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EPIDEMIOLOGY OF OVARIAN CANCER: AN UPDATED SYSTEMATIC REVIEW (2019-2021)

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Abstract:

Background: *Ovarian cancer (OC) is expected to cause 239,000 new cases and 152,000 deaths globally each year. Almost all benign and malignant ovarian tumors are caused by one of three types of cells: epithelial cells, stromal cells, or germ cells. The prevalence of OC varies significantly across the countries. Several risk factors have been associated with OC incidence. Among these risk factors are Family history, menarche and menopause age, pregnancy, lactation, obesity, and contraceptives use.*

Aim: *To assess the epidemiology of ovarian cancer in females, including risk factors, diagnosis, survival, racial differences and other characteristics.*

Methods: *Studies related to our subject were explored using PubMed and Google scholar databases during 2019 to 2021. The included searching keywords were "Ovarian cancer (OC), Epidemiology, Risk factors, OC diagnosis, OC survival, OC racial and ethnic characteristics" and were used in various combinations. The inclusion criteria were original studies reported ovarian cancer epidemiology conducted on females and full text- articles.*

Results: *A total of 125 articles were obtained, only eleven articles were eligible for the inclusion criteria. The involved studies were conducted on a total number of 62459 participants. Out of 11 studies included, 3 studies were published in 2019, 7 studies in 2020 and 1 study in 2021. Four studies were cross-sectional, six cohort studies and one study based on data from SEER program.*

Conclusion: *The average age of the OC patients in our sample was 52.5 years. Granulosa tumours and high-grade serous carcinoma were the most common histological characteristics of ovarian cancer. Non-Hispanic black women were shown to have a greater overall mortality risk than non-Hispanic white women. More research is needed to investigate the involvement of unknown risk factors in the development of ovarian cancer.*

Keywords: Ovarian cancer (OC), Epidemiology, Risk factors, OC diagnosis, OC survival and OC racial and ethnic characteristics.

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INTRODUCTION:

Ovarian cancer (OC) is expected to cause 239,000 new cases and 152,000 deaths globally each year. Eastern and Central Europe had the highest rates. A woman's lifetime risk of acquiring OC is one in 75, and her likelihood of dying from the condition is one in ten thousand. The illness usually manifests itself late in life. **[1]** The total 5-year relative survival rate globally fluctuates between 30% and 40%, with minor improvements (2–4%) since 1995. **[2]**

Almost all benign and malignant ovarian tumors are caused by one of three types of cells: epithelial cells, stromal cells, or germ cells. In affluent nations, more than 90% of malignant ovarian tumors are epithelial in origin, 5%–6% are sex cord-stromal cancers (e.g., granulosa cell tumors, thecomas, and so on), and 2%–3% are germ cell tumors (e.g., teratomas, dysgerminomas, etc.). **[3]**

Epithelial OC is a diverse disorder with different histologic subtypes in cellular origin, etiology, molecular abnormalities, gene expression, and prognosis. Malignant OC, also known as carcinomas, are classified into five histotypes: high-grade serous (HGSOC), endometrioid (ENOC), clear cell (CCOC), mucinous (MOC), and low-grade serous (LGSOC). The types account for 70, 10, 10, 3, and 5% of malignant ovarian cancer incidences. **[4]**

The prevalence of OC varies significantly across the countries. The greatest age-adjusted incidence rates are found in industrialized countries, such as North America and Central and Eastern Europe, where rates often surpass 8 per 100,000 people. South America (5.8 per 100,000) has the highest rates, whereas Asia and Africa have the lowest (3 per 100,000). **[5]** Within the United States, racial variations in incidence and mortality mirror worldwide variation, with rates most significant among Whites, intermediate for Hispanics, and lowest among Blacks and Asians. **[6]**

