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Ovarian cancer epidemiology in the era of collaborative team science

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Abstract

Purpose—Over the past decade, a number of consortia have formed to further investigate genetic associations, pathogenesis, and epidemiologic risk and prognostic factors for ovarian cancer. Here, we review the benefits that ovarian cancer consortia provide as well as challenges that have arisen. Methods for managing key challenges are also discussed.

Methods—We review the structural organization and some of the milestone epidemiologic publications of five consortia dedicated to the study of ovarian cancer, including the Ovarian Cancer Association Consortium (OCAC), the Ovarian Tumor Tissue Analysis (OTTA) consortium, the Ovarian Cancer Cohort Consortium (OC3), the Collaborative Group on Epidemiological Studies of Ovarian Cancer (The Oxford Collaborative Group) and the Ovarian Cancer in Women of African Ancestry (OCWAA) consortium.

Results—As ovarian cancer is a rare and heterogeneous disease, consortia have made important contributions in the study of risk factors by improving statistical power beyond what any single study, or even a few studies, would provide. Thus, a major accomplishment of consortial research is enhanced characterization of histotype-specific risk factor associations. Additionally, consortia have facilitated impressive synergy between researchers across many institutions, spawning new collaborative research. Importantly, through these efforts, many challenges have been met, including difficulties with data harmonization and analysis, laying a road map for future collaborations.

Conclusions—While ovarian cancer consortia have made valuable contributions to the ovarian cancer epidemiological literature over the past decade, additional efforts comprising of new, well-

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designed case-control studies are needed to further elucidate novel, histotype-specific risk and prognostic factors which are not consistently available in existing studies.

Keywords

ovarian cancer; consortium

Introduction

In recent decades, epidemiological approaches to investigating complex diseases have undergone a shift toward the utilization of multi-disciplinary and collaborative consortia [1, 2]. By definition, a scientific consortium is “a group of scientists from multiple institutions who have agreed to participate in cooperative research efforts involving, but not limited to, pooling of information from more than one study for the purpose of combined analyses and collaborative projects” [1, 3]. The primary and unique advantage of consortial research is the ability for researchers to pool data to investigate risk and prognostic factors associated with rare cancers and cancer histotypes that otherwise could not be addressed with the resources and study population sizes available to researchers at a single institution [3].

Because ovarian cancer meets the NIH definition of a rare disease (i.e., a disease affecting less than 200,000 people in the United States per year), ovarian cancer consortia are particularly relevant and warranted in an era of collaborative epidemiology. Consortial research in ovarian cancer is made all the more necessary by evidence demonstrating that ovarian cancer is not one disease, but rather several subtypes of disease, defined based on tumor histology, grade, and mutational status [4–7]. To this end, several consortia have been established over the past decade to identify genetic and/or environmental risk and prognostic factors associated with this rare, complex, and heterogeneous disease. As a leading cause of cancer death in women, with no early detection methods or screening protocols, an increased understanding of factors related to ovarian cancer risk and survival is necessary to improve prevention efforts and clinical outcomes. Further, with increasing recognition of the heterogeneity of risk factor associations for ovarian cancer, combining data across studies is necessary to evaluate whether risk factors differ for ovarian cancer histotypes.

Herein, we provide an overview of existing ovarian cancer consortia, which have served an integral role in clarifying risk and prognostic factors associated with invasive epithelial ovarian cancer. We also summarize the important benefits, challenges and limitations associated with pooling pre-existing data from consortium studies. Lastly, we discuss future directions that may offset the current challenges associated with consortia work.

