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Research Article

Coexistence of Endometrial Cancer, Polycystic Ovarian Syndrome and Metabolic Syndrome

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Abstract

Background: Metabolic syndrome including obesity, hypertension, insulin resistance, diabetes, and dyslipidaemia have been reported to increase risk of developing multiple cancers, particularly endometrial cancer (EC). Observations linking high blood pressure, abnormal glucose metabolism, and insulin resistance to EC have been mostly from retrospective studies which provided less conclusive evidence because of self-reported disease history and anthropometry without adjustment for body mass. Also, polycystic ovarian syndrome is being linked.

Objective: Present study was conducted to study association of EC, PCOS and Metabolic syndrome.

Materials and Methods: During the period of analysis, a total of 1744 gynaecological cancer (GC) patients were admitted. EC comprised of 3.5% of GC, which significantly increased over the years, 3% (6 of 195 patients) EC out of all GC in 2007 and 8.9% (14 of 157 patients) in 2015.

Results: EC was found to be increasing even in this part. Of the total 62 patients of EC, 36 (58.1%) were obese, 20% had Metabolic Syndrome (12 Type I EC and one Type II EC) and 8% had PCOS. Most women who were part of the study fall in age group 40 - 49 years.

Conclusion: In the present study almost 20% patients provided the evidence of metabolic syndrome and 8% were diagnosed with PCOS. Obesity, metabolic syndrome and PCOS can be considered as important risk factors for EC because they promote endogenous hyperestrogenemia. PCOS, Metabolic Syndrome is seen to increase the risk of subsequent EC. EC patients have linkage to PCOS and metabolic syndrome. Both ways investigations are essential.

Keywords: *Endometrial Cancer; Polycystic Ovarian Syndrome; Metabolic Syndrome*

Background

Decades back Sommers (1957) reported that women with endometrial cancer had a 'habitus', obesity, diabetes or glucose intolerance and hypertension. This was later confirmed by McMohan (1974). However, observations linking high blood pressure, abnormal glucose metabolism, and insulin resistance to EC were mostly from retrospective studies. These retrospective studies provided less conclusive evidence because of self-reported disease history and anthropometry without adjustment for body mass. Weiderpass., *et al.* [1] later reported that there was an association of hypertension with EC in obese women. But the association between hypertension and EC was inconclusive, because of some reports of positive association and others of no association. Elisabete., *et al.* (2000) did not find any

effect of hypertension after adjustment for Body mass index (BMI). However, they did observe an effect of hypertension among obese women, compatible with the hypothesis that Metabolic syndrome with obesity, hypertension and insulin resistance, was a risk factor for EC. Friedenreich., *et al.* (2002) also reported that Metabolic syndrome including obesity, hypertension, insulin resistance, diabetes, and dyslipidaemia increased the risk of developing multiple cancers, particularly EC. Obesity and polycystic ovarian syndrome (PCOS) were both known to be associated with insulin resistance, which lead to elevated insulin levels and increased insulin-like growth factor I (IGF-I) expression. Elevated IGF-I expression, which may occur through decreased sex hormone-binding globulin, the phosphorylated-akt (p-akt) pathway, and/or the aromatase pathway, lead to high local and/or systemic estrogen concentrations [2] which have linkage to EC. Soliman., *et al.* reported that women with EC were more likely to have low adiponectin levels than controls, even after adjusting for BMI. This suggested that insulin resistance was independently associated with EC (Soliman., *et al*. 2006). Three prospective studies have evaluated circulating estrogen levels and EC risk in postmenopausal women, with consistent strong positive association, 2 - 4 times risk in relation to high versus low hormone levels, but this relationship has not been studied in premenopausal women (Eliassen 2007, Luhn., *et al.* 2013, Brown 2015).

Objective of the Study

Present study was conducted to know association of EC, PCOS and Metabolic syndrome.

Materials and Methods

During the period of analysis a total of 1744 gynaecological cancer (GC) patients were admitted to gynaecology inpatient of a rural institution in Central India. EC comprised of 3.5% of all GC, patients. Cases of EC increased over the years, 3% (6 of 195 GC patients) in 2007 and 8.9% (14 of 157 GC patients) in 2015, significant difference (P value < 0.05). Though overall GC patients decreased but those of EC increased. However, EC still remained third GC amongst all GC after cancer cervix and ovary.