Several risk factors have been associated with OC incidence. Among these risk factors are Family history, menarche and menopause age, pregnancy, lactation, obesity, and contraceptives use. A family history of the disease is one of OC's most critical risk factors. First-degree relatives of probands have a 3- to 7-fold greater risk, especially if numerous relatives are afflicted, and the disease manifests itself at a young age. **[7]** Early menarche and late menopause, according to the ongoing ovulation theory, enhance risk by increasing the number of ovulatory cycles. According to the gonadotropin theory, late age at menopause slows the surge of postmenopausal gonadotropin hormones, thereby lowering risk. **[8]**

The relationship between pregnancy and OC risk has been thoroughly researched. Pregnancy produces anovulation and decreases pituitary gonadotropin production, supporting both the 'incessant ovulation' and the 'gonadotropin' ideas. Indeed, parous women have a 30-60% lower risk than nulliparous women, and each additional full-term pregnancy reduces risk by around 15%. **[9]**

AIM OF WORK

The current systematic review was performed to identify the prevalence and epidemiology of ovarian cancer in females, including risk factors, diagnosis, survival and racial characteristics.

METHOD AND SEARCH STRATEGY:

This systematic analysis follows the PRISMA checklist guidance for systematic review and meta-analysis **[10]**. Two databases were used for searching purpose; PubMed and Google scholar databases during 2019-2021. The two databases were used to search for studies conducted on our main subject "epidemiology of ovarian cancer in females. The studies were published in 2019 and 2021.

The searching process involved using of various keywords, including “Ovarian cancer (OC), Epidemiology, Risk factors, OC diagnosis, OC survival and OC racial and ethnic characteristics". The involved keywords were used in several combinations in order to obtain all possible articles. All the titles produced from this primary exploration were revised.

ELIGIBILITY CRITERIA:

After reviewing the titles of the obtained articles, only articles focused on epidemiology of ovarian cancer were included, whereas articles conducted on OC before 2019 were excluded. Also, articles conducted on endometriosis associated ovarian cancer were excluded. The second step included reviewing the abstract of the remaining articles conducted on epidemiology of ovarian cancer to select only articles written in English language and original articles; whereas articles such as review articles, letters to editors, case series and cases reports were excluded. The final stage included original articles written in English language and reported epidemiology of ovarian cancer; these articles were further explored to exclude non-available full-text articles, duplicate articles and articles with unsatisfying content such as articles with overlapped or incomplete data. The full description of the search strategy is shown in figure 1.

