Pathol. Oncol. Res. (2012) 18:135–148
DOI 10.1007/s12253-011-9482-8

REVIEW

Modern Trends into the Epidemiology and Screening of Ovarian Cancer. Genetic Substrate of the Sporadic Form

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Received: 28 September 2011 / Accepted: 21 November 2011 / Published online: 9 December 2011

Abstract Ovarian cancer (OC) is a heterogeneous disease, including a broad spectrum of histological subtypes and demonstrating diverse biological behavior. Epithelial-derived ovarian malignant tumours constitute the predominant and most lethal form of the disease. Age, genetic predisposition, gynecological and reproductive factors and environmental factors are the main risk factors that increase the risk for acquiring OC. Vaginal examination, ultrasonography and measurement of blood serum levels of tumour markers, especially CA125 constitute the first-line screening modalities for OC, whereas second-line testing involves more accurate imaging techniques such as color Doppler ultrasound of the lesion or/and a CT scan. Sex steroid hormone pathway genes, cell cycle genes, DNA repair genes, oncogenes and onco-suppressor genes have been associated with a genetic susceptibility to sporadic OC. In the present review we focus on the major oncogenes and onco-suppressor genes in the sporadic form of the disease. Each tumour subtype is associated with a unique molecular signature, as revealed by current genetic and biomarker profiling studies. Different OC pathways emerge early in the process of carcinogenesis, ultimately leading to clinically different tumour types. As mutations acquired early during tumourigenesis will be present in all later stages, large-scale gene expression profiling using DNA microarray analysis techniques can help to classify ovarian cancers into clinically relevant subtypes.

Keywords Ovarian cancer · Risk factors · Symptoms · Screening · Oncogenes and onco-suppressor genes

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Introduction

Ovarian cancer (OC) is considered to be the leading cause of death from gynecological malignancy in the Western world [1] and the 5th most common type of cancer among women in both Europe and the United States [2, 3]. Its incidence is higher in the US, Europe and Israel and lower in Japan and in the developing countries [4]. In the United States, the incidence of OC is higher for Caucasian women than for African-American or Asian-American counterparts. Ethnicity however does not appear to be a risk factor for OC, since women who have immigrated from low-risk countries to high-risk areas, such as North America, exhibit increased OC rates similar to those expected for native-born women [5], demonstrating environmental influences on the appearance of the disease.

OC is a heterogeneous disease, including a broad spectrum of histological subtypes and demonstrating diverse biological behavior. In general, ovarian tumours may develop from one of three cell types: epithelial cells, sex cord-stromal cells (including granulosa, theca, and hilus cells), or germ cells (oocytes). 40% of all ovarian tumours are non-epithelial in origin, their lesions rarely progressing to malignancy. Non-epithelial ovarian cancer approximately accounts for 10% of all ovarian cancers [6]. This review will focus exclusively on epithelial-derived ovarian malignant tumours, which constitute the predominant and most lethal form of the disease. Epithelial ovarian cancer (EOC), which accounts for approximately 90% of all ovarian malignancies [7, 8], is primarily a disease occurring in post-menopausal women, usually between the sixth and seventh decades of life [6, 9]. Epithelial ovarian carcinomas are themselves a heterogeneous group of neoplasms that exhibit a wide range of tumour morphologies, clinical manifestations, and underlying genetic alterations. Upon diagnosis of

malignancy, ovarian tumours are surgically staged to determine how far they have extended beyond the ovary [10]. Stage I indicates confinement to the ovary. Stage II tumours extend beyond the ovary to adjacent pelvic structures such as the fallopian tube or uterus. Stage III indicates metastasis to the peritoneum and/or regional lymph nodes. Stage IV tumours have metastasized beyond the peritoneum to distant sites.

OC constitutes a challenge for both the clinical and research fields. Most often diagnosed at an advanced stage of disease, mainly due to lacking of specific symptoms, roughly 2/3 of women present with metastatic disease at diagnosis [6]. Despite advances in cytoreductive surgery and combination chemotherapy, reflected in the moderately improved 5-year survival rates and improved quality of life, long-term mortality remains unaltered, with most patients returning with more aggressive disease, usually chemoresistant.

Tumour staging at diagnosis, tumour histological subtype, extent of residual disease following initial cytoreductive surgery and performance status are considered the four major prognostic factors of OC [6, 11, 12]. Considering the survival discrepancy between the early and late diagnosis of OC [13], there has been much emphasis in developing effective screening methods as well as new tumour markers in order to detect OC at an early stage [14].

Risk Factors for Developing Ovarian Cancer

Several factors have been identified as increasing the risk of acquiring OC. These can be grossly categorized into: i) age, ii) genetic predisposition, iii) gynecological and reproductive factors and iv) environmental factors.

Age

Epithelial ovarian cancer is predominantly a disease occurring in perimenopausal and postmenopausal women, with 80% to 90% of ovarian cancers occurring after the age of 40 [6]. The peak incidence of invasive epithelial ovarian cancer occurs around 60 years of age [9]. Less than 1% of ovarian cancers occur before the age of 20, mainly germ-cell tumours. The majority of ovarian tumours are sporadic (roughly 90%) in appearance, with genetic predisposition (hereditary or familiar OC) accounting for only 5–10% of cases [12]. Hereditary ovarian cancer is believed to occur about 10 years earlier [15]. Data from the Gilda Radner Familial Ovarian Cancer Registry further suggest a significant trend in hereditary ovarian cancer toward an earlier age at diagnosis with each successive generation (a phenomenon known as “anticipation”) [16].

