

## A Focused Review on the Risk Factors Associated With the Ovarian Cancer

Dr. Manasa R<sup>1</sup>, Dr. Rachana M S<sup>1</sup>, Dr. Rashmitha R<sup>1</sup>

<sup>1</sup>Pharm D, Department of Pharmacy Practice, Rajiv Gandhi University of Health Sciences, Bengaluru, Karnataka, India.

Corresponding author: Dr. Manasa R, Pharm D, Department of Pharmacy Practice, Rajiv Gandhi University of Health Sciences, Bengaluru, Karnataka, India.

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### ABSTRACT

Ovarian cancer (OC) remains one of the most challenging gynecological malignancies due to its heterogeneous biological behavior, lack of effective early screening methods, and poor survival outcomes when diagnosed at advanced stages. Hormonal, lifestyle, and environmental factors suggestively show impact on the disease susceptibility and advancement. This review focuses on the advances and knowledge of the risk factors, protective effects and evolving strategies for the early detection and cure of OC. Genetic predisposition, mainly Lynch syndrome and mutations in Breast Cancer Gene 1 and Breast Cancer Gene 2, signifies a large contributor to disease risk. Protecting interferences such as tubal ligation, oral contraceptive use, and lactation have been allied with a reduced risk of OC, however factors like optimal timing, duration, and long-term effects remained uncertain. The complex and multifactorial nature of ovarian carcinogenesis is highlighted by several factors like obesity, endometriosis, chronic inflammation, and environmental exposures. These factors highlight the necessity of personalized strategies for risk assessment and prevention of ovarian cancer. This review also emphasizes the limitations of current screening methods, especially among the high-risk populations, such as the need for better and early detection methods. Novel approaches such as biomarker discovery, automated analytical techniques, and longitudinal research appear to be promising strategies for enhancing screening accuracy and clinical outcomes. Additionally, disparities exist in genetic testing availability, awareness, and preventive care which needs to be addressed. A multidisciplinary approach for integration of genetic counselling, lifestyle modification, and advanced diagnostic technologies is critical for reduction of disease burden and improving survival in ovarian cancer.

**KEYWORDS:**Ovarian Cancer, Epithelial Ovarian Cancer, Malignant neoplasms, Lynch Syndrome, BRCA1/2 Mutations, Endometriosis, Tumors.

