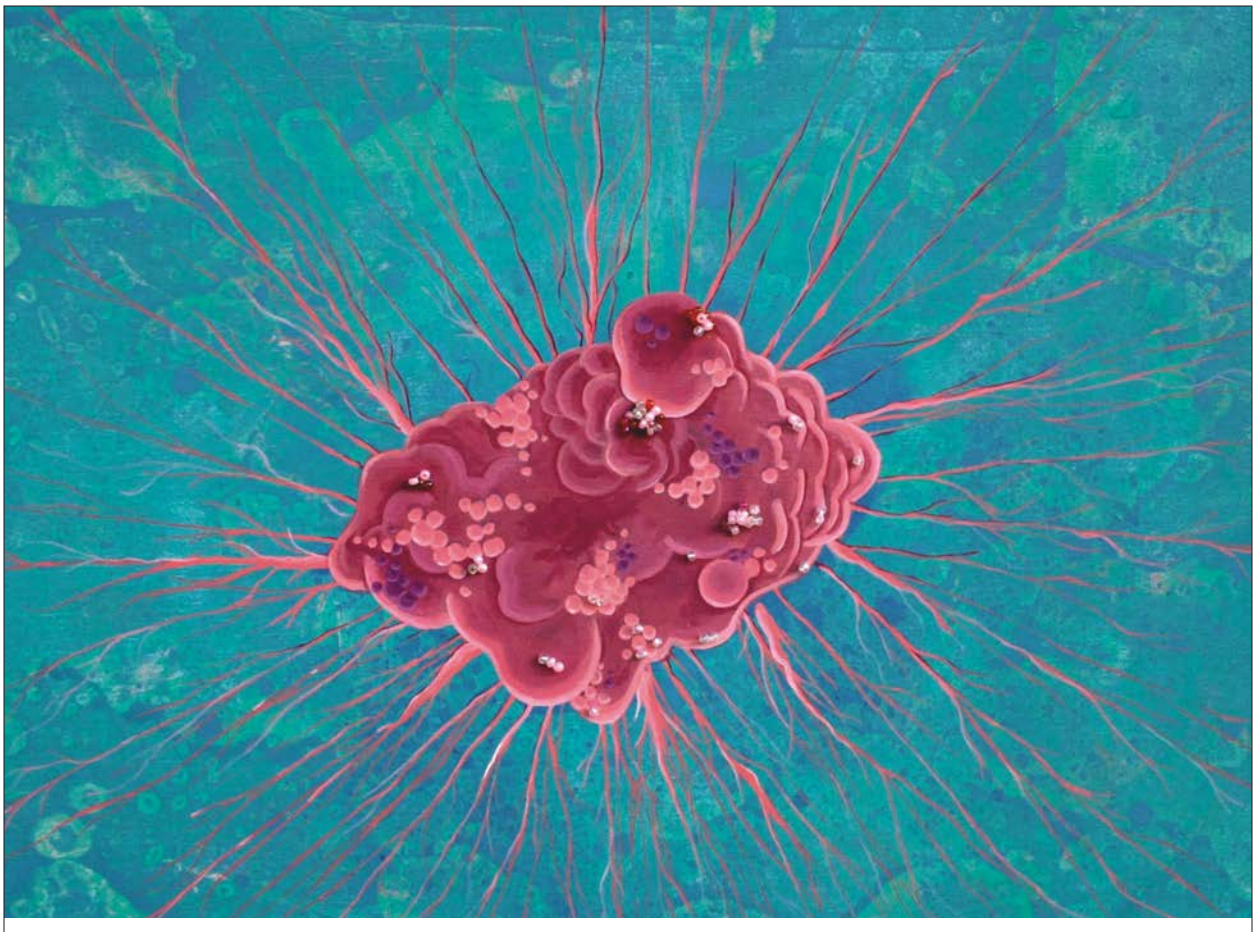

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# Risk Factors for Epithelial Ovarian Carcinoma in India: A Case Control Study in Low-Incidence Population

