Risk Factors for Ovarian Cancer: A Literature Review

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Abstract

Ovarian cancer is the third type of gynecologic cancer in terms of prevalence after cervical and uterine cancer. The disease is known as the silent killer as it is slowly spread without a diagnosis, which leads to the worst prognosis and high mortality rate. Libya shows low disease incidence while the high mortality rate is seen in developed countries due to a lack of proper diagnostic and treatment options. This research aims to understand the various risk factors of ovarian cancer described in literature. Based on the literature review related to various factors which are the demographic, reproductive history, hormonal factors, genetic factors, lifestyle such as diet and BMI. Various controversial in literature exist on the effect of these factors and their association with risk factors.

Keywords: *Ovarian cancer, Risk factors, conceptual, literature review.*

Introduction

Background: Ovarian cancer is the fifth leading cause of death from cancer in women aged 35-74. An approximate one in 78 women would develop ovarian cancer in the course of their lifetime. The American Cancer Society predicts there will be about 22,280 additional ovarian cancer cases diagnosed by the year 2020, and more than 14,240 people will die from ovarian cancer. The five-year survival rate is over 90 percent when women are diagnosed and treated in the early stages. Owing to the non-specific signs of ovarian cancer and the lack of early detection testing, about 20 percent of all cases are detected early, either in stage I or II. The survival rate may be as low as 28 percent if caught in stage III or higher. Each woman diagnosed with ovarian cancer has a different profile due to the nature of the disease, so it is difficult to provide a general prognosis[1].

In Libya, the number of cancer cases increased from 12.7 in 2008 to 14.9 million in 2012[2]. According to the[3], the significant cases are of breast cancer, representing 11.7 % of the cases. The number of cases in 2019 reached 6308, and the number of death due to cancer is 3375. It is significantly important to understand cancer types, distribution, and risk factors in order to provide insights to protect communities and individuals. Ovarian cancer is one of the most severe types of cancer. The primary issue of ovarian cancer is that it is considered a silent disease as early detection is viewed as a challenge. This is the reason many types of research try to examine the risk factors in order to help make the early association of the disease in susceptible individuals. In this research, we aim to provide a quantitative approach in order to generalize an understanding of the risk factors of ovarian cancer in women in Libya.

According to[4], Ovarian cancer is considered the seventh most commonly diagnosed cancer among women worldwide. In Libya, ovarian cancer accounts for 4.6 % of cancer affecting women, according to the International Agency for Research on Cancer, 2018. May risk factors are associated with ovarian cancer, such as obesity, use of fertility medication, long ovulation cycles throughout life due to lack of children. Some elements showed to reduce the risk of ovarian cancer, such as breastfeeding, pregnancy, and the use of oral contraceptives [5]. The majority of the cases is related to family history through inheritance of mutated autosomal dominant gene [6].

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Ovarian cancer is considered one of the most types of cancers affecting women in the world. The incidence of ovarian cancer increased to reach 4.6 % in 2018. The disease does not show symptoms in the early stage, but it becomes symptomatic when it has already spread to other parts of the body. Screening for the condition is not practical due to false-positive, which may lead to unnecessary surgical procedures. Understanding the risk factors is essential to help educate the women community about the risk factors and preventive measures in order to reduce the incidence of the disease and get an earlier diagnosis to provide a better prognosis. This paper aims to provide a review of literature of the various risk factors for ovarian cancer. Among the risk factors examined in the study are awareness, obesity, nature of the diet, ovulation information such as the age of menarche and age of menopause, pregnancy, breastfeeding, use of oral contraceptives, and family history. Scholars have controversial opinions about these risk factors and associations with ovarian cancer.

Literature Review:

Theoretical Framework: It allows for formal theories to be contextualized and for research to help choose the research design and analysis plan [7,8].

