

ARE THERE PRECURSOR LESIONS FOR OVARIAN CANCER: A REVIEW

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SUMMARY

Precancer is a very early noninvasive lesion that has genetic abnormalities, loss of cellular control functions, some phenotypic characteristics of invasive cancer, and predicts a significant likelihood of developing invasive cancer. Currently, there is no consensus on the existence of ovarian cancer precursor lesions, though many dysplasias in the ovary have been found to date. Our inability to detect precancer in the ovary has hampered early detection efforts. After review of current literature, inclusion cysts, deep surface invaginations and papillomatosis, commonly referred to as "putative ovarian precancer lesions" appear to correlate with known genetic alterations found in the advanced disease in predisposed cohorts. Although we suggest that screening for these lesions would underestimate the ovarian cancer risk in general population, data on chemoprevention studies offers new hope for combating this deadly disease.

Key words: precancer; inclusion cysts; papillomatosis

INTRODUCTION

Ovarian cancer is one of the leading causes of cancer death in women in Europe and the United States. It is the deadliest among gynecological malignancies. Patients with an early stage disease have generally a favorable prognosis, yet most ovarian tumors are diagnosed in a late aggressive stage, with extensive intraperitoneal spread of disease, leading to a poor prognosis [1]. Factors that hinder our capability to detect, prevent and cure ovarian cancer are the lack of defined precursor lesions, the lack of appropriate animal models and reliable biomarkers for disease detection, the late stage of presentation, the inaccessible organ location, and poor understanding of the underlying biology of the ovary. Therefore, the ongoing identification of precursor lesions, development of animal models and disease biomarkers and strategies for manipulation of the immune response will hopefully offer prospects for progress in this difficult-to-treat disease.

HOW DOES OVARIAN CANCER ARISE?

The majority of ovarian cancers are epithelial in origin. The ovary is an endocrine gland responsible for production of female sex hormones and egg cells. The epithelial tumors are believed to arise from the surface mesothelial layer of the ovary and account for nearly 90% of all ovarian cancer cases, whereas, non-epithelial tumors comprise sex cord-stromal, germ cell and gonadoblastoma types [2]. The histologic classification of human ovarian neoplasms is remarkably intricate since the ovary has a greater diversity of tumors than any other organ in the body, with more than 40 histological entities contributing to the World Health Organization (WHO) classification of ovarian epithelial tumor types. These most important types are serous, mucinous, endometrioid, clear cell, transitional, mixed, and undifferentiated. Each of the

epithelial ovarian tumor cell types is additionally subdivided into benign, borderline (low malignant potential or LMP) and malignant categories. Whether these three categories are a biologic continuum of stepwise progression to malignancy or whether they represent separate entities that arise *de novo* is a controversy in the ovarian cancer research field [3]. In spite of the progress in the elucidation of the ovarian cancer molecular pathways, many reports yet fail to consider the disease heterogeneity, grouping together tumor samples of dissimilar histological types, subtypes, stages, grades, or laterality of ovarian cancer, patient's age, ethnicity or genetic background. This simple view of ovarian cancer causes discrepancies in data analyses, and slows down the search for biochemical markers and targeted treatments. Ovarian tumors should be studied against each specific morphologic category, given that they arise as a result of a distinct set of molecular alterations and entail distinct putative precursor lesions [4]. Therefore, heterogeneity in ovarian cancer histology contributes to complexity in ovarian preneoplasia.

In general, during malignant transformation carcinomas become less differentiated than the epithelium of their origin. On contrary, during ovarian malignant transformation morphologically simple surface epithelium transforms into very complex histological structures similar to nonneoplastic epithelia of the gynecologic tract [5]. This phenomenon is difficult to understand, since the ovary derives from the mesonephros, while the uterine tubes, endocervix and endometrium originate from the Müllerian ducts. Serous carcinomas of the ovary are morphologically similar to uterine tube carcinomas; mucinous tumors bear a resemblance to those arising in the endocervix; endometrioid ovarian carcinomas are similar to carcinomas of the endometrium, while clear cell tumors are comparable to a variant of endometrial carcinoma [6]. This similarity may explain why animal models of ovarian carcinoma develop only one histologic subtype.

