



REVIEW ARTICLE

OVARIAN CANCER

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ABSTRACT:

Ovarian cancer (oc) is the seventh most normally recognized cancer amongst girls within the international and the tenth maximum commonplace in china. Epithelial oc is the maximum predominant pathologic subtype, with five major histotypes that fluctuate in origination, pathogenesis, molecular alterations, chance elements, and analysis. Genetic susceptibility is manifested with the aid of uncommon inherited mutations with excessive to moderate penetrance. Genome-extensive association research have additionally diagnosed 29 not unusual susceptibility alleles for oc, inclusive of 14 subtype-precise alleles. Numerous reproductive and hormonal factors can also lower chance, including parity, oral contraceptive use, and lactation, at the same time as others together with older age at menopause and hormone substitute therapy confer expanded dangers. Those associations vary via histotype, specially for mucinous oc, probable reflecting differences in etiology. Endometrioid and clear cellular oc proportion a comparable, precise sample of institutions with accelerated risks among ladies with endometriosis and decreased dangers associated with tubal ligation. Oc risks related to other gynecological conditions and techniques, which includes hysterectomy, pelvic inflammatory sickness, and polycystic ovarian syndrome, are less clear. Other viable chance elements include environmental and way of life factors which includes asbestos and talc powder exposures, and cigarette smoking. The epidemiology offers clues on etiology, number one prevention, early detection, and probably even therapeutic strategies.

INTRODUCTION:

Ovarian most cancers (oc) accounts for an predicted 239,000 new instances and 152,000 deaths international annually¹. The best costs (eleven.Four in keeping with a hundred,000 and 6.Zero in keeping with one hundred,000, respectively) are seen in japanese and significant europe. Even though china has a particularly low incidence rate (four.1 in step with one hundred,000), the large populace translates to an predicted fifty two,one hundred new instances and 22,500 related deaths in 20152. In assessment, 21,290 cases and 14,180 related deaths are anticipated to occur in the U.S.A. In the course of the identical year³. A girl's lifetime threat of growing oc is 1 in 75, and her danger of loss of life of the disorder is 1 in 1004. The sickness typically affords at late level when the 5-12 months relative survival rate is handiest 29%. Few instances (15%) are diagnosed with localized tumor (stage 1) whilst the 5-12 months survival fee is 92percent⁴. Strikingly, the overall five-12 months relative survival rate generally ranges among 30%–forty% across the globe and has seen handiest very modest increases (2%–four%) considering 19955. Regardless of the public fitness significance.

Lethal disorder isn't always absolutely understood. This assessment is split into 5 sections: pathologic type, descriptive epidemiology, genetic epidemiology, chance and preventive factors, and precis and conclusions.

Pathologic type of OC:

Nearly all benign and malignant ovarian tumors originate from one in all 3 mobile types: epithelial cells, stromal cells, and germ cells. In advanced international locations, greater than 90% of malignant ovarian tumors are epithelial in beginning, 5%–6% of tumors constitute intercourse cord-stromal tumors (e.G., granulosa mobile tumors, thecomas, etc.), and 2%–3% are germ cell tumors (e.G., teratomas, dysgerminomas, and so on.)⁶. The pathology and classification of ovarian tumors are defined in detail by way of chen et al.⁷. Maximum epidemiologic research, which includes the present review, specializes in epithelial oc. Epithelial oc reflects a heterogeneous ailment with histologic subtypes (histotypes) that fluctuate of their cell starting place, pathogenesis, molecular alterations, gene expression, and prognosis⁸⁻¹¹. Malignant oc, additionally called carcinomas, are created from five main histotypes: excessive-grade serous (hgsoc; 70%), endometrioid (enoc; 10%), clear cellular (ccoc; 10%), mucinous (moc;

