Gynecologic Oncology xxx (2017) xxx–xxx

Contents lists available at ScienceDirect

Gynecologic Oncology

journal homepage: www.elsevier.com/locate/ygyno

Review Article

Genetic epidemiology of ovarian cancer and prospects for polygenic risk prediction

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HIGHLIGHTS

- Contribution of high and moderate penetrant genes to ovarian cancer heritability
- Contribution of common low risk alleles to ovarian cancer heritability
- Implications of genetic risk discovery for clinical risk prediction and prevention

ARTICLE INFO

Article history:
Received 16 May 2017
Received in revised form 28 September 2017
Accepted 2 October 2017
Available online xxxx

Keywords:
Ovarian Cancer
Susceptibility
GWAS
Next generation sequencing
Clinical genetic testing

ABSTRACT

Epithelial ovarian cancer (EOC) is a heterogeneous disease with a major heritable component. The different histotypes of invasive disease – high grade serous, clear cell, endometrioid and mucinous – are associated with different underlying genetic susceptibility and epidemiological and lifestyle risk factors, all of which contribute to the different biology and clinical characteristics of each histotype. A combination of familial and population based sequencing studies, and genome wide association studies (GWAS) have identified a range of genetic susceptibility alleles for EOC comprising rare but highly penetrant genes (e.g. *BRCA1*, *BRCA2*) that are responsible for familial clustering of ovarian cancer cases; more moderate penetrance susceptibility genes (e.g. *BRIP1*, *RAD51C/D*, *MSH6*); and multiple common but low penetrance susceptibility alleles identified by GWAS. Identifying genetic risk alleles for ovarian cancer has had a significant impact on disease prevention strategies; for example it is now routine clinical practice for individuals with germline *BRCA1* and *BRCA2* mutations to undergo risk reducing salpingo-oophorectomy. Because ovarian cancers are commonly diagnosed at a late clinical stage when the prognosis is poor, the continued development of genetic risk prediction and prevention strategies will represent an important approach to reduce mortality due to ovarian cancer. Advances in genomics technologies that enable more high-throughput genetic testing, combined with research studies that identify additional EOC risk alleles will likely provide further opportunities to establish polygenic risk prediction approaches, based on combinations of rare high/moderate penetrance susceptibility genes and common, low penetrance susceptibility alleles. This article reviews the current literature describing the genetic and epidemiological components of ovarian cancer risk, and discusses both the opportunities and challenges in using this information for clinical risk prediction and prevention.

Contents

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https://doi.org/10.1016/j.ygyno.2017.10.001
0090-8258/

1. Epithelial ovarian cancer: the clinical and public health challenge

Epithelial ovarian cancer (EOC) causes around 125,000 deaths globally per year. Over the last 40 years, long term survival rates have changed very little. About 70% of women with ovarian cancer are diagnosed with advanced stage disease (stages III/IV), of whom only ~30% will survive more than 5 years. By contrast, women diagnosed with earlier stage (stage 1) disease have a 5-year survival rate >90%. Our understanding of the biology of EOC is limited, and complicated by disease heterogeneity. Invasive EOC represents 90% of all malignant ovarian tumors and comprises four major histological subtypes; high-grade serous, endometrioid, clear cell and mucinous, which have different clinical courses and survival rates. The most common histotype is high-grade serous ovarian cancer (HGSOC) and these cases represent the major clinical problem. The different histotypes probably have distinct cells of origin and can be characterized by different germline and somatic genetic changes that result in the perturbation of different molecular pathways. Even within the different histotypes there is likely to be substantial clinical and molecular heterogeneity [1,2]. The standard treatment for EOC consists of maximal cytoreductive surgery followed by administration of platinum and taxane-based chemotherapy. Most patients with advanced stage (III/IV) EOC initially respond well to primary treatment with surgery and chemotherapy; but cancer usually recurs with a drug-resistant phenotype.

