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Solid Tumour Section

Review

Ovary: Epithelial tumors

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Identity

Note

Ovarian epithelial tumours are thought to arise from the simple cuboidal surface epithelium of the ovary, and account for 75% of all ovarian tumours, and 90-95% of ovarian malignancies.

Classification

Note

Ovarian epithelial tumours are classified according to the following histological subtypes:
serous,
mucinous,
endometrioid,
clear cell,
Brenner,
transitional cell,
small cell,
mixed mesodermal and
undifferentiated.
Usually each subtype can be classified as benign, borderline (low malignant potential, LMP), or malignant (invasive).

Serous tumours are further subdivided into the following:
Serous cystadenoma
Borderline serous tumour
Serous cystadenocarcinoma
Adenofibroma
Cystadenofibroma

Mucinous tumours are further classified as:
Mucinous cystadenoma
Borderline mucinous tumour
Mucinous cystadenocarcinoma
Adenofibroma

Clinics and pathology

Etiology

Epidemiology studies have provided data showing increased risk for ovarian cancer with greater numbers of ovulation cycles. Multiple pregnancies and use of oral contraceptives are thought to have a protective effect because of decreased ovulation and hormonal influences. There are two theories explaining for the association of decreased risk with decreased number of ovulation cycles:
1. "Theory of incessant ovulation": repeated ovarian follicular rupture and subsequent repair results in increased likelihood of genetic alterations within the surface epithelium.
2. The "Gonadotrophin Theory" hypothesis: persistent stimulation of the ovaries by gonado-trophins, together with local effects of endogenous hormones, results in increased proliferation and mitotic activity of the surface epithelium. This is consistent with ovarian cancer being associated with high gonadotrophin states such as the menopause, and less commonly associated with low gonadotrophin states such as oral contraceptive use and high parity.

Epithelial ovarian carcinoma develops sporadically in about 90-95% of patients. Environmental and dietary factors are thought to have a role. These include use of talc on the perineum and vulva, asbestos, pelvic irradiation, viruses (particularly mumps), high-fat diet, and lactose consumption. Other factors are associated with an increased number of ovulation cycles: low parity, delayed childbearing, early menarche and late menopause. However, genetic factors are the most important risk factor for ovarian epithelial carcinoma (See Genetics section of this review for further details).
Factors that decrease the risk for ovarian cancer

predominantly reduce the number of ovulation cycle's woman encounters-such as the use of oral contraceptives, breast-feeding and multiparity. Long-term use of oral contraceptives has reduced the risk of ovarian cancer by more than 50% in unselected women. Decreased risk of ovarian cancer has also been associated with tubal ligation and hysterectomy.

Epidemiology

Epithelial ovarian cancer is the sixth most common cancer in women and is the second most common female genital tract malignancy after endometrial cancer. They are usually found in postmenopausal women and are the commonest cause of death among women with gynaecologic malignancies in the USA, accounting for approximately 15,000 deaths annually. The annual lifetime risk for ovarian cancer is 1.4 per 100 women in the USA. Epithelial ovarian cancer can occur in females as young as 15, however the mean presentation age is 56 years. The age-specific incidence gradually rises and peaks at 70 years of age (55 per 100,000 Caucasians), whereas it affects only 3 women per 100,000 before 30 years of age. The median age for ovarian adenocarcinoma (which accounts for 85-90% of all malignant tumours) is between 60-65 years. The LMP ovarian tumours present at a younger age; the mean age of diagnosis is 48 years, and no large peak of incidence is observed. Brenner tumours are diagnosed in peri- or postmenopausal women. The incidence of ovarian epithelial tumours varies globally, with highest rates being observed in Scandinavia, Israel and North America, whereas the lowest rates are found in developing countries and Japan. A racial predisposition to ovarian epithelial tumours is apparent, with lower risks for black women. Clear cell adenocarcinoma is more prevalent in Japanese than western countries.

Clinics

Most early ovarian carcinomas and the serous and mucinous cystadenomas are asymptomatic. Two-thirds of patients present with extensive intra-abdominal metastases. Patients with advanced carcinomas usually present with vague abdominal swelling or discomfort, abdominal bloating, dyspepsia and early satiety, lack of appetite, malaise, urinary frequency and weight change (either gain or loss). Pelvic examination revealing firmness, fixation, nodularity, lack of tenderness, ascites, or cul-de-sac nodules are indicative of malignancy. 50% of all ovarian carcinomas are bilateral. Malignant serous tumours constitute over 40% of invasive epithelial carcinomas. Both borderline and malignant serous tumours are often bilateral.

Mucinous carcinomas are diagnosed at stage I in approximately half of patients, whereas serous tumours are usually diagnosed at advanced stages.

Brenner tumours are virtually always benign, and the exceptional malignant cases resemble transitional cell carcinoma of the bladder. As with the other types of ovarian neoplasm, it is usually asymptomatic until it has grown to a large size.

Pathology

Serous

Benign serous tumours are loculated, have a single layer of flattened or cuboidal epithelium and the absence of mitoses. Papillae are sometimes present on the external or internal surfaces.

Histological analysis of borderline serous tumours reveals papillary cystic pattern, stratification, tufting, increased mitotic figures and cytologic atypia.

Malignant serous tumours are soft, multiloculated, partially cystic, partially solid tumours with friable papillae. Their capsule may be smooth or irregular or show papillary projections. Internal papillae are soft and tan in colour. Cyst fluid is clear, thin and colourless.

Histological review of malignant serous tumours indicates significant stromal invasion. Calcifications (Psammoma bodies) are present in one-third of patients. Characteristic microscopic features include finger-like papillae with fibrovascular core, covered by multilayered cuboidal or columnar epithelium, hyperchromatic nuclei, prominent nucleoli, frequent mitoses, Psammoma bodies and desmoplasia (invasion of stroma with fibrosis).

Mucinous

Benign mucinous tumours are larger than serous tumours, and may grow to an enormous size. They are usually unilocular cysts or may have a few septae, with a smooth external surface. The cyst fluid is slimy, yellow and clear. Mucinous tumours are the most heterogeneous group of epithelial tumours. Benign mucinous tumours have a single layer of tall, columnar cells and clear, mucin-producing cells, with a bland stroma.

Borderline mucinous tumours have complex patterns, two to three cell layer stratification, cytological atypia and mitotic figures. Carcinoma is diagnosed when the stratification exceeds three cell layers or if there is a significant stromal invasion. Mucinous cystadenocarcinomas contain a smooth capsule, are cystic, multiloculated and large tumours (can be 50 cm in diameter). The cystic fluid is clear, yellow and sticky. Their microscopic appearance resembles intestinal adenocarcinoma. Multiple glands comprising mucin-containing cells are present, demonstrating nuclear atypia, hyperchromasia with prominent nuclei and desmoplasia.

