Ovarian cancer: a short review

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Ovarian cancer is one of the leading causes of female cancer deaths in the most developed countries. The reason may lie in absence of early key signs and symptoms that can clearly distinguish ovarian cancer from the other benign conditions. Moreover, ovarian cancer is highly heterogeneous disease with multiple histological subtypes, of those, epithelial tumors are the most common form. New methods brought new insight into molecular background of different subtypes of ovarian cancer and depicted new paths leading to personalized treatment. This short review is focused on some aspects of this disease.
Key words: ovarian cancer, epithelial tumors, mutations, array comparative genomic hybridization (array CGH)

Ovariálne nádory: krátky prehľad
Nádorové ochorenia vaječníkov predstavujú jednu z najčastejších onkologických príčin úmrtia žien vo vysokorozvinutých krajinách. Podstata môže spočívať v absencii skorých príznakov a symptómov, ktoré jasne odlišujú nádorové ochorenia ovárií od iných nezhubných stavov. Nádory vaječníkov sú navyše značne heterogénnou skupinou s rôznymi podtypmi, z ktorých sa najčastejšie vyskytujú epitelové nádory. Nové metódy odkrývajú podstatu ochorenia a ponúkajú možnosť personalizovaného prístupu k terapii. Predkladaný článok sa venuje niektorým aspektom tohto závažného typu ochorenia.
Kľúčové slová: nádory vaječníkov, epitelové nádory vaječníkov, mutácie, array komparatívna genómová hybridizácia (array CGH)

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Introduction

Ovarian cancer is the fifth-most common cause of cancer death in women in the USA and the other developed countries. According to the American Cancer Society ovarian cancer was responsible for 14 240 cancer-related deaths in 2016 and estimates that there will be diagnosed 22 440 new cases of ovarian cancer in the US in 2017[1]. The age-standardized incidence has been estimated at 9.4 per 100 000 population in more developed areas, and 5 per 100 000 population in less developed areas[2]. Slovakia has one of the highest incidence rate among the European countries. In 2010, there were 511 registered cases of ovarian cancer what represents standardized incidence of 11.3 per 100 000 population. Out of registered cases, 277 women died from ovarian cancer in 2010[3].

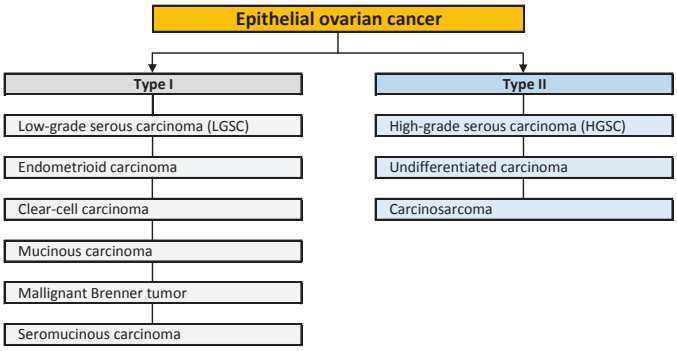
Relatively poor prognosis and high death rate is linked to the late presentation in most cases. The symptoms of ovarian cancer are often subtle, painless, and may mimic much more common disorders such as dyspepsia, irritable bowel syndrome, menstruation and menopause[4]. Symptoms commonly associated with ovarian cancer involve abdominal distension, abdominal or pelvic bloating, abdominal mass, loss of appetite and abdominal or pelvic pain, then diarrhea, isolated abdominal pain, weight loss, change in bowel habits, constipation, urinary frequency or urgency, dyspepsia, and abnormal vaginal bleeding[4].

There are several accepted risk factors that increase the probability of developing ovarian cancer, including increasing age (over 55), nulliparity, early menarche or late menopause (all associated with number of ovulation cycles), familial history of ovarian and other types of cancer, overweight[5,6]. Contrary, there are some positive factors that lower the risk of ovarian cancer, including full-term pregnancies, breast feeding, oral contraceptives[1,6]. The role of diet in the development of ovarian cancer is not clearly understood and results are often controversial[7].

