Risk factors associated with epithelial ovarian cancer in Sri Lankan women: A case-control study

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Abstract- Despite the emergence of novel treatment modalities, mortality rates due to ovarian cancer remain high, and its incidence has been rising over the past two decades. Although numerous studies have been conducted in developed countries to evaluate the risk factors associated with ovarian cancer, there is a dearth of such information in the South Asian region, which includes Sri Lanka. Therefore, this study aimed to assess the risk factors contributing to epithelial ovarian cancer among women over the age of 40 years in the district of Colombo, Sri Lanka.

A population-based case-control study was conducted among 91 consecutively selected newly diagnosed patients with epithelial ovarian cancer (EOC) residing in the Colombo district who were identified from tertiary care hospitals, versus systematically selected 377 community controls with no ovarian masses. A pre-tested, judgmentally validated interviewer-administered risk assessment questionnaire targeting reproductive, genetic, and lifestyle-related risk factors, which was supplemented by a questionnaire on lifestyle and physical activity levels validated for Sri Lanka was used. Unconditional Multiple Logistic Regression was performed in the analysis. The risk factors associated with epithelial ovarian cancer were: being educated beyond G.C.E (O/L) (AOR=4.2, 95% CI:2.0-9.0), being employed at some point in life (Adjusted Odds Ratio (AOR)=2.3, 95% CI:1.1-4.8), age ≥50years (AOR= 2.6, 95% CI:1.2-5.3), being menopaused (AOR=5.1, 95% CI:2.4-10.8), positive family history of breast/ovary/colon cancer in a first-degree relative (AOR=10.2, 95% CI:3.7-28.6), exposure to abdominal X-rays (AOR=3.4, 95% CI:1.2-9.8). On the other hand, having irregular menstrual cycles (AOR=0.4, 95% CI:0.2-0.9), breastfeeding ≥ 24 months (AOR=0.1, 95% CI:0.06-0.4), and taking oral contraceptive pills (OCP) for ≥2years (AOR=0.1, 95% CI: 0.03-0.3) were found to be protective against EOC. Both modifiable and non-modifiable risk factors related to reproductive and genetic domains contribute to epithelial ovarian cancers.

Index Terms- Epithelial ovarian cancers, risk factors, case-control study, Sri Lanka

I. INTRODUCTION

While being the third commonest gynecological cancer and the sixth most common cancer among females in Sri Lanka[(1)], ovarian cancer is also rated at fourth place among the top ten cancers with the highest mortality rates[(2)]. One in every 131 Lankan females is at risk of developing ovarian cancer during her lifetime, with an age-adjusted incidence of 5.7/100,000 female population[(1)], and an estimated 5-year prevalence of 5.5 % (n=1828)[(3)]. Although the incidence of ovarian cancer in Sri Lanka had remained stable from 1995-2010, the mortality rates increased between 2003 and 2010 among the older age groups[(4)].

Epithelial ovarian cancer (EOC) is the commonest ovarian cancer, accounting for 90-95% of all ovarian malignancies[5]. They are often detected at advanced stages, and hence the prognosis is usually poor[6]. The other ovarian cancer types are germ cell, sex cord-stromal, metastatic and miscellaneous. The mechanism of ovarian cancer development is explained in the literature using two theories: the "incessant ovulation" theory and the theory of "elevated gonadotropin levels". During the ovulatory process, there could be repeated damage and subsequent repairing of the surface epithelium of the ovary leading to DNA damage resulting in an increased risk for ovarian cancer development[7]. In the instances where there is exposure to high levels of circulating pituitary gonadotropins, the stimulation of ovarian surface epithelium would increase the risk of malignant changes[8].

Unlike other malignancies, only a few factors are known to contribute to EOC. These are related to reproductive function, hormonal, genetic, and environmental factors. Among these, the best-known risk factors are advanced age and the presence of susceptibility genes such as BRCA1 and BRCA2[9].