Borderline/LMP

Borderline/LMP tumours are characterised by epithelial multilayering of more than 4 cell layers, and less than 4 mitoses per 10 high-power field, mild nuclear atypia, increased nuclear/cytoplasmic ratio, slight-to-complex branching of epithelial papillae and pseudopapillae, epithelial budding and cell detachment into the lumen

and no destructive stromal invasion. Borderline mucinous tumours have similar gross morphology to their benign counterparts, cysts with smooth surfaces. The epithelial layer is characterised by stratification of 2-3 layers, nuclear atypia, enlarged nuclei and mitotic figures.
Approximately 25% of borderline tumours show cell proliferations on the outer surface only. Of these, 90% develop peritoneal implants, which can be invasive or non-invasive. Both have a similar appearance, glandular or papillary proliferations with cell detachments, sometimes Psammoma bodies, cellular atypia and desmoplastic fibrosis. However, epithelial cells infiltrate the stroma in the invasive implants.

Brenner tumours
Brenner tumours are solid or cystic, yellow-tan colour and firm upon gross examination. Histological examination of Brenner tumour reveals epithelial nests or cysts of cells, resembling urothelium, separated by a cellular, fibrous stroma (composed of spindle-like cells). The nuclei are relatively uniform, lacking pleomorphism, hyperchromasia or macronucleoli, and mitoses are not identified. There is a moderate amount of eosinophilic cytoplasm.

Clear Cell Carcinoma
Clear cell carcinoma accounts for 5-12% of ovarian adenocarcinomas. The gross appearance of clear cell carcinoma shows a smooth, lobulated external surface. These tumours are usually solid and firm, but can be cystic. They have a yellow-tan colour. Microscopic examination reveals cells arranged in tubules, nests or cysts, with clear, glycogen rich cytoplasm, sharply demarcated cell borders, and hyperchromatic, pleomorphic nuclei. "Hobnail" cells with nucleus standing on a stalk of cytoplasm are visible microscopically.

Endometrioid Carcinoma
Endometrioid carcino-mas are solid, white, firm tumours with smooth or irregular surfaces. They may contain a cystic component and have areas of necrosis and haemorrhage. Histological analysis reveals glands, or glands mixed with solid areas, round-oval vesicular, clear nuclei with prominent nucleoli. Endometrioid carcinoma is indistinguishable from endometrial carcinoma.

Mixed Mesodermal
They are usually large variegated lesions with necrotic and haemorrhagic regions, and may have adhesions. Microscopic examination reveals serous or endometrioid epithelial component displaying squamous differentiation. Stroma may comprise spindle cell or soft tissue differentiation including cartilage, skeletal muscle or smooth muscle.

Treatment

The primary treatment of epithelial ovarian cancer is aggressive surgical tumour debulking, including total abdominal hysterectomy and bilateral salpingo-oophorectomy. Most women with ovarian epithelial tumours, except some stage Ia patients, receive chemotherapy. Postoperative treatment usually involves taxane-platinum combination chemotherapy; cisplatin or carboplatin with paclitaxel is the usual first-line treatment. High response rates, about 80%, are obtained, however most patients relapse, and other combination therapies fail. The mean disease-free interval for patients with stage III and IV disease is about 18 months. Only 20-30% of stage III and IV cases are long-term survivors. Postoperative intraperitoneal chemotherapy or external radiation therapy are used to treat patients with minimal residual disease. Clear cell adenocarcinoma is usually resistant to platinum-based chemotherapy. A strong association exists between ovarian mucinous tumours and appendiceal mucinous neoplasms. Consequently the appendix should be removed in patients with mucinous neoplasms. Repeat laparotomy or peritoneal lavage is required to remove gelatinous material in the persistent recurrences of Pseudomyxoma peritonei. Brenner tumours are cured with surgical resection. Prophylactic oophorectomy at an early age has significantly reduced the risk of coelomic epithelial cancer. Oral contraceptives have a protective effect against ovarian cancer in carriers of BRCA1 or BRCA2 mutations.

Evolution

Epithelial ovarian cancer initially spreads by direct seeding of the peritoneal surfaces, and is found on the underside of the diaphragm, paracolic gutters, bladder, cul-de-sac, surface of liver, mesentery and serosa of large and small bowel, omentum, uterus and paraaortic and pelvic lymph nodes. The tumour cells may remain confined to the surface of the coated abdominal viscera without penetrating it. They may also spread to the pleural cavity, lungs and groin lymph nodes. Mucinous tumours tend to form large masses, whereas serous tumours tend to distribute more diffusely, and are more often bilateral. Endometrioid and clear cell tumours usually invade locally and retroperitoneally. Sometimes mucus-secreting ovarian carcinomas fill the peritoneal cavity with a gelatinous neoplastic mass, referred to as pseudomyxoma peritonei.

Prognosis

The most important determinant for a favourable prognosis is diagnosis of ovarian carcinoma at an early stage. The prognosis of invasive epithelial ovarian cancer is poor, and relates to stage (see Tables 1 and 2), tumour grade and residual disease after surgery. The prognosis or early-stage ovarian invasive cancers and borderline tumours of all stages is significantly better. 5-year survival rates for patients with stage I disease are more than 90%, but less than 25% for advanced stage cancers. Patients with borderline tumours have an excellent prognosis. Age at diagnosis and the presence

of invasive peritoneal implants are associated with a poorer prognosis in borderline tumours. The recurrence rate is 20%, with a mean time from diagnosis to relapse is 3.1 years in women with
borderline serous tumours with non-invasive implants. However, borderline serous tumours with invasive implants have much higher recurrence rates of 32-45%, which occur much earlier (median time 24 months).

Clear cell adenocarcinoma has a worse prognosis that the other histological subtypes as it is resistant to platinum-based chemotherapy. Some data suggests familial ovarian cancers have prolonged survival in comparison to the nonfamilial cases. In one study, patients with familial ovarian cancer exhibited a 67% 5-year survival, in comparison with a 17% 5-year survival in the nonfamilial ovarian cancer cases.

