were diagnosed with type 1 endometrial cancer.

Table 1. Clinical characteristics of the study population

	Women with endometrial cancer (n=1,104)
Age at diagnosis (years, median/range)	54 (26-88)
Type 1 (number, %)	872 (79%)
Type 2 (number, %)	232 (21%)
Premenopause (number, %)	483 (44%)
Postmenopause (number, %)	621 (56%)
Histological stage	
Stage I (number, %)	851 (77%)
Stage II (number, %)	115 (10%)
Stage III (number, %)	119 (11%)
Stage IV (number, %)	19 (2%)

BMI is associated with the stages of endometrial cancer regardless of subtypes of endometrial cancer and menopausal status

Overall, the median BMI in patients with stage I or stage II or stage III or stage IV was 24.01 (range from 15.2 to 40.2) kg/m² or 23.44 (range from 13.6 to 37.3) kg/m² or 23.43 (range from 16 to 32.4) kg/m² or 23.9 (range from 19.1 to 28.9) kg/m², respectively (Table 2).

We then divided the patients into type 1 and type 2 endometrial cancer (two groups) to investigate the association between BMI and stages of cancer (Table 3). In type 1 endometrial cancer, the median BMI in patients with stage I or stage II or stage III or stage IV was 24.01 (range from 15.2 to 40.2) kg/m² or 23.44 (range from 17.7 to 37.3) kg/m² or 23.43 (range from 16.6 to 32.4) kg/m², 20.83 (range from 19.1 to 22.6) kg/m², respectively.

In type 2 endometrial cancer, the median BMI in patients with stage I or stage II or stage III or stage IV was 24.03 (range from 17.7 to 40.2) kg/m² or 22.89 (range from 13.6 to 34.3) kg/m² or 23.44 (range from 16 to 30.8) kg/m², 23.44 (range from 19.5 to 28.9) kg/m², respectively (Table 3).

We further divided the patients into premenopausal and postmenopausal groups (Table 4). In premenopausal patients, the median BMI in patients with stage I or stage II or stage III or stage IV was 23.71 (range from 17.2 to 40.2) kg/m² or 22.76 (range from 13.6 to 37.3) kg/m² or 22.37 (range from 16.6 to 32.4) kg/m², 23.68 (range from 21.4 to 28.9) kg/m², respectively. In postmenopausal patients, the median BMI in patients with stage I or stage II or stage III or stage IV was 24.17 (range from 15.2 to 40) kg/m² or 23.44 (range from 16.1 to 34.3) kg/m² or 23.83 (range from 16.4 to 30.8) kg/m² or 22.45 (range from 19.1 to 25.0kg/2) kg/m², respectively.

BMI was then analysed using multiple linear regression analysis with type, stage and menopausal status and their interactions as explanatory variables. The results showed that there was no statistically significant difference in BMI between subtypes in endometrial cancer (p=0.5069). There was also no statistically significant difference in BMI between premenopausal women and postmenopausal patients (Table 5, p=0.9071), and this was consistent for different stages of endometrial cancer (menopausal status and stage interaction p=0.4342). There was a highly statistically significant difference in BMI between patients with different stages (Table 5, p<.0001), and this difference was consistent between different subtypes of endometrial cancer (stage and type interaction p=0.1989) and menopausal status (stage and menopausal interaction p=0.4342). The estimated mean BMI using least square means from the multiple linear regression analysis was presented in Table 5.

Table 2. Overall BMI distribution among the different stages of endometrial cancer

	BMI (median, range) (kg/m²)
Stage I (n=851)	24.01 (15.2-40.1)
Stage II (n=115)	23.44 (13.6- 37.3)
Stage III (n=119)	23.43 (16 – 32.4)
Stage IV (n=19)	22.61 (19.1 -28.9)

Table 3. The BMI distribution among the different stages of endometrial cancer according to the subtypes of endometrial cancer

	Type 1 (n=872) BMI (median, range) (kg/m²)	Type 2 (n=232) BMI (median, range) (kg/m²)
Stage I	24.01 (15.2-40.2)	24.03 (17.7-40)
Stage II	23.44 (17.7-37.3)	22.89 (13.6-34.3)
Stage III	23.43 (16.65-32.4)	23.44 (16-30.8)
Stage IV	20.83 (19.1-22.6)	23.44 (19.5-28.96)

Table 4. The BMI distribution among the different stages of endometrial cancer according to menopausal status

	Premenopause (n=483) BMI (median, range) (kg/m²)	Post menopause (n=621) BMI (median, range) (kg/m²)
Stage I	23.71 (17.2-40.2)	24.17 (15.2-40)
Stage II	22.76 (13.6-37.3)	23.44 (16.1-34.3)
Stage III	22.37 (16.6-32.4)	23.83 (16.4-30.8)
Stage IV	23.68 (21.4-28.9)	22.45 (19.1-25.0)

Table 5. Least square means of BMI by type, stage and menopause status from multiple linear regression

	BMI (kg/m²)	95% Confidence Limits (kg/m²)		Pr > F
Type				0.5069
Type 1	23.19	22.31	24.06	
Type 2	23.56	22.87	24.25	
Stage				<.0001
I	24.77	24.41	25.13	
II	23.21	22.44	23.97	
III	22.99	22.33	23.65	
IV	22.52	20.58	24.46	
Menopause				0.9071
Premenopause	23.41	22.50	24.32	
Postmenopause	23.34	22.60	24.05	

The proportion of overweight/obese is not different between type 1 and type 2 endometrial cancer

We further analysed the proportion of overweight or obese women between type 1 and type 2 endometrial cancer based on The WHO classification of BMI for Asian/Indian women (Table 6). In type 1 endometrial cancer, 32% (274 of 855) patients were normal weight, while 66% (565 of 855) patients were overweight or obese. In type 2 endometrial cancer, 35% (82 of 235) patients were normal weight, while 61% (143 of 235) patients were overweight or obese. There was no difference in the proportion of patients who were overweight or obese between type 1 and type 2 endometrial cancer (p>0.05).