Genetic Predisposition

Genetic predisposition is considered the most important risk factor for OC. Hereditary ovarian cancer accounts for 5–15% of all ovarian malignancies [17]. Clinically, genetic predisposition is interpreted as either a positive family history (for breast, uterine, ovarian, prostate or colorectal cancer), mainly on behalf of first-degree relatives (sister, mother, father) or as the presence of known high-risk gene mutations. A number of high-risk genes have been identified so far. However, two well-defined inheritable genetic aberrations have received the highest attention. Mutations in the breast cancer-associated genes, BRCA1 and BRCA2, and mutations of DNA mismatch-repair (MMR) genes describing the HNPCC (Hereditary Non-Polypoid Colorectal Cancer) syndrome, often termed Lynch II [12, 17]. BRCA1 and BRCA2 carriers account for approximately 90% of the ovarian cancers in the hereditary breast-ovarian cancer (HBOC) syndrome [18–23] and some 65–85% of all hereditary ovarian cancers [24–26]. HNPCC syndrome is characterized by tumours located anywhere within the genitourinary (ovary, endometrium, prostate) and gastrointestinal systems and is attributed to mutations in at least four DNA mismatch-repair (MMR) genes (MLH1, MSH2, MSH6 and PMS2). The aberrations in the Lynch syndrome account for another 10–15% of hereditary ovarian carcinomas [24, 25, 27]. In both the above categories of genetic aberrations, pedigree analysis suggests autosomal dominant transmission with variable degree of penetrance [17]. The risk of OC is the cumulative result of the number of affected first and second degree relatives on both the maternal and paternal sites. Approximately 2/3 of mutations concern BRCA1, with the estimated OC risk for a BRCA1 mutation carrier varying between 11% and 66% [17], mean risk 39% [28]. BRCA2 accounts for the remaining 1/3 of cases of the hereditary breast-ovarian cancer syndrome, with the corresponding risk around 10–20% (revised in [17]). It becomes evident that a comprehensive family history is fundamental, in order to enable early recognition of high-risk populations and prompt intervention.

Reproductive and Gynecological Factors

Early menarche and late menopause have frequently been proposed to influence the risk for OC. Although early menarche has never been sufficiently statistically proven to be an independent risk factor, old age at menopause has earned a lot of ground in OC risk assessment, being frequently identified in studies as a statistically-verified independent risk factor for OC [29, 30]. At present, there are two distinct pathogenetic theories in support of the above. Firstly, the theory of incessant ovulation, i.e. the lifetime number of ovulatory cycles is an index of a woman’s ovarian cancer

risk. Secondly, the excessive gonadotropin stimulation of the ovaries during the reproductive years. Other reproductive habits include nulliparity, refractory infertility [31] and prolonged treatment with fertility drugs [32]. For the latter, serious questions have been raised, supporting that the relationship between fertility treatment and OC is not a causal one, but rather that they are both the result of the underlying pathophysiology of infertility [33]. The use of hormone replacement therapy for treating menopausal symptoms is also considered a risk factor for OC. In a prospective study of 44241 postmenopausal US women, Lacey and coworkers reported that women who used oestrogen replacement therapy for 10 or more years were at significantly increased risk of OC and that the risk increased significantly and consistently with increasing duration of use [34]. Finally, polycystic ovary syndrome [35] and pelvic inflammatory disease -mainly endometriosis- further elevate OC risk, the latter especially for endometrioid and clear cell histologies [36].

Environmental, Dietary and Lifestyle Factors

Exposure of the ovaries to pelvic contaminants and toxic agents, such as the mumps virus [37] have been occasionally implicated as potential carcinogens for the ovaries [38], as a result of an industrialized lifestyle. Moreover, a diet high in saturated fats, obesity and cigarette smoking have been found to elevate the risk of disease [39, 40]. Smoking in particular was found to double a woman's risk of developing mucinous ovarian cancer in a meta-analysis by Jordan et al. [41], while stopping smoking returns the risk to normal in the long term. The authors concluded that smoking may thus be one of the few modifiable factors offering potential for primary prevention of mucinous ovarian cancer [41]. Finally, the use of talc powder for genital hygiene has been related with serous rather than mucinous OC [42, 43].

Risk Factors for Epithelial Ovarian Cancer According to Histological Subtype

Over the last decade, an emerging trend has appeared for recognizing histology-specific risk factors in OC in an attempt to justify the diversity of clinical outcome in OC patients. It is therefore believed that risk factors for OC may differ according to different OC histological types [44, 45]. Reproductive factors such as parity and OCP use were similarly inversely associated with OC risk in all four major EOC types (mucinous, serous, endometrioid, clear cell), while non-reproductive factors, including BMI and cigarette smoking, showed different associations for different cancer histologies. Kurian et al. mentioned that unique associations include an inverse relation of serous cancer risk to body mass index, a positive relation of mucinous cancer risk to cigarette smoking, and a weakly positive relation of endometrioid cancer risk to body mass index. Risk of all histological types was unassociated with age at menarche, age at menopause, a history of infertility, noncontraceptive oestrogen use, and alcohol consumption [44, 45]. Furthermore, Tung et al. demonstrated that non-mucinous but not mucinous tumours were significantly associated with menstruation years and lifetime ovulatory cycles. Duration of breast-feeding was significantly and inversely related to non-mucinous tumours but not to mucinous tumours. Among all tumour types, endometrioid tumours were the most strongly related to pregnancy and tubal ligation, while clear cell tumours were the only type that was associated with non-contraceptive hormone use [45]. These results strongly suggest that different OC histological types represent etiologically distinct diseases, with different pathogenetic mechanisms, distinct molecular basis and subsequent clinical outcome.

