Arch Gynecol Obstet (2014) 289:237–239
DOI 10.1007/s00404-013-3114-3

NEWS AND VIEWS

The heterogeneity of ovarian cancer

I. Meinhold-Heerlein · S. Hauptmann

Published online: 10 December 2013

Abstract Ovarian cancer carries the worst prognosis of all gynecological malignancies. This is mainly due to its resistance against commonly used cytostatic drugs as well as the lack of a screening method for its detection at an early stage. Both basic and translational research have shown over the past decades that ovarian cancer as a medical term includes several types of tumors with different phenotypes, molecular biology, etiology, tumor progression, and even different prognosis. In this issue of *Archives of Gynecology and Obstetrics*, J. Dietel presents a review article about novel findings of the etiopathogenesis of ovarian cancer and the role that fallopian tubes may play. He also outlines the implied clinical consequences. Here, we give a brief overview of the heterogeneity of ovarian cancer to introduce the topic.

Keywords Ovarian cancer · Heterogeneity · Borderline tumors of the ovary · Pathogenesis

Introduction

Although in the clinical routine ovarian cancer is regarded and treated as a single disease, there is evidence that the term "ovarian cancer" comprises a variety of tumor types that differ in morphology, prognosis, etiology, and molecular biology.

I. Meinhold-Heerlein (✉) · S. Hauptmann
Department of Gynecology and Obstetrics, University Hospital Aachen, Pauwelsstraße 30, 52074 Aachen, Germany
e-mail: imeinhold@ukaachen.de

I. Meinhold-Heerlein · S. Hauptmann
Institute of Pathology, Hospital Düren, Düren, Germany

Basic research has led to the conclusion that ovarian cancers may (at least) progress along two different pathways: Type I cancers are highly differentiated ("low grade") and develop via typical precursor lesions, such as cystadenomas and borderline tumors. Although serous cancers represent the predominant histological subtype of the type I pathway, low-grade mucinous and endometrioid carcinomas as well as malignant Brenner tumors are also included in this category (group). Type II cancers are poorly differentiated ("high grade") and develop rapidly without known or morphologically visible precursor lesions ("de novo development"). This group includes poorly differentiated serous, endometrioid, clear cell and transitional cell carcinomas [1].

For a long time, borderline tumors of the ovary ("tumors of low malignant potential", LMP tumors), that behave like a "carcinoma in situ" showing a malignant phenotype but not passing the basal membrane, have been seen as an own entity. Meanwhile, several types of borderline tumors are known to develop from benign cystadenoma thereby representing a precursor lesion of highly differentiated (e.g., low grade) ovarian cancer. Although they may show a minimal invasion that this microscopic finding does not influence their favorable prognosis. In addition, borderline tumors can exhibit peritoneal implants mainly located in the omentum. These implants may impress "invasive" or "non-invasive" and do not impair the patient's prognosis. When borderline tumors relapse, they remain as borderline tumors in the majority of cases. However, they can also return as invasive cancer [2, 3] (http://www.ago-online.org).

In conclusion, several significant findings have been accepted as state of the art of science: (a) the term ovarian cancer summarizes different types of cancers with different pathways of development; (b) the grading of serous cancers does not represent a continuum, but two different diseases

(low- and high-grade cancers); (c) serous borderline tumors can (rarely) progress to highly differentiated ("low grade") tumors; (d) mucinous borderline tumors progress to invasive cancers more often; (e) ovarian endometriosis and clear cell ovarian cancers are associated [4].

This article will address significant scientific findings about the morphologic, prognostic, etiopathogenetic, and molecular heterogeneity of ovarian cancer and may therefore prepare the reader for J. Dietels detailed article about the role of the fallopian tube in the etiopathogenesis of ovarian cancer.

