TUBAL LIGATION, REPRODUCTIVE EXPERIENCES AND RISK OF OVARIAN CANCER- A PROSPECTIVE STUDY

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ABSTRACT

BACKGROUND

Ovarian cancer is the most lethal malignancy of the female reproductive system. Risk of ovarian cancer increases with age, but the rate of increase slows after the menopause. Tubal ligation confers long-term protection against ovarian cancer. This observational study examines the factors affecting the ovarian cancer risk and also studies the correlation between ovarian cancer risks with reproductive experiences.

MATERIALS AND METHODS

This study was conducted at Department of Obstetrics and Gynaecology, Government Medical College, Kottayam, Kerala, for a period of one year. Information was collected from 112 women diagnosed with ovarian cancer as treatment group and 336 women without ovarian cancer as control group. A binary logit regression analysis was conducted to study the factors that are affecting the ovarian cancer. The Chi-square test was done to find the association of ovarian cancer risk with different reproductive experiences.

RESULTS

We found that months of lactation, tubal ligation and oral contraceptive pills had a negative impact on ovarian cancer risk. Our study also proved that age of first pregnancy, age of menarche and age of menopause had a significant association with ovarian cancer risk.

CONCLUSION

Our findings signify the importance of providing awareness to the public regarding the prevalence, symptomatology, screening/diagnostic techniques, treatment modalities and prognosis of ovarian cancer. The dual benefits of tubal ligation need to be made aware among the public and tubal sterilisation rates have to be enhanced. We recommend the promotion of tubal ligation as a permanent method of contraception in those who have completed their families.

KEYWORDS

Tubal Ligation, Oral Contraceptive Pills, Reproductive Experiences, Binary Regression Analysis.

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BACKGROUND

Ovarian cancer is the most dangerous gynaecological malignancy. Furthermore, it is a highly fatal disease with the worst prognosis among the gynaecological cancers because it is often diagnosed at an advanced tumour stage. Early detection and newer therapeutic methods to lessen mortality have been largely unsuccessful since the origin and pathogenesis of ovarian cancer are poorly understood.[1]

A recent research report concludes that ovarian cancer is a collection of different subtypes with distinct developmental origins.[2] The report summarises emerging evidence that most ovarian cancers arise from the female reproductive tract, not the ovaries per se and spread to the ovary. This awareness has changed thinking about screening and early detection, risk factors and most importantly preventive measures, especially in women known to be at higher risk.[3] Gynaecological surgeries including tubal ligation and hysterectomy may alter ovarian cancer risk by protecting the ovary from ascending carcinogens or damaging the utero-ovarian artery altering hormonal function. In addition, tubal ligation may increase immunity against the surface glycoprotein human mucin 1 (MUC1).[4-6]

Tubal ligation is the most common form of birth control used in the world. A reduced risk of ovarian cancer has consistently been seen following tubal sterilisation in both case control and cohort studies. The protective effect of tubal sterilisation on ovarian cancer appeared to persist for many years after the procedure. Alternatively, tubal sterilisation diminishes the risk of ovarian cancer by

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obstructing ascend of potentially harmful carcinogenic agents such as talc, contraceptive foams or gels, uterine growth factors or retrograde menstruation.

Various studies are conducted in developed world on the relationship between tubal ligation and ovarian cancer risk. But, very limited studies are conducted in developing nations to explore the impact of tubal ligation on ovarian cancer. Hence, we investigated the factors including tubal ligation that are affecting ovarian cancer risk as well as the association of reproductive experience with ovarian cancer risk.

MATERIALS AND METHODS

Study Population

This study was conducted at the Department of Obstetrics and Gynaecology (OB-GYN), Government Medical College, Kottayam, and it was an observation study. The Regional Committee for Medical Research Ethics had approved the study protocol of this research. The duration of study was from August 2015 to July 2016. Information was collected from 112 women diagnosed with ovarian cancer as treatment group and 336 women without ovarian cancer as control group. Information regarding this research was informed to the patients and written consents were obtained from each of them. The information needed for this study was collected by using semi-structured questionnaire, ultrasound report and tumour marker measurements.