Incessant Ovulation Theory: The constant theory of ovulation reveals that ovulation traumatizes the ovarian surface, as the breakdown of follicles leads to rapid repair and damage to the ovarian surface epithelium. The process of continuous damage to the injuries and the proliferation of the ovary surface's epithelium places strain on the ovary cells, thereby increasing the risk of the reverse transcription[9,10]. Often a hundred years ago, women had several children, and ovulation was often hindered by pregnancy and lactation. Scientific evidence of a reduction of the risk of epithelial ovarian cancer by pregnancy or oral use of hormonal contraceptives by using a decreasing number of life - long ovulations. For women with and without ovarian cancer, an essential correlation between high overall ovulation and cancer was found when calculating the total lifetime ovulation number. There are also reports that in some instances of infertility, such as polycystic ovarian syndrome, people are highly at risk for developing ovarian cancers[10–12]

Gonadotrophin Theory: The gonadotrophins theory notes that prolonged exposure to gonadotropin enhances the oestrogen production of ovarian surface epithelium and may contribute to malignant transformation. Gonadotrophins can either directly affect ovarian surface epithelium, enhance transformation, or indirectly encourage the production of estrogen [10]. The rates of gonadotrophin are increasing with age and exceptionally high in menopause, in line with the age-specific ovarian cancer rate. Pregnancy and the oral contraceptive pill are lower circulating levels of pituitary gonadotrophin[13,14], although significant increases in oestrogen and human chorionic gonadotrophin (h CG) levels are observed during pregnancy[13,14]. Females with polycystic ovary syndrome seem to have a low follicle stimulant hormone and high luteinizing hormone and an elevated risk of ovarian cancer, thus supporting a gonadotrophin theory at the expense of an incessant ovulation hypothesis. Some epidemiological evidence disputes the theory of gonadotrophin. Breastfeeding women have higher Follicle-stimulating hormone levels, but evidence indicates that breastfeeding is preventive [15]. On the other hand, there has been evidence of lower rates of gonadotrophin in some ovarian cancer patients and of a higher risk of developing cancer for women with a specific low circulating gonadotrophin [10].

Hormonal Theory: The hormonal theory partly seeks to solve such conflicts and suggests an increase in the risk of cancer due to excess androgen stimulation of ovary cells. In contrast, a progesterone stimulation of the cell surface protects the cancer formation[13,14]. Androgens are produced by the ovary at a higher rate than estrogens by the developing follicles and the primary sexual steroids within the follicle fluid. It was suggested to expose cysts of epithelial incorporation found close follicle formation to elevated androgen rates. The only progestin pill that does not inhibit ovulation reduces ovarian cancer's chance to the same or higher level than the combined contraceptive pill. Progesterone levels remain high during pregnancy, and the concentrations of the dwarf circulating androgens are high. Pregnancy protection has been suggested to be consistently high in progestin levels over the course of 8-9 months, rather than by suppressing ovulation[10].

The Inflammation Theory: The ovular cycle is an inflammatory response that is strongly correlated with the invasion of leucocytes and the development of inflammatory intermediaries such as cytokines. The ovary surface epithelium cells in the surface proliferate when the pre-ovulatory follicles expand to support the changing follicle and then cell death, as the follicle wall is thin. A significant stage in the development and metastatic expansion of every tumour is the extracellular matryl proteolytic (ECM). The breakdown of the ova

and the release of the ovum leads to an increase in progesterone synthesis in ovular granulose cells, now free from paracrine control. Progesterone production around ovulation helps to maintain the completeness of DNA in the damaged ovary cells in the apoptosis wave and pre-ovulation fragmentation of DNA. Cortisol could be involved in the control of ovulation-borne inflammations. The infection can block an endogenous ovary inflammatory reaction and inhibit ovulation, causing an acute inflammatory response. These anti-inflammatory agents are thought to operate through a shared pathway based on the suppression of gene transcription factor activity, which may, after that, decrease transcript of growth factors, chemokines, and proteases, including cyclooxygenase (COX)-2, VEGF, and various interleukins and chemical chemokines. It can stimulate cell proliferation, invasion, and cell death resistance [10].

Discussion

Risk factors for ovarian cancer

Demographic Factors: Ovarian cancer is considered among scholars to be anage-related disease. The disease usually happens after menopause. According to[16,17], It indicates that ovarian cancer incidenceis more common in women over 65 years of age. Based on many studies,[18,19] indicate that the average range of ovarian cancer diagnosis among women is between 50 to 79 years. Another study also associates another factor to age: the prognosis or treatment outcome studies indicate treatment at a younger age can lead to better prognosis[18–20]. Scholars contribute to the notion that older patients receive less aggressive treatment than younger patients [21]. The age factor in prognosis is still controversial; other studies, such as [22], indicate no correlation between age and prognosis [22].