Ovarian Cancer Symptoms

Ovarian cancer has long been called "the silent killer", because it usually isn't discovered until its advanced stages. It is estimated that by the time of diagnosis only 15% of ovarian cancer is localized to the ovary, 17% is regional, and 62% occurs as distant disease [38]. The reason for this is by no means the lack of symptoms, but rather the lack of disease-specific symptoms and the misinterpretation -on the patients' behalf- of the existing symptoms or more often signs of an ovarian tumour. Given the fact that ovarian tumourigenesis is complex and many histological subtypes of OC exist, it is difficult to explain why some women remain asymptomatic until distant metastases, while others gradually develop warning signs (caused either by infiltration of local tissues or by pressure phenomena to adjusting organs) and seek help sooner. Early signs of OC include vague abdominal discomfort, bloating and occasionally vague pelvic pain, often confused with menstrual cramps. When the tumour has reached a substantial size, it can cause pressure phenomena to the adjusting organs such as the colon and the urinary bladder, causing changes in bowel movements (mainly constipation) and urination frequency [46]. Menstrual changes, vaginal bleeding or discharge and pain during intercourse are also reported [47]. The percentage of women who are completely or nearly asymptomatic until advanced disease, is unknown. A case–control study in the early 1990s involving 811 women reported 16% of women with borderline tumours, 7% with early cancer and 4% with advanced cancer experienced no symptoms before diagnosis [46]. These women usually present directly with late stage disease with symptoms such as ascites, pleural

effusions or unexplained lower back pain, the latter due to metastatic foci in the retroperitoneal space, all of which imply distant extra-abdominal disease. Finally, sensation of premature stomach fullness and/or reduced appetite, as well as mild unexplained fatigue, are considered common clinical characteristics of various malignancies. One of the most important clinical signs in ovarian cancer is a fixed irregular pelvic mass, which is usually discovered by vaginal palpation during a routine gynecological examination [48, 49].

Current Screening Modalities in Ovarian Cancer

Risk assessment is important in OC. All women with a positive family history of cancer, regardless of the type, should have an annual thorough clinical gynecological examination (including abdominal auscultation and palpation, vaginal examination, with emphasis in the douglas space and lower rectal examination) and a comprehensive family history recorded, especially women around menopause (older than 40 years). Current first-line screening modalities for OC include vaginal examination, ultrasonography (mainly transvaginal ultrasound) and measurement of blood serum levels of tumour markers, especially CA125 [50, 51]. Second-line testing, usually follows a positive or inconclusive first-line test result [51]. Second-line testing involves more accurate imaging techniques such as color Doppler ultrasound of the lesion or/and a CT scan. Where necessary, exploratory laparotomy or/and ovarian tumour biopsy are performed to distinguish between cases.

The use of serum tumour markers for the early detection of OC has largely focused on CA125, a heavily glycosylated high molecular-weight mucin (MUC 16) [50, 52, 53]. CA125 is basically a marker of epithelial tissue turnover and is produced by a variety of tissues, including mullerian (endocervical, endometrial, tubal) and coelomic (peritoneum, pericardium, mesothelial cells of the pleura) epithelia [54]. In a review by Badgwell et al. 2007 [50], it was reported that significant expression of CA125 has been observed in 80% of ovarian cancers at a tissue level [55], but variations have been noted according to OC histotype. In tissue arrays, CA125 is expressed by 85% of serous, 68% of papillary, 65% of endometrioid, 40% of clear cell and 36% of undifferentiated adenocarcinomas, but in only 12% of mucinous cancers [56]. Therefore CA125 elevation is predominantly associated with serous tumours, the most common and most lethal subtype of ovarian cancer. Serum levels directly correlate with the level of CA125 protein production in tumour cells and appear to reflect a state of active tumour growth [56, 57].

CA125 has relatively high sensitivity for advanced stage OC, yet sensitivity declines when it comes to detecting early stage OC [58]. Serum CA125 levels are elevated in 50–60% of patients with early stage ovarian cancer and in 90% of patients diagnosed with late stage ovarian cancer [59]. Furthermore, Nakae et al. demonstrated that among 32 patients with ovarian cancer, 34 patients with benign ovarian tumours, and 31 healthy women, CA125 had a sensitivity of 84.4% and a specificity of 66.3% in predicting this disease [60]. CA125 specificity is relatively poor, since it is elevated in a number of benign ovarian conditions such as menstruation, first trimester pregnancy, endometriosis, adenomyosis and salpingitis [50], or even in other types of cancer, including carcinomas of the breast and lung [61, 62]. Furthermore, recent studies that investigated demographic and clinical factors predicting CA125 values, have highlightened the need to interpretate CA125 values on the basis of the individual's age-specific risk [63] and demonstrated that initial CA125 testing should be personalized primarily for menopausal status [64]. It becomes evident that CA125 alone is less effective when used to screen premenopausal women and should be limited for the screening of postmenopausal ones.

Specificity improves when CA125 is combined with other biomarkers, such as HE4 (Human Epididymis Protein 4). When compared to CA125, HE4 possesses higher sensitivity in detecting stage I ovarian cancer [65], plus it is more specific than CA125, i.e. has less false-positive results in non-malignant ovarian conditions [66, 67]. In combination with HE4, CA125 has been found to identify ovarian cancers preoperatively with 94% sensitivity [65]. When used in combination to detect early-stage disease, CA-125 and HE4 perform better than either marker alone and can be used to stratify patients into high- and low-risk groups [68, 69].

