ORIGINAL ARTICLE

CHROMOSOMAL ABNORMALITIES IN ENDOMETRIAL AND OVARIAN CARCINOMAS

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ABSTRACT

Development and progression of human malignancies involve multiple genetic changes including chromosomal instabilities such as translocations, deletions, and inversions. Chromosomal abnormalities were observed in 23 cases with ovarian and endometrial cancer by cytogenetic studies using a GTG (G bands by trypsin using Giemsa) banding technique. Specific chromosome bands were frequently involved, and were most frequent on chromosomes 1, 2, 3, 5, 12 and 17. Clonal alterations were observed at the cancer breakpoints, such as 1q21, 1q32, 3p21, 7q22, 11q23 in ovarian and 1p36, 1q32, 2p12, 3p21, 7q22, 9q34, 11p15, 11q23, 12q13, 14q11, 14q32, 16p13, 21q22 in endometrial cases. These findings provide evidence that multiple genetic lesions are associated with the pathogenesis of endometrial and ovarian cancer.

Key words: Endometrial cancer, Ovarian cancer, Cytogenetics

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INTRODUCTION

Endometrial and ovarian carcinomas are the most common malignancies of the female genital tract. Most of these neoplasms are associated with chromosomal abnormalities and show a constellation of rearrangements such as translocations, deletions, and inversions [1-5]. However, understanding of the molecular genetic and cytogenetic changes associated with ovarian tumor development and disease progression has been limited because of the extreme complexity of the abnormalities [2]. Cytogenetic abnormalities have diagnostic and prognostic value in ovarian carcinoma [2,5,6]. Some chromosomal breakpoints and fragile sites observed in cancer cases are accepted as cancer breakpoints and fragile sites [7,8]. Among the 30 gene-richest bands, cancer breakpoints and fragile sites colocalize at 1p36, 1q21, 7q22, 8q24, 11p15, 11q13, 11q23, 12q13, 16p13, and 19p13 [7,8]. Chromosome breakage is a manifestation of chromosomal instability. Chromosomal deletions in cancer cells are often found to contain tumor suppressor genes [7,8]. Structural rearrangements of chromosome arms 1p, 1q, 3p, 3q, 6q, 7p, 9q, 11p, 11q, 17q, 19p, and 19q were identified in ovarian tumors [1-3,5]. Taken together, these findings suggest that certain chromosomal abnormalities are important in the pathogenesis of ovarian and endometrial cancers. Because of this, we carried out cytogenetic analyses after short-term cultures of 23 endometrial and ovarian tumors. We here describe the chromosomal changes we found.

MATERIALS AND METHODS

Freshly operated tumor samples were obtained from 38 patients who had undergone surgery for endometrial and ovarian carcinomas at the hospital section of the Obstetrics and Gynocology at the Medical School of Çukurova University, Adana, Turkey. Fifteen were excluded from the study because of bacterial contamination, detachment, or presence of necrotic tissue, thus leaving 12 endometrial and 11 ovarian tumors for study. All tissues were examined macroscopically at the Pathology Department, Medical School, Çukurova University, Adana, Turkey, and came from invasive epithelial tumors. The study was approved by the Ethical Boards of the Medical School.

The tissues were disaggregated in a solution of trypsin-EDTA. The cell lines were initiated in tissue culture flasks (25 cm²) in Chang complete medium supplemented with penicillin-streptomycin to establish primary cultures [9]. The flasks were harvested for cytogenetic analysis after 7 to 10 days by exposure to colcemid followed by hypotonic treatment and fixation in methanol: acetic acid (3:1). The slides were incubated at 37°C for 2 days. Chromosomal analyses from tissue cultures were performed according to standart cytogenetic methods using the Giemsa banding technique [10]. The GTG (G bands by trypsin using Giemsa) banded slides were used for cytogenetic analysis and karyotype descriptions were made according to the International System for Human Cytogenetic Nomenclature (ISCN) [11].

RESULTS

Of the 38 tumor samples, 15 were excluded from the study because of bacterial contamination, detachment, or the presence of necrotic tissue. Karyotypic patterns were analyzed in 12 endometrial carcinomas and 11 ovarian carcinomas. All samples were from invasive epithelial tumors and characterized histologically as follows: of the endometrial tumors, four were at grade III, seven at grade II and one at grade I, while of the ovarian tumors, one was at grade III, five at grade II and five at grade I. The patients did not all show the same stage of cancer progression and there was no relationship between the complexity of chromosome constitution and the cancer progression.

