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EPITHELIAL OVARIAN CANCER TYPE II PATHOGENESIS

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ABSTRACT

The epithelial ovarian cancer (EOC) is the most lethal gynecologic cancer. Approximately 75% of the women are not diagnosed with EOC until the cancer has spread outside the ovary, leading to a 5-year mortality rate of 70%. Studies in recent years increasingly put forward the idea that EOC can no longer be considered a unitary disease. Clinical and molecular evidence shows that the different histological types are separate entities with specific patterns of disease progression and each type requires a different therapeutic approach.

KEYWORDS*: epithelial ovarian cancer, cancer genetic.*

Epithelial ovarian cancer is a major health problem, ranking 5th among the incidence of cancers in western countries [1-4]. The death rate by EOC exceeds the total rate of cervical and endometrial cancer deaths [5]. EOC cases can be divided into two broad categories, based on the model of tumour progression and molecular genetic alterations, classified as type I and type II [6,7].

Histopathologically, EOCs type we are low-grade cancers including low-grade serous, low-grade endometrioid or mucinous tumours and some subtypes of clear cell carcinomas, showing a slow evolution and relative genetic stability. They arise from morphologically recognizable precancerous lesions such as endometriosis, ovarian cortical inclusion cysts or borderline tumours [8].

EOCs type II includes high-grade serous or undifferentiated carcinomas and carcinosarcoma, and are tumours of increased aggressiveness and fast dissemination during their clinical evolution. EOC type II rarely arises from morphologically recognizable precursors [9].

Recent literature shows that peritoneal carcinoma in EOC seems to originate either in the ovarian epithelium (40%), the distal fallopian tubes/oviductal fimbriae (50%), or the peritoneum itself (primary peritoneal adenocarcinoma, 10%) – a theory supported by the common origin of these tissues from embryonic pleuripotential mesothelial coelomic epithelium [10]. In the case of advanced carcinomatosis, the tumorous tissue shows similar histological and immunohistochemical features, making the determination its origin virtually impossible.

All cancers have a genetic basis, consisting of congenital or *de novo* mutations or other genetic errors caused by multiple factors. About 10% of

high-grade serous ovarian, fallopian or peritoneal cancers are hereditary, while the remaining 90% of cases are triggered by breeding and environmental factors such as nulliparity, polycystic ovarian disease and use of ovulation induction medications, hormone replacement therapy in menopause. Multiparity, as well as the use of oral contraceptive for at least five years, can reduce the risk of developing the disease by 30-60%. Obesity, endometriosis and pelvic inflammatory disease are among common predisposing conditions. These risk factors are linked by inflammatory processes arising either from uninterrupted ovulation or oxidative stress induced by the presence of menstrual blood in the pelvic peritoneum as a result of retrograde menstruation. Other predisposing factors are advanced age and a family history of ovarian and breast cancer. Hysterectomy, tubal ligation and oophorectomy lead to a considerable reduction of cancer risk [11].

Hanahan and Weinberg described six hallmarks of malignant cell growth: sustained stimulation of cell cycle, lack of sensitivity to growth inhibitor signals, the ability to avoid apoptosis, unlimited replication potential, angiogenesis, tissue invasion and metastasis [12].

The genes responsible for cancer induction are classically divided into two major categories: proto-oncogenes (activated into oncogenes by gain-of-function mutations) and tumour suppressor genes (converted into oncogenes by loss-of-function mutations).

The proto-oncogenes encode for polypeptides playing a role in the initiation and intracellular transduction of signals regarding cellular growth and differentiation. Among the main cellular proto-oncogenes which have been documented to play an important role in the EOC pathology are the HER2 or ERBB2, KRAS and BRAF genes. The oncogenic activity of HER2 is due to gene amplification and protein overexpression and was observed in 25% of ovarian cancers, where it is associated with a poor prognosis. KRAS or BRAF mutations were highlighted in 86% of low-grade ovarian carcinomas, as well in borderline ovarian tumours and epithelium from ovarian cystadenomas, suggesting an important role in tumour progression from benign to malignant.

Normally, tumour suppressor genes act by limiting the cell growth. In case of neoplasia, both copies of these genes are inactivated or mutated (by deletion). The loss-of-function of tumour suppressor genes causes cell cycle alterations which result in excessive cellular growth. Among the tumour suppressor genes whose inactivation triggers EOC, the BRCA1, BRCA2, PTEN, and TP53 genes have been better documented.

BRCA1 and BRCA2 act to regulate DNA repair, cell cycle progression, apoptosis and maintenance of genome integrity. BRCA1/2 mutation carriers show a 40% risk probability to develop EOC at the age of 70. Histologically, 18% of cases are high-grade serous tumours, endometrioid tumours and clear cell carcinoma.