Results

Of the total 62 patients of EC 36 (58.1%) were obese. Mean BMI was 29.30 kg/m^2, with range of 21 - 45 kg/m^2. Mean BMI for Type I EC was 29.3 kg/m^2 and for Type II EC also 29.2 kg/m^2, insignificant difference (p-value - 0.9). Five (8.06%) patients (all Type I EC), had PCOS, and hypertension. One (1.61%) was having ischaemic heart diseases (IHD) also. Five (8.06%) patients (3 Type I and 2 Type II EC), had diabetes as well as hypertension, 2 (3.23%) both Type I EC, had diabetes, hypertension as well as IHD and 6 (9.6%) (all Type I EC) had other significant history like thyroid disorder.

Of the 4 (6.4%) patients of EC who were of younger than 40 years, 2 (50%) were obese, of them one had PCOS and other hypothyroidism. Two non-obese women with EC did not have any other disorder. Of the 19 women who were of 40 - 49 years, 9 (47%) were obese and amongst them one (11%) had hypertension, one (11%) had IHD, and 7 (63.6%) did not have any lifestyle disorders. Amongst the ten non-obese patients, one (10%) had hypertension, one (10%) hypothyroidism and the rest 8 (80%) did not have any lifestyle disorder. Of the 25 cases of 50 - 59 years, 16 (64%) were obese. One (6.2%) of the obese with EC had hypertension, 2 (12.5%) had diabetes as well as hypertension and one (6.2%) had hypertension, diabetes as well as IHD. Of nonobese women of 50-59 years with EC, one (11.1%) had hypertension, one (11.1%) had PCOS and did not have any significant history. Of 11 cases of 60 - 69 years with EC, 7 (63.6%) were obese, one (14.2%) had hypertension, 2 (28.5%) had diabetes as well as hypertension and one (14.2%) had diabetes, hypertension as well as IHD. Amongst 4 non-obese cases of EC one (25%) had IHD. Over all 56 EC cases did not have PCOS, 6 (9.67%) had. However, of the 62 patients of EC, 16 (28.1%) of 57 of Type I EC and 1 (20%) of 5 Type II had clinical signs of hyperandrogenism and oligo/anovulation.

Of Type II EC cases 28.57% had hyperandrogenemia (free testosterone > 3.0 pg/ml). 80.9% of Type I EC and 50% of Type II DHEA-S between 35 - 200 ug/dl and in 19.05% Type I EC and 50% of Type II EC had DHEA-S > 200 ug/dl. Only five (8.77%) patients of Type I EC out of 57 and one of 5 Type II EC cases had polycystic ovaries on ultrasonography. Almost 20% of the total 62 patients could be termed to have metabolic syndrome (12 Type I EC and one Type II EC) (Table 1 and Table 2).

	Life Style Disorders										
Age group (years)	**Obesity**	**Hypertension (HTN)**	**Breast Cancer**	**Ischaemic Heart Disease (IHD)**	**PCOD**	**DM + HTN**	**DM + HTN+ IHD**	**Others**	**None**	**Total**	**%**
< 40 years	Obese	0	0	0	1	0	0	1	0	2	50.00
	Non obese	0	0	0	2	0	0	0	0	2	50.00
	Total	0	0	0	3	0	0	1	0	4	6.45
40-49 years	Obese	1	0	1	0	0	0	0	7	9	47.37
	Non obese	1	0	0	0	0	0	1	8	10	52.63
	Total	2	0	1	0	0	0	1	15	19	30.65
50-59 years	Obese	1		0	1	3	1	1	9	16	64.00
	Non obese	1	1	0	1	0	0	0	6	9	36.00
	Total	2	1	0	2	3	1	1	15	25	40.32
60-69 years	Obese	1	0	0	0	2	1	1	2	7	63.64
	Non obese	o	0	0	0			2	2	4	36.36
	Total	1	0	0	0	2	1	3	4	11	17.74
>70 years	Obese	0	0	0	0	0	0	0	2	2	66.67
	Non obese	0	0	0	0	0	0	0	1	1	33.33
	Total	0	0	0	0	0	0	0	3	3	4.84
Total	n	5	1	1	5	5	2	6	37	62	100.00
		8.06	1.61	1.61	8.06	8.06	3.23	9.68	59.68		

Table 1: *Age, obesity and lifestyle disorders.*

Obesity - BMI >27.5 (Asian criteria).