Overview of Ovarian Cancer Consortia

OCAC

The Ovarian Cancer Association Consortium (OCAC; http://ocac.ccge.medschl.cam.ac.uk/) is an international consortium established in 2005 to foster genetic association studies and to identify rare variants and novel genes that cause and predispose to ovarian cancer [8]. OCAC consists of more than 76 ovarian cancer studies worldwide and currently includes 21,891

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ovarian cancer cases and 29,271 controls from four continents (North America, Europe, Asia and Australia). The majority of the studies enrolled cases between 1992 and 2010; 25 studies are currently enrolling participants. Because the main objective of OCAC was to assess genetic associations, eligible studies were limited to those in which a DNA specimen was obtained. Soon after the establishment of OCAC, a core database of epidemiologic data was developed; data were sent to the OCAC data-coordinating center (Duke University) and centrally harmonized. OCAC also formed an Epidemiologic Working Group (EWG), which addresses issues related to data harmonization, analytic approaches and ongoing and planned projects. To date, OCAC analyses have resulted in the publication of eleven epidemiologic risk and prognostic factor pooled analyses, many of which have demonstrated histotype-specific associations (ovarian cancer subtypes defined by histology) [9–19].

OTTA

The Ovarian Tumor Tissue Analysis (OTTA) consortium, which developed out of tumor tissue-based collaborations among OCAC-participating studies, combines centralized pathology review with centralized biomarker-based histotyping to achieve the integration of accurately classified patient-level tumor information with epidemiologic data. OTTA has published a tissue-based signature to more accurately characterize tumor histology and grade [20]. Additionally, OTTA facilitated a recent pooled analysis of 12 studies that included 2,933 women with ovarian cancer and examined whether tumor expression of the progesterone receptor (PR) and estrogen receptor (ER) were associated with histotype-specific survival [21]. OTTA collaborators have several ongoing projects using tissue-based biomarkers, often using tissue microarrays (TMAs), to understand ovarian cancer heterogeneity to understand ovarian cancer heterogeneity.

OC3

The Ovarian Cancer Cohort Consortium (OC3; http://sites.google.com/a/channing.harvard.edu/oc3/) was established in 2012 to bring together prospective epidemiologic cohorts that have collected data on ovarian cancer diagnoses. The original goals of the OC3 were to identify histotype-specific risk factors and to develop risk prediction models that take histotypes into account. There are currently 24 studies participating in OC3, with 6,285 cases among 1,344,765 women. A baseline dataset of core ovarian cancer risk factors assessed at study enrollment was developed based on the OCAC epidemiologic dataset to facilitate potential collaborative projects with OCAC. Data from participating studies were sent to the coordinating center (Brigham and Women’s Hospital) and centrally harmonized. OC3 has a 12-member steering committee that has monthly conference calls to discuss data harmonization and analysis. Additionally, several OC3 participating studies have joined with OCAC to perform GWAS. OC3 investigators recently published a manuscript on differences in traditional ovarian cancer risk factors by histotype [7] and harmonized analyses of potential ovarian cancer biomarkers (e.g., androgens) are underway. OC3 is currently collecting data from follow-up questionnaires and beginning pooled studies of non-centrally assembled archived tumor tissue.

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Oxford Collaborative Group

The Collaborative Group on Epidemiological Studies of Ovarian Cancer (https://www.ceu.ox.ac.uk/research/epidemiological-studies-of-ovarian-cancer) is a pooling project of data from both case-control and prospective cohort studies of ovarian cancer, with data from 58 studies on over 30,000 women with ovarian cancer. The Oxford Collaborative Group began in 2005; they centrally harmonized data at Oxford University and have published detailed analyses on oral contraceptives, smoking, body size, and menopausal hormone therapy [22–25]. Overlap between this group and studies contributing data to OCAC and OC3 is high, although studies from OCAC and OC3 include cases diagnosed more recently than the Oxford Collaborative Group dataset.