There are other limitations that render CA125 ineffective for early stage OC screening. Cut-off levels (30 or 35 U/mL) that are used for identifying a positive CA125 test have only been established for patients with clinically overt disease. This value is not recommended for screening asymptomatic patients. It must be made clear that, like for most tumour markers, there is a meaning only when evaluating CA125 changes in serum overtime, i.e. there is a need for serial measurements. There is no reason in evaluating absolute values of the marker since there are inter-individual variations (in the absence of identifiable benign disease, some women have individual baselines that exceed the usual 35 U/ml cut-off for 99% specificity [70, 71]), as well as variations according to age, OCP use and menstrual status [63, 64]. Meantime, CA-125 remains a valuable tool for monitoring response to chemotherapy and for detecting disease relapse following treatment [72, 73].

Specificity of screening can be improved by combining CA125 with trans-vaginal ultrasonography (TVS) in a two-stage strategy or by sequential monitoring of CA125 values over time [50]. TVS is a noninvasive technique that provides detailed images of ovary size and shape, facilitating

the detection of ovarian masses. Theoretically, a combination of CA125 and ultrasound could achieve a specificity of 99.9% [74], however large-scale studies evaluating its ability to identify early-stage tumours have so far reported mixed results [75–77]. Furthermore, even in the most optimistic reports, it is clear that TVS can only detect tumours that cause a significant increase in ovarian volume [77]. This is especially worrisome in the case of serous-type tumours which may spread rapidly from the ovary to other pelvic sites prior to ovarian enlargement. TVS screening may also be prone to false-positive results because it cannot always distinguish malignant ovarian tumours from benign adnexal masses, such as cysts and fibromas, which are highly prevalent among postmenopausal women [78, 79]. Since TVS has not demonstrated adequate sensitivity to warrant its use in screening general populations, an important limitation to its widespread use, is the cost of annual screening for the entire postmenopausal population, given the prevalence of ovarian cancer and difficulties in identifying women at increased risk [51].

Major Oncogenes and Onco-suppressor Genes in the Pathophysiology of Sporadic Ovarian Cancer

Ovarian cancer is thought to result from an accumulation of genetic alterations, however the exact nature of alterations remains largely unknown. Approximately 10% of ovarian cancers arise in the setting of known genetic predisposition, the majority of which are associated with germline mutations in the BRCA1 and BRCA2 genes [17]. The majority of OC cases (90%) are sporadic in origin.

On the basis that cancer is primarily a genetic disease, like other cancers, ovarian tumourigenesis can be described as a multi-step process in which each step is thought to correlate with one or more distinct mutations in major regulatory genes. During the last 30 years several genes have been associated with a genetic susceptibility to sporadic OC, summarized mainly into 4 groups: sex steroid hormone pathway genes, cell cycle genes, DNA repair genes, oncogenes and onco-suppressor genes [80]. The last category of genes involves genes whose coupled balanced action regulate cell growth, proliferation and differentiation and are considered essential for the maintainance of tissue cellular homeostasis.

While hereditary ovarian cancer syndromes are characterized by an inherited susceptibility to ovarian cancer on the basis of identified germline mutations of varrying penetrance in one allele of a susceptibility gene (mainly BRCA1 and BRCA2) [17], sporadic ovarian cancer results from a serial stepwise accumulation of acquired and uncorrected mutations in somatic genes, without any germline mutation playing a role. The genetic component of sporadic OC has been an object of research in the last decade. The widespread use of gene-expression profiling techniques has drastically boosted research on sporadic OC. Microarray technology enables the analysis of expression levels of thousands of genes simultaneously and is widely used to identify prognostic gene-expression profiles for all types of cancer [81, 82].

Oncogene and Onco-suppressor Gene Mode of Action—General Principles

Oncogene or oncosuppressor gene activation in human cancer can result from increased gene copy number or structural changes, leading to increased expression of the gene product or production of an altered protein, respectively [83, 84]. The normal proto-oncogene can be converted into an active oncogene by deletion or point mutation in its coding sequence, gene amplification, and by specific chromosome rearrangements [83]. Structural changes may take the form of point mutations or rearrangements, the latter usually resulting from chromosomal aberrations such as translocations and inversions. Changes resulting in increased gene expression include gene amplification, enhanced transcription or translation, and mRNA or protein stabilization [84]. Mutational activation of oncogenes and/or often coupled with non-mutational inactivation of tumour suppressor genes, is probably an early event in the oncogenic pathway of sporadic tumours of the female genital tract, followed by more, independent mutations in at least four other genes, the chronological order of which is likely less important [83–86].

Ovarian Tumourigenesis - the Dualistic Model

The vast histological variety of ovarian malignant tumours, the diversity in tumour behaviour and course of disease even within the same histological subgroup, makes the treatment of OC profoundly difficult. A tumour progression model unifying the basic pathogenetic mechanism, mode of progression (tumour spread), molecular and genetic characteristics related to prognosis was clearly lacking. However, it was evident that there were similarities between OC tumours belonging to different groups, i.e. low-grade serous (often termed serous borderline), mucinous and endometrioid carcinomas, although distinct in cell type origin, pursue an indolent course that may last for up to 20 years [87, 88], while high-grade serous carcinomas are more aggressive in nature [89].

Genetic and biomarker profiling studies of ovarian cancer have revealed that each tumour subtype is associated with a unique molecular signature (revised in [17] and [90]). For

example, gene expression profiling has demonstrated that ovarian clear cell tumours are distinctly different from other forms of ovarian cancer and rather share more in common with clear cell tumours of other organs, such as renal clear cell carcinomas [91]. Even within one histological subtype, ovarian tumours exhibit differences in biological behaviour reflected in distinct expression profiles. Bonome et al. [92] found that serous borderline tumours (which account for 10-15% of serous ovarian neoplasms and are known to pursue an indolent course, associated with vastly improved survival [87, 88]), cluster separately from high-grade serous carcinomas in hierarchical clustering analyses and are genetically more similar to normal ovarian surface epithelium than to advanced high-grade serous tumours [92], the latter exhibiting more aggressive behaviour.