PCOS- Polycystic ovarian syndrome.

Investigation	**Values**	**Endometrial Carcinoma**					
		Type I		**Type II**		**n**	**%**
		Total	**%**	**Total**	**%**		
Free testosterone	0.7 - 3.0 pg/ml	15	71.43	1	50.00	16	69.57
	> 3.0 pg/ml	6	28.57	1	50.00	7	0.30
	Total	21	100	2	100	23	100
DREA-S	35 - 200	17	80.95	1	50.00	18	78.26
	201 - 430	4	19.05	1	50.00	5	21.74
	> 430	0	0.00	0	0.00	0	0.00
	Total	21	100	2	100	23	100
Polycystic ovaries on USG	Present	5	8.77	1	20.00	0	0.00
	Absent	52	91.23	4	80.00	56	90.32
	Total	57	0	5	0	62	100
Oligo/anovulation ± Clinical hyper-androgenism	Present	16	28.1	1	20.0	17	27.4
	Absent	41	71.9	4	80.0	45	72.6
	Total	57	91.9	5	8.1	62	100.0

Table 2: *Types of Endometrial carcinoma and Polycystic ovarian syndrome.*

Discussion

A relationship between EC and PCOS was first suggested in the 1940s and 1950s (Jackson 1957). Later others confirmed these findings (Ramzy 1979, Coulam 1983, Esobedo 1991). Some studies have reported up to 30% premenopausal cases of EC having PCOS [3]. Present study revealed 8% cases having PCOS and 20% having Metabolic syndrome. It was assumed that elevated endogenous estrogen in PCOS patients led to EC. However, obesity and insulin resistance were not fully recognized as potential risk factors for EC at the time when the studies were done. Given that many women with PCOS were obese and had IR, it was not obvious whether PCOS was truly an independent risk factor. However recent study revealed women under 50 years with PCOS had four times the risk of EC compared with controls. An increased risk remained when the researchers controlled for BMI. However, there was no adjustment made for insulin resistance [4]. A familial tendency towards EC was suggested, first degree relatives had an increased risk of developing the disease, especially for disease at younger age (< 55 years) (Olikainen 2005, Lucentefirte 2009).