### I. INTRODUCTION

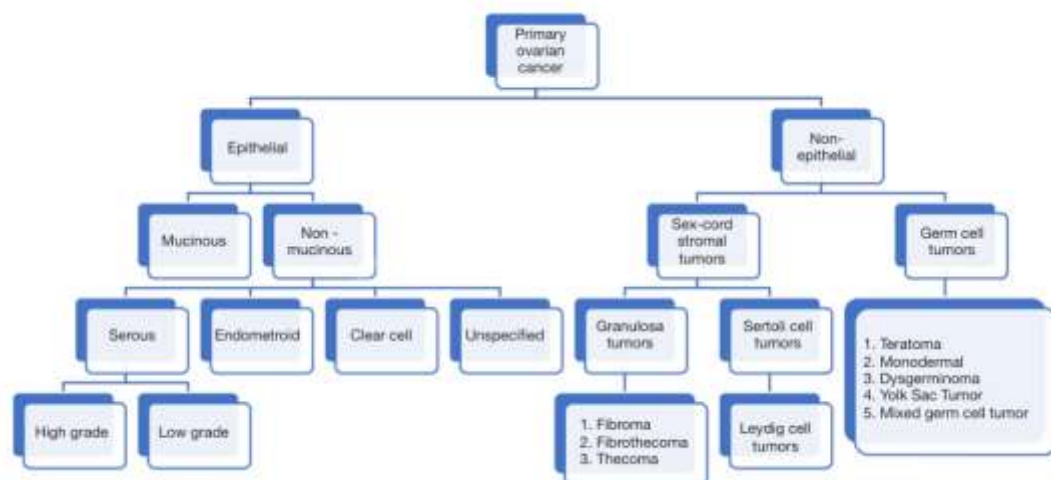
OC is a heterogeneous disease(1).It is among the most prevalent cancers of the gynecology. After uterine and cervical cancer, it ranks third. It also has the highest risk of death and the worst prognosis. It also has the maximum death proportion and the nastiest prognosis(2). Although OC is three times more dangerous than breast cancer, it is less frequent. By 2040, experts predict a sharp increase in the cancer's fatality rate. Early detection of the illness is challenging because the symptoms are frequently not very distinct. For this reason, most patients present with advanced disease(3).It ranks as the seventh most frequent cause of death for women worldwide. Due to the difficulty of diagnosing this cancer in its early stages, it is usually found in its advanced stages, leading to inappropriate treatment(4). Most OCs appear after menopause, when aberrant ovarian activity causes no symptoms and the ovaries no longer perform a physiological role. Ovarian cancers typically do not manifest symptoms until they are large or have spread because of this and the ovaries' deep location within the pelvis.(5)Type I OC is characterized by well-known ovarian precursor lesions, while Type II OC is characterized by poorly documented tumors that may originate from the tubal and/or ovarian surface epithelium. To reduce the fatality rate from ovarian cancer, it is essential to understand these characteristics(3). Sporadic mutations cause most ovarian malignancies.(6) OC can spread outside of the ovary in three different ways. First, after the tumor has penetrated the ovarian capsule, it may immediately infiltrate nearby organs. Second, the tumor cells may be able to travel through the lymphatics that connect the lymph nodes such as

pelvic and para-aortic. Metastases of lymph node occur in up to 20% of early-stage malignancies as well as most progressive phase tumors. OC cells may move into the peritoneal cavity from areas where the tumor has penetrated the ovarian capsule. Because it causes tumor cells to expand throughout the peritoneal cavity, this type of spread is especially harmful. Tumors in stage I are limited to the ovaries. One or both ovaries with pelvic extension are affected by stage II malignancies. One or both ovaries with verified peritoneal metastases outside the pelvis and/or regional lymph node metastases are considered stage III malignancies. Distant metastasis is a characteristic of stage IV cancers. A woman has a 1 in 75 lifetime risk of acquiring ovarian cancer and a 1 in 100 chance of dying from the illness. The disease typically appears late, with a 5-year relative survival rate of only 29% (4). OC is not a singular illness. The term has expanded to encompass primary peritoneal and fallopian tube malignancies, as well as a variety of morphomolecular kinds for which more targeted therapies may be possible (7). Every stage of OC can have symptoms (6). They only have small positive predictive effects for the condition, though, because they are typically generic and common in women without OC (8). The methods by which cancer grows and the cell of genesis of OC have long been disputed. Conventional theory of ovarian

carcinogenesis proves, Mesothelium (ovarian surface epithelium) is which all the tumors are originated from, and the following metaplastic changes in the development of various cell types like serous, endometrioid, clear cell, mucinous, and transitional cell. These cell types share similarities in appearance with the endocervix, bladder, gastrointestinal system, fallopian tube, and endometrial, respectively (9). With an emphasis on both well-established and recently discovered determinants based on accessible scientific data, this study aims to give a thorough overview of the numerous risk factors that contribute to the development of ovarian cancer.

**TYPES OF OVARIAN CANCER**

Nine research examined various subtypes of OC. Research indicates that up to 90% of OC are epithelial, with the remaining 90% being non-epithelial. The majority of epithelial OC are not mucinous; about 3% are. Serous (70%), endometrioid (10%), clear cell (10%), and unknown subtypes (5%) are also seen in non-mucinous. Recent studies have distinguished between two forms of serous carcinomas: high-grade and low-grade. Non-epithelial malignancies are less invasive than epithelial cancers (10). One of three cell types—epithelial cells, stromal cells, or germ cells—is the source of almost all benign and malignant tumors (11).



