Original Research Article

A retrospective analysis on the association between aetiology and symptomatology of ovarian carcinoma at a tertiary care centre

Kumari Ankita*, Tushar Tatyaba Palve, Rajashree Thatikonda, Dishant Upadhyay

Department of Obstetrics and Gynecology, Grant Medical College and Sir JJ Group of Hospitals, Mumbai, Maharashtra, India

*Correspondence:
Dr. Kumari Ankita,
E-mail: ankitamegha21@gmail.com

ABSTRACT

Background: Ovarian cancer is a leading cause of cancer related mortality in women, but is often diagnosed during late stages since the symptomatology at onset of illness is often vague and inconsistent. Mortality and morbidity in carcinoma ovary patients are found to reduce dramatically when definitive diagnosis is arrived upon at early stages. Thus, the aim of our study was to analyse the symptomatology of diagnosed cases of carcinoma ovary with its known aetiology to elicit significant associations that may aid in diagnostic cues for this elusive disease. This study aimed to analyse the symptomatology of diagnosed cases of carcinoma ovary with its etiological factors.
Methods: In a retrospective design, data was collected from hospital records and interviewing known cases of ovarian cancer, age at presentation, age at first child birth, parity, BMI, family history, chief complaint at presentation was analysed.
Results: Abdominal pain was the chief complaint in majority of patients. Majority of the patients were having parity less than 2. Over one-third of patients had obesity. Age at presentation, age at first child birth, and parity were not associated or correlated with each other. Age at first child birth was significantly higher (27 years vs 22 years) in those having positive family history for ovarian cancer.
Conclusions: Later age of first child birth, obesity and parity less than 2 were found to have positive association with carcinoma ovary.

Keywords: Age at first child birth, Ovarian cancer, Parity

INTRODUCTION

Among various gynaecological cancers, ovarian cancer emerges as one of the most enigmatic, standing as the second leading cause of mortality in females globally. It claims more lives than any other disease affecting the female reproductive system.[1] According to the National Cancer Institute, an estimated 19,170 new cases of ovarian cancer were reported in 2023, with an estimated 13,270 deaths. Furthermore, the incidence rate of new cases of ovarian cancer was 10.3 per 100,000 women per year, and the mortality rate was 6.3 per 100,000 women per year.

The 5-year relative survival rate for ovarian cancers was 50.8%.[2]

The non-specific nature of its symptomatology increases the likelihood of overlooking the diagnosis in the early treatable stages. Recognition of these symptoms frequently occurs in the advanced stages, typically at stage III or stage IV. Manifesting as a blend of abdominal fullness, bloating, nausea, abdominal distention, early satiety, fatigue, altered bowel movements, urinary symptoms, back pain, dyspareunia, and weight loss, these symptoms often present in a vague manner several months before the formal diagnosis of ovarian cancer.

Ovarian cancer is linked to several risk factors, predominantly affecting postmenopausal women. The incidence of the disease rises with age, leading to advanced stages and reduced survival rates. Parity, as suggested by some case-control studies, plays a protective role, with a higher age at childbirth associated with a lower risk of ovarian cancer. A significant risk factor is a positive family history of breast or ovarian cancer, with a personal history of breast cancer further elevating the risk.[3]

The identification of high-risk individuals is traditionally based on established risk factors closely tied to the incidence rate of the disease. Ovarian cancer, being a complex condition, relies on medical background, with family history standing out as the most critical risk factor. Recognized risk factors encompass older age, genetic predisposition, family history, previous cancer occurrences, nulliparity, late menopause, early menarche, hormone replacement therapy (HRT), tobacco smoking, and dietary fat intake, obesity, lack of physical activity

Objective of this study was to investigate clinical symptoms, parity, age at first child birth, lifestyle factors like obesity and establish relation between various risk factors and etiologies.

METHODS

A retrospective observational study was carried out at Cama and Albless Hospital in Mumbai from January 2023 to January 2024, after getting clearance from Institutional Review Board.

Target population included all indoor cases of histopathologically confirmed cases of ovarian cancer admitted for debulking surgery.