OCWAA

With worse ovarian cancer survival among African-American (AA) women compared to whites, there is a need to further understand the epidemiology of ovarian cancer among women of African Ancestry. To date, only the African American Cancer Epidemiology Study (AACES) has enrolled enough AA women to conduct adequately-powered analyses of risk factors for incidence but less so for evaluating factors influencing survival of this difficult to detect and treat cancer [26]. No single study has an adequate sample size to address either risk factor or prognostic factors within ovarian cancer histotypes, reflecting the logistical challenges of studying less common cancers in minority populations. To better understand racial differences of ovarian cancer, it is therefore critical to pool resources from multiple studies to form the Ovarian Cancer in Women of African Ancestry (OCWAA) consortium. Although data have not yet been pooled, it is hoped that this emerging consortium will succeed to combine information from multiple large case-control and cohort studies to provide the opportunity to estimate the effect of differential exposures to risk factors on differences in race-specific incidence and survival.

Benefits of Consortial Analyses

Increased power to evaluate rare outcomes

The most important advantage of conducting a consortium analysis is the ability to conduct well-powered investigations of risk and prognostic factors that otherwise could not be addressed with individual epidemiological investigations. This advantage is particularly relevant for uncovering risk and prognostic factors associated with each of the ovarian cancer histotypes—and especially among the less common histotypes (e.g., endometrioid, mucinous and clear cell tumors). In fact, recent publications from OCAC [9–15, 19], The Oxford Collaborative Group [22, 24, 25], and OC3 [7] substantiate previous evidence in individual studies that there is considerable heterogeneity of individual risk factor associations across ovarian cancer histotypes and that the histotypes are different diseases.

Pooled analyses can also provide the statistical power required to conduct relevant stratified analyses, including examining associations between exposures and ovarian cancer endpoints by additional epidemiological factors such as race, ethnicity, menopausal status, family history of ovarian cancer and obesity status. Further, the enhanced statistical power provided by combined analyses allows for the study of rare exposures, such as a family history of

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ovarian cancer and genetic susceptibility, the detection of modest associations, and enables investigators to assess interactions between genetic and environmental risk factors [27, 28]. The large samples size afforded by consortia efforts also enhances risk model prediction, allowing for extensive risk factor coverage. For example, the recently published risk prediction model using OCAC data was able to fit models stratified on age (<50 vs. ≥50) and could also fit interaction terms between hysterectomy and menopausal hormone therapy, as this interaction has been shown in prior analyses of ovarian cancer risk [29]. This is of particular importance in genetic association analyses such as with genome-wide association studies (GWAS) where the challenge of multiple comparisons is an essential consideration and was the primary motivation for the formation of OCAC. OCAC provides the large sample sizes required in GWAS projects and has resulted in a number of publications in high impact journals such as *Nature Genetics* [30–34]. Although some GWAS SNPs have been identified without stratifying by histotype, it is notable that many associations found in EOC overall are likely driven by high-grade serous tumors, the most prevalent EOC histotype. This assertion has been supported when genetic associations initially detected for all histotypes combined are often observed to increase in significance in the more homogenous sample of high-grade serous cases [33, 35]. Further, a recent GWAS showed associations specific to the mucinous histotype [32] and in the most recent OncoArray analysis using OCAC data, with the largest number of cases and controls to date, all 10 newly discovered GWAS SNPs associations were histotype-specific. Two were specific to the less common mucinous ovarian cancer cases, four were specific to low-grade serous ovarian cancer and three were specifically associated with high-grade serous ovarian cancers [36].

Establishing consensus

In addition to uncovering important histotype-specific risk factor associations, consortial analyses also serve as an authoritative source for establishing consensus when previous investigations were inconclusive or when single studies could not adequately address an important research question. For example, prior to 2012, existing scientific literature consistently demonstrated that endometriosis was associated with an increased risk of ovarian cancer, but the reported associations between endometriosis and the invasive histotypes were inconsistent. However, more recently, consistent histotype-specific findings reported in two pooled analyses from OCAC [37] and OC3 [7] solidified that endometriosis is more strongly associated with clear cell and endometrioid tumors than with other ovarian cancer histotypes.

Similarly, unopposed estrogen menopausal hormone therapy has been consistently associated with an increased risk of ovarian cancer; however, associations with estrogen plus progestin therapy were largely inconsistent. Through a combined analysis of case-control, cohort, and clinical trial study data, the Oxford Collaborative Pooling Project confirmed an increased risk of ovarian cancer per 5 years of estrogen plus progestin use [22].

