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Title: The Importance of Screening for Early Detection of Ovarian Cancer: Epidemiological Review

Running Title: Early Detection of Ovarian Cancer

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Abstract – Objective: *Ovarian cancer, although not possessing a high incidence, is still the most common cancer-related deaths among women diagnosed with a gynecologic malignancy. The present study aims to highlight the epidemiology, risk factors of this disease and the significance of development of improved early detection strategies.*

Materials and Methods: *This study was conducted using current published English studies by searching PubMed and Google Scholar. The search strategy included the keywords "ovarian cancer", "diagnosis", "risk factors", "screening", "epidemiology". Studies on incidence and mortality were also considered. Case reports were excluded.*

Results: *The highest incidence and mortality rates are observed in Central and Eastern Europe, while rates are relatively low in Asia and Africa. These rates are highest among the white population (14.3 per 100,000) and lowest among blacks (10 per 100,000) and Asians (9.7 per 100,000). The risk factors for this disease includes a family history, hormonal factors, nutrition and diet and physical activity, with some of them playing protective roles in reducing risk of ovarian cancers. There are no reliable screening methods for ovarian cancers. The most common diagnosis methods include a transvaginal ultrasound and a blood test to detect CA125 markers.*

Conclusions: *The mortality rate of ovarian cancer is gradually increasing; thus, preventative measures are required to reduce lifetime risk of ovarian cancers and improve mortality rate.*

KEYWORDS: *Ovarian Cancer, Epidemiology, Risk Factors, Screening, Diagnosis, Mortality, Incidence*

INTRODUCTION

Ovarian cancer is the second most common gynecologic malignancy and the most common cancer-related deaths among women[1]. Most women with ovarian cancer present with advanced stage, which is defined as the metastasize of 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 45%[3]. However, when the cancer is diagnosed at earlier stages, FIGO Stages I to IIA, the 5-year survival rate approaches 80%[4]. Despite recent advances in treatment strategies, relapses occur in most women[5]. 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 slightly increase survival; the 10-year survival rate being approximately 35%, in most countries[6]. 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.

MATERIALS AND METHODS

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This review was conducted using current published English full-text articles by searching PubMed and Google Scholar. The search terms included the following keywords: “ovarian cancer”, “diagnosis”, “risk factors”, “screening”, “epidemiology”. Studies on incidence and mortality were also considered. Case reports were excluded.

RESULTS

Epidemiology

There is a geographic variation in the incidence and mortality of ovarian cancer (Table 1)[7]. The highest incidence and mortality rates are observed in Central and Eastern Europe, while rates are relatively low in Asia and Africa. These rates are highest among the white population (14.3 per 100,000) and lowest among blacks (10 per 100,000) and Asians (9.7 per 100,000)[3]. 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 women who are post-menopausal, and the median age at time of diagnosis is 63 years[10]. Ovarian cancer is relatively rare in women below the age of 45 years. Over 80% of ovarian cancers are observed in women over 45 years of age. In cases where protective factors are absent, the risk of ovarian cancer approaches 2.7% [11].

Table. 1. Geographic variation in incidence and mortality rates of ovarian cancer per population of 100,000 as of 2020 (Age-Standardized rate). Drawn from ref. [7].

Geographic Regions	Incidence	Mortality
Central and Eastern Europe	30.7	17.2
Northern Europe	23.8	13.2
Southern Europe	22.5	11.7
Northern America	22.4	10.9
South-Eastern Asia	22	14.9
Western Europe	19.6	11.2
Western Asia	18.8	13.6
South-Central Asia	16.8	13.2
Australia and New Zealand	16.8	9.8
Northern Africa	16.4	11.9
Eastern Africa	16.3	13.7
Central America	16	10.6
Western Africa	15.6	13.2
Eastern Asia	15.5	10.7
South America	15.4	10.1
Southern Africa	12.6	9.1

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Middle Africa	12.6	10.7

Risk Factors and Protective Factors

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

Family History

One of the most important risk factors for ovarian cancer is a family history of either breast and/or ovarian cancer. Women whose first-degree relatives are diagnosed with ovarian cancer experience a 3-fold increase in risk of developing the cancer themselves[12]. 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 family history is of great importance when it comes to ovarian cancer incidence rate[13]. Most hereditary ovarian cancers are attributed to BRCA1 and BRCA2 gene mutations[14]. By the age of 80 years, it is estimated that the cumulative risk of ovarian cancer is 44% in patients who are BRCA1 mutation carriers and 17% in BRCA2 mutation carriers[15]. Screening for mutations have shown that approximately 15% of ovarian cancers are associated with BRCA1 and BRCA2 gene mutations[16].