STAGE	DEFINITION
Stage I	Growth limited to ovaries
Stage Ia	Growth limited to one ovary, no ascites, no tumour on external surface, capsule intact
Stage Ib	Growth limited to both ovaries, no ascites, no tumour on external surface, capsule intact
Stage Ic	Tumour either stage Ia or Ib, but with tumour on one or both ovaries, with capsule ruptured, with ascites present containing malignant cells, or with positive peritoneal washings
Stage II	Growth involving one or both ovaries with pelvic extension
Stage IIa	Extension and/or metastases to the uterus and/or tubes
Stage IIb	Extension to other pelvic tissues
Stage IIc	Tumour either stage IIa or IIb, with tumour on the surface of one or both ovaries, but with capsule(s) ruptured, with ascites present containing malignant cells, or with positive peritoneal washings
Stage III	Tumour involving one or both ovaries with peritoneal implants outside the pelvis and/or positive retroperitoneal or inguinal nodes. Superficial liver metastases equal stage III. Tumour limited to the true pelvis but with histologically proven malignant extension to small bowel or omentum
Stage IIIa	Tumour grossly limited to the true pelvis with negative nodes but with histologically confirmed microscopic seeding of abdominal peritoneal surfaces.
Stage IIIb	Tumour involving one or both ovaries with histologically confirmed implants of abdominal peritoneal surfaces, none exceeding 2cm in diameter. Nodes are negative.
Stage IIIc	Abdominal implants >2cm in diameter and/or positive retroperitoneal or inguinal nodes.
Stage IV	Growth involving one or both ovaries with distant metastases.

Table 1. Definitions of the FIGO classification scheme for Staging Primary Ovarian Carcinoma (taken from Jones, 2000).

STAGE No	PATIENTS TREATED	SURVIVAL3-yr (%)	SURVIVAL 5-yr (%)
I	5,559	87.5	82.1
II	3,364	72.1	64.5
III	2,530	47.0	38.1
IV	492	20.7	14.0
TOTAL	11,945	71.6	65.4

Table 2. Survival Rates of Ovarian Carcinoma according to Disease Stage (adapted table from Jones, 2000).

Genetics

Inherited predisposition
As mentioned in the Aetiology section, genetic factors are the most important risk factor for ovarian epithelial carcinoma. Having 1 or 2 first-degree relatives with ovarian cancer increases the lifetime risk to 3-5% and 39% respectively. Three hereditary syndromes in which familial aggregation of ovarian carcinoma occurs have been described:
Hereditary breast-ovarian cancer syndrome: clusters of breast and ovarian cancer among first- and second-degree relatives.
Hereditary nonpolyposis colorectal cancer syndrome, HNPCC, or Lynch Cancer Family syndrome II): ovarian cancer develops in a proband whose close

relatives have had cancers of the colon, breast, ovary, endometrium, urinary tract, uterine and other malignancies.
Site-specific ovarian cancer syndrome of unknown origin in which two or more first-degree relatives have ovarian cancer.
All 3 patterns of familial ovarian cancer are consistent with autosomal-dominant transmission of one or more genes responsible for the development of >1 cancers, with incomplete penetrance and variable expression. The age of diagnosis of hereditary epithelial ovarian cancer is approximately 10 years earlier than its sporadic counterpart.

Breast-Ovarian Syndrome

Of the about 10% of ovarian epithelial cancers thought to have a hereditary component, 90% are associated with breast-ovarian syndrome. This syndrome is associated with two genes, BRCA1 at 17q21, and BRCA2 at 13q12.3 (see below), which are involved in DNA repair and transcription regulation. Mutations are distributed throughout the entire coding regions of BRCA1 and BRCA2, and most result in truncation of the protein. Germline mutations in BRCA1 account for about 80% of hereditary breast-ovarian cancers. Germline mutations of BRCA2 account for about 10-35% of familial ovarian cancers. BRCA1 is associated with a 26% cumulative risk for ovarian cancer for most mutation carriers, and a much higher risk, 85%, in a small subset. Women with a germline BRCA1 mutation have an about 40% risk of developing ovarian cancer by 70 years of age. BRCA2 increases susceptibility to a smaller degree. The lifetime risk for developing ovarian cancer in BRCA2 mutation carriers is 27%. However the risks of developing ovarian cancer associated with germline mutations of BRCA1 and BRCA2 vary according to the population studied. A study by revealed a lifetime risk of ovarian cancer of 40-60% for BRCA1 mutation carriers, whereas another one found a 25-30% risk for BRCA1 mutation carriers. Approximately 1/4000 in the general population has a mutation of BRCA1, although some populations have much higher incidences, for example the Ashkenazi Jews. Patients with breast cancer who had BRCA1 or BRCA2 mutations had a tenfold increased risk of developing ovarian cancer.
The variable penetrance of BRCA1 suggests that other genetic and non-genetic factors contribute to the pathogenesis in these individuals. One such modifier is a VNTR polymorphism, 1-kb down-stream of HRAS. BRCA1 carriers with rare alleles of the VNTR had an 2.11 increased risk of developing ovarian cancer compared with the common alleles (p=0.015).
About 50% of familial ovarian cancers are not associated with germline BRCA1 or BRCA2 mutations. Linkage and LOH analysis has suggested a susceptibility gene for familial ovarian cancer at 3p22-p25. LOH of 3p33-p25 is higher (52%) in non-BRCA1/BRCA2 familial ovarian cancers than in the BRCA1 (29.7%) group.

HNPCC

Mutations of the mismatch repair genes (MMR) including MLH1, MSH2 and MSH6 are present in HNPCC syndrome (Lynch 2 Syndrome). This represents the second most common type of ovarian cancer with a hereditary component.

Site-Specific Ovarian Cancer Syndrome

The least common of the familial ovarian cancers is the site-specific ovarian cancer syndrome, in which ovarian cancer is the dominant cancer. It has been suggested that site-specific ovarian cancer is a variant of breast-ovarian syndrome attributable to mutation in either BRCA1 or BRCA2, and not a distinct clinical entity.

Early onset ovarian carcinoma (<30 years age)

Germline DNA from women with ovarian carcinoma diagnosed before 30 years of age were screened for mutations in BRCA1, BRCA2, MSH2 and MLH1. 2/101 women with invasive ovarian cancer.

Other familial cases

There have been several reports of small cell carcinoma, a rare form of ovarian carcinoma, occurring in multiple family members, suggesting a genetic predisposition to this tumour. Several familial cases of ovarian carcinomas have been associated with germline P53 mutations.

