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Research Article

Endometrial Cancer in Low Resource Settings, Challenges!

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Abstract

Background: Endometrial cancer (EC) reported to be 5th most common cancer, contributed to 4.8% cancers in women with 320 000 new cases worldwide and 49,154 new cases diagnosed 8911 deaths in USA in 2012. Earlier EC was reported as twelth most common cancer amongst all cancers, most common gynecological (gyn) cancer in western women, with rates four to five times lower in developing countries and Japan.

Objective: Present study was conducted to know about any change in trends of EC cases and their profile in low resource settings.

Materials and Methods: During analysis period 51,656 women attended gyn outpatient of rural institute, 14,727 (28.5%) were admitted. Of hospitalised gyn patients, 1744 (11.8%) had gyn cancers (GC). Of them 62 (3.5%) were of EC, third position after cervical cancer (CC 73.5%), ovarian cancer (OC 19.1%).

Results: Of 1744 GC patients 192 (11.0 %) were of less than 40 years, 4 (6.5 % of EC) of EC, 143 (11.1% of CC) of CC, 45 (11.1% of OC and other GC) OCOGC. Ratio of EC amongst all GC cases was highest between 40 to 60 years. Youngest woman with EC was of 27 years, oldest 70 years. Many women (32.2%) with EC had early age of menarche (AOM) 11 years, 16 (25.8%) 12 years, only one (1.6%) 15 years, mean 12.2 years in Type I EC, 13.2 years Type II. There were only 5(8.1%) nullipara women. There was no evidence of delayed menopause. Most women had sterilization (89%). Very few had used oral combination contraceptive pills that too for few cycles.

Conclusion: Present study revealed significant cases of EC in young women, with low resources. Most were multipara and had sterilization done. A lot of research is needed.

Keywords: *Endometrial Cancer; Young Age; Parity; Early Menarche*

Background

Endometrial cancer (EC) has been reported to be the 5th most common cancer among women. It accounted for 4.8% of all cancers in women with 320 000 new cases diagnosed, worldwide in 2012 [1]. Earlier Ferlay (2010) reported EC as twelfth most common cancer amongst all cancers. EC has been reported as the most common gynecologic cancer (GC) in western women. Over all 49,154 new cases and 8911 deaths were reported from USA in 2012 (US Cancer Statistics Working7). Rates in developing countries and Japan were four to five times lower than USA [2]. Earlier Arafa., *et al.* [3] reported that EC was the fourth most common cancer in women after breast, colorectal and lung cancers. Annual incidence was estimated at 10 - 20 per 100,000 women and was increasing [4,5]. However around 75% cases were diagnosed at early stage with the tumor confined to the uterus [6]. In the UK, the incidence in older women (aged 60 - 79 years) increased by more than 40% between 1993 and 2007, similar to most European countries [7]. Colombo., *et al.* [8] reported more than 90% cases in women older than 50 years of age, with a median age of 63 years. In India it has been reported to occur in 4 to 4.4/100,000 women [2,9,10]. National Cancer Registry Programme of Indian Council of Medical Research [11] reported significant increase in EC in urban registries from four metros. In Bangalore the Annual percentage change (APC) was 7.4% between 1986 - 2009 and 7.3% in Mumbai registry between 2005 and 2010 compared to 1.7% between 1982 and 2004. The increase in incidence was more in last five years than in previous 22 years. Bangalore, Delhi and Mumbai Population Based Cancer Registries (PBCR) showed a significant increase in AARs (Age adjusted rates) between 45-54 years of age. Chennai Population Based Cancer Registry recorded an increase due to increase in cases between 55- 64 years of age [11].

Objective of the Study

Present study was conducted to know about any change in trends of EC cases and their profile in low resource settings.

Materials and Methods

Present study was done after approval of ethics committee of the institute. Analysis of histopathologically proved EC cases was done. It had two segments. First was search of records of inpatients who were diagnosed to have GC. In second segment analysis of cases of EC was done. During the period of analysis 51,656 women attended gynaecology outpatient of the institute, of which 14,727 (28.5%) were admitted. Of hospitalised gyn patients, 1744 (11.8%) were of GC, 62 (3.5% of all GC) of EC, third position after cervical cancer (CC) (73.5%) and ovarian cancer (OC) (19.1%). EC remained third commonest GC.

