REVIEW

Ovarian cancer in the world: epidemiology and risk factors

Zohre Momenimovahed[1,2]
Azita Tiznobaik[2,3]
Safoura Taheri[4]
Hamid Salehiniya[5,6]

[1]Department of Midwifery and Reproductive Health, School of Nursing and Midwifery, Qom University of Medical Sciences, Qom, Iran; [2]Department of Midwifery and Reproductive Health, School of Nursing and Midwifery, Tehran University of Medical Sciences, Tehran, Iran; [3]Department of Midwifery and Reproductive Health, School of Nursing and Midwifery, Hamedan University of Medical Sciences, Hamedan, Iran; [4]Department of Midwifery and Reproductive Health, School of Nursing and Midwifery, Ilam University of Medical Sciences, Ilam, Iran; [5]Social Determinants of Health Research Center, Birjand University of Medical Sciences, Birjand, Iran; [6]Epidemiology and Biostatistics Department, School of Public Health, Tehran University of Medical Sciences, Tehran, Iran

Aim: Ovarian cancer is one of the most common gynecologic cancers that has the highest mortality rate. Considering the fact that knowledge on the incidence, mortality of ovarian cancer, as well as its risk factors is necessary for planning and preventing complications, this study was conducted with the aim of examining the epidemiology and risk factors of ovarian cancer in the world.

Materials and methods: In order to access the articles, Medline, Web of Science Core Collection, and Scopus databases were searched from their start to the year 2018. Full-text, English observational studies that referred to various aspects of ovarian cancer were included in the study.

Results: In total, 125 articles that had been published during the years 1925–2018 were entered into the study. Ovarian cancer is the seventh most common cancer among women. Increased risk factors of cancer have led to an upward trend in the incidence of cancer around the world. In 2018, 4.4% of entire cancer-related mortality among women was attributed to ovarian cancer. Although the incidence of cancer is higher among high Human Development Index (HDI) countries, the trend of mortality rate tends to be reversing. Various factors affect the occurrence of ovarian cancer, from which genetic factor are among the most important ones. Pregnancy, lactation, and oral contraceptive pills play a role in reducing the risk of this disease.

Conclusion: This study provides significant evidence about ovarian cancer. Considering the heavy burden of ovarian cancer on women's health, preventive measures as well as health education and early detection in high risk groups of women are highly recommended. Although some risk factors cannot be changed, a focus on preventable risk factors may reduce the risk of ovarian cancer. More studies are needed to explore the role of unclear risk factors in ovarian cancer occurrence.

Keywords: Ovarian cancer, epidemiology, risk factor

Introduction

Cancer is the most common cause of mortality in most parts of the world,[1] and currently is the most common impediment to achieving desirable life expectancy in most countries.[2] Ovarian cancer is one of the most common gynecologic cancers that rank third after cervical and uterine cancer.[2] It also has the worst prognosis and the highest mortality rate.[3] Although ovarian cancer has a lower prevalence in comparison with breast cancer, it is three times more lethal,[4] and it is predicted that, by the year 2040, the mortality rate of this cancer will rise significantly.[2] The high mortality rate of ovarian cancer is caused by asymptomatic and secret growth of the tumor, delayed onset of symptoms, and lack of proper screening that result in its

Correspondence: Hamid Salehiniya
Social Determinants of Health Research Center, Birjand University of Medical Sciences, Birjand, Southern Khorasan, Iran
Email alesaleh70@yahoo.com

diagnosis in the advanced stages. Thus, silent killer is a name that has been given to this cancer.[4–6]

Like many cancers, the incidence of ovarian cancer varies across the world.[7] The epidemiological diversity of ovarian cancer in different regions can be attributed to the risk factors that account for the occurrence of ovarian cancer.[8] The highest prevalence of ovarian cancer is seen in non-Hispanic white women (12.0 per 100,000), followed by Hispanic (10.3 per 100,000), non- Hispanic black (9.4 per 100,000), and Asian/ Pacific Islander women (9.2 per 100,000).[9] However, due to differences in access to diagnostic and therapeutic services, the mortality of ovarian cancer has a different pattern, and the highest mortality rate is seen in African populations.[10] The statistics show that between one third to two fifths of the total cancer cases can be prevented by eliminating and reducing risk factors.[2] Considering the fact that knowledge on the incidence, mortality, and geographical diversity of ovarian cancer as well as its risk factors is necessary for planning and preventing complications, and since we could find no comprehensive study on the risk factors of ovarian cancer in the world, the aim of this study was to examine the trends in incidence and mortality across the world and to present all possible factors associated with OC.

