17 Epidemiology and Risk Factors for Ovarian Cancer

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17.1 Introduction

The International Agency for Research on Cancer reported that in 2012 gynecological cancers accounted for 20% of the 14.1 million new cancer cases and 8.2 million cancer deaths in females. Of this, 239,000 new cases were diagnosed as OC and caused 1,52,000 deaths [1].

By 2020, an estimated 182,602 cases of gynecological cancer will be diagnosed in Indian women which would be 30% of the total cancers among females [2].

In the United States, an estimated 22,440 new cases of OC were diagnosed in 2017 accounting for 5% of the total cancer-related deaths. Over the past two decades, OC rates have declined by about 1.1% per year in whites and 0.4% per year in black women with a similar decrease in mortality (2% per year versus 1% per year) [3].

The median age at diagnosis is 63 years, and the lifetime risk of having OC is 1 in 75 (1.3%) with the mortality rate of approximately 25% for all stages of OC. The 5-year survival rate for OC is low (46.5%) as 60% of women are diagnosed in later stages where the survival incidence is on an average 29%. Early-stage cancer is diagnosed only in 15% women though the survival rate is as good as 92% [4].

17.2 Geographic Distribution

A wide geographic variation is observed for OC with the highest rates (>8 per lakh) being observed from developed nations like North and Central America and Eastern Europe. South Asia and Africa account for the lowest incidence of less than 3 per lakh with South America being between the two (5.8 per lakh) [5] which are in congruence with the variations observed across the globe [4]. Figure 17.1 exhibits the wide geographic distribution of ovarian cancer all over the globe [1].

Maximum decline in OC-related mortality has been seen in major developed countries like the European Union, America, and Australia (10%, 16%, 12%, respectively). The fall was larger for the young and the middle-aged women. Latin American countries had lower rates with a modest decline of only 2.1% noted in Japan [6].

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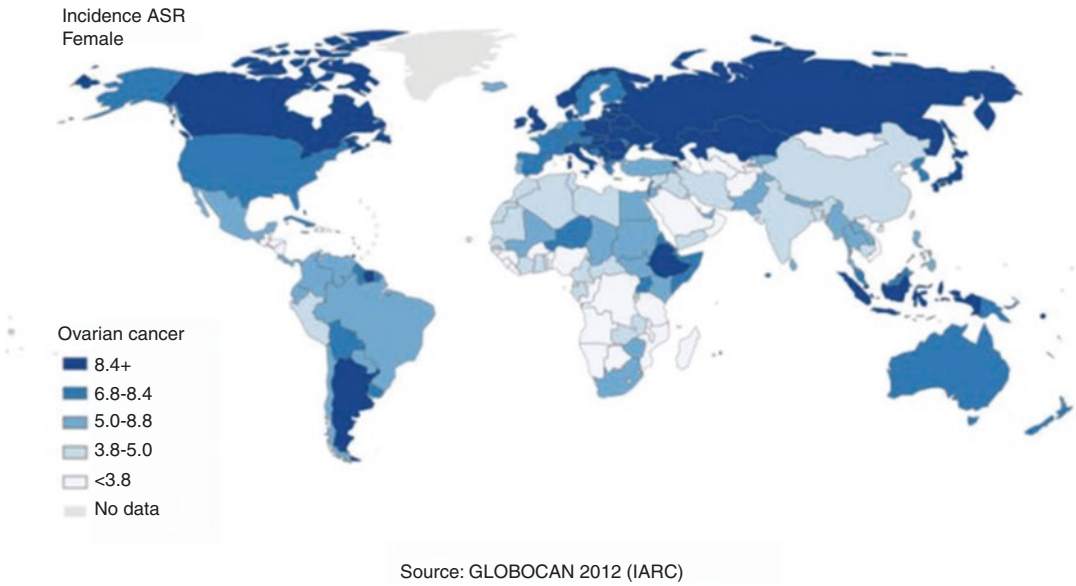

Fig. 17.1 Geographic distribution of ovarian cancer. Adapted with permission from Ferlay J., Soerjomataram I., Ervik M., Dikshit R., Eser S., Mathers C., Rebelo M., Parkin D.M., Forman D., Bray, F. GLOBOCAN 2012 v1.0, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 11 [Internet]. Lyon, France: International Agency for Research on Cancer; 2013. Available from: http://gco.iarc.fr/today/home