Socioeconomic Status: Socioeconomic status is sometimes viewed as one of the predictors of ovarian cancer[23]. The socioeconomic status has an indirect effect on the diagnosis and prognosis of ovarian cancer, as high social and economic status is related to increased patient awareness of symptoms, lifestyle, time of response to symptoms, and health care access to the diagnostic and treatment facilities[24,25]. A study done by[26]showed a negative relationship between educational level and the risk of ovarian cancer in a case-control study. In another study by (27) showed that low social status is linkedto more advanced illness.

Reproductive History

Menstrual-related factors: The association between the number of ovulation cycles and the risk of development of ovarian cancer is well established in the literature. A controlled study done by[28] indicated an inverse relationship between the number of ovulation cycle and the chance of development of ovarian cancer; the study indicated that if a woman did not have ovulation cycles for 7 or 8 years, it decreased the risk by 4 times [28]. The findings are supported by incessant ovulation theory. Other research uses these theories as to the base of protective measures, as any factors that reduce ovulation such as pregnancy and the use of oral contraceptives. Still, some controversy among scholars as a lack of ovulation caused by menstrual disorders is associated with an increased risk of ovariancancer [29].

Some of the risk facts for ovarian cancer are connected to the ovulation time during the female lifetime. The longer the ovulation time, the higher the incidence of ovarian cancer occurrence. The ovulation time is prolonged in case of the absence of children and pregnancy and breastfeeding as ovulation pauses during pregnancy and sometimes lactation. According to[5], not having children doubles the risk of developing ovarian cancer [5]. Other researchers, such as [30], indicate that the longer the ovulation period in the female lifetime, the higher the chance of ovarian cancer. The ovulation time can be extended by early menstruation and late menopause [30].

Age of menarche and menopause: Although the result of some studies showed a relationship between the early onset of menarche and the risk of ovarian cancer[31], other researchers reported that the age of menarche and menopause does not affect the risk of ovarian cancer[32]. Menopause also is associated with this type of cancer, and the connection is more reliable. According to[33], there is a direct correlation between menopause in late age and increased risk of ovarian cancer [33,34]. Another factor is the number of menstrual cycles in a lifetime, and this factor shows no impedance association with ovarian cancer as it is always associated with other factors [6].

Many studies support the notion that pregnancy provides protection against ovarian cancer; examples are[13,35]. The nature of pregnancy and delivery also plays a role in the risk of development of ovarian cancer.[36] performed a case-control study to understand the effect of various pregnancy criteria and their contribution as

a risk factor for ovarian cancer. The study indicated that both natural childbirth or induced abortion and the number of pregnancies decreased ovarian cancer risk [36].

Age at childbirth: The women's age at childbirth is also considered as a factor that affects ovarian cancer development. A study done by[11], The study postulated an inverse relation and the risk of ovarian cancer, and the study indicated that the older age in pregnancy, the lower the risk of ovarian cancer[11]. These findings are well supported in other studies' literature[35,37]. The studies indicated that the increase of 5 years at the first childbirth decreases the risk of ovarian cancer by 10%[38].

Hormonal factors:

Contraceptive method: The role of oral contraceptives in reducing the risk of ovarian cancer is established in the literature. Many studies support this postulation, such as[37,39]. According to [36], in a case-control study in Canada, the study proved the role of hormonal contraceptive pills in the reduction of all histological types of epithelial ovarian cancer, except for mucinous tumors[16,36]. The study also indicated that with each year's use of oral contraceptive pills by 7%[36]. The length of use of oral contraceptives is also an essential factor, and The reduced risk can continue for up to 10–15 years after the cessation of pills[37,40].

Similar to most of the risk factors of ovarian cancer, controversy about the role of oral contraceptives in reducing ovarian cancer is also documented in various studies. According to [41,42], The study indicated no relation between the use of contraceptive method and the risk of ovarian cancer[41,42].

Hormone replacement therapy (HRT): The hormonal replacement therapy is done after the age of menopause, where estrogen-progesterone (female hormones) replaces natural body hormones, which stops during the age of menopause, The aim is to reduce menopausal symptoms, such as hot flashes and vaginal discomfort[43].

