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Challenges and Opportunities in Studying the Epidemiology of Ovarian Cancer Subtypes

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Abstract

Purpose of review—Only recently has it become clear that epithelial ovarian cancer (EOC) is comprised of such distinct histotypes--with different cells of origin, morphology, molecular features, epidemiologic factors, clinical features, and survival patterns—that they can be thought of as different diseases sharing an anatomical location. Herein, we review opportunities and challenges in studying EOC heterogeneity,

Recent findings—The 2014 World Health Organization diagnostic guidelines incorporate accumulated evidence that high- and low-grade serous tumors have different underlying pathogenesis, and that, on the basis of shared molecular features, most high grade tumors, including some previously classified as endometrioid, are now considered to be high-grade serous. At the same time, several studies have reported that high-grade serous EOC, which is the most common histotype, is itself made up of reproducible subtypes discernable by gene expression patterns.

Summary—These major advances in understanding set the stage for a new era of research on EOC risk and clinical outcomes with the potential to reduce morbidity and mortality. We highlight the need for multidisciplinary studies with pathology review using the current guidelines, further

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Conflict of Interest

Jennifer Anne Doherty, Lauren Cole Peres, Chen Wang, and Gregory P. Way each declare no potential conflicts of interest.

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molecular characterization of the histotypes and subtypes, inclusion of women of diverse racial/ethnic and socioeconomic backgrounds, and updated epidemiologic and clinical data relevant to current generations of women at risk of EOC.

Keywords

Epithelial ovarian cancer; histotype; gene expression subtype; survival; pathology

Introduction

Ovarian cancer is the most deadly gynecologic cancer, with only 46% of women surviving five years after diagnosis [1]. Over the past decade it has become clear that invasive epithelial ovarian cancer (EOC) represents a group of tumor types that, despite arising in a similar anatomical location, have different cells of origin, morphology, molecular features, epidemiologic factors, clinical characteristics and survival [2–5]. Furthermore, reproducible gene expression-based molecular subtypes of the most common histotype of EOC, high grade serous cancers (HGSC), have been observed in multiple studies [6–8]. Understanding similarities and differences in epidemiologic, pathological, molecular, and clinical features by biologically relevant subtypes is essential in order to reduce morbidity and mortality from EOC, as has been achieved with breast cancer [9,10]. For breast cancer, subtype-specific risk factors have been described [11–14], targeted treatments are effective in improving clinical outcomes [15,16], and differences in the incidence and mortality of subtypes [17,18] has set the stage to identify causes of racial, ethnic and socioeconomic disparities [19]. Similar research in EOC is in its infancy partially because it is a rare cancer (incidence 11.9 per 100,000) [20] but also because the recent major paradigm shifts in the understanding of EOC point to the need to approach EOC research in new ways.

Major Paradigm Shifts in EOC Histotype Classification

Invasive EOC has traditionally been separated according to histologic appearance, including serous, endometrioid (EC), clear cell (CCC), and mucinous (MC) histotypes. Immunohistochemical (IHC) markers have recently enabled the refinement of traditional histologic categorization schemes into more homogeneous “molecular” subgroups. As well, IHC markers have served to highlight differences between low- and high-grade tumors within each of the serous and EC groups [21,22] such that 1) HGSC and low grade serous (LGSC) are understood to develop along different pathways and are not part of a continuum of disease as was previously believed, and 2) many high-grade EC tumors have close similarities to HGSC. These distinctions have been included in the new 2014 World Health Organization (WHO) diagnostic classification guidelines [23]. Also, converging lines of research support that most HGSC arise from the fallopian tubal fimbriae [24,25], while EC and CCC likely arise from endometriotic lesions [26–29], and a high proportion of advanced stage MC are now considered to be metastases from other primary tumor sites [5,22]. The new diagnostic guidelines are considerably more reproducible across pathologists and may more accurately reflect biological differences since there are clearer survival differences between histotypes. This is well-illustrated in the study by Kommoss et al. [30] where an expert pathologist used the 2014 WHO guidelines to re-review diagnostic slides from a 2002

clinical trial for which he had originally classified the tumors, with only 54% concordance between his two reviews. Another pathologist independently reviewed the same slides using the 2014 WHO guidelines, and concordance between the two pathologists' reviews was 98%. While there was originally no survival difference between histotypes, the MC and CCC histotypes classified in the later review had markedly worse survival [30]. Conceivably, epidemiologic research that defined histotypes using prior guidelines may have failed to identify histotype-specific etiologic differences that may yet exist when more accurate histotypes are defined by the 2014 WHO guidelines. Since evidence was accumulating over time to support the new classification for many years before it was published (e.g., reviewed in [5]), and as early as 2010 was demonstrated to be highly reproducible across trained pathologists [31], the extent of misclassification in existing EOC studies likely depends on the years of diagnoses, and whether cases were reviewed by expert gynecologic pathologists.

