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EDITORIAL

Epidemiologic paradigms for progress in ovarian cancer research

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Editorial

In the US, though ovarian cancer is the 11th most common cancer in women, it is the fifth most common cause of cancer death [1]. Despite the development of some personalized novel treatment approaches, survival has not substantially improved, in part due to the late stage at diagnosis in most patients. This decade has marked a very exciting time in ovarian cancer research with the paradigm-shifting understanding that ovarian cancer is not one disease, but comprises a constellation of different disease histotypes with varying etiology and pathways of development, characterized by distinct mutational profiles, cells of origin/precursor lesions, and histology [2, 3]. As these changes in understanding become incorporated into epidemiologic research, we will make greater progress in reducing the incidence and mortality from this highly lethal cancer. Further showing the importance of ovarian cancer as a public health issue, congress designated funds to review the state of the science of ovarian cancer as part of the Gynecologic Cancer Education and Awareness Act (also known as Johanna's law). In 2015, the Centers for Disease Control tasked the Institute of Medicine (IOM) to "make recommendations for public and private sector efforts that could facilitate progress in reducing the incidence of and the morbidity and mortality from ovarian cancer," with an emphasis on advancing research on ovarian carcinogenesis across the cancer continuum [4].

Notably, several recommendations in the report are particularly relevant to the implementation of population-based studies of ovarian cancer risk and survival. These span primary prevention, screening/early detection, and secondary prevention. With respect to primary prevention, a key recommendation was to "identify and evaluate the underlying mechanisms of both new and established risk factors for ovarian cancers…accounting for the various ovarian cancer subtypes [4]." The ultimate goal of such work is to improve upon risk prediction models to identify high-risk women who could benefit from prevention measures. To date, risk models have had low predictive capacity [5–9], in part due to the heterogeneity of risk factor associations across tumor histotypes [10] and the relatively few strong risk factors identified for the most common and deadly histotype, high-grade serous tumors. In addition, the IOM committee recommended that researchers "focus on the development and assessment of early detection strategies that extend beyond current imaging modalities and biomarkers and that reflect the pathobiology of each ovarian cancer subtype [4]," given that CA-125 and transvaginal ultrasound screening protocols have not led to significant reductions in mortality from ovarian cancer [11–14]. Finally, population science can play a role to "develop more effective pharmacologic and nonpharmacologic therapies…that take into account the unique biology and clinical course of ovarian cancer [4]." To achieve these goals, it is critical to consider new approaches in conducting epidemiologic studies of ovarian cancer risk and survival

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and to take advantage of consortium-based efforts to study this relatively rare, yet heterogeneous and deadly, disease. This Special Issue contains a commentary and cutting-edge research that addresses the IOM recommendations and seeks to set the stage for advancing epidemiologic research on ovarian cancer into the next decade.

Thus, the call for papers for this Special Edition requested submission of original research articles, particularly those coming from consortia or collaborative work, that incorporated the following: (a) evaluating traditional risk factors in a new context (e.g., recent birth cohorts, different racial/ethnic populations) or novel risk factors, (b) considering associations across tumor histotypes (within and across anatomic sites) or with potential precursor lesions, (c) assessing factors associated with screening and survival, and (d) commentaries about approaches to advance population-based research on ovarian cancer. In this Issue, we include 10 original, peer-reviewed research articles and one commentary that highlight crucial research meeting the recommendations set out by the IOM report.

Traditional and new risk factors

Oral contraceptive use is well established as a protective factor for ovarian cancer in many studies. However, most of these studies evaluated populations born before the 1950s that had access to early, more potent formulations of contraceptives. Notably, Webb et al. shows that the potential impact of oral contraceptive use on ovarian cancer incidence rates over time shows evidence that the decline in incidence observed for birth cohorts who had access to oral contraceptives may be lessening among later birth cohorts. To examine this in more detail, the issue highlights studies examining oral contraceptives and other established risk factors from studies comprising women from later birth cohorts. These studies showed that newer, lower hormone oral contraceptives might only reduce risk with very long-term use, with a suggestion of an increased risk for short-term use in some studies (Bethea et al., Koushik et al., Shafrir et al.). These studies illuminate a critical need in ovarian cancer research to evaluate the efficacy of newer contraceptives and contraceptive methods (e.g., hormone intrauterine devices). Such work will require the development of new case-control studies among women from later birth cohorts who had access to these contraception approaches and continued follow-up of recent prospective studies, such as the UK Biobank. In addition, two articles from a prospective (Bethea et al.) and consortial case-control study (Peres et al.) show that traditional risk factors have the expected associations with ovarian cancer risk in African-American women, an understudied population in ovarian cancer research. While the individual studies have too few cases on their own to examine associations for the rare histologic subtypes, the Commentary (Cannioto et al.) describes a new initiative to develop a consortium pooling together all existing (and future) data from African-American women. Finally, one article illustrates work in a more novel area examining local inflammation to the peritoneal cavity, by reviewing all work on pelvic inflammatory disease (Su et al.). Given the challenges of assessing local inflammation in the peritoneal cavity, creative studies using multiple approaches will be needed to understand its role in ovarian cancer development.