Inclusion criteria

The inclusion criteria were all cases of histopathologically confirmed carcinoma ovary, post debulking surgery with or without chemoradiation, willing to give informed consent for participation.

Exclusion criteria

The cases those were not selected for debulking surgeries, cases of suspicious ovarian mass under evaluation, ovarian mass not confirmed for carcinoma by histopathology were excluded.

Data collection

The medical records of ovarian cancer patients admitted during this period were thoroughly examined. Patients and their primary care givers were then interviewed to gather information on history, chief complaints at the time of diagnosis, patient's age at diagnosis, obstetric history providing records of the parity and age at first child birth, Family history, Obesity etc.

Sample size calculation

Using the prevalence of ovarian carcinoma at 3.5% (p=0.035), margin of error at 6% (d=0.06), sample size of 36 was arrived upon.[4]

Statistical analysis

Collected data was tabulated using Microsoft Excel 2007 and analysed using Statistical Package for Social Sciences version 23. Quantitative data points were found to be normally distributed (Shapiro-Wilk Test p>0.05) and hence parametric tests were used for data analysis. Unpaired t test was used to assess difference in distribution of numerical data across categories, while Pearson's correlation coefficient was used to assess the correlation amongst quantitative data. Qualitative analysis was done using Fischer's Exact test.

RESULTS

Study included of total n=36 patients, of these n=5 was discharged patients lost to follow up and we were unable to conduct interview, hence data was collected for n=31 subjects. Chief complaints of the patients at the time of presentation are tabulated in Table 1.

Table 1: Percentage of combinations of chief complaints.

Chief complaints	Number of patients	%
Abdominal pain	6	19.35
Abdominal pain, abdominal distension by mass	5	16.13
Abdominal distension by mass	5	16.13
Abdominal pain, fatigue, bloating, weight loss	3	9.68
Abdominal pain, P/V bleeding	2	6.45
P/V bleeding	2	6 .45
Abdominal distension by fluid	2	6.45
Abdominal pain, abdominal distension by fluid	2	6.45
Abdominal distension by fluid, other	1	3.23
Abdominal pain, abdominal distension by fluid, fatigue, bloating, weight loss	1	3.23
Abdominal distension by fluid fatigue, bloating, weight loss	1	3.23
Abdominal pain, other	1	3.23
Grand total	31	100

Majority of the patients had chief complaint of abdominal pain (n=20) while n=5 (16.13%) had abdominal distension by mass as the solitary chief complaint whereas abdominal pain along with abdominal distension accounts for (n=5, 16.13%). Fatigue, bloating and weight loss present with

abdominal pain was seen in (n=3, 9.68%) as well as with abdominal distension in (n=3 3.23%) of cases. Bleeding per vaginum was the chief complaint in 6.45% cases (n=2) while abdominal pain was the chief complaint in 6.45% cases (n=2).

Individually, frequency abdominal pain accounts for majority of the cases as one of the chief complaints followed by abdominal distension. Fatigue, bloating and weight loss was seen in 31% cases (n=5). P/V bleeding was major presenting complain in 12% of cases (n=4). Only one of the patients (3.2%) had presented with the complaint of urinary retention (Figure 1).
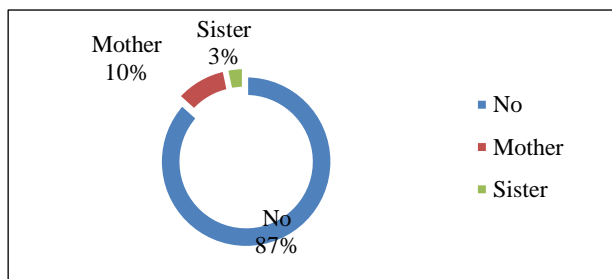
Figure 1: Distribution of positive family history across subjects.

Patients with parity 2 and 3 constituted majority of the cases (32.3% each) whereas 12.9% (n=4) cases had 4 living issues and 9.7% (n=3) cases had 5 living issues.