Characteristics of EOC Histotypes

Molecular Features

Nearly all HGSC have *TP53* mutations [32] and frequent homologous recombination deficiency, largely explained by somatic/germline BRCA1/2 alterations (33% in The Cancer Genome Atlas (TCGA)[7]). Thus, HGSC is genetically highly unstable as reflected by widespread copy number alterations (CNA) [7] with considerable tumor heterogeneity [33,34]. In contrast LGSC has intact TP53 function and very few CNA; LGSC also has much higher frequencies of *KRAS* and *BRAF* mutations than HGSC [35], but mutation rates may differ by stage [36]. The other histotypes rarely harbor *TP53* mutations, and instead have mutations in *KRAS* (MC), *CTNNB1* (EC), *PTEN* (EC) and *PIK3CA* (CCC) [5,22,37].

Pathology review of cell type is now highly reproducible and is considered the "gold standard" for histotype classification. In some cases, IHC markers can help with classification. Extending this work, an algorithm using eight IHC markers (WT1, TP53 (p53), CDKN2A (p16), HNF1B, PGR (PR), TFF3, ARID1A, and VIM (Vimentin)) assessed using tumor microarrays (TMA) has been developed to predict the five major histotypes [21,38]. The authors report that it correctly classified tumors 93% of the time based on expert pathology review. The algorithm designated most high-grade carcinomas (including many high-grade EC) as HGSC, reflecting the tumor's immunophenotype as well as underlying molecular abnormalities. As well, in that study population reduced marker sets, which may be easier to implement clinically, were reported to have reasonable prediction accuracy; a four marker panel including WT1, TP53, NAPSA, and PGR had 87% accuracy, and a six marker panel additionally including CDKN2A and TFF3 had 91% accuracy [21].

While there is no question that there are well-defined molecular differences between EOC histotypes, it is also becoming clear that there are similarities across cancers arising in different organ sites. Molecular similarities between serous fallopian tube and ovarian cancers, and to a lesser extent serous primary peritoneal carcinoma have been noted [39] (While serous fallopian tube and ovarian cancer have comparable epidemiologic factor profiles, primary peritoneal cases tend to be older, more obese, and have higher parity [39–41]). Also, HGSC is similar to basal-like breast cancer and a serous-like subtype of endometrial cancer in terms of somatic CNA, *TP53* mutations, *BRCA* mutations and

epigenetic silencing, and *CCNE1* and *MYC* amplification [42]. Understanding the molecular similarities between these cancer types may provide additional opportunities to decipher causal associations for modifiable factors and possible treatment options.

Epidemiologic Factors

Misclassification of histotypes and differences between studies in their categorization may interfere with the ability of studies to identify true differences in risk factors across histotypes; still, histotype-specific risk factor associations have been uncovered even using prior classification guidelines in large pooled studies. Table 1 provides a summary of results from the Ovarian Cancer Association Consortium (OCAC) [43–46], the Ovarian Cancer Cohort Consortium (OC3) [47], the Collaborative Group on Epidemiological Studies of Ovarian Cancer [48–52], and the Million Women's Study [53]. Because these are generally based on earlier histotype definitions, many of the studies were not able to present results separately by LGSC and HGSC. For some factors, there is an association with EOC overall which is stronger among specific histotypes (e.g., for parity and tubal ligation, inverse associations are more pronounced for EC and CCC). For other factors, associations are only present for specific histotypes (e.g., cigarette smoking and increased risk of MC, and suggestive decreased risk of CCC and EC; and estrogen-only hormone therapy and increased risk of serous and EC). Differences in the incidence of histotypes have been observed by race, with a higher incidence of CCC in Asian women [54]. Genetic risk varies by histotype as well, though genome wide association studies of the rarer histotypes are generally underpowered [55]. The *HNF1B* locus represents an intriguing example of genetic heterogeneity; different SNPs in this gene are associated with serous versus CCC tumors [56].