Though many researchers consider ovarian surface epithelium (OSE) as the site of origin of ovarian neoplasms, some believe that the ovarian tumors are derived from the Müllerian tissue, claiming that the proof for metaplasia of the OSE to produce such tumors is weak [7].

Most of the genetic animal models of ovarian cancer created to date do not replicate the histological diversity of human disease [8-11]. They are usually not of the epithelial type, but rather of germ, stromal or granulose cell type and cause fast developing, late-stage disease presenting at an early age. These experimental models, while important for the understanding of the role of individual genes in ovarian cancer, may not be entirely adequate for studying the preneoplastic and early neoplastic stages of the disease. On the contrary, according to Stewart and colleagues, ovarian lesions induced by the coadministration of carcinogens and hormones display all stages of tumorigenesis, including initiation, promotion, and progression. Characterization of 7,12-dimethylbenz(alpha)anthracene (DMBA) murine model of ovarian cancer revealed the appearance of putative preneoplastic lesions of epithelial cell origin with progressive histology, strongly resembling human, and assumed to represent precursors of ovarian cancer clonal development [12].

THERE CURRENTLY IS CONTRADICTING EVIDENCE REGARDING THE EXISTENCE OF PRENEOPLASTIC LESIONS IN THE OVARY

Current literature identifies the following entities as precursors for ovarian cancer: a) epithelial inclusion cyst, b) deep invagination of the surface epithelium into stroma, c) epithelial pseudostratification, d) surface papillomatosis, e) ovarian endometriosis, f) benign tumor, and g) borderline tumor [13, 14]. Some of these lesions have been designated as ovarian dysplasia or OIN (ovarian intraepithelial dysplasia) [15]. Ovarian cancer can also form from the normal appearing ovarian surface epithelium without identifiable precursor lesions [16]. Additionally, the pathologist Louis Dubeau and other supporters of the alternative hypothesis of Müllerian origin of ovarian cancer regard the components of the secondary Müllerian system, such as paraovarian/paratubal cysts, rete ovarii, endosalpingiosis, and endomucinosi, as possible precursors in ovarian tumorigenesis [7].

The majority of human ovarian malignant tumors occur sporadically, while only 10% are inherited in the form of either a) breast and ovarian cancer syndrome linked to mutations in BRCA1 and BRCA2 tumor suppressor genes, responsible for 65-75% of all hereditary cases, b) site-specific ovarian cancer, or c) ovarian cancer associated with Lynch syndrome II or hereditary non-polyposis colorectal cancer.

For the identification of histopathologic and genetic lesions that precede the development of human epithelial ovarian cancer, researchers have used prophylactically removed ovaries from high-risk women with mutations in

the BRCA1 or 2 genes, normal ovaries from women with other carcinomas of the female genital tract (including normal ovaries contralateral to unilateral ovarian cancer), surface epithelium and inclusion cysts adjacent to areas of invasive ovarian cancer, normal ovaries from identical twins of ovarian cancer patients, and ovaries removed because of suspicious ovarian cancer screening findings [13-15, 17, 18].

For an accurate historical perspective on ovarian preneoplasia, seminal work of Gusberg and Deligdisch needs to be highlighted. They were the first investigators to bring the notion of ovarian cancer precursor lesions 23 years ago. A detailed morphometric and histological analysis was performed on the ovaries removed for prophylaxis from identical twin sisters of women with invasive carcinoma of the ovary [18], and in a later study atypical nuclear and cellular ultrastructural features in the areas of nonmalignant epithelium adjacent to the region of early invasive ovarian carcinomas were detected [15]. In a more recent karyometric study of ovarian preneoplasia, Brewer et al. showed that the alterations in nuclear chromatin pattern observed in the epithelia lining of inclusion cysts and in the underlying stroma of ovaries, either cancerous or at high risk for cancer, imply the presence of preneoplastic lesions in histologically normal tissue [14].