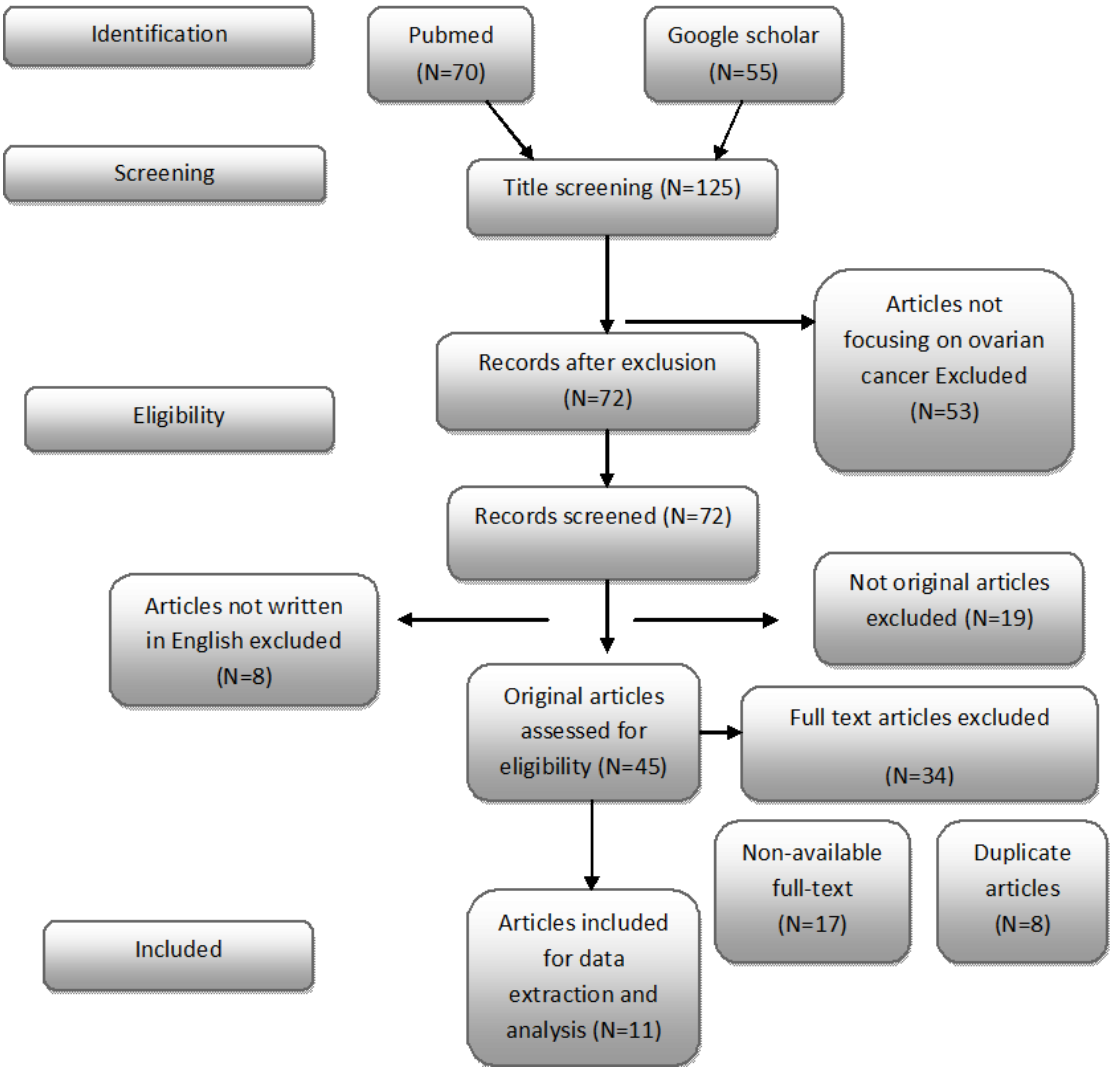

Fig 1: Planning of Eligible criteria

DATA REVIEWING AND ANALYSIS:

Articles were reviewed for abstracts and the full-text to extract the data of interest and transfer data into a pre-designed an excel sheet. The selected data were then revised through the excel sheet and then the data was transferred to one stable to summarize the chosen data to facilitate the analysis of data.

RESULTS:

This systematic review included eleven articles that met the eligible criteria **[11-21] (Table 1).** The included studies were either published in 2019 **[11, 16, 20],** 2020 **[12, 13, 14, 15, 17, 18, 21]** or 2021 **[19].** Four studies were cross-sectional **[12, 16, 18, 19],** six cohort studies **[11, 13, 14, 15, 17, 21]** and one study based on data from SEER program between 1995-2015 **[20].**

The included studies involved a total of 62459 ovarian cancer patients**.** In study was conducted on 50,780 women who underwent CA125 testing; 456 were diagnosed with ovarian cancer and 1,321with non-ovarian cancer **[14].** One study included 53 formalin-fixed, paraffin-embedded ovaries of epithelial ovarian cancer patients **[12].** Another study included 4905 consecutive adult patients presenting with an adnexal mass **[13].** A study was conducted on 720 non-epithelial ovarian cancers cases among all ovarian malignancies in the Danish Cancer Registry **[15].** A study included 23 diagnosed ovarian cancer cases registered during 2015–2017 **[16],** and one study

included 6111 women treated for ovarian cancer in Sao Paulo from January 2000 to December 2018 **[17].** Another study was conducted on fifty-nine patients with primary epithelial ovarian cancer **[18].** One study was performed on advanced ovarian cancer receiving or not active treatment **[19].** Another study included women with epithelial ovarian cancer from the SEER Program between 1995–2015 **[20].** The last study included Women with FIGO stage III and IV epithelial ovarian and Fallopian tube cancers **[21].**