Structural alterations present in more than one cell were termed clonal alterations. Thirteen patients had clonal chromosomal abnormalities, eight had non clonal abnormalities, and two cases had normal karyotypes. Most specimens exhibited complex karyotypes with many numerical and structural changes (Table 1). Numerical changes were seen in six cases: case O5 had karyotype 54,XX with numerical changes at chromosomes 9, 10, 12, 14, 15 and 20. Aneuploidy was observed in case E5. Cases O11, E1, E6 and E7 showed near-triploid, tetraploid and polyploid modal numbers with heterogenous structural abnormalities. Eleven showed a variety of structural abnormalities and five had only one structural abnormality. Deletions, translocations, inversions, gaps or breaks, acentric fragments, double minutes, radials and endoreduplications were observed in varying proportions. Translocations were found in four cases. Case E1 had t(19;22)(q13;p13) and t(21;22)(p13;q13), while case E2 had t(14;21)(q11; q11), case O5 had t(3;7)(q;q) and case O4 had t(1;22)(qter;p). Two cases (13 cells of E6 and five cells of O11) had double minutes and one case with triradial and quadriradials (seven cells of E6) (Table 1).

The cancer breakpoints and fragile sites observed are shown in Table 2. Chromosomes 3, 5, 1, 12, 17 and 2 (cited according to their frequency) were most frequently involved in structural abnormalities (Table 3 and 4 and Figure 1). Structural rearrangements acquired on chromosomes 2, 4, 7, 8, 9, 10, 11, 13, 15, 17, 18 and X in ovarian cancers and on chromosomes 14, 19, 20 and 22 in endometrial cancers.

DISCUSSION

Understanding the molecular basis of the initiation and progression of ovarian and endometrial cancer will be strongly dependent on advanced cytogenetic and molecular genetics. In this cytogenetic study we described the chromosomal findings detected in 23 endometrial and ovarian tumors, only two had normal karyotypes, and possibly fibroblast-derived instead of tumorigenic tissues [12-14]. Although five tumors revealed only one simple structural change, the karyotypes of the other 16 tumors were quite complex. Our results indicate that several chromosomal regions were non randomly involved in abnormalities. The patients did not all show the same stage of histological grade and there was no relationship between the complexity of chromosome constitution

Pazarbasi A[1,*], Kasap M[1], Demirhan O[1], Vardar MA[2],
Suleymanova-Karahan D[1], Doran F[3]

Table 1. Chromosomal abnormalities in 12 endometrial (E1-12) and 11 ovarian (O1-11) carcinomas. The complete karyotypes are listed. When more than one karyotype was identified within individual samples, the number of cells of each type is shown in square brackets.