Inclusion Criteria of Treatment Group

Women admitted to the Department of OB-GYN who had carcinoma ovary as defined by ultrasound and tumour markers and who were willing to participate in the study were selected.

Inclusion Criteria of Control Group

Women admitted to the Department of OB-GYN who did not have carcinoma ovary as excluded by ultrasound and tumour markers and who were willing to participate in the study were selected as control group.

Information on demographic characters, reproductive experiences and tubal ligation were recorded from the patients using a standard questionnaire.

Statistical Analysis

The data collected was entered into Microsoft Excel worksheet. Percentages were used to express the qualitative data. In order to find out the factors that contributes to the ovarian cancer risk, a binary logistic regression analysis was carried out. A binary regression model was used to quantify the linkage between ovarian cancer risk and various factors that contribute to it.

To examine the factors influencing ovarian cancer, the logit model with most likely variables was fitted and was estimated using the maximum likelihood method. The logit model postulates that the probability of ovarian cancer, P is a function of an index variable Z summarising a set of the explanatory variables (Xi). In fact, Z is equal to the logarithm of the odds ratio, i.e. ratio of probability (P) of ovarian cancer to the probability (1-P) of non-ovarian cancer and it can be estimated as linear function of explanatory variables.[7] The functional form of the logistic model maybe given by equation 1.

The functional form of the model is specified as follows-

$Y = P/(1-P)$……(1).

Where, Y = Ovarian cancer status of the patients (1 if the patient has ovarian cancer and 0 for non-ovarian cancer patients).

$\ln P/(1-P) = Z = F(X_1, X_2, X_3, X_4, X_5, X_6)$……(2).

Where,

Z = Vector of explanatory variables.

X_1 = Tubal ligation.

X_2 = Months of lactation.

X_3 = Oral Contraceptive Pills (OCP).

X_4 = Age more than 45 years.

X_5 = Early menarche.

X_6 = Talc use.

Chi-square test was carried out to study the association of ovarian cancer risk with different reproductive experience. Minimum 95% confidence interval and p value <0.05 was considered statistically significant. Statistical Package for Social Sciences (SPSS) was used to analyse the data.

RESULTS

The results of our study are depicted in the following tables and figures. The Chi-square value = 24.7, p value=0.000, OR=11.533 and 95% CI=(1.793-74.196), which implies that age more than 45 years is a significant risk factor for carcinoma ovary, increasing the risk 11.6 times (Table 1).

Age in Years	Ovarian Cancer Group		Control Group		P value
	Number	%	Number	%	
<45	10	8.9	111	33.0	0.000
>45	102	91.1	225	67.0	

Table 1. Association of Ovarian Cancer Risk with Age of Patients

The association between level of education and ovarian cancer risk was significant. The Chi-square is 52.1 and p value is 0.000 (Table 2). We found that 37.5% of cases and 10.7% of controls had no formal education (Figure 1).

Level of Education	Ovarian Cancer Group (Numbers)	Control Group (Numbers)	P value
No formal education	42	36	0.000
Primary	54	162	
Secondary and above	16	138	

Table 2. Association of Ovarian Cancer Risk with Level of Educational

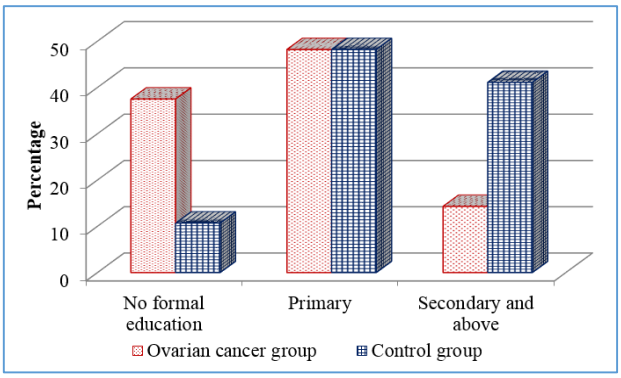

Figure 1. Distribution of Study Population According to Level of Education

We found significant association between age of pregnancy and ovarian cancer risk. Chi-square=17.3 and p value=0.001, implies that a later age of first pregnancy (>30 years) is a significant risk factor for carcinoma ovary (Table 3). 62.5% of cases and 81.3% controls had their first pregnancy before 30 years of age (Figure 2).