Taken together, the establishment of ovarian cancer consortia have strengthened our understanding of the etiology of ovarian cancer and have added greatly to our knowledge that the individual ovarian cancer histotypes are different diseases with different risk factor profiles. While vital strides have been made towards establishing consensus and enhancing

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risk-prediction capabilities, we acknowledge there are important challenges associated with consortial research and that much work remains in further elucidating the epidemiology of epithelial ovarian cancer.

Challenges and considerations associated with consortial research

Study Design

The large sample sizes afforded by consortial research do not remove potential biases associated with certain epidemiologic study designs. For example, while most of the 76 OCAC-participating studies are population-based or hospital-based case-control designs, there are also 25 case-only studies, five prospective cohort studies and an additional five nested case-control sample sets from prospective cohorts. Thus, given the different types of biases that can ensue from varying ascertainment methods, it is imperative to attempt to account for differences in study design in analyses when data is pooled from several types of studies. While we acknowledge these potential challenges, it is important to emphasize that the majority of studies included in OCAC epidemiological pooled analyses are population-based case-control studies utilizing controls identified through random digit dialing, or through population registries, electoral rolls, surveys, or by municipality/neighborhood.

In instances where data have been pooled from both population-based and hospital-based case-control studies, two approaches that have been commonly employed in OCAC analyses include assessing between-study heterogeneity based upon study design, or excluding hospital-based case-control studies in sensitivity analyses. These approaches may be particularly important when studying modifiable lifestyle exposures such as physical inactivity, smoking, alcohol consumption and BMI, because women who volunteer to serve as controls in population-based studies may represent a sample of women who are healthier than the general population, which could result in a more extreme point estimate. On the contrary, a hospital-based study utilizing a control group comprised of patients diagnosed with non-neoplastic conditions may be unhealthier than the general population, thus potentially biasing a point estimate towards the null.

Differences in case-control versus cohort studies are also an important concern given the potential for recall bias in case-control studies which cannot be mitigated by analytic methods. One noteworthy example of a consortia paper which identified different associations by study design included the Oxford group’s study of hormone therapy usage [22]. Specifically, current hormone therapy use, as opposed to former use, was shown to be the most relevant exposure in cohort studies, whereas current hormone therapy use in case-control studies generally yielded null results [22]. On the contrary, the Oxford group also recently reported that ever use of oral contraceptive (OC) was associated with a reduced risk of ovarian cancer for all three study designs evaluated (i.e., the risk estimate was 0.74 for prospective studies, 0.69 for population-based case-control studies and 0.81 for hospital-based case-control studies) [38].

Lastly, in the OC3, in which all participating studies are prospective cohort studies, there is less concern about the potential for recall or other types of ascertainment bias, because in most studies, exposure data were collected many years prior to the diagnosis of ovarian

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cancer. However, because the OC3, to date, only uses baseline exposure data, exposures that change over time, such as BMI, use of menopausal hormone therapy and other medications, may be misclassified. Although this misclassification is likely to be non-differential, it can nevertheless lead to an underestimate of the true exposure-disease association, which can reduce power, particularly for studies of rare histotypes. Also, because ovarian cancer is rare, most prospective studies have few cases; thus, even when combining cases from several prospective studies, as the OC3 did, the total number of cases still remains low.

In summary, the potential limitations of differing study designs and data ascertainment methods, while challenging, can usually be addressed in the statistical analysis by evaluating differences in estimates of association by study design (for population-based case-control studies, hospital-based case-control studies, and/or cohort studies) or by examining whether the association with the exposure of interest changes over time since enrollment (for cohort studies). Identifying differences by study design or over time can help to understand the nature of the relationship between the exposure of interest and the outcome. For example, if an exposure is only associated with cases that occur shortly after the baseline questionnaire (in a cohort study), that might suggest reverse causation rather than a causal effect of the exposure of interest. Therefore, this potential limitation of consortial research can actually be leveraged to provide additional insight into the exposure-disease relationship.