Since women with a strong family history of ovarian cancer have an elevated probability of developing the disease, ovaries removed prophylactically from such asymptomatic patients provide an excellent opportunity to identify preneoplastic changes [17]. In spite of the common presence of inclusion cysts in older women [3], and the ongoing controversies, many groups [14, 19], favor the concept of epithelial inclusion cyst, cortical invagination, epithelial pseudostratification, surface papillomatosis, and stromal hyperplasia as potential ovarian premalignant histologic features, since these have been more often detected in women harboring BRCA1/2 mutations or women with contralateral ovarian carcinoma, compared to controls [20, 21]. Some of the studies have shown that the cancer-prone ovaries and their OSE cells have a preneoplastic phenotype that is the background from which ovarian cancer develops [5, 20, 22], thereby providing a starting point to look for genetic changes responsible for disease initiation.

Due to the unique pathophysiology of ovarian cancer, information cannot be easily extrapolated from the study of other cancers to the analysis of ovarian cancer. Contrary to other solid neoplasms that fit the multistep progression model of tumorigenesis, with their identifiable precursors and molecular genetic alterations, ovarian carcinoma has been difficult to classify in the same fashion.

In spite of the common knowledge that ovarian cancer originates from the OSE and inclusion cysts, seldom have putative precursor lesions been seen in these sites of malignancy [13]. First, ovarian cancer is a disease without recognizable early symptoms and warnings, most often diagnosed in the advanced form. Hence, majority

of existing tissue specimens available for analysis represent late stage disease and do not contain the earliest preneoplastic changes. Second, human ovary is small, located deep in the pelvis, and therefore inaccessible for inspection, compared to the other parts of the female reproductive tract. Dysplasias arise in the ovary, as in the cervix and uterus, but have rarely been reported because they are easily unnoticed and have not thoroughly been searched for by pathologists with expertise in gynecologic malignancies. Dysplasias can be detected only by extensive sectioning of the ovaries for histologic assessment. Another reason why dysplasias have rarely been found in the ovary is frequent physical absence of the surface epithelial layer from human ovarian surgical or autopsy specimens. This layer is brittle, easily dries out, and gets disrupted and detached by handling the organ during removal or gross pathologic examination.

Contrary to the above-mentioned studies in cancer-prone ovaries, some researchers have not supported the presence of preneoplasia or they have reported conflicting results within their own studies. Several groups did not find statistically significant differences in the frequency of inclusion cysts, cortical invaginations, pseudostratifications and papillomatosis in the OSE of BRCA1/2 carriers vs. non-carriers [23-25]. It is not certain whether these ovaries were comprehensively sampled and whether the penetrance of the disease in the families of study subjects was taken into account. Scientists from Fox Chase Cancer Center suggested that ovarian morphological features are associated with age and menopausal status, and not the BRCA1/2 status [25]. This may explain the controversial reports on the correlation between ovarian morphology and BRCA genotype.

Benign epithelial tumor, another candidate precursor for ovarian cancer, is usually removed by surgery after detection. Therefore, its preexistence, malignant transformation and natural history within the ovary are unknown. Also, benign ovarian tumor appears on average 10-15 years later than ovarian carcinoma of the same cell type [26], making it an unlikely candidate for an ovarian cancer precursor. Benign serous epithelium rarely coexists with the advanced serous carcinoma, which usually overgrows it by the time of diagnosis [13].

Epidemiologic and histopathologic studies have recognized a clear link between endometriosis and endometriosis-associated ovarian cancers, namely the endometrioid and clear cell subtypes. Prowse and colleagues have examined endometrioid and clear cell ovarian carcinoma samples with coexisting endometriosis for the loss of heterozygosity (LOH) on multiple chromosomes and provided molecular genetic evidence that endometriosis is indeed a precursor for ovarian cancer [27].

LMP tumors of the ovary have been methodically investigated to allow for a differential diagnosis from benign to malignant neoplasms. These tumors have an atypical epithelial proliferation without stromal invasion. It has been proposed that the precursor for the low-grade serous carcinoma of the ovary is the serous LMP tumor,

since they both usually coexist in the clinical cases. As of high-grade serous carcinomas, they do not coexist with, or originate in LMP tumors, but instead develop directly from the surface epithelium. Likewise, mucinous LMP tumors may represent a precursor variant of mucinous carcinoma of the ovary [28]. Endometrioid carcinomas show frequently endometrioid LMP areas, implying that LMP endometrioid tumor may be a precursor for endometrioid carcinoma [29].

