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ORIGINAL ARTICLE

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Comparison of alterations of chromosome 17 in carcinoma of the ovary and of the breast

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Abstract Breast and ovarian carcinomas share a region of allelic loss on chromosome 17q25, suggesting that these tumours may arise by similar molecular pathways. We analysed paraffin-embedded tissues from 84 sporadic ovarian carcinomas and 42 sporadic infiltrating ductal carcinomas of the breast for abnormalities on chromosome 17. Loss of heterozygosity (LOH) of at least one informative marker on 17q was identified in 49 of 82 (60%) ovarian carcinomas, as against only 6 of 40 (15%) informative breast carcinomas (P<0.0001). In ovarian carcinoma, LOH was most commonly observed for GH on 17q23 (56%), and was also frequently observed at 17q21 (46%). In contrast, LOH of D17S1330/CTT16 on 17q25 was observed in only 19% of ovarian tumours. LOH in breast carcinomas was most frequently observed at 17q21 (16%), less frequently at 17q23 (7%) and not identified at all at 17q25 in any breast cancers. Immunohistochemical analysis demonstrated overexpression of the *p53* gene product in 38 of 84 (45%) ovarian carcinomas, as against 10 of 42 (24%) breast carcinomas (P=0.0195). *p53* immunoreactivity was significantly associated with LOH in ovarian and breast cancers. Immunohistochemical expression of HER2/*neu* was observed in 6 of 84 (7%) ovarian and 3 of 42 (7%) breast carcinomas. There was no relationship between HER2/*neu* immunoreactivity and LOH. Although sporadic carcinomas of breast and ovary share some regions of allelic loss on chromosome 17q, differences in other alterations on this chromosome suggest divergent pathways of tumour development.

Key words Ovary · Breast · Carcinoma · Loss of heterozygosity · Chromosome 17

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Introduction

Chromosome 17 is one of the most frequent targets of genetic damage in human neoplasia [25]. In particular, three genes on chromosome 17 have been linked to the development of breast cancer: *p53*, *BRCA1* and HER2/*neu*. Analyses of breast cancers have implicated additional genes with tumour suppressor function. Studies of allelic loss using loss of heterozygosity (LOH) of polymorphic genetic markers on chromosome 17 have implicated the existence of one or more additional tumour suppressor genes on the long arm of chromosome 17 distal to *BRCA1* [6, 17, 23, 29]. As further evidence of this, a *BRCA1*-deficient chromosome 17 has been shown to suppress tumorigenicity when transfected into a *p53*-positive breast cancer cell line [28].

Recently, deletion mapping of microsatellite markers was used to define a 3-cM region on 17q25, distal to the genetic marker D17S1330, containing a putative tumour suppressor gene inactivated in carcinoma of the breast [16]. This region of 17q25 allelic loss has recently been shown to be shared with ovarian carcinomas [15]. Other alterations of chromosome 17 have also been associated with both breast and ovarian cancer, including germline mutations in the *BRCA1* gene [12, 21] and other regions of LOH [1, 23].

We have undertaken a comparative study of 84 sporadic ovarian and 42 sporadic breast carcinomas to compare alterations of chromosome 17 between these tumours. We have analysed allelic loss in three regions of 17q proximal to the area of 17q25 (flanked by D17S722 and D17S802) already shown to contain a putative tumour suppressor gene [15]. In addition, we used immunohistochemistry to analyse the expression of *p53* and

HER2/*neu* (located on 17p13 and 17q12, respectively), which have both been shown to be involved in the development of breast [5, 27] and ovarian [9, 24] cancer.

Methods

Based on review of haematoxylin and eosin-stained slides and availability of formalin-fixed, paraffin-embedded tissue, 84 invasive ovarian adenocarcinomas and 42 infiltrating ductal carcinomas of the breast were identified with confluent areas of neoplasm (at least 80% by visual examination). The histological subtypes of the ovarian carcinomas were papillary serous (26), endometrioid (28), mucinous (4), clear cell (14) and others (12: transitional cell carcinomas, carcinosarcomas, and tumors of mixed histological patterns). Anonymized tissue specimens were used in accordance with informed consent provided by each patient at the time of surgery, as approved by the institution's Internal Review Board. Two paraffin tissue blocks, one each of neoplastic and nonneoplastic tissue, were selected from each case. DNA was extracted from paraffin sections as previously described [10] and digested overnight in 100 μl of 50 mmol/l TRIS pH 8.3 with 200 ng/μl proteinase K at 37°C. Samples were then boiled for 8 min, cooled on ice, and spun for 5 min to pellet the debris. DNA extraction was performed in batches with a reagent-only negative control.