Given the greatly improved survival rates associated with early stage ovarian cancer, clinical intervention strategies that either detect EOC at the earliest most treatable stages, or prevention strategies for women at greatest risk may be effective approaches to reduce the burden of EOC. Unfortunately, signs and symptoms of ovarian cancer are usually absent in early stage disease. Even when they are present, symptoms are often subtle and may vary by EOC histotype [3]. There are currently no effective screening approaches for detecting early stage EOC. Serum CA-125 testing is useful for differential disease diagnosis, but has not been shown to be an effective early-stage screening approach due to its low sensitivity and specificity [4,5]. HE4 is another candidate ovarian cancer screening marker, although it has not been extensively tested in clinical trials [6]. Vaginal ultrasonography can also be used to detect adnexal masses consistent with ovarian cancer, but once again this does not appear to be effective for detecting early stage EOC [7]. Using a combination of genetic, epidemiology and lifestyle risk factors to identify women at greatest risk of EOC in the population, followed by effective clinical intervention strategies could represent a powerful population based strategy to reduce mortality associated with the disease

1.1. Genetic epidemiology of epithelial ovarian cancer

1.1.1. Epidemiological and lifestyle risk factors

Several epidemiologic studies have suggested that exposure to endogenous and exogenous hormones play an important role in ovarian cancer etiology [8]. Oral contraceptive (OC) use [9] and parity [10] are both protective, with decreasing risks associated with increasing duration of OC use and increasing parity. Younger age at menarche, breastfeeding and hysterectomy are associated with a reduction in EOC risk, while the use of menopausal hormone therapy (MHT) (particularly estrogen only therapy), is associated with an increase in EOC risk [9,11–16]. In a large trial, long-term post-menopausal hormone use was associated with increased EOC risk [17], which is consistent with several cohort studies [18–21]. A meta-analysis indicated a 20% increase in ovarian cancer risk per 5 years of postmenopausal estrogen use [12]. Tubal ligation is another well-established EOC risk factor [22] which is inversely associated with EOC risk.

Some risk factors have been reported to be associated with specific histotypes of ovarian cancer. Olsen et al. found obesity to be weakly associated with an increased risk of low-grade serous invasive tumors but there was no association with invasive high-grade serous disease [23]. In the same study, high body mass index (BMI) was associated with increased risk of borderline serous, invasive endometrioid, and invasive mucinous ovarian cancer histotypes. It is also well established that endometriosis is risk factor for clear cell and endometrioid ovarian cancer, but not for high-grade serous or mucinous histotypes [24]. A meta-analysis has found an association between smoking and mucinous EOCs, an inverse association for risks of endometrioid and clear cell EOCs, and no association with high-grade and borderline serous histotypes [25]. Menopausal hormone therapy appears to be more associated with an increased risk of serous and possibly endometrioid histotypes compared to other subtypes [15,18]. Finally, oral contraceptive use (ever/never) is associated with reduced risk for the serous and endometrioid subtypes, with a suggestive, but not significant, increase in risk in mucinous and clear cell EOC [15]. Recent larger studies have reported reduced risk in all subtypes other than mucinous with oral contraceptive use, with an increase in risk of mucinous EOC as duration of oral contraceptive use increases [26,27].

1.1.2. Germline genetic risk factors

Family history remains one of the strongest EOC risk factors. A woman with a first-degree relative with ovarian cancer has a threefold increased risk of developing the disease compared to women with no family history. Studies of twins show that the majority of this familial risk is due to inherited genetic factors, rather than environmental and lifestyle factors shared within families [28]. Inheriting damaging mutations in highly penetrant susceptibility genes is the strongest predictor of inherited risk for ovarian cancer. Mutations in two genes, *BRCA1* [29] and *BRCA2* [30], confer high-penetrance susceptibility to both ovarian and breast cancer [30,31]. The risks of ovarian cancer conferred by *BRCA1* and *BRCA2* mutations have been estimated from both family and population based studies. In family studies, the cumulative risks of ovarian cancer by age 80 years are estimated to be 44% in *BRCA1* mutation carriers and 17% in *BRCA2* mutation carriers [32]. Risk estimates are generally lower in population based studies; in a combined analysis of 22 different studies average ovarian cancer risks were 39% (95% confidence interval (CI) 18%–54%) in *BRCA1*-mutation carriers and 11% (2.4%–19%) in *BRCA2*-mutation carriers [33]. The prevalence of mutations in these genes also contributes to the different risk of EOC observed in different populations. For example, *BRCA1* and *BRCA2* mutations are substantially more prevalent in Ashkenazi Jewish compared to non-Ashkenazi Jewish populations which may explain why average lifetime risks are higher in this population (54% for *BRCA1* and 23% for *BRCA2*) [34]. These genes are responsible for most families containing multiple cases of breast and ovarian cancer [35,36] and combined they account for approximately a third of the heritable risk of ovarian cancer [37]. However, in a study of 283 ovarian cancer families, only 27% of families containing just two first degree relatives

Please cite this article as: M.R. Jones, et al., Genetic epidemiology of ovarian cancer and prospects for polygenic risk prediction, Gynecol Oncol (2017), https://doi.org/10.1016/j.ygyno.2017.10.001