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## ABSTRACT

A case-control study to identify the risk factors for ovarian carcinoma in Tiruchirapalli district, Tamilnadu, India a low incidence population was conducted. The invasive epithelial ovarian cancer case patients were 37. The control group consisted of 74 healthy women, matched according to age categories. Subjects were interviewed in person regarding socio demographic and reproductive characteristics. The unconditional logistic regression was performed and tests of statistical significance were based on difference in the log likelihoods and all p values were 2-sided. In logistic regression analysis, the risk of ovarian cancer was strongly related to the increased physical activity (OR: 3.227, 95% CI: 1.143, 9.108), intake of high fat (OR: 6.286, 95% CI: 0.779, 50.701) early age at menarche (OR: 6.389, 95% CI: 2.143, 19.047), post menopausal status (OR: 3.22, 95% CI: 1.417, 7.316). The use of contraceptive methods, tubal ligation, one birth, late menarche was found to be inversely associated with ovarian cancer risk. The risk of ovarian cancer decreased 80% by one birth event, 40% by use of contraceptives and tubal ligation and six times reduced risk for menarche at later age. The present study thus clearly typified this neoplasm as hormone dependent and it is possible to establish that "ovulation" mechanism determine the level of risk for ovarian cancer in this study population. In addition, the difference in the distribution of histologic subtypes in this population compared with high-incidence populations may point to further differences in risk factors.

**Key words:** Ovarian cancer, risk factors, menarche, menopause

## INTRODUCTION

Ovarian cancer is the 6th most common cancer and the 7th cause of cancer deaths among women worldwide (Boyle and Levin, 2008). The lack of specific symptoms, effective screening and early diagnostic techniques makes ovarian cancer as a highly dreadful malignancy (Chornokur *et al*., 2013). Survival is directly related to stage with a 5 year survival of 93% for those diagnosed with localized disease and only 31% for those with distant disease. There are considerable variations in the incidence of ovarian cancer across countries (Greenlee *et al*., 2000;

Shanmughapriya *et al*., 2013a), with the highest rates in industrialized western nations and the lowest rate in developing countries (Shanmughapriya *et al*., 2013b). The incidence in Europe is 13.92 per 100,000 females, whereas India has a relatively low incidence only one half of the incidence as in Northern countries. However, the incidence rate of ovarian carcinoma among women in urban Chennai has increased during the period 1982-1984 to 2006-2008 from 4.9-6.1 per 100,000 females (NCRP., 2010). The incidence of ovarian cancer has been reported to be low but with a steady increase in the age standardized prevalence rate of ovarian cancer by 3% per year in different state registries over a period of time (Murthy *et al*., 2009).

Majority of ovarian cancers (80-90%) are epithelial ovarian tumours (EOCs). The etiology and precursor lesions of EOCs are poorly understood and predicted to be multifactorial and in part because EOCs tend to have a complex and heterogeneous histology that defies a simple biological explanation (Janardhan *et al*., 2015). Several genetic studies are beginning to unravel different pathogenic pathways to the different EOC subtypes. Several epidemiological and clinical risk factors are known to influence a women's life time risk for ovarian cancer. Reproductive behaviors and the use of hormonal therapies are the main clinical risk factors for ovarian cancer (Riman *et al*., 2004). In addition to these epidemiological factors a family history of ovarian cancer is another major risk that can contribute to the evaluation of a women's ovarian cancer life time risk. Population based case control studies have described a 2-3 fold increased risk in first degree relatives of ovarian cancer patients (Parazzini *et al*., 1991).

Many epidemiologic studies have been conducted on ovarian cancer but vast majority being on high incidence populations in Europe and North America. However, data on low incidence populations such as Asians is sparse, with few recent reports (Zhang *et al*., 2004). Unlike in high incidence populations where the ovarian cancer incidence is stable (Parazzini *et al*., 1991) or actually decreasing (Gnagy *et al*., 2000) the incidence of the disease in low incidence populations is on rise with no exception to India (Janardhan *et al*., 2015).

To the best of the knowledge this is the first epidemiological study analyzing the risk factor associated with the development of ovarian cancer among women from Tiruchirapalli district, Tamilnadu, India. Such emerging studies from low incidence countries such as India can provide useful etiological information on EOC. To address this issue detailed demographic, reproductive, family history and other risk factor information from 37 women with invasive ovarian carcinoma and 74 community based control subjects from Tiruchirapalli, Tamilnadu, India were obtained.

## MATERIALS AND METHODS

**Case patients:** After institutional review board approval (IEC No: DM/2010/101/21) was obtained, a total of 50 women with clinical diagnosis of ovary cancer were found through the oncology department of Dr G. Vishwanathan hospital between May, 2010 and June, 2011. Inclusion criteria for cases were defined to be women less than 75 years of age, who had been residents of Trichirapalli district for at least 10 years and histopathologically diagnosed with epithelial ovarian cancer. All cases were incident and had received no treatment for the condition prior to the study. Of these, 4 were excluded from the study because they refused to participate (1 case patient), or were unavailable for follow-up (2 case patients) or they could not be contacted (1 case patient). A total of 46 case patients were interviewed, representing a response rate of 92% of the eligible living patients. Later 9 case patients were excluded as their ovarian tumors were not invasive and epithelial origin, leading to a final total of 37 patients with invasive Epithelial Ovarian Carcinoma (EOC).

