Review Article

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The Importance of Early Detection of Ovarian Cancer: Epidemiology and Risk Factors

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ABSTRACT

Background: Although not having a high incidence, ovarian cancer still leads to the most common cancer-related death among women diagnosed with gynecologic malignancies. The present study aims to highlight this disease's epidemiology, risk factors, and the significance of developing improved early detection strategies.
Methods: Articles were accessed from PubMed and Google Scholar without a time limit. Full-text English studies that mentioned epidemiology and risk factors of ovarian cancer were included in this review.
Results: The highest incidence and mortality rates are observed in Central and Eastern Europe, while rates are relatively low in some parts of Asia and Africa. The risk factors for this disease include family history, hormonal factors, nutrition, diet, and physical activity. We also discussed some protective factors. There are no reliable screening methods for ovarian cancers. The most common diagnostic methods include a pelvic exam, a transvaginal ultrasound, and several imaging tests.
Conclusions: The mortality rate of ovarian cancer is gradually increasing; thus, preventative measures are required to reduce the lifetime risk of ovarian cancers and improve the mortality rate.

Keywords: Diagnosis, Epidemiology, Incidence, Ovarian Cancer, Risk Factors, Screening

INTRODUCTION:

Ovarian cancer ranks fifth in the most common cancer-related deaths among women, accounting for more deaths than any other reproductive malignancy [1].

Most women with ovarian cancer present with an advanced stage, defined as metastasizing the tumour to the pelvis or another area in the abdomen [2]. According to the International Federation of Gynaecological Oncologists (FIGO), Stages IIA to IV are advanced. In such cases, the 5-year overall survival rate is approximately 49% [3]. However, when the cancer is diagnosed at earlier stages, FIGO Stages I to IIA (Table 1) [4], the 5-year survival rate approaches 80% [5]. Despite recent advances in treatment strategies, relapses occur in most women [6]. The gold standard treatment of advanced ovarian cancer includes cytoreductive surgery and platinum-based chemotherapy. Although there have been improvements in treatment, it has only managed to increase survival slightly; the 10-year survival rate being approximately 35% in most countries [7]. In this review, the major risk factors and current screening and diagnosis methods will be discussed to highlight the importance of early detection of ovarian cancer.

Table 1. FIGO Staging of Ovarian Cancer (Source: Reference 4)

FIGO Stage	Characteristics
Stage I	Tumour is retained in the ovaries
Stage IA	Tumour in one ovary, no ascites
Stage IB	Tumour in both ovaries, no ascites
Stage IC	Tumour in one or both ovaries with ascites
Stage II	Tumour involves one or both ovaries and extends into the pelvis
Stage IIA	Extends or implants on the uterus or fallopian tubes, no ascites
Stage IIB	Extends to other pelvic tissues
Stage IIC	Extends to other pelvic tissues with ascites
Stage III	Tumour involves one or both ovaries with peritoneal metastasis outside the pelvis or lymph node metastasis
Stage IIIA	Tumour limited to the pelvis
Stage IIIB	Metastasis beyond the pelvis (<2 cm)
Stage IIIC	Peritoneal metastasis beyond pelvis (>2 cm)
Stage IV	Distant metastasis

Methods:

This review was conducted using published English full-text articles by searching PubMed and Google Scholar without a time limit. Pubmed was searched with the following terms: “ovarian cancer”, “ovarian neoplasms” [MeSH Term], “risk factors” [MeSH Term], “incidence” [MeSH Term], “mortality”, “epidemiology”, and a combination of them. Google Scholar was searched with the entry terms. Case-control studies, systematic reviews, meta-analyses, literature reviews, and all cohort studies (prospective and retrospective) were included, while case reports, case series, and articles mentioning animal studies were excluded.

Incidence, Mortality, and Survival:

There is a geographic variation in the incidence and mortality of ovarian cancer (Table 2), with an AS (age-standardized) incidence rate of 6.6 per 100,000 (Table 2 & Figure 1). The highest AS incidence rate was observed in Central and Eastern Europe, while the AS rates are relatively low in Eastern Asia and Southern and Central Africa. The AS rates are highest among the non-Hispanic white population (11.0 per 100,000) and lowest among the non-Hispanic black population (9.1 per 100,000) and Asians (9.4 per 100,000) [3] ,and this is among the Unit-

Table 2. Geographic variation in incidence and mortality rates of ovarian cancer per population of 100,000 as of 2020 (Age-Standardized rate) (Source: Globocan 2020).