Hormonal Factors

Recent studies indicate that use of oral contraceptives is associated with a reduced risk of all histological subtypes of ovarian cancer[17-19]. 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 serous tumour by approximately 60% compared with patients who have never used oral contraceptives (odds ratio = 0.40; 95% CI: 0.26-0.62)[20]. It has been shown that this reduction of risk may last up to 15 years after discontinuation of oral contraceptives[21].

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[22]. An epidemiologic review of the literature suggested that vegetables are highly likely to reduce risk of ovarian cancers[23]. The review also concluded that frequent consumption of whole grain foods and low-fat milk has a protective effect against ovarian cancers.

Physical Activity

Physical activity has been shown to have a protective effect and thus reduces the risk of ovarian cancer[24]. A Canadian case-control study concluded that moderate to high levels of occupational and recreational activity was associated with a decreasing risk of ovarian cancer[25]. These results may suggest that moderate levels of physical activity decreases ovarian cancer risk and a sedentary lifestyle increases ovarian cancer risk, however, these studies offer inconsistent findings, hence more future studies are required to assess different types of physical activity, while taking into consideration the intensity and duration of activity and their association with ovarian cancer risk[26,27].

SCREENING AND DIAGNOSIS

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Most often ovarian cancers present with few symptoms during the early stages making it increasingly difficult to diagnose. Some of these symptoms include nausea, abdominal pain, bloating, loss of appetite, and urinary tract issues among others[28].

An effective strategy for early detection of ovarian cancer is yet to be developed and 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 and high rate of mortality. Only 20% of ovarian cancer patients are diagnosed at an early stage, with 5-year survival rates exceeding 90%, compared to late-stage diagnosis that offers 5-year survival rates of 17-39%[29].

The current gold standard screening method is detection of blood serum levels of cancer antigen 125 (CA125). Although this method has been extensively studied, it does not propose valuable results in that these studies have shown low positive values and high rates of false positives causing unnecessary distress to patients and unnecessary surgical interventions[30]. There have currently been only 2 trials that investigated the impact of screening on mortality benefit. 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[31]. The trial randomized the patients to no intervention or annual screening using just the transvaginal ultrasound or serum CA125, interpreted according to the Risk of Ovarian Cancer Algorithm, along with transvaginal ultrasound (multimodal screening). The trial showed a test sensitivity of 86.2% (95% Confidence Interval (CI) 80.8-90.6) with the multimodal screening and 63.3% (95% CI 55.4-70.6) with transvaginal ultrasound alone. The second trial was the Prostrate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial in the United States[32]. 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 overdiagnosis of 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, was not statistically significant. Additionally, the UKCTOCS trial showed a significant stage shift at time of diagnosis in those in the multimodal screening compared to no screening.

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 benefit. Nevertheless, early detection and screening strategies are continuously being developed. To accurately reduce mortality, it is imperative that future early detection strategies focus on reducing the high false positive rates; risk stratification to improve outcomes in average to high risk women; and identification of other promising biomarkers as a first-line test.

CONCLUSIONS

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 an increase in deaths compared to other gynecologic malignancies. The risk factors discussed in this review have been identified as the most common risk factors among women with this disease, with some being protective factors, such as oral contraceptive pills and physical activity, that play a prominent role in reducing the risk of ovarian cancer. The need for improved early detection and screening strategies remains of the utmost importance for reducing early onset of ovarian cancer and improving 5-year overall survival rate.

CONFLICT OF INTEREST:

The author declares that there are no conflicts of interest.

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