Data sharing

Individual level data from epidemiologic studies are typically sent to a central data-coordinating center for cleaning, checking and harmonization to create one dataset for data analysis. Most institutions require data transfer agreements (DTAs) to share individual-level data which can be cumbersome involving oversight of the individual institute’s legal team. Existing consortia have addressed some of these data-sharing challenges. For example, the OCAC core epidemiologic dataset contains de-identified data; thus it can be sent to individual institutions without requiring additional DTAs. The OC3 has a template DTA, which many participating studies’ institutions accepted when forming the OC3, thus reducing the amount of time to receive approval to share data. This template DTA covers how and where data will be stored, who will have access, approval for future projects, and other institution-specific requirements for data sharing.

Harmonization

Data harmonization efforts are almost always necessary when combining data across multiple studies [39]. This often involves combining data across disparate categories, resulting in a loss of granularity. While there are benefits in terms of increasing sample size, there are disadvantages in combining categories and potentially dampening the measured association by including, for example, moderately exposed individuals in the same category as highly exposed individuals because of lack of information or inconsistent categorization of data across study instruments. For example, in the OC3, some studies collected information on duration of oral contraceptive use using categories, while other studies queried total duration in continuous years.

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The loss of granularity in an exposure across multiple studies can sometimes be addressed or assessed through sensitivity analyses. If there is a subset of studies that collected information in a similar manner, analyses can be limited to the more granular data from a smaller number of study subjects. However, this approach requires careful consideration of the differences between individual studies (e.g., age or race of study participants) that may influence the risk factor association of interest. Analyses restricted to a limited number of studies with specific data should evaluate the primary exposure association in the subset of pooled study data to demonstrate that it is consistent with the results from the larger pooled study data, before interpreting results based on a subset of studies with additional (potentially more detailed) data.

Missing data/variables

A major challenge in conducting consortial research is missing data, which can be broadly categorized into two categories: 1) respondent-level missing data on study variables that were assessed by investigators (e.g. respondent could not recall exposure or preferred not to answer) and 2) study-wide missing data due to exposures or clinical variables of interest that were not assessed by investigators. Unfortunately, if missing data is not random, this could potentially yield biased results, while large amounts of missing data can result in a lack of statistical power to conduct important analyses.

There are established methods to address respondent-level missing data. For example, when assembling harmonized risk factor data from 11 case-control studies in OCAC to construct a risk prediction model including 17 risk factors, all variables, except age, were found to have some missing data [29]. In fact, 80% of the participants were missing information on at least one risk factor and the amount of missing data for any individual variable ranged from 1% – 46%. In this scenario, rather than limit the analysis to participants with complete data or drop risk factors from the model, the missing data were imputed, resulting in an increased sample size and improved power [29]. In this example, epidemiologic variables were imputed through the development of a Bayesian model that provided a sequence of conditional models for case-control status, the risk factors and indicators of whether they were missing or not missing at random. Missing data was modeled as a function of other risk covariates and incorporated using Markov Chain Monte Carlo. Missing SNP data was modeled using a multinomial model with probabilities for the number of rare alleles given an informative Dirichlet prior distribution centered at genotype probabilities assuming Hardy-Weinberg equilibrium and a mass parameter in the Dirichlet equivalent to 1,000 observations. Genotype probabilities were calculated using the minor allele frequency estimated from studies in OCAC not used in the analysis.

Addressing study-wide missing data can be more challenging. While case-control studies in OCAC obtained data on the majority of well-established risk/preventive factors for ovarian cancer (e.g., parity, oral contraceptive use, and family history of ovarian or breast cancer), data on less established factors (e.g., body powder, analgesic medication use and tubal ligation) were not included in the questionnaires for one or more studies in the U.S. and Australia, and these data were entirely absent among studies conducted in Asia. Further, additional factors that may be relevant to ovarian cancer etiology or prognosis (e.g.,

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autoimmune disease or pelvic inflammatory disease) have not routinely been captured in case-control or cohort studies.