Classification of ovarian cancer

Ovarian cancer is highly heterogeneous disease with different histological subtypes. Primary ovarian tumors fall into four main groups according to the type of cells from which cancer can develop: epithelial, sex cord-stromal, germ cell, and mixed-cell type ***(Figure 1)***.

Figure 1. *Histological subtypes of ovarian cancer and classification of epithelial ovarian cancer based on tumor histology and grade (reviewed in 24)*



Epithelial ovarian carcinoma is the most common form and comprises approximately 90% of all cases[6]. Histological subtypes of epithelial ovarian cancer include serous, endometrioid, clear cell, mucinous, malignant Brenner tumors, and mixed-cell type tumors, which are not longer included in the 2014 WHO classification.

Epithelial ovarian cancer may be grouped based on their clinicopathologic features and genetic profile into two types ***(Figure 2)***. Type I involves slowly developing tumors including low-grade serous carcinoma, endometrioid carcinoma, clear-cell carcinoma, mucinous carcinoma then very rare malignant Brenner tumors, and seromucinous carcinoma. Most type I tumors are believed to arise from endometriosis or borderline serous tumors. This group of cancer accounts for about 25% of ovarian malignancies and cause 10% deaths. Type II comprised more aggressive tumors including the high-grade serous carcinomas, high-grade endometroid, and rare undifferentiated carcinomas and carcinosarcomas. Tumors of this type are believed to arise from fallopian tube. Type II accounts for 75% of ovarian cancers and cause 90% of deaths[8,9].

Ovarian sex cord-stromal tumors are formed by cells that normally give rise to cells surrounding the oocytes and contain the cells that produce ovarian hormones[10]. These tumors are presented in younger patients as a low-grade disease and are usually not aggressive. Surgery is a key treatment with generally favorable prognosis. They accounts for about 7% of all primary ovarian cancer[10]. The World Health Organization reclassified this group ovarian cancer into pure stromal tumors, pure sex cord tumors, and mixed sex cord-stromal tumors[11].

Germ cell tumors of the ovary are uncommon tumors developing from the ovarian germ cells. These tumors are frequently unilateral, and despite they are aggressive, they are generally curable and treatable if found early[12]. Germ cell tumors account for about 20-25% of ovarian neoplasms, but only 5% are malignant. Group of germ cell tumors includes, in order of frequency: dysgerminomas, immature teratomas, yolk sack tumors, and mixed germ cell tumors. Less common germ cell tumors include embryonal carcinomas, choriocarcinomas, and malignant struma ovarii tumors[13].

