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Editorial

EDITORIAL

Precancerous Lesions of Ovarian Cancer—A US Perspective

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A major challenge to realizing the goals of early detection and prevention of ovarian cancer is a lack of comprehensive knowledge of the natural history of precancerous lesions. Precancerous lesions are abnormal tissues that often precede the development of invasive carcinoma, which could be a risk factor, a true precursor, or an in situ component of the carcinoma. Unlike cancers arising in the endometrium, cervix, colon, breast, and prostate, where the early events of carcinogenesis can be studied because their precursor lesions have been well established, this is not the case for ovarian high-grade serous carcinoma (HGSC), the most common and lethal type of ovarian cancer. In recent years, technology has enabled the generation of molecular evidence that suggests that serous tubal intraepithelial carcinoma (STIC) of the fallopian tube is likely the precancerous lesion of most HGSCs (1–5). While molecular and epidemiologic data are emerging to support this paradigm, the clinical utility of a STIC diagnosis remains to be determined. A STIC comprises contiguous atypical epithelial cells with morphological and molecular features resembling an invasive HGSC. STICs reside in the fimbriated ends of fallopian tubes, from which some STIC cells may be by exported to ovaries and peritoneal tissues, where they progress to HGSCs. As such, HGSCs are often advanced diseases at the time of diagnosis (Figure 1). The prevalence of STICs is reported to be as high as 10% in *BRCA1/2* mutation carriers (6), but little is known about the incidence of STICs in the general population.

The study by Trabert et al. appearing in this issue of the Journal is a timely report that begins to address this question (7). The report highlights the importance of descriptive epidemiology and the value of using combined data from cancer registries across a country to better understand the clinical characteristics and public health burden of uncommon diseases. Through the North American Association of Central Cancer Registries (NAACCR), the authors were able to access data on fallopian tube and ovarian carcinomas diagnosed between 1999 and 2012 from 30 high-quality cancer registries spread across the entire United States. The authors are to be congratulated on this important study.

The authors used a variety of coding algorithms based on ICD coding and histology in an attempt to identify STICs from previously collected data. Using specific histologic criteria available between 2008 and 2012, 53% of women who were diagnosed with fallopian tube carcinoma in situ had tubal intraepithelial carcinoma, and 29% of these were classified as STICs. This suggests a high prevalence of STICs among patients with fallopian tube carcinoma in situ. Most interestingly, the authors observed a statistically significant increase in the incidence rate of fallopian tube carcinoma in situ and STIC from 2005–2007 to 2011–2012. In contrast, there was no increase in ovarian HGSC over the same time period. The timing of the increase coincides with the introduction of the Sectioning and Extensively Examining the Fimbriated end (SEE-FIM) protocol by pathologists in major medical centers to comprehensively and systemically evaluate the entire fallopian tube, especially the fimbriated ends (2). Before the SEE-FIM era, fallopian tubes were most often examined in one or two representative tissue sections sampled from the midportion, and the fimbriated ends were usually not assessed. The report by Trabert et al. is an example demonstrating how the adoption of a new pathology practice in tissue sampling can impact the measurement of incidence in a disease state.

Another important observation from this study is that the five-year cause-specific survival rates for both tubal intraepithelial carcinoma and serous tubal carcinoma *in situ* were high, 97.1% and 96.0%, respectively, compared with less than 50% for late-stage HGSC of the fallopian tube and/or ovary. The

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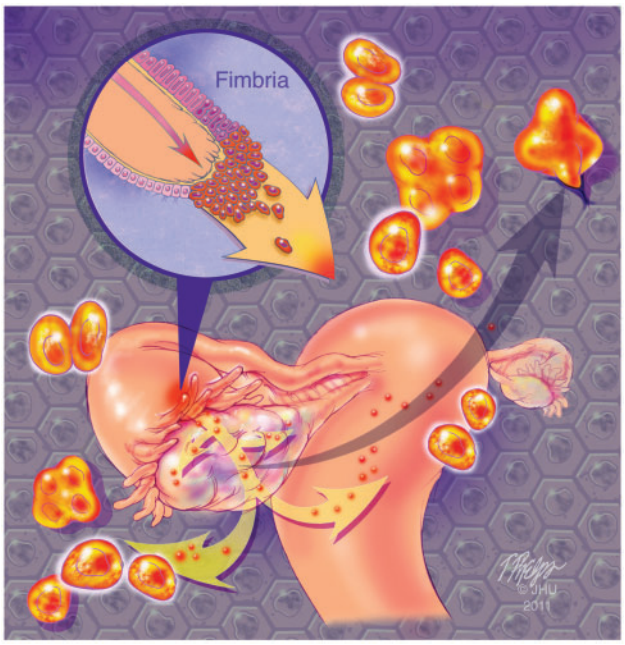

Figure 1. The tubal paradigm in the development of ovarian cancer. High-grade serous carcinoma originates from serous tubal intraepithelial carcinoma (STIC) on the fallopian tube surface where normal tubal epithelial cells are transformed to a premalignant and pre-invasive state. STIC cells detach from their tubal residence and disseminate to the ovary and peritoneal soft tissues, where they grow as mass lesions and clinically present as advanced stage disease at the time of diagnosis.

favorable survival associated with STIC as compared with invasive carcinoma suggests an opportunity for preventive interventions if we can identify women with STICs who are at risk of developing ovarian cancer. The data also suggest that there is a subset of women who undergo risk-reduction salpingo-oophorectomy (RRSO) but subsequently progress to invasive cancer, suggesting that the STIC cells may have spread to the peritoneum before surgery.

The authors acknowledge that additional data will be needed to generate robust US population–based estimates of incidence and mortality for STICs. This includes pathological validation of the diagnosis of STIC using rigorous and standardized criteria, and separate validation of the coding algorithms used. Capturing information on the numbers of STIC lesions a patient has, as well as the details of diagnostic tissue processing employed, may also be informative. More efforts are also needed to illuminate the biology of STICs and other fallopian tube lesions, especially for those incidental cases preceding the development of invasive cancer. Not all STICs are created equal, as some are proliferatively active and others dormant. A related lesion, "p53 signature," is characterized by normal-appearing histology, a p53 immunostaining pattern compatible with a *TP53* missense mutation, and no or very low proliferative activity (8,9). It is currently unclear whether and to what extent p53 signatures are related to STIC and HGSC. Thus, it would be important for cancer registries to incorporate diagnostic codes for all potential precursor lesions so that we can track their clinical behavior, which would help us understand whether they are a public health problem.

Ultimately, as has been accomplished for cervical dysplasia, more accurate measures of incidence and morbidity and mortality statistics of STICs and related precancerous lesions would provide a foundation for identifying subgroups of individuals at high and low risk for developing HGSC. Moreover, assessing the impact of population-based interventions on the incidence of STICs and ovarian HGSC is important. These include introduction of new pathological criteria as well as preventive strategies such as salpingectomy. The recent enthusiasm of the National Cancer Institute (in the form of Beau Biden Cancer MoonshotSM initiatives) in constructing comprehensive, dynamic, and multidimensional atlases of precancerous lesions and their surrounding microenvironment provides a welcome jump start to this effort.

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