Several epidemiological studies have examined the association between reproductive factors and the risk of EOC. While some of the observational studies have reported an inconsistent association between the age at menarche and ovarian cancer risk [10], a meta-analyses had shown an inverse association[11, 12]. Lengthy irregular menstrual cycles have been found to be a protective factor for EOC[13, 14]. Nulliparity exposes the woman to a greater number of ovulatory cycles, thereby increasing the risk of ovarian cancer[15-17]. Conversely, increasing parity with decreasing ovarian cancer risk has been observed in a number of studies, conducted in different settings, including Europe, United States of America, and Asia[18-20]. An inverse association between EOC risk and breastfeeding for a longer duration was reported in a number of studies[21, 22]. Inconsistent associations were reported for women who had attained menopause after 50years of age in some studies[17, 23, 24]. Exogenous hormonal factors such as oral contraceptive pill (OCP) and hormone replacement therapy have been studied in relation to EOC, where a protective effect that increases with the duration of the OCP usage, lasting for at least 15–20 years after the cessation of its use has been noted[21, 25-27].

Studies on lifestyle-related factors such as obesity, smoking, alcohol, diet, and their relationship with EOC risk have reported inconsistent results. Although a number of studies have been conducted in developed countries to elucidate the risk factors attributable to EOC, there is a scarcity of such information from the South Asian region including Sri Lanka. The impact of already known risk factors could vary across the different regions of the world[28]. Hence, information related not only to the influence of known risk factors whose impact may differ due to the genetic make-up and the lifestyle of the Lankan women, but also about possible unexplored risk factors for ovarian cancers is urgently required in the local setting. Keeping this in mind the present study was conducted to determine the risk factors attributed to EOC in women over 40 years of age in the district of Colombo, Sri Lanka.

II. METHODS AND MATERIALS

A population-based case-control study was designed, and cases were selected from Gynae-oncology unit of the National cancer hospital, Maharagama, and all the other tertiary care hospitals in the district of Colombo, Sri Lanka between 02nd October 2016 to 31st January 2019. Women who were scheduled for an explorative laparotomy on the suspicion of an ovarian tumor were also requested to participate in the study. Histologically confirmed, newly diagnosed (within at least 3 months) patients with an EOC of any stage (according to FIGO staging), who were over 40 years of age, residing in the district of Colombo for a period not less than one year were recruited as cases. Patients with germ-cell, sex cord-stromal, Kruckenberg tumours, patients with ovarian cancer recurrences or other gynaecological malignancies, and those who were mentally and physically not fit enough to give informed consent (e.g. under intensive care) were excluded from this study. Using probability proportionate to cluster sampling technique, females over 40 years of age, residing in the district of Colombo, Sri Lanka for a time exceeding one year, who were confirmed to be free of an abnormal ovarian mass by the ultrasound scan assessment were selected as controls. Women who had been diagnosed with any other gynaecological malignancy were excluded. A final sample of 96 cases and 383 controls were recruited based on a standard formula. In order to increase the statistical

power, four controls were selected per case from the same Divisional Secretariat division of residence of the case or from the closest Divisional Secretariat division. A pre-tested interviewer administered risk assessment tool measuring the reproductive, genetic and lifestyle factors evaluated for judgmental validity, and a lifestyle physical activity questionnaire (LTPAQ) validated for breast cancer patients in Sri Lanka[29], were used to collect data. Anthropometric measurements were taken according to standard protocols. Inter-rater reliability for risk assessment tool, and the LTPAQ was assessed using the same sample of subjects. The life event calendar was used in all the interviews. Informed consent was obtained prior to the interviews. Due ethical clearance was obtained from the Ethics Review Committee of the Faculty of Medicine, University of Colombo, Sri Lanka.

The information of the study variables were as follows; Age at recruitment (40-49years, 50-59 years, 60-69 years, and ≥70 years) civil status (married, unmarried, widow, separated), ethnicity (Sinhala, Tamil, Muslim, Burgher,) employment status (unemployed, ever employed, currently employed), level of education (No school education, Grade 1-5, Grade 6-10, G.C.E O/L, G.C.E A/L, technical education and University education and beyond), the age at menarche (≤11 years, >11 years), parity (Parous, Nulliparous), regularity of menstrual cycles (regular periods ≤ 35 days, irregular periods (lengthy cycles)>36 days), the duration of breastfeeding (Breastfeeding not done, breast feeding≤24 months, ≥ 24 months), the age at menopause (<55 years, ≥55years) and the duration of exposure to Oral Contraceptive Pills (OCP) (Not used, <2years, ≥ 2years), any family history of ovarian/ breast/colorectal cancers among first degree relatives (Yes, No), exposure to passive smoking (Yes, No), occupational activities (low, moderate, high), household activities (low, moderate, high) and Waist to Hip Ratio(<0.86, ≥0.86). Each explanatory variable was re-categorized into 2 categories to be used for univariate analysis followed by multivariate analyses.