In the study, 13% ovarian cancer cases had family history of ovarian or breast cancer. Age at first child birth was found to be significantly higher (27.25 years vs 22 years) in those having a positive family history of ovarian carcinoma (Unpaired t test, p=0.037). 32.14% ovarian cancer cases (n=10) in our study had age of first child birth beyond 25 years and those with first age at pregnancy 20 years and less contributed to just 25% of the cases.

It was observed that that 29.032% (n=9) of the ovarian cancer patients were obese women (pre-debulking BMI >25.0 kg/m^2).

Table 2: Distribution of frequency of obesity in the subjects.

Obesity (BMI>25.0 Kg/m^2)	Number of patients
No	22
Yes	9
Grand total	31

Complaints at presentation do not appear to vary across those having family history vs history of poor lifestyle/obesity (p>0.05, Fischer exact test). Age at presentation of illness, age of first child birth, parity was neither associated nor correlated with each other (Pearson's correlation coefficient p>0.05).

Chief complaints at presentation did not vary by age of presentation to hospital, age of first child birth or parity. (Unpaired t test- p>0.05).

Age at presentation to hospital, age at first child birth and parity were not different across groups those having vs not having obesity (Unpaired t test, p>0.05).

Those having lower age of first child birth (mean-20years vs 23 years) were more likely to have complaints of fatigue at presentation (Unpaired t test- p=0.009). Those having lower age of first child birth (19.67 yrs vs 23.47 yrs) were more likely to have complaints of weight loss at presentation (unpaired t test, <0.001).

Age at first child birth was found to be significantly higher (27.25 yrs vs 22 yrs) in those having family history (Unpaired t test, p=0.037).

DISCUSSION

Ovarian cancer stands as a prominent contributor to cancer incidence and mortality globally. The elevated mortality rate associated with ovarian cancer stems from the asymptomatic and discreet growth of tumors, delayed manifestation of symptoms, and the absence of effective screening methods, leading to diagnoses occurring in advanced stages. Consequently, the term "silent killer" has been coined to describe the insidious nature of this cancer.[5,6]

The study pinpoints genetic, environmental, and lifestyle factors influencing the heightened or diminished risk associated with this lethal disease. The interplay of these factors has undoubtedly influenced the varied patterns and trends observed in ovarian cancer incidence and mortality worldwide.

In the current study, the most prevalent symptom was abdominal pain, observed in 17 patients (54%) and the second most common symptom following abdominal pain was abdominal distension by mass, noted by 10 patients (32.2%). Fatigue, bloating and weight loss was seen in 31% cases (n=5). Only one of the patient (3.2%) had presented with the complaint of urinary retention. This aligns with findings from a study by Friedman et al, where 55.1% of patients reported abdominal pain, while 30.4% exhibited distension.[7] Results from a subsequent case-control study conducted at the Memorial Sloan-Kettering Cancer Center validated these findings. The researchers noted notable distinctions in symptoms between ovarian cancer patients and the control group, highlighting that abdominal pain, bloating, reduced appetite, fatigue, urinary frequency, and constipation were significantly more prevalent among cases, and the most common symptom was found to be abdominal pain.[8,9]

Anovulation is induced by pregnancy, leading to the inhibition of pituitary gonadotropin secretion, aligning with both the 'incessant ovulation' and 'gonadotropin'

hypotheses. The 'incessant ovulation' hypothesis suggests that an elevated frequency of ovulatory cycles contributes to an increased rate of cellular division involved in repairing the surface epithelium following each ovulation. This, in turn, is thought to heighten the likelihood of spontaneous mutations. The 'gonadotropin hypothesis' ascribes the observed impact to gonadotropins, including luteinizing hormone and follicle-stimulating hormone. According to this hypothesis, these hormones play a key role in influencing the cellular processes that contribute to the documented effects.[10] Notably, women with a history of childbirth exhibit a 30-60% reduced risk compared to those without children, and each additional full-term pregnancy further diminishes the risk by around 15%.[11,12] In our study, majority of the patients were having parity less than 2 (66%), this is consistent with previous findings that document a decreased risk of ovarian cancer with increased parity.