Missing variables can be even more problematic in cohort studies because data collection was not primarily focused on ovarian cancer epidemiology. For example, in OC3-participating cohorts, some well-established ovarian cancer risk/preventive factors were not consistently obtained in questionnaires (e.g. breast-feeding duration and endometriosis). Specifically, among 21 studies included in the OC3 analysis of risk factor differences by histotype, only 6 studies had collected information on endometriosis. Thus, study-wide missing data limits the effective sample size because imputation in this context is more challenging. However, one possible solution is to impute the data based upon the distribution of the variable of interest in the most similar study with complete data. This approach is currently being used in a risk prediction model that is being developed in collaboration between OCAC and the OC3. Indicator variables, interaction terms, and multiple imputation (described above) in pooled analyses are additional ways to address missing data.

Data analysis

Data analysis in consortia usually comes in one of two forms: 1) a two-step process involving analyses in individual studies followed by meta-analysis yielding a weighted summary estimate of association [40] or 2) a pooled analysis of all data combined. Both data pooling methods are associated with important strengths and weaknesses that warrant further discussion. The appeal of meta-analysis is that it allows for the studies with more detailed information on confounders to have complete adjustment, without having to limit adjustment to variables available in all studies. Additionally, investigators can quantify, and account for, between-study heterogeneity by reporting random-effects summary estimates when significant heterogeneity is observed. However, the major drawback of meta-analysis is that studies with few observations may yield unstable effect estimates and may need to be excluded from the meta-analysis. This is particularly problematic when both the exposure and the outcome are rare. For example, in the OC3 analysis of differences in risk factor associations by histotype, the association of first-degree family history of ovarian cancer with the rarer histotypes yielded wildly different relative risks across studies because, by chance, some studies had only one exposed individual, yielding relative risks that were either infinity or negative infinity [7]. Thus, most studies that use meta-analysis as the main approach often use a pooled approach when examining differences by histotype or when performing stratified analysis.

The major benefit of pooling data via a combined dataset is the improvement in statistical power associated with analyzing one large dataset, which also allows for well-powered subgroup analyses. However, as noted above, many studies have missing data on important potential confounders. Therefore, pooled analyses may suffer from residual confounding, which should be addressed in sensitivity analyses that compare minimal vs. more complete adjustment in the studies with more complete information. Furthermore, the combined dataset approach is most appropriate when no between-study heterogeneity is noted. Thus, many investigators utilize the two-stage approach as described above and if no heterogeneity is observed, a pooled analysis utilizing a combined dataset is performed. This approach has

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the added benefit that analysts can easily compare the study-specific estimates yielded in their analysis with published results (if they are available).

Communication

A successful consortium, yielding efficient data collection, harmonization and data analyses requires clear and consistent communication, participation and expertise of its contributing members. Although the data-coordinating center may bear the majority of the burden, at least initially, much input and feedback from participating studies is required for quality control and ensuring that the harmonized data reflects the original studies to the greatest degree possible. For data analysis projects, feedback from both the data-coordinating center and the individual studies participating in the project is crucial. Thus, communication is a key component of consortial research.

Although both the OC3 and OCAC have regular conference calls to discuss ongoing projects, both also have annual in-person meetings to help foster communication. Initially, the OCAC consortium had semi-annual meetings; over time this meeting has become annual meeting. These meetings have been critical for the success of OCAC by providing a venue for face-to-face interactions with a large number of participants, ~80 individuals attended the 2016 OCAC meeting, which allowed a discussion of detailed information as well as allowed investigators to reach consensus quickly, when necessary.