Earlier Brinton., *et al.* reported that women with BMI of 32 kg/m^2 or greater were four times more likely to develop EC compared to women with BMI of less than 23 kg/m^2, while women with BMI of 35 kg/m^2 or greater had six times the risk (Brinton 1992). In the present study also Brean BMI was more than 29. Swanson also reported that heaviest women were at the highest risk of developing EC (Swanson., *et al*. 1993). In the present study also 58% women were obese. In another study a woman's current weight and weight gain throughout adulthood were most predictive of risk of developing EC [1]. Obese women may have lower circulating levels of sex hormone binding globulin, leading to increased steroid hormone activity, alterations in the concentration of insulin-like growth factor and its binding proteins, and insulin resistance. All of which may contribute to the increased risk of EC [5]. This is because of the greater likelihood of developing an estrogen-responsive EC in women with a higher level of circulating estrogen. Accordingly, severely obese women were more likely to present with stage I disease (77 versus 61 percent), low grade histology (44 versus 24 percent) or a less aggressive histologic subtype (endometrioid: 87 percent versus serous or clear cell: 75 percent) (Everett., *et al.* 2003). Boren (2010) reported obesity to account for 17 - 46% of all cases of EC. A recent study found that overweight women had twice the risk than normal-weight women, while obese women carried four to five times the risk (Lu., *et al.* 2011). Additionally, the length of time, a woman remained overweight also affected her chances of developing cancer and age at disease. Lu., *et al.* (2011) also reported that patients who gained 35% or more weight in their 20s were diagnosed with EC 10 years earlier than women who reported a 5% or less weight change in their 20s. In the same study, women who remained overweight throughout their adulthood were five times more likely to develop EC than their normal-weight counterparts. Mauland., *et al.* (2011) reported more stage I and stage II cancers in obese women with a trend towards improved prognosis in these patients. In a meta-analysis of 19 prospective studies including over three million women, each increase of 5 kg/m^2 in BMI incurred a significantly increased risk of developing EC [6]. Researchers reported an increase in obesity and metabolic syndrome amongst ever married women of reproductive age from 11% to 15% in India and the rural population was not an exception (Ramachandran 2010, Kalra 2012). However, some studies revealed elevated BMI associated with less aggressive EC (Mauland 2011). May be because of this, several authors reported a trend towards better survival in the overweight compared with slender women (Temkin 2007, Munstedt 2008). However, others reported no difference (Jeong., *et al*. 2010) and even poorer survival for women with higher BMI (Gruenigen 2006). The literature regarding the association between hypertension and EC is inconclusive with reports of positive association and no association too. Elisabete's did not find any relation to hypertension after adjustment for BMI, however, an relationship with hypertension among obese women, compatible with the hypothesis that metabolic syndrome, obesity, hypertension and insulin resistance was a risk factor for EC (Saltzman 2008). Friedenreich., *et al.* also reported that metabolic syndrome including (obesity, hypertension, insulin resistance), diabetes, and dyslipidaemia increased the risk of developing multiple cancers, particularly EC (Friedenreich., *et al.* 2011). Further it has been suggested that metformin, a drug widely used to treat infertile women with PCOS, may have a role in preventing endometrial hyperstimulation by lowering insulin concentrations and restoring ovulation (Hardiman 2003). Several studies have evaluated the impact of metformin on ovarian or EC outcomes, namely cancer recurrence or overall survival (Ko 2014, Nevadunsky., *et al.* 2014). Ko., *et al.* (2015) reported that in a population-based cohort of > 500,000 women, when patients using metformin were compared to those using Sulfonyl-

ureas there was no reduced risk of EC. However, there has been scant evidence regarding the impact of metformin upon the development of EC. In the present study it was revealed that almost 60% of cases were obese. The difference between mean BMI of Type I and Type II EC was insignificant (p-value - 0.9). Of the 62 patients, 5 (8.06%) had only hypertension (all Type I EC), one (1.61%) was having only IHD (Type I EC), 5 (8.06%) had PCOS (all Type I), 5 (8.06%) had diabetes and hypertension (3 Type I and 2 Type II), 2 (3.23%) had diabetes, hypertension with IHD (both Type I) and 6 (9.6%) had other significant disorder thyroid disorders (all Type I). There is evidence that obese diabetic women have the highest risk of developing disease (Anderson., *et al.* 2001). Ko (2014) reported diabetes as a risk factor for Type I EC, however the association was not for Type II EC. This was supported by Nevadunsky (2014) also. Vigneri (2009) reported that the relative risk is greatest (about twofold or higher) for EC with diabetes. In another study 66% of patients were found to have insulin resistance at the time of diagnosis of EC, half of the insulin-resistant women did not have a history of diabetes (Burzawa 2011).

It has been assumed that elevated endogenous estrogen in PCOS patients led to EC. Further work is needed to detail the exact role of insulin resistance in EC development.

A 10-fold increased risk with a family history of EC at age younger than 50 years, breast or ovarian cancer and complex endometrial hyperplasia has been reported [7].

Findings of present study are also in concordance with literature that family history of risk diabetes, breast cancer, and presence of PCOS and EC may be risk factors for development of EC [8-37].

Conclusion

In the present study almost 20% women had evidence of metabolic syndrome and 8% had evidence of PCOS.

Findings of present study confirm the hypothesis that the important risk factors of EC include obesity, metabolic syndrome and PCOS by endogenous hyperestrogenemia. The numbers are small and more studies are needed.

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