**Control subjects:** During the same period, 74 population based control subjects were recruited and interviewed. The community controls were recruited by curbside sampling from four different taluks one urban (Tiruchirapalli) and three rural areas (Lalgudi, Musiri, Thuraiyur) of Tiruchirapalli district with the assistance from local community councils. The criteria for controls were women not to have a neoplasm, bilateral oophorectomy nor have been on long term dietary modification. Women recruited for controls were matched with cases by age and geographical area. The controls were obtained according to age by frequency matching in 10 year categories in a ratio of 2 to each case.

**Histological classification:** Each study engaged a single pathologist to review the pathology reports, tumor blocks of ovarian cancer patients and to classify the invasiveness and histology of their cancers. Borderline tumors were excluded from the study. Pathology records were systematically reviewed and tumors were classified as serous, mucinous, endometeroid and clear cell or brenner tumor.

**Questionnaire and interview:** Questionnaires were administered in a standardized manner to all case patients and control subjects. The questions concerned primarily with the reproductive factors (age at marriage, parity, number of full term birth, induced and spontaneous abortions, use of contraceptives, age at menarche, menopause status, age of menopause) and medical histories (use of hormone replacement therapy and oral contraceptives, tubal ligation, hysterectomy, other surgery), screening histories and socio demographic information (smoking, alcohol, education). Data were collected by face to face interview using the structured questionnaire after obtaining the written consent of subjects. The interviews usually took 15 min and were conducted by the first author with the assistance of a female public health nurse.

**Statistical methods:** All data were reviewed for completeness by the corresponding author at the end of each interview. The data was coded and analyzed using the SPSS package (SPSS., 2000). Univariate analysis was first under taken to screen potentially significant variables. The case control analysis of the data, odds ratio and the corresponding 95% confidence intervals was calculated by unconditional logistic regression and maximum likelihood estimation. Tests of statistical significance were based on difference in the log likelihoods, and all p values are 2 sided.

## RESULTS

Study cases were predominantly from Tiruchirapalli city and Musiri the important urban and rural parts of Tiruchirapalli district. All the EOC cases recruited in the study were detected at an advanced stage (III-IV) with serous (78.4%) as the predominant histotype. The mean age of the case patients was 48.31 years ±2.28 (Mean±SE) compared with a mean age of control subjects of 48.03 years ±2.38. There was no age difference between the cases and the controls ($t = 0.84$, $p = 0.934$) reflecting a successful age frequency matching. The number of EOC cases generally rose reaching a peak at age 41-50 and declined there after.

Table 1 summarizes the distribution of demographic and socio-economic characteristics of the study groups. A significant association was observed between physical activity (in relation to occupation) and ovarian cancer risk. Women involved in highest physical activity experienced a 3 fold statistically significant increase in cancer risk compared with least active women (OR = 3.227; 95% CI = 1.143, 9.108). A positive association was observed between intake of non-vegetarian diet