**CLASSIFICATION OF OVARIAN CANCER**

**RISK FACTORS**

**NON-MODIFIABLE RISK FACTORS**

**AGE**

Age has been proven to be one risk factor for an onset of OC. OC has been observed to be

more common among patients with more ovulatory cycles, such as those who have late menopause and are younger at menarche. Malignant neoplasms are more likely to form when there are more ovulatory cycles since this results in more cellular divisions.

Most people consider OC to be a postmenopausal condition. The median age for a diagnosis is between 50 and 79 years old, though these vary by region as previously mentioned. Several studies have also demonstrated that growing older increases the likelihood of acquiring a more aggressive tumor(12).

### **FAMILY HISTORY**

A family history of either breast or ovarian cancer is the most significant risk factor for ovarian cancer. An inherited genetic problem accounts for about 25% of all instances of ovarian cancer(13). The risk of ovarian cancer is roughly exponentially higher for women with a family history of breast or ovarian cancer. According to reports, 4% and 12% of patients with ovarian cancer, respectively, have a family history of breast or ovarian cancer. It is yet unclear whether women with a family history will be similarly affected by prevalent risk factors for ovarian cancer, particularly those that are modifiable. The type of family history affects the risk of ovarian cancer(14). According to a case-control research, women are more likely to acquire ovarian cancer if their mother or sister had a family history of breast, uterine, or ovarian cancer ( $P < 0.001$ )(10).

### **BRCA1/BRCA2 MUTATIONS**

Genetic factors account for about 10% of ovarian cancer cases. Germline mutations in the BRCA1 or BRCA2 genes are the most prevalent of these risks(15). Germline BRCA mutations are thought to affect 3.5% of individuals with ovarian cancer, and they may be linked to 10–20% of cases of ovarian cancer. In this patient population, the risk of ovarian cancer ranges from 27% to 44% for those with BRCA2 and BRCA1 mutations, respectively. In contrast, non-mutated populations had a lifetime risk of ovarian cancer of less than 1.5%. In addition to high-penetrance (high-risk) BRCA alleles, a number of low-penetrance (low-risk) alleles, including mutations in the BRCA1-interacting helicase 1 (BRIP1), RAD51 Paralog C (RAD51C), RAD51D, and partner and localizer of BRCA2 (PALB2) genes, may account for the increased risk of ovarian cancer. The odds ratio of 14.1 for BRIP1, 5.2 for RAD1D, and a relative risk of 2.9 for PALB2(16). With percentages of at least 50% for BRCA1 and 20% for BRCA2, women with these mutations have a markedly increased risk of ovarian cancer. When women with BRCA1 or BRCA2 gene mutations undergo a salpingo-oophorectomy as a prophylactic intervention, the incidence of ovarian cancer is greatly reduced, and

overall mortality is also significantly reduced(13). An excellent model for the carcinogenesis of HGSOc is the germinal BRCA mutation(16). The discovery of dysplastic epithelium in the fallopian tube in women with hereditary mutations in BRCA1 and BRCA2 led to a new paradigm for the genesis of ovarian cancer(17).

### **LYNCH SYNDROME**

The autosomal dominant cancer predisposition syndrome known as Lynch syndrome, causes about 3% of cases of colorectal cancer(18). Ten to fifteen percent of the cases of hereditary OC are caused by Lynch syndrome;(19) those with a family history of Lynch syndrome have a 6–8% lifetime chance of developing this cancer(20). Eighty-two to eighty-four percent of ovarian tumors linked to Lynch syndrome occur in stage I or II and are non-mucinous(21). A genetic mutation in one of the four mismatch repair genes (MHL1, MSH2, MSH6, and PMS2) causes Lynch; the most prevalent mutations in these people are MSH2 and MLH1(22). Endometrioid and clear cell ovarian tumors are the most prevalent forms of OC in these people(23).