Geographic Regions	Incidence	Mortality
Central and Eastern Europe	10.7	5.6
Northern Europe	8.8	4.9
Polynesia	8.8	6.6
Northern America	8.1	4.1
South-Eastern Asia	8.1	5.2
Southern Europe	8.0	4.1
Micronesia	7.3	7.3
Western Europe	7.1	4.3
Melanesia	7.0	5.2
Western Asia	6.6	4.6
World	6.6	4.2
Australia and New Zealand	6.4	3.9
South Central Asia	6.2	4.4
Central America	6.1	3.7
South America	5.8	3.6
Northern Africa	5.7	3.9
Eastern Asia	5.7	3.3
Western Africa	5.6	4.4
Eastern Africa	5.5	4.3
Southern Africa	4.9	3.3
Caribbean	4.6	3.2
Middle Africa	4.4	3.5

ed States population. The factors that explain the variations in incidence rates and the trends in incidence and mortality include variations in oral contraceptive usage, family history, exercise, and hormonal factors [8,9]. The high incidence of ovarian cancer is associated with increasing age, especially in post-menopausal women, and the median age at diagnosis is 63 years [3]. Ovarian cancer is relatively rare in women below the age of 45 years. Over 80% of ovarian cancers are observed in women over 45. In cases where protective factors are absent, the lifetime risk of ovarian cancer approaches 2.7% [10].

Risk Factors and Protective Factors:

Although age is a determining factor for the risk of ovarian cancer, additional factors, such as those discussed next, may also play a substantial role in increasing ovarian cancer risk

Genetic Factors:

Family History

One of the most critical risk factors for ovarian cancer is a family history of breast and/or ovarian cancer. Women whose first-degree relatives have been diagnosed with ovarian cancer experience a 3-fold increase in the risk of developing the cancer themselves [11]. In a study on the relative risk (RR) of ovarian cancer in first-degree relatives, the relative risk is higher for first-degree relatives who have been diagnosed at <50 years than for those >50 (RR 4.7 vs. 2.5, p = .0052). These results suggest that

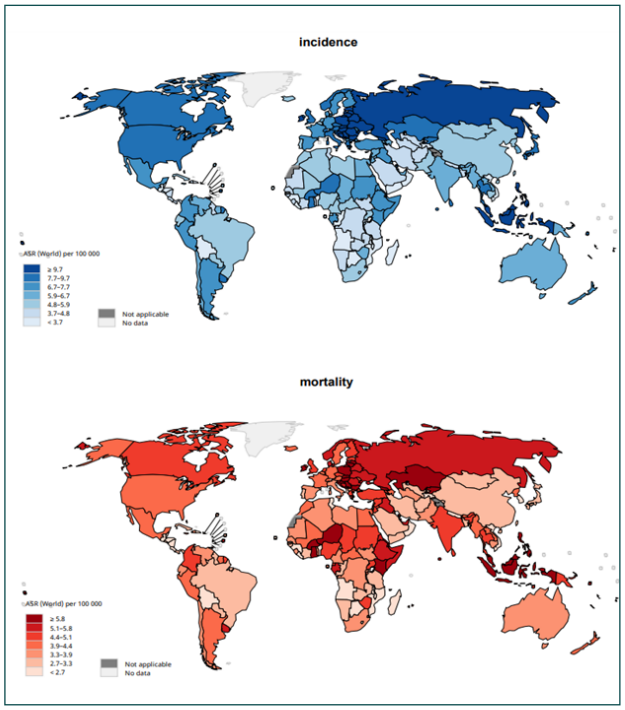

Figure.1. Global incidence and mortality age-standardized rates of ovarian cancer, all ages. Data Source: https://gco.iarc.fr/today (accessed 17 May 2022).

family history is of great importance regarding ovarian cancer incidence rate [12].

BRCA Mutations

Most hereditary ovarian cancers are attributed to BRCA1 and BRCA2 gene mutations [13]. By the age of 80 years, it is estimated that the cumulative lifetime risk of ovarian cancer is 44% in patients who are BRCA1 mutation carriers and 17% in BRCA2 mutation carriers [14]. Screening for mutations has shown that approximately 15% of ovarian cancers are associated with BRCA1 and BRCA2 gene mutations [15].

Hormonal Factors:

Contraceptives

Recent studies indicate that oral contraceptives are associated with a reduced risk of all histological subtypes of ovarian cancer [16,18]. A case-control study established that oral contraceptive usage is a protective factor for serous ovarian cancer, the most common subtype of ovarian cancer, as it significantly reduced the risk of a serous tumour by approximately 60% compared with patients who have never used oral contraceptives (odds ratio (OR) = 0.40; 95% CI: 0.26-0.62) [16]. It has been shown that this risk reduction may last up to 30 or more years after discontinuation of oral contraceptives [20].

Reproductive Factors:

Menstruation-related factors

Several studies described the association between ovulation cycles and the risk of ovarian cancer [21,22]. A Vietnamese case-control study displayed a significant relationship between increasing years of ovulation and escalating risk of ovarian cancer [23]. Another case-control study indicated that, in women who experienced an absence of an ovulation cycle for 8.7 years, the risk of ovarian cancer was reduced by four times (OR = 0.23; 95% CI: 0.10-050) [24]. This is referred to as the "incessant ovulation" theory, which posits that the risk of ovarian cancer rises due to recurring trauma to the ovarian epithelium that occurs during ovulation. Hence, any event that reduces ovulation offers a protective effect against ovarian cancer [25].