17.3 Risk Factors

The two predominant hypotheses for OC that have emerged after decades of research are the incessant ovulation and the gonadotropin hypothesis. According to the former theory, with the increasing number of ovulatory cycles, there is an increase in the rate of cellular division associated with the repair of ovarian epithelium in turn increasing the chances of spontaneous mutations [7]. Entrapment of the ovarian surface epithelium within the ovarian stroma and its subsequent differentiation, proliferation, and malignant transformation may occur due to estrogen stimulation. These occur more likely especially with high gonadotropin levels (luteinizing hormone [LH] and follicle-stimulating hormone [FSH]) and form the basis of gonadotropin hypothesis [8, 9].

17.3.1 Age

Early age at menarche and late age of menopause increase the number of ovulatory cycles, thereby increasing the risk of development of OC, though many studies do not support the same [10]. Gong et al. analyzed 22 case-control and five cohort studies in their meta-analysis and reported a statistically significant inverse association between menarcheal age and OC risk (RR = 0.85; 95% CI, 0.75–0.97), but the association was restricted to invasive and borderline serous ovarian cancer [11].

Similar inconsistent results have been reported with regard to age at menopause. In the EPIC cohort of 327,396 women, menopausal age more than 52 had an increased risk compared to <45 years (>52 vs ≤45: HR, 1.46; 95% CI, 1.06–1.99; P-trend 0.02) [12]. A collaborative report from NHS and NHS-II found an increased association of increasing age at menopause with endometrioid tumors and not serous invasive or mucinous tumor [13]. To conclude, with all the available evidence, the effect of age at the ends of the reproductive spectrum is small.

17.3.2 Pregnancy and Parity

Pregnancy exerts a strong protective effect on ovarian cancer by causation of anovulation and

decreased pituitary gonadotropins. Gaitskell et al. in their prospective Million Women Study (MWS) showed that nulliparous females had a 29% increase of ovarian cancer risk compared to women even with a single child with significant variation for histological subtype. There was no significant increase in serous to a modest increase for mucinous but a substantial increase for clear cell and endometrioid tumors [14].

A large case-control study from Denmark found a significant decrease in the risk of serous borderline OCs with increasing parity ($p < 0.01$), whereas infertility was associated with an increased risk (OR = 3.31; 95% CI, 2.44–4.49) [15]. Similar results were reported by Koushik et al. [16].

17.3.3 Breastfeeding

Prolactin release after delivery helps in the establishment of lactation and switches off LH and FSH secretion in turn causing anovulation. So breastfeeding (BF) has a protective effect in the development of ovarian cancer [9]. Tsilidis and colleagues showed that there was no significant association of risk of OC with breastfeeding [12]. In a recent meta-analysis by Li et al. including 17,137 women with ovarian malignancy, a 30% risk reduction was seen with up to 6 months of BF as compared to no BF with a significant decrease in epithelial variety. When duration of BF was considered, the relative risks for <6 months, 6–12 months, and >12 months were 0.85, 0.73, and 0.64, respectively, thus showing that there is a linear trend toward ovarian cancer risk and duration of BF [17]. Sung et al. observed that first birth and first 6 months of BF had a greater protective effect than subsequent births and additional months of BF [18].

17.3.4 Oral Contraception

Consistent reports of the protective effect of oral contraception on development of ovarian cancer exist in the literature with the protective effect increasing with the duration of use [16, 19, 20].

Koushik et al. reported that ever use was not associated with risk overall but >10 years of use versus no use reduced the risk especially for invasive OC [16], whereas another study showed that if use was 5 years or more, the risk was halved [9].

The EPIC trial showed that oral contraceptive use for ≥10 years decreased the risk of ovarian cancer by 45% compared to ≤1 year of use, though ever users had significant lower risk of OC [12].

No particular oral contraception formulation or ovarian cancer histiotype is associated with risk reduction [21]. A lower risk of ovarian cancer with progestin only contraception has also been seen [22].

Across the globe, the choice of contraceptive method usage varies. Huang et al. in the prospective Shanghai Women's Health Study showed that with intrauterine device use of longer than 20 years, there was a reduction of 38% for OC compared to never users [23]. With levonorgestrel intrauterine system (LNG-IUS), a lower incidence of OC has been seen [24]. To conclude, still further research is needed to establish the effect of different formulations and modes of contraception on ovarian cancer risk.

