Chapter

Risk Factors for Ovarian Cancer

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Abstract

Ovarian cancers remain a perplexing group of diseases that continue to raise questions over their etiology and clinical behavior. They are the most fatal of gynecological cancers. Despite a global lifetime risk of only 1–2%, they contribute the highest mortality and the lowest 5-year (overall) survival rate of just 35%. The three broad histological groups: epithelial, sex cord-stromal and germ cell cancers have different biologic behavior and may constitute different clinical disease entities. Of the eight subtypes in the epithelial group, high-grade serous are universally the most common and have the worst prognosis. Globally making 65–85% of all ovarian cancers, most of the focus on risk factors has been directed on the epithelial group but the importance of other primary malignancies cannot be overemphasized as a step towards understanding their etiology and clinical behavior. The normal ovary has none of the epithelia that produce the range of epithelial ovarian cancers or there is an obvious premalignant stage, symptoms are very vague, screening and early diagnosis are difficult and indeed unrewarding. No specific etiology is known for any of the histologic groups. However, commonly mentioned risk factors like increasing age, genetics, nulliparity, prolonged infertility, use of fertility drugs, high animal fat, obesity, endometriosis, polycystic ovary syndrome, previous history of cancer, use of hormone replacement therapy, pelvic inflammatory disease and smoking may not apply to all the subtypes, while factors like increasing parity, breast feeding, use of oral contraceptive pills, hysterectomy, tubal ligation and use of antioxidants may differ in the degree of protection they provide. There may also be geographical and probably racial variations in the relevance of some of the risk factors. Thorough understanding of the predisposing and protective factors of the various histologic subtypes is an important step understanding the disease and therefore improving treatment outcome or providing effective prevention.

Keywords: risk factors, ovarian cancers, histologic subtypes, variation

1. Introduction

Ovarian cancer (OC) is an important public health problem with a lifetime risk of 1–2%. Recent estimates indicate that 295,414 cases are expected in 2018 with about 184,000 of victims dying from the disease [1]. This reflects an increase of over 54,000 cases in incidence and 32,000 cases in mortality compared with earlier figures [2, 3]. Public screening for ovarian cancer has been neither feasible nor beneficial due to a lack of most appropriate screening test for the range of malignancies produced by the ovary. Use of tumor markers is largely unreliable since different tumor markers are secreted by different histological varieties and up to 50% of early disease may be associated with insignificant rise of tumor markers [4, 5]. Besides tumor markers could be raised by non-malignant conditions as well

as other malignancies [6–8]. Cancers of the lung, pancreas, colorectal, breast and non-Hodgkin's lymphomas are associated with a rise in CA125 [9, 10] which is also raised in benign conditions such as endometriosis, ovarian cyst, leiomyoma uteri and pelvic inflammatory disease [4, 8, 11]. Only 50% of early OC is associated with raised CA125 making it unreliable for early diagnosis. More than 75% of OC are diagnosed in late stages of disease [12–14] when prognosis is very poor. Screening did not reduce mortality in two large trials [12, 15].

The ovaries are totipotential in their ability to form wide histologic varieties of cancers with different biology, natural history and possibly mechanism of onset [16–18]. These heterogeneous tumors differ in their clinical behavior including response to treatment and prognosis. Knowledge of the cause or genesis of OCs is very scant and the available hypotheses do not explain observed disease phenomena [19, 20]. The uniqueness of OC in having no known premalignant stage, no reliable screening tool, very vague symptoms in early and advanced stages make identification of at risk group important for prevention, early diagnosis and possibly as a step towards defining its etiology.

The World Health Organization classifies ovarian cancers based on histologic origins of the cells, as epithelial, sex cord-stromal and germ cell tumors [16, 21] (**Table 1**). The epithelial ovarian cancers are made up of eight histologic subtypes with different cellular origin, pathogenesis, gene expression and response to treatment [13, 16, 17]. The most common type, serous cyst adenocarcinoma with two distinct subtypes may be arising from the fallopian tube epithelium. The high grade serous accounts for 85% of the epithelial ovarian cancers and up to 80% of

Histological
I. Epithelial tumors
A. Serous cyst adenocarcinoma
B. Mucinous Cyst adenocarcinoma
C. Endometrioid
D. Clear cell (mesonephroid)
E. Brenner's
F. Mixed epithelial
G. Undifferentiated
H. Unclassified
II. Sex cord-stromal tumors
A. Granulosa
B. Androblastoma
C. Gynandroblastoma
D. Unclassified
III. Lipid cell tumors
IV. Germ cell tumors
A. Dysgerminoma
B. Endodermal sinus tumors
C. Polyembroyoma
D. Choriocarcinoma
E. Teratoma
F. Mixed tumors
V. Gonadoblastoma
VI. Soft tissues not specific to the ovary
VII. Unclassified
VIII. Metastatic

Table 1.
WHO histological classification for ovarian cancers.

ovarian cancers generally [22]. It is the most challenging in terms of treatment outcome. Mucinous adenocarcinomas have cells similar to the cervical epithelium, endometrioid cancer cells resemble the endometrium, while Brenners tumors have transitional epithelium akin to that of the bladder [19].

