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Risk of Ovarian Cancer Compare to benign Ovarian Disease among Women in Indian Scenario

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Abstract: ***Introduction: Ovarian cancer is one of the most common cancers of women in India. This study aimed to find out the risks such as age, menopausal status, age at menopause, age at menarche, parity, age at first pregnancy, use of oral contraceptives, domicile status, literacy, occupation and BMI of ovarian in comparison with benign ovarian diseases in females. Methods: In this study 100 ovarian cancer patients and 100 women with benign ovarian diseases, who attended at Out Patient Door (OPD) of IPGME&R and SSKM Hospital, Kolkata, India during the period from January, 2010 to December, 2016 were included. Results: Significant risk of ovarian cancer was found in women who attained menopause after 55 years of age (OR-17.60), early menarche (OR-4.76), late menarche (OR-3.35), unmarried (OR-5.26), nulliparous (OR-7.10), late age at first pregnancy (OR-8.30) and related to the occupation (OR-0.44). No increased risk was found in OCP users(OR- 0.36) and occupation (OR-0.44). Patients with a high BMI were at a higher risk (OR-6.65). Discussion: Several risk factors which had already been established by researchers. But the studies were based on different populations of different geographical areas. This study is based on the females of eastern India. Thus the risk factors established through this study may help for early detection and prevention of ovarian cancer in this region.***

Keywords: Cancer, ovarian cancer, benign ovarian disease, risk factors, India

1. Introduction

Ovarian cancer is one of the most common leading gynecological cancer in worldwide as well as India. (Age standardized incidence rate: 6.6/100000). Ovarian cancer has poor prognosis among all gynecological carcinoma [1]. In Indian scenario ovarian cancer is third leading side of cancer among female next to cervical and breast cancer [2, 3]. No comprehensive study has been conducted as yet to assess the risk factors of ovarian cancer in eastern India. Postmenopausal status, early menarche (<12 years), late menopause (>55 years), late age at first pregnancy (>30 years) and non- lactation increase the susceptibility of ovarian tissue to hormonal variations. The risk of developing ovarian cancer is also reducedOral contraceptives pill (OCP) users with pathogenic mutations in the *BRCA1* or *BRCA2* gene [4]. Identification of patients at high risk is essential as early diagnosis and treatment can increase not only the overall but also the disease-free survival of patients with ovarian cancer. The configuration of cancer risks was similar to those found in positive family history, but their total degrees of risk were higher [5].Early menarche and late menopause, which are important risk factors for BC, may be genetically predetermined in a subgroup of patients [6].

H-O Adami et al suggested that nulliparous women are at a significantly higher risk of developing ovarian and breast cancer, especially in those with a BRCA1 or BRCA2 mutation [7, 8] while Mark Clemons et al found that multiparity is a protective risk factor for breast cancer [9]. Parity has been shown to be an independent risk factor for ovarian and breast cancer [7, 10]. Early age at first childbirth and hyperlactation reduces the risk of ovarian and breast cancer in BRCA1 and BRCA2 carriers, and has also been shown to regulate normal cell differentiation [7, 11]. Butt Z et al found that with increasing duration of lactation the risk ofbreast cancer is significantly reduced [12]. Women who are more than 30 years of age at first child birth, are at higher risk of developing ovarian and breast cancer [7, 13]. Ovarian cancer risk factors were observed among urban women compared to rural women [14] and the same trend has also been observed in Indian breast cancer women [15]. Gajalaksmi et al suggested that late menarche, early menopause, early first child birth, multiparty and hyperlactation were protective factors against breast cancer in southern India [16]. Increased body mass index (BMI) has been shown to correlate with increased risk of ovarian cancer in both premenopausal and postmenopausal women and obesity is significantly associated with a worse prognosis in early stage ovarian cancer [17]. Higher BMI was a significant risk for ovarian cancer compared to women having normal BMI. High BMI is a good predictor of ovarian cancer risk in postmenopausal women [18]. This study aimed at identifying the risks of ovarian cancer related to hormonal status, domicile status, literacy, age, occupation, use of oral contraceptives, duration of symptoms and BMI in comparison with women with benign ovarian diseases in Eastern India.

2. Material and Methods

Patient Selection

In this study 100 ovarian cancer patients and 100 women with benign ovarian diseases who attended at Out Patient Door (OPD) of IPGME&R and SSKM Hospital, Kolkata, India during the period from January, 2014 to December, 2016 were included. Information related to demography of the patients was obtained by direct interview with the patients. After clinical examination all patients were subjected to true-cut biopsy or FNAC for the confirmation of their diagnosis. Information of these patients was maintained in the department of G & O in this institute.