three%), and coffee-grade serous (lgsoc; <five%)^{8,9}. Within each of these categories, despite the fact that most customarily amongst serous and mucinous, are tumors of Uncertain malignant behavior called borderline or low malignant capability (lmp) tumors that contain microscopic capabilities of malignancy with out frank invasion into surrounding stroma¹². The cellular foundation and pathogenesis of oc isn't always nicely understood and, curiously, most tumors appear to originate from other gynecological tissues and contain the ovary secondarily. Morphological and genetic research have given rise to numerous speculation of origination, in particular for high-grade serous tumors that lack a clean development model^{13,14}. Compelling facts endorse high and coffee grade serous neoplasms originate from fallopian tube epithelium, ccoc and enoc from endometriotic cysts associated with endometriosis, and moc from transitional cell nests on the tubal-mesothelial junction^{15, sixteen}. Hgsoc and lgsoc are both concept to get up from tubal epithelium despite the fact that through separate pathways. Strange lesions in the fimbriated end of the fallopian tube (serous tubal intraepithelial carcinomas) display comparable morphology and tp53 signatures as hgsoc tumors suggesting the neoplastic procedure may originate at those tubal lesions and shed onto the ovary wherein they aggressively progress¹⁷⁻¹⁹.

Descriptive epidemiology:

OC incidence reveals huge geographic variant (discern 1)³². The best age-adjusted occurrence prices are located in evolved parts of the world, inclusive of north the united states and crucial and eastern europe, with charges normally exceeding 8 in keeping with a hundred,000. Prices are intermediate in south america (five.8 consistent with one hundred,000), and lowest in asia and africa (≤ 3 per one hundred,000).



Fig. Ovarian cancer incidence exhibits wide geographic variation.

Migration from international locations with low charges to those with high charges results in more risk^{33,34} underscoring the significance of non-genetic hazard factors. Inside the america, racialDifferences in incidence and mortality mimic the located global variant with prices maximum amongst whites, intermediate for hispanics, and lowest amongst blacks, and asians⁴. Variant within large nations consisting of china additionally mimics global variant with incidence and mortality higher inside developed, urban regions as opposed to less developed, rural regions³⁵. In most advanced countries, largely such as north the usa and europe, oc incidence and mortality has regularly declined since the 1990s^{4,36-forty}. Conversely, historically less evolved international locations with latest financial growth and life-style modifications have seen increases in incidence and mortality quotes. In china, the increase is plain best amongst rural girls as opposed to those in greater advanced, city regions^{2, forty one}.

Genetic epidemiology:

One of the most full-size danger factors for oc is a own family records of the disease⁴². First-degree family of probands have a 3- to 7-fold multiplied chance, especially if multiple loved ones are affected, and at an early age of onset^{43-forty seven}. Uncommon excessive penetrant mutations in the brca1 and brca2 genes substantially growth lifetime risk⁴⁸ and account for most people of hereditary instances and 10%–15% of all cases^{49-fifty seven}. Data from the breast cancer linkage consortium suggest the threat of oc thru age 70 years is up to 44% in brca1 families⁵⁸ and tactics 27% in brca2 families⁵⁹. Hereditary non-polyposis colorectal most cancers syndrome (hnpcc)⁶⁰ may account for at least 2% of instances and confer as much as a 20% lifetime risk^{48,61-64}. Ladies with mutations in dna repair genes, such as bripl1, rad51c, and rad51d have envisioned lifetime dangers of five.8%, five.2%, and 12%, respectively^{65, sixty six}. Deleterious mutations in brca1/2 and different double-strand dna destroy restore genes are extra strongly associated with hgsoc susceptibility even though they do arise in different tumor subtypes⁶⁵⁻⁶⁷.

Threat elements and preventive elements

Hormonal and reproductive risk elements:

Epidemiological research has truly implicated hormonal and reproductive factors in the pathogenesis of oc. Main hypotheses have emerged to in shape the data⁸⁴. The 'incessant ovulation' hypothesis posits that the number of ovulatory cycles will increase the rate of mobile division related to the restore of the floor epithelium after each ovulation, thereby growing spontaneous mutations⁸⁵. The correlation among increasing numbers of lifetime ovulations and higher risk⁸⁶⁻⁸⁹ are constant with this hypothesis. The 'gonadotropin speculation' attributes the impact to gonadotropins, inclusive of

lutinizing hormone and follicle-stimulating hormone⁹⁰. Each of those proposed mechanisms offer a framework to interpret the epidemiologic information on both endogenous correlates of reproductive hormone exposure and exogenous resources of hormones. A more targeted overview is available via rima et al.^{Ninety one}.