III. STATISTICAL ANALYSES

The data analysis was done using SPSS 22.0 version. The reliability of the study instruments was checked using Cohen Kappa coefficient. Chi-square test was deployed to assess the statistical significance of categorical data, while the t-test was used in relation for quantitative data. Data were analyzed for descriptive statistics, and associations were assessed using univariate logistic regression followed by multiple logistic regression. The independent variables for the multiple logistic regression model were selected based on a p-value of less than 0.25 originating from the univariate analysis. Thirty-nine variables that were found to have p values less than 0.25 and other biologically important variables were selected for the multiple logistic regression. Variables associated with ovarian cancer at a significant level below 0.05 were kept in the multivariate model following purposeful selection. Possible interactions were checked by adding 2 variables at a time, including interaction term into the LR analysis. Multicollinearity was assessed at each step when adding or deleting a variable by using a correlation matrix.

IV. RESULTS

In total, 91 cases and 377 controls were included in the final analysis giving rise to a 93.8% and 98.4% response rate for cases and controls, respectively. The mean age of the cases was 56.64 years (SD+ 9.35 years), whereas the mean age of the controls was 51.8years (SD+ 8.34 years).

A greater proportion of both cases and controls were over 50 years of age, and were married, Sinhalese, educated beyond ordinary level examination, and were skilled workers and non-manual workers (table number 1).

Table 1: Socio-demographic characteristics of the study participants

Socio-demographic characteristic	Cases (%)	Controls (%))
Age		
40-49 years	23(25.3%)	167(44.3%)
50-59 years	29(31.9%)	149(39.5%)
60-69 years	32(35.2%)	45(11.9%)
>70 years	7(7.7%)	16(4.2%)
Civil status		
Married	62(68.1%)	341(90.5%)
Unmarried	19(20.9%)	26(6.9%)
Divorced	1(1.1%)	4(1.1%)
Widow	9(9.9%)	6(1.6%)
Ethnicity		
Sinhala	79(86.8%)	332(88.1%)
Tamil	5(5.5%)	30(7.9%)
Muslim	7(7.7%)	11(2.9%)
Burgher	0(0%)	4(1.1%)
Level of education		
No school education	6(6.6%)	6(1.6%)
Grade 1-5	5(5.5%)	0(0%)
Grade 6-9	17(18.7%)	28(7.4%)
Up to G.C.E. O/L[#]	33(36.3%)	182(48.3%)
Up to G.C.E A/L[##]	19(20.9%)	112(29.7%)
Technical Education `	1(1.1%)	28(7.4%)
Up to university education or beyond	10(11.0%)	21(5.6%)
Employment status		
Unemployed	34(37.4%)	269(71.4%)
Ever employed	27(29.7%)	17(4.5%)
Currently employed	30 (33.0%)	91(24.1%)
Social class[(30)]		
I -Leading professions	3(3.3%)	33(8.8%)
II- Lesser professions	15(16.5%)	57(15.1%)
III- Skilled workers and non-manual workers	65(71.4%)	256(67.9%)
IV-Partly skilled workers	2(2.2%)	18(4.8%)
V-Unskilled workers	6(6.6%)	13(3.4%)

[#] General Certificate of Education Ordinary level

[##]General Certificate of Education Advance level

Table 2: Distribution of the cases by histology and staging

Disease characteristic		No. (%)
Histopathological diagnosis	Serous papillary cyst adenocarcinoma	74(81.3%)
	Endometrioid adenocarcinoma	09(9.9%)
	Mucinous cystadenocarcinoma	05(5.5%)
	Clear cell adenocarcinoma	03(3.3%)
Staging (FIGO)	Stage I	12(13.2%)
	Stage II	34(37.4%)
	Stage III	29(31.9%)
	Stage IV	15(16.5%)

The commonest histopathological entity was serous papillary cyst adenocarcinoma; accounting for 81.3% of all EOC, belonging to FIGO stage II (37.4%) at the time of surgery (table number 2).