PTEN is a tumour suppressor gene activated as an oncogene by gene deletion or DJ1 oncogene expression. PTEN expression correlates with endometriosis in EOC.

TP53 encodes the p53 protein, the function of which is to respond to various cellular aggressions by regulating the target genes that induce cell cycle arrest, apoptosis, senescence, DNA repair or metabolic changes. TP53 mutations are associated with 50% of EOC cases.

Also, an important role in triggering EOC is played by microsatellite instability. Changes that accumulate in a specific DNA sequence, generated by the inactivation of intranuclear proteins involved in the DNA repair process, are mirrored by microsatellite instability. Genetic changes occur either through epigenetic inactivation of the M2H1

gene or through mutations of the MSH2, MSH6, PMS1, PMS2 genes.

The pathogenic molecular mechanisms leading to carcinogenesis are completely different between type I and type II EOC.

Table I. *Genetic basis of EOC*

Genetic cause	EOC type I	EOC type II
p53 overexpression	no	yes
BRCA1/2 mutation	no	yes
PTEN, BRAF, KRAS mutation	yes	no
Microsatellite instability	no	yes

The best documented hereditary cancers showed cell cycle control deficiencies responsible for 10% of high-grade serous ovarian cancers, 16% of high-grade serous fallopian cancers and 10% of high-grade serous peritoneal cancers [13]. Hereditary cancers include:

- Hereditary breast and ovarian cancer syndrome (20%) – associating specific mutations in BRCA1/2 and leading to serous ovarian tumours type II. These mutations appear rarely in the general population (0.1% estimated frequency) but are very powerful in the neoplastic process development. This is the reason women inheriting BRCA1/2 mutation are advised to undertake salpingo-oophorectomy – generally after the age of 40 – to reduce the risk of EOC. In the case of BRCA1 mutations, surgical intervention decreases the risk of EOC by 70% in women with no previous occurrence of breast cancer and by 85% in women with a history of breast cancer [14].
- Hereditary ovarian cancer syndrome (5%) – evolves mainly to serous ovarian cancers of type I.
- Hereditary non-polyposis colorectal cancer (Lynch II syndrome) – responsible for about 5% of hereditary epithelial ovarian cancers. The tumours usually occur at younger ages and histologically are described as mucinous, endometroide and clear cell cancers. The syndrome is caused by germline mutations of mismatch repair (MMR) genes, designated to troubleshoot possible mistakes of DNA replication process. For MMR mutation carriers, the risk of cancer before the age of 70 reaches 60% for endometrial cancer, 85% for the colorectal cancer and 12% for the ovarian cancer [15].

While in 10% of ovarian cancers, such as the hereditary ones, the molecular mechanism of tumorigenesis has been established, for the remaining 90% sporadic cancers, potential reproductive and environmental trigger factors remain under discussion. To understand the pathogenesis of high-grade sporadic EOC, animal model studies constitute an opportunity. Few animals develop spontaneous ovarian tumours, of which mainly hens and non-human primates such as macaques.

Despite anatomical dissimilarities, laying hens develop adenocarcinoma, providing information about the association between uninterrupted ovulation and spontaneous ovarian cancers [16]. According to a four year study carried out by Barua & colab. on 155 laying hens, 32% of the birds developed ovarian cancer and 8%, oviductal tumours [17]. Studying EOC in hen models is supported by similarities to humans in histological investigation, stages and metastasis. Even at the molecular level, these tumours shows similarities to human ovarian cancers: the p53 alterations are common in hen ovarian adenocarcinomas and directly related to the number of ovulations in throughout life [18]. Like in high-grade human ovarian cancers, hen RAS mutations are rare. Overexpression of HER2 acts as a marker for serous carcinomas of endometrial origin [19].

Similarly, in macaques, 23% of ovarian tumours are epithelial and very similar to human cases in terms of histological type and model of progression and metastasis [20].

Recent data shows that the common denominator of biological events such as ovulation, endometriosis and pelvic inflammatory disease linked to the EOC is inflammation. Inflammatory mediators, as well as some cytokines produced by the immune cells and activated *in situ* (TNF2, IL-1 and IL-6) were singled out as promoters of EOC genesis, growth and progression [21]. The uninterrupted ovulation theory, considered among the major EOC factors is built upon the hypothesis of a long-lasting inflammatory process. The ovarian surface epithelium adjacent to the ovulatory site is repeatedly exposed to an inflammatory and oxidative environment, resulting in an increased risk of malignant transformation. After laying an egg, both the process of ovulation and the repair process at the ovulatory site are accompanied by the release of large amounts of cytokines/chemokine and enzymes involved in extracellular matrix remodelling, including prostaglandins, bioactive eicosanoids, plasminogen activators, collagenases, interleukins and growth factors. A recruitment of activated immune cells occurs simultaneously. The overall result of these events is a global activation of pro-inflammatory networks [22]. Although genetic information is crucial in the initiation and development of the neoplastic process, it is thought that inflammation plays an important role in promoting tumour progression and metastasis. The inflammatory mediators are generated by the tumour cells as well as bt the peritumoral tissues suffering the invasion process.