The age of women included in the studies of our results was categorized: less than 50 and more than 50 in one study **[14].** The average age of the OC patients was 54.5 years in one study **[18]** and 52.66 in another study **[19].**

Two studies performed genetic testing among ovarian and non-ovarian cancer patients **[11, 14].** One study included 30.9% of patients with ovarian cancer, whereas 24.1 % had breast cancer **[11].** Another study detected the presence of ovarian cancer in 0.9% and non-ovarian cancer in 2.6% **[14].** In ovarian cancer patients, the most prevalent pathogenic variants were BRCA1 (8.7%), BRCA2 (5.8%), CHEK2 (1.4%), BRIP1 (0.9%), MSH2 (0.8%), and ATM (0.6%) **[11].**

One study **[12]** discovered variations in the expression levels of nerve growth factor, tyrosine kinase receptor A, and vascular endothelial growth factor in various stages of epithelial ovarian cancer.

One study investigated the most prevalent ovarian cancer symptoms and risk factors **[16, 18**]. In one study **[16],** the most prevalent symptoms were irregular menstruation and abdominal pain in premenstrual women, as well as abdominal distention in postmenopausal women, and lower abdominal discomfort followed by abdominal distension in another study **[18].** In addition, past pregnancies, previous surgeries, and menstrual cycle disturbances were identified as risk factors **[16].**

Two studies **[16, 18]** looked at the histopathological features of ovarian cancer. In one study **[16],** granulosa tumors were the most prevalent histological subtype and high-grade serous carcinoma in another **[18].**

One research examined the diagnostic prediction for ovarian cancer malignancy **[13].** In 3441 patients (70 %), the outcome was benign, and in 978 cases, the prognosis was malignant (20%).

One study investigated the occurrence and prognosis of non-epithelial ovarian cancer **[15].** Germ cell tumors and sex cord-stromal tumors accounted for 49.9 % of ovarian malignancies (38.6 %).

One study evaluated how hospital features affected the overall survival of patients with epithelial ovarian cancer **[17].** In ten years, high-volume hospitals and teaching hospitals were related to low-death risk.

One study **[19]** examined the performance of ovarian cancer patients in terms of function and cancer-related fatigue (CRF). Patients with ovarian cancer have a high degree of function, as indicated by handgrip strength. They also reported moderate CRF and impaired upper and lower limb function.

Two studies evaluated the racial differences in ovarian cancer survival and genetic testing **[11, 20].** One study stated that testing was lower in blacks than whites **[11].** Another study **[20]** discovered that non-Hispanic black women were at a higher risk of overall mortality than non-Hispanic white women. Hispanic women fared no better than non-Hispanic white women in terms of survival. Non-Hispanic Asian/PI women had a relatively lower risk than non-Hispanic white women. Compared to non-Hispanic white women, the risk of not having surgical intervention remained high among non-Hispanic black women and Hispanic women. Compared to non-Hispanic white women, non-Hispanic black women, non-Hispanic Asian/PI women, and Hispanic women all had a considerably higher chance of dying within the first 12 months following a cancer diagnosis.

One study compared the 5-year disease-free survival (DFS) and relative survival (RS) of patients with advanced ovarian cancer before and after the adoption of centralized primary treatment **[21].** Regardless of the main treatment, there was an increase in 5-year RS from 24% to 37% and an increase in median RS from 27 months to 44 months. The 5-year DFS was much longer after centralization, and centralization was revealed to be a significant independent predictor for both survival and DFS. [21]

DISCUSSION:

Ovarian cancer is the third most frequent gynecologic malignancy, following cervical and uterine cancer. It also has the most fatalities and the poorest outcome. Even though ovarian cancer is less prevalent than breast cancer, it is three times fatal**.[22]** Ovarian cancer has a high death rate due to silent and hidden tumor development, delayed onset of symptoms, and a lack of effective screening, which results in detection in the advanced stages. As a result, this malignancy has been dubbed the "silent killer." **[7]**

The current study aimed to assess the epidemiology of ovarian cancer in females, including risk factors, diagnosis, survival, racial differences, and other characteristics .