Many studies investigated the effect of hormonal replacement therapy on the risk of developing ovarian cancer. Some studies indicated that the combination of estrogen-progesterone therapy after menopause does not increase the risk of ovarian cancer even in long-term use[44]. The great controversy is associated with hormonal replacement therapy as a risk factor. Some studies indicated an increased risk of developing ovarian cancer, especially with estrogen use. The duration of the therapy is also a factor; more than 10 years of use of estrogen may increase the risk of ovarian cancer. While according to[45]. The risk of ovarian cancer increases regardless of the type of medication (estrogen or progesterone), duration, method of use, or dosage. All factors may be associated with an increased risk of developing ovarian cancer[45]. Many studies support this postulation. According to[46], oral type of hormone therapy may be linked to an increased risk of ovarian cancer in women who did not receive a hysterectomy[46]. Estrogen alone is linked to an increased risk of ovarian cancer[47], while the combination of estrogen and progesterone reduces ovarian cancer risk [44].

Use of Infertility treatments: Infertility treats increase ovulation, which, based on "incessant ovulation theory,"leads to an increased chance of developing ovarian cancer [9]. Many studies support this postulation; still, the overall results are controversial. The hormones used in fertility mediations are used to stimulate the ovaries to produce ova and hormones to increase the change of pregnancy. The use of fertility drugs is associates with a risk factor for developing ovarian cancer. According to [48], the connection between the use of fertility hormones and ovarian cancer is controversial [48]. They may be associated with devolving borderline tumors. Other scholars, such as [49], argue that the use of fertility medicine has no association with ovarian cancer. The association between fertility medicine and borderline ovarian cancer is also not confirmed[6]. However, numerous studies prove the association between some of the infertility treatment drugs and ovarian cancer. Drugs such as clomiphene citrateand gonadotropin are proved to increase ovarian cancer risk in a cohort study, and the result worsens with the dose increase[50]. Other drugs, such as Menotropin, produced similar results[51].

Lactation: The relation between breastfeeding and the development of ovarian cancer is inverse in nature. According to [52], the risk of developing ovarian cancer decrease by 8 % with every five months of breastfeeding.[6,52]. The relation between lactation in terms of duration, number of children, and the chance of development of ovarian cancer is inverse in nature [53]. According to [54], the study indicated a decrease chance of ovarian cancer by 22% in the case of lactation and lactation duration of an average of 18 months. The documented reduction of risk is related to two types of endometrioid and clear cell ovarian cancers[54].

Genetic Factors:

Family History: Family history is the most critical risk factor in the development of ovarian cancer. According to [5], the case of ovarian cancer is genetic in 5–10% of the cases. The reason is that genetic mutation and gene abnormalities are passed through families using autosomal dominant genes, which means that the female is likely to present symptoms of the diseases even if she got the gene from only one parent[55,56]. Another factor is linked to ovarian cancer, which is the female history of breast cancer and uterine cancer, which has been linked to increased incidence of ovarian cancer in many studies such as[57].

BRCA Mutations: The increased risk scarily for families, which shows Hereditary breast-ovarian cancer syndrome, which is represented in two types BRCA-1 and BRCA-2, both entails genetic abnormalities. According to [58,59], the genetic mutation in the syndrome increases the risk of both breast cancer and ovarian cancer in families [58,59]. The risk is amplified at the age between forties and fifties years of age. The risk is between 30- 60 %[48,58,59]. In the case of BRCA1, the risk of development of ovarian cancer is between 15- 45%, while in the case of BRCA2, the risk is reduced to 10-40%[59].

A study done in the united states shows that the chance of developing ovarian cancer if one of the first-degree relatives was diagnosed with the disease in five in one hindered. The risk would increase to seven in a hundred if the women had two relatives diagnosed with ovarian cancer[6,58].

Lifestyle Factors:

Nutrition and Diet: Diet and nutrition are essential factors in a personal lifestyle that significantly affects the general health condition of the individual. Similar to all the risk factors associated with ovarian cancer, Diet and nutrition are also provide controversial findings among the studies. The nature of food is believed to be an essential factor in the development of many diseases, including ovarian cancer. In a study done by[60], a positive correlation between the risk of ovarian cancer and daily consumption of fish, while the negative correlation with a daily intake of milk[60]. Other studies associate ovarian cancer with higher cholesterol intake and reduce vegetable consumption[13].