Results

Of the 1744 GC cases, 192 (11.0% of GC) were of less than 40 years, 4 (6.5% of EC) of 192 were of EC, 143 (11.1% of CC cases) of CC and 45 (11.1% of OC and other GC) of OCOGC. Over all 651 (37.5%) women were of 40 - 49 years, 19 (30.6% of all EC) of EC, 481 (37.5% of all CC) of CC and 151 (37.32% of all OCOGC) of OCOGC. Total 462 women (26.4% of all GC) were of 50 - 59 years, 25 (40.3% of all EC) of EC, 334 (26% of all CC) of CC and 103 (25.9% of all OCOGC) of OCOGC. Total 303 (17.3 % of all GC) women were of 60 - 69 years, 11 (17.7% of all EC) of EC, 228 (17.8% of all CC) of CC and 71 (17.7% of all OCOGC) of OCOGC and 129 (7.3% of all GC) patients were of more than 70 years of age, 3(4.8% of all EC) of EC, 97 (7.6% of all CC) of CC and 29 (7.4% of all OOGC) of OCOGC. The mean age of the women with EC was 52.30 ± 9.27, with range of 27 to 70 years. Maximum cases of EC [25 (40.3%)] were of 50 - 59 years, quite a few [19 (30.6%)] 40-49 years also. The mean age of the patients of OCOGC was 46.52 ± 7.58, youngest 21 and eldest 60 years. Mean age of CC cases was 47.21 ± 3.48, youngest 25 and eldest 80 years. Most cases of EC were of 40 to 60 years, 6.5% were of less than 40 years and 4.8% of 70 years. While the patients of EC were highly significantly older than cases of CC (p-value 0.001) and of OCOGC cases (p-value 0.05) (Table 1) still the eldest EC case was 70 years and of CC 80 years. The mean parity of patients with EC was 3 (SD ± 1.61), 82.53% para 2 or higher. Only 8% were nullipara. Of the 62 patients, 48 (77.4%) had undergone tubectomy and mean interval since tubectomy was 24.5 ± 6.5 years, minimum 12 years and maximum 41 years. Overall only 5 (8%) women had never become pregnant, 2 truly infertile, 2 widows with no birth and one was single woman with no pregnancy. Of the 62 patients of EC only 10 (16.1%) had used oral combination contraceptive pills, (3 for 2 years and 2 for 3 years) that too many years back. One woman after using intrauterine contraceptive device (IUCD) for 3 years, used OCPs for few months and then got sterilization done. Twenty (32.2%) patients had menarche (AOM) at the age of 11 years and around 16 (25.8%) at 12 years, 18 (29.0%) at 13 years, 7 (11.2%) at 14 years and only 1 (1.6%) at 15 years. Mean AOM was 12.2 years in cases of Type I EC and 13.2 years in cases of Type II EC. Of the 62 patients of EC, 50 (80.64%) were postmenopausal and 20% premenopausal (Table 2 and 3). Of the 50 postmenopausal women, 22 (44%) had attained menopause within last 5 years, 10 (20%) 6 - 10 years, 8 (16%) 11 - 15 years, 7 (14%) 16-20 years back and 3 (6%) more than 20 years. Two (3.2%) premenopausal patients with EC also had last child birth (LCB) 11 - 15 years before the diagnosis.

Age in years	Endometrial Cancer		Cervical cancer		Other gynaecological Cancers	
	n	%	n	%	n	%
< 40	4	6.5	143	11.1	45	11.3
40-49	19	30.6	481	37.5	151	37.8
50-59	25	40.3	334	26.0	103	25.8
60-69	11	17.7	228	17.8	71	17.8
>70	3	4.8	97	7.6	29	7.3
Total	62	100.0	1283	100.0	399	100.0
Mean	52.30 ± 9.27		47.21 ± 3.48		46.52 ± 7.58	
Range	27-70 yrs		25- 80 yrs		24-60 yrs	

Table 1: *Age of patients.*

Age (Years)	Endometrial Carcinoma									
	Nullipara		Para 1		Multipara		Grandmultipara		N	%
	N	%	N	%	N	%	N	%		
<40	1	25	1	25	2	50	0	0	4	6.45
40 - 49	1	5.26	1	5.26	17	89.47	0	0	19	30.64
50 - 59	4	16	2	8	16	64	3	12	25	40.32
60 - 69	0	0	0	0	5	45.45	6	54.54	11	17.74
≥ 70	0	0	0	0	2	66.66	1	33.33	3	4.83
Total	6	6.67	4	6.45	42	67.74	10	16.12	62	100