Parity and infertility:

The association among being pregnant and oc hazard has been studied significantly. Being pregnant causes anovulation and suppresses secretion of pituitary gonadotropins and is for that reason steady with each the 'incessant ovulation' and the 'gonadotropin' hypotheses. Certainly, parous ladies have a 30%-60% lower chance than nulliparous women^{85,ninety two,ninety nine,103-107,115,117,123-126} and each additional full-term pregnancy lowers danger by means of approximately 15p.^{C98,one hundred and five,127}. Research in african american¹²⁸ and asian¹²⁹, a hundred thirty populations have yielded comparable results. The protecting impact associated with parity is evident across the primary histotypes despite the fact that perhaps barely weaker for serous carcinomas, with kind of 20% decrease hazard in parous women, versus different subtypes, particularly clear mobile and endometrioid that display 50%–70% discounts in risk^{28-30,131,132}. Akin to the breast most cancers literature, case-control research with health facility controls have pronounced multiplied risk with past due age at the start start (>30 years of age)^{92,ninety seven,ninety eight,106,108,123,133-136}, however not among research with population controls^{96,ninety eight,137}. Latest information also shows that oc hazard does no longer range by the time c program language period between the first and closing birth¹³⁸. It's miles doubtful whether or not spontaneous or induced abortions impact oc danger.

Barely lower risk^{85,ninety two,97,ninety eight,104,one zero five,139-141} while others have reported threat to be increased^{107,126}, or now not affected^{96,99,a hundred,102,106,a hundred and fifteen,123,125,142}. Triggered abortions were associated with decrease danger in numerous studies^{105,one hundred forty,141}, however now not others^{96,108,139}. In regards to spontaneous abortions, positive^{100,123,139}, inverse¹⁰², and null associations^{103,one hundred twenty five,one hundred forty with risk} have been said. Interpretation of this literature is tough due to the identified capacity for take into account bias must be 'abortions' right here no longer pregnancies but higher to give up at recollect bias.¹⁴³ Infertility is a time period this is used to explain a heterogeneous institution of biologically wonderful situations ranging from genital tract infections and tubal disturbances to medical conditions inclusive of endometriosis and polycystic ovarian syndrome (pcos)^{one hundred forty four,one hundred forty five}. Infertility seems to be a chance issue in most studies^{92,98,102,106,a hundred and fifteen,123,125,126,136,144}, but no longer all^{105,146}. The inconsistent consequences may additionally replicate the failure to take a look at the diverse kinds of infertility one after the other.

Lactation:

Lactation suppresses secretion of pituitary gonadotropins and ends in anovulation, mainly within the preliminary months after delivery¹⁵⁷. Both the incessant ovulation and gonadotropin hypotheses could be expecting lactation reduces the danger of oc. In fact, most studies suggest a slight shielding effect from breastfeeding, with odds ratios approximating Zero.6–zero.798,^{ninety nine,102,124-126,158-161}, even though a few have not^{96,100,one hundred fifteen}. Few research have explored the association through tumor subtype, with one file of the finest chance reduction for endometrioid tumors¹⁶² while another found the most powerful discount amongst mucinous cancers³⁰. A latest meta-analysis indicates a massive defensive effect (summary rr=0.68, ninety five% ci: 0.61–0.76) for breastfeeding that elevated with longer period (precis rr=0.Eighty five, 0.Seventy three, and zero.Sixty four for <6 months, 6–12 months, and >one year of total breastfeeding duration)¹⁶³. For that reason, lactation protects in opposition to epithelial oc, especially for long-time period length.