As presented so far in this review, numerous microscopic alterations occur in the ovaries of the high-risk and low-risk women, generally thought of as precursors to invasive cancer. However, correlative studies have not been conclusive for various aforementioned reasons. Therefore, as discussed below, we feel that pathologic evaluation should be coordinated with molecular-genetic identification and classification of these lesions as ovarian cancer precursors.

GENETIC CHANGES OCCURRING IN PUTATIVE OVARIAN PRENEOPLASTIC LESIONS

Many recent studies have supported the hypothesis that each ovarian carcinoma subtype represents a biologically and pathogenetically distinct entity [13, 19]. Gene expression profiling has revealed distinctive, though somewhat overlapping, signatures for each ovarian carcinoma subtype. High-grade, invasive serous type is distinguished by mutations in p53 and BRCA1/2 genes, LOH on multiple chromosomes, the absence of microsatellite instability (MI), and most probably arises *de novo* from morphologically normal or dysplastic epithelium within inclusion cysts or the OSE [30]. On contrary, p53 mutations are rare in all other subtypes. Serous LMP tumor of the ovary is characterized by KRAS and BRAF oncogenic mutations, and arises probably via a multistep sequence [31]. Data suggest greater similarities in molecular genetic characteristics among benign, LMP and malignant mucinous tumors, compared to the serous ones. Mucinous ovarian carcinoma contains KRAS mutations and also develops via a benign-borderline tumor-carcinoma sequence [32]. Furthermore, high-grade endometrioid carcinoma is similar to its serous counterpart, while low-grade endometrioid ovarian carcinoma carries PTEN and CTNNB1 mutations, MI, and has ovarian endometriosis for a precursor [33]. Clear cell carcinoma of the ovary shares the same precursor, but is characterized by mutations of TGFbetaR2, overexpression of HNF-1beta, BRCA dysfunction and MI [16]. With the introduction of laser capture microdissection (LCM) technology in 1996, these genetic lesions, as discussed below, have been more carefully studied in pure cell populations within the heterogeneity of the ovary [10, 27, 34, 35].

Alteration of p53, such as mutation, allelic loss or protein overexpression, is the most frequent genetic event in ovarian cancer, however it is most commonly associated with the advanced disease [36]. The genetic evidence

for benign or borderline serous tumors as precursors of ovarian cancer is not very convincing. Most studies failed to detect p53 mutations in these tumors. It has been shown that benign-appearing epithelium in continuity with serous carcinoma had similar mutational and cytogenetic changes, which could mean that either the benign component already had the genetic abnormalities and was predisposed to transformation, or that there is morphologic maturation of malignant epithelium that does not indicate a benign precursor lesion [37]. Furthermore, while p53 immunoreactivity was found in these tumors, subsequent genetic analysis revealed no mutation. In a recent study using comparative genomic hybridization (CGH), Osterberg et al. showed a number of genetic alterations that differed greatly between stage I and borderline ovarian serous tumors [38]. However, both tumor categories had loss at chromosome 17, which harbors p53 and BRCA1 genes, with 30% of borderline tumors having this loss.

ARE THERE PREVENTIVE MEASURES FOR THE PRENEOPLASTIC STATE IN THE OVARY?

Unlike breast or cervical cancer prevention, in which efforts to decrease incidence and mortality focus on detection of well-defined preinvasive lesions, primary ovarian cancer prevention is impractical due to the low incidence, lack of risk and response biomarkers and difficulties in sampling ovarian tissue. Therefore, we need to concentrate efforts on women at increased risk for ovarian cancer, and to enhance chemoprevention and prophylactic surgery among them [39]. The nonsurgical preventive choices include laparoscopically-directed biopsies and noninvasive imaging techniques, such as optical coherence tomography and fluorescence spectroscopy, for identification and follow-up of selected high-risk patients with significantly atypical ovarian epithelium [40]. Prospective evaluations of these women would then be required to reveal the natural history of precursor lesions in their ovaries [15].

Three chemopreventive agents are currently utilized in ovarian cancer: oral contraceptives (OCs), retinoids and Cox-2 inhibitors. It has been shown that ovarian cancer risk decreases with increased duration of OC use, continuing for up to ten years, and returning to baseline approximately 15 years after the last regular use of OCs [41]. The protective effect of OCs is due to the increased apoptosis of the OSE cells and the inhibition of gonadotropin release from the pituitary gland. Studies in women and in primates suggested that progesterin is the active component in OCs [42].