The odds ratios for the risk factors associated with EOC are summarized in table 3. The risk of having EOC was 2.6 times higher among women aged 50 years or older compared to those aged below 50 years (AOR= 2.6, 95% C.I: 1.2- 5.3). Women who had been employed any time during life were at higher risk of developing EOC compared to women who had never been employed (AOR=2.3, 95% C.I:1.1-4.8). Those who were educated beyond GEC O/L were at higher risk of developing EOC compared to their counterparts (AOR=4.2, 95% C.I: 2.0-9.0).

The risk of having EOC was 60% less among women with a lengthy menstrual cycle >35 days (AOR=0.4, 95% C.I: 0.2-0.9). The women who had continued breastfeeding beyond 24 months were protected against EOC compared to women who had never breastfed and women who had not continued breastfeeding up to 24 weeks (AOR=0.1, 95% C.I:0.06-0.4). The risk of getting EOC was reduced by 90% among the women who had taken OCP for more than two years, compared to women who had taken OCP for less than 2 years and who had never taken OCP (AOR=0.1, 95% C.I: 0.03-0.3). Menopaused women were found to be having a risk five times greater for developing EOC (AOR=5.1, 95% C.I:2.4-10.8). The risk of having EOC was 10 times high among women who gave a history of breast, ovarian or colonic cancer among their first-degree relatives, compared to the women who did not have such positive family history (AOR=10.2, 95% C.I: 3.7-28.6). Those who had ever been exposed to abdominal X-ray were 3 times more likely to develop EOC (AOR=3.4, 95% C.I:1.2-9.8).

Table 3: Risk factors associated with epithelial ovarian cancer

Predictor variable	Cases (%)	Controls (%)	Unadjusted OR (95% C.I)	Adjusted OR (95% C.I)
Age at recruitment				
Age ≥50 years	68(74.7%)	210(55.7)	2.4(1.4-3.9)	2.6(1.2-5.3)

*Age< 50 years	23(25.3%0	167(44.3%)	Ref	Ref
Employment				
Ever employed	57(62.6%)	108(28.6%)	4.2(2.6-6.7%)	2.3(1.1-4.8)
*Never employed	34(37.4%)	269(71.4%)	Ref	Ref
Income				
< Rs. 30,000	14(15.4%)	34(9.0%)	1.8(0.9-3.6)	1.4(0.5-4.0)
*≥ Rs. 30,000	77(84.6%)	343(91.0%)	Ref	Ref
Level of education				
≤ (GCE) Ordinary Level	61(67.0%)	216(57.3%)	1.5(0.9- 2.5)	4.2(2.0-9.0)
*> (GCE) Ordinary Level	30(33.0%)	161(42.7%)	Ref	Ref
Age at menarche				
Menarche< 11 years	21(23.1%)	39(10.3%)	2.6(1.4-4.7)	2.4(0.9-6.3)
*Menarche≥ 11 years	70(76.9%)	338(89.7%)	Ref	Ref
Menstrual regularity				
Irregular periods >36 days	17(18.7%)	117(31.0%)	0.5(0.3-0.9)	0.4(0.2-0.9)
*Regular periods≤35days	74(81.3%)	260(69.0%)	Ref	Ref
Parity				
Nulliparous	32(35.2%)	47(12.5%)	3.8(2.2-6.4)	1.4(0.4-4.7)
*Parous	59(64.8%)	330(87.5%)	Ref	Ref
Duration of breastfeeding				
≥24 months	47(51.6%)	297(78.8%)	0.3(0.2-0.5)	0.1(0.06-0.4)
*<24months[1]	06(6.6%)	27(7.1%)	Ref	Ref
No breastfeeding[1]	38(41.8%)	53(14.1%)		
Duration of OCP use				
OCP used ≥ 2 years	09(9.9%)	144(38.2%)	0.1(0.04-0.2)	0.1(0.03-0.3)
*OCP used> 2 years[2]	14(15.4%)	45(11.9%)	Ref	Ref
Never used[2]	72(79.1%)	188(49.9%)		
Menopausal status				
Postmenopausal	62(68.1%)	153(40.6%)	3.1(1.9-5.9)	5.1(2.4-10.8)
*Premenopausal	29(31.9%)	224(59.4%)	Ref	Ref
Age at menopause				
Age at menopause ≥55 years	10(16.13%)	14(9.15)	1.9(0.8- 4.6)	1.1(0.3-3.9)
*Age at menopause < 55 years	52(83.87%)	139(90.85%)	Ref	Ref
Family History of Breast/Ovary/Colon among first-degree relatives				
Yes	23(25.3%)	25(6.6%)	4.8(2.6-8.9)	10.2(3.7-28.6)
*No	68(74.7%)	352(93.4%)	Ref	Ref