Table 1: Demographic and socioeconomic characteristics of cases and controls

| Characteristics | Cases (n = 37) | Controls (n = 74) | OR (95% CI) | p-value |
|---|---|---|---|---|
| **Education** | | | | |
| 0 | 16 | 18 | 2.667 (0.61, 11.7) | 0.191 |
| 1-5 | 8 | 16 | 1.500 (0.32, 7.12) | 0.610 |
| 6-10 | 7 | 25 | 0.840 (0.18, 3.97) | 0.826 |
| 11-12 | 3 | 6 | 1.500 (0.22, 10.08) | 0.677 |
| College | 3 | 9 | 1.000 (Ref) | - |
| | | | | p-trend = 0.289 |
| **Employment** | | | | |
| Unemployed | 15 | 44 | 1.00 (Ref) | - |
| Part time | 11 | 20 | 1.613 (0.63, 4.13) | 0.319 |
| Full time | 11 | 10 | 3.327 (1.14, 9.11) | 0.027 |
| | | | | p-trend = 0.084 |
| **Food** | | | | |
| Vegetarians | 1 | 11 | 1.00 (Ref) | - |
| Non vegetarians | 36 | 63 | 6.286 (0.78, 50.7) | 0.084 |
| Narcotics | | | | |
| Yes | 9 | 10 | 2.057 (0.75, 5.61) | 0.159 |
| No | 28 | 64 | 1.00 (Ref) | - |
| **Frequency of narcotics** | | | | |
| 0 | 28 | 64 | 1.00 (Ref) | - |
| 0-15 years | 4 | 8 | 1.143 (0.32, 4.11) | 0.838 |
| 15-30 years | 3 | 2 | 3.429 (0.54, 21.66) | 0.190 |
| >30 years | 2 | - | - | - |
| | | | | p-trend = 0.631 |
| **Age at menarche** | | | | |
| ≤ 12 | 16 | 6 | 6.389 (2.14, 19.05) | 0.001 |
| 13-15 | 17 | 46 | 1.00 (Ref) | - |
| 15-17 | 4 | 22 | 0.391 (0.140, 1.537) | 0.001 |
| | | | | p-trend = 0.000 |
| **Menopause** | | | | |
| Post | 23 | 23 | 3.220 (1.42, 7.32) | 0.005 |
| Peri | 14 | 51 | 1.000 (Ref) | - |
| **Age at menopause**[a] | | | | |
| ≤40 | 2 | 6 | 0.182 (0.03, 1.2) | 0.076 |
| 41-45 | 5 | 10 | 0.227 (0.05, 0.09) | 0.044 |
| 45-50 | 5 | 1 | 1.000 (Ref) | - |
| >50 | 11 | 6 | 2.727 (0.26, 29.07) | 0.406 |
| | | | | p-trend = 0.046 |

[a]Only case patients and control subjects who attained menopause

and EOC. Women on non-vegetarian diet showed a 6 fold increase in cancer risk compared with women on vegetarian diet (6.286, 0.779 and 50.70). Risk of EOC was found to be positively associated with the use of narcotics (2.057, 0.754 and 5.615). Also there observed strong trend of increasing risk with increasing years of narcotics usage.

The grading distribution of cases and controls according to various reproductive factors are presented in Table 2. Compared to nulliparous women, parous women are at reduced risk of EOC. An 81% reduction of risk (0.190, 0.028 and 1.274) was found to be associated with one birth event. As generally reported an inverse relationship between the number of pregnancies and number of full term births was not observed among the population. Instead a linear increase of risk with the increase in number of full term births and number of pregnancies were noted.

Among gravid women, a history of spontaneous or induced abortions was found to be associated with 40% increased risk on comparison with never abortion. The observed increased cancer risk due to incomplete pregnancies than that of full term pregnancies further supports the hypothesis of incessant ovulation.

Table 2: Comparison of reproductive risk factors between cases and controls

| Characteristics[b] | Cases (n = 33) | Controls (n = 70) | OR (95% CI) | p-value |
|---|---|---|---|---|
| **No. of parity** | | | | |
| 0 | 3 | 2 | 1.000 (Ref) | - |
| 1,2 | 5 | 30 | 0.161 (0.02, 1.42) | 0.104 |
| >3 | 25 | 38 | 0.676 (0.09, 5.12) | 0.704 |
| | | | | p-trend = 0.062 |
| **Number of live births** | | | | |
| Nulliparous | 3 | 2 | 1.000 (Ref) | - |
| 1-2 | 12 | 42 | 0.190 (0.03, 1.27) | 0.087 |
| 3-4 | 11 | 22 | 0.333 (0.05, 2.29) | 0.265 |
| 5-6 | 7 | 4 | 1.556 (0.17, 14.65) | 0.699 |
| | | | | p- trend = 0.05 |
| **Induced abortion** | | | | |
| Yes | 17 | 30 | 1.454 (0.63, 3.37) | 0.382 |
| No | 16 | 40 | 1.000 (Ref) | - |
| **Spontaneous abortion** | | | | |
| Yes | 4 | 3 | 1.601 (0.25, 10.29) | 0.620 |
| No | 29 | 67 | 1.000 (Ref) | - |
| **Contraceptive use** | | | | |
| Yes | 4 | 12 | 0.667 (0.20, 2.25) | 0.513 |
| No | 29 | 58 | 1.000 (Ref) | - |
| **Tubal ligation** | | | | |
| Yes | 12 | 36 | 0.540 (0.23, 1.26) | 0.155 |
| No | 21 | 34 | 1.00 (Ref) | - |

[b]Data based on married women only

The contraception methods generally adopted in the study population were IUDs and tubal ligation. We found a reduction in the risk of ovarian cancer forever and never use of each of these methods for contraception. Thus use of IUDs and tubal ligation was associated with lower risk (0.667, 0.198, 2.250 and 0.540, 0.231, 1.263, respectively) of EOC.