Benign gynecologic conditions and gynecologicsurgical:

Procedure numerous gynecologic situations were examined as threat elements for oc, which includes pcos, endometriosis, and pelvic inflammatory sickness (pid). Pcos is a multi-factorial sickness often characterised by weight problems, hirsutism, infertility, and menstrual abnormalities. Because of unopposed endogenous estrogen and/or elevated androgens, girls with pcos have an expanded danger for endometrial cancer. The affiliation between pcos and oc chance changed into investigated using statistics from the cancer and steroid hormone look at, a population-based totally case-manipulate study¹⁵⁵. Amongst 476 histologically confirmed epithelial oc cases and 4,081 controls, 7 cases (1.Five%) and 24 controls (0.06%) suggested a records of pcos (or=2.5, ninety five% ci: 1.1–five.9)^{one hundred fifty five}. The restricted records was inadequate for a consensus announcement that pcos is a hazard factor¹⁶⁴. Larger research that modify for ability confounders are clearly wanted. Endometriosis is one of the most common gynecological problems, affecting 10%–15% of ladies in reproductive years¹⁶⁵. No matter being taken into consideration a benign condition, endometriosis has been connected with oc within the scientific literature because 1925. Sayasneh and colleagues¹⁶⁵ carried out a scientific evaluation of 8 research; seven suggested an elevated hazard of oc, with impact sizes ranging from 13-19. The most powerful associations with endometriosis are obtrusive among endometrioid and clear mobile histologies^{30,a hundred sixty five,166}, constant with molecular data that helps endometrial epithelium because the foundation of those subtypes⁸. In addition, pearce and colleagues¹⁶⁷ identified an accelerated hazard of lowgrade serous oc (or=2.11, ninety five% ci: 1.39–three.20) amongst girls with endometriosis in addition to for endometrioid (or=2.04, ninety five% ci: 1.67–2.48) and clear cell cancers (or=three.05, 95% ci: 2.43–3.84).

Each the endometrium and fallopian tube. The affiliation between endometriosis and endometrioid and clean mobile ovarian carcinomas may additionally constitute shared threat factors¹⁶⁵, genetic susceptibility¹⁶⁸, and/or pathogenesis¹⁶⁹ instead of a causal association. Pid causes infection of the endometrium, fallopian tubes, and ovaries. Research evaluating the affiliation among pid and oc chance have yielded inconsistent results^{103,one hundred seventy-172}. Lin and colleagues¹⁷³ evaluated this association in a massive nationwide cohort from chinese taiwan that included sixty seven,936 ladies with pid (42 of whom later developed oc) and a hundred thirty five,872 women with out a records of pid (48 of whom evolved oc). A records of pid turned into a massive danger thing (adjusted hr=1.Ninety two, ninety five% ci: 1.27–2.Ninety two), specifically among topics identified with pid before the age of 35 and girls who had as a minimum 5 episodes of pid. Other research located no association^{171,172}. In the danish malova

(malignant ovarian tumor) case-manage look at of 2,three hundred women, pid history become associated with expanded threat of ovarian borderline tumors however now not with invasive oc174. Rasmussen et al. Numerous gynecologic techniques appear to influence the threat for oc. It's miles well established that amongst excessive risk women, bilateral prophylactic oophorectomy decreases danger by at the least 90percent176. Numerous research have recognized a discounted risk related to both a hysterectomy or tubal ligation ranging from 30%–40%92,102,177-183 with the highest hazard reductions determined amongst endometrioid and clear cellular histotypes30,181,184-187. Furthermore, the risk reduction from these methods seems to ultimate for at the least 10–15 years, which argues against screening bias (due to selective removal of subclinical ovarian tumors)116,178,188,189. Even though it is unknown how these techniques lessen the hazard of oc, it's been proposed that thru retrograde menstruation (i.E. Menstrual fluid flows backwards into the fallopian tubes rather than leaving the body through the vagina) endometrial tissue implants on peritoneal and ovarian surfaces (endometriosis) and turns into invasive, growing into endometrioid or clear mobile ovarian carcinomas13,a hundred ninety. This hypothesis is supported through epidemiological studies that show the most powerful associations with tubal ligation and endometriosis for enoc and ccoc.