Cytogenetics

Cytogenetics Morphological

There is far more cytogenetic data available on ovarian carcinomas than for the other subtypes of ovarian tumours (germ cell tumours, sex-cord stromal tumours). At present, there are over 400 published karyotypes of ovarian carcinomas. The cytogenetic aberrations are non-random and complex. However, no pathognomonic rearrange-ments have been identified thus far. The karyotypes often show severe aneuploidy, with hypodiploid or near-triploid stemline chromosome numbers. The different subtypes of ovarian carcinoma show no marked cytogenetic differences, except seropa-pillary tumours more frequently display chromosome aberrations than the other subtypes. Complex chromosomal aberrations are present in invasive carcinomas, but not in benign or LMP tumours. The complexity of the karyotypes obtained from advanced tumours has obscured the initiating events in the pathogenesis of these tumours. Often normal karyotypes or simple cytogenetic aberrations were found in low-grade tumours. However, a correlation exists between karyotypic complexity and tumour grade. Simple chromosome changes (numerical changes only or a single structural rearrangement) were found in well-differentiated carcinomas, whereas complex karyo-types were found in poorly

differentiated tumours. Patients with aberrant tumour karyotypes, particularly complex ones, were associated with short survival. Approximately 10-20% of ovarian carcinomas display homogeneously staining regions (hsr), although the loci they contain are unknown. However dmin are rarely observed. The most prevalent numerical changes are gains of chromosomes 1, 2, 3, 6, 7, 9, 12 and 20 losses of chromosomes 4, 8, 11, 13, 14, 15, 17 and 22. Structural rearrangements primarily involve deletions and unbalanced translocations involving 1p, 1q, 3p, 3q, 6q, 7p, 10q, 11p, 11q and 12q. In the review of 244 primary ovarian adenocarcinomas 201/244 tumours displayed clonal chromosomal abnormalities and hsr were identified in 20 cases.

Using log-rank and proportional hazards regression analysis, it has been found that the presence of a chromosome breakpoint in any of 21 nonrandomly involved regions and breaks in 9 distinct regions (1p1, 1q2, 1p3, 3p1, 6p2, 11p1, 11q1, 12q2, and 13p1) were associated with reduced patient survival rate and time. Furthermore, only breakpoints within 1p1 and 3p1 retained independent, deleterious effects on survival and clinical variables associated with survival. In one review, 37% of serous LMP tumours displayed chromosomal anomalies, commonly trisomies of 7, 8 and 12. A much higher proportion, 91%, of invasive serous carcinomas of low-grade malignancy display clonal chromosomal abnormalities. A combination of karyotyping and microsatellite analyses identified a small deletion of 6q27, between D6S149 and D6S193, in both benign and advanced ovarian epithelial tumours, suggesting the presence of a putative tumour suppressor gene which is involved in the early events of the genesis of this tumour.

Invasive serous and undifferentiated ovarian carcinomas have complex cytogenetic rearrangements, including amplification of oncogenes. Complex chromosomal anomalies are rarely found in mucinous and endometrioid carcinomas (mainly in advanced stages), and are never found in serous LMP tumours. Epithelial ovarian tumours are characterised by gains at 3q, 8q and 20q, often with high level amplification. Thus the cytogenetic profiles of ovarian carcinomas differ from that of ovarian granulosa cell tumours; trisomy 14 and monsomy 22 are rarely found in ovarian carcinomas. Chromosome 1 and 3 abnormalities are the commonest aberrations found in ovarian metastatic tumours. Cytogenetic investigation of 11 individuals with bilateral ovarian carcinoma showed identical baseline

karyotypes, suggesting both tumours arise from the same transformed cell, rather than the tumours arising independently.

46/52 ovarian carcinomas had complex karyotypes, often with a stemline chromosome number that was approaching near-triploid or hypodiploid. Chromosome losses of X, 22, 17, 13, 14 and 8, (lost in <20 tumours) were most frequent (compared to the nearest euploid level). Chromosomal gains were less prevalent, trisomy 20 was found in 10 tumours. The most common structural rearrangements are deletions and unbalanced translocations, which frequently involved 19p13 (n=26), 19q13 (n=14), 1p36 (n=13), 11p13 (n=13), 3p12-13 (n=12), 1q23 (n=11), and 6q21 (n=10). In a study, 26/36 ovarian carcinomas displayed aberrant karyotypes. Chromosomal gains of 1, 2, 3, 6, 7, 9 and 12 were common, as were losses of chromosomes X, 4, 8, 11, 13, 15, 17 and 22. Structural rearrangements frequently involved 1p, 1q, 3p, 3q, 7p, 9q, 11q, 17q, 19p and 19q. In a cohort of 54 tumours, the breakpoints of structural anomalies preferentially involved 1p35, 1p11-q21, 3p11-23, 7p, 11p, 11q, 12p13-q12 and 12q24. Loss of the X chromosome and trisomy 7 were the most common numerical changes. A third of all ovarian carcinomas have deletions of distal 11p. The frequent occurrence and variability of the deletions of chromosome 1, both the distal half of 1q and 1p34-36, and the frequent observations of similar entities in other tumour types suggest that they are secondary, non-specific changes. Deletions and unbalanced translocations resulting in loss of 3p, particularly of 3p13-21 are recurrently found in ovarian carcinomas, but not as sole anomalies.

The cytogenetic findings of 370 cases of ovarian adenocarcinoma can be found listed on the Mitelman Database of Chromosome Aberrations in Cancer (http://cgap.nci.nih.gov/Chromosomes/ Mitelman). The imbalances arising from the cytogenetic rearrangements listed in the database are summarised in Table 3. Of the cases listed, 36% had polyploid karyotypes (with chromosome numbers ranging between 58 and 127), 28% had hyperdiploid karyotypes (with 48-57 chromosomes), 22% had hypodiploid karyotypes (<45 chromosomes), and only 14% were peridiploid (45-47).

Very little is known about the sequence of cytogenetic and genetic events accompanying the progression of disease from early to advanced disease. This question has been addressed by analysing the cytogenetic data in the Mitelman Database of Chromosome Aberrations in Cancer and proposed that ovarian carcinomas undergo >3 modes of karyotypic evolution:

Phase I: 1-7 imbalances

Phase II: with 8-15 imbalances

Phase III: with >15 imbalances

Their analyses hypothesised that the temporal order of imbalances were as follows: 1q-, 6q-, +7 and +8q occurred early, -4, -8, +1q, +12 and +20 were intermediate imbalances, and the remaining imbalances were late events. It has been concluded that karyotypic evolution in ovarian carcinomas followed at least 2 cytogenetic pathways. The first pathway involved chromosomal gains of +7/+8q/+12 and was associated with low-stage and low-grade tumours. The second pathway involved chromosomal losses of 6q- and 1q- was found in tumours of moderate stage and grade. The

early stages of karyotypic evolution result from the step-wise acquisition of changes resulting in Phase I tumours. Chromosome instability resulted in the transition to Phase II tumours, possibly as a result of extensive telomere crisis and breakage fusion breakage cycles, which is linked to imbalances characteristic of the 6q-/1q- pathway.

Consequently, low-grade and borderline tumours cannot progress unless they have mixed-pathway features. The 6q-/1q- pathway was associated with triploidization. The 6q-/1q- pathway is instrumental in the progression of ovarian carcinomas. The proposed pathway of karyotypic evolution in ovarian carcinomas is summarised in Figure 1.