The fimbriated end of the fallopian tube has morphologic and molecular similarities with high grade serous ovarian cancers which also expresses TP53 signature suggesting that neoplastic process may be originating from tubal epithelium and shed into the ovary where aggressive neoplastic process proceeds [14, 19]. Low-grade serous ovarian cancers share similar histiogenesis but progress through a separate pathway and has different prognosis [18, 23, 24]. It represents less than 5% of the epithelial cancer [25].

The sex cord-stromal tumors are a heterogeneous group, which include several histologic subtypes (**Table 1**). Apart from adult granulosa tumor that affects women in their fifth decade, sex cord-stromal tumors mainly affect women in the second or third decade of life and account for about 5% of malignancies in women 15–24 years [26]. Several subtypes are associated with genetic predisposition, including in patients with Peutz-Jeghers syndrome [27].

The germ cell tumors, which include dysgerminomas, immature teratoma, embryonal tumors and endodermal sinus tumors form only 1.5–5% of OC. Approximately one-third are dysgerminomas, another third immature teratomas and a further one-third include the rest three (embryonal tumors, endodermal sinus tumors, choriocarcinoma and mixed cell types) [19, 28]. Malignant germ cell tumors of the ovary may be developing through similar pathways with testicular germ cell tumors but the ovarian have greater histological complexity than most solid somatic tumors.

This diversity in genesis may partly explain the observed differences in clinical behavior.

2. Hypothesis for ovarian carcinogenesis

Development of OC has remained a mystery since hypotheses advanced do not convincingly explain the observed phenomena. It is important to explain how other surface epithelia form aggressive primary neoplasm in a separate organ.

The 'incessant ovulation' theory explains that repetitive ovulatory micro trauma to the ovarian surface in association with the tubal epithelium results in carcinogenesis through mistakes in repair of the damaged surface epithelium [29, 30]. While this hypothesis partly explain serous cystadenocarcinoma, it fails to explain other subtypes in the epithelial group and does not offer plausible explanation for the germ cell tumors and the sex cord-stromal tumors.

The pituitary "gonadotropin hypothesis" indicates that high levels of estrogens and gonadotropins such as luteinizing hormone and follicle-stimulating hormone would over stimulate the ovarian epithelium causing increased proliferation and subsequent malignant transformation [31, 32].

The "inflammation hypothesis" proposes that factors such as endometriosis, pelvic inflammatory disease and other inflammatory conditions may stimulate cancer formation [31, 33].

These theories have failed to provide plausible genesis for ovarian cancer therefore new hypothesis have been proposed [19, 34].

Understanding a clear etiology is far from site, a thorough global analysis of the risk factors of the disease may be a good starting point to unraveling the etiology and therefore an effective strategy towards disease control and prevention. It is however expected that the range of tumors may very well differ in risk factors and epidemiology.

3. Predisposing factors

Predisposing and protective factors for ovarian cancers vary according to histologic type [13, 18]. Although most studies concentrate on epithelial ovarian cancers, particularly serous cystadenocarcinoma, which tends to form the major global disease burden, risk factors to other histologic types are important prerequisite to their genesis and will be considered in this review.

4. Racial and geographical risk

Ovarian cancer is a cosmopolitan disease as it occurs in every geographical location and in every race [1, 30]. Epithelial ovarian cancer is the commonest subtype all around the world with high-grade serous accounting for 60–85% of cases [22, 35–38].

Highest incidence of OC is found among white females in Northern and Western Europe and in North America with age adjusted incidence exceeding 8.4/100,000 [1, 30]. Recent statistics from the US show a decline in incidence from 16.6/100,000 in 1985 to 11.8/100,000 in 2018 [39]. Incidence is also high in New Zealand and among Jewish women in Israel but low in Africa and Asia with estimated rates of <3/100,000 [37]. Japan, though reported to have low incidence is experiencing a rising trend in the disease of recent [40].

All regions of North America show higher incidence of invasive ovarian cancer among white women [41].