Parity

Several studies have continually displayed the protective effect of parity against ovarian cancer [21,26,27]. A case-control study showed that parous women had a lower risk of getting ovarian cancer of any subtype than nulliparous women under 55 years. The OR for serous cancer was 0.65 (95% CI: 0.56–0.77), for mucinous cancer 0.66 (0.52–0.83), for endometrioid cancer 0.52 (0.40–0.68), for clear-cell cancer 0.30 (0.19–0.46) and for other types 0.59 (0.43–0.80). However, in women 55 years and older, the ORs were 0.86 (0.75–0.99), 0.78 (0.57–1.07), 0.61 (0.47–0.79), 0.44 (0.29–0.66) and 0.74 (0.57–0.95), respectively. Increased pregnancy also displayed a consistent reduction in risk [28].

Age at childbirth

Several studies showed that older age during pregnancy is associated with a decreased risk of ovarian cancer [27,29]. Whiteman et al. indicated that women 30 years of age or older at either first or last birth experienced a 30-50% lower risk of ovarian cancer than those who were less than 20 years of age at first birth or 25 years at last birth [30]. Despite these results, the association between age at first birth and ovarian cancer risk is still unclear.

Lifestyle Factors:

Diet and Nutrition

A Canadian case-control study on the link between dietary B-vitamin and ovarian cancer suggested that a diet high in vitamin B6 and folate was inversely associated with the risk of ovarian cancer [31]. An epidemiological review of the literature suggested that vegetables are highly likely to reduce the risk of ovarian cancers by 39% [32,33]. The review also concluded that frequent consumption of whole-grain foods and low-fat milk protects against ovarian cancers. Blank et al. showed an increase of 28% in the risk of ovarian cancer in women consuming greater amounts of fat. However, a 30% increase in risk was observed in association with animal fat intake [34]. Larsson et al. investigated the relationship between dairy intake and ovarian cancer risk, and the results indicated a 60% greater risk for invasive ovarian cancer [35].

Physical Activity and Obesity

Physical activity has been shown to have a protective effect and thus reduce the risk of ovarian cancer [36]. A Canadian case-control study concluded that moderate to high occupational and recreational activity levels were associated with a decreasing risk of ovarian cancer [37]. These results may suggest that moderate physical activity decreases ovarian cancer risk and a sedentary lifestyle increases ovarian cancer risk. Several other case-control studies investigated the association between recreational physical activity and ovarian cancer risk, ranked by BMI [37,39]. However, only two case-control studies showed that higher activity levels in obese women are related to risk reduction [37,39]. Another case-control study indicated an inverse relationship between vigorous physical activity and ovarian cancer risk [40]. Notwithstanding the results, these studies offer inconsistent findings. Hence more future studies are required to assess different types of physical activity while considering the intensity and duration of activity and their association with ovarian cancer risk [41,42]. On the other hand, obesity has also been found to be a risk factor for ovarian cancer. Delort et al. indicated that a high waist to hip ratio (WHR) increased the risk of ovarian cancer (OR=2.93 for WHR=0.801-0.85, 95% CI: 1.94-4.42; OR=8.58 for WHR>0.85, 95% CI: 3.77-19.52). This study also explained that central adiposity is the main factor of ovarian cancer, suggesting the conversion of androgens in adipose tissue [43]. Rodriguez et al. observed a 36% increase in the risk of ovarian cancer in obese women who had never used postmenopausal estrogens and also noted that ovarian cancer mortality increased in taller women [44]. Beehler et al., via a hospital-based case-control study, showed that premenopausal women (<50 years), who were obese, had an increased risk of ovarian cancer (adjusted OR= 2.19; 95% CI: 1.19-4.04) as opposed to post-menopausal women and those who were considered normal/underweight [45].

SCREENING AND DIAGNOSIS:

Most often, ovarian cancers present with few symptoms during the early stages, making them increasingly difficult to diagnose. Some symptoms include nausea, abdominal pain, bloating, loss of appetite, and urinary tract issues, among others [46]. The stage at diagnosis primarily depends on the epithelial subtype. Most serous ovarian carcinomas are diagnosed at FIGO Stage III (51%) and IV (29%) [47], with the presence of swelling of the abdomen caused by ascites48. On the other hand, endometrioid, mucinous, and clear cell carcinomas are diagnosed at FIGO stage I (58%-64%) [47]. Only 20% of ovarian cancer patients are diagnosed at an early stage, with an approximate 5-year survival rate of 90%, compared to late-stage diagnosis that offers 5-year survival rates of 17%-39% [49]. The relative 5-Year survival rate at each FIGO stage is summarized in Table 3.