LOH of genetic markers on chromosome 17q was identified using primers designed to analyse five informative repeat sequences on chromosome 17q (Table 1): D17S855 and D17S1323 (dinucleotide microsatellite markers intragenic to *BRCA1* on 17q21, GenBank U15595); EDH17B (a 12-bp insertion-deletion flanking 17beta-hydroxysteroid dehydrogenase on 17q21 near *BRCA1* [11]); GH (a tetranucleotide repeat at the human growth hormone locus on 17q23, GenBank J03071 [22]); and D17S1330/CTT16 (a trinucleotide repeat on 17q25, GenBank G07947). All of these markers are proximal to the defined area of interstitial deletion on 17q25 flanked by markers D17S722 and D17S802 [15].

PCR was performed with an initial denaturation step of 4 min at 94°C coupled to 35 cycles of 1 min at 94°C, 2 min at the primer-specific annealing temperature (Table 1), and 2 min at 72°C, followed by a 7-min completion step at 72°C. Ten microlitres of PCR product were loaded in parallel onto 8% neutral polyacrylamide and 3% agarose gels (1.5% NuSieve, FMC Bioproducts, Rockland, Me. and 1.5% agarose, Gibco-BRL, Grand Island, N.Y.) with 10 μl of 1×TBE buffer and 3 μl of loading dye. The gels were stained in 0.5 μg/ml ethidium bromide and photographed with a Polaroid camera using an ultraviolet light source. Allelic loss in neoplastic tissue was determined visually as loss of more than 50% of the intensity of one allele relative to the other in neoplastic compared to non-neoplastic tissue.

Immunohistochemical analysis of p53 protein in ovarian tumours was performed in conjunction with an earlier study [9]. Immunoreactivity for p53 protein was assessed using antibody PAb1801 (Oncogene Science, Uniondale, N.Y.), a murine monoclonal antibody specific for a denaturation-resistant epitope between amino acids 32 and 79 of the human p53 protein [3]. Using the same block of neoplastic tissue selected for PCR analysis, tissue sections of 4 μm thickness were pretreated with microwaving in 10 mM citrate buffer and incubated overnight at room temperature with the primary antibody at a 1:1000 dilution as previously described [9]. Following 1 h of incubation with a 1:200 dilution of biotinylated antimouse IgG (Vector mouse ABC kit, Burlingame, Calif.), the tissues were incubated for 30 min at room temperature with 1 μg/ml streptavidin-alkaline phosphatase (BRL Life technologies, Bethesda, Md.). The samples were then incubated in the dark for 1 h with nitroblue tetrazolium and 5-bromo-4-chloro-3-indolyl phosphate substrate (BRL) for chromogen development. Tumours were considered to be positive in the presence of diffuse staining (confluent areas of tumour in which at least half of the nuclei stained as estimated by visual examination).

Immunohistochemical analysis of HER2/*neu* amplification was performed using the monoclonal antibody clone TAB-250 (mAb1, Triton Laboratories, Alameda, Calif.), which recognizes an epitope on the external domain of the HER2/*neu* gene product. Deparaffinized tissue sections were sequentially incubated for 20 min with 1.5% H_2O_2 in methanol (to quench endogenous peroxidase activity) and for 10 min in 20% normal horse ("suppressor") serum. Following overnight incubation at room temperature with primary antibody at a concentration of 1:50, the slides were incubated sequentially with secondary biotinylated (horse anti-mouse)

Table 1 Loci used for analysis of allelic loss on chromosome 17q in carcinomas of the ovary and of the breast

Locus	Location of microsatellite marker	Primer Sequence	Annealing temperature (°C)	Approximate size (bp)
EDH17B (17 beta-hydroxysteroid dehydrogenase)	17q21	5′-GCAAAGACGGGGTCTCATTCT-3′ 5′-AGAAGGTGAAGAACTCATCCA-3′	55°	255
D17S855 (*BRCA1*)	17q21	5′-ACACAGACTTGTCCTACTGCC-3′ 5′-GGATGGCCTTTTAGAAAGTGG-3′	57°	150
D17S1323 (*BRCA1*)	17q21	5′-TAGGAGATGGATTATTGGTG-3′ 5′-AAGCAACTTTGCAATGAGTG-3′	55°	155
GH (growth hormone)	17q23	5′-TCCAGCCTCGGAGACAGAAT-3′ 5′-AGTCCTTTCTCCAGAGCAGGT-3′	54°	243
D17S1330 (CTT16)	17q25	5′-TGGCTAGTGGACAAAGTGGT-3′ 5′-GGGAACAAATAATGAACAAAA-3′	51°	174