Tumor histotypes and precursor lesions

As it has become increasingly clear that ovarian cancer is not one disease, with multiple potential cells of origin, including the ovary, fallopian tubes, and endometriosis/endometrial tissue, it is crucial to employ consortia to increase power to investigate associations by histotypes. Importantly, the commentary describes key ovarian cancer population-based consortia and discusses the advantages and challenges of this research approach (Cannioto et al.). Studies in this issue leverage two of the largest consortia, including the Ovarian Cancer Association Consortium (Babic et al., Minlikeeva et al.) and the Ovarian Cancer Cohort Consortium (Ose et al.). The latter study pools data on insulin-like growth factor I (IGF-I) from prospectively collected blood samples and shows a clear, but unexpected, inverse association, despite the well-established positive association of ovarian cancer with height [15] (which is associated with higher IGF-I). This suggests an opportunity to better understand the role of growth hormones in ovarian cancer development, which given that IGF-I was similarly associated across all histotypes suggests that it may influence either very early carcinogenesis or late stage tumor development. Further, endometriosis has now been proposed to be a precursor lesion for the endometrioid and clear cell histotypes of ovarian cancer. Also, some hypothesize that endometrioid ovarian tumors represent metastases from endometrial tumors. Two articles in this issue address these questions (Poole et al., Kelemen et al.) using different approaches. Poole et al. examined the association of endometriosis with both ovarian and endometrial cancer risk in a prospective study with confirmation of endometriosis onset. While endometriosis was associated with higher ovarian cancer risk, particularly of the endometrioid and other nonserous histotypes, it was not associated with endometrial cancer. This suggests that endometriosis likely is not a common precursor of these two cancers. These results were consistent with findings from Kelemen et al., that endometriosis of the ovary was associated with a lower risk of having synchronous endometrial and ovarian

cancer versus ovarian cancer alone. However, the molecular profiles of synchronous tumors differed from single-site disease, suggesting that at least a small portion of ovarian tumors may be metastases from the endometrium. Overall, these studies support the continued examination of putative precursor lesions in ovarian cancer development, including precursors of the serous subtype, as well as relationships of ovarian tumors with other reproductive cancers.

Screening and survival

Although no current screening protocol is recommended for population use, CA-125 has the best predictive capacity of any known biomarker to date [16]. Screening trials that used changes in CA-125 over time as opposed to a hard cut-point generally performed better with respect to shifting diagnosis to earlier stages [11–14], suggesting that improved understanding of how levels of this marker are regulated may inform screening protocols. Babic et al. leveraged data from the Ovarian Cancer Association Consortium to evaluate predictors of CA-125 in cases at the time of diagnosis. Notably, race and prior oral contraceptive use were associated with CA-125 independent of tumor characteristics. If such findings were extended to prospective studies, it may be possible to identify individualized cut-points or changes over time based on participant characteristics that can improve early detection. Further, relatively few population-based studies have examined associations of pharmacologic and nonpharmacologic factors [17], such as aspirin use and physical activity, which have been associated with survival for other cancers [18–20]. Given increasing evidence that pre-diagnosis risk factors influence tumor development, considering exposures both before and after diagnosis is required to fully characterize survivorship in ovarian cancer patients. This approach is evidenced by Minlikeeva et al., who examined the relationship of comorbidities and common drugs for their treatment with survival in the Ovarian Cancer Association Consortium. Notably, some differences in association were observed by histologic type, demonstrating the need to consider tumor heterogeneity in the survival context. Future work leveraging existing studies with pre- and post-diagnosis exposure data in the consortial setting, as well as new studies following patients at regular intervals after diagnosis, is needed to identify potential future interventions for ovarian cancer patients.

Summary

Ovarian cancer is a complex, heterogeneous disease with poor outcomes. Because of its relative rarity, it is less studied compared to some other female cancers (e.g., breast cancer). However, consortial initiatives as outlined in Cannioto et al. provide unique opportunities to identify factors that can influence prevention recommendations, improve ability to target surgical interventions to high-risk women, and support lifestyle changes among patients to enhance survival and quality of life. That said, time trends in reproductive factors over the last several decades, occurring with the backdrop of increasing obesity and changes in diet, as well as the need to assess completely novel exposures (e.g., psychosocial stress, GIS-based measures) and windows of susceptibility (e.g., pre- vs. postmenopause), will require development of new cohort and case-control studies to advance understanding in the short- and long-term [21]. Further, consortia and new studies should include diverse populations as well as integrate tumor tissue to better assess alternate markers of tumor heterogeneity that may help elucidate etiologic pathways by which exposures influence disease development. We hope that this issue begins to address the IOM recommendations, providing a roadmap for the coming decade to reduce morbidity and mortality of ovarian cancer through the implementation of population-based research.