Age at First Pregnancy in Years	Ovarian Cancer Group (Numbers)	Control Group (Numbers)	P value
<20	22	103	0.001
20-30	48	170	
>30	30	46	
Not applicable	12	17	

Table 3. Association of Ovarian Cancer Risk with Age at First Pregnancy

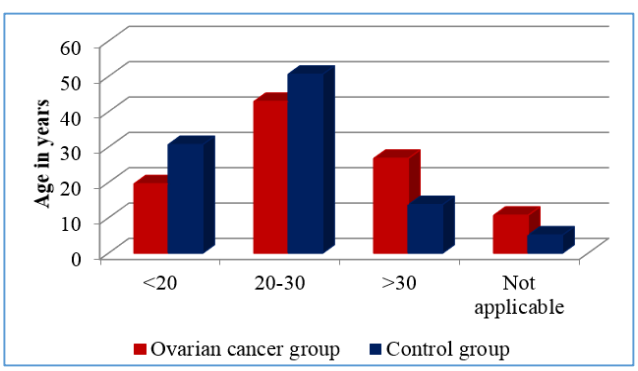

Figure 2. Distribution of Study Population According to Age at First Pregnancy

The association between ovarian cancer risk and duration of lactation was statistically significant. The Chi-square=80.0, p value=0.000, OR=0.069 and 95% CI= (0.033-0.146), which implies that breastfeeding more than 2 years is protective against carcinoma ovary, decreasing the risk by 6% (Table 4).

Duration of Lactation	Ovarian Cancer Group		Control Group		P value
	Number	%	Number	%	
<1	50	44.6	49	14.6	0.000
1-2	42	37.5	100	29.8	
>2	8	7.1	170	50.6	
Not applicable	12	10.7	17	5.1	

Table 4. Association of Ovarian Cancer Risk with Duration of Lactation

We found a significant association between parity and ovarian cancer risk. The Chi-square value is 15.3 and p value is 0.000, which implies that increased parity decreases the risk for carcinoma ovary (Table 5).

Parity	Ovarian Cancer Group		Control Group		P value
	Number	%	Number	%	
Nullipara	12	10.7	17	5.1	0.000
Primipara	14	12.5	14	4.2	
Multipara	86	76.8	305	90.8	

Table 5. Association of Ovarian Cancer Risk with Parity

The association between mode of delivery and ovarian cancer risk was statistically significant at 95% confidence interval (Table 6).

Mode of Delivery	Ovarian Cancer Group		Control Group		P value
	Number	%	Number	%	
Vaginal	74	66.1	202	60.1	0.017
LSCS§	26	23.2	117	34.8	
Not applicable	12	10.7	17	5.1	

Table 6. Association of Ovarian Cancer Risk with Mode of Delivery

§Lower segment caesarean section.

We found a significant association between history of infertility and ovarian risk cancer (Table 7).

History of Infertility	Ovarian Cancer Group		Control Group		P value
	Number	%	Number	%	
Yes	10	8.9	1	0.3	0.000
No	90	80.4	318	94.6	
Not Applicable	12	10.7	17	5.1	

Table 7. Association of Ovarian Cancer Risk with History of Infertility

Table 8 depicts the distribution of ovarian cancer and age of menarche. Chi-square value = 31.3, p value = 0.000, OR = 5.27 and 95% CI = (2.54-10.95), implies that early menarche <12 years is a risk factor for cancer ovary increases the risk by 5.3%.