The OC3 has annual meetings in concert with the annual meeting of the NCI Cohort Consortium. The OC3 steering committee, which consists of 12 members, also has monthly conference calls to discuss ongoing analyses. At the annual meeting, OC3 members review ongoing analyses, provide feedback on current and upcoming projects and approve new project proposals. Although many of the discussions at the annual meeting overlap with the steering committee calls, the annual meeting is an opportunity to get feedback from members who are not on the steering committee, discuss projects in more detail, and make plans for future investigations.

How to Meet Challenges: Future Directions in Ovarian Cancer Research

While the establishment of several ovarian cancer consortia has served as an impetus for advancing our knowledge of ovarian cancer risk, much of the etiology of the disease remains unknown and we know very little about whether there are modifiable factors that may improve prognosis among women diagnosed with ovarian cancer. Thus, in recognition that existing data within the consortia have not yet been fully exploited, existing consortia are continually working to address current gaps in knowledge relevant to ovarian cancer etiology and prognosis. For example, the OTTA consortium continues to use tissue-based biomarkers to further our understanding of ovarian cancer histotypes and how they might develop through different etiologic pathways. Additionally, OCAC-participating studies have combined to form a long-term survival consortium. Furthermore, the OC3 is collecting updated data (i.e., data from post-baseline questionnaires), to assemble both pre- and post-diagnosis information that might be used to better understand predictors of ovarian cancer prognosis.

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Despite these efforts, there remains a need for new, well-designed, multi-site case-control studies designed to carefully, objectively and consistently assess putative risk and prognostic factors that have not yet been definitively associated with ovarian cancer risk or prognosis (e.g., the role of inflammation in risk and prognosis or the role of post-diagnostic physical activity in survivorship). An important limitation of existing consortia is that most subjects were enrolled prior to 2010 [9–18], yielding decade-old data for most studies. Since exposures have changed over time, such as recent formulation changes in oral contraceptives, the impact of these changes cannot be addressed using existing data. As it appears there are no major ongoing epidemiologic data collection efforts, it is not possible to assess effects of changes in exposure in well-established risk factors within existing consortia. Additionally, since definitions and practice has changed over time, older studies are likely to have misclassification of the histotypes. Further, novel etiologic hypotheses that require new exposure assessment cannot be addressed in existing studies. It is also clear that the definition of disease going forward will rely on the molecular characterization of the tumor. However, many of the epidemiologic studies in existing consortia have not obtained tumor tissue and therefore, disease heterogeneity cannot be assessed through molecular markers. Additionally, as most of the known ovarian cancer risk factors seem to be less strongly related to the high-grade serous histotype [7], the most common and aggressive type, there remains an urgent need to identify high-grade serous-specific risk factors. Thus, additional pooling efforts, using high-quality epidemiological and clinical data, are needed to gain a better understanding of ovarian cancer etiology, as well as for the targeted development of novel prevention approaches.

One way to meet the challenges associated with the reliance upon pre-existing consortia data is to prospectively plan multi-site case-control studies in which data pooling is part of the planning [27, 41]. The AACES, a multi-center, population-based case-control study of ovarian cancer in African-American women [26] is a successful example of this approach. Additionally, researchers focusing on other cancer types are also conducting similar types of analyses. Two notable examples include the international case-control study of adult glioma and meningioma [42] and the InterLymph Consortium [43]. Additional examples of successful prospectively planned pooled analyses of cohort data include the SEARCH program and the European Investigation on Cancer and Nutrition (EPIC) studies [44, 45].

In conclusion, we have shown that ovarian cancer consortia have facilitated and advanced epidemiologic and genetic research that has been mostly focused on ovarian cancer risk. Although, these efforts continue, important limitations exist and further considerations of how to overcome existing challenges are necessary. With the shift in trend from ‘cottage industry’ epidemiology to collaborative epidemiology of the twenty-first century [2], more prospectively planned pooled analyses, utilizing standardized study designs, data collection and analytical methods, are warranted to further elucidate factors associated with EOC etiology and prognosis [41].

Supplementary Material

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