One of the cyclooxygenase isoenzymes, COX-2, a component of inflammatory pathways, is highly expressed in EOC, correlating with prognosis of adverse events such as relapses or ascites [23]. Chronic users of aspirin, nonsteroidal anti-inflammatory drugs or acetaminophen (paracetamol) show a considerable lower risk of developing EOC [24].

According to a recent hypothesis, high-grade serous ovarian cancers would originate in the fallopian epithelium and the iron-induced oxidative stress after the retrograde menstruations is suspicioned as pathogenic mechanism. The floating fimbriae into the peritoneal fluid containing blood from retrograde menstruation are exposed to catalytic action of iron and genotoxic effects of reactive oxygen species (ROS) generated by haemolysis of erythrocytes by activated macrophages in the pelvic peritoneum. The inflammatory response induced in the fallopian epithelium under physiological conditions could be the start of EOC type II pathological tumorigenesis pathway [24]. Logically, retrograde menstruation – with an impact on fallopian fimbriae – is intimately linked to the uninterrupted ovulation.

The same aspects explained the prophylactic role of tubal ligation in the prevention of serous "ovarian" cancer by blocking retrograde menstruation mechanism. In order to highlight the role of tubular epithelium in ovarian tumorigenesis, Kim and colab. showed that in Dicer-Pten double-knockout mice, fallopian tube developed a high-grade serous carcinoma which subsequently spread to the ovary and evolved as metastasis into the abdominal cavity, leading ultimately to the death of the mice within 13 months [25]. Given that ovariectomized mice develop high-grade epithelial cancers and the tubal removal at early age prevents ovarian cancer, the fallopian origin of serous ovarian cancer is demonstrated [26].

When prophylactic bilateral salpingo-oophorectomy started to be practiced, 3-8% of BRCA1/2 mutation women carriers highlighted a number of neoplastic outbreaks – not interesting the ovarian surface but the distal tubal epithelium. Thus, the serous tubal intraepithelial carcinoma (STIC) as precursor lesion for type 2 cancers was evidenced. The STIC lesions are characterized by nuclear

atypia, epithelial stratification, overexpression of TP53, increased proliferation (estimated by the immunohistochemical assessment of the nuclear antigen Ki-67) and the absence of stromal invasion. In later stage of their evolution, it invades the underlying stroma. In two large studies about serous ovarian cancer in advanced stages, STIC lesions occur in 50% of cases in the distal fallopian tube, along with pathogenetic changes in TP53 [27]. It is considered that fallopian tube epithelial cells containing STIC undergoes an exfoliation process, reach ovarian surface and penetrate ovarian structures being incorporated into ovarian inclusion cysts – a process already known in relation with the follicular development in the ovulatory process.

Another variant of serous carcinoma type II is the primary peritoneal serous carcinoma. Although the estimated incidence is 10% of all EOC type II, the last decade registered an increase of 13% per year – perhaps through better identification of stem cells. [28]. It can be speculated that even in this case, the onset of tumorigenesis was due to inflammation and oxidative stress after retrograde menstruation.

It should be noted that under the action of certain mutagenic factors (probably chronic inflammation, on similar manner to ovarian cancer) the tumorigenesis processes follows different patterns – also müllerian tumour of the peritoneum being type I (becoming primary peritoneal borderline tumours) and type II (becoming peritoneal carcinomatosis).

References

1. Siegel R, DeSantis C, Virgo K, Stein K, Mariotto A, Smith T, Cooper D, Gansler T, Lerro C, Fedewa S, Lin C, Leach C, Cannady RS, Cho H, Scoppa S, Hachey M, Kirch R, Jemal A, Ward E., Cancer treatment and survivorship statistics 2012; *CA. Cancer J. Clin* 2012; 62(4):220-41.

2. Vaughan S, Coward JI, Bast RC Jr, Berchuck et al., Rethinking ovarian cancer: recommendations for improving outcomes. *Nat Rev. Cancer* 2011; 11(10): 719-25.

3. Diaz-Padilla I, Malpica AL, Minig L, Chiva LM, Gershenson DM, Gonzalez-Martin A., Ovarian low-grade serous carcinoma: a comprehensive update, *Gynecol Oncol* 2012; 126(2):279-85.