Statistical analysis

Statistical Analysis was performed with help of Epi Info (TM) 3.5.3. EPI INFO is a trademark of the Centers for Disease Control and Prevention (CDC). Both univariate and multivariate analysis had been done to find the Odds Ratio with 95% confidence interval and corresponding p-values. Under univariate analysis bivariate frequency tables were used to find the Odds Ratio with their 95% confidence interval and under multivariate analysis Multiple Logistic Regression has been used to find the Odds Ratio with their 95% confidence interval after adjusting the confounding factors. Also descriptive statistical analysis was performed to prepare different frequency tables and to calculate the means with corresponding standard errors. Chi-square test was applied as the measures of associations.

3. Results and Analysis

Distribution of age in cases and controls

The mean age (mean± s.d.) of cases was 46.06±9.88 years with range 31-70 years and the median age was 46 years. The mean age (mean± s.d.) of controls was 46.63±9.73 years with range 31-70 years and the median age was 44 years. T-test showed that there was no significant difference in mean age of the cases and controls (p>0.05), (Table 1). Thus the cases and controls were matched for age.

Risk of ovarian cancer according tomenopausal status, age at menopause and menarche in cases and controls

Among the ovarian cancer patients 56(56.0%) were postmenopausal and 16(28.6%) had late menopause (age at menopause >55 years) but in controls, 45(45.0%) were postmenopausal and 1(2.2%) had late menopause. Under univariate analysis significant risk of ovarian cancer was found 17.60[OR-17.60(2.23, 138.81); p=0.001] times more for late menopause and multivariate analysis significant risk of ovarian cancer was found 15.20[OR-15.20(1.86, 124.25); p=0.011] times more for late menopause. No significant risk was found for menopausal status [OR-1.56(0.89, 2.72); p=0.119] under univariate analysis and [OR-1.10(0.50, 2.44); p=0.802] under multivariate analysis (Table 2). Among the ovarian cancer patients, 26(31.0%) had early menarche (age at menarche <12years), 16(21.6%) had late menarche (age at menarche >13 yrs). In controls, 8(8.6%) had early menarche, 7(7.6%) had late menarche. Under univariate analysis significant risk of ovarian cancer was found 4.76[OR-4.76(2.01, 11.25); p<0.001] times more for early menarche and 3.35[OR-3.35(1.30, 8.65); p=0.009] times more for late menarche but under multivariate analysis significant risk of BC was found 5.41[OR-5.41(2.15, 13.59); p<0.001] times more for early menarche and 3.51[OR-3.51(1.27, 9.71); p=0.015] times more for late menarche (Table 2).

Risk of ovarian cancer according marital status, parity, age at first pregnancy, OCP users, family history of any cancer and BMI in cases and control

In ovarian cancer women, 14(14.0%) were unmarried, 18(18.0%) were nulliparous, 29(35.4%) were having age at first pregnancy (>30 years), 22(26.8%) had a history of lactation less than 6 months and 12(14.6%) had used at least once OCP during their child bearing period. In control women, 3(3.0%) were unmarried, 3(3.0%) were nulliparous, 6(6.2%) were having age at first pregnancy>30 years, and 31(32.0%) had used at least once OCP during their child bearing period (Table 3). Under univariate analysis significant risk of ovarian cancer was found 5.26[OR-5.26(1.46, 18.93); p=0.005] times more for unmarried, 7.10 [OR-7.10 (2.02, 24.95); p=0.001] times more for nulliparous, 8.30 [OR-8.30(3.24, 21.29); p<0.001] times more for late age of first pregnancy. No significant risk was found for OCP users [OR-0.36(0.17, 0.77); p=0.006]. Under multivariate analysis significant risk of ovarian cancer was found 4.34[OR-4.34(1.11, 10.19); p=0.009] times more for unmarried, 3.20 [OR-3.20 (1.32, 11.21); p=0.005] times more for nulliparous, 7.05 [OR-7.05(2.69, 18.49); p<0.001] times more for late age of first pregnancy (> 30 years). No significant risk was found for OCP users [OR-0.40(0.18, 0.89); p=0.024].In ovarian cancer women, 6(6.0%) had family history of cancers. In control women, 1(1.0%) had family history of cancers. No significant risk was found for women having family history of any cancer 6.32[OR-6.32(0.75, 53.5); p=0.120] under univariate analysis. No significant risk was found for women having family history of any cancer 7.69[OR-7.69(0.83, 71.25); p=0.072] under multivariate analysis (Table 3).In ovarian cancer women, 52(52.0%) had high BMI (BMI>25 kg/m^2). In control women, 14(14.0%) had high BMI (Table 3). Under univariate analysis significant risk of ovarian cancer was found 6.65 [OR-6.65(3.35, 13.24); p<0.001] times more for high BMI women. Under multivariate analysis significant risk of ovarian cancer was found 6.65 [OR-6.65(3.35, 13.24); p<0.001] times more for high BMI women (Table 3). t-test showed that BMI of the patients was significantly higher than that of control (t_{198}-5.71; p<0.001),(Table 1).