Clinical Potential

Patterns of histotype-specific incidence and survival differ considerably by stage. The majority of HGSC and LGSC are diagnosed at an advanced stage, whereas the majority of EC, CCC and MC are diagnosed at an early stage [5]. Sixty percent of women with EOC present with distant disease, with a median five year survival of only 29% [57]. For distant stage, survival for MC and CCC is dramatically low (particularly in the years directly after diagnosis), with better survival for EC and LGSC, than HGSC [58–60]. Five-year survival for localized/regional disease is considerably better at 82% [57], with the worst survival for HGSC followed by CCC and MC, and the best survival for EC and LGSC [5]. African American women experience worse survival than women of European ancestry, while women of Asian ancestry tend to have better survival [61]. This could in part be due to differences in distributions of histotypes across racial/ethnic groups but is also likely impacted by disparities in access to care and treatment [62].

At present, the standard of care for EOC is surgical debulking, or removal of the tumor burden from throughout the peritoneal cavity, and combination platinum/taxane-based chemotherapy [63]. MC and CCC appear to be less responsive to these regimens and CCC are also more likely to recur than the other histotypes given the same treatment [64–68]. Nevertheless, the clinical care model is still a "one size fits all" approach. A gene expression analysis across LGSC, EC, MC and CCC has also revealed two classes of tumors

significantly correlated with progression free survival; the better outcome group had a higher proportion of low-grade, early-stage disease and of MC and a lower proportion of CCC [69]. It is imperative that histotype is taken into account in EOC clinical trials so that histotype-specific clinical care guidelines can be developed to improve treatment effectiveness. In breast cancer, the major molecular subtypes (luminal A, luminal B, triple negative/basal-like, normal-like and HER2 type) have different response patterns to available therapies [18,70,71], and targeted treatments have been developed (e.g., the anti-HER2 monoclonal antibody trastuzumab for the HER2 subtype and poly adenosine diphosphate-ribose polymerases (PARP) inhibitors for the basal-like subtype) [15,16]. While these treatments have garnered some success, their effectiveness is not widespread [16,72], indicating the need for additional research to identify novel subtype-specific molecular targets that can be used alone or in combination with current therapies to improve survival. The question of whether the molecular features of histotypes remain constant through treatment is important; remarkably, it is possible for lung adenocarcinomas to transform to small-cell lung cancers after developing resistance to EGFR inhibitors [73]. It is unknown whether such transformations occur in EOC histotypes.

Characteristics of HGSC Molecular Subtypes

Gene Expression Subtypes

Several studies have reported that HGSC tumors separate into four distinct molecular subtypes based on mRNA expression patterns [6–8]. In the only study to date that examined epidemiologic factors and risk of these subtypes, differences in associations were observed for age at diagnosis, race, breast-feeding, and first-degree family history of breast or ovarian cancers [74]. To cleanly separate tumors into subtypes, some researchers have removed samples that were difficult to cluster [6,7], so the reported subtypes may not capture the full complexity of the disease. The subtypes are commonly referred to as mesenchymal, immunoreactive, proliferative and differentiated [7]. Generally, the mesenchymal subtype has the worst survival, and the immunoreactive subtype has the most favorable survival. Hofree et al. defined genetic subtypes of HGSC by performing network-based clustering on germ-line and somatic variant data from TCGA, but these subtypes are not concordant with the gene expression subtypes [75]. A recent analysis of genotyping accuracy has raised questions about the quality of sequencing-based variant calls in TCGA's HGSC samples [76] which may affect the findings in Hofree et al. [75]. Given the exploratory nature of molecular clustering and limitations of the approaches used, more research is needed about how many underlying molecular subtypes exist [77–79] and if they are consistent across populations [80].

Tumor Micro-environment

Patterns of gene expression are thought to arise because of transcriptional programs active in cancer cells as a consequence of the amplification of a gene or genes in a pathway. However, alternative explanations also exist. It is possible that subtypes are merely approximations of tumor subgroups sharing similar molecular mechanisms [81]. It is also possible that some tumors efficiently recruit tumor microenvironment substrate while others do not. In many cancer types, RNA expression profiling of tumor tissue is influenced by different stromal

cell-types in the tumor micro-environment [82–84]. Still another possibility has little to do with the cancer itself: maybe cancer cells express the same markers but certain individuals have a variable response based on constitutive factors. This may have important implications for treatment. For example, a tumor of the mesenchymal subtype arising through epithelial-to-mesenchymal transition (EMT) might be treated by EMT inhibitors, while a tumor arising from an increased recruitment of stromal support cells could focus on disabling this recruitment.