17.3.5 Hormone Replacement Therapy (HRT)

Despite the well-known ill effects of HRT on women's health, Ness et al. reported that 12% postmenopausal women with a mean age of 66 years still take HRT [21]. The evidence suggest that HRT is the risk factor for ovarian cancer. Initial studies mainly focused on unopposed estrogen therapy (ET) and OC risk. Studies both support [25–27] and refute [28, 29] the association of OC risk with unopposed ET therapy. But a recent reanalysis of 52 epidemiological studies reported that 55% women who used HRT develop OC and the risk was increased even with <5 years of use. The risk mostly increased for serous and endometrioid type, and the risk remained despite stoppage of HRT even up to the next 10 years [30].

Combined estrogen and progestin therapy (EPT), though initially deemed to have no association or was weakly protective [31, 32], has been shown to have increased risks as well.

Greiser and colleagues observed that risk of ovarian cancer was increased 1.28-fold with ET compared to 1.1-fold increase with EPT, though no differential impact of the formulation was noted on histological subtypes [26].

Thus, HRT use in women is associated with a small but significant risk of OC.

17.4 Lifestyle Factors

17.4.1 Smoking

Cigarette smoke contains carcinogenic chemicals like benzo[a]pyrenes, which is a potent mutagen and carcinogen found in cigarettes. Women exposed to cigarette smoke have benzo[a]pyrene DNA adducts in their ovarian follicular cells which may increase the risk of DNA damage [33].

Some studies [34–36] reported that smoking was not a risk factor for ovarian cancer. A study published in *The Lancet* journal analyzed the effect of smoking on ovarian cancer for 28,000 women from a total of 51 studies. They reported that current smoking rather than past history was associated with an excess of mucinous tumors mainly of the borderline histology (49% mucinous invasive and 125% borderline). A reported decrease in endometrioid and clear cell tumors was noted which is in congruence with the fact that smoking decreases the risk of endometrial cancer. Thus, the overall increase in incidence is small though nonsignificant [37].

Mettler and colleagues in their pooled analysis showed that cigarette smoking had differing strengths of association with different histological subtypes of ovarian cancer. Maximum association was with invasive and borderline mucinous tumors to the tune of 31% and 83%, respectively, in current smokers. The association between smoking and risk of low- and high-grade serous OC was insignificant though a significant increase was noted for serous borderline tumors among former and not current smokers [38].

There has been a global increase in female smoking. Serous ovarian cancers are the most lethal of them, but most studies have found that this histological type does not have an increased association with smoking [37, 39–41].

Various studies have shown a protective effect of smoking on endometrioid OC, but quite a good number found no association between the same [39, 41–44].

A decreased risk for clear cell ovarian cancer was seen in some studies [37, 39, 44], though others found an increased but nonsignificant association between the same [42, 43].

17.4.2 Diet and Vitamin Intake

A null association was observed with intake of vitamins A, C, and E and folate and ovarian cancer though some association was observed with greater vitamin intake especially carotenoids with endometrioid histology [45]. Schulz et al. noted that higher intake of vegetables, whole grain foods, and low-fat milk have some evidence for decrease in OC risk [46]. The meta-analysis of EPIC cohort and the Netherlands cohort including 430,476 women with 1522 OC cases found that high intake of saturated fats elevates the OC risk (HR = 1.21, 95% CI, 1.04–1.41) [47]. Yin et al. found no strong evidence of vitamin D decreasing the risks [48]. A very recent Mendelian randomization study found single nucleotide polymorphisms (SNPs) that were associated with circulating levels of vitamin D and increased risk of OC [49].

17.4.3 Asbestos and Talc

IARC has notified that evidence suggested that exposure to asbestos in humans causes OC [50]. A 75% excess risk of OC with asbestos exposure occurs though the effect is negated upon histopathological confirmation of the reported OC cases [51].

Talc like asbestos is a silicate mineral. Though mechanistic, pathological, and animal studies are not supportive of the carcinogenic properties of

talc on ovarian epithelium [52], studies both supporting [53, 54] and refuting the same have been reported in literature [55]. Thus IARC classified genital talc use as possibly carcinogenic in humans [56].