Within Europe too, there is difference in incidence and mortality across the region. Using WHO data base of 28 European countries from 1953 to 2000, Bray et al. reported Nordic countries, Austria, Germany and the United Kingdom to have the highest trend in the 1960s but the trend tended to decline over the recent years while Southern European countries showed an upward trend. Similarly, central and eastern European countries with hitherto low incidence are experiencing a rising over time [12, 35] . In the most recent 5-year period (2003–2007), the incidence of ovarian cancer was highest in Eastern/Southern Europe, followed by Northern Europe, and Western Europe [22] Asian sub region reports lower rates than Europe and America [2, 3].

South Eastern Asia have highest rate in the subcontinent and Eastern Asia has the lowest rate.

Migration to areas of high risk increases the risk of disease therefore cultural and dietary factors may be responsible for the observed difference. Japanese immigrants to the US have equivalent risk as natives [42].Racial variations in the incidence of ovarian cancer are best observed in the USA. Age adjusted incidence rate are higher in whites than in non-whites and Indians in the USA have lowest mortality from ovarian cancer. While Caucasian Americans have higher disease incidence, African-Americans have 1.3 times higher disease mortality and lower survival rates even with equal access to care [43]. They also experienced poorer 5-year survival rates irrespective of stage of diagnosis [44, 45].

From the Surveillance Epidemiology and End Result (SEER)database (1992–1998), AA experienced a fall in 5-year survival rates from 47.9 to 40.3%, while their Caucasian counterparts witnessed an improved survival from 40.7 to 45% in the same period. The observed disparities have been linked to interplay of socioeconomic, environmental, genetic and epigenetic factors [43].

Determining the incidence of ovarian cancer in four US populations of heterogeneous racial-ethnic composition, Weiss and Paterson found 19–42% lower incidence among Japanese, Chinese, Hispano and black women compared with white women [44]. The observed difference is primarily due to lower rates of serous and papillary tumors. Chinese women also had decreased incidence of mucinous

tumors, while Hispano and black women had lower incidence of endometrioid-clear cell tumors.

The incidence of non-epithelial cancers remains fairly constant between the races; especially germ cell tumors which has remained stable in incidence for three decades [44]. However, data from SEER suggest that the incidence of sex cord-stromal tumors is significantly lower among white women compared with black women (0.18 *vs.* 0.35 per 100,000 person years; relative risk, 0.53; 95% confidence interval (95% CI): 0.42–0.67) [46].

OC rates from Africa though reported to be low must be considered in the background of health circumstances in the region of lack of cancer registries, poor utilization of health facilities and rudimentary statistics.

Ovarian cancer is reported to be more common in developed countries than developing nations but over the last three decades, ovarian cancer incidence has remained stable in high-risk countries, while an increasing trend has been reported in low-risk countries.

5. Age as a risk factor

Increasing age is a risk factor for ovarian cancer which is generally considered a disease of the older women. Globally, the annual incidence regardless of age is 42 cases/100,000 women. Data from US SEER, ovarian cancer is rare before the age of 40 years and incidence rises steadily after the fifth decade to reach a peak at 80–84 years, when the age specific incidence is 61.3/100,000 women. More than half of cases of ovarian cancers are diagnosed in women over 65 year [47].

In the United States, the annual incidence is 61.3 per 100,000 for women aged 75 and 79 years.

In the UK, the overall incidence of a symptomatic ovarian cyst in a premenopausal female being malignant is approximately 1:1000 increasing to 3:1000 at the age of 50 years although 1000 women under the age of 50 years develop ovarian cancer annually in the UK [48–50]. Most diagnose are other histologic subtypes like borderline tumors and germ cell tumors. EOC are generally reported to be uncommon in young premenopausal women in the UK [50]. Women aged 65 years and above make 64% of mortality from OC [47, 50]. Young premenopausal women are more commonly affected by germ cell tumors and borderline tumors in most reports from European literature [35, 51].

Similarly, a meta-database analysis of 5055 ovarian cancer patients of 4 prospective phase III intergroup trials identified 294 (5.8%) patients under the age of 40 years from European studies. Young age appeared a strong independent protective on overall incidence of EOCs as well as prognostic factor for PFS and OS [52].

The issue of age and ovarian cancer diagnosis may however be different among non-Europeans races. Reports from India show much younger age affected than most European papers for EOC. Murtha et al. reported increased risk after 35 years with peak at ages of 55–64 years. Saini et al. have reported mean age of 55 years Basu et al. had 48.8 ± 11.2 years while Mondel had 48 years and Jindal et al. had a mean of 48 years. Malik from Pakistan found mean age for EOC to be 49.5 ± 13 years [53–57].

Mostafa et al. from Egypt reported a mean age of 47 years for epithelial ovarian cancers, with 1% of cases affecting women of 30 years and only 3% occurring in older women of 70 years [58].

From African subcontinent, findings contradict increasing age as a risk factor for EOC as reports show young premenopausal women to be mostly affected with serous cystadenocarcinoma, which is the most common histiotype. There is increasing report of rising incidence of ovarian cancer from Africa [38, 59–61].