In an attempt to integrate most of the clinical, histopathological and molecular genetic findings concerning OC, Shih and Kurman [89] proposed a two-pathway progression model for ovarian carcinogenesis. In this model, ovarian tumours are divided into two broad categories designated as type I and type II. These designations refer to pathways of tumourigenesis and are not specific histopathological terms. Type I tumours include all major histotypes (low-grade serous carcinoma, mucinous carcinoma, endometrioid carcinoma, malignant Brenner tumours and clear cell carcinoma). Type II tumours are composed of what are currently classified as moderately and poorly differentiated serous carcinoma (high-grade serous carcinoma), malignant mixed mesodermal tumours (carcinosarcomas), and undifferentiated carcinoma.

The tumourigenic pathway for type I tumours is characterized by clearly recognized, well-defined precursor lesions, namely, cystadenoma, atypical proliferative tumour, and noninvasive carcinoma. The latter two non-invasive tumours have traditionally been combined into one category designated as "borderline." These tumours exhibit low-grade nuclear and architectural features and develop slowly in a stepwise manner from the precursor lesion. Type I tumours are associated with distinct molecular changes that are rarely found in type II tumours, such as BRAF and KRAS mutations, both of which activate the oncogenic MAPK signaling pathway [93]. Mutually exclusive KRAS and BRAF mutations are observed in 65% of serous borderline tumours but are rarely seen in high-grade serous carcinomas [94, 95]. KRAS mutations also occur in ~60% of mucinous, 5–16% of clear cell and 4–5% of endometrioid type I carcinomas [89]. PTEN silencing mutations, which typically result in constitutive PI3K signaling, occur in ~20% of type I endometrioid neoplasms [96] The MAPK and PI3K pathways are also related. They eventually converge upon a common downstream translation factor, notably eIF4B [97], which may represent an important signaling axis in Type I tumour development. WNT and TGF-β signaling pathways are also implicated in type I tumourigenesis, based on the presence of β-catenin mutations in 16–54% of endometrioid tumours and TGF-β RII mutations in 66% of type I clear cell tumours [89]. It is worth mentioning that the mutational profile of type I OC affects pathogenetic mechanisms involved in the process of epithelial-to-mesenchymal transition [98, 99].

In contrast, type II tumours have no morphologically recognizable intermediate stages, arising directly from the surface epithelium or inclusion cysts. These tumours exhibit a high-grade mitotic index, evolve rapidly and are associated with an early and more aggressive metastatic potential. Molecular alterations associated with type II tumours include frequent mutations of p53 in high-grade invasive serous carcinomas and malignant mixed mesodermal tumours [89, 100–102]. Type II tumours are comprised almost exclusively of high-grade serous carcinomas but also include two less common subtypes, mixed epithelial and undifferentiated carcinomas. Type II ovarian tumours are overwhelmingly TP53 mutated (50–80%) and may also exhibit gene amplification and overexpression of HER2/neu (20–30%) [103, 104] and PI3K/AKT2 (12–18%) oncogene pathway [105]. It is of note that alterations of AKT2 have been associated with tumour aggressiveness and poor prognosis [105].

This dualistic model for ovarian tumourigenesis, later reviewed and improved by others [17, 90] reconciles the inconsistency in the current classification of ovarian tumours that regards borderline tumours as a distinct entity unrelated to invasive carcinoma and provides a morphological and molecular genetic framework for future studies aimed at elucidating the pathogenesis of ovarian cancer. Lynch et al. improved the model by the addition of a pathogenetic mechanism for hereditaty OC [hereditary BCRA1 and BCRA2 mutations, along with somatic p53 mutations (Knudsen two-hit hypothesis), complicated by genotoxic injury], unifying all pathogenetic cascades of ovarian tumourigenesis in a satisfactoty explanation of the diversity and yet the common features of low-grade and high-grade behaviour in OC [17].

Thus, different ovarian cancer pathways emerge early in the process of carcinogenesis, ultimately leading to clinically different tumour types. As mutations acquired early during tumourigenesis will be present in all later stages, large-scale gene expression profiling using DNA microarray analysis techniques can help to classify ovarian cancers into clinically relevant subtypes.

Major Oncogenes in Sporadic Ovarian Cancer

Ras Family Genes

The RAS gene superfamily are G-proteins, known to act as molecular switches in the transduction of cellular signals critical for a wide range of normal developmental events as

well as pathological processes. Activating mutations in the Ras gene family members are found in 30% of all human tumours [106]. In mammals, there are three functional Ras genes, H- (Harvey) ras, N- (neuroblastoma) ras, and K- (Kirsten) ras, located on different chromosomes that appear to be expressed ubiquitously [106, 107]. Their actions are mediated through the MAP kinase pathway [108]. The functions of RAS genes in the female genital tract have only started to be unveiled [83–85]. In the ovaries, RAS, most likely KRAS that is highly expressed in granulosa cells of growing follicles, appears crucial for mediating the gonadotropin-induced events associated with the unique physiological process of ovulation. In mouse models, a mutated form of K-RAS (active KrasG12D mutant) results in the complete disruption of normal follicular growth, cessation of granulosa cell proliferation, blockage of granulosa cell apoptosis and differentiation. When coupled with additional mutations, such as PTEN disruption, ovarian surface epithelial cells expressing the same PTEN/KrasG12D mutations rapidly become ovarian surface epithelial serous cystadenocarcinomas [106]. In humans, mutations in the K-RAS gene have been reported in approximately 60% of borderline ovarian tumours, in nearly 70% of low-grade ovarian tumours, and in 50% of ovarian mucinous adenocarcinomas and often in the adjacent benign epithelium [89, 109, 110].