Materials and methods
Search engines
In order to access the articles, Medline, Web of Science Core Collection (Indexes = SCI-EXPANDED, SSCI, A & HCI Timespan) and Scopus databases were searched from their start to the year 2018.

Search strategy
At first, the search strategies were defined to increase validity of the review. In order to search the articles, a systematic and accurate review of the published articles was carried out by two researchers independently, and a list of potential articles was prepared. The views of a specialist and expert librarian were used to ensure the comprehensiveness of searching strategies and reviewing resources. Searching for articles was carried out with no time limit using keywords such as; ovarian cancer, incidence, mortality, risk factor, and a combination of them in English language. All keywords were checked within PubMed Medical Subject Heading (MeSH). Then, to ensure the adequacy of the search, a manual search was also done in valid journals, followed by a manual search for the references of full-text articles and

systematic reviews. All retrieved articles were entered into a database in the Endnote X7.

Inclusion criteria
The criteria for entering the study included the following: Full-text articles (retrospective and prospective cohort and case-control studies), English language articles, the use of keywords in the title or abstract (ovarian cancer, incidence, mortality, risk factors, and a combination of these terms).

Exclusion criteria
Case reports, case series, systematic reviews, and animal studies were excluded.

Results
Characteristics of the selected studies
In total, 145 articles that had been published during the years 1925–2018 were entered into the study. In the initial search, 588 articles were obtained from databases, and 46 articles were extracted by manual search. After removing repetitive articles using EndNote software, 493 articles were selected for review. After reviewing the titles and abstracts, 322 articles that were unrelated to the purpose of study and were not consistent with the criteria of the study were removed. Furthermore, 26 articles were also removed for scientific reasons (editorial: 5, qualitative: 6, duplicate: 9, not available full text: 6). Finally, 145 articles that had been published during the years 1925–2018 were entered into the study (Figure 1).

The types of ovarian cancer
Different subtypes of ovarian cancer were discussed in nine studies. Studies show that up to 90% of all OC have epithelial origin and the remaining OC have non-epithelial origin.[11–13] Among epithelial OC, 3% are mucinous and others are non-mucinous.[14] Non-mucinous are further found to have serous (70% of non-mucinous), endomterioid (10%), clear cell (10%), and unspecified subtypes (5%).[14–16] According to recent studies, serous carcinomas are divided into two separate subtypes: high grade and low grade.[17,18] Compared to epithelial cancers, non-epithelial cancers are less invasive.[19]