Most reports suggest EOC to be the commonest but predominantly seen in young premenopausal, generally parous women [38, 60, 61].

A global report by the International Federation of Gynecology and Obstetrics (FIGO) has noted that the highest incidence of ovarian cancer was moving towards a younger age group, although the majority of patients with epithelial cancer were more than 50 years in age [38].

It is interesting that high grade serous cyst adenocarcinoma remains the commonest variety while literature from USA, Europe, Israel and Australia find it in older women above 65 years, in Asia, the Arab world and Africa, it is observed in young premenopausal women. Research for this important difference is worthwhile.

Early menarche is considered a weak predictor of ovarian cancer risk and women whose menarche was earlier than 12 years are at increased risk of epithelial tumors [62, 63]. Meta-analysis of 22 case–control studies and 5 cohort studies has reported a statistically significant inverse association between menarcheal age and ovarian cancer risk (RR = 0.85; 95% CI: 0.75–0.97) [62], but this association is most significant in invasive serous and borderline tumors. In this respect, 'incessant ovulation' theory as possible cause of tumor genesis provides plausible explanation [30, 34]. No association was found when menarche begins after age 16 years. Late menarche has not been shown to be protective [64].

Women who experience natural late menopause are at increased risk [13, 34, 65]. Odds ratios for late natural menopause were reported as low as 1.19 and as high as 1.25 (95% CI: 0.95–1.49) [65]. These findings may suggest that earlier menarcheal age and late natural menopause might increase risk of ovarian cancer by increasing a woman's lifetime number of ovulations. Results from the Nurses' Health Study (NHS) confirmed increased risk of endometrioid epithelial cancers with late natural menopause but not of serous or mucinous cancers (RR = 1.3, 95% CI: 1.04–1.22). Furthermore, the European Prospective Study into Cancer and Nutrition Cohort (EPIC) age at menopause >52 years was associated with increased risk compared with 45 years or less [66].

6. Infertility and use of ovulation induction drugs

Infertility either by itself or in association with some of its causes like endometriosis, is a risk factor and prolonged period of infertility is associated with higher risk [67].

A large cohort study, involving 54,362 women with infertility in the Danish fertility clinics (1963–1998) used parity specific cancer incidence and reported significantly increased from infertility (1.46, 95% CI: 1.24–1.71) [68].

Whittemore et al. analyzed 12 US case–control studies between 1957 and 1985, with 2197 cases of ovarian cancer and 4144 controls and confirmed higher risk in nulligravid subfertile women compared with controls [20].

However, study by Ness with 5207 cases of ovarian cancer and 7705 controls found only a weak association between infertility and epithelial ovarian cancer (OR 1.16, 95% CI: 1.02–1.31) [69].

Drug treatment of infertility may further increase risk as untreated infertile nulliparous women have 1.5–2-fold risk, while women who received treatment and failed to conceive have even higher risk [70].

Use of ovulation induction agents like clomiphene citrate, gonadotropins are associated with three times higher general population [69] particularly prolonged use of clomiphene (for more than 12 cycles). This is associated with rise in risk for invasive and borderline cases by about 11.1-fold compared with infertile women with no clomiphene use [67].

Use of gonadotropins is also associated with increased risk [31, 70]. There are, however, a number of studies that show no increased risk of OC with use of ovulation induction agents [71].

However, studies that report increased risk do of borderline tumors only not high grade serous.

7. Genetic factors

More than one-fifth of OC cases are hereditary from highly penetrant autosomal dominant genetic susceptibility [72]. Although accounting for only a limited number of cases, heredity is a strong risk factor for OC. The lifetime risk of a woman who has a first degree relative with OC is 5% compared with 1.4% in a woman without. The risk rises to 7% if two members of the family are affected [73]. These rate has been thought to be a probable underestimate as a British study has shown that where two close relatives (not necessarily first degree) are affected, the risk may be as high as 30–40% [73, 74]. The risk for confirmed carriers of BRCA at the age of 70 may be as high as 63% [73, 75]. Ovarian cancer in a first degree relative, has been shown to be a strong positive indicator of early onset epithelial cancer and positively associated with non-mucinous tumors [76].

The three main clinical types of genetic ovarian cancers include site-specific, hereditary breast and/or ovarian cancer (HBOC) and hereditary non-polyposis colorectal cancer (HNPCC) or Lynch II syndrome [77].

The first two syndromes are related to inheritance of BRCA1 and BRCA 2. Patients with HNPCC have inherited mismatch repair genes (MLH1, MLH2, MLH6, PMS1, PMS2 and possibly some other yet unidentified genes).