The link between diet and ovarian cancer development is established through ecological studies that determined the correlation between the two variables. The nature of food is a contributing factor in ovarian cancer. According to[61,62], some foods are associated with an increased risk of ovarian cancer, such as meat and certain fats, while foods such as vegetables and fruits showed decreased risk in relation to ovarian cancer. Also, some micronutrients (vitamins and minerals) are associated with a reduced risk of developing ovarian cancer [61,62]. The number of carbohydrates in the diet also hasan influence on increasing the risk of developing ovarian cancer. However, the association is not actively supported. It is open for debate among scholars; according to [56,63], the effect of the carbohydrate is through the glycaemic index (GI) and glycaemic load (GL);glycaemic index refers to the food ability to increase the amount of insulin present in the blood, while the glycaemic load deals with the number that the food will raise the blood sugar level [56,63]. The carbohydrates are ranked based on the glycaemic index and glycaemic load as it affects the blood insulin levels. And that depends on the nature and the degree of processing of the carbohydrate source[6].

Libya is one of the Mediterranean countries. The food pattern consumption in the mediation region is different from any other part of the world, which leads scholars to study these patterns, and it is an effect on the lifestyle and disease occurrence. The Mediterranean diet is one of the recommendations by the [64] to help reduce blood glucose levels and blood pressure as well. The Mediterranean diet plan is based on increased consumption of foods rich in long-chain n-3 fatty acids and monosaturated fats, mostly present in olive oil, which is an essential ingredient in the Mediterranean diet plan. The link between the use of such fats and diet plans is supported by some researches such as[6,65,66]. In Mediterranean countries such as Greece, Spain, and Italy, these studies indicate a low incidence of ovarian cancer in the Mediterranean region. That is contributed to the nature of the diet. Although many studies have examined the role of diet in ovarian cancer, the complete connection is not established, and it is suggested that the diet does not have a major impact on the incidence of ovarian cancer occurrence[6].

Obesity and physical activity: Factors as obesity and the nature of the diet are considered an enormous risk fact in developing ovarian cancer[59].

In general terms, obesity is a dangerous condition for general body health. An obese individual isat risk

of developing many conditions such as heart conditions, type 2 diabetes, high cholesterol, high blood pressure, and atherosclerosis, which may lead to coronary heart disease and stroke[67].

In relation to ovarian cancer, the effect of obesity is not an exception. Many studies indicated increased mortality from ovarian cancer in obese patients[68]. Many indications are used in studies as an indication of obesity, Body mass index (BMI), the waist-hip ratio is reported by[69]. However, controversy still exists as some studies, such as[14,70], only indicated the association between obesity and ovarian cancer prognosis and menopause condition. According to[70], that obesity before the age of menopause is associated with an increased risk of ovarian cancer[7014].

The apparent association between ovarian cancer and physical activities is not yet established. However, some studies, such as[71], suggest that the inverse correlation between physical activity and risk of ovarian cancer as increase physical activity reduces risk[71].

The effect of smoking, alcohol, and caffeine consumption: Smoking, in general, has an adverse effect on health. It is also believed to have similar effects as a risk factor in ovarian cancer, according toLeitzmann et al. (2009). The study linked long-term smoking up to 20 years with obesity as it leads to double the risk of ovarian tumors[72], while [13]associate smoking with increased mortality of ovarian cancer by up to 25%. While, many studies only link smoking to one type of ovarian cancer, which is mucinous epithelial tumors[73,74]. Alcohol is studied for its relation to ovarian tumors. Several researchers around the world believe that alcohol [75]. In a study by [76], both caffeine and alcohol are believed to increase the risk of ovarian mucinous tumors[76].

Conclusion

The review of literature indicated various risk factors for ovarian cancer that are related to various factors which are the demographic, reproductive history, hormonal factors, genetic factors, lifestyle such as diet and BMI. Various controversial in literature exist on the effect of these factors and their association with risk factors. The factors may differ based on the geographic location of the patient. The need for a comprehensive prediction model for the ovarian risk factors that can help predict disease incidents.

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