### **MODIFIABLE RISK FACTORS**

#### **HORMONE REPLACEMENT THERAPY**

After menopause, combination estrogen-progesterone therapy did not raise the risk of ovarian cancer, according to the findings of a case-control study(24). According to Hempling et al.'s analysis of the effects of postmenopausal hormone therapy exposure, even long-term usage of HRT is not linked to ovarian cancer(2). However, in those who have never had a hysterectomy, oral hormone therapy is associated with an increased risk of ovarian cancer(25). Researchers think that using estrogenic techniques is associated with an increased risk of ovarian cancer, especially for ten years or longer(26). A case control study's findings demonstrated that while hormone therapy using estrogen alone raises the risk of ovarian cancer, it has no appreciable impact on the patient's chance of survival. The progesterone component of a combination hormone therapy lowers the incidence of ovarian cancer, according to a case-control study. According to Morch et al., hormone therapy is linked to an elevated risk of ovarian cancer regardless of the length of usage, formulation, estrogen dose, type of regimen, type of progesterone, and mode of administration(10).

### INFERTILITY DRUGS

Ovarian cancer is an uncommon but fatal illness. It is challenging to look at the connection between infertility treatments and ovarian cancer because both nulliparity(25)and infertility are risk factors for the disease. According to the incessant ovulation idea, continuous ovulation can cause damage to the ovary epithelium, which can lead to the development of ovarian cancer. Consequently, any factor that reduces ovulation can prevent ovarian cancer(27). The use of gonadotropin(28)and clomiphene citratehas been linked in several studies to an increased risk of ovarian cancer. The results of a cohort study indicated that nulliparous women's risk of ovarian cancer increases with increasing dosage of clomiphene citrate and showed an increase in ovarian cancer after clomiphene citrate exposure(29).

### ENDOMETRIOSIS

Numerous studies have shown that endometriosis and ovarian cancer are related in a number of ways. A cohort study found that age, living in an urban area, having a high or low income, depression, pelvic infection, and not having children all increased the risk of ovarian cancer in people with endometrium(20). Inflammation and the genes PTEN, CTNNB1 ( $\beta$ -catenin), KRAS, microsatellite instability, and ARID1A are associated with endometriosis-related ovarian cancer. Compared to other types of the disease, endometriosis-associated ovarian cancer is discovered at a lower stage and at a younger age(30). Endometriosis raises the risk of ovarian cancer (SIR=1.43 [1.19–1.71]), and a hysterectomy may prevent ovarian cancer before or at the time of endometriosis diagnosis(31).

### OBESITY

One study looked at the association between obesity and ovarian cancer survival, stage at diagnosis, histotype, and reproductive, anthropometric, and lifestyle factors in a cohort of over one million UK women who completed a health questionnaire between 1996 and 2001, with an average follow-up of 17.7 years. The results showed that 8697 (66%) of the 13,222 women (1.1%) who were diagnosed with ovarian cancer died from the disease. The stage upon diagnosis had a substantial impact on survival (stage IV versus I, RR = 10.54, 95% CI: 9.16–12.13).By histotype, the survival rate of high-grade tumors is lower than that of low-grade ones. Survival appeared to decline with increasing age at

diagnosis (per five years, RR = 1.19, 95% CI: 1.15–1.22) and high pre-diagnosis BMI (an overall 6% higher risk for each five-unit increase in BMI). It was only statistically significant for serous carcinomas (per five-unit increase in BMI, RR = 1.06, 95% CI: 1.02–1.11). Furthermore, a lower survival rate (current versus never: RR=1.17, 95% CI: 1.07–1.27) was linked to smoking(32).Other risk factors for OC include smoking, obesity, being overweight, and using perineal talc. The molecular processes that underlie the association between obesity and overweight and OC are unclear and inconsistent(33).Low levels of physical activity, obesity, malnutrition, breastfeeding duration, and socioeconomic position have all been associated with an increased risk of ovarian cancer. A lower risk of ovarian cancer has been linked to leading a healthy lifestyle that includes health-promoting habits like exercise, a balanced diet, and effective stress management. A retrospective design study involving 112 cancer patients in Argentina from 2012 to 2019 that assessed characteristics such being overweight or obese and having metabolic cancer.The most common neoplasms linked to being overweight were breast cancer, digestive system cancer, ovarian cancer, prostate cancer, and thyroid cancer, according to a retrospective design study that included 112 cancer patients in Argentina between 2012 and 2019 and evaluated factors like being overweight and obese and presenting metabolic syndrome(13).