Table 2 Allelic loss on 17q in carcinoma of ovary and of breast

	LOH of any 17q marker[a]	LOH of 17q21 *(17HSD, D17S855, D17S1323)*	LOH of 17q23 (GH)	LOH of 17q25 *(D17S1330/ CTT16)*	LOH of 17q21 only[b]	LOH of 17q23–25 only 25 only[b]
Ovarian carcinoma	49/82 (60%)	33/72 (46%)	29/52 (56%)	11/57 (19%)	10/65 (15%)	10/65 (15%)
Breast carcinoma	6/40 (15%)	5/32 (16%)	2/27 (7%)	0/30 (0%)	3/29 (10%)	1/29 (3%)

[a] Of tumours informative for any of the analysed markers on chromosome 17q
[b] Of tumours informative for markers on 17q21 *and* either 17q23 or 17q25

Table 3 Allelic loss on 17q and immunohistochemical expression of *p53* and HER2/*neu* in histological subtypes of ovarian carcinoma

Histological subtype of ovarian carcinoma	LOH of any17q marker[a]	LOH of 17q21 (17HSD, D17S855, D17S1323)	LOH of 17q23 (GH)	LOH of 17q25 (D17S1330/ CTT16)	LOH of 17q21 only[b]	LOH of 17q23–25 only[b]	*p53* gene product	HER2/*neu* gene product
Papillary serous	16/25 (64%)	12/22 (55%)	8/13 (62%)	4/20 (20%)	6/21 (29%)	2/21 (15%)	16/26 (61%)	0/26 (0%)
Endometrioid	20/27 (74%)	13/23 (57%)	13/17 (68%)	3/17 (18%)	3/20 (15%)	5/20 (25%)	14/28 (50%)	1/28 (4%)
Mucinous	0/4 (0%)	0/4 (0%)	0/4 (0%)	0/4 (0%)	0/4 (0%)	0/4 (0%)	1/4 (25%)	3/4 (75%)
Clear cell	6/14 (43%)	2/12 (17%)	3/10 (30%)	1/8 (13%)	1/10 (10%)	2/10 (20%)	2/14 (14%)	0/14 (0%)
Other[c]	7/12 (60%)	6/11 (55%)	5/8 (63%)	3/8 (38%)	0/10 (0%)	1/10 (10%)	5/12 (42%)	2/12 (17%)

[a] Of tumors informative for any of the analyzed markers on chromosome 17q
[b] Of tumours informative for markers on 17q21 *and* either 17q23 or 17q25
[c] Includes 2 mixed papillary serous-endometrioid carcinomas, 4 transitional cell carcinomas, 4 undifferentiated carcinomas and 2 carcinosarcomas

antibody, avidin–biotin complex reagent (ABC Elite kit, Vector Laboratory Systems, Burlingame, Calif.) and chromogen reaction solution [3,3′-diaminobenzidine tetrahydrochloride (Sigma, St. Louis, Mo.) in 0.04% H_2O_2]. Tumours were not considered positive unless confluent tumour cells demonstrated intense, discrete staining of the cytoplasmic membrane.

Statistical analysis (Chi-square except where noted) was performed using Statview vers. 4.01 (Abacus Concepts, Berkeley, Calif.).

Results

As summarized in Table 2, loss of at least one informative marker on 17q was identified in 49 of 82 (60%) ovarian carcinomas, as against only 6 of 40 (15%) informative breast carcinomas (P<0.0001). Allelic loss of any informative markers at 17q21 was always accompanied by LOH of others at this locus. In ovarian carcinoma, LOH was most commonly observed for GH on 17q23 (56%), and was also frequently observed at 17q21 (46%). LOH of D17S1330/CTT16 on 17q25 was observed in only 19% of ovarian tumours. When histological subtypes of ovarian cancers were analysed separately (Table 3), there was very similar prevalence of LOH among papillary serous and endometrioid carcinomas, but much less LOH of 17q in clear cell carcinomas and none at all in any of four mucinous carcinomas. LOH in breast carcinomas was most frequently observed at 17q21 (16%), less frequently observed at 17q23 (7%), and not identified at all at 17q25 in any breast cancers. Examples of LOH are illustrated in Fig. 1.