Incidence
Population growth, increased risk factors of cancer, decreased pregnancy and duration of lactation, as well as tube ligation have led to an upward trend in the incidence
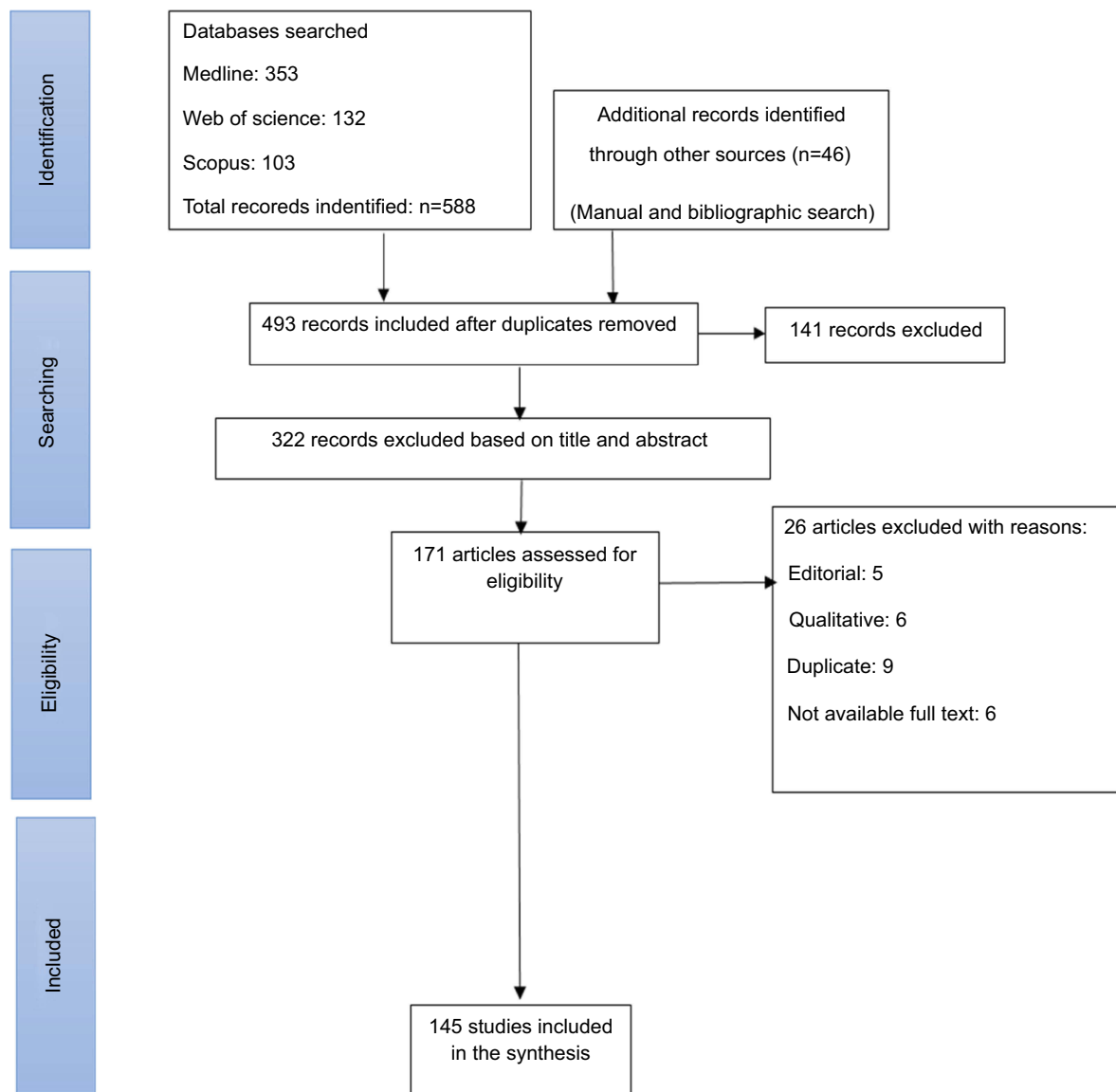
Figure 1 Flowchart of the included eligible studies in review.

of cancer around the world.[2,20,21] Ovarian cancer is the seventh most common cancer among women[2] and, in the absence of protective factors, the lifetime risk of ovarian cancer is about 2.7%.[21] According to Globoccan, 295,414 cases of ovarian cancer have been identified in 2018, accounting for 3.4% of all cancer cases in women.[2] The Age Standardized Rate (ASR) of ovarian cancer is estimated to be 6.6 in 2018.[2] The incidence of epithelial ovarian cancers varies in different age and race groups.[9] The incidence of this cancer is higher among transitioned countries,[2] and approximately 30% of ovarian cancer cases occur in European countries.[22] In 2012, the highest rates of ovarian cancer occurred in China (14.60% of all cases), India (11.33% of all cases), and the US (81.8% of all

cases).[22] In that year, 22,240 cases of ovarian cancer were detected in the USalone.[9] Among the Asian countries, Singapore, Kazakhstan, and Brunei have the highest standardized incidence rate of ovarian cancer.[23]

Mortality

In 2018, 184,799 deaths occurred due to ovarian cancer, accounting for 4.4% of the entire cancer-related mortality among women.[2] Based on Globoccan 2018, the ASR of ovarian cancer mortality is 3.9.[2] Although the incidence of cancer is higher among high Human Development Index (HDI) countries, the trend of mortality rate tends to be reversing.[2] The highest mortality rate in Asia is seen in India, and the mortality rate has decreased in Europe and

North America in recent years, especially among young people.[24] The mortality-to-incidence ratio is high among African women, indicating their lack of access to suitable treatment.[10] Two-thirds of ovarian cancer mortality is attributable to high-grade serous carcinoma.[12] The FIGO's high stage at diagnosis and surgery,[25] and the presence of comorbidity[26] are among the most important predictors of high mortality in ovarian cancer.

Risk factors

Table 1 shows factors related to ovarian cancer.