A cohort of 114 ovarian neoplasms was analysed, including benign, borderline and invasive carcinomas by conventional and molecular cytogenetics.

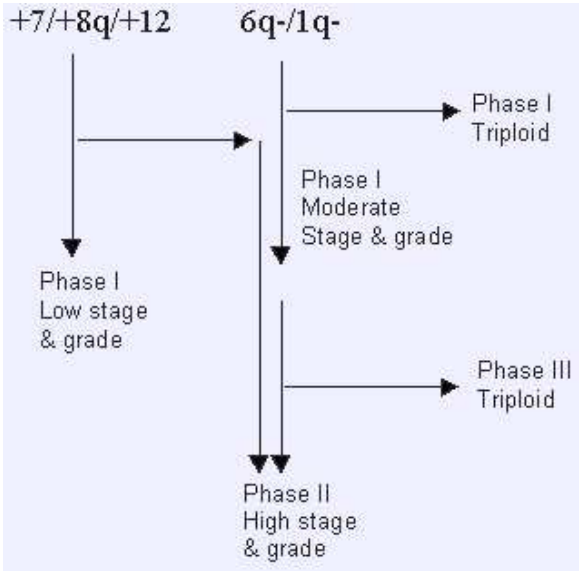

Figure 1. Summary of karyotypic evolution in Ovarian carcinomas (taken from Hoglund et al., 2003)

Imbalance	Frequency of imbalance in ovarian carcinoma (n=316), as a %
+1q10-q32	24
+2p12-q37	9
+3q10-q29	18
+6p24-p10	10
+7p22-q36	16
+8q10-q24	11
+12p13-q24	20
+20p13-q13	11
-1p36-p32	28
-1q31-q44	24
-2p15-p23	18
-4p16-q35	27
-5p15-q34	20
-6q15-q27	40
-7p22-p15	22
-7q31-q36	21
-8p23-q24	30
-9p24-p21	20
-10p15-p11	22
-11p15-p13	27
-13p13-q34	28
-14p13-q32	29
-15p13-q26	31
-16p13-q24	25

-17p13-q25	30
-18p11-q23	23
-19p13-q13	21
-21p13-q22	22
-22p13-q13	31
-Xp22-q28	39

Table 3. A summary of the frequency of imbalances in ovarian carcinomas (table from Hoglund et al., 2003, data from Mitelman Database of Chromosome Aberrations in Cancer).

The chromosome abnormalities were categorised as follows:
Group 1: Abnormalities found in all subtypes. This included losses of chromosomes 6, 8, 10, 11, 15, 16, 17, 18, 19, 20, 21, 22 and X together with 6q24-qter deletions; and gains of chromosomes 1, 3, 5 and 12.
Group 2: Abnormalities present in malignant but not benign subtypes. This included losses of chromosomes 2, 7, 13 and 14, and gains of chromosome 4 and marker chromosomes.
Group 3: Abnormalities unique to invasive carcinomas such as loss of chromosome 4, 6q16-q24 deletions, gains of chromosomes 2, 7, 8, 9, 10, 16, 17, 18, 19, 20 and 21, and structural rearrangements of 3p, 3q, 13q and 21q.
The presence of cytogenetic aberrations common to all subtypes suggests these tumours develop by progression.
The main conclusions from cytogenetic investi-gations of ovarian epithelial tumours are as follows:
Nonrandom breakpoints in ovarian adenocarcinoma do not occur independently.
Breakpoints in 1p3 and 11p1 are early events, and associated with poor prognosis.
Breakpoints in 1p1, 3p1 and 1q2 distinguish a class of ovarian tumours, and breakpoints at 1p1 and 3p1 are associated with a poor prognosis.

Cytogenetics Molecular

Interphase cytogenetics demonstrated a high frequency of gain of copy number of 20q13.2 (70%) and cyclin D1 (CCND1 at 11q13, 72%) which were associated with poor prognosis. Another study addressing amplification of 20q12-q13.2 using a series of FISH probes in 24 sporadic
and 7 hereditary ovarian carcinomas found amplification of at least one of the regions in 54% of sporadic cases and all of the hereditary cases, and amplification of AIB1 (20q12), a steroid receptor coactivator correlated with poor survival.
Online access to summaries of the recurrent DNA copy number amplifications and losses identified by CGH in ovarian epithelial neoplasms (and other tumour entities) can be viewed at http://www.helsinki.fi/cmg/cgh_data.html, and undergo regular updates. The criteria for recurrent losses and gains employed were as follows. For losses, 10% of the cases should have the loss, and there must be at least 3 aberrant cases. Highly frequent aberrations which do not meet the criteria of 10% of cases or 3 cases are indicated by parentheses-such as 1p21-p31. Recurrent amplicons were defined as at least 3 cases and >5% frequency display the amplicon. The recurrent losses and gains are summarised in Table 4.

Ovarian Neoplasm Subtype	**Loss**	**Amplification**	**Percentage (number of cases)**
Ovarian Cancer	(1p21-p31)		7 (5/72)
	1p34.1-p34.3		11 (5/44)
		1q	7 (5/71)
		2p15p22	4 (1/24)
		2q22-q24	5 (1/20)
		3cen-q23	4 (1/24)
		3q25-q27	13 (6/47)
	4q21-q32		16 (30/184)
	4q32-qter		16 (15/91)
	4q32-qter		16 (15/91)
	5q12-q23		16 (30/184)
		6p21	7 (3/144)
		6q13-qter	5 (1/20)

	6q16-qter		13 (23/184)
		7q36	7 (2/27)
	8p21-pter		17 (32/184)
		8q	4 (1/24)
		8q22-qter	18 (8/44)
	9p		10 (16/159)
		9p24	4 (1/27)
	9q		13 (17/136)
		10p15	4 (1/27)
	10q11-qter		17 (10/59)
		12p12	19 (9/47)
		12p12	9 (4/47)
	12q24-qter		10 (14/140)
	13q12-q21		18 (24/135)
	13q21-q32		12 (18/160)
	16p		13 (12/93)
	16q		23 (24/184)
	17p		20 (37/184)
	17q11.2-q32		23 (31/137)
		17q21-qter	6 (3/47)
		18p11.3	4 (1/27)
	18q12-qter		18 (33/184)
	19p		23 (10/44)
	19q		16 (11/69)
	21q		10 (12/116)
	22q		18 (17/93)
	Xp		19 (35/184)
	Xq		19 (9/47)
	Xq11.2-q21		13 (12/89)
	Xq21-qter		24 (16/68)
Primary epithelial ovarian cancer	4p15.2		18 (5/28)
	4q23-q24		18 (5/28)
	4q26-q27		18 (5/28)
	5q14		14 (4/28)
	5q15		14 (4/28)
	9p22-p24		11 (3/28)
	9q22-q31		18 (5/28)
	13q14		14 (4/28)
	13q31-q32		21 (6/28)
	14q24.3-q31		14 (4/28)
	15q21.1		25 (7/28)
	18q21		11 (3/28)
Ovarian Inherited (BRCA1 & BRCA2)		1q32-qter	10 (2/20)
		3q26.1	10 (2/20)
		5p	5 (1/20)
		6p22-p24	10 (2/20)