BRCA genes are common in the Ashkenazi Jewish population where 29–41% of ovarian cancer is believed to be secondary to inheriting one of three founder mutations in *BRCA*1 and *BRCA*2, against 10% in non-Ashkenazim [78].

BRCA 1 gene is an oncosuppressor gene located at chromosome 17q, it participates in chromatin remodeling and crucial steps in cell cycle [79].

OC associated with BRCA mutations are diagnosed at a younger age and are of high-grade serous type. In one study, the average age at diagnosis of OC in BRCA1 and BRCA2 mutation carriers was 52 and 62 years, respectively [77, 80]. BRCA mutations do not seem to play a significant role in the development of mucinous or borderline ovarian tumors. The BRCA associated OCs also tend to have better clinical outcome with longer overall survival and recurrence-free interval than sporadic cancers [77].

There is no standard clinical definition of hereditary breast and ovarian cancer syndrome but affected families may be identified from:

- Several cases of breast cancer diagnosed before the age of 50 years.
- One or more cases with ovarian cancer in the family.
- One or more relatives with both breast and ovarian cancer.
- The presence of a BRCA1 or BRCA 2.
- However, many women without a family history may still have a gene mutation associated with their BRCA1 or BRCA 2.

Lynch syndrome (LS) or hereditary non-polyposis colon cancer (HNPCC) refers to germline mutations in MMR genes (*MLH1*, *MSH2*, *MSH6*, *MLH3* and *PMS2*),

which lead to the loss of expression of one of the MMR proteins. Clinically, LS is associated with higher risk of colorectal cancers that have specific predilection to location proximal to splenic flexure [72, 81]. Confirmed case of Lynch syndrome is associated with 6–10% life time risk of OC of early onset. MLH1 carriers are often diagnosed of ovarian cancer at average age of 52 years and MLH2 carriers at age of 45 years [82, 83].

HNPCC syndrome is also associated with cancers of the stomach, small bowel, hepatobiliary tract, pancreas, renal pelvis, ureter, breast, prostate and brain (particularly glioblastoma) [72, 84]. The OCs associated with LS are commonly endometrioid and clear cell varieties [82, 85] and tend to be diagnosed at a relatively early stage with high stage-specific survival rate compared with non LS type [86, 87].

The Li-Fraumeni syndrome is an autosomal dominant syndrome characterized by heterozygous germline mutation in TP53. It is the most frequently mutated gene in human cancer thus the syndrome is associated with development of multiple cancers at young age. About 50% will develop first tumor at age of 30 years [88] and up to 35% will develop multiple tumors in their lifetime [89]. Li-Fraumeni syndrome associated OC, though not the most common but tend to occur at around 39.5 years [90].

Peutz-Jeghers syndrome(PJS) is a rare autosomal dominant condition occurring in 1 in 25,000–30,000 livebirths [91] characterized by benign hamartomatous intestinal polyps with very low tendency to malignancy, cutaneous lesions increased risk of OC in addition to cancers of breast, colon, rectum, pancreas, stomach, testicles and lungs. Tumor suppressor gene STK11(LKB1), located on chromosome 19p13.3 is responsible for this syndrome. OC risk is as high as 18–21% [92]. The ovarian cancers associated with this syndrome are sex cord tumor with annular tubules (SCTATs) in addition to a range of other gynecological cancers [92, 93].

Mutations in double strand breaks repair system like *CHEK2, RAD51, BRIP1* and *PALB2* are also associated with increased risk of various types of ovarian cancer [89, 94]. To date, more than 16 genes are known to be involved in the mechanism of hereditary ovarian tumorigenesis and new ones are being discovered [77, 95].

8. Use of perineal talc

Talc, a metamorphic mineral composed of silicon, magnesium and oxygen, is a common component of genital powders. Applied by women for moisture absorption to prevent perineal chafing and rashes, talc has similarities to and co-occurs with asbestos in its natural form, which is a known carcinogen [96, 97]. Contamination of talc with asbestos was hypothesized to have a causal role in ovarian carcinogenesis [13, 98]. The finding of talc materials in ovarian cancer specimens supports this argument [99]. The International Agency for Research on Cancer(IARC) in 2006, classified genital talc use as possibly carcinogenic to humans based on evidence from epidemiologic studies (carcinogen group 2B) [100, 101].

Although the biological basis of talc carcinogenicity is not clear, direct physical contact with ovarian epithelium may cause chronic inflammation and retrograde transport of talc particles through the reproductive tract as suggested by some workers may occur [98]. An immune mechanism may also be the case.