Risk of BC according to socioeconomic factors

In ovarian cancer women, 23(23.0%) were from rural area, 24(24.0%) were not having any formal education (illiterate) and 19(19.0%) were working women. In control group, 7(7.0%) were from rural area, 12(12.0%) were not having any formal education (illiterate) and 35(35.0%) were working women. Under univariate analysis significant risk of ovarian cancer was found 3.97 [OR-3.97(1.62, 9.74); p<0.001] times more for rural women, 2.32 [OR-2.32(1.08, 4.94); p=0.027] times more for the women not having any formal education (illiterate). No significant risk was found for working women [OR-0.44 (0.23, 0.83); p=0.069]. Under multivariate analysis significant risk of ovarian cancer was found 5.28 [OR-5.28(1.08, 25.72); p=0.039] times more for rural women. Under multivariate analysis no significant risk of ovarian cancer was found [OR-0.70 (0.70, 2.93); p=0.629] for the women not having any formal education (illiterate) and [OR-0.46 (0.23, 0.89); p=0.070] for working women (Table 4).

4. Discussion

In this study, it was established some risk factors associated with ovarian cancer among women in eastern India. Different factors have been found to be good predictors for risk of ovarian cancer. Hypotheses to explain its etiology must take into account not only the carcinogenic agents to which a woman is exposed throughout her life, but also the action of these carcinogens within the context of anovarian cancer resistant host. Risk factors are broadly classified into

those useful in clinical practice, which is significantly influencing the odds of developing ovarian cancer in an individual woman, and those that are significant in public health trends in the population [43]. Among the risk factors which are important in population – hormonal factors are of important value. Early age at menarche, late age at menopause, late age at first childbirth and nulliparity are the common hormonal risk factors which have been discussed thoroughly in western data [19-22]. In this study, the risk of ovarian cancer was significantly increased in women who attained menopause after 55 years of age (OR-17.60). Similarly, risk was increased in women who had early menarche (OR-4.76), as well as in women with late menarche (OR-3.35). However, no risk was associated with the menopausal status of the patient (OR-1.56). Multiparity, age at first pregnancy <30yrs and hyperlactation play a major role in breast cancer protection [23]. In this study, the risk of developing ovarian cancer was significantly increased in women who were unmarried (OR-5.26) and nulliparous (OR-7.10). Late age at first pregnancy (OR-8.30) also placed the women at a significantly higher risk. DariuszSzpureket al. demonstrated that incidence of ovarian cancer is rising in urban Indian women compared to rural Indian women [14]. This data suggests that incidence of breast cancer is higher in rural women than in urban women, and rural women are a significantly greater risk (OR- 3.97) as compared to their urban counterparts. The western data suggests that females who use any kind of OCP have a slightly increased risk of breast and ovarian cancer; whereas females who never used OCP have reduced risk of breast and ovarian cancer [4, 24, 25, 26], but use of OCP in Indian women is not a significant risk factor for breast cancer [27]. No increased risk (OR- 0.36) was found in ovarian cancer patients using OCP in this study.

The inverse relationship of educational level with cancer risk observed in western countries is due lack of knowledge and awareness regarding cancer screening [28, 29]. This result suggests that risk of ovarian cancer (OR-2.32) is higher in illiterate women compared to literate women in eastern India. This data suggests that illiterate women are at a higher risk of ovarian due to negligence of symptoms of ovarian cancer and lack of cancer awareness. Patients with a family history of related cancers were at a higher risk (OR-6.32) of ovarian cancer, whereas no increased risk was seen related to the occupation of the patient with ovarian cancer (OR-0.44). Several relationships including BMI, dislipidemia, postmenopausal status, hormonal status and parity have been observed in this study. The higher BMI was significant risks for ovarian cancer patients compare to controls women. High BMI was a good predictor for risk of ovarian cancer in postmenopausal women [18]. Patients with a high BMI were at a higher risk (OR-6.65). It was seen that sedentary habits and high calorie food intake leads to increase BMI as well as chance of ovarian cancer. As housewives are prone to develop high BMI due to increase in fat mass of the body, it can be hypothesized that physically inactive women are high risk of ovarian cancer compare to normal women.