### SMOKING

Even though many researchers think smoking cigarettes has no effect on a woman's chance of developing ovarian cancer before or after menopause(34). According to a study, smoking a pack of cigarettes every day for 20 years doubles the risk of developing benign mucinous tumors, borderline tumors, and malignant tumors(35). The duration and intensity of smoking raise the incidence of borderline cancers, according to cohort research(5).It was thought that smoking could raise an individual's risk of dying from ovarian cancer by as much as 25%(36). According to a study, smoking is not linked to other histological forms of ovarian cancer, although raising the incidence of epithelial mucinous tumors. Another research has also verified this outcome. The risk of ovarian cancer is unrelated to the age at which smoking began(2).

### PCOS

Women with polycystic ovarian syndrome (PCOS) have a 60% higher risk of OC. Obesity,

diabetes, inflammation, metabolic syndrome, and aging are some of the risk factors for PCOS. It is unclear, though, if PCOS itself or other risk factors like diabetes and obesity are to blame for the increased risk of endometrial cancer. Hyperinsulinism, hyperglycemia, insulin resistance, and hyperandrogenism are among the metabolic traits unique to PCOS that increase the risk of cancer. Furthermore, common inherited genetic variations may be the cause of this association between PCOS and endometrial cancer(33).

### **PROTECTIVE FACTORS ORAL CONTRACEPTIVES**

Most research findings show that using oral contraceptives is linked to a lower risk of ovarian cancer of all histological types(37). The use of hormonal contraceptive tablets is linked to a considerable decrease in all histological categories of epithelial ovarian cancer, except for mucinous tumors, according to the findings of case-control research conducted in Canada. The study's results showed that the OR for each year of usage of these medications was 0.98 (0.93-1.04) for mucinous tumors and 0.89 (0.85-0.93) for non-mucinous tumors(38). An oral contraceptive pill lowers the incidence of fatal and advanced ovarian cancer compared to less advanced instances, according to the findings of case-control research(39). According to a study, using combination oral contraceptive pills annually lowers the risk of ovarian cancer by 7% (OR=0.93 [0.90-0.96]), and this reduction is particularly noticeable when using them for the first time before the age of 25(40). The duration of usage is more significant, even if there is an inverse link between the age at which a hormonal contraceptive pill is used and the risk of ovarian cancer(41). Although several studies have not demonstrated the preventive benefit of oral contraceptive, the risk decrease can last for up to 10–15 years after stopping tablets(42). A case control analysis revealed no connection between the incidence of ovarian cancer and the usage of contraceptive techniques (except from tube ligation)(43).

### **BREASTFEEDING**

The number of breastfed children, the length of nursing, and the risk of OC have all been found to be inversely correlated by researchers(44). A case control study's findings demonstrated that nursing lowers the risk of ovarian cancer by 22%, and that this risk falls with a longer lactation period—an average of 18 months of breastfeeding.

The study found that endometrioid and clear cell ovarian tumors had the greatest risk reduction(45). They also agreed with other researchers' findings that the length of lactation lowers the risk of non-mucinous malignancies(40).

### **PREGNANCY CHARACTERISTICS**

The risk of ovarian cancer is increased by preterm labor, according to a case control study(46). The investigation by Skold et al. has verified this finding(47). A study's findings indicated that having a male baby increases the incidence of mucinous ovarian cancer by two times(46). While Skold et al. found no connection between newborn weight and ovarian cancer, a study found that low birth weight among term infants has a protective effect on the mother's ovarian cancer(48). Additionally, pre-eclampsia and numerous pregnancies were not found to be associated with the mother's cancer incidence(47).