		6q21-q22	5 (1/20)
	6q25-qter		15 (3/20)
	8p23		40 (8/20)
		8q23-q24.1	30 (6/20)
		12p	5 (1/20)
		12q13-q21	5 (1/20)
	18p11.2-pter		15 (3/20)
	18q21-qter		20 (4/20)
		20p	5 (1/20)
	Xp		15 (3/20)
	Xq12-21		15 (3/20)
Ovarian cancer, sporadic & inherited	1p34-p36		25 (4/18)
	4q31.3-q35		19 (3/16)
	9q31-q34		40 (8/16)
	10q23-q26		25 (4/16)
	11q23-q25		19 (3/16)
	16p		19 (3/16)
	16q22-q24		38 (6/16)
	17p		19 (3/16)
	19		19 (3/16)
	22q12-q13		25 (4/16)
	Xp		19 (3/18)

Table 4. Recurrent amplifications and losses in epithelial ovarian tumours, including hereditary neoplasms (data taken from **http://www.helsinki.fi/cmg/cgh_data.html**)

Other studies have identified gain of chromosome 8 in 1/10 ovarian carcinomas.

A study of 31 primary ovarian carcinomas in Chinese women by CGH identified several non-random changes in copy number including gains of 3q (17 cases, 55%) with a minimum region of gain of 3q25-q26, 8q (16 cases, 52%), 19q (12 cases, 39%), Xq (11 cases, 35%), 1q (10 cases, 32%), 12p12-q13 (10 cases, 32%), 17q (10 cases, 32%) with a minimum region of gain at 17q21, and 20q (9 cases, 29%); together with losses of 16q (9 cases, 29%), 1p (7 cases, 23%), 18q (7 cases, 23%) and 22 (7 cases, 23%). High copy number amplifications were observed at 3q25-q26 (4 cases), 8q24 (3 cases) and 12p11.2-q12 (3 cases). The commonest imbalances detected by CGH of epithelial neoplasms were gain of 3q25-26, gain of 8q24, loss of 16q, and loss of 17pter-q21. 12p gains were seen in 8/44 cases, which has been reported previously in both ovarian and testicular germ cell tumours. Another study by Hauptmann et al., 2002 using CGH to analyse ovarian carcinomas identified frequent gains of 3q, 6p, 7, 8q and 20, together with losses of 4q, 6q, 12q, 13q and 16q, which have supported the available cytogenetic data.

CGH was used to screen a mucinous ovarian carcinoma and a Brenner tumour coexisting in different ovaries of the same female. Amplification of 12q14-q21 was identified in both tumours, in the presence of other copy number changes, 4 such changes in the Brenner tumour and 6 in the mucinous carcinoma.

Correlation of CGH data with Clinical data

In a large study of 106 primary ovarian carcinomas, the CGH findings were correlated with clinical parameters such as tumour grade of differentiation. 103 tumours displayed imbalances. Amplifications of 8q, 1q, 20q, 3q and 19p were frequent findings present in 69-53% of the tumours. Underrepresentations of 13q, 4q and 18q were also common, present in 54-50% of cases. Underrepresentation of 11p and 13q and overrepresentation of 8q and 7q correlated with undifferentiated ovarian carcinoma, whereas 12p underrepresentation and 18p overrepresentation were more commonly associated with well-differentiated and moderately differentiated tumours. These findings corroborate other CGH studies including.

A CGH study of a cohort of 12 ovarian clear cell carcinomas revealed similarities to the data of other subtypes of epithelial neoplasms, such as gains of 8q and 17q and losses of 19p. They also correlated their findings with disease status (i.e. disease free, recurrent disease, or death from disease). DNA copy number changes present in over 20% of cases included overrepresentation of 8q11-q13, 8q21-q22, 8q23, 8q24-qter, 17q25-qter, 20q13-qter and 21q22; and

underrepresentation of 19p. Overrepresentation of 8q11-q13, 8q21-q22, 8q23, 8q24-qter was more common in disease-free patients than in those with recurrent disease or who had died. Conversely, overrepresentation of 17q25-qter, 20q13-qter was more frequent in patients with recurrent disease or non-survivors, than in disease-free patients. This data suggests ovarian clear cell carcinoma develop along 2 cytogenetic pathways.
In a study correlating CGH genomic imbalances with clinical endpoints in 60 ovarian carcinomas, the following associations were found:
Loss of chromosome 4 with high-grade tumours.
Gains of 3q26-qter, 8q24-qter and 20q13-qter and low-grade and low-stage tumours.
Deletion of 16q24 and >7 independent genomic imbalances and reduced survival times.
Tumour grade correlated better with genomic progression than clinical stage.

CGH findings of Sporadic and Hereditary Ovarian Carcinoma

CGH profiles were compared from sporadic and hereditary (3 BRCA1 and 1 BRCA2 mutation carriers) ovarian cancers. The commonest imbalance included amplification of 8q22.1-qter (66.6%), 1q22-32.1 (41.1%), 3q (75%) and 10p (33.2 %), and deletion of 9q (41.6%) and 16q21-q24 (33.3%). Deletions of 9q were found in all 3 BRCA1 carriers and 2/8 sporadic tumours, and deletions of 19 were found in 2/3 BRCA1 carriers and none of the sporadic cases. These findings suggest preferential somatic losses of chromosome 9 and 19 in BRCA1 mutation carriers. In contrast, another study identified extensive similarity by CGH between sporadic and hereditary ovarian carcinomas, except for 2q24-q32. CGH analysis of a further 36 hereditary tumours found the majority of imbalances to be similar to that of sporadic tumours (Gains: 8q23-qter, 3q26.3-qter, 11q22, 2q31-32; losses: 8p21-pter, 16q22-qter, 22q13, 12q24, 15q11-15, 17p12-13, Xp21-22, 20q13, 15q24-25, 18q21). However some imbalances were identified that were specific to hereditary tumours, including deletions of 15q11-15, 15q24-25, 8p21-pter, 22q13 and 12q24, and gains of 11q22, 13q22 and 17q23-35. Deletions of 15q11-15 and 15q24-25 were found in 16/36 and 12/36 cases respectively which implicated hRAD51 and other tumour suppressor genes in these loci in the genesis of hereditary ovarian cancer.