Table 2: *Age, Parity of Endometrial carcinoma.*

Age	Socioeconomic class	Endometrial cancer					
		Permanent Contraception			Temporary Contraception		
		Tubectomy	Vasectomy	None	OCPs	IUCD	None
< 40 years	Upper	1	1	0	2	0	0
	Upper Middle	0	0	0	0	0	0
	Middle	1	0	0	1	0	0
	Lower Middle	0	0	1	1	0	0
	Lower	0	0	0	0	0	0
40-49 years	Upper	0	0	0	0	0	0
	Upper Middle	10	0	0	0	1	9
	Middle	7	2	0	3	1	5
	Lower Middle	0	0	0	0	0	0
	Lower	0	0	0	0	0	0
50-59 years	Upper	0	1	1	0	0	2
	Upper Middle	13	2	1	2	1	13
	Middle	5	0	0	1	1	3
	Lower Middle	2	0	0	0	0	2
	Lower	0	0	0	0	0	0
60-69 years	Upper	3	0	1	0	0	4
	Upper Middle	4	0	0	0	1	3
	Middle	1	0	2	0	0	3
	Lower Middle	0	0	0	0	0	0
	Lower	0	0	0	0	0	0
>70 years	Upper	0	0	0	0	0	0
	Upper Middle	0	0	0	0	0	0
	Middle	1	0	1	0	0	2
	Lower Middle	0	1	0	0	0	1
	Lower	0	0	0	0	0	0
Total	62	48	7	7	10	5	47
		62			62		
Total Percentage	100	77.42	11.29	11.29	16.13	8.06	75.81

Table 3: *Age, economic class contraception.*

IUCD: Intrauterine Contraceptive Device; OCPs: Oral Contraceptive Pills.

Discussion

EC is believed to be a disease of the affluent. Epidemiological studies revealed more than 40 % incidence attributed to excess body weight and may be lack of physical activity too. Many researchers [12-14] have reported that alterations in endogenous hormone metabolism provide the main link between EC risk, physical inactivity and excess body weight. EC with an increasing incidence in the last decades has become the most common cancer of the female genital tract in developed countries [15], with an incidence of 12.9 per 100,000 women diagnosed annually [16] and a mortality rate of 2.4 per 100,000, but there were more than 14-fold variations in the incidence in some countries [17]. Unlike most other cancers, the numbers of new cases of EC have risen in recent years, an increase of over 40% in the United Kingdom between 1993 and 2013 [18]. In UK, around 7,400 cases and in Europe around 88,000 of EC were diagnosed annually [7]. Over all 41% of world's EC cases diagnosed in 2012 were from Asia and Northern Europe. Eastern Europe and North America together contributed to 48% of diagnosed EC cases [19]. International agency for research in cancer (IARC) in its most recent report of world cancers estimated that approximately 320,000 women were diagnosed with EC and around 76,000 women died of EC worldwide each year, making it the sixth most common cancer in women [19].

Galaal., *et al.* reported the lifetime risk of EC 1.6% in women of developed countries, compared to 0.6% in developing countries [18]. In developing countries the incidence was 5.9 and mortality of 1.7 per 100,000 women [20,21]. The average woman's lifetime risk for EC was approximately 2 - 3% (Ma 2013). Dinkelspiel., *et al.* reported that in the US, EC was the most frequently diagnosed GC, fourth most common cancer in women [22], representing 6% of all cancer cases in women [23]. In India, low rates have been reported, 4.3 per 100,000 [2]. Dey., *et al.* [24] reported six times higher incidence in urban areas compared to rural. PBCR from India, reported EC as tenth leading cause of cancer in women during the years 1982-83, constituting 1.5 % of body cancers with AAR of 1.9/100,000 women. However, by the year 2008-2009 it became 6th leading cause of cancer in women, constituting 4.2% of all body cancers with AAR of 6.2/100,000 women due to various reasons. The populations have displayed rapid changes in life styles, dietary practices and socioeconomic milieu and these factors might have affected occurrence of EC. The highest APC, has been observed in the incidence of EC amongst all body cancers in PBCR in India between the years 1982-83 and 2008-09 [11]. In seven hospital based cancer registries (HBCR) from India under NCRP, EC was amongst top 10 sites. Chandigarh accounted for 3.8% of all body cancers in women.

In a earlier local study, in the rural region, analysis of GC cases of 15 years, revealed EC contributing to only 2.0% of all GC (1985 - 1999). In the recent analysis it was 3.5%, significant rise in a decade. Over all 1479 women were diagnosed with histopathologically confirmed cancers of various organs, 629 were of GC, 42.52% of all cancers in women. CC was the most common cancer (80%) of all GC, (81.9% between 1985 -1996 and 76% between 1997 - 1999). No woman with CC was from the upper economic class but 25% and 8.6%, cases respectively of EC and OC, were from upper economic class. Almost all the rest were from the middle and lower middle class [25].