Morphology

Pathologists classify the grading and the histological subtypes of ovarian cancer. They distinguish between serous, endometrioid, mucinous, clear cell, transitional cell and undifferentiated cancers, as well as carcinosarcomas. Kurman et al. [4, 5] have proposed a progression model, which groups several histological subtypes into "low grade" (type I) or "high grade" (type II) cancers. Type I cancers are often diagnosed as early stage tumors, are highly differentiated serous, endometrioid, mucinous and clear cell cancers and develop via benign and borderline tumors. Type II tumors are often diagnosed as advanced stage tumors, are poorly differentiated serous, endometrioid, and undifferentiated cancers. The morphologic heterogeneity is reflected on a molecular level. Every subtype is characterized by a specific molecular pattern, which can be evaluated with expression, mutation, and methylation analyses, respectively [reviewed in 4, 12].

Prognosis

The tumor stage, which is determined during the primary surgery, is one important prognostic factor of ovarian cancer. The 5-year overall survival of FIGO stage I cancers accounts for almost 90 %, whereas the survival of FIGO stage III/IV cancers accounts for only approximately 40 % [6].

Residual tumor, tumor grading and the histological subtype are additional significant prognostic factors.

Even the advanced stage type I cancers show a more favorable prognosis when compared to type II cancers [6]. By contrast, type I cancers barely respond to chemotherapy. We have previously shown the prognostic difference of low- and high-grade cancers [7] and it is noteworthy that the prognostic outcome can vary within one single histological subgroup of tumors.

In addition to the tumor-associated, there are patient-associated and therapy-associated prognostic factors: The patient-associated factors include age (the 5-years survival decreases with increasing age) and performance status. The therapy-associated factors include the quality of surgery (accuracy of staging, radicality of debulking, lymph node dissection, avoidance of tumor rupture) as well as the application of chemotherapy [6].

Etiopathogenesis

For a long time, the following assumptions formed the understanding of etiology, pathogenesis, and progression of ovarian cancer:

- The origin of ovarian cancer and the trigger of its evolution are unknown.
- The growth of cancer starts at the ovarian surface.
- A differentiation occurs during tumor progression.
- The peritoneal spread is typical, whereas distant metastases happen seldom and late.
- Borderline tumors represent an own, independent entity of disease.

Over the last two decades, molecular research on ovarian cancer has brought novel findings which in part are inconsistent with some of the previous theories:

- Serous borderline tumors can progress into an invasive cancer; mucinous borderline tumors progress into an invasive cancer more often.
- Serous borderline tumors can present "invasive peritoneal implants".
- Ovarian endometriosis is associated with endometrioid and clear cell ovarian cancer.
- Mucinous and transitional cell carcinomas may develop from para-ovarian transitional epithelial cell nests.
- The female peritoneal tissue keeps the ability to form all kinds of epithelial cells of muellerian origin ("Muellerian metaplasia of mesothelial cells").
- Morphologic, clinically pathologic and molecular analyses lead to the suggestion that there are at least two types of ovarian cancer progression.
- Ovarian cancers with BRCA1 and two mutations often show serous tubal intraepithelial carcinomas ("STICs"), which represent the probable origin of the disease. STICS have also been found in asymptomatic (healthy) women carrying BRCA1 and two mutations.

Obviously, there are several ways of pathogenesis that lead to ovarian, tubal, or peritoneal cancer. Based on the hitherto conception and Kurman's progression model, Fleming et al. have proposed several alternatives of ovarian cancer origination: (a) malignant transformation is eased by regenerative changes of ovarian surface epithelial cells after ovulation; (b) ovulation leads to invagination of

surface epithelial cells, forms inclusion cysts which transform via muellerian metaplasia into cancer; (c) epithelial cells from the rete ovarii region with stem cell character are the point of cancer origin [4, 5, 8]. In addition, latest research suggests that hereditary ovarian cancer (associated with BRCA mutations) rather develops from the fallopian tube than from the ovarian surface—see J. Dietels review article in this issue of *Archives of Gynecology and Obstetrics* [9].

Molecular pathology

The morphologic differences of serous type I and type II tumors are reflected by molecular differences: type I tumors are genetically stable; two-thirds of them carry KRAS, BRAF and ERBB2 mutations. Most of them lack p53 mutations [10, 11]. Low-grade endometrioid cancers carry CTNNB1, PTEN and PIK3CA mutations. More than 50 % of the low-grade mucinous tumors carry KRAS mutations. Low-grade clear cell tumors often carry PIK3CA mutations [12].