Genes involved and proteins

Note

In addition to involvement of germline mutations of BRCA1, BRCA2 and the mismatch repair genes in the predisposition of ovarian epithelial tumours (see Genetics: Inherited Predisposition section), many studies have investigated somatic changes at specific loci. The somatic aberrations are summarised below according to whether the studies involved allelotyping or analysing specific genes (which is further subdivided into oncogenes and tumour suppressor genes).

Allelotyping/LOH/MSI

Cytogenetic and loss of heterozygosity (LOH) studies have implicated many regions of the genome in the pathogenesis of ovarian cancer. Numerous allelotype studies have been performed on ovarian carcinomas and identified frequent losses of 1p, 4p, 5q, 6p, 6q, 7p, 8p, 8q, 9p, 9q, 11p, 11q, 12p, 12q, 13q, 14q, 15q, 16p, 16q, 17p, 17q, 18q, 19p, 21q, 22q and Xp. However most of these studies examined ovarian serous adenocarcinoma. From the few studies that have analysed LOH of benign and LMP tumours, LOH is rarely found at most loci, with the exception of the X chromosome in LMP tumours. LOH analysis of early-stage malignant and borderline ovarian tumours displayed similar LOH patterns suggesting that malignant ovarian tumours may develop from benign and borderline tumours. Frequent allelic losses are found at 5p15.2, 5q13-21, 6p24-25, 6q21-23, 6q25.1-27, 7q31.1, 11p15.5, 11p13, 11q22, 11q23.3-qter, 17p13.3 and 17p11.2, suggesting the presence of tumour suppressor genes involved in ovarian carcinoma. Microcell-mediated chromosome transfer of normal chromosome 11 and 17 confirmed the presence of tumour suppressor gene(s) on these chromosomes. Complete suppression of tumourigenicity was obtained by transfer of chromosome 11, whereas reduced in vivo and in vitro growth rates together with increased latency period were obtained by the transfer of chromosome 17. Furthermore transfer of 17p11.2 had the same effect as transfer of the entire chromosome. Microsatellite analysis has suggested the presence of a tumour suppressor gene at 22q11-q12 (between D22S301 and D22S304). This was also supported by microcell-mediated chromosome transfer of chromosome 22 into ovarian carcinoma cell line SKOV3 which resulted in complete abrogation of anchorage-independent growth and a dramatic reduction of in vitro doubling times and tumourigenicity in nude mice.
The pattern of allelic loss differs according to the histological subtypes of epithelial ovarian cancer.
Clear cell adenocarcinoma predominantly demonstrates LOH of 1p, 19p and 11q. Serous adenocarcinoma demonstrates allelic losses in >50% of cases of 1p, 4p, 5q, 6p, 8p, 9q, 12q, 13q, 15q, 16p, 17p, 17q, 18p, 18q, 19p, 20p and Xp. Endometrioid adenocarcinoma frequently demonstrated LOH of 7p, and mucinous adenocarcinoma demonstrated recurrent LOH at 17p13.1. LOH analysis using RFLP markers in 6q24-q27 demonstrated allelic loss at a few or all loci in 17/33 ovarian serous tumours, 1/15 ovarian mucinous tumours, and 2/12 ovarian clear cell tumours. Allelic loss of 1p31 has been found in about 40% of ovarian

carcinomas, where the maternally imprinted tumour suppressor gene ARH1(NOEY2) resides. Approximately 1/3 of epithelial ovarian tumours of all stages demonstrate LOH of 9p. 69% of 78 ovarian epithelial tumours displayed LOH of 17p13.1 where TP53 is located. Allelic loss at 10q23.3 flanking PTEN and within PTGN have been found in 45% of ovarian epithelial cancers (n=68). Loss of PTEN expression was associated with elevated phosphorylated AKT levels. No microsatellite instability (MSI) was apparent among the 23 benign cystadenomas and 31 LMP ovarian tumours examined using 69 microsatellite markers. Thus these findings suggest MSI is not a pathogenic mechanism in the development of LMP tumours, and abnormalities of the DNA mismatch repair mechanisms are not involved. In contrast, about one-third of endometrioid carcinomas and up to 40% of serous LMP tumours displays MSI, although in serous LMP tumours the MSI is low level.

LOH of 3p14.2, 11p15.5, 11q23.3, 11q24, 16q24.3 and 17p13.1 are more frequent in advanced than lower stage tumours. LOH of 3p14.2 correlated with tumour metastasis, whereas LOH at 11p15.5 and 11q23.3 were associated with reduced survival. LOH of 11q22.3 was associated with reduced survival and a serous histology, meanwhile LOH of 11q24-25 correlated with a higher tumour stage, serous histology, presence of residual tumour, but not with survival. LOH of 1p36 is associated with poor histological grade.

Tumour Suppressor Genes

Alterations in tumour suppressor genes such as P53, RB1, ARH1 (NOEY2), BRCA1 are involved in ovarian carcinogenesis.

P53

Allelic deletions of 17p or P53 mutations occur frequently in ovarian carcinoma. P53 mutations are found in about 50-80% of tumours when analysed by complete gene sequencing. LOH of P53 is also a frequent finding in ovarian carcinomas, ranging from 30% to 80%. P53 mutations have been found in ovarian carcinoma and borderline ovarian tumours. Invasive serous and undifferentiated ovarian carcinomas are characterised by P53 mutations with protein accumulation, extensive allelic loss of chromosome 17 and complex cytogenetic aberrations. Functional wild-type P53 is required for chemo- and radio-sensitivity due to its role in apoptosis. Thus mutation of P53 followed by loss of the wild-type results in resistance to therapy. Of the ovarian neoplasms that express nuclear P53, 90% of them have mutations of P53 which increases the half-life of the P53 protein. 50% of advanced ovarian carcinomas have overexpressed or mutant P53 which correlates with high grade and poor survival, but not with chemoresponsiveness. However, P53 does not appear to be involved in the pathogenesis of clear cell adenocarcinoma.

CDKN2A

Homozygous deletions or intragenic mutations of CDKN2A (p16INK4A) are also found in ovarian epithelial tumours. CDKN2A encodes an inhibitory protein of cyclin-dependent kinase 4. The CDKN2A complex blocks phosphorylation of the Retinoblastoma (RB) protein. Phosphorylation of the RB protein is a prerequisite for cells to enter the S phase of the cell cycle. Thus CDKN2A is a negative regulator of the cell cycle.