In HGSC, mesenchymal and immunoreactive tumors have significantly lower tumor content [85]. This is consistent with a model where these signatures arise at least in part from stromal gene expression. Mesenchymal tumors are associated with a strong stromal reaction and increased desmoplasia while immunoreactive tumors have high levels of infiltrating T-cells [6]. Recently, a pathology-based scoring system recapitulated the TCGA-defined subtypes [86]. The authors propose a scoring scheme for proliferative as tumors with "proliferative and solid growth architecture," and differentiated as tumors with "papillary growth and glandular architecture." This classification scheme was highly reproducible, with a reported overall average consistency of 74% across scores from six pathologists.

HGSC subtypes should be considered at both the tissue and cellular level. It may be possible that a single tumor expresses the signatures of multiple subtypes across different cells, which is masked when observed in bulk. New experimental techniques provide the opportunity to interrogate such hypotheses directly. This phenomenon has been observed in 66 single cells in a HGSC tumor [87] and a subset of glioblastoma tumors by single cell profiling [88]. However, it has been recently shown that glioblastoma tumors are inherently heterogeneous by chance [89], and more single cell data is required to fully explore this phenomenon. Single cell RNAseq can reveal the types of cells in a complex mixture [90]. Measuring single cells sidesteps the need for deconvolution methods and overcomes many difficulties inherent to estimating differential cell type proportions in bulk tumor mixtures. Droplet-based methods can profile tens of thousands of single cells from a sample [91], but require fresh tissue and are costly [92]. For deep characterization of many samples, reductions in sequencing costs and analytical approaches that use single cell sequencing to inform deconvolution of bulk tumors will continue to improve the feasibility of these methods for large studies.

Clinical Potential

There is some evidence that response to treatment varies by HGSC gene expression signatures. A recent study reported that women with the proliferative and mesenchymal subtypes benefit from experimental treatment (Bevacizumab) over standard chemotherapy [93], which raises the possibility that similar subtype-specific variations in response to other actively developing therapeutics for EOC, such as PARP inhibition and immune therapies [94,95] might exist. For example, immunoreactive tumors may be good candidates for immunotherapy [79]; an open-label single-arm Phase II trial has been initiated to evaluate efficacy and safety of pembrolizumab anti-PD-1 monotherapy in these cases [96]. For mesenchymal tumors, TGF-beta inhibition may be considered since the TGF-beta pathway is significantly up-regulated compared to other subtypes, which aligns well with other

supervised expression studies reporting worse clinical outcomes associated with this pathway [97–100].

Challenges and Limitations in Studying Epidemiology of Cancer Subtypes

Potential Biases in Tissue-based Studies

Given the demonstrated heterogeneity of EOC, it is critical to perform studies that have accurate histotyping and to acquire tissue for HGSC subtyping and other molecular studies. It is logistically difficult to obtain fresh frozen tissue for large studies, but advances in molecular assays that can be performed using archival formalin-fixed paraffin-embedded tumors provide the opportunity to obtain a more representative case group. Still, there are several potential sources of bias that are important to recognize, and if possible, quantify (Figure 1). As many as 18% of women with EOC do not receive surgery [101] (although biopsy tissue or ascitic fluid are sometimes available). Use of neoadjuvant therapy prior to surgery, which is likely to influence the populations of tumor cells that remain for surgical removal, has been increasing from approximately 9% in 2004 to 23% in 2013 [102]. Archival specimens typically must be requested from a large number of hospitals, and some proportion of the specimens will not be available for various reasons (e.g., the hospital does not retain the blocks, or does not have the staffing necessary to identify, pull and send the blocks to researchers). Even if blocks are available, the slide/block that was used for the original diagnosis may not be available or the hospital may not be willing to release that block for research purposes. In fact, sometimes only blocks from other sites, most commonly the omentum, are available, and the degree to which the tumor is similar when it is collected from metastatic sites is not well-characterized. As with most cancer types, tumor heterogeneity comes into play but since EOC tumors are typically very large, appropriate sampling of the tumor is an important consideration, particularly with respect to necrosis and cellularity of the sample. For TMAs, it is important to take cores from different parts of the tumor and have multiple replicates to try to assess heterogeneity. Additional attrition occurs through the processing and extraction processes, and failure of quality control measures specific to the assay of interest. The extent to which the cases lost at each of these steps differ from the cases that are included introduces bias.