Case #	No of M*	HG**	Endometrial Cancer
E1	35	III	40~79,XX, fra(1q11) (q32), fra(3p21), fra(5q31), fra(7q22), fra(9q34), fra(11q23), fra(14q24), fra(15q22), fra(17q21), del(12p13), dup(2p11-12), inv11(p15;q23), inv(21p13;q22)[2], t(19:22)(q13;p13), t(21;22)(p13;q13), 2p+[2]
E2	26	II	46;XX, chtb(2p13), chtb(5q31)[3], chtb(7q22), chtb(17q21)[7], del(7q34), del(11p15), fra(11q23), fra(Xq27), i(2p13), t(14;21)(q11;q11)
E3	22	II	46;XX, chtb(5q31), del(11p15),(q23), fra(17q21)
E4	57	I	46;XX,gap(1p36),(q32)[2],gap(3p21), gap(5q31)[4], fra(5q31)[2], fra(7q22), fra(14q32)
E5	41	III	25-46,XX, gap(1p21),(p36),(q32), gap(3p14)[4],(q21)[2], gap(5q22),(q31), chtb(1p13), del(3q21,p21), del(5p15), fra(5q31)[2], fra(6q25), fra(11q23), inv(9)(q12;34), heteroploidi(7)(q22), 1ph+, 3qh+
E6	85	II	19-141,XX, del(1p13),(p21)[4],(p36)[2],(q32)[3], del(3p21,q21)[8],(q25)[2],(p14,q21), del(4p15)[2], del(5p15), del(6q11),(q15),(q21), del(9q12), del(12p13)[4], del(16q23), del(Xq26)[2], fra(1p21),(p36),(q42), fra(4q21), fra(5q31)[3], fra(10p13)[2], fra(12q13), fra(13q22), fra(14q24), fra(16p13), fra(X)(p22),(q27), chtb(1p36)[2],(q21)[2], chtb(2p13),(q11)[2],(q21)[2],(q35)[3], chtb(3p21)[2], chtb(4p11),(p15), (q11),(q21), chtb(5q12),(q31), chtb(6q21), chtb(7q11), chtb(9q22)[3], chtb(10p13), chtb(12p13),(q13)[2], chtb(16p13), chtb(17p13)[2],(q11),(q21), chtb(20p11), chtb(Xq26), gap(12q24), gap(13q14)[3],(q22)[3], gap(15q15)[3], dup(5q22), der(7,17)(p ,p) i(Xq), dm[13], ace, tr and qr [7]
E7	79	III	38-92,XX, gap(1q32), gap(3p21)[3], fra(1)(q21),(q32)[4], fra(3p21), fra(5q31)[8], fra(9q34), fra(10q23), fra(12q13), fra(17q25), del(4p15), del(5p15)[3], del(21q22), 13p+
E8	12	II	46;XX, fra(3p14), fra(6q21), fra(12q24)[2], fra(Xq26)
E9	60	II	46;XX, del(3p25), chtb(3q11), fra(9q34), fra(11q23)
E10	18	II	46;XX, fra(12q24)
E11	11	II	46;XX, fra(2q35)
E12	42	III	46;XX
Case #	No of M*	HG**	Ovarian Cancer
O1	60	II	46,XX, fra(1)(q21), (q32), fra(2q35), fra(3)(p25),(q27), fra(7q22), fra(1q23), fra(14)(q11),(q24), chtb(1p36), chtb(5q12), chtb(10q23), chtb(12q13), chtb(14q11), del(2q35), del(18q23)
O2	20	II	46,XX, fra(1q21), chtb(4q11), chtb(5q31), chtb(17q24)
O3	35	I	46,XX, fra(1q32), chtb(8q21)
O4	10	III	46,XX, chtb(1q21), t(22p;1qter)
O5	35	II	54,XX,+9x3,+10x3,+12x5,+14,+15,+20x3 [35]/ t(3q;7q)
O6	42	I	46,XX, gap(5q31)[2]
O7	24	I	46,XX, 2qh+, fra(3)(p14)[2],(p21),(q11)[2],(q21),(q27), 9qh+
O8	19	II	46,XX, gap(1q21)
O9	11	I	46,XX
O10	48	II	46,XX, 2qh+[13]
O11	27	I	47-77,XX, gap(2q23), chtb(3)(p25)[2],(q11), chtb(9p22), dup(4q11→ter)[27], dup(18q11→ter)[27], del(4p15), del(5p15)[5], del(11q23), del(13p11)[2], del(15p11), inv(12p10;q13)[3], dm[5]/ +12[7]