K-ras mutations appear to play a minor role in the pathogenesis of invasive ovarian carcinomas; their role seems to be more important in borderline ovarian tumours that exhibit low malignant potential [95, 109, 111, 112]. Activating mutations in codons 12 and 13 of KRAS occur frequently in carcinomas and result in the constitutive activation of KRAS that contributes to tumourigenesis [93, 113–116]. Varras et al. [111] analyzed the pattern of K-, H- and N-ras codon 12 point mutations, in 74 tissue specimens of epithelial ovarian tumours in the Greek population, and showed that K- and H-ras gene mutations were detected in 23% and 6% cases with primary invasive ovarian carcinomas, respectively; while N-ras gene mutations were not detected. Furthermore, in 33% borderline ovarian tumours a H-ras gene mutation was detected. In epithelial ovarian neoplasms K-ras codon 12 gene mutations show a wide variation fluctuating between 4% and 39% in invasive carcinomas and 20–48% in borderline malignant tumours. Back in 1998, Zachos et al. demonstrated that transcriptional regulation of the c-H-ras1 gene by the P53 protein is implicated in the development of human endometrial and ovarian tumours [112]. The mutational profile of BRAF, a downstream mediator of KRAS, has also been studied [93, 109]. To determine the role of mutations in BRAF and KRAS in ovarian carcinoma, Singer et al. analyzed both genes for three common mutations (at codon 599 of BRAF and codons 12 and 13 of KRAS) [95]. Mutations in either codon 599 of BRAF or codons 12 and 13 of KRAS occurred in 68% of invasive micropapillary serous carcinomas (MPSCs; low-grade tumours) and in 61% of serous borderline tumours (precursor lesions to invasive MPSCs). None of the low-grade tumours contained both BRAF and KRAS mutations, while no BRAF or KRAS mutations were detected in a series of 72 aggressive high-grade serous carcinomas of the same study. The apparent restriction of these BRAF and KRAS mutations to low-grade serous ovarian carcinoma and its precursors suggests that low-grade and high-grade ovarian serous carcinomas are characterized by different mutations and therefore develop through independent pathways. Mayr et al. [109] in a series of 100 ovarian tumours, demonstrated that 92 cases (92%), including all serous carcinomas (100%), did not show a mutation of BRAF. Eight cases (8%), including five serous borderline tumours (31%), contained a mutation. In all serous borderline tumours, codon 600 was affected. There was no BRAF mutation in mucinous borderline tumours. Both previous studies [95, 109] demonstrate that mutations of either K-RAS or BRAF are frequent in borderline tumours but are not found in invasive serous carcinomas and are very rare in other invasive subtypes. This supports the notion of different pathological pathways. Ratner et al. [117] evaluated the histological distribution of a variant allele of KRAS at rs61764370 (termed KRAS-variant) across different subtypes of epithelial OC and found that the prevalence of the KRAS-variant varied between subtypes, being highest in non-mucinous cancers, and being rarely found in patients with mucinous ovarian cancers. The researchers support that the KRAS-variant is identified in over 25% of non-selected OC patients and is found in 61% of OC patients from HBOC (hereditary breast ovarian cancer syndrome) families previously considered uninformative for gene mutations and support the hypothesis that the KRAS-variant is a new genetic marker of an increased risk of developing OC, and, additionally, that this allele of KRAS may be a new HBOC locus.

c-Myc

c-Myc is a transcription factor that regulates the expression of many genes. The c-Myc gene is amplified in both hematopoietic and solid neoplasms, including more than 30% and 40% of endometrioid and clear cell carcinomas, respectively. The over-expression of c-Myc has been reported in 30% of all ovarian tumours, but most frequently in serous adenocarcinomas [108].

HER Receptor Family

Epidermal growth factor receptor (EGFR) (also referred to as ERBB1/HER1) is over-expressed in 30–70% of high-grade serous ovarian carcinomas. The relationship between

EGFR over-expression and clinical prognosis is not clear, with some reports suggesting a clear prognostic importance [118]. Increased EGFR signaling is detected more often in metastases than in primary epithelial ovarian cancer tumour samples [119]. c-ERBB2 (HER2/neu) is a member of the type I tyrosine kinase receptor family HER (i.e., ERBB). HER2 expression in ovarian cancer varies widely; over-expression is found in 20–30% of serous ovarian high-grade carcinomas, but rarely in low-grade and borderline tumours [103]. It has been reported that approximately 40% of HBOC cases over-express HER2. Puputti et al. reported the allelic imbalance of the HER2 variant in sporadic serous ovarian cancer [120]. Increased HER2/neu expression in OC is correlated with poor survival [83–85].

AKT-2

Amplification of AKT-2 has been detected in 12.1% of samples of ovarian carcinomas [83, 84]. Over-expression of AKT-2 can also occur in ovarian carcinomas negative for AKT-2 amplification. The significance of the PI3K/AKT (including PIK3CA, PIK3CB, PIK3R1, AKT1 and AKT2) pathway in ovarian cancer is well documented [121]. Evidence of deregulation of the PI3K/AKT signalling pathway in ovarian cancer includes gain-of-function mutations and amplifications of PI3-kinase genes, amplification of AKT2 and allelic imbalance and mutations of PTEN [122]. Previous studies have reported that patients with alterations of AKT2 have a poor prognosis with amplification of AKT2 being especially frequent in undifferentiated tumours, suggesting that AKT2 alterations may be associated with tumour aggressiveness and overall poor prognosis [105]. The finding of copy number gains of AKT2 [123], but not the related genes AKT1 or AKT3, suggests a particular significance of AKT2 over-expression in serous ovarian tumourigenesis. In addition, the over-expression of AKT2, but not other AKT family members, has been shown to lead to the up-regulation of β1 integrins, increased invasion, and metastasis of ovarian cancer cells [124].