In vitro and in vivo studies have shown that fenretinide (4-HR), and other synthetic vitamin A derivatives, retinoids, can prevent ovarian carcinoma [43]. The proposed mechanisms of action of retinoids in human ovarian carcinoma cell lines are inhibition of proliferation and

induction of cell cycle arrest and apoptosis [44]. Brewer and colleagues have shown that 4-HPR acts through different mechanisms in premalignant ovarian surface cells and cancer cells, with a preventive effect in premalignant, and a treatment effect in cancer cells [45]. An Italian clinical trial of fenretinide was associated with a lower incidence of ovarian carcinoma in women with early breast cancer, but only during the intervention [43, 46].

COX-2 inhibitors, such as celecoxib, are a class of non-steroidal anti-inflammatory drugs. Observational studies of ovarian carcinoma have implied a risk reduction with the use of some NSAID derivatives on a regular basis [47, 48]. In vitro analysis has suggested that inhibition of COX-2 leads to downregulation of local prostaglandins that may result in interactions with downstream mediators of the OSE cell apoptosis inhibiting rupture of the epithelial lining of the dominant follicle [49]. The very recent study of celecoxib in women at elevated risk of ovarian carcinoma presented a rationale argument for the continued examination of this agent in clinical and preclinical trials [50].

CONCLUSION

Precancer is a very early noninvasive lesion that has genetic abnormalities, loss of cellular control functions, some phenotypic characteristics of invasive cancer, and predicts a substantial likelihood of developing invasive cancer. The objective of this review was to present the most up to date literature on the existence of ovarian preneoplasia, without making a judgment with regards to its clinical significance. The assumption has been that, as with other cancers, gross dysplasia found in ovarian tissue specimens represents a precursor lesion. Based on this, researchers have restricted their clinical correlative studies on women at increased risk for ovarian cancer, with reasoning that those findings would also apply to cases of sporadic ovarian cancer.

It is evident, based on the above-described studies that high-risk women carry ovarian precursor lesions with genetic alterations, which may lead to a suitable environment for neoplastic transformation. Nevertheless, the argument for precursor lesions in the ovaries of low-risk women is not as strong. As low-risk women represent the majority of invasive ovarian cancer cases, population-wide genetic screening tests for disease biomarkers are currently not warranted. This is also reflected in the disappointing sensitivity and specificity of CA125 and proteomics screens. In spite of the obstacles related to ovarian cancer prevention and screening, there is hope. As shown in this review, the use of OC provides strong protection against ovarian cancer. Additionally, it would be interesting to see the results of the ongoing fenretinide and COX-2 inhibitor preventive trials. Future studies entailing epigenetic screens, such as DNA methylation patterns, may equally provide useful clinical data in this endeavor.

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ПОСТОЈЕ ЛИ ПРЕКУРСОРНЕ ЛЕЗИЈЕ КАРЦИНОМА ЈАЈНИКА – ПРЕГЛЕД ЛИТЕРАТУРЕ

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КРАТАК САДРЖАЈ

Преканцер је врло рана неинвазивна лезија са генетским поремећајима, извесним фенотипским обележјима инвазивног тумора, губитком контроле ћелијских функција, која са великом вероватноћом може да прерасте у инвазивни тумор. Засад још нема консензуса о постојању прекурсорних лезија за рак јајника премда су досад откривене многе дисплазије. Неспособност да се открије преканцер јајника успорила је напоре за раним откривањем болести. На основу прегледа актуелне литературе, по свој прилици, постоји корелација између инклузионих циста, дубоких површинских инвагинација и папиломатоза, често означених као „путаивне преканцерске лезије јајника“, и генетских промена у знапредовалој болести код предиспонираних болесница. У овом прегледном чланку су описане теорије о развоју рака јајника, наведени су контрадикторни докази о постојању

премалигних промена у јајнику, описане су генетске промене у тим лезијама, као и одговарајуће мере превенције. Иако мала учесталост рака јајника не оправдава скрининг у општој популацији, подаци о хемопревентивним студијама уливају наду у борби против ове често фаталне болести.

Кључне речи: преканцер јајника; инклузионе цисте; папиломатоза

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