Several case–control studies report association between perineal talc use and ovarian cancer and data from Women Health Initiative support this association also support this fact [98, 102–104]. Furthermore, a prospective study has confirmed association with serous cystadenocarcinoma and talc use. However asbestos-free talc has been in use in cosmetic products at least in most developed countries and later case–control studies show no association between use of talc and ovarian cancer [104]. Other case–control studies found increased risk by 92% that is a relative risk of 1.92 [98]. A study by Cook et al. reported 1.60 relative risk of ovarian cancer with use than non-use. This is an increase of 60%. Finally, a meta-analysis of about 20 published

works reported 35% increased risk of cancer in women who used talc [102]. Scientific evidence has weighed heavily against the makers of talc products who recently lost over 4 billion dollars to a group of 22 women who developed ovarian cancer following talc use adding a court evidence to ovarian carcinogenesis by talc [105].

9. Diet and ovarian cancer

Diet has been directly or indirectly related to risk of ovarian cancer though very few studies specify the histologic subtype in relation to dietary types. Diet may be modifying the risk of ovarian cancer through effect on endogenous hormones, antioxidant activity or other anticarcinogenic mechanisms. There is however a unanimous finding of reduced incidence of ovarian cancer with higher intake of vegetables especially for epithelial ovarian cancer [106–111]. The average finding is a reduction of risk by about more than 50%. High dietary fiber, carotenoids total ligands and phytochemicals are associated with reduced risk [112].

Dairy products have received conflicting results. While over the years, studies showed no associations between dairy intake and ovarian cancer of any type [113, 114]. Faber et al. using the Danish population-based case–control studies reported increased risk especially with milk and lactose but decreased risk with cheese [115]. An interesting study by Merritt et al. using data from New England case–control study examined including histological subtypes and tumor aggression in relation to intake of dairy foods. They reported decreased risk of serous borderline and mucinous cancer with higher intake of calcium and vitamin D. High Vitamin D intake was also found to be inversely related to serous borderline and endometrioid cancers [116]. Merritt et al. found no evidence between lactose intake and risk of ovarian cancer [116].

High intake of total fat, animal fat, cholesterol and saturated fats may be associated with increased risk. Meta-analysis of 16 independent studies reported significant increase in risk of ovarian cancer with high intake of total saturated and trans fats with serous cancers being especially susceptible to dietary fats than other histologic subtypes [117, 118]. Huncharek and Kupelnick reported a RR of 1.70 or an increased risk of 70% in patients with high fat intake [117], however Bertone et al. found no association with intake of fats alone but associated increased with when combined with high intake of eggs [119]. High intake of eggs alone are reported to increase risk [111, 120]. This effect has been linked to high dietary cholesterol which may be increasing risk of ovarian cancer through increased circulating estrogens [111, 121].

Although the link between ovarian cancer and high intake of meat has been controversial with some studies finding no association [122], majority report positive association between high intake of red and processed meat with epithelial ovarian cancer, while poultry and fish have either no relative increase or observed reduction in risk [123–126].

High alcohol consumption has been studied in reasonable depth and only few studies show no association [127] while others show a reduction in risk with minimal and moderate intake of alcohol [128, 129]. The observed phenomenon may be due to the anti-oxidants in the wine and alcohol rather than the alcohol itself [130]. While tea consumption has not been associated with risk of ovarian cancer, coffee is associated with modest reduction of risk [131, 132].

High dietary intake of B carotene is reported to be protective against epithelial ovarian cancer; in a meta-analysis of over 3782 subjects, a modest 16% reduced risk was found [133]. Supplemental selenium (>20 μg daily) is associated with 30% risk reduction [134]. This fact, however, does not support use of selenium as a preventive strategy [135]. These antioxidants may be reducing risk by limiting oxidative stress to the ovarian epithelium.

The effect of vitamin D, particularly D3, has been of interest because of its ability to cause apoptosis of cancer cells in vitro and the demonstrated increased risk of ovarian cancer in vitamin D deficient Europeans [136], more research is necessary to define clinical implication of these findings as some researchers propose supplementation of vitamin D for preventive purposes [137].

10. Smoking

Association between cigarette smoking and ovarian cancer is not as clear as other cancers like lungs oropharynx and lungs that are very well documented [138]. However, metabolites of nicotine which are potent hydrocarbons and carcinogens like cotidine and benzopyrene have been isolated in follicular fluid and OC has been induced in rodents with cyclical hydrocarbons [139].

Cigarette smoking is associated with increased risk of mucinous ovarian cancers [140–143] but the effects on other histologic types is less clear. A Norwegian study, found increased risk of invasive borderline cancers in addition to mucinous [140]. Smokers however have a deficit of endometrioid tumors.