We found 13% of our cases to have a family history of ovarian carcinoma. While the majority of ovarian cancer cases are sporadic, approximately upto 10% can be attributed to the inheritance of an ovarian cancer susceptibility gene as seen in a study conducted in Department of Clinical Genetics, North Trent Regional Genetics Service, Sheffield Children's Hospital to review the different types of ovarian cancer family history and the genes that give rise to them.[13]

In postmenopausal women, the primary origin of circulating estrogens is the aromatization of androgens occurring in adipose tissue.[10] In our study, it is seen that 29.032% (n = 9) cases were obese or overweight with sedentary lifestyle. In a 2007 meta-analysis encompassing 28 population studies, it was observed that overweight and obese women exhibited an elevated risk of ovarian cancer in comparison to those with normal weight.[14]

It was found that complaints at presentation do not appear to vary across those having family history vs history of poor lifestyle/obesity (p>0.05, Fischer exact test).

The age at presentation of illness, age of first child birth and parity are neither associated nor correlated with each other (pearson's correlation coefficient p>0.05).

Age at first child birth was found to be significantly higher (27.25 yrs vs 22 yrs) in those having family history of ovarian carcinoma. (Unpaired t test, p=0.037). A family history of ovarian cancer is acknowledged as a potent risk factor for the development of ovarian cancer, indicating an inherent genetic predisposition to the disease. This is supported by a two-sample Mendelian randomization study showing a causal association between female infertility and increased risk of epithelial ovarian cancers.[15] Rodriguez et al investigated the association between self-reported infertility and mortality from ovarian cancer in 676,526 female participants in the Cancer Prevention Study II (CPS-II). Their findings suggested that infertility, even without concurrent exposure to fertility drugs, could potentially elevate the risk of fatal ovarian cancer.[16]

Patients with a younger age at first childbirth were more prone to reporting fatigue and weight loss at presentation as a presenting complaint (Unpaired t test- p<0.05). While none of the epidemiological studies reviewed by us demonstrated a significant effect of age at first birth on prognosis of ovarian carcinoma, the link between difference in presenting symptoms across those having lower age of first child birth warrants further investigation.[17]

The study revealed that delayed age at first childbirth was associated with an increased risk, in contrast to women who initiated motherhood before the age of 23 years. 32.14% ovarian cancer cases in our study had age of first child birth beyond 25 years and those with first age at pregnancy 20 years and less contributed to just 25% of the cases. There's a decreased risk by about 10% for each 5-year increment in age at first childbirth as supported by a case control study conducted by Adami et al in 1994.[18,19]

Positive family history of ovarian carcinoma is associated with a significantly higher age at time of first child birth while the patients having a lower age of first child birth were more likely to have complaints of weight loss/fatigue at time of presentation. However, symptomatology of ovarian cancer was not found to be affected by family history, obesity, age at presentation or parity.

High mortality rate associated with ovarian cancer is consequent to a delay in definitive diagnosis progression to an advanced stage, characterized by the spread of the disease beyond the pelvic region. Notably, when the diagnosis is reached upon at an early stage (stage I) of ovarian cancer, the survival rate reaches close to 90%, highlighting the potential for positive outcomes without the need for modifications to current therapeutic approaches.[20]

Our study was not without limitations, having an observational retrospective design based on hospital record and interview of patients, our study was subject to recall bias, and many known risk factors such as age of menarche, use of contraceptive methods, use of talc powder, duration of breast feeding etc. could not be uniformly analysed.

CONCLUSION

Despite efforts to implement screening measures, multiple screening trials did not demonstrate a reduction in mortality rates for ovarian cancer. Aim of this study was a close analysis of the symptomatology of presenting chief complaints vis-à-vis the risk factors, emphasising the significance in raising the index of clinical suspicion of carcinoma ovary, thereby aiding in early diagnosis. Our study suggests at the possibility of a positive family history of ovarian carcinoma marking the patient prone to later

child birth, or even infertility. Based on our findings and the studies documenting this association, we recommend that those females in reproductive age having infertility, or later age of first child birth to be periodically screened for carcinoma ovary by transabdominal ultrasonography and assay of blood tumor markers. While many risk factors are non-modifiable, directing attention towards addressable risk factors as well as health education holds the potential to mitigate the overall risk of ovarian cancer.