5. Conclusion

Being one of the first of its kind, this study looked into the distribution pattern of risk factors of ovarian in eastern India. From this study it was demonstrated clearly that early ovarian function, late age at first childbirth, late menopause and nulliparity are important risk factors of ovarian cancer. However, two other variables i.e. use of OCP and occupational status were not found to correlate significantly with the development of ovarian cancer. Also some factors such as illiteracy and domicile status, which are directly or indirectly related to the awareness of ovarian cancer, are found to be potential risk factors for ovarian cancer. Thus it may be said that creating awareness regarding these risks, among the women of eastern India, may help in early detection and treatment of ovarian cancer in this region. This being one of the largest case control studies in eastern India, it conclusively showed premenopausal status, early menopause,multiparity, early age at first pregnancy, urban background, literacy and no family history of related cancers to be associated with a significantly reduced risk of ovarian cancer.

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Table 1: Distribution of age and BMI in cases and controls

	Case (n=100)	Control (n=100)	p-value
Mean Age (mean± s.d.) years	46.06±9.88	46.63±9.73	>0.05
BMI (kg/m^2), (Mean ± s.d.)	22.70 ±2.76	25.22 ±3.44	<0.001

>0.050 -not significant

Table 2: Risk of Ovarian cancer according to menopausal status and age at menopause, menarche

Menopausal status, age at menopause and menarche		Case n(%)	Control n (%)	Univariate OR with 95% CI, p-value	Multivariate OR with 95% CI, p-value
Menopausal Status	Post	56(56.0)	45(45.0)	1.56(0.89, 2.72); p=0.119	1.10(0.50, 2.44); p=0.802
	Pre	44(44.0)	55(55.0)		
Age at Menopause	>55 years	16(28.6)	1(2.2)	17.60(2.23,138.81); p=0.001*	15.20(1.86, 124.25); p=0.011*
	≤55 years	40(71.4)	44(97.8)		
Early Menarche	<12 years	26(31.0)	8(8.6)	4.76(2.01, 11.25); p<0.001*	5.41(2.15, 13.59); p<0.001*
	12-13 years	58(69.0)	85(91.4)		
Late Menarche	>13 years	16(21.6)	7(7.6)	3.35(1.30, 8.65); p=0.009*	3.51(1.27, 9.71); p=0.015*
	12-13 years	58(78.4)	85(92.4)		

* Significant level (≤0.05), >0.050 -not significant, n= Number of patients, %- Percentage

Table 3: Risk of Ovarian cancer according to marital status, parity, age at first pregnancy and OCP users

Risk factors		Case n(%)	Control n (%)	Univariate OR with 95% CI, p-value	Multivariate OR with 95% CI, p-value
Marital status	Unmarried	14(14.0)	3(3.0)	5.26(1.46, 18.93); p=0.005*	4.34(1.11, 10.19); p=0.009*
	Married	86(86.0)	97 (97.0)		
Parity	Nulliparous	18(18.0)	3(3.0)	7.10 (2.02, 24.95); p=0.001*	3.20 (1.32, 11.21); p=0.005*
	Parous	82(82.0)	97 (97.0)		
Age at first pregnancy	>30 years	29(35.4)	6(6.2)	8.30(3.24, 21.29); p<0.001*	7.05(2.69, 18.49); p<0.001*
	≤30 years	53(64.6)	91(93.8)		
OCP Users	Yes	12(14.6)	31(32.0)	0.36(0.17, 0.77); p=0.006*	0.40(0.18, 0.89); p=0.024*
	No	7 0(85.4)	66(68.0)		
Family history of cancer	Yes	6(6.0)	1(1.0)	6.32(0.75,53.5); p=0.120	7.69(0.83, 71.25); p=0.072
	No	94(94.0)	99(99.0)		
BMI (kg/m^2)	≥25	52(52.0)	14(14.0)	6.65(3.35,13.24); p<0.001*	4.39(1.95,9.86); p<0.001*
	<25	48(48.0)	86(86.0)		

Table 4: Risk of Ovarian cancer according to socioeconomic factors

Socioeconomic factors		Case n(%)	Control n (%)	Univariate OR with 95% CI, p-value	Multivariate OR with 95% CI, p-value
Domicile Status	Rural	23(23.0)	7(7.0)	3.97(1.62,9.74); p<0.001**	5.28(1.08, 25.72); p=0.039*
	Urban	77(77.0)	93(93.0)		
Education	Not having formal education	24(24.0)	12(12.0)	2.32(1.08, 4.94); p=0.027*	0.70(0.17, 2.93); p=0.629
	Having formal education	76(76.0)	88 (88.0)		
Occupation	Working Women	19(19.0)	35(35.0)	0.44(0.23, 0.83); p=0.069	0.46(0.23,0.89); p=0.070
	House-wife	81(81.0)	65(65.0)		