Major Onco-suppressor Genes in Sporadic Ovarian Cancer

p53

It has been reported that loss of function and mutations of p53 are involved in ovarian cancer, and possibly these alterations can be used as a prognostic factor [83, 84, 112]. p53 is an example of a prototype tumour suppressor gene that promotes cell cycle arrest/apoptosis in cells with DNA damage. Mutations of this gene are frequently encountered in many human malignancies, including 50–80% of high-grade ovarian serous carcinomas [17], particularly associated with an aggressive invasive phenotype [100, 101] and poor prognosis. However, p53 mutations are rarely seen in other OC types or borderline serous tumours. p53 mutations have also been detected in ovarian inclusion cysts adjacent to cystadenocarcinomas, in microscopic ovarian cancer, and in tubular intraepithelial carcinomas removed prophylactically from patients with BRCA1 mutations, suggesting that the p53 inactivation may be a relatively early event in ovarian cancer pathogenesis [108, 125]. Serous endometrial carcinomas are also p53 mutation-positive as are the "dysplastic" ovarian surface cells from prophylactic salpingo-oophorectomies. Spandidos and Zachos in 1998 suggested the transcriptional regulation of the c-H-ras1 proto-gene by the P53 protein to be implicated in the development of human endometrial and ovarian tumours [112]. Mutation of the p53 gene at the locus 17p13.1 is the most common single genetic alteration in sporadic human epithelial OC. The p53 protein contains four functional domains: a transcriptional activation domain, a tetramerization domain and two DNA binding domains. In addition to possessing transcriptional activating properties, transcriptional repression has been described, although binding sites are less well characterized [126]. Either loss of wild type p53 function, gain of oncogenic function or the ability to activate p53 inappropriately severely compromises the capacity for controlled cellular proliferation and growth. The majority of p53 mutations are missense mutations that cause single residue changes, largely occurring in the DNA binding domain [126, 127]. p53 mutations in OC are considered an index of poor prognosis, earlier disease relapse, and non-response to cis-platinum first line chemotherapy [128, 129]. There is also evidence that p53 mutation status can be a general predictor of radiation resistance in advanced stages of ovarian cancer [130].

PTEN

PTEN, a tumour suppressor gene located at chromosome 10q23.3, is one of the most frequently mutated genes in human cancer and acts as a tumour suppressor by dephosphorylating the plasma membrane lipid second messenger phosphoinositide-3,4,5-triphosphate (PIP3) generated by the action of PI3Kinases back into PIP2. This dephosphorylation is important because it results in the inhibition of the AKT signalling pathway; so with the loss or dysfunction of this gene and encoded protein, the proliferation of transformed cells continues unabated [131]. Mutations of PTEN are tightly associated with endometrioid metaplasias, endometriun hyperproliferation, therefore with the endometrioid type of ovarian and uterine carcinomas (revised in [17]). Reduced PTEN protein expression has been reported in both endometrial hyperplasias and advanced endometriosis [132–

134]. Somatic PTEN mutations were identified in 4/20 (20%) endometrioid ovarian carcinomas and in 7/34 (21%) benign endometrial ovarian cysts but in just 2/24 (8%) of the ovarian clear cell carcinomas studied by Sato et al. [134]. Common PTEN loss of heterozygosity (LOH) in both carcinoma and endometriosis was found by Sato et al. in 60% of endometrioid ovarian carcinomas with synchronous endometriosis and 50% of ovarian clear cell carcinomas with synchronous endometriosis. These observations and data suggest that endometrioid carcinomas may arise from malignant transformation through the loss of heterozygosity in MMR in benign or oestrogen-stimulated endometrium, endometrial hyperplasia or even endometriosis (revised in [17]).

BRCA1 and BRCA2

BRCA1 and BRCA2 (breast cancer susceptibility genes) genes are mostly responsible (approximately in 80% of cases) for the appearance of cancer in hereditary breast ovarian cancer syndrome. However, somatic mutations (de novo mutations, unrelated to inherited susceptibility) of these genes can also occur, resulting in sporadic forms of breast or ovarian cancer. Such mutations (mainly deletions) account for roughly 5–6% of all ovarian cancer cases [108]. Among its many biological functions, the BRCA1 protein is involved in DNA repair. BRCA2 is a tumour suppressor that shows similar but less common associations with HBOC as compared with BRCA1 [17]. BRCA2 is thought to be involved in the maintenance of chromosomal stability and to possess an important role in recombination-mediated double-strand DNA break repair [17, 83, 84]. In sporadic OC, BCRA1 and BCRA2 mutations are considered a prognostic index of poor response to single-agent chemotherapy (particularly platinum-based), while absent/low BRCA1 protein expression is a favourable prognostic marker [135–138].

Protective Factors Against Developing Ovarian Cancer

Suppression of ovulation and/or diminished lifetime exposure to gonadotropins, mainly oestrogens, is currently considered the key molecular mechanism with the strongest protective effect against EOC. Thus, factors associated with ovulation suppression, such as increasing numbers of full-term pregnancies, late menarche and early menopause, prolonged lactation and oral contraceptive use are associated with a decrease in ovarian cancer risk.