17.4.4 Obesity

Adipose tissue converts androgens to estrogens, and increase in body mass index (BMI) has been associated with OC risk mainly in premenopausal women [57, 58], but some studies also found an association with postmenopausal women [59, 60]. Increase in different histological types of OC has been also seen [59, 61, 62].

17.4.5 Physical Activity

Olsen and colleagues suggested a modest inverse relationship between the level of physical activity and the risk of ovarian cancer, though the benefit did not vary for different histological subtypes. Thus, regular physical activity should be the norm considering its beneficial outcome on weight control and hence a better bone and heart health [63].

17.4.6 Drugs

The inflammatory etiology of ovarian cancer [64] wherein inflammatory mediators released during ovulation initiate cell transformation and a similar inflammatory process in endometriosis support the protective anti-inflammatory role of aspirin and NSAIDs. Aspirin is an irreversible COX-1 inhibitor, and this inhibition is more important for decrease in risk for ovarian malignancy as OC tissue overexpress COX-1.

In the analysis of more than 7500 patients, aspirin use was associated with decreased risk of OC, more so for regular users of low dose [65]. Aspirin use for cardiovascular disease prevention has reported a 12% reduction in cancer incidence with ≥3 years of daily aspirin use, especially for female genital cancers [66]. In contrast regular use of NSAIDs was seen as protective in comparison to aspirin [67].

Interestingly, evidence is emerging for the role of metformin in OC prevention and treatment. In a very recent retrospective study by Wang et al., patients with OC who regularly use metformin had a longer progression-free survival and overall survival than who did not take or discontinued metformin and in nondiabetic OC controls [68].

Thus, further research is warranted, keeping in mind potential drug adverse effects on long-term use.

17.5 Gynecological Conditions and Risk of Ovarian Cancer

Benign conditions like endometriosis, pelvic inflammatory diseases (PID), and PCOS have all been evaluated as potential risk factors for development of OC.

Endometriosis has been long linked to the development of OC. A systematic review reported increased risk of OC especially of endometrioid, clear cell, and low-grade serous tumors [69, 70].

PCOD is known to be associated with endometrial cancer due to unopposed estrogens and androgens. Literature is scarce on the association of PCOD with OC [71, 72].

Studies are inconclusive about the association between PID and ovarian cancer [73–77]. PID was found to be a risk factor especially in women <35 years [75] though an increased association was seen with borderline tumors [76], especially of the serous variety and not mucinous [77].

17.6 Gynecological Surgery and Ovarian Cancer

Various mechanisms by which tubal ligation acts as a protective barrier are an early screening effect, alteration of ovarian function, mechanical barrier against ascending carcinogenic agents, and prevention of endometrial and proximal fal-

lopian tube ascent [78]. Tubal ligation has been shown to decrease the risk of ovarian cancer. Cibula and colleagues showed a decreased risk for epithelial OC by 34% though a risk reduction was also noted for endometrioid and serous variety and not mucinous OC [79].

The role of prophylactic oophorectomy in decreasing OC has been well established especially among high-risk women [80, 81]. This is discussed in detail in Chap. 20.

Hysterectomy has also been identified to reduce OC risk of endometrioid and clear cell type as is with tubal ligation [82, 83].

17.7 Conclusion

Ovarian cancer is one of the common cancers in women and the leading cause of mortality. Lifestyle modification with avoidance of occupational hazards and appropriate and timely prophylaxis in high-risk women can go a long way in decreasing the risk and mortality associated with ovarian cancer. Promotion of breastfeeding for a minimum of 6 months, regular and consistent use of contraception, prescription of HRT to women who are in actual need of it, and, most importantly, monitoring of one's own health will help prevent many more cases.

Key Points

- Ovarian cancer is one of the most commonly diagnosed cancers and the cancer-related cause of mortality among women.
- The highest rates have been recorded from the most developed nations probably because of the increased screening protocols.
- Early and increased use of oral contraceptives has contributed to declining rates observed in developed countries.
- In developing countries reduced parity, decreased physical activity, and a higher dietary saturated fat intake may be playing a crucial role in the increasing trends observed.
- Lifestyle modifications will play a definitive role in further decreasing the associated morbidity and mortality.

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