Demographic factor
Age

The epithelial ovarian cancer is an age-related disease, and is considered mainly a postmenopausal disease.[10,27] Increased incidence of this cancer is more pronounced in women over 65 years of age.[28] According to previous studies, median age at diagnosis is 50–79 years.[27,29,30] The relationship between age and the outcome of ovarian cancer is uncertain. Although many researchers have pointed out that the younger age of ovarian cancer is associated with the improved outcome,[29,31,32] other stated age is not an independent prognostic factor.[33] Older age in this disease is associated with more advanced disease and lower survival rate.[27,34] Older women are

treated less aggressively in contrast with younger ovarian cancer patients, and, thus, survival is lower in these group.[35] An age of over 64 years is one of the predictors of mortality in people with ovarian cancer.[25]

Reproductive factors
Menstrual-related factors

Tung et al[36] stated that non-mucinous tumors are strongly associated with menstrual periods (odds ratio=1.5 for the highest vs the lowest quartile) and ovulation cycles (odds ratio=2.8 for the highest vs the lowest quartile). In numerous studies, researchers indicated an inverse relationship between ovulation cycles and the risk of ovarian cancer.[37,38] The result of a case-control study showed that, in women who have not had an ovulation cycle for 8.7 years, the risk of ovarian cancer was reduced by 4-times (OR=0.23 [0.10–0.50]).[39] These findings support the theory of "incessant ovulation". Based on this theory, ovulation without interruption can contribute to the incidence of ovarian cancer by damaging the epithelium of ovaries; therefore, any factor that contributes to the reduction of ovulation can have a protective effect against ovarian cancer.[40] However, Moorman et al[41] believed that, contrary to the lack of ovulation due to pregnancy or the use of oral contraceptives, the lack of ovulation caused by menstrual disorders is associated with an increased risk of ovarian cancer.

Table 1 Factors related to ovarian cancer in the world

Factors		Protective	Predisposing	Controversial
Demographic	Age		✓	
Reproductive	Menstrual-related factors		✓	
	Age of menarche and menopause			✓
	Parity	✓		
	Pregnancy characteristics			✓
	Higher age of childbirth	✓		
Gynecologic	Pelvic inflammatory disease			✓
	Endometriosis		✓	
Hormonal	Contraceptive methods	✓		
	Hormone Replacement Therapy (HRT)			✓
	Infertility treatments			✓
Genetic	Family history		✓	
	BRCA mutations		✓	
	Lynch syndrome		✓	
Lifestyle	Nutrition and Diet			✓
	Obesity and physical activity			✓
	Alcohol, caffeine and cigarettes			✓
Other	Lactation	✓		
	Lower socioeconomic status		✓	

Age of menarche and menopause

Although the result of some studies showed a relationship between the early onset of menarche and risk of ovarian cancer,[42,43] other researchers reported that age of menarche and menopause has no effect on the risk of ovarian cancer.[44–49]

Parity

Results of several studies suggest that pregnancy has a protective role against ovarian cancer.[38,45,49–52] Based on the results of a case-control study, the risk of ovarian cancer is reduced in women with live birth ($P<0.001$) or induced abortion ($P<0.05$), and this risk decreases with an increase in the number of live birth cases ($P<0.001$). The result of a case-control study showed that, for every full-term pregnancy, OR is equal to 0.76 [0.69–0.85] for non-mucinous tumors and 1.03 [0.88–1.21] for mucinous tumors.[53] The result of a study showed that increased pregnancy is associated with a consistent reduction in the relative risk of invasive ovarian cancer (odds ratio for each additional birth=0.81 [0.75–0.85]), epithelial cancer (0.81 [0.77–0.86]), stromal cancer (0.84 [0.72–0.98]), and germ-cell cancer (0.71 [0.48–1.05]).[54] However, Poole et al[34] stated that pregnancy decreases the risk of less aggressive disease compared to an advanced disease.

Pregnancy characteristics

Jordan et al,[55] in a case-control study, showed that preterm labor increases the risk of ovarian cancer (OR=1.48 [1.02–2.15]). This finding has been confirmed in Skold et al's[56] study. The results of a study showed that the delivery of a male infant is associated with a 2-times increase in the risk of mucinous ovarian cancer (OR=2.19 [1.15–4.17]).[55] Mucci et al[57] concluded that low birth weight among term infants has a protective effect on the mother's ovarian cancer, while Skold et al[56] did not find any relationship between infant's weight and ovarian cancer. Skold et al[56] also rejected the role of pre-eclampsia and multiple pregnancies in the occurrence of cancer in the mother. However, Calderon-Margalit et al,[58] in a cohort study, concluded that pre-eclampsia increases the risk of ovarian cancer by more than 2-times (HR=2.59 [1.35–4.94]).