Exposure to passive smoking				
Yes	15(16.5%)	26(6.9%)	2.7(1.3-5.3)	3.2(1.0-10.1)
*No	76(83.5%)	351(93.1%)	Ref	Ref
Exposure to abdominal X-ray				
Yes	14(15.4%)	30(8.0%)	2.1(1.1-4.2%)	3.4(1.2-9.8)
*No	77(84.6%)	347(92.0%)	Ref	Ref
Waist-to-hip ratio				
Waist/Hip ratio≥0.86	53(58.2%)	179(47.5%)	1.7(1.1-2.8)	0.8(0.4-1.6)
*<0.86	38(41.8%)	198(52.5%)	Ref	Ref
Occupational activities				
Low	32(35.2%)	108(28.6%)	1.4(0.8-2.2)	1.5(0.7-3.4)
*Moderate[3]	40(44.0%)	195(51.7%)	Ref	Ref
*High[3]	19(20.8%)	74(19.7%)		
Household activities				
Low	53(58.2%)	218(57.8%)	1.0(0.6-1.6)	1.3(0.6-2.8)
*Moderate[4]	19(20.9%)	106(28.1%)	Ref	Ref
*High[4]	19(20.9%)	53(14.1%)		

*Reference
[1] Duration of breastfeeding <24 months and subjects with no history of breastfeeding were taken as reference
[2] Duration of OCP use <2 years and subjects with no history of OCP use were taken as reference
[3] Moderate and high levels of occupational activities were taken as the reference value
[4] Moderate and high levels of household activities were taken as the reference value

V. Discussion

In the present study women, who were aged 50 years or more, who had been educated beyond GCE (O/L), who had been employed any time during life, who had already attained menopause, who had a positive family history of carcinoma of the breast/ovary/colon in a first-degree relative, and who had been exposed to abdominal X rays were at risk of developing EOC. Women who were found to be having irregular menstrual cycles lasting> 35 days, who had continued breastfeeding > 24 months, and who had used OCP for more than 2 years were protected against EOC.

We adhered to the following measures in the methodology to minimize the bias introduced in a case control study. For the present study, cases were recruited from all the tertiary care hospitals in the Colombo district, Sri Lanka, and controls were selected from the community in the Colombo district, where the cases also were residents. This ensured the greatest level of comparability since they represented the same source population from where the cases originated[(31)]. We used incident cases, since in case-control studies they are better preferred compared to the prevalent cases[(31)], as the individuals may modify their exposure to the elements of concern once cancer/disease is diagnosed, or due to complications caused by the disease. In our study, due to the limited number of cases identified during the limited period, we recruited four controls per case, thereby improving the statistical power of the study. In order to mitigate recall, bias a life event calendar was given to both cases and controls with enough time to complete before answering, so as to facilitate

reflecting and recalling through a sequence of events in their lives. Verification of exposure details was done by referring to medical records, thereby minimizing recall bias. The study population consisted of subjects from diverse educational backgrounds, hence their literacy rates understandably were different. Therefore, the administration of interviewer-administered questionnaires reduced the missing data, at the same time minimizing information bias.