Age of Menarche in Years	Ovarian Cancer Group		Control Group		P value
	Number	%	Number	%	
<12	53	47.3	68	20.2	0.000
>12	59	52.7	268	79.8	

Table 8. Association of Ovarian Cancer Risk with Age at Menarche

The association between duration of menstrual bleeding and ovarian cancer risk was found statistically significant (Table 9). Chi-square value = 40.65 and p value = 0.000, which means prolonged menstrual bleeding (>5 days) increases the risk for ovarian malignancy.

Duration of Menstrual Bleeding in Days	Ovarian Cancer Group		Control Group		P value
	Number	%	Number	%	
<5	44	39.3	244	72.6	0.000
>5	68	60.7	92	27.4	

Table 9. Association of Ovarian Cancer Risk with Duration of Menstrual Bleeding

The length of menstrual cycle has no significant association on the occurrence of cancer ovary (Table 10). The Chi-square value was 0.779 and p value was 0.677.

Length of Menstrual Cycle	Ovarian Cancer Group		Control Group		P value
	Number	%	Number	%	
Polymenorrhoea	32	28.6	83	24.7	0.677
Normal	69	61.6	222	66.1	
Oligomenorrhoea	11	9.8	31	9.2	

Table 10. Association of Ovarian Cancer Risk with Length of Menstrual Cycle

We found significant association between ovarian cancer and age of menopause (Table 11). Chi-square value was 56.7 and p value = 0.000, which means that late menopause (age >50 years) increases the risk of ovarian malignancy.

Age of Menopause in Years	Ovarian Cancer Group		Control Group		P value
	Number	%	Number	%	
<50	32	28.6	146	43.5	0.000
>50	67	59.8	75	22.3	
2	13	11.6	115	34.2	

Table 11. Association of Ovarian Cancer Risk with Age of Menopause

The estimated coefficients of the binary regression model for ovarian cancer risk are presented in Table 12. The estimated model seems to perform satisfactorily with R^2 value of 0.62. Many of the estimated coefficients are statistically significant and have expected signs. Age of women more than 45, early menarche and talc use had positive impact on ovarian cancer risk. Months of lactation, tubal ligation and OCP had a negative impact on ovarian cancer risk.

Variables	B	S.E.	Wald	df	Sig.
Age >45 years	2.445	0.95	6.628	1	0.01***
Months of lactation	-2.673	0.383	48.668	1	<0.001***
OCP	-2.873	0.625	21.12	1	<0.001***
Tubal ligation	-2.46	0.463	28.197	1	<0.001***
Early menarche	1.663	0.373	19.893	1	<0.001***
Talc use	2.271	0.701	10.486	1	0.001***
Constant	4.741	1.132	17.537	1	<0.001***

Table 12. Binary Logit Regression Estimates of the Determinants of Ovarian Cancer Risk

***Significant at 0.01.

DISCUSSION

The risk of developing ovarian cancer gets higher with age. Ovarian cancer is rare in women younger than 40. Most ovarian cancers develop after menopause. Women, those between the ages of 65-84 years have ovarian cancer incidence rates two to three times the rates of younger women. They also are more likely to be initially diagnosed with metastatic ovarian cancer to a greater extent than are younger ovarian cancer patients. Although, older women may lose their reproductive capacity in middle age and few oocytes are observed after menopause. They do not lose their potential to be at higher risk for ovarian cancer than younger women.[8] In the present study, age more than 45 years is a significant risk factor for carcinoma ovary. Lack of education is a significant risk factor for carcinoma ovary because patients may be ignorant of the signs and symptoms of this malignancy. A number of factors could influence the association between education level and cancer risks including access to medical care, the prevalence of exposure to important cancer risk factors, such as cigarette smoking and obesity and the likelihood of cancer screening utilisation.[9]