Age at childbirth

Results of a case-control study indicated that older age in pregnancy is associated with a decreased risk of ovarian cancer[59] relative to the number of pregnancies. This result has been confirmed in other studies.[51,52,54] Adami et al[54] stated that, for every 5-year increase in the age at first childbirth, the risk of ovarian cancer would be reduced by up to 10% (OR=0.89 [0.84–0.94] epithelial cancer, 0.92 [0.77–1.10] stromal cancer, 0.92 [0.65–1.32] germ-cell cancer, 0.93 [0.80–1.09] borderline tumors).

Gynecologic factors

Pelvic inflammatory disease

The role of inflammation and pelvic inflammatory disease in the occurrence of ovarian cancer is controversial among experts. Ness et al,[60] in a case-control study, supported the hypothesis that suggests inflammation contributes to the onset of ovarian cancer. On the other hand, Jia et al[61] concluded that events associated with inflammation in the ovary (such as repairing the damaged ovary) are associated with an increase in the release of cancer cells in the tissues around the ovary. Thus, they stated that ovulation and other events associated with inflammation in the ovary contribute to an increased risk of ovarian cancer. In line with this, a case-control study referred to the role of chlamydia trachomatis infection in the development of ovarian cancer.[62] Wong et al[63] stated that, although chlamydia trachomatis inflammation may contribute to the development of ovarian cancer, chlamydia is a common pathogen in the genital area, and it is difficult to determine the exact relationship between the two. Merritt et al,[64] in a case-control study in 2008, had an opposite view, and stated that chronic inflammation has no role in the development of ovarian cancer. Lin et al[65] reported that there is a link between PID and ovarian cancer (HR=1.92 [1.27–2.92]). In a cohort study, Rusmussen et al[66] reported that inflammation associated with serous ovarian cancer is not associated with the risk of other types of ovarian cancer. The result of another case-control study suggested that, although there is a relationship between pelvic inflammatory disease (PID) and ovarian cancer, this risk is higher in the cases of recurrent PID (OR=1.88 [1.13–3.12], $P=0.014$).[67]

Endometriosis

The relationship between endometriosis and ovarian cancer has been shown in various studies through various mechanisms. The results of a cohort study showed that, in people with endometrium, aging, living in urban areas, low or high income, depression, pelvic infection, and lack of childbearing increase the risk of ovarian cancer.[68] In 1925, Sampson[69] proposed a link between endometriosis and ovarian cancer based on the theory of malignant changes of endometriosis. Inflammation and

the PTEN, CTNNB1 (β-catenin), KRAS, microsatellite instability, and ARID1A genes are involved in the occurrence of endometriosis-associated ovarian cancer.[70] THe results of a cohort study showed that endometriosis increases the risk of ovarian cancer (SIR=1.34 [1.16–1.55]) and this risk is higher in endometrioid (SIR=1.64 [1.09–2.37]) and clear cells (SIR=3.64 [2.36–5.38]).[71] Compared to other types of ovarian cancer, endometriosis-associated ovarian cancer is detected at a younger age and lower stages.[70] Melin et al[72] stated that, although endometriosis increases the risk of ovarian cancer (SIR=1.43 [1.19–1.71]), hysterectomy may have a protective effect against ovarian cancer before or at the time of endometriosis diagnosis. Stewart et al,[73] in a cohort study, stated that nulliparous women with endometriosis are 3-times more likely to develop ovarian cancer (HR=3.11 [1.13–8.57]). They stated that, although hysterectomy plays a protective role against ovarian cancer, unilateral oophorectomy/salpingo-oophorectomy without hysterectomy increases the risk of ovarian cancer by 4-times (HR=4.23 [1.30–13.77]). Erzen and Kovacic[74] believed that the relationship between endometriosis and ovarian cancer is affected by the age of the patient. The incidence of epithelial ovarian cancer in women with endometriosis rises from 4.99 in less than 30 years to 35.81 in more than 50 years per 10,000 people per year.[75] In a case-control study, researchers concluded that hyperestrogenism or exogenous is a risk factor for the onset of ovarian cancer after endometriosis.[76] Cottreau et al[77] believed that the use of danazol for the treatment of endometriosis is associated with a 3.2-times increased risk of ovarian cancer [1.2–8.5]. They stated that there is no such a risk in the consumers of leuprolide/nafarelin.