The present study revealed that women of age >50 years have a higher risk of getting EOC and according to previous studies, median age at diagnosis is 50–79 years[32, 33]. In the present study, education beyond GCE (O/L) was found to be a statistically significant risk factor. This could be explained by the fact that those who aspire for higher education voluntarily delay starting a family which could have negative implications on their risk of ovarian cancer. Similarly, a study conducted on 1,031 cases of invasive EOC and 2,411 controls from 1992-1999 in Italy reported a higher risk of developing cancer among the women who had achieved the highest level of education[34]. A study conducted in the Shanghai area had shown a statistically significant increase in the incidence of EOC among professionals, technical workers, and scientists[35]. In the present study, it was the women who were ever involved in a job who were found to be having a higher risk of EOC. However, subgroups of the occupations could not be analyzed in relation to EOC in the present study, since the sample size in each occupational category was small.

Having lengthy menstrual cycles as a result of fewer ovulations has been shown to be a protective factor against EOC in the present study. Some other studies have also reported an inverse association between irregular lengthy cycles and EOC[14, 36], while one study had found no association[37].

In the present study, the risk of developing EOC was reduced by 90% in women who continued breastfeeding for a period of exceeding 24 months. Similar inferences were made in two meta-analyses and one population-based study; Here it was shown that breastfeeding for a period over 12 months conferred a significant protective effect[22], a reduction of the risk by 8% for each additional 5 months to the duration of breastfeeding[38], and breast feeding for beyond 18 months[39]. On the contrary, another study revealed no statistically significant association[40]. During pregnancy and lactation, ovulation is suppressed, and the gonadotrophin levels are also reduced. The subsequent reduction in oestradiol levels could be the plausible physiological mechanism behind this protective effect[41, 42].

In our study, OCP use for$\geq$ 2 years was found to have a protective effect against EOC. Similar findings were reported by the Collaborative Group on Epidemiological Studies of Ovarian Cancer[43], and also by a population-based, case-control study[27] where they had concluded that longer the duration of OCP use, the better the protective effect was.

In the present study, the risk associated with menopause for the development of EOC was 5.1 times higher compared to that for those women who were yet to reach menopause. In the published studies, direct information on the risk conferred by the menopausal status on EOC is scarce. One such study revealed that the ovarian cancer risk dramatically increases around the peri-menopausal age and in the immediate post-menopausal period, and thereafter continues to pose a significant risk as the ovary ages[44].

In our study, a positive family history of carcinoma of the breast, ovary or colon in a first-degree relative was a statistically significant risk factor for the development of EOC in the index subject. The findings of our study were also consistent with the findings of the other studies published in the literature[13, 18, 45]. In our study, due to the limited sample size, women with a first-degree relative with cancers that were known to have a genetic link were grouped together. Hence, the familial risks conferred by individual cancers could not be elicited.

In the present study, ever exposure to abdominal X-rays during a lifetime was found to be a statistically significant risk factor. The evidence on the effect of abdominal X-rays on ovarian cancer is sparse in the literature. A univariate analysis performed in a case-control study conducted to explore the effect of diagnostic X-rays and the risk of EOC among Jewish women showed no association between exposure to abdominal or pelvic X-rays within 10 years or more[46].

The limitations of our study were as follows: Even though we used life event calendars, the effect of recall bias on the information on lifetime physical activity levels could not be completely corrected. Our study was a retrospective case-control study, and therefore causal relationships could not be elicited. It was not possible to carry out subgroup analysis as the number included in each category of histopathological subtypes of EOC was small.

In conclusion, having irregular menstrual cycles lasting more than 35 days, breastfeeding for an average of 24 months or longer, and use of OCP for 2 years or more were found to be protective factors against EOC after adjusting for possible confounding factors. Being a woman aged 50 years or older, having been educated beyond G.C.E (O/L), being employed at some point in life, being menopaused, having a positive family history for carcinoma of the breast/ovary/colon in a first-degree relative, and having been exposed to abdominal X-rays were found to be risk factors after adjusting for possible confounding factors.

The association between reproductive, genetic, and lifestyle risk factors and epithelial ovarian cancer, needs to be further studied using prospective research methodologies followed by Mendelian Randomization studies to triangulate causal relationships and to eliminate confounding bias.

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