*Metaphases; **Histological Grade

Table 2. Breakpoints and clonal alterations observed per chromosome in endometrial and ovarian cancer. Boldface represents cancer breakpoints.
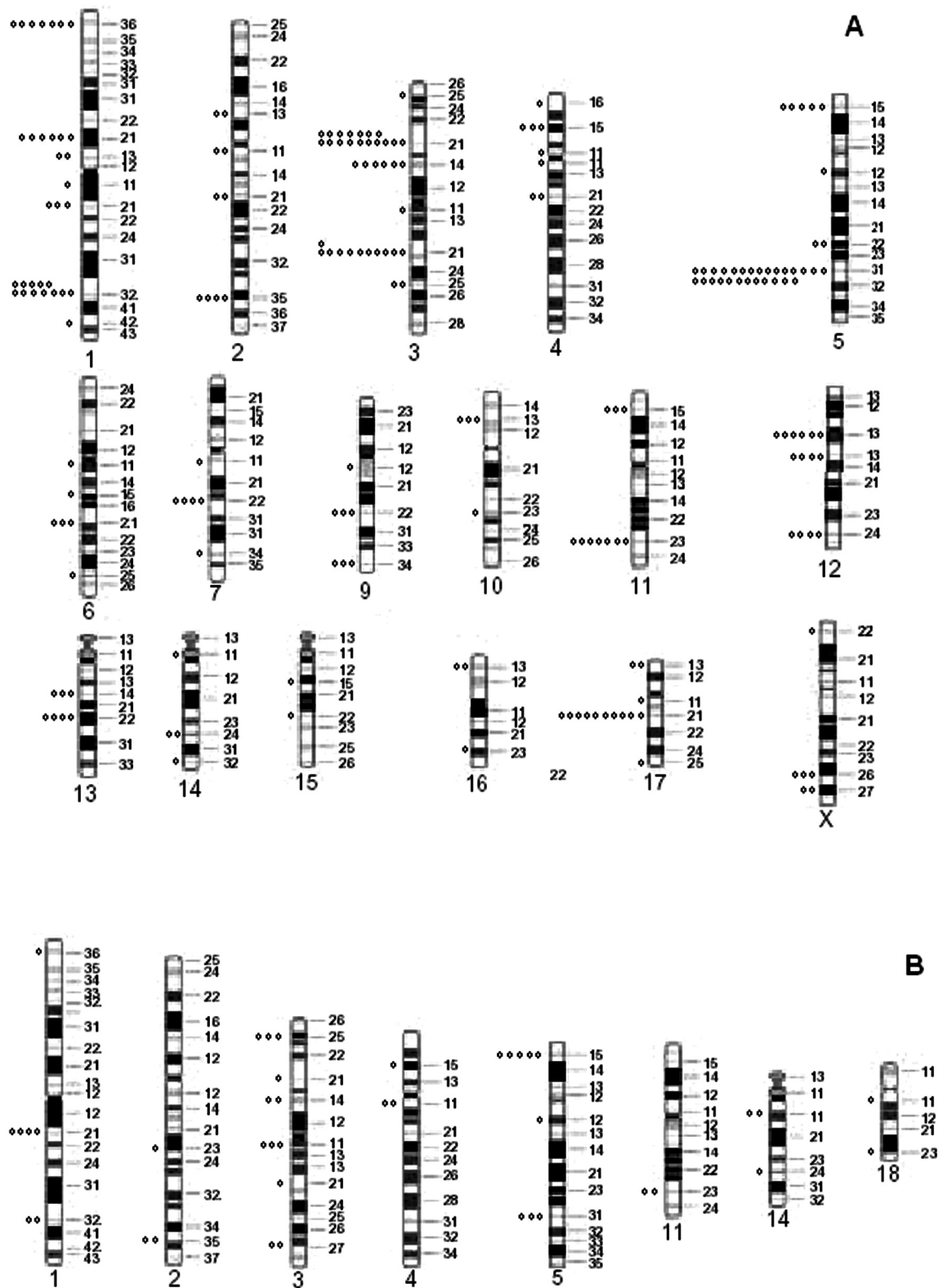
Chromosome Number	Endometrial Cancer	Ovarian Cancer
1	1p13[2], p21[6], **p36[7]**, q11, **q21[3]**, **q32[12]**, q42	**1p36, q21[4], q32[2]**
2	2p13[2], q11[2], q21[2], q35[4]	2q23, q35[2]
3	p14[6], **p21[17]**, p25, q11, q21[11], q25[2]	p14[2], **p21**, p25[3], q11[3], q21, q27[2]
4	4p11, p15[3], p16, q11, q21[2]	4p15, q11[2]
5	5p15[5], q12, q22[2], q31[27]	5p15[5], q12, q31[3]
6	6q11, q15, q21[3], q25	
7	7q11, **q22[4]**, q34	**7q22**
8		8q21
9	9q12, q22[3], **q34[3]**	9p22
10	10p13[3],q23	10q23
11	11p15[3], **q23[7]**	**11q23[2]**
12	12p13[6], **q13[4]**, q24[4]	**12q13**
13	13q14[3], q22[4]	13p11
14	**14q11**, q24[2], **q32**	**14q11[2]**, q24
15	15q15, q22	15p11
16	**16p13[2]**, q23	
17	17p13[2], q11, q21[10], q25	17q24
18		18q11, q23
20	20p11	
21	**21q22**	
X	Xp22, q26[3], q27[2]	

and cancer progression.