Study Design Considerations

Beyond collection of the tumor samples themselves, demographics, lifestyle behaviors, and clinical factors are important for multivariate analyses of risk, progression and survival. Population-based case-control studies are essential for studying EOC risk because it is a rare disease. Since they rely on population–based cancer registries, which identify essentially all cases in a well-defined geographic region, they have the potential to produce a representative distribution of histotypes in the population of interest. Also, accurate response proportions for EOC cases can be calculated and differences between responders and non-responders can be evaluated using data from cancer registries (e.g., age, histotype, geographic region, receipt of surgery and chemotherapy, residual disease, time between diagnosis and death). Older and more advanced EOC patients are most difficult to enroll and tend to be underrepresented in case-control studies. Rapid case ascertainment allows for the identification of eligible cases as early as one to two months after diagnosis, though

representation of rapidly fatal cancers is still problematic. In the North Carolina Ovarian Cancer Study [103], even with rapid case ascertainment, approximately 4% of eligible cases were deceased at ascertainment suggesting that the most aggressive cases were not enrolled. Further examination showed that ~15% of African American cases were deceased at ascertainment, highlighting the need to understand the underlying basis of this disparity [104]. While selection bias is a concern for case-control studies, for tissue-based studies, to the extent that it is approved by Institutional Review Boards, tissue can be requested even for non-responders.

Most existing EOC population-based case-control studies in the U.S. have focused on disease risk and many do not have clinical and outcome data. Also, nearly all were completed before 2010 [105], with epidemiologic data less representative of current exposures that may affect risk and survival (e.g., differences in oral contraceptive formulations, changes in the prevalence of obesity). Because these studies are often conducted in a large geographic region with many hospitals where diagnoses have occurred, requesting medical records and abstracting them for clinical and prognostic variables is time-consuming and costly, and often there is an unavoidably large proportion of missing data.

Hospital-based studies have the potential to increase inclusion of aggressive EOC cases and provide improved access to medical records and clinical data, and collection of serial samples pre- and post-treatment. Women can be approached for enrollment when they are being evaluated for suspected EOC. However, it is difficult to accrue large numbers of cases from a single institution so a multi-institutional effort with related complexities is required. Prospective cohort studies, to the extent that they have complete follow-up and identification of EOC cases, are able to collect data on the most aggressive cases prior to diagnosis. However, it is very difficult to obtain a sizable number of cases of EOC. Since cohort studies are not typically disease-focused, important risk factor data are often incomplete, and critical pathologic data, clinical and prognostic factors, as well as tumor tissue are often not available. Although clinical trials have detailed pathologic, prognostic and outcome data, their eligibility criteria typically result in a highly selected patient population which is unlikely to be representative of the spectrum of histotypes. Racial/ethnic minorities also tend to be underrepresented in clinical trials. For any of these study designs, careful consideration about the degree of accuracy of the existing histotypes is important to determine whether re-classification or re-review is needed. Adding tumor marker assays could help with updating tumor classification but likely results in a loss of sample size as described above.

Importance of Consortia and Interdisciplinary Approaches

Because of the low incidence of EOC and the need to study risk and survival separately by histotype and molecular subtype, efforts to pool existing data from many studies are essential. In addition to the previously noted consortia, OCAC and OC3, the newly formed Ovarian Cancer in Women of African Ancestry (OCWAA) consortium addresses disparities in risk and survival in African American women by pooling data from existing case-control and cohort studies. Work emerging from this group is likely to provide new insights into risk, prognosis and treatment of EOC because of differences in genetic background and

exposures to epidemiologic factors. Formation of these consortia do not remedy possible misclassification from earlier histotype assignments and the lack of available clinical and prognostic variables as well as tumor tissue. The Ovarian Tumor Tissue Consortium (OTTA) includes tissue-based studies and focuses on tumor biomarkers and survival [106,107], with several large efforts underway. Compilations of systematically harmonized public gene expression datasets such as curatedOvarianData [108] are complementary resources. Although these consortia and compendia represent large numbers of studies, analyses of the rarer histotypes, MC, LGSC, and CCC, remain underpowered. Bringing together multidisciplinary teams including pathologists, epidemiologists, bioinformaticians, biostatisticians, genome biologists, and clinicians to leverage existing data and conceptualize novel and more powerful approaches will accelerate advances.