Table 6. The proportion of BMI distribution in women with endometrial cancer according to subtypes

	Type 1 (n=872)	Type 2 (n=232)	P value
Under weight (number, %)	16 (1.8%)	10 (4.2%)	>0.05
Normal weight (number, %)	274 (32%)	82 (35%)	>0.05
Overweight (number, %)	395 (46.2%)	107 (45.5%)	>0.05
Obese (number, %)	170 (20%)	36 (15.3%)	>0.05

Discussion

In this retrospective study with a large sample size of Chinese women, we found that the higher BMI the lower stage of endometrial cancer at diagnosis, which may suggest patients with higher BMI have better clinical outcomes. This negative association persisted after adjusting for age, menopausal status and subtypes of cancer.

Most of the risk factors for developing endometrial cancer involve high levels of estrogens and obesity is associated with excessive levels of estrogen [20, 21], indicating obesity increases the risk of developing endometrial cancer. However the association of obesity and endometrial cancer survival is unclear and controversial due to the study populations [6, 9]. In our current study, we found that the median BMI of women diagnosed with stage 1 endometrial cancer was significantly higher than in women diagnosed with stage II or III. Interestingly, we further found that there was no difference in BMI between stage II and stage III cancer, suggesting that this negative relationship is restricted to early stage endometrial cancer. A recent study with small sample size (n=94) reported that patients with the increased body fat were more likely to have stage 1 endometrial cancer [22]. Stage I endometrial cancer normally has the best prognosis, while stage IV commonly has a worse prognosis with a median survival time within nine to ten months [23]. Taken together our result indirectly suggests that patients with higher BMI may

have better clinical outcomes. Our current findings are surprising to contrast with a recent systemic review study which suggested that obesity associates higher mortality rate of endometrial cancer in general population [6]. However another study showed that 66% of survivors of endometrial cancer were over-weight or obese after diagnosis [24], suggesting obesity is negatively associated with survival. The difference between our current study and Arem's study [6] could be due to the ethnicity. In general, the BMI in Asian (Chinese) is smaller than in Caucasian and the association between obesity and risk for developing endometrial cancer vary across ethnicities [10]. In addition, factors such as ages at diagnosis that influence cancer survival also differ from different population. We have previously reported that ages at diagnosis of endometrial cancer in Chinese population is significantly younger than Caucasians [17].

Over 70% endometrial cancer is often detected at stage I (Stage Breakdown by CCG, 2014) and over 70% of women with type I endometrial cancer are obese [12, 13]. In our current study we also found that over 77% endometrial cancers were diagnosed at stage I and only 13% endometrial cancers were at stage III or IV at diagnosis in Chinese population. Our data is consistent with these studies further suggesting higher BMI is associated with stage I endometrial cancer. The underlying mechanism of this negative association in unknown but it could be associated with abnormal vaginal bleeding. Abnormal vaginal bleeding is one of the main clinical symptoms of endometrial cancer in premenopausal and postmenopausal women and increased unopposed estrogen (E2) which is associated with obesity is associated with abnormal vaginal bleeding.

Endometrial cancer traditionally divides into type 1 and type 2 and menopausal status is one of risk factors for developing endometrial cancer. We then further analysed this negative association taking into account subtypes of cancer and menopausal status. We further found that the negative association between BMI and stage was seen in both type 1 and type 2 cancer as well as seen in both premenopausal women and postmenopausal women, suggesting the negative association between BMI and the stage of endometrial cancer is consistent between different types of endometrial cancer and between women with different menopausal status.

Type 1 endometrial cancer is the prototypical estrogen-dependent cancer. Traditionally, one of the main cited risk factors for developing type I endometrial cancer is obesity [25], and over 70% of women with type 1 endometrial cancer are over-weight or obese [12, 13]. Women with type 2

endometrial cancer are more likely to be older, of normal weight, and multiparous compared to women with type I [26-28]. In our current study, 66% of women with type 1 endometrial cancer were over-weight or obese, consistent with previous studies; however, 60% of women with type 2 endometrial cancer were also over-weight or obese. Obesity is associated with excessive levels of estrogen [20, 21], which is a risk factor of developing endometrial cancer, and estrogen may also be involved in the pathogenesis of type 2 endometrial cancer [14-16]. Taken together our data support other findings which suggested obesity may also be involved in developing type 2 endometrial cancer. Our previous study reported that the age at diagnosis of endometrial cancer in Chinese population is approximately 10 years younger than Caucasian reported in the literature, and they are more likely to be pre-menopause [17]. This may support the hypothesis that estrogen may also be involved in the pathogenesis of type 2 endometrial cancer.

We acknowledge that there are some limitations of this study. First the age at menopause was self-reported. Secondly, the number of patients with stage IV was small and future study with large sample size of stage IV of endometrial cancer to confirm our conclusions is necessary.

In conclusion, our data demonstrate that in a population of Chinese women with endometrial cancer, BMI is negatively associated with the stages of endometrial cancer, regardless of the subtypes of endometrial cancer and menopausal status. In addition, the proportion of patients with over-weight or obese in type 1 endometrial cancer is not different with type 2 endometrial cancer. Our data support hypothesis that obesity may be also involved in the pathogenesis of type 2 endometrial cancer. Therefore our study suggests that obese women with endometrial cancer may have better clinical outcomes, regardless of menopausal status, and that clinicians should be aware that obese women may also develop type 2 endometrial cancer.

Acknowledgments

Competing Interests

The authors have declared that no competing interest exists.

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