Ovarian cysts

Some types of benign ovarian cysts may act as a precursor of malignant ovarian tumors. According to a case-control study, ovarian cyst is associated with increased risk of borderline ovarian tumors (OR=1.3 [0.9–1.8]), and this risk increased among women who were undergoing surgery.[78] In addition, complex ovarian cysts significantly increase the risk of malignancy in postmenopause.[79] However in another study, complex cysts in postmenopausal women were not the immediate precursors of ovarian cancer.[80] Crayfold,[81] in a cohort of women, indicated that

removal of ovarian cysts was not associated with a decrease in ovarian cancer related mortality.

Tubal ligation

The risk of ovarian cancer was reduced in women with tubal ligation.[82–85] In a cohort study, tubal ligation was associated with a 20% reduction in risk of high-grade serous carcinoma.[86] Women with tubal ligation have a decreased risk of invasive serous cancer (19%), invasive mucinous cancer (32%), clear cell cancer (42%), and endometrioid cancer (52%).[82,85] No association was found between tubal ligation and low-grade serous tumors.[82,86] Younger age at tubal ligation was not associated with increased protective effects of this method.[82] A mechanical barrier for carcinogenic agents can reduce ovarian cancer after tubal ligation.[87]

Hormonal factors
Contraceptive methods

Results of most studies indicate that the use of oral contraceptive methods is associated with a reduced risk of all histological types of ovarian cancer.[36,51,88,89] Results of a case-control study in Canada indicated that the use of hormonal contraceptive pills is associated with a significant reduction in all histological types of epithelial ovarian cancer, except for mucinous tumors. According to the findings of this study, OR for each year of use of these pills was 0.89 [0.85–0.93] for non-mucinous tumors and 0.98 [0.93–1.04] for mucinous tumors.[53] The result of a case-control study showed that oral contraceptive pill (OCP) decreases the risk of fatal and advanced ovarian cancer compared to less advanced cases.[34] Royar et al[89] stated that, each year, use of combined oral contraceptive pills reduces the risk of ovarian cancer by 7% (OR=0.93 [0.90–0.96]), and this reduction is more pronounced during the first use at the age of less than 25 years. Although there is an inverse relationship between the time of using hormonal contraceptive pill, the age of its use, and the risk of ovarian cancer, the duration of consumption is more important.[51,59] This risk reduction can persist for up to 10–15 years after the discontinuation of pills,[90] however the protective effect of oral contraception has not been proven in many studies.[50] In a case-control study, no relationship was found between the use of contraceptive methods (except for tube ligation) and the risk of ovarian cancer.[37]

Hormone replacement therapy (HRT)

The result of a case-control study showed that combined estrogen-progesterone therapy after menopause does not increase the risk of ovarian cancer.[91] Hempling et al[92] examined the effect of exposure to post-menopausal hormone therapy, and stated that HRT is not associated with ovarian cancer, even in long term use. However, Glud et al[93] stated that oral hormone therapy is associated with an increased risk of ovarian cancer in people who have not previously had a hysterectomy. Researchers believe that the use of estrogenic methods, especially for 10 years or more, is associated with an increased risk of ovarian cancer.[94] The result of a case-control study showed that, although hormone therapy with estrogen alone increases the risk of ovarian cancer, it has no significant effect on the survival of the patient.[95] Rossing et al,[91] in a case-control study, stated that the progesterone component of a combined hormone therapy reduces the risk of ovarian cancer. Mørch et al[96] believed that, regardless of the duration of use, formulation, estrogen dose, type of regimen, type of progesterone, and method of use, hormone therapy is associated with an increased risk of ovarian cancer.

Infertility treatments

Ovarian cancer is a rare and, at the same time, a fatal disease. Regardless of infertility treatments, nulliparity itself[97] and infertility are risk factors of ovarian cancer, so it is difficult to investigate the relationship between infertility treatment and ovarian cancer. The "incessant ovulation theory" states that ovulation without interruption can contribute to the development of ovarian cancer by damaging the ovary epithelium, and, therefore, any factor that contributes to the reduction of ovulation can have a protective effect against ovarian cancer.[40] Several studies have indicated an association between the increased risk of ovarian cancer and the use of clomiphene citrate[98] and gonadotropin.[99] The results of a cohort study showed an increase in ovarian cancer after exposure to clomiphene citrate, and indicated that the risk of ovarian cancer increases with increasing dosage of clomiphene citrate among nulliparous women.[98] The results of a case-control study indicated that the use of ovulation-inducing drugs, especially hMG, increases the risk of epithelial ovarian tumors.[100] Although several studies have suggested a relationship between the risk of ovarian cancer and the use of ovulation-inducing drugs, this risk was not significant in many studies.[46,101–105] In a cohort study of 54,362 women, Jensen et al[106] reported that the risk of ovarian cancer does not increase with the use of clomiphene citrate, gonadotropins, human chorionic gonadotrophin, and gonadotrophin releasing hormone, and there is no relationship between duration of use, duration of follow-ups, or pregnancy. Brinton et al (2001)[99] suggested that an increased risk of ovarian cancer among people who take ovulation-inducing drugs requires a more attention to the choice of individuals.