Chromosomes 3, 5 and 1 were (sequenced according to their frequency) most frequently involved in structural abnormalities in both endometrial and ovarian cases. Involved in structural clonal alterations were chromosomes 1, 2, 3, 4, 5, 6, 7, 9, 10, 11, 12, 13, 16, 17, 21, X in endometrial cases, and chromosomes 1, 3, 5, 12, 14 in ovarian cases. In endometrial cases, deletion of chromosome 3, the most frequent structural alteration observed, was found in 13 cells of cases E5, E6 and E9, while no deletion of chromosome 3 was found in ovarian cancers. Deletions generally cause the loss of tumor suppressor genes [15-19]. Molecular studies have shown loss of heterozygosity (LOH) on 3p, which seems to be a common event in endometrial tumors and related to LOH in the *FHIT* (fragile histidine triad) and the *hMLH1* locus [13]. According to Imamura *et al.* [13],

these losses contribute to the progression of the tumor to an undifferentiated stage, aggressive behavior, or metastatic potential. In another study [14], various deletions (3p13, 21, 22, 26) of chromosome 3p were associated with the development of uterine cervical carcinoma in Indian patients. Del(3)(q13q23) was the most consistent aberration observed in six of nine gastric and esophageal adenocarcinomas [15]. Through positional cloning of the 3q21 breakpoint, a novel gene, *DIRC2*, reported to encode a multi membrane-spanning protein that represents a new member of the major facilitator superfamily (*MFS*) of transporters, and these fragilities associated with sporadic and familial renal cell carcinomas [16].

Although the second most frequent clonal alterations that we observed was located on chromosome 5, the most frequent clonal alteration we observed in both tumor groups was 5q31. The q31 band of chro-

Pazarbasi A[1],*, Kasap M[1], Demirhan O[1], Vardar MA[2],
Suleymanova-Karahan D[1], Doran F[3]

Figure 1. Localization of breakpoints and clonal alterations observed in endometrial (A) and ovarian (B) cancers.

Table 3. Frequency of abnormalities observed per chromosome in endometrial cancer (listed in decreasing order).

Chromosome Number	Number of Abnormalities (total metaphases analyzed)	Abnormality (%)
3	40 (488)	**8.20**
5	35 (488)	**7.17**
1	32 (488)	**6.55**
12, 17	14 (488)	**2.86**
2	12 (488)	**2.45**
9, 11	9 (488)	**1.84**
4	8 (488)	**1.63**
13	7 (488)	**1.43**
6, 7, X	6 (488)	**1.22**
10, 14, 21	4 (488)	0.81
16	3 (488)	0.61
15, 18, 22	2 (488)	0.40
19, 20	1 (488)	0.20

Table 4. Frequency of abnormalities observed per chromosome in ovarian cancer (listed in decreasing order).

Chromosome Number	Number of Abnormalities (total metaphases analyzed)	Abnormality (%)
3	12 (315)	**3.80**
5	9 (315)	**2.85**
1, 12	7 (315)	**2.22**
2, 4, 14	3 (315)	0.95
11, 18	2 (315)	0.63
7, 8, 9, 10, 13, 15, 17	1 (315)	0.31

mosome 5 has been the subject of intensive studies as it is a gene-rich area. It contains genes of known biological function, including growth factor, growth factor receptor, hormone receptor and neurotransmitter receptor [17].

The third most frequent clonal alteration that we observed was located on chromosome 1. One of the clonal alteration in endometrial cases was at 1p36. Four genes, mapping to 1p36, have been proposed as candidate tumor suppressor genes: *Heir-1* (*ID3*), a neuroectodermally expressed member of the Id family of developmental negative regulatory genes; *TNFR2*, one of two tumor necrosis factor receptor genes; *PITSLRE*, a cell cycle-regulated kinase gene with homology to human *CDC2*; and *DAN*, a transcription factor gene homologous to a mouse tumor suppressor gene. Two additional genes, the transcription factor regulator *E2F2* and the paired-box-containing gene *PAX7*, were recently mapped to 1p36 and are thus additional potential candidate suppressor genes. Disruption of one or more of these candidate genes could play a role in the development of endometrial cancer [6].