LOH confined to informative markers on 17q21 (with retention of heterozygosity of more distal markers) was present in 3/29 (10%) breast carcinomas and 10/65 (15%) ovarian carcinomas. Conversely, allelic loss confined to distal 17q (i.e., LOH of 17q23 or 17q25 with retention of heterozygosity of 17q21) was observed in 1/29 (3%) breast cancers, as opposed to 10/65 (15%) ovarian

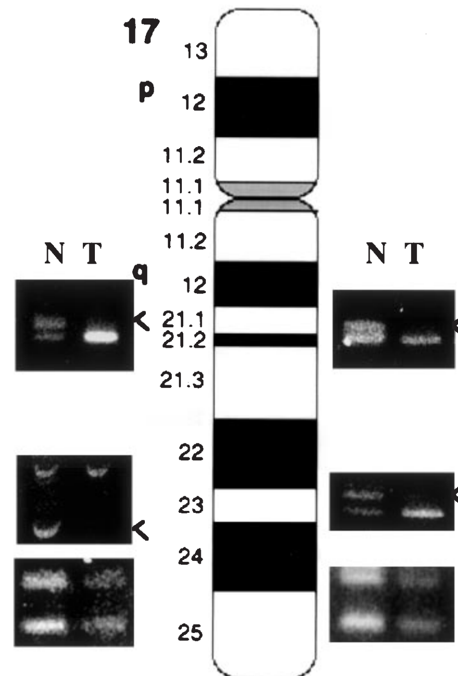

Fig. 1 Loss of heterozygosity on chromosome 17q in carcinomas of the ovary and breast. Microsatellites were amplified from paired samples of nonneoplastic tissue (*N*) and tumour (*T*). Informative tissues possessed two microsatellite alleles, indicated by PCR products of slightly different sizes. Loss of heterozygosity (*LOH*) was indicated by absence of one fewer of these two bands in neoplastic than in nonneoplastic tissue, as shown for markers at 17q21 and 17q23 (*arrows*) in both the breast (*left*) and the ovarian (*right*) carcinomas illustrated. LOH was more commonly seen in carcinomas of the ovary than of the breast. Losses at 17q21 and 17q23 were more frequent than at 17q25 in both tumour types. Breast tumours demonstrated LOH at 17q21 more frequently than of 17q23, while the opposite was true for ovarian tumours

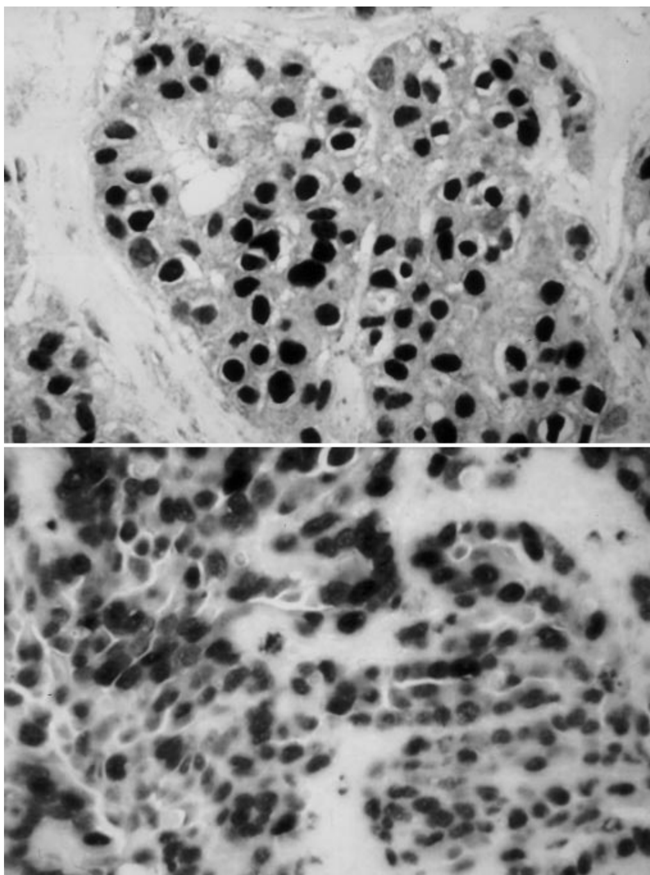

Fig. 2 Immunoreactivity for the *p53* gene product in carcinomas of breast and ovary. Diffuse nuclear staining results from accumulation of p53 protein, indicative of a missense mutations in the *p53* gene, as demonstrated in the carcinomas of breast (*upper*) and ovary (*lower*) as illustrated above. Overexpression of the *p53* gene product was significantly more frequent in carcinomas of the ovary than of the breast. NBT-BCIP-stained immunochemical preparations