4. Jemal A, Siegel R, Ward E, Murray T, Xu J, Smigal C, Thun MJ, Cancer Statistics 2006. *CA Cancer J. Clin* 2006; 56(2):106-30.

5. Cannistra SA, Cancer of the ovary, *N. Engl. J. Med* 2004; 351(24): 2519-29

6. Shih IeM, Kurman RJ., Ovarian tumorigenesis: a proposed model based on morphological and molecular genetic analysis. *Am J Pathol.* 2004, 164(5):1511-8.

7. Cho KR, Shih IeM., Ovarian cancer. *Annu Rev Pathol.* 2009; 4:287-313.

8. Dubeau L., The cell of origin of ovarian epithelial tumors. *The Lancet Oncology*, 2008, 9(12):1191-1197

9. Landen I.P, Birrer M. I, Sood AK, Early events in pathogenesis of epithelial ovarian cancer. *J. Clin Oncol* 2008; 26(6): 995-1005.

10. Cohn ED, Alvarez DR, Chapter 12: High-grade serous carcinomas of the ovary, fallopian tube and peritoneum, in *Gynecologic oncology: clinical practice & surgical atlas*, 1st ed., Editors: Karlan J.B, Bristow ER, LI J.A, Mc. Grow Hill Medical, 2012, 217-237, ISBN 978-0-07-174926-8.

11. Riman T, Nilsson S, Persson I.R., Review of epidemiological evidence for reproductive and hormonal factors in relation to the risk of epithelial ovarian malignancies, *Acta Obstet Gynecol Scand.* 2004, 83(9):783-95.

12. Hanahan D, Weinberg RA, The hallmarks of cancer, *Cell*, 2000, 100(1):57-70.

13. Paun M, Paun I, Sindroamele de cancer ginecologic ereditar, *Obstetrica şi Ginecologia*, 2012; 60(4): 219-225.

14. Heemskerk-Gerritsen BA, Kriege M, Saynaeve C, Association of Risk-Reducing Surgery With Cancer Risks and Mortality in *BRCA* Mutation Carriers, *JAMA* 2010; 304(24): 2695-2696

15. Jacobs J, Menon U, Can ovarian cancer screening saves lives? The Question Remains Unanswered, *Obstetrics and Gynecology*, 2011, 118(6): 1209-1211.

16. Fredrickson TN, Ovarian tumors of the hen. *Environ Health Perspect.* 1987, 73:35-51.

17. Barua A, Bitterman P, Abramowicz JS, Dirks AL, Bahr JM, Hales DB, Bradaric MJ, Edassery SL, Rotmensch J, Luborsky JL, Histopathology of ovarian tumors in laying hens: a preclinical model of human ovarian cancer. *Int J Gynecol Cancer*. 2009; 19(4):531-9.

18. Hakim AA, Barry CP, Barnes HJ, Anderson KE, Petitte J, Whitaker R, Lancaster JM, Wenham RM, Carver DK, Turbov J, Berchuck A, Kopelovich L, Rodriguez GC., Ovarian adenocarcinomas in the laying hen and women share similar alterations in p53, ras, and HER-2/neu. *Cancer Prev Res (Phila).* 2009; 2(2):114-21

19. Nofech-Mozes S, Khalifa MA, Ismiil N, Saad RS, Hanna WM, Covens A, Ghorab Z., Immunophenotyping of serous carcinoma of the female genital tract. *Mod Pathol.* 2008; 21(9):1147-55.

20. Cline JM, Wood CE, Vidal JD, Tarara RP, Buse E, Weinbauer GF, de Rijk EPCT, van Esch E, Selected background findings and interpretation of common lesions in the female reproductive system in macaques, *Toxicol. Pathol* 2008; 36(7):142s-163s.

21. Clendenen TV, Lundin E, Zeleniuch-Jacquotte A, Koenig KL, Berrino F, Lukanova A, Lokshin AE, Idahl A, Ohlson N, Hallmans G, Krogh V, Sieri S, Muti P, Marrangoni A, Nolen BM, Liu M, Shore RE, Arslan AA., Circulating inflammation markers and risk of epithelial ovarian cancer. *Cancer Epidemiol Biomarkers Prev.* 2011; 20(5):799-810.

22. Macciò A, Mantovani G, Turnu E, Artini P, Contu G, Volpe A., Preovulatory human follicular fluid in vitro inhibits interleukin (IL)-1 alpha, IL-2, and production and expression of p55 chain IL-2 receptor of lymphomonocytes. *Fertil Steril.* 1994; 62(2):327-32.