References

1. Cancer Facts & Figs (2015) Atlanta: American Cancer Society
2. Jarboe EA, Folkins AK, Drapkin R, Ince TA, Agoston ES, Crum CP (2009) Tubal and ovarian pathways to pelvic epithelial cancer: a pathological perspective. Histopathology 55(5):619
3. Kurman RJ, Shih Ie M (2011) Molecular pathogenesis and extraovarian origin of epithelial ovarian cancer-shifting the paradigm. Hum Pathol 42(7):918–931
4. IOM. Ovarian Cancers (2016) Evolving paradigms in research and care. Ovarian cancers: evolving paradigms in research and care. IOM, Washington (DC)
5. Hartge P, Whittemore AS, Itnyre J, McGowan L, Cramer D (1994) Rates and risks of ovarian cancer in subgroups of white women in the United States. The Collaborative Ovarian Cancer Group. Obstet Gynecol 84(5):760–764
6. Li K, Husing A, Fortner RT et al (2015) An epidemiologic risk prediction model for ovarian cancer in Europe: the EPIC study. Br J Cancer 112(7):1257–1265
7. Pfeiffer RM, Park Y, Kreimer AR et al (2013) Risk prediction for breast, endometrial, and ovarian cancer in white women aged 50 y or older: derivation and validation from population-based cohort studies. PLoS Med 10(7):e1001492
8. Rosner BA, Colditz GA, Webb PM, Hankinson SE (2005) Mathematical models of ovarian cancer incidence. Epidemiology 16(4):508–515
9. Clyde MA, Palmieri Weber R, Iversen ES et al (2016) Risk prediction for epithelial ovarian cancer in 11 United States-based case-control studies: incorporation of epidemiologic risk factors and 17 confirmed genetic loci. Am J Epidemiol 184(8):579–589
10. Wentzensen N, Poole EM, Trabert B et al (2016) Ovarian cancer risk factors by histologic subtype: an analysis from the ovarian cancer cohort consortium. J Clin Oncol 34(24):2888–2898

11. Buys SS, Partridge E, Black A et al (2011) Effect of screening on ovarian cancer mortality: the Prostate, Lung, Colorectal and Ovarian (PLCO) cancer screening randomized controlled trial. JAMA 305(22):2295–2303
12. Kobayashi H, Yamada Y, Sado T et al (2008) A randomized study of screening for ovarian cancer: a multicenter study in Japan. Int J Gynecol Cancer 18(3):414–420
13. van Nagell JR Jr, DePriest PD, Ueland FR et al (2007) Ovarian cancer screening with annual transvaginal sonography: findings of 25,000 women screened. Cancer 109(9):1887–1896
14. Jacobs IJ, Menon U, Ryan A et al (2016) Ovarian cancer screening and mortality in the UK Collaborative Trial of Ovarian Cancer Screening (UKCTOCS): a randomised controlled trial. The Lancet 387(10022):945–956
15. Schouten LJ, Rivera C, Hunter DJ et al (2008) Height, body mass index, and ovarian cancer: a pooled analysis of 12 cohort studies. Cancer Epidemiol Biomarkers Prev 17(4):902–912
16. Zhu CS, Pinsky PF, Cramer DW et al (2011) A framework for evaluating biomarkers for early detection: validation of biomarker panels for ovarian cancer. Cancer Prev Res (Phila) 4(3):375–383
17. Poole EM, Konstantinopoulos PA, Terry KL (2016) Prognostic implications of reproductive and lifestyle factors in ovarian cancer. Gynecol Oncol 142(3):574–587
18. Elwood PC, Morgan G, Pickering JE et al (2016) Aspirin in the treatment of cancer: reductions in metastatic spread and in mortality: a systematic review and meta-analyses of published studies. PLoS ONE 11(4):e0152402
19. Dieli-Conwright CM, Lee K, Kiwata JL (2016) Reducing the risk of breast cancer recurrence: an evaluation of the effects and mechanisms of diet and exercise. Curr Breast Cancer Rep 8(3):139–150
20. Schoenberg MH (2016) Physical activity and nutrition in primary and tertiary prevention of colorectal cancer. Visc Med 32(3):199–204
21. Epidemiology Working Group Steering Committee, Ovarian Cancer Association Consortium (2017) Current gaps in ovarian cancer epidemiology: the need for new population-based research. JNCI under review: NCI