Table 3. Relative 5-Year Survival Rate for Ovarian cancer for each FIGO stage, for all races and epithelial subtypes. Data Source: SEER Registry, National Cancer Institute, 2017

FIGO Stages	Relative 5-Year Survival Rate
Stage I	89%
Stage II	71%
Stage III	41%
Stage IV	20%

An effective strategy for the early detection of ovarian cancer is yet to be developed. It is one of the main reasons for the delay in diagnosis and treatment of this disease, leading to poor outcomes, lower rates of 5-year overall survival in patients with advanced carcinomas, and a high mortality rate.

There are currently no reliable screening methods for detecting ovarian cancer. However, the cancer antigen 125 (CA125) test can be performed and has been proven helpful as a tumour marker to aid in guiding treatment for patients known to have ovarian cancer. Although this method has been extensively studied, it does not propose valuable results. These studies have shown low positive values and high rates of false positives causing unnecessary distress to patients and futile surgical interventions [50].There have currently been only two trials that investigated the impact of screening on mortality benefits. The largest trial of the two trials was conducted in the UK as part of the UK Collaborative Trial of Ovarian Cancer Screening (UKCTOCS) between 2001 and 2005, with more than 200 000 women [51]. The trial randomized the patients to no intervention or annual screening using the transvaginal ultrasound or serum CA125, interpreted according to the Risk of Ovarian Cancer Algorithm and transvaginal ultrasound (multimodal screening). The trial showed a test sensitivity of 84% (95% CI: 79-88; 199 of 237) with the multimodal screening and 73% (95% CI 66-79; 161 of 221) with transvaginal ultrasound alone. The second trial was the Prostrate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial in the United States [52]. The PLCO trial randomized more than 70 000 women to usual care or annual screening for detection of CA125 in blood and transvaginal ultrasound for the first 4 years, then 2 years of CA125 only. The PLCO trial resulted in overdiagnosing low malignant tumours, resulting in these women undergoing surgery. The PLCO trial suggested no significant improvement in ovarian cancer mortality compared to the UKCTOCS trial, which showed a decrease in mortality. However, it was not statistically significant. Additionally, the UKCTOCS trial showed a significant stage shift at the time of diagnosis in the multimodal screening group compared to the no screening group.

Diagnosis of ovarian cancer begins with a pelvic examination. However, according to Ebell et al., pelvic exams lack accuracy as a diagnostic test for ovarian cancer and fail to distinguish benign from malignant lesions. For a diagnostic test to be effective, it should be sensitive and specific and have both a high positive predictive value (PPV) and a high negative predictive value (NPV). The sensitivity and specificity of the pelvic exam were 0.44 and 0.98, respectively, and for distinguishing between benign and malignant, they were within the range of 0.43 to 0.93 for sensitivity and from 0.53 to 0.91 for specificity [53]. Another diagnostic test is the transvaginal ultrasound, which had a sensitivity of 85.0%, specificity of 98.7%, a positive predictive value of 14.01%, and a negative predictive value of 99.9%. Although the transvaginal ultrasound accurately identifies ovarian tumours, it is also futile in differentiating benign lesions from malignant lesions [54]. Another test is an ovarian biopsy, which according to Thabet et al., displayed a sensitivity and specificity of 100% ± 0 (19 out 19) and 88% ± 26 (seven out eight), respectively [55], proving the high efficacy of this test. Other imaging tests include MRIs, with sensitivities and specificities for malignancy ranging between 91–92% and 91–100%, respectively [56]; and Positron emission tomography-computed tomography (PET/CT) scan, with a sensitivity of 52–58% and specificity of 76–78% [57].Despite these trials, the data does not support the need for screening for ovarian cancers in the general population due to indefinite evidence of mortality benefits. Nevertheless, early detection and screening modalities are continuously being developed. To reduce mortality accurately, future early detection strategies must focus on reducing the high false positive rates, risk stratification to improve outcomes in average to high-risk women, and identifying other promising biomarkers as a first-line test.

Conclusion:

Ovarian cancer-related deaths are most common in women diagnosed with a gynecologic malignancy with increasing mortality and incidence rate. The difficulty in detecting this disease at an early stage due to lack of symptoms results in increased deaths compared to oth-

er gynecologic malignancies. The risk factors discussed in this review have been identified as the most common risk factors among women with this disease. We also discussed some protective factors, such as oral contraceptive pills and physical activity, that significantly reduce the risk of ovarian cancer. The need for improved early detection and screening strategies remains of the utmost importance for reducing the early onset of ovarian cancer and improving the 5-year overall survival rate.

Footnotes:

Conflicts of Interest:
The author declares no conflict of interest.

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