Genetic factors
Family history

The most important risk factor for ovarian cancer is a family history of breast or ovarian cancer.[9] Personal history of breast cancer is associated with an increase in the risk of ovarian cancer (OR=3.7 [1.8–7.7]).[107] The results of a case-control study showed that the risk of ovarian cancer increases in women with a family history of breast, uterine, or ovarian cancer in their mother or sister ($P<0.001$).[37]

BRCA mutations

More than one-fifth of ovarian cancers are due to mutations in tumor suppressor genes,[108] and 65–85% of inherited ovarian tumors result from germline mutations in *BRCA* genes.[109] Although the risk of ovarian cancer in carriers of *BRCA1* and *BRCA2* mutations is less than 3% by the age of 40, this risk increases to 10% by the age of 50.[12] The 10-year risk of developing ovarian cancer in individuals with breast cancer is 12.7% and 6.8% in the carriers of *BRCA1* and *BRCA2* mutation.[12] Cumulative risk of ovarian cancer up to the age of 80 is 49% in *BRCA1* mutation carriers and 21% in *BRCA2* mutation carriers.[110] About 25% of breast cancer deaths in stage I are due to the occurrence of ovarian cancer.[111] Salpingo-oophorectomy in BRCA-positive individuals reduces the risk of ovarian cancer by 75%.[112] Since, most epithelial cancers originate from the fallopian tube, salpingectomy decreases the risk of ovarian cancer by 35–50%.[113]

Lynch syndrome

Lynch syndrome is an autosomal dominant cancer predisposition syndrome that is responsible for 1–3% of all colorectal cancer.[114] Lynch syndrome is responsible for 10–15% of the total inherited ovarian cancer cases,[115] and the lifetime risk of this cancer in individuals with a family history of Lynch syndrome is 6–8%.[116] Most of the ovarian cancers associated with Lynch syndrome are non-mucinous, and 82–84% of them are in stage I or II.[115] Lynch occurs due to a hereditary mutation in one of the four mismatch repair genes (*MHL1*, *MSH2*, *MSH6*, and *PMS2*),[12] and *MSH2* and *MLH1* are the most common mutations in these individuals.[117] The most common

types of ovarian cancer in these individuals are endometrioid and clear cell ovarian cancers.[116]

Lifestyle factors

Nutrition and diet

According to the findings of a case-control study, there is a positive correlation between daily intake of fish and the risk of ovarian cancer ($P<0.05$), and this correlation is negative for daily intake of milk ($P=0.05$).[37,118] Results of a case-control study showed that the risk of ovarian cancer is associated with a higher cholesterol intake (OR=1.42 [1.03–1.97]), and this risk is reduced by consumption of vegetables (OR=0.77 [0.60–1.04]), vitamin supplement (OR=0.49 [0.30–0.81]), beta-carotene (OR=0.31 [0.11–0.91]), and B-complex vitamins (OR=0.61 [0.36–1.05]).[119] McCann et al[120] refer to the protective role of phytoestrogens in the development of ovarian cancer, and believe that a plant-based diet plays an important role in the reduction of hormone-related cancers.[120,121] The results of a case-control study showed that saturated fat is associated with an increased risk of ovarian mucinous tumors.[53] Ong et al[122] revealed that an increased concentration of vitamin D in plasma may reduce the risk of ovarian cancer. This risk reduction is also seen in the case of calcium and lactose consumption.[118]