The menstrual factors in relation to EOC were evaluated. Menarcheal age was inversely associated with risk. Menarche at age 15 or more, relative to ≤12 appeared to be associated with a statistically decreased risk (0.391, 0.140 and 1.537). A linear trend of increasing age at menarche was significantly associated with a decreased risk ($p<0.001$). Menopausal status was associated with three fold increased risk of EOC (3.22, 1.417 and 7.316). Age at natural menopause was found to be related to ovarian cancer risk. A direct trend of increasing age at menopause was associated with increased but not a significant risk of EOC.

## DISCUSSION

The results of the present study showed a statistically significant positive association between physical activity and ovarian cancer. Similar results were observed in the Iowa women's health study with highest category of physical activity had a two-fold increase in risk (Bain *et al*., 1996). Recent studies conducted to understand the moderate to vigorous physical activity and leisure time sitting in relation to ovarian cancer risk, revealed no association between physical activity and ovarian cancer, whereas prolonged sitting was associated with higher risk (Hildebrand *et al*., 2015; Huang *et al*., 2015a). Given the heterogeneity of ovarian cancer and changes in hormone levels, it could be possible that physical activity may only be relevant to certain cancer subtypes or during specific life periods.

Increased consumption of fat has been cited as a possible cause of increased incidence of ovarian cancer in Asia (Herrinton *et al*., 1994) with significant dose response relationship

(Huncharek and Kupelnick, 2001) which was found to be similar in the present study. Animal meat is a high source of fat and influence the development of ovarian cancer by altering serum hormone concentrations (Dorgan *et al*., 2003).

Compared to nulliparous women parous women are at reduced risk of ovarian cancer with a significant risk reduction by one birth event. Studies have shown that reproductive factors such as parity and oral contraceptive use are associated with lower ovarian cancer risk. The finding of the present study that the parity is protective is consistent with the literature (Bodelon *et al*., 2013; Gay *et al*., 2015). A full or near term pregnancy may induce permanent change in the pituitary mediated hormonal production or cause a decidual reaction that decreases the susceptibility of the ovarian and pelvic surface epithelium to malignant transformation (Cramer, 1999). But interesting and controversial to all other previous studies (Pasalich *et al*., 2013; Yavuzcan *et al*., 2014; Gay *et al*., 2015), it has been observed in the present study that the risk of ovarian carcinoma increased with increasing number of parity and live births with a reduced risk with one birth event. A number of reasons can be explained for this unusual trend. Firstly several studies have reported late age at last child birth, long interval between first and last live birth were more important than the total number of pregnancies (Godard *et al*., 1998). But the general customs in the study population is women getting married at very early age and hence early first and last child birth with no long intervals between the births. The results of the present study are consistent with incessant ovulation, gonadotrophin by Harlow and Ehross hypothesis. According to Harlow and Ephross (1995), menstrual cycles occurring between ages 25 and 39 are most likely to be ovulatory and pregnancies occurring between these ages have a greater potential to interrupt ovulatory cycles. Moreover gonadotrophin levels increases with increasing age and are particularly high during menopause. Due to the prevailing customs women from the study population end up their full term pregnancies or live childbirth before they reach their ovulatory age and excessive gonadotrophin exposure during ovulatory age without parity increases oestrogenic stimulation of the ovarian surface epithelium leading to malignant transformation (Cramer and Welch, 1983).

Further the present study has also reported tubal ligation or use of contraceptives to be protective against EOC. The tubal ligation could possibly have an effect via reduction in utero-ovarian blood flow resulting in altered local hormonal and growth factor levels, or via its protection against the ascension of inflammants. Studies have shown that the use of oral contraceptives and other contraceptive methods including intrauterine devices and tubal ligation to reduce ovarian cancer risk (Permuth-Wey and Sellers, 2009; La Vecchia, 2006; Huang *et al*., 2015b).

## CONCLUSION

The present study found that one birth event, use of contraceptives, tubal ligation, consumption of food items low in fat would be protective against EOC. The present study focused on socioeconomic, demographic and reproductive variables appropriately and has thus increased the knowledge about risk factors for this disease from such an unnoticeable population. The limitation of the study is that the number of women recruited is small and mostly dravidians. The risk factors analyzed clearly showed the EOC of the study population to be hormone dependent with consistent association between ovulatory events or ovulation associated with ovarian inflammation. Future investigations should focus on other details of hormonal alterations in order to clarify processes involved in ovarian carcinogenesis.

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