Conclusions and Future Directions

Despite considerable effort, progress in identifying modifiable factors to prevent EOC and reduce mortality from this disease has been elusive. Approaching research with the understanding that EOC comprises biologically-relevant histotypes with distinct cells of origin provides an opportunity to more accurately identify etiologic risk factors, prognostic relationships and appropriate treatment strategies. The rarity of the disease and the degree of heterogeneity requires large sample sizes and multidisciplinary initiatives. While the molecular features of HGSC have been studied more than those of the other histotypes, in-depth characterization of all of the histotypes, and more precise characterization of HGSC subtypes, is needed to further reduce misclassification and increase power to detect subtype-specific associations.

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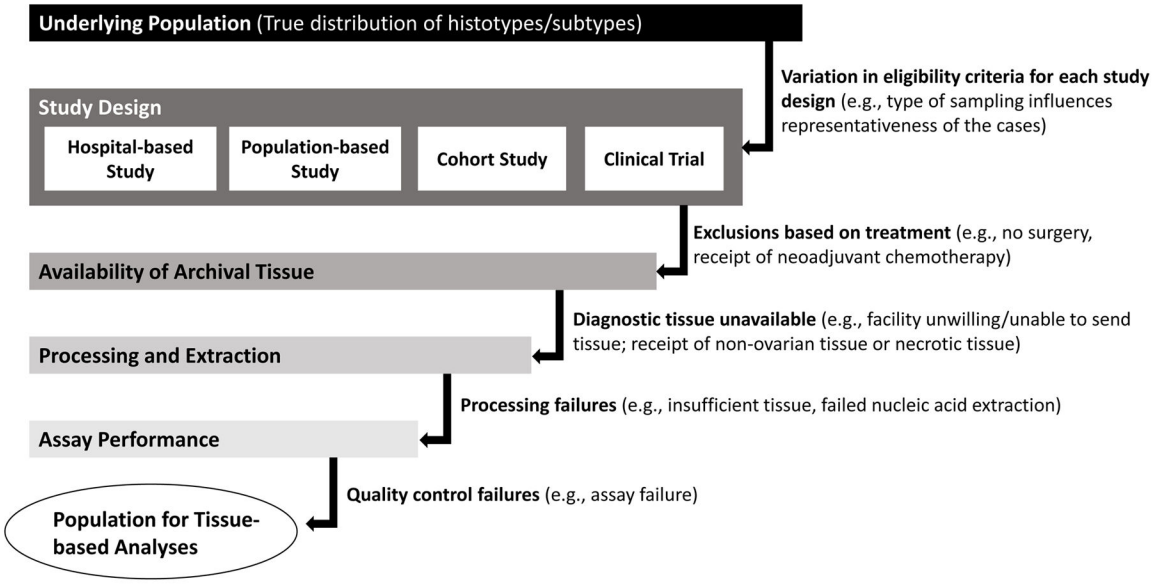

Figure 1.
Sources of bias in tissue-based studies of ovarian cancer

Table 1

Selected epidemiologic factors and EOC risk by histotype in three ovarian cancer consortia: Ovarian Cancer Cohort Consortium (OC3), Ovarian Cancer Association Consortium (OCAC) and the Collaborative Group on Epidemiological Studies of Ovarian Cancer