This systematic review included eleven articles that met the eligible criteria **[11-21].** The average age of the OC patients was 54.5 years in one study **[18]** and 52.66 in another study **[19].** According to National Cancer Institute **[23],** ovarian cancer incidence rises with age, especially after 45, with an average age of diagnosis of 63 years.

However, a study from Japan **[24]** stated that clear cell carcinoma (an ovarian cancer subtype) was more prevalent in women under 50 in the Japan cohort (30.2 %). Still, serous carcinoma was more common in the US cohort (50.8 %). According to another study based on data from the Surveillance, Epidemiology, and End Results (SEER) cancer registry **[25],** 26% of mucinous ovarian malignancies were detected in women under 44.

Our study results indicated that in ovarian cancer patients, the most prevalent pathogenic variants were BRCA1 (8.7%), BRCA2 (5.8%), CHEK2 (1.4%), BRIP1 (0.9%), MSH2 (0.8%), and ATM (0.6%) **[11].** A study by Morgan et al. (2019) supports our current results. It found that pathogenic BRCA1/2 mutations were found in more than 10% of women diagnosed with ovarian cancer before 60. **[26].**

Our results indicated that the most prevalent symptoms associated with ovarian cancer were irregular menstruation and abdominal pain in premenstrual women, as well as abdominal distention in postmenopausal women, and lower abdominal discomfort followed by abdominal distension in one study **[16]** and past pregnancies, previous surgeries, and menstrual cycle disturbances were the most reported risk factors in another study **[18].** In a study from Palestine, extreme generalized fatigue, unexplained weight loss, and 'increased abdominal size on most days were the most commonly reported symptoms **[27].** In a study carried out by Roberts et al. (2019) has found that severe PTSD symptoms had a twofold increased risk of ovarian cancer compared to women who had no trauma experience **[28].**

In our study, variations in nerve growth factor (NGF) expression levels, tyrosine kinase receptor A, and vascular endothelial growth factor in various stages of epithelial ovarian cancer were associated with OC **[12].** A study by Garrido et al. (2020) has found that Metformin showed an ability to inhibit NGF-induced proliferation and angiogenic potential in epithelial ovarian cancer. **[29, 30]**

In our study, the histopathological features of ovarian cancer reported were granulosa tumors **[16]** and high-grade serous carcinoma **[18].** The findings of study by Abreu et al. (2020) are coherent with these results. It stated that the most common histopathological type of OC was high-grade serous carcinoma that accounted for 48% **[31].**

In our study, the occurrence and prognosis of non-epithelial ovarian cancer were Germ cell tumors (49.9 %) and sex cord-stromal tumors of ovarian malignancies (38.6 %) **[15].** Non-epithelial ovarian tumors are rare cancers that develop from the ovary's germ cells, sex cord cells, and stromal cells. Non-epithelial tumors are distinguished from epithelial tumors, which often emerge from the exterior lining of the ovaries or the fallopian tube epithelium. This histological differentiation is based on the World Health Organization's ovarian tumor categorization and has significant genomic, epigenetic, and clinical consequences. **[32]** Non-epithelial ovarian tumors account for 8–10% of ovarian malignancy cases, with around 2200 new cases diagnosed each year in the United States. This diverse tumor category includes malignant ovarian germ cell tumors (MOGCT), malignant sex cord-stromal tumors (SCST), and other malignancies. These categories are further classified into many histological and clinically distinct groupings. These cancers afflict younger individuals more than epithelial malignancies, with some forms most commonly appearing in the juvenile population. Because non-epithelial ovarian cancers are rare and heterogeneous, high-quality evidence is scarce to guide clinical therapy for individuals with these tumors. **[33]**