Several epidemiological studies have found parity to be significantly protective against OC (see reviews [12, 38, 48]. Overall, multiparas appear to have a risk reduction as high as 40–60% as compared to nulliparas ([139, 140]). What is more, it appears there is an inverse correlation between the number of births and risk assessment. It is estimated that each full-term pregnancy confers a 16–22% risk reduction [139, 140], independent of maternal age at first pregnancy [141]. Pregnancies resulting in spontaneous abortion or early termination lead to no significant change in OC risk [139, 142]. Prolonged lactation has been reported to be associated with a slight additional reduction in OC risk [139, 143]. It appears that the reprogramming of the ovary/pituitary axis during pregnancy, labor and subsequent lactation induces changes to the hormonal environment of the ovaries, leading to cessation of ovarian epithelium turnover and suppression of the ovulatory process, resulting in OC protection.

In the same spirit, oral contraceptive pill (OCP) use is considered to exert major protective effects against OC, to such an extent as to be used as a means for the prevention of the disease in high-risk patients (OCP-1,OCP-2). Duration of OCP use seems important (see reviews [12, 48]). Risk reduction for OC by 40%, 53% and 60% was reported with OCP use for 4.8 and 12 years, respectively [38]. Interestingly, the protective effect of oral contraceptives appears to persist even after discontinuation of use [144]. This significant protective effect seems to be independent of oestrogen dose [145]. Ten years of OCP use by women with a family history appeared to reduce their risk to levels below the general population baseline [146]. Furthermore, a combined effect for risk reduction has been observed by the combination of parity and OCP use [29]. Other pharmacological agents which may lower OC risk are acetaminophen, aspirin [147] and vitamin D [148], possibly through inhibition of inflammatory processes and oxidative stress.

Additionally, gynecological procedures involving hysterectomy and tubal ligation have been associated with an average 67% risk reduction in OC. This protective effect appears to last for at least 20 to 25 years after surgery [149, 150].

Clinical Management

The risk of ovarian cancer is reduced by 50% or more in unselected women with long-term use of oral contraceptives ([151, 152]). To evaluate the potential benefit of oral contraceptive use in women at high risk for ovarian cancer, Narod et al. [153] studied 207 patients with BRCA1 or BRCA2 mutations and ovarian cancer and 161 of their sisters, who served as controls. Their findings suggested that oral contraceptive use protects against ovarian cancer in carriers of either the BRCA1 or BRCA2 mutation.

Meijers-Heijboer et al. [154] conducted a prospective study of 139 women with pathogenic BRCA1 or BRCA2 mutations without a history of breast cancer; 76 underwent

prophylactic mastectomy and 63 remained under regular surveillance. They found that prophylactic bilateral total mastectomy reduced the incidence of breast cancer at 3 years of follow-up. Eisen and Weber [155] stated that prophylactic mastectomy is "clearly the right choice for some women. For the remainder, oophorectomy and tamoxifen in conjunction with intensive screening that includes breast MRI is a viable alternative". They noted the need for underlying and novel prospective studies to define the role of prophylactic surgery, new chemopreventive agents, and optimal screening strategies.

Kauff et al. [156] and Rebbeck et al. [157] reported the results of studies indicating that prophylactic oophorectomy in carriers of BRCA1 or BRCA2 mutations can decrease the risk of breast cancer and BRCA-related gynecological cancer. In the study of Kauff et al. [156], of 98 women who had salpingo-oophorectomy, 3 developed breast cancer and 1 developed peritoneal cancer. Among the 72 women who chose surveillance alone, breast cancer was diagnosed in 8, ovarian cancer in 4, and peritoneal cancer in 1. In the study of Rebbeck et al. [157], 6 of 259 women who underwent prophylactic oophorectomy (2.3%) received a diagnosis of stage I ovarian cancer at the time of the procedure; 2 women (0.8%) received a diagnosis of papillary serous peritoneal carcinoma 3.8 and 8.6 years after bilateral prophylactic oophorectomy. Among the controls, 58 women (19.9%) received a diagnosis of ovarian cancer, after a mean follow-up of 8.8 years. With the exclusion of the 6 women whose cancer was diagnosed at surgery, prophylactic oophorectomy significantly reduced the risk of coelomic epithelial cancer.

"Synthetic lethality" as a treatment for cancer refers to an event in which tumor cell death results from lethal synergy of 2 otherwise nonlethal events. Fong et al. [158] used this model to treat breast cancer cells that have homozygous loss of the tumor suppressor genes BRCA1 or BRCA2 with a PARP inhibitor, resulting in the induction of selective tumor cytotoxicity and the sparing of normal cells. The method aims at inhibiting PARP-mediated single-strand DNA repair in cells with deficient homologous-recombination double-strand DNA repair, which leads to unrepaired DNA breaks, the accumulation of DNA defects, and cell death. Heterozygous BRCA mutant cells retain homologous-recombination function and are not affected by PARP inhibition. In vitro, BRCA1-deficient and BRCA2-deficient cells were up to 1,000-fold more sensitive to PARP inhibition than wildtype cells, and tumor growth inhibition was also demonstrated in BRCA2-deficient xenografts. Fong et al. [158] reported a phase 1 clinical trial of an orally active PARP inhibitor olaparib (AZD2281 or KU-0059436) in 60 patients with mainly breast or ovarian cancer, including 22 BRCA mutation carriers and 1 who was likely a mutation carrier but declined genetic testing. Durable objective antitumor activity was observed only in confirmed carriers of a BRCA1 or BRCA2 mutation; no objective antitumor responses were observed in patients without known BRCA mutations. Twelve (63%) of 19 BRCA carriers with ovarian, breast, or prostate cancers showed a clinical benefit from treatment with olaparib, with radiologic or tumor-marker responses or meaningful disease stabilization. The drug had an acceptable side-effect profile and did not have the toxic effects commonly associated with conventional chemotherapy. Fong et al. [158] concluded that PARP inhibition has antitumor activity in BRCA mutation carriers.

Conflict of Interest Statement All authors state that they do not have any financial interests or connections, direct or indirect that might raise the question of bias in the present work.

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