The 12q13-15 region was involved in six cells of three cases in our study. It contains several genes (including an oncogene) of potential importance for

Pazarbasi A[1,*], Kasap M[1], Demirhan O[1], Vardar MA[2],
Suleymanova-Karahan D[1], Doran F[3]

neoplastic development, for example, *SAS, SP1, INT-1, GLI, CHOP, CDK4* and *MDM2* [19-21]. Molecular studies have shown that these genes are often coamplified, although there have also been cases with only one or two of these genes included in the amplicon [20,21]. The presence of an additional copy of chromosome 12 with an altered gene at 12q13 may contribute to the development of a malignancy. The *HMGI-C* gene encodes a member of the high-mobility-group proteins, which are non histone nuclear proteins able to bind AT-rich regions in the minor groove of DNA through three so-called AT-hook domains and may affect transcription by acting as architectural proteins. They have been found overexpressed in human and experimental malignancies [21]. Rearrangements of the *HMGI-C* gene are the consequence of chromosomal aberrations involving the 12q13-15 region where the *HMGI-C* gene is located [21].

Based on data on breakpoints at the 2q35-q37 region, a genetic link between some carcinomas has been suggested for a common pathway of the development of these tumors. This region include paired box protein (PAX3) gene [22]. However, the role of the PAX3 gene in rearrangements in chromosome 2 in endometrial and ovarian carcinomas remains to be determined.

The *THY1* gene was mapped to the 11q23~24, which has been identified by both Taetle *et al*. [1] and Garba *et al*. [22] to have a high incidence of LOH in ovarian cancer. The location of the *THY1* gene at this region makes this a suitable tumor suppressor gene for ovarian cancer. The *THY1* gene was found to be exclusively expressed in the two non tumorigenic cell clones [23]. In contrast, *THY1* expression was not determined in the tumorigenic ovarian cell lines. We observed clonal alterations at this region in both carcinoma types in our study. The mechanism of how *THY1* expression is abolished in ovarian cancer cells remains elusive.

We observed fragility at 7q22 in both endometrial and ovarian tumors. That observed in endometrial tumors was a clonal alteration. Genes mapped to the 7q22 region include the human cut-like1 gene (*CUTL1*), human mismatch repair gene (*PMS2L*), erythropoietin gene (*EPO*), and asparagine synthetase gene (*ASNS*). The fact that most structural rearrangements involving 7q22, suggest the hypothesis that this site contains a critical region of single or multiple genes, that when mutated or deleted results

in malignant transformation. Whether this involves a structural alteration of a putative tumor suppressor gene remains to be clarified [24].

Two main cytogenetic subgroups have been identified in published cases of ovarian tumors with chromosome abnormalities: tumors with simple karyotypic changes and tumors with complex karyotypic abnormalities. Simple karyotypic changes are defined as simple numerical changes, whereas complex karyotypic changes are multiple numerical and structural abnormalities of chromosomes. We found that aberrations may be of significance in the pathogenesis of ovarian cancer and may provide valuable information for further investigation at the molecular level. Simple karyotypic changes, including trisomy 12, 10, 7, 8, 5 (in decreasing order of frequency) have been considered as primary chromosomal changes in ovarian cancer [5]. The 54,XX karyotype with complex numerical changes at chromosomes 9, 10, 12, 14, 15 and 20, which we found in case O5, have not been previously reported. These chromosomes may play a specific role in the pathogenesis of ovarian cancer. Because trisomy 10 has been observed in some benign tumors and in normal tissues that surround malignant tumors, it may contribute to the transformation of normal tissues and/or the initiation of tumorigenesis [5]. Marked aneuploidy represents this aggressive phenotypic behavior at a cytogenetic level. However, chromosomal aberrations need not necessarily be associated with advanced-stage disease. We observed two normal 46,XX karyotypes in a highly malignant endometrial (E12) and an ovarian (O9) cancer.

In conclusion, this study has shown that specific chromosome bands, frequently involved in clonal alterations and breakpoints, may indicate the regions in which to search for new dominant oncogenes or recessive tumor suppressor genes. Our cytogenetic findings provide strong evidence that multiple genetic lesions are associated with the development of endometrial cancers, and that deletions of 3p13, p21, p23, q21 and q25 may play a specific role in the pathogenesis of such cancers. Chromosomal abnormalities have been known to occur in malignant tumors for a long time [1-5]. This study adds little to the understanding of the field of ovarian cancer cytogenetics; the results for endometrial cancer are more novel and could be improved by analyses of more cases.

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