RB

Abnormalities of the RB gene in epithelial ovarian cancers have been found by immunohistochemical analysis and molecular approaches, however they are thought to affect a minority of tumours and are possibly a late event in tumourigenesis.

GATA4

No expression of GATA4, a transcription factor gene located at 8p23.1, was found in the majority of serous carcinomas, whereas it is expressed in most mucinous carcinomas, suggesting that these tumour types develop along discrete pathogenic pathways.

RNASET2

Reduced expression of RNASET2 (RNASE6PL), located at 6q27, was found in 30% of ovarian cancers. Transfection of RNASET2 cDNA into ovarian cancer cell lines suppressed tumourigeni-city, suggesting it to be a candidate tumour suppressor gene.

BRCA1

Somatic mutations of BRCA1 and BRCA2 have not been found in sporadic ovarian neoplasms, however allelic losses including 17q21, were BRCA1 is located, were common. This suggests that additional tumour suppressor genes are required in the molecular aetiology of sporadic tumours, one proximal to BRCA1, the other on 17p.

Oncogenes

Alterations in oncogenes KRAS, MYC and ERBB2 are frequently involved in ovarian carcinogenesis.

RAS

KRAS mutations are found in 30% of ovarian carcinomas, and are frequently observed in
mucinous adenoma and thus may be an early event in the pathogenesis of ovarian mucinous tumours. KRAS mutations are present in 40-50% of mucinous LMP tumours and mucinous carcinomas, and also in one-third of serous LMP tumours. Amplification of KRAS has been reported in 3-5% of ovarian cancers. In one study, KRAS2 amplification occurred in 2/53 of ovarian epithelial tumours, (6 borderline serous, 2 low grade serous, 31 high grade serous; 4 low grade mucinous; 2 low grade endometrioid, 8 high grade endometrioid), and only in the aggressive types (2 high grade serous tumours). A mutation in codon 12 of KRAS has been identified in small cell carcinoma.

HRAS acquires transforming activity either as a result of substitution mutations or by increased expression of the normal gene. Mutated HRAS lack GTPase activity, resulting in dysregulation of cell growth.

Growth Factor Receptors

Abnormal cell signalling mediated by protein kinases can result from alterations of the growth factor receptors in ovarian epithelial neoplasms. These include

ERBB2 (HER2/Neu) receptor which is amplified and overexpressed in 9-30% of ovarian cancers. The ERBB2 oncogene located at 17q21 encodes a membrane receptor that binds a glycoprotein similar to transforming growth factor-a and is correlated with poor survival of patients.

CSF1R (formerly fms, macrophage colony stimulating factor receptor), is expressed in many ovarian cancers, but not benign ovarian tumours or normal ovarian surface epithelium. Amplification of CSF1R has been reported in 3-5% of ovarian cancers.

ECGF1, the platelet-derived endothelial growth factor, shows significantly higher levels in primary epithelial ovarian tumours and was more abundant at the higher stages (III and IV than lower stages), also more prevalent in the mucinous than in the serous adenocarcinomas.

EGFR which encodes the transmembrane receptor for epidermal growth factor is expressed by most advanced carcinomas and is associated with poor prognosis.

MYC

Amplification of MYC oncogene, 8q24, occurs in 10-20 % of ovarian cancers, and in about one-third of advanced ovarian carcinomas. MYC amplification is more frequently found in the serous subtypes than the mucinous subtypes. MYC encodes a DNA-binding nuclear-associated protein that regulates cell proliferation. Dividing cells have increased amounts of nuclear c-myc, whereas quiescent cells express negligible quantities. MYC amplification is often indicative of biologically aggressive tumours. MYC amplification was not associated with prognosis or survival. Significantly higher levels of p62c-myc were found in serous papillary ovarian carcinoma. LMP tumours expressed MYC at values intermediate between that of normal ovary tissue and carcinoma.

PI3K/AKT2

Amplification, altered expression, and malfunction of several protein kinases and phosphatases are involved in the pathogenesis of ovarian epithelial neoplasms, in particular the phosphatidylinositol 3-kinase (PI3K) pathway. Increased PI3K activity is important in the growth and dissemination of ovarian cancer cells. The PIK3CA gene which encodes the catalytic subunit of PI3K, and its downstream effector AKT2 are amplified in primary ovarian tumours. Overexpression of AKT2 is found in high-grade and late-stage tumours. Mutation and/or down-regulation of the PI3K phosphatase PTEN/MMAC1 are frequently observed in ovarian endometrioid carcinomas. AKT2 mediates some of the transforming signals of RAS and SRC which are mutated and overexpressed/activated respectively in late-stage tumours. Downregulation of the cGMP-dependent protein kinase PKG and upregulation of MAP2K6 (MEK6) were significantly correlated with the genesis of ovarian cancer. Amplification of AKT2 has been reported in 3-5% of ovarian cancers.

Other oncogenes

Amplification of other oncogenes such as FGF3 (formerly INT2) and MDM2 have been reported in 3-5% of ovarian cancers. As mentioned in the Molecular Cytogenetics section, high level amplification of 20q12-q13.2 is a frequent finding in ovarian carcinomas, and a gene located at 20q11.2-12, TGIF2, was amplified and over-expressed in 14 ovarian cancer cell lines. EIF5A2 is a candidate oncogene for the 3q25-q26 amplification in ovarian carcinomas. Over-expression of the Kallikrein gene, KLK4, located at 19q13.4, has been found in 69/147 ovarian tumours and is indicative of a poor prognosis. NME1 is thought to have a role in ovarian neoplastic process. Elevated levels of inhibin are found in most postmenopausal women with mucinous ovarian cancers.

Oncogenes involved in endometrioid carcinoma

Overexpression of BCL2 is present in about 90% of endometrioid carcinomas, and MSI is present in about one-third of cases, as has been described in endometrioid endometrial carcinomas. Over-expression of P53, EGFR, ERBB2 and ERBB3 was also detected in ovarian endometrioid carcinoma.

Expression Profiling

Expression microarrays were used to compare differential expression between 7 early stage ovarian carcinomas and 7 late stage ovarian carcinomas, and showed that several genes are aberrantly regulated to the same extent in both groups. Genes which function in cell-cell interaction such as cadherin 11 (CDH11), cadherin 2 (CDH2) and nidogen (NID) were downregulated in most tumours. Genes involved in invasion and metastasis such as matrilysin (MMP7), gelatinase (MMP9), matrix metalloproteinase 10 and 12 were upregulated in most tumours.

Several other expression profiling studies have been undertaken which identified differentially expressed genes between serous and mucinous carcinomas; and also identified differences in gene expression during progression of ovarian carcinoma.

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