### **TUBAL LIGATION**

Tubal ligation decreased the incidence of ovarian cancer in women(49). Tubal ligation was linked to a 20% lower risk of high-grade severe cancer in a cohort analysis. (53) Inverse serous cancer (19%), invasive mucinous cancer (32%), clear cell cancer (42%), and endometrioid cancer (52%) are all less common in women who have had tubal ligation(37). Lower grade serous cancers and tubal ligation did not appear to be related. Increased protective benefit of tubal ligation were not linked to younger age at the procedure. Following tubal ligation, a mechanical barrier for carcinogenic substances can lower the risk of ovarian cancer(2).

### **RECENT RESEARCH HIGHLIGHTS**

BMC Public Health evaluated overall learning worldwide from 1990 to 2001 and anticipated risks to 2050 in a 2025 cross-sectional study. It established that environmental and occupational disclosures like air pollution, industrial chemicals, and endocrine-disrupting combinations are progressively renowned as substantial contributors to OC, predominantly in women aged 20-49. Occupational hazards in segments like agriculture, manufacturing, and healthcare were associated with advanced occurrence ratios, feasible due to sustained exposure to carcinogens and hormone-disrupting vehicles. This study also emphasized regional discrepancies, with low- and middle-income countries undergoing a growing concern of OC due to a restricted approach to early discovery

and added exposure to environmental threats. Urbanization and industrial trends are allied with higher risk, mainly in rapidly developing regions. Whereas BRCA1/2 mutations persist as the most compelling genetic risk factors, newer research is discovering the role of polygenic risk scores and epigenetic variations in foreseeing susceptibility. Hormonal impacts such as early menarche, late menopause, and nulliparity continue to be confirmed as risk accompaniments, while oral contraceptive use and tubal ligation are confirmed as protective. Obesity, endometriosis, and chronic inflammation are gradually implicated in the pathogenesis of definite subtypes like clear cell and endometrioid OCs. Developing indications suggest that dietary patterns, physical inoperativeness, and talc-based product use may also play contributory roles, though findings remain mixed.

## II. DISCUSSION

### GAPS IN KNOWLEDGE

Despite the fact that we are aware of several contributors to the development of OC such as hormonal, genetic, and lifestyle factors, there still exist several crucial knowledge gaps. Reports of association of risk factors like air pollution, industrial chemicals, and endocrine-disrupting compounds are well known, whereas the systematic pathways of association with OC are inadequately understood. Occupational risks in agriculture, healthcare, and manufacturing are noted, yet dose response relationships are not well defined. Lynch syndrome and BRCA1/2 remain as a well-known risk factor, while interventions among environmental, lifestyle exposures and genetic predisposition is not explained in detail. Novel tools like polygenic risk scores and epigenetic profiling demonstrate potential. But the predictive accuracy of these tools remains uncertain for diverse populations. Certain factors are known to be associated with increased risk such as early menarche, delayed menopause, and nulliparity, but the biological pathways responsible for these associations are yet to be understood. The positive effects of oral contraceptives, breastfeeding, and tubal ligation are well known, though the optimal timing and duration required for maximum benefit remains unclear. OC is also related with obesity, endometriosis, and chronic inflammation, but further investigations on subtype analysis with specific risk factors (e.g., clear cell vs. serous carcinoma) is essential. Evidence on several other agents such as dietary factors, talc use, and physical activity lacks consistency, with contradictory