By contrast, serous high-grade cancers are genetically instable; more than 80 % carry p53 mutations [10, 11], many of them show an overexpression of CCNE1 (coding for Cyclin E1) and/or have an active Jak/STAT signaling pathway; very few high-grade cancers show the above-mentioned mutations, which are characteristic of type I tumors. In addition, carcinosarcomas of the ovary show a similar molecular pattern in comparison to type II tumors [7, 12].

The majority of hereditary ovarian carcinomas are caused by BRCA1 and/or BRCA2 mutations thereby representing approximately 10 % of all ovarian cancer cases. Both BRCA1- and BRCA2-associated ovarian cancers are each characterized by distinct clinical and molecular characteristics. Interestingly, expression profiles of sporadic cancers can be allocated to BRCA1 or BRCA2 profiles, respectively. This leads to the assumption that BRCA-associated signaling pathways play a role also in the development of sporadic cancer. This is also known as the "BRCAness"of sporadic cancers [9].

Ovarian cancer development seems to depend on homeobox allotype genes (HOX genes), which play an important role in the embryonic phase when tissue differentiation occurs: HOXA 9, 10 and 11 cause the normal differentiation of fallopian tube, endometrium, and cervical epithelial cells. It has been shown that these genes are also active in different types of ovarian cancer and may provide the genetic background for serous, mucinous, and endometrioid carcinomas [13].

In the future, it will be necessary to develop specific therapies based on different types of ovarian cancer. For this, the molecular characterization may provide the essential tool.

Conflict of interest There is no conflict of interest for both authors.

References

1. Shih Ie M, Kurman RJ (2004) Ovarian tumorigenesis: a proposed model based on morphological and molecular genetic analysis. Am J Pathol 164(5):1511–1518
2. Du Bois A, Ewald-Riegler N et al (2009) Borderline-Tumoren des Ovars—eine systematische übersicht. Geburtsh Frauenheilk 69:807–833
3. Seidman JD, Kurman RJ (2000) Ovarian serous borderline tumors: a critical review of the literature with emphasis on prognostic indicators. Hum Pathol 31(5):539–557
4. Kurman RJ, Shih Ie M (2010) The origin and pathogenesis of epithelial ovarian cancer: a proposed unifying theory. Am J Surg Pathol 34(3):433–443
5. Kurman RJ, Shih Ie M (2008) Pathogenesis of ovarian cancer: lessons from morphology and molecular biology and their clinical implications. Int J Gynecol Pathol 27(2):151–160
6. Heintz AP, Odicino F et al (2006) Carcinoma of the ovary. FIGO 26th annual report on the results of treatment in gynecological cancer. Int J Gynaecol Obstet 95(Suppl 1):161–192
7. Meinhold-Heerlein I, Bauerschlag D et al (2005) Molecular and prognostic distinction between serous ovarian carcinomas of varying grade and malignant potential. Oncogene 24(6):1053–1065
8. Fleming JS, Beaugie CR et al (2006) Incessant ovulation, inflammation and epithelial ovarian carcinogenesis: revisiting old hypotheses. Mol Cell Endocrinol 247(1–2):4–21
9. Jazaeri AA (2009) Molecular profiles of hereditary epithelial ovarian cancers and their implications for the biology of this disease. Mol Oncol 3(2):151–156
10. Bauerschlag DO, Schem C et al (2009) The role of p53 as a surrogate marker for chemotherapeutical responsiveness in ovarian cancer. J Cancer Res Clin Oncol 136(1):79–88
11. Hauptmann S, Denkert C et al (2002) Genetic alterations in epithelial ovarian tumors analyzed by comparative genomic hybridization. Hum Pathol 33(6):632–641
12. Shih Ie M, Kurman RJ (2005) Molecular pathogenesis of ovarian borderline tumors: new insights and old challenges. Clin Cancer Res 11(20):7273–7279
13. Hennessy BT, Coleman RL et al (2009) Ovarian cancer. Lancet 374(9698):1371–1382