The reproductive experience of the study participants included in the study are age of first pregnancy, months of lactation, parity, age of menarche, duration of menstrual bleeding and age of menopause. Women who have been pregnant and carried it to term before age 26 have a lower risk of ovarian cancer than women who have not. The risk goes down with each full-term pregnancy. Women who have their first full-term pregnancy after age 35 or who never carried a pregnancy to term have a higher risk of ovarian cancer. Inverse associations between menarche age and ovarian cancer risk were observed in most subgroups; however, the significant association was restricted to invasive and borderline serous ovarian cancer. Menopause at an age more than 50 years also increases the risk of ovarian cancer. In our study, the length of menstrual cycle has no impact on the occurrence of ovarian cancer. In the present study, it was found that increased parity decreases the risk for carcinoma ovary; infertility predisposes to cancer ovary. A later age of first pregnancy (>30 years) is a

significant risk factor for carcinoma ovary. Breastfeeding may lower the risk even further. Breast feeding more than 2 years is protective against carcinoma ovary.

Tubal ligation may reduce the chance of developing ovarian cancer by up to two-thirds. Our study also showed that tubal ligation reduces ovarian cancer risk. Several mechanisms have been proposed to explain the protective effects of tubal ligation on ovarian cancer risk. Tubal ligation has been hypothesised to reduce blood flow to the ovary resulting in altered levels of hormones and growth factors, block the retrograde flow of carcinogenic or inflammatory agents from the vagina into the peritoneal cavity and induce immunity to mucins, which are over expressed in ovarian cancer.[10-11] In the study of Dubeau indicates that most ovarian cancers arise from tissues embryologically derived from the mullerian ducts.[12] Ovarian cancer cells are believed to originate from exfoliated endometrial cells and are associated with endometriosis[13] and mutations in the ARID1A gene.[14] In disparity, many serous high-grade cancers are anticipated to originate from the distal fimbrial end of the fallopian tube.[15] Tubal ligation is significantly more protective for endometrioid and clear cell cancers than for serous high-grade cancer because the location of the ligation near the uterotubal junction prevents the retrograde transport and ovarian seeding by cells originating from the endometrium, but not the distal tubes.

Women who used oral contraceptives had a lower risk of ovarian cancer. The mechanisms underlying this noticeable reduction have not been well-defined. However, many studies confirm that ovulation with its associated disruption and subsequent repair of the ovarian epithelium can lead to the acquisition of genetic damage in ovarian epithelial cells and in turn to ovarian cancer in susceptible individuals.[16] Our study found a similar result. This reduced risk continues for many years even after the pill is stopped. The study of Hankinson et al (1993) indicated that the talc use before pregnancy can be a risk factor for ovarian cancer than use after pregnancy.[17] The lifetime application of talc is also associated with increased risk of ovarian cancer.[18] The latency for development of ovarian cancer is more than 15 years. The potential effect of talc on the ovaries depends on migration of talc through a patent genital tract.

CONCLUSION

We studied the factors that are influencing the ovarian cancer risk. These factors include tubal ligation, age of women more than 45, early menarche, use of talc, durations of lactation and OCP. We did a binary logit regression analysis to find out the factors influencing the ovarian cancer risk. Our study also investigated the association between ovarian cancer and reproductive history including age of first pregnancy, months of lactation, parity, age of menarche, duration of menstrual bleeding and age of menopause. We used Chi-square test to estimate the association of ovarian cancer and reproductive history. The results of binary logistic regression analysis showed that months of lactation, tubal ligation and OCP had a negative impact on ovarian cancer risk. Our study proved that age of first pregnancy, age of menarche and age of menopause had a significant association with ovarian cancer risk.

Lack of education is a risk factor for cancer ovary. This finding signifies the importance of giving awareness to the public regarding the prevalence, symptomatology, screening/diagnostic techniques, treatment modalities and prognosis of ovarian cancer. The dual benefits of tubal ligation need to be made aware among the public and tubal sterilisation rates have to be enhanced. We recommend the promotion of tubal ligation as a permanent method of contraception in those who have completed their families. Oral contraceptive pill use has to be propagated as a temporary contraceptive method due to its added advantage. We recommended further studies involving large samples comparable to those done in Western countries.

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