REFERENCES

1. Board PA. Ovarian Epithelial, Fallopian Tube, and Primary Peritoneal Cancer Treatment (PDQ®): Patient Version. PDQ Cancer Information Summaries [Internet]. 2002.
2. National Cancer Institute. Cancer stat facts: ovarian cancer, 2023. Available at: https://seer.cancer.gov/statfacts/html/ovary.html. Accessed on 17th March 2023.
3. Momenimovahed Z, Tiznobaik A, Taheri S, Salehiniya H. Ovarian cancer in the world: epidemiology and risk factors. Int J Womens Health. 2019;11:287-99.
4. Torre LA, Trabert B, DeSantis CE, Miller KD, Samimi G, Runowicz CD, et al. Ovarian cancer statistics, 2018. CA: Canc J Clini. 2018;68(4):284-96.
5. Badgwell D, Bast JRC. Early detection of ovarian cancer. Dis Markers. 2007;23(5-6):397-410.
6. Vergote I, Amant F, Ameye L, Timmerman D. Screening for ovarian carcinoma: not quite there yet. Lancet Oncol. 2009;10(4):308-9.
7. Friedman GD, Skilling JS, Udaltsova NV, Smith LH. Early symptoms of ovarian cancer: a case–control study without recall bias. Fam Pract. 2005;22(5):548-53.
8. Olson SH, Mignone L, Nakraseive C, Caputo TA, Barakat RR, Harlap S. Symptoms of ovarian cancer. Obstet Gynecol. 2001;98(2):212-7.
9. Risch HA. Hormonal etiology of epithelial ovarian cancer, with a hypothesis concerning the role of androgens and progesterone. J Natl Cancer Inst. 1998;90(23):1774-86.
10. Cramer DW, Welch WR. Determinants of ovarian cancer risk. II. Inferences regarding pathogenesis. J Natl Cancer Inst. 1983;71(4):717-21.
11. Reid BM, Permuth JB, Sellers TA. Epidemiology of ovarian cancer: a review. Can Biol Med. 2017;14(1):9.
12. Adami HO, Lambe M, Persson I, Ekbom A, Adami HO, Hsieh CC, et al. Parity, age at first childbirth, and risk of ovarian cancer. Lancet. 1994;344(8932):1250-4.
13. Cook J. Family history of ovarian cancer. Curr Obstet Gynaecol. 2002;12(1):47-51.
14. Casagrande JT, Louie EW, Pike MC, Roy S, Ross RK, Henderson BE. "Incessant ovulation" and ovarian cancer. Lancet. 1979;314(8135):170-3.
15. Fan Z, Song H, Yuan R, Peng Y, Jiang Y. Genetic predisposition to female infertility in relation to epithelial ovarian and endometrial cancers. Postgrad Medi J. 2023;99(1168):63-8.
16. Rodriguez C, Tatham LM, Calle EE, Thun MJ, Jacobs EJ, Heath CW. Infertility and risk of fatal ovarian cancer in a prospective cohort of US women. Canc Cau Control. 1998;9:645-51.
17. Cramer DW, Hutchison GB, Welch WR, Scully RE, Ryan KJ. Determinants of ovarian cancer risk. I. Reproductive experiences and family History. JNCI. 1983;71:711.
18. Toufakis V, Katuwal S, Pukkala E, Tapanainen JS. Impact of parity on the incidence of ovarian cancer subtypes: a population-based case-control study. Acta Oncolog. 2021;60(7):850-5.
19. Adami HO, Lambe M, Persson I, Ekbom A, Hsieh CC, Trichopoulos D, et al. Parity, age at first childbirth, and risk of ovarian cancer. Lancet. 1994;344(8932):1250-4.
20. Wong AS, Auersperg N. Ovarian surface epithelium: family history and early events in ovarian cancer. Reproduct Biol Endocrinol. 2003;1:1-8.