Survival of patients who smoke is also found to be worse than that of non-smokers [142, 144]. Studies have confirmed the increased risk of mucinous epithelial cancers in smokers to be directly proportional to the pack-years of smoking [145, 146]. A twofold increased risk of mucinous epithelial cancers is the generally observed phenomenon [141, 143, 146], but could be up to fourfold increase in women who have smoked for 40 years or more [146].

There is a suggestion however that with the deficit in clear cell and endometrioid cancer and despite the increase in borderline and mucinous cancer smoking may not be associated with overall increase in ovarian cancer mortality [144].

11. Endometriosis and risk of ovarian cancer

OC prevalence in women with endometriosis is higher than the general population 1.32–1.9 [147]. A recent systemic review agrees with this modest increase in risk of endometrioid, borderline and clear cell cancers with endometriosis [148]. Some reports suggest about two to threefold increase in risk [149]. This association between endometriosis and OC is not a proof of causality for the histiotypes.

It is more common in patients with longstanding or recurrent endometriosis and removal of endometrioma is not preventive towards development of OC [150]. The increased risk might be due to high estrogen concentration or due to gene mutations caused by oxidative stress due to iron in the endometriotic cyst [151].

12. Polycystic ovarian syndrome

PCOS is the commonest endocrine disease in women of reproductive age with incidence of about 20% [152]. Associated with infertility, obesity and abnormal gonadotropin secretion, PCOS is associated with 2.5-fold increased risk of epithelial ovarian cancer [153]. The risk of ovarian cancer in women with PCOS is greatest in lean women and those who never used oral contraceptive pills [153, 154].

A systemic review involving eight studies and a meta-analysis found increased incidence of borderline serous cancer in patients with PCOS [155]. Proteomic biomarkers for identification of patients with PCOS who are at increased risk of ovarian cancer may be useful for early diagnosis but the clinical use of these markers need further verification [156].

13. Pelvic inflammatory disease

Inflammation has been implicated in ovarian carcinogenesis but studies investigating the association between pelvic inflammatory disease (PID) and ovarian cancer risk are few and inconsistent with some studies reporting positive association [157, 158] and others excluding such association [159, 160]. A pooled reanalysis of 13 studies reported increased risk of borderline ovarian tumors in women who had multiple episodes of pelvic inflammation [157]. This association may be pronounced among Asian women [158]. Rasmussen et al. in a population-based cohort study recently reported increase in risk of serous ovarian cancer in patients with PID [157]. Therefore we can conclude that repeated episodes of PID is associated with statistically significant risk of borderline and serous cancers but not non-epithelial cancers which have been found not to be associated with PID [158].

14. Hormone replacement therapy (Hrt) and risk of ovarian cancer

Women who use menopausal hormone therapy are at an increased risk for ovarian cancer. A review and meta-analysis of data published between 1966 and 2006 concluded that current use of postmenopausal hormone therapy (HT) increased the risk of ovarian cancer by 30% compared with never use of HT [161]. Estrogen alone was thought to confer higher risk than combined estrogen and progesterone which is refuted by finding from data from million women study [162, 163]. Recent studies indicate that using a combination of estrogen and progestin for 5 or more years significantly increases the risk of serous and endometrioid OC in women with intact uterus, but for women who have had hysterectomy, 10 or more years of use is associated with increased risk [161, 164, 165]. In a recent pooled analysis of 52 epidemiological studies, the risk of serous cancer was 51.4% and that of endometrioid was 48.6% [164]. The increase has been interpreted to mean one extra OC in 1000 users and one extra mortality in 1700 user [166]. There is more risk with prolonged use irrespective of the type of HRT, regimes used or mode of administration.

15. Obesity

Obesity may be increasing risk of ovarian cancer significantly [166–168]. Obese women (BMI > 30 kg/m^2) who have not used menopausal hormone replacement therapy (MHR) had 25–80% increased risk compared with women with normal BMI (18.5–24.9) no relationship between BMI and OC in women with family history. Obesity is associated with an almost 80% higher risk of ovarian cancer in women 50–71 who had not taken hormones after menopause. For women who have not used HRT, evidence shows risk of ovarian cancer to increase by 10% with every 5 kg/m^2 increase in BMI (Collaborative Study). Higher BMI in young adulthood is reported to increase risk of premenopausal ovarian cancers [167].

Evidence from meta-analysis of 14 studies shows that slightly worse survival in obese women with ovarian cancer compared to non-obese women (pooled HR = 1.17, 95% CI: 1.03–1.32) [169].

Obesity may be increasing this risk for ovarian cancer through increasing inflammatory biomarkers and increase in hormonal factors especially androgens which is important in development of mucinous tumors [170].

Histologic subtypes associated with obesity include low-grade serous, mucinous tumors and endometrioid cancers. No association was found between high grade serous and obesity therefore reducing BMI is unlikely to reduce the incidence of

high grade serous cancers [171]. Moreover, obese women with HGSC have poorer outcome than their non-obese counter parts [172].