In this current study, the diagnostic prediction for ovarian cancer malignancy was 70 % benign and malignant in 20% **[13].** A study by Chen et al. (2020) assessed the efficacy of ultrasound features in improving the diagnostic prediction of ovarian tumors. It showed that ultrasound, in addition to other ultrasound features as the Risk of Malignancy Index (RMI1), HE4 model, Rajavithi-Ovarian Cancer Predictive Score (R-OPS), improved the prediction of OC malignancy **[34].**

Our results showed that patients with ovarian cancer have a high degree of function and cancer-related fatigue (CRF), as indicated by handgrip strength. They also reported moderate CRF and impaired upper and

lower limb function **[19].** Cancer-related fatigue (CRF) is a severe illness that can last for years following treatment for many cancer survivors. Early and chronic weariness, functional deterioration, depression, and cognitive problems are symptoms. A qualitative assessment of clinical studies by Inglis et al. (2019) evaluated dietary treatments for the prevention and treatment. Dietary consumption influences tiredness levels before, during, and after cancer treatment. Increased protein consumption may aid in the preservation of lean mass and body composition. Dietary patterns that lower inflammation, such as the Mediterranean diet and other plant-based diets, tend to be tolerated for cancer survivors and may help with tiredness. Energy levels in cancer survivors may be improved by taking ginseng, ginger, or probiotics. Nutritional therapies should be evaluated as a treatment option for fatigued cancer survivors alone or in conjunction with other interventions. **[35]**

In the current systematic review, racial differences in ovarian cancer survival and genetic testing were lower in blacks than whites **[11].** In contrast, non-Hispanic black women were at a higher risk of overall mortality than non-Hispanic white women. Hispanic women fared no better than non-Hispanic white women in terms of survival. Non-Hispanic Asian/PI women had a relatively lower risk than non-Hispanic white women. Compared to non-Hispanic white women, the risk of not having surgical intervention remained high among non-Hispanic black women and Hispanic women. Non-Hispanic white women, non-Hispanic black women, non-Hispanic Asian/PI women, and Hispanic women all had a considerably higher chance of dying within the first 12 months following a cancer diagnosis **[20].** A study by Chapman-Davis et al. (2021) supports these findings. It indicated that Non-Hispanic Whites were more likely to be referred due to family cancer history compared to all other races. In contrast, Non-Hispanic Blacks, Hispanics, and Asians were more likely to be referred owing to personal cancer history. At genetic testing, non-Hispanic Blacks and Hispanics were more likely to have advanced-stage cancer **[36].**

In our study, the 5-year disease-free survival (DFS) and relative survival (RS) of patients with advanced ovarian cancer before and after the adoption of centralized primary treatment were compared **[21].** Regardless of the primary treatment, there was an increase in 5-year RS from 24% to 37% and an increase in median RS from 27 months to 44 months. The 5-year DFS was much longer after centralization, which was revealed to be a significant independent predictor for both survival and DFS. A Korean study evaluated the Relative Survival of Ovarian Cancer. The study showed that all patients had a 5-year relative survival rate of 61.1 % at the time of diagnosis **[37].**

CONCLUSION:

The current systematic review aimed to update knowledge on the epidemiology of ovarian cancer and risk factors, predictors, racial inequalities, and survival. The average age of the OC women in our sample was 52.5 years. Granulosa tumors and high-grade serous carcinoma were the most common histological characteristics of ovarian cancer. Non-Hispanic black women were shown to have a greater overall mortality risk than non-Hispanic white women. In addition, the most common pathogenic mutations associated with OC were BRCA1, BRCA2, CHEK2, BRIP1, MSH2, and ATM.

Furthermore, ovarian cancer patients had a high level of function in terms of function and cancer-related fatigue (CRF), as measured by handgrip strength. Although certain risk factors are unchangeable, focusing on controllable risk factors may lower the chance of ovarian cancer. More research is needed to investigate the involvement of unknown risk factors in the development of ovarian cancer.

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