Obesity and physical activity

The results of a study showed that obesity reduces the risk of survival in ovarian cancer (HR=3.40 [1.16–9.99]), and increases the risk of death caused by the disease (HR=0.58 [0.35–0.96]).[123] Central adiposity is associated with an increased risk of ovarian cancer, indicating the conversion of androgen in the peripheral tissues.[124] Rodriguez et al[125] reported a 36% increase in the risk of ovarian cancer among obese people who have never used postmenopausal estrogen treatment, and stated that obesity and tallness increase the mortality of ovarian cancer. Anderson et al,[126] in a cohort study, reported that waist–hip ratio is associated with an increased risk of ovarian cancer (RR=1.59 for high quartile vs low quartile [1.05–2.40]). However, Kotsopoulos et al[127] stated that height, weight, and adiposity are not related to the prognosis of ovarian cancer. Beehler et al[128] believed that the relationship between obesity and risk of ovarian cancer is related to menopause condition. Beehler et al,[128] in a case-control study, showed that obesity before menopause is associated with an increased risk of ovarian cancer (adjusted OR=2.19 [1.49–4.04]), although it is not associated with the risk of ovarian cancer at post-menopausal age. Leitzmann et al[129] suggested that obesity, with its hormonal mechanism,

increases the risk of ovarian cancer and, in addition to that, increases the mortality of affected individuals.[38] On the other hand, researchers in a case-control study concluded that physical activity is associated with a reduction in the risk of ovarian cancer.[130] However, this result has not been confirmed by other studies,[131,132] Anderson et al[126] stated that leisure-time physical activity is associated with an increase in the incidence of ovarian cancer (RR=:1.42 for high activity vs low activity [1.03–1.97]).

Alcohol, caffeine, and cigarettes

Several researchers around the world believe that alcohol does not increase the risk of ovarian cancer,[46,133–137] but Goodman and Tung[138] argue that alcohol's relation to ovarian cancer is related to the type of alcohol. Schouten et al[139] believed that drinking alcohol in the form of wine, beer, or liquor is not associated with an increased risk of ovarian cancer. However, the result of a case-control study showed that caffeine and coffee consumption may increase the risk of ovarian cancer in women before menopause.[135]

Although many researchers believe that cigarette smoking does not change the risk of ovarian cancer in women before and after menopause,[135,140] Jordan et al[141] state that smoking a pack of cigarettes daily for 20 years is associated with a doubled risk of benign mucinous tumors, borderline tumors, and malignant tumors (OR=2.7 [1.6–4.4] for benign tumors, OR=2.7 [1.7–4.4] for borderline tumors, and OR=2.1 [0.9–5.0] for malignant tumors). Gram et al,[142] in a cohort study, showed that the length and amount of smoking increases the risk of borderline tumors. Kim et al[38] believed that smoking increases the risk of death in people with ovarian cancer by up to 25% (HR=1.25 [1.01–1.54]). Marchbanks et al[143] stated that, although smoking increases the risk of epithelial mucinous tumors (OR=2.9 [1.7–4.9]), it is not associated with other histological types of ovarian cancer. This result has also been confirmed in other studies.[46,52,136,144–146] The age at smoking onset is not associated with the risk of ovarian cancer.[147]

Other

Lactation

Researchers have reported an inverse relationship between the duration of breastfeeding, the number of breast-fed children, and the risk of ovarian cancer.[50,148] Results of a case-control study showed that lactation reduces the risk of ovarian cancer by 22% (OR=0.78 [0.64–0.96]), and this risk decreases with longer lactation period (OR=0.56 [0.32–0.98] for 18 months average duration of breastfeeding

vs none). In this study, the most risk reduction was related to endometrioid and clear cell ovarian cancers.[149] Tung et al[36] were also in agreement with the views of other researchers, and stated that the duration of lactation reduces the risk of non-mucinous tumors (OR=: 0.4 for the highest vs the lowest quartile). However, there was no such a protective effect against mucinous tumors in this study.

Socioeconomic status

The socioeconomic status is one of the predictors of incidence and survival of ovarian cancer.[150] Access to healthcare,[151] patient awareness about the symptoms of ovarian cancer, timely response to symptoms, lifestyle, and underlying illnesses justify the link between socioeconomic status and ovarian cancer.[152] The result of a case-control study showed a negative relationship between educational level and the risk of ovarian cancer.[153] In the Brewster et al's [154] study, a weaker social status was associated with the more advanced illness.

Conclusion

The aim of this study was to review the epidemiological aspects and the risk factors of ovarian cancer in the world. Ovarian cancer, as one of the major gynecological cancers, kills many women around the world, and this mortality varies from country to country. The findings of this study showed that various factors affect the occurrence of ovarian cancer, from which genetic, environmental and lifestyle factors are among the most important ones. Many factors such as pregnancy, lactation, and oral contraceptive pills play a role in reducing the risk of this disease.

Disclosure

The authors report no conflicts of interest in this work.

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