Oral contraceptives and other types of contraception:

The epidemiological literature during the last numerous decades has always pronounced that use of oral contraceptives is inversely related to the chance of oc. The protective effect increases with longer period of use98,102,191-195 with about a 20% reduced chance for every 5 years of use that persists many years after use has ceased115,124,193,196-two hundred. Furthermore, the hazard discount does not appear to be unique to any specific oral contraceptive formulation195,201 or oc histotype, despite the fact that oral contraceptive use appears less powerful for mucinous cancers in a few studies23,27,28,30,118,131,200. Oral contraceptive use corresponds to the prevention of approximately 30,000 oc instances each 12 months and has already prevented an anticipated 200,000 oc cases and one hundred,000 deaths over the last 50 years200. Progestin-simplest contraceptives have been less studied, in general due to the low occurrence of use, but the available records propose they will additionally decrease risk of oc124,193,202. Exceptionally few studies have tested methods of contraception aside from oral contraceptives. The use of an intrauterine tool (iud) has been related to decreased oc hazard in numerous studies182,203,204 while the nhs cohort discovered multiplied risks205, however, there was a low prevalence of iud use in that populace which occurred previous to the more moderen iud formulations. Similar to oral contraceptives, any protective effect related to iud use may be established upon period of use. Huang and colleagues203 evaluated iud use and oc hazard within the shanghai girls's health examine cohort and discovered lengthy-term iud use of at the least 20 years was related to a 38% reduction in danger. Iud use is the most not unusual contraceptive method in china with a occurrence rate of approximately 50% amongst ladies of reproductive age206. The authors advise that the excessive incidence of lengthy-time period iud use and the associated sturdy defensive impact may additionally make contributions to the low occurrence of oc located in china203. Vasectomy has been evaluated in affiliation with oc hazard and findings were inconclusive205, despite the fact that ness and colleagues182 stated that vasectomy may confer a small reduction in hazard (adjusted or=zero.77, ninety five% ci: zero.Sixty one–zero.Ninety nine), possibly because of reduced exposure to sperm.

By means of histotype:

Hormone substitute remedy (hrt) not like oral contraceptive use that has a properly-set up benefit on oc risk, the association with hrt is less clean. Hrt reduces the secretion of gonadotropins and need to therefore decrease chance, however the decreased levels are still better than pre-menopausal women207. Conversely, postmenopausal hrt may additionally decorate estrogen-brought about proliferation of ovarian cells and therefore growth risk208. Initial studies on the topic have targeted on unopposed estrogen therapy (et) amongst postmenopausal ladies. Numerous case-control98,209,210, cohort211 and meta-analysis212,213 research have determined no association with period of use, even though two have located either a sizeable or suggestive trend in increased risk23,214. More current research suggest that oc hazard is elevated in ever users of hrt215-218 and large will increase are visible for longer durations of use219-223. For example, in the nhs cohort both present day and past hrt users of 5 or extra years had a considerably better threat than by no means customers ($rr=1.41$, ninety five% ci: 1.07–1.86 and $rr=1.52$, 95% ci: 1.01–2.27, respectively), however no association with chance was seen for users of much less than 5 years for either current or past users ($rr=1.01$, ninety five% ci: 0.70–1.41 and $rr=0.88$, ninety five% ci: 0.64–1.19, respectively)219. The authors concluded that the elevated hazard appeared to be driven largely by period as opposed to through repute of use. Conversely, a collaborative re-evaluation of 52 epidemiological research located oc risk was improved in current hrt users, even those with much less than five years of use224. Moreover, danger decreased over time after cessation of use, despite the fact that a small extra in risk turned into nevertheless observed even 10 years after preventing long duration hrt. Mixed estrogen and progestin use and oc danger have best recently been evaluated in studies with sufficient statistical electricity. It's been hypothesized that progestin promotes apoptosis while estrogen promotes proliferation of ovarian epithelial cells225 for this reason the outcomes of unopposed et are idea to be greater negative to the ovaries than estrogen plus progestin (ept)225.