Risk Factors	Serous		Endometrioid		Clear Cell		Mucinous	
	Direction of Association	RR or OR (95% CI)[a]	Direction of Association	RR or OR (95% CI)[a]	Direction of Association	RR or OR (95% CI)[a]	Direction of Association	RR or OR (95% CI)[a]
Cigarette smoking (Current vs. never smokers) [44,47,48]	Null	0.99 (0.94–1.05)	Modest Inverse	0.93 (0.79–1.09)	Modest Inverse	0.95 (0.74–1.21)[b]	Positive	1.27 (1.01–1.59)
		0.89 (0.76–1.04)		0.84 (0.69–1.02)		0.74 (0.56–0.98)		1.31 (1.03–1.65)
		0.99 (0.91–1.08)		0.81 (0.70–0.94)		0.80 (0.63–1.01)		1.79 (1.47–2.17)
Tubal ligation [43,47,53]	Weak Inverse	0.91 (0.79–1.06)	Strong Inverse	0.60 (0.41–0.88)	Strong Inverse	0.35 (0.18–0.69)	Inconsistent	1.01 (0.60–1.71)
		0.81 (0.74–0.89)		0.48 (0.40–0.59)		0.52 (0.40–0.67)		0.68 (0.52–0.89)
		0.84 (0.77–0.92)		0.54 (0.43–0.69)		0.55 (0.39–0.77)		0.99 (0.84–1.18)
BMI (Per 5 kg/m^2 increase) [45,47,50]	Null	0.97 (0.93–1.01)	Positive	1.07 (0.99–1.16)	Null	1.04 (0.92–1.17)	Positive	1.08 (0.96–1.20)
		0.98 (0.94–1.02)		1.17 (1.11–1.23)		1.06 (0.96–1.17)		1.19 (1.06–1.32)
		1.00 (0.96–1.04)		1.07 (1.01–1.13)		1.05 (0.95–1.15)		1.15 (1.07–1.23)
Endometriosis [26,47]	Null (High- grade)[c]	1.11 (0.70–1.74)	Positive	2.32 (1.36–3.95)	Positive	2.87 (1.53–5.39)	Null	1.62 (0.58–4.51)
		1.13 (0.97–1.32)		2.04 (1.67–2.48)		3.05 (2.43–3.84)		1.02 (0.69–1.50)
		N/A		N/A		N/A		N/A
Estrogen-only hormone therapy (Ever vs. never use) [46,49]	Positive	N/A[d]	Positive	N/A[d]	Null	N/A[d]	Null	N/A[d]
		1.57 (1.23–2.00)		1.82 (1.10–3.03)		0.80 (0.38–1.68)		0.80 (0.38–1.69)
		1.59 (1.45–1.75)		1.42 (1.19–1.69)		0.88 (0.71–1.10)		0.91 (0.66–1.24)
Oral contraceptive use (Duration per 5-year increase of use) [47,51]	Inverse	0.85 (0.81–0.89)	Inverse	0.86 (0.77–0.95)	Inverse	0.86 (0.74–1.00)	Null	1.02 (0.80–1.31)
		N/A		N/A		N/A		N/A
		22.1% (SE 2.9) reduction in risk		27.1% (SE 4.8) reduction in risk		21.3% (SE 7.3) reduction in risk		6.7% (SE 5.8) reduction in risk
Parity (Per term pregnancy) [47,52]	Weak Inverse	0.93 (0.92–0.95)	Inverse	0.78 (0.74–0.83)	Strong Inverse	0.68 (0.61–0.76)	Weak Inverse	0.91 (0.84–0.99)
		N/A		N/A		N/A		N/A
		0.87 (0.83–0.91)		0.72 (0.66–0.77)		0.56 (0.49–0.65)		0.85 (0.77–0.93)
Breastfeeding Duration (Per year for OC3 and per month for the Collaborative Group) [47,52]	Inverse	0.94 (0.86–1.03)	Inverse	0.85 (0.69–1.05)	Null	1.03 (0.81–1.33)	Inverse	0.88 (0.63–1.23)

Risk Factors	Serous		Endometrioid		Clear Cell		Mucinous	
	Direction of Association	RR or OR (95% CI)[a]	Direction of Association	RR or OR (95% CI)[a]	Direction of Association	RR or OR (95% CI)[a]	Direction of Association	RR or OR (95% CI)[a]
		N/A		N/A		N/A		N/A
		0.98 (0.97–0.99)		0.98 (0.98–1.00)		1.00 (0.97–1.03)		0.97 (0.95–1.00)

RR: relative risk, OR: odds ratio, CI: confidence interval, SE: standard error, N/A: not applicable

[a]The order of the RRs from top to bottom is OC3, OCAC, and the Collaborative Group on Epidemiological Studies of Ovarian Cancer. For tubal ligation, the Million Women Study was included instead of the Collaborative Group. For parity and breastfeeding, a pooled analysis of nine studies in the Collaborative Group was used instead of the full set of studies in the Collaborative Group on Epidemiological Studies of Ovarian Cancer.

[b]Although cigarette smoking overall was not associated with risk of clear cell ovarian cancer in OC3, an inverse association was observed for pack-years (Per 20 pack-years: RR=0.68, 95% CI=0.53–0.89).

[c]Among LGSC, a strong positive association was observed for women with a history of endometriosis (OC3: RR=3.77, 95% CI=1.24–11.48; OCAC: OR=2.11, 95% CI=1.39–3.20).

[d]OC3 evaluated hormone therapy use overall but not by type of therapy.