Molecular background of ovarian cancer

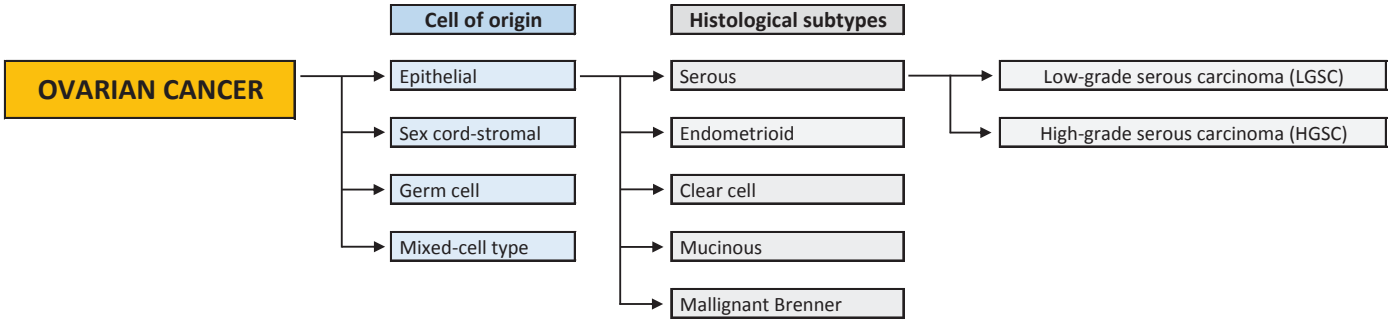
Although majority of ovarian cancers are sporadic, family history is one of the strongest risk factors. Approximately 10% of ovarian cancers are hereditary and, of those, 90% cases are closely associated with germline mutations in *BRCA1* (17q21.31) and *BRCA2* (13q13.1) genes[14]. Pal et al., 2005 performed full genes sequencing of *BRCA1* and *BRCA2* genes in cohort of 232 women with epithelial ovarian carcinomas [15]. Invasive ovarian carcinoma was diagnosed in 209 women, 32 women (15.3%) had mutations in *BRCA1* or *BRCA2* genes. Of these, 20 women had mutations in *BRCA1*, 12 in *BRCA2* gene, respectively. Variants of uncertain significance were detected in 8.2% of women with invasive ovarian carcinoma. No mutations were identified in women with borderline or invasive mucinous tumors. Among the *BRCA* mutation-positive women, 63% had serous tumors. A family history of breast and/or ovarian carcinomas was reported in 65% of relatives of *BRCA1* carriers, 75% *BRCA2* carriers, and 43.5% non *BRCA1/2* carriers, respectively[15]. Interestingly, *BRCA2* mutations show clearly genotype-phenotype correlation. Central part of the gene (nt 3035-6629 in exon 11) is named ovarian cluster region and are associated with increased risk of ovarian, rather than breast cancer. Studies on *BRCA1* mutations are less conclusive[16].

Some other malignant syndromes may develop ovarian cancer as one of their symptoms. Hereditary non-polyposis colorectal cancer (HNPCC, or Lynch syndrome) exhibits ovarian cancer as an extracolonic manifestation of Lynch syndrome II subtype. Lynch syndrome is caused by mutations in mismatch repair (MMR) genes, including *MSH2*, *MLH1*, *MLH6*, *PMS1*, and *PMS2*. Women with a germline mutation in one of the MMR genes *MLH1*, *MSH2* or *MSH6* have 6-8% life time risk of ovarian cancer[17]. Grindedal et al.,[18] performed a retrospective study of 144 women with ovarian cancer due to mutations in mentioned genes. They found 51 women (35.4%) had a mutation in *MLH1*, 78 (54.2%) had a mutation in *MSH2*, and 15 (10.4%) had a mutation in *MSH6*. They also found that overall survival of women with mutation in MMR genes is better than those with *BRCA1/2* mutation[18]. Ovarian cancers associated with Lynch syndrome are predominantly clear-cell or endometrioid in histology[19].

Peutz-Jeghers syndrome (PJS) is an autosomal dominant inherited disorder which is characterized by interstinal hamartomatous polyps, mucocutaneous melanin deposition, and increased risk of cancer, including ovarian and breast. In most PJS patients germ line inactivating mutations of the *STK11/LKB1* gene (19p13.3) has been indentified[20]. Women with PJS have an increased incidence of rare sex cord tumor with annular tubules (SCTAT). SCTAT accounted for 1.4% of ovarian sex cord-stromal tumors and are all benign[21].

To screen other germ line mutations in 12 tumor suppression genes, Walsh et al.[22] used targeted capture and massively parallel genomic sequencing. Study was conducted on

Figure 2. *Classification of epithelial ovarian cancer based on clinicopathologic and molecular features (reviewed in 24)*



360 women with ovarian carcinomas. 24% carried germ-line loss-of-function mutations: 18% in *BRCA1* or *BRCA2* and 6% in *BARD1*, *BRIP1*, *CHEK2, MRE11A, MSH6, NBN, PALB2, RAD 50, RAD51C,* and *TP53*[22]. However, the risk associated with majority of these genes is not well understood yet.