Drug use:

Epidemiological proof linking pid and endometriosis to improved oc risk shows inflammation performs an essential position in ovarian carcinogenesis. Further, animal and in vitro research suggest aspirin inhibits the growth of oc335-337. Several prospective338,339 and case-control340-344 studies have located an inverse association between aspirin and nonsteroidal anti-inflammatory drugs (nsaids) and oc prevalence, even though different research have said no association345,346. Prizment and colleagues339 investigated those capsules the use of facts from a prospective cohort of about 20,000 girls from the iowa women's fitness examine. Compared to girls who reported no need of aspirin, the relative risks of oc for folks who used aspirin < 2, 2–five times, and ≥ 6 instances per week have been 0.83, 0.77, and 0.61, respectively ($p=0.04$) however no affiliation become discovered among nsaid use and risk. Conversely, in the nhs i and ii338 everyday use of nsaids changed into defensive ($hr=0.81$, 95% ci: 0.64–1.01) however aspirin use changed into no longer ($hr=1.11$, 95% ci: 0.92–1.33). No dose-response courting with increased

frequency or duration of use turned into determined, and results did not differ when stratifying by using tumor histology³³⁸ A developing body of proof helps a role for the antidiabetic agent, metformin, within the prevention and remedy of a couple of cancers³⁴⁷. Extra studies have located reduced incidence and mortality amongst metformin treated groups³⁴⁹. Given the absence of appropriate screening assessments, the potential for use of metformin as a chemo preventive agent deserves in addition exploration.

Conclusions:

OC is a main cause of most cancers occurrence and mortality worldwide. This evaluate describes the importance of the trouble and summarizes epidemiological studies that have recognized genetic, environmental, and way of life elements which can growth and decrease risk of this deadly ailment. These factors have possibly impacted the diverse styles and trends of oc prevalence and mortality seen across the globe. Extended and earlier use of oral contraceptives has very probably contributed to the declining developments found in most evolved nations even as decreased parity and modifications in weight-reduction plan and bodily pastime could play a function within the growing traits determined in several international locations with financial boom. Most danger elements display sizable heterogeneity across the 5 histologic subtypes indicating one of a kind etiologies, in particular between mucinous and non-mucinous subtypes. The truth that risk element associations guide universal models of pathogenesis for the man or woman histotypes supply weight to causality, even though such inference is limited. Mendelian randomization studies, which exclude motives consisting of bias, confounding and opposite causality, have inferred a likely causal effect of bmi on danger of non-hgs oc and of vitamin d on threat of invasive and hgs oc. Extra epidemiological research of instrumental variables and incorporating tumor histopathology are needed to refine effect estimates for histotypes and decorate causal inference. Even though most of the hazard factors can't be changed, reflecting the contribution of genetics and unavoidable exposures, some of others may be altered. Growing parity and oral contraceptive use decrease threat of oc. The equal is probably genuine, but to a weaker diploma, of lactation, normal bodily activity and avoidance of cigarettes. An individual's chance is in component a end result of the cumulative effect of exposures. Numerous danger prediction fashions for oc had been evolved to estimate absolute threat based on one's chance issue profile³⁵⁰⁻³⁵³. Forty seven for women with common parity (2 full-term pregnancies) and oral contraceptive use (5 years) with stronger protection conferred with higher parity and period of use ($r=zero.33$, 4 full term pregnancies and 10 years of use). Notably, modifiable elements can mitigate relative hazard of unavoidable exposures including later age of menopause. For instance, reducing bmi from 30 to 24.

Kg/m², utilizing oral contraceptives for 5 years, and forgoing hormone remedy use, the relative chance of a girl who reaches menopause at 60 is mitigated from three.Five to 0.99. It's miles essential to emphasise that the mounted chance elements aside from fairly penetrant gene mutations confer neither big increases in threat nor account for all of the variability inside the incidence of this sickness. Hence, additional reasons of oc are but to be recognized. Extra research is needed to higher recognize the heterogeneous etiology of this lethal ailment, on the way to better prevention and early detection strategies.

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