The average age of diagnosis of EC in the US was 61 years [26]. Vishwanthan., *et al.* (2014) in their study reported 13% patients of less than 50 years of age in Kerala, the mean was 55.5 years, the range of 45 to 80 years. Balasubramaniam., *et al.* [2] from Mumbai reported 37.7% women with EC of less than or equal to 50 years. Rathod., *et al.* from Bangalore reported mean age 56 Years with range of 30 to 80 years (Rathod 2014). In the present analysis the mean age for Type I EC cases was 52.01 ± 9.28 and Type II EC cases was 55.6 ± 7.44. Type I cancer was diagnosed at a younger age but with insignificant difference (p-value 0.40). Age is lower than that reported in western studies [26,27]. Maximum cases of EC [25 (40.3%)] were of 50 - 59 years and 19 (30.6%) of 40 - 59 years. The mean age of the patients of OCOGC was 46.52 ± 7.58, youngest 21 and oldest 60 years and of CC cases, mean age was 47.21 ± 3.48, youngest 25 and eldest 80 years, younger than other reports. Bhurgri., *et al.* reported the mean age of EC cases in Pakistan as 56.7 + 12.4years [28]. Fujita., *et al.* [29] reported the mean age as 59.4 + 10.5 years in Japanese women. It seems that more research is needed as trends seem to be changing. In the present analysis of the 62 patients of EC, 29 (46.7%) were rural and 33 (53.2%) urban. Most of the patients (60%) seeking health services from the health facility were rural but more EC patients were urban (53.2%). Dey., *et al.* reported six times higher incidence of EC in urban regions compared to rural [24]. This aspect also needs more studies.

Decades back Henderson [30] reported that nulligravida women had two to three times risk of developing EC compared to parous women. Infertile women were found to have 3.5 times higher risk than fertile women. Parazzini., *et al.* [31] also reported that risk of EC was inversely related to parity. Though nulliparity could be a manifestation of infertility, there was evidence that infertility treatments

were independent risk factors for developing EC [32]. Yang., *et al.* [33] found that parity and infertility independently contributed to EC, parity being the predominant predictor. It has been reported that multiparity protects against EC [29,34,35]. A woman's EC risk decreased with each child she had. Giving birth to at least one child is associated with 35% risk reduction and the risk decreased with every subsequent birth [36,37]. However in the present study most women were multipara, only 8% were nullipara, 4 (6.5%) para one, 13 (21%) para two, 20 (32.3%) para three, 10 (16.1%) para four, 6 (9.7%) para five and 4 (6.4%) were para six or higher. Maximum parity was 8. The mean parity of EC patients was 3 (SD ± 1.61) and 82.53% patients were para 2 or higher. No one had used drugs for infertility. Older age at first birth [37] as well as last birth [38] have been reported to be associated with lower risk [32]. However, early marriage and low age at first pregnancy are common in India. If pregnancy occurs at an older age, the effect persists till the perimenopausal age which is a high risk period for EC [36]. Women in India complete their family early, the protective effect of parity and older age at first birth does not seem to be the operating factor. This may be one reason why parity did not play a protective role. It is also possible that this may be the reason for EC occurring at an younger age when the protective effect of early pregnancy wanes off. Further research is needed.

Early menarche has been reported to be associated with EC in several studies. The effect of early menarche on EC, more so with EC in younger women was reported years back [30]. Menarche at the age of ≥ 15yrs has 34% less risk compared to menarche before 11years and menopause at the age of ≥ 55yrs has 53% more risk than menopause between 45 - 49 years [39]. Increased risk of EC associated with early menarcheal age has been attributed to a longer lifetime exposure to endogenous estrogen with deficient progesterone associated with anovulatory cycles [40]. Late menopause associated with increased risk was probability due to a longer lifetime exposure to endogenous estrogen [39-42]. MacPherson., *et al.* reported the relative risk of EC 0.62 in women with menopause between 45 - 49 years of age (McPheson 1996). Bajracharya., *et al.* reported that if a patient is nulliparous and obese and reaches menopause at age 52 years or later, she had a 5-fold increase in the risk of EC [43]. In the present analysis of the 62 patients, 48 (77.4%) had undergone tubectomy (mean duration since tubectomy was 24.5 years, minimum 12 years and maximum 41 years) and 7 (11.2%) women's husbands had vasectomy. Few had used OCP that too for short duration. The findings in the present study revealed most patients had early menarche but there was no evidence of delayed menopause. Menstruation span to endogenous estrogen exposure was probably same to western population. Limitation of study was out patient cases were excluded. Only histopathologically confirmed inpatients cases were included. So, over all incidence of GC and EC could have been little different but the advantage was all confirmed cases were included [44-49].

Conclusion

EC seem to be occurring in young women and increasing. However, it remained third GC after CC and OC. Most women with EC did not belong to upper economic class. Most women had many pregnancies and births. A lot of research is needed.

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