Epithelial ovarian tumors are heterogeneous in the term of histological features and molecular profiling. Each subtype is characterized by the presence of certain gene mutations. The Cancer Genome Atlas Research Network[23] reported that high-grade serous ovarian cancer (or type II) is characterized by *TP53* mutations in almost all tumors (96% of 489 high-grade serous ovarian adenocarcinomas). On the other hand, *TP53* is rarely affected in type I tumors, except mucinous one. These tumors are characterized by mutations in regulators of the mitogen-activated protein kinase (MAPK) pathway (e.g. *KRAS* or *BRAF*), as well as a number of other genomic variants, including *PIK3CA*, *PTEN*, *ARID1A*, *CTNNB1*, *CDKN2A*[24]. These evidence underline the prediction that low grade serous carcinoma is unlikely to be a precursor lesion for high grade serous carcinoma but rather they are two separated entities.

The array comparative genomic hybridization is a method for genome-wide screening for genomic abnormalities. Caserta et al.[25] performed BAC array CGH in ovarian adenocarcinoma in 10 patients with familial history[25]. The most common findings were loss of 6q (4 cases with mosaic loss of 6q), 9p (4 cases), 10q (3 cases), 21q (3 cases), 22q (4 cases); and gain of 8q and 9q (8 cases) and 12p (1 case). They observed two cases with monosomy X, and two cases with a micro deletion of 17p terminal. Some cases showed genomic profile with total or mosaic segmental gain on chromosomes 2p, 3q, 4q, 7q and 13q[25].

Gunn et al.[26] used array CGH to identify somatic chromosomal aberrations in 90 clinically relevant genes in18 ovarian tumors. They found one patient was positive for *HER2* gene amplification, four positive for *CCNE1* gene amplification and four for *MYC* gene amplification. They detected high level amplification of *KRAS* in one patient, as well as in *CCND2*. Other two high-risk patients had amplification of *CCND3*, and *PLAG1* genes. In patients with high level *CCNE1* amplification was observed co-amplification of *CCND1*, *CCND3*, *MYC* and *ETV6* genes; high level amplification of *CCND3* tumors was accompanied with co-amplification of *MYC* and *AKT2* genes; and high level of *MYC* tumors showed co-amplification of *JAK2*, *FGFR3*, and *MYB* genes. One tumor with high level *MYC* gene amplification also showed bi-allelic *PTEN* gene deletion. Eight tumors were positive for amplification of the chromosome 3q26 region which contains *MECOM*, *SnoN/SKiL*, and *ECT2* genes. All these genes were showed to be implicated in ovarian pathogenesis in high grade serous carcinomas. Interestingly, no *TP53* aberration has been detected which points to the fact that primary mechanism of *TP53* lost of function is caused by point mutations[26].

Ovarian cancer screening and prevention

High mortality rate of ovarian cancer is mainly associated with lack of key signs of disease and absence of reliable screening tests[24]. Currently, the most widely used screening methods are transvaginal ultrasound and serum cancer antigen CA-125 but the efficacy of this approach is disputable. Partridge with co-workers estimated the risk of ovarian malignancy among asymptomatic women with abnormal transvaginal ultrasound and CA-125. They concluded that screening for ovarian cancer using simultaneous CA-125 and transvaginal ultrasound did not reduce ovarian cancer mortality and was associated with high false-positive tests[27]. Falls positive results may lead to unwanted surgery which is associated with its own risks and its benefit may be questionable.

To prevent development of ovarian cancer prophylactic surgical removal of the ovary may be considered in some cases. Bilateral salpingo-oophorectomy can be recommended for women with identified *BRCA1* or *BRCA2* gene mutations and strong family history of ovarian cancer associated syndromes, for women who are 35-40 years of age and have completed childbearing. However, this intervention is link to physical and psychosocial issues[28].

Conclusion

Ovarian cancer is highly heterogeneous disease characterized by several histological subtypes, which are, in turn, characterized by their own molecular profile. Introduction of the genome-wide technologies such as aCGH or next-gene sequencing brought new insights into understanding the fundamental of disease, classification, prognostics and treatment. Searching for specific changes on the gene level can help to predict the course of disease and find the suitable targeted treatment for women.

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Poďakovanie

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