Recent systemic review of 43 studies involving more than 3 million women concludes that the evidence is inconsistent that obesity is a definite risk factor for ovarian cancer [173]. This finding may be due to the dominance of HGSC which risk is not affected by obesity.

16. Protective factors that reduce risk of ovarian cancer.

16.1 Pregnancy

Pregnancy is thought to be protective against ovarian cancer [13, 47, 65]. Pregnancy whether uncompleted or term confers a protective benefit against epithelial ovarian cancer. Increasing parity is associated with a reduction in the risk of ovarian cancer [36, 63, 65, 174]. Pregnancy may be protective against all histological subtypes. A Swedish study has reported reduced risk for epithelial, stromal and germ cell tumors, but less consistent decrease in borderline cancers [63].

However, it appears that the protective effect of pregnancy (and breast feeding) so called reproductive factors, may be more significant in the West, parts of the US and among Jewish women as reports of ovarian cancer of all histologic subtypes in parous women in developing countries is so widespread and requires further research [38, 53, 55, 57, 59, 60]. The significance of this phenomenon is that the protective effect of pregnancy may be lost in the face of other more important risk factors that need to be defined.

All theories of ovarian carcinogenesis are not plausible explanation for the observed protective effect of pregnancy, therefore pregnancy-induced clearance of malignant cells has been proposed [63] which must to be case in all races to be an acceptable hypothesis.

16.2 Breastfeeding

Breast feeding exerts a strong protective effect with long-term breast feeding being more protective especially against epithelial cancers [175]. The mechanism may be by suppression of gonadotropins through unovulation, resulting in depressed production of plasma estradiol and unovulatory cycles [65, 176]. Breastfeeding also reduces the levels of gonadotropins, especially luteinizing hormone [176], which may be causal mechanism for ovarian carcinogenesis [177].

Meta-analysis of 12 US studies and 9 studies from developed countries showed an inverse association between breastfeeding and ovarian cancer risk [175]. Women who breast fed for up to 6 months showed duration-dependent benefit with women who breastfed for long having more protection. Breast feeding may be reducing risk of epithelial cancers by up to 30% compared with women who did not breast feed.

16.3 Oral contraceptives

The use of oral contraceptives decreases the risk of developing OC and the benefit may be enjoyed up to 25–30 years after stopping the pill [178, 179]. COCP use is associated with about a 40–50% lower risk compared with never use [178, 180]. Length of pill use appears to influence the degree of protection, with a relative risk of 0.4 for more than 5 years reported in pooled European and US studies [178, 181].

The protective benefit may be experienced even in high risk women though there is not enough evidence for use of the pill for chemoprophylaxis [180, 182, 183]. Women who use the pills for more than 5 years enjoy more protection of about 50% reduction [179]. This protection is enjoyed by women of all ages and parities.

Therefore while HRT is associated with increasing risk, the pills are associated with reduced risk a position both have similar active ingredients and estrogen has been blamed in ovarian carcinogenesis.

16.4 Hysterectomy/tubal ligation

Observational epidemiologic evidence strongly support tubal ligation and hysterectomy to be associated with a decrease in the risk of ovarian cancer, by approximately 26–30% [184]. Having fallopian tubes tied hysterectomy and unilateral oophorectomy may reduce risk by up to 67% [184, 185].

Patients with BRCA1 but not with BRCA2 are found to benefit from the protection conferred by tubal ligation to OC [186]. Tubal ligation and hysterectomy reduce risk of low grade more than high grade serous cancers. Risk of endometrioid cancer is almost halved. Tubal ligation is not observed to reduce the risk of mucinous tumors [187].

16.5 Physical activity and exercise

Physical activity may be beneficial in both risk reduction of inflammation, decreasing body fat and frequency of ovulation. Survivors of ovarian cancer may also experience general health benefit of physical activity [188]. The specific effect of physical exercise on ovarian cancer in general and the various histologic subtypes have shown inconsistent results. The most consistent result obtained by research is that of increasing risk by prolonged sedentary life style physical inactivity [188, 189].

Considering direct effect of physical activity however, some studies report no effect on the risk of ovarian cancer [190, 191] while other studies report risk reduction [190, 191]. The reduction of risk may be to epithelial cancers. Physical activity may not be affecting sex cord-stromal and germ cell cancers of the ovary.

17. Conclusion

The risk of ovarian cancer in women is modified by a number of biologic, hormonal, lifestyle and geographic factors the extent of which differs between the histologic varieties. There may be racial or regional variation in the extent to which these factor increase risk or protect against particularly the most common histologic subtype.

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