outcomes across geographic regions. Currently, validated biomarkers for population-wide screening does not exist. Approaches such as liquid biopsies (ctDNA, exosomal miRNAs) are promising, but are still under experimentation and lack clinical normalization. This gap may contribute to diagnosis at later stages, which persists to be a major driver for suboptimal survival results. Many women are still unaware of the symptoms and risk factors of OC, which contributes to persistence of health literacy gaps. Disparities in the healthcare infrastructure and resource constrained environments has restricted the access to genetic testing, preventive surgery, and specialized care. Incidence trends show that regional differences like unexplored cultural, dietary, and environmental influences justifies further research. The most pressing gaps include the systematic knowledge of environmental exposures, integration of genetic and lifestyle risks, development of effective screening tools, and addressing worldwide discrepancies in awareness and access to care. Future research should focus on wide-range longitudinal assessments, routine molecular investigations, and international collaboration to improve prevention strategies and lower the worldwide burden of OC, but disputes exist regarding the most accurate testing strategy for OC. Very limited existing studies evaluate the tests for early examination of symptoms in the primary healthcare settings, where most women with OC first present. Before diagnosis of OC there is no proof found about the association between reproductive, anthropometric, and other lifestyle factors such as alcohol, physical activity, and education level. However, it limits the approach that defends a recommendation of general screening for OC. Determination of protein patterns in blood serum or gene expression profiling for early detection is still under consideration.

### NEED FOR EARLY SCREENING IN HIGH-RISK WOMEN

Due to lack of applicable population wide screening tools and elusive symptoms OC is often diagnosed at advanced stages. When compared to the overall population, women with carriers such as BRCA1/2 mutations, with Lynch syndrome, or a strong family history have a comparatively increased lifetime risk. Survival outcomes can be improved in these groups by early detection as progression is more likely linked to stage at diagnosis. BRCA1 mutation carriers confront up to a 40-60% lifetime risk, while BRCA2 carriers confront 10-20%. Risk of endometrioid and clear cell subtypes is elevated due to Lynch syndrome.

Oral contraceptive usage and tubal ligation act as protective factors, while nulliparity, early menarche and late menopause increase the risk of OC. The mechanisms of several risk factors that contribute to development of OC are incompletely understood such as, obesity, endometriosis, and possible exposure to talc or endocrine-disrupting chemicals. Screening tools for general population like Transvaginal Ultrasound (TVUS) and CA-125 serum testing are the most reviewed approaches, but lack specificity and sensitivity. In women with higher risk to the development of OC, these tools can be used in combination with risk-reducing strategies (e.g., prophylactic salpingo-oophorectomy). Liquid biopsies (ctDNA, exosomal miRNAs) and AI-driven imaging analysis are emerging and promising methods but are yet to be validated for use in clinical practice and universally accepted screening protocol does not exist for high-risk women. Test results that are false positives may lead to redundant therapeutic interventions, whereas false negative results may lead to delay in diagnosis. It is imperative for biomarker discovery and further longitudinal studies to enhance risk stratification and screening intervals. In high-risk women, since the disease may progress silently and has the stake of poor prognosis at advanced stages it is crucial to implement early screening to improve OC outcomes. Novel methods such as risk factor-based stratification, genetic testing, and emerging biomarker technologies represent as the most assuring in effective early detection.

### III. CONCLUSION

Because of its unstable evolution, improper screening methods, and poor survival rates at advanced stages, OC stays as substantial health suffering in women. Lynch syndrome and BCRA1/2 mutations remain the chief risk factors, whereas lifestyle, hormonal, and environmental factors have principal effect on disease susceptibility and progress. Factors such as oral contraceptives, tubal ligation and breastfeeding which act as protective interventions need more evidence about the time and duration. The data obtained from environmental exposures, obesity, endometriosis, and chronic inflammation highlight the interventions regarding complexity of ovarian carcinogenesis. More importance should be provided for future research, automatic studies, biomarker discoveries, and longitudinal research analysis to improve the screening procedure, especially for high-risk women. More concentration must be provided towards local

differences in genetic testing, knowledge, and anticipatory management and a multidisciplinary methodology which incorporates genetic counselling, lifestyle changes, and the state-of-the-art diagnostic tools is the most prominent plan to decrease the rate and improve survival in OC.

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