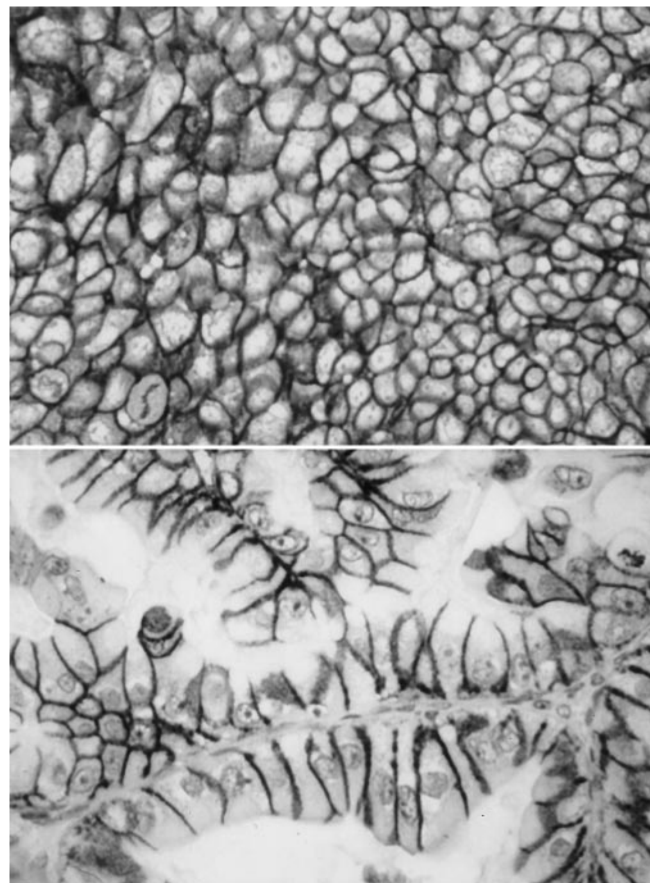

Fig. 3 Immunoreactivity for the HER2/*neu* gene product in carcinomas of breast and ovary. Tumours were considered to overexpress the gene product if they demonstrated diffuse, strong decoration of the cell membrane, as demonstrated in the illustrated examples of infiltrating carcinoma of the breast (*upper*) and mucinous carcinoma of the ovary (*lower*). Immunohistochemical analysis identified overexpression of HER2/*neu* in 7% of ovarian and breast carcinomas. DAB-stained immunochemical preparations

carcinomas (P=0.0169). Three of 27 ovarian carcinomas informative for markers on 17q21, q23 and q25 showed LOH at all informative loci, indicating possible loss of the entire chromosomal arm. None of 15 breast carcinomas informative at all loci showed widespread chromosomal loss.

The results of immunohistochemical analysis of the p53 protein are illustrated in Fig. 2 and summarized in Table 4. Diffuse nuclear accumulation of p53 protein, indicating a missense mutation in the gene itself, was identified in 38 of 84 (45%) ovarian carcinomas, as against 10 of 42 (24%) breast carcinomas (P=0.0195) Immunoreactivity for p53 was more common in papillary serous and endometrioid ovarian carcinomas than in clear cell and mucinous tumours (Table 3). In cancers of the ovary p53 immunoreactivity was associated with LOH on 17q: 29 of 36 (81%) p53-positive tumours demonstrated LOH of at least one 17q marker, as opposed to 20 of 26 (43%) p53-negative ovarian carcinomas (P=0.0007). A similar correlation was observed in breast cancer: 4 of 9 (44%) p53-positive breast carcinomas demonstrated LOH of at least one 17q marker, as opposed to 2 of 31 (6%) p53-negative breast carcinomas (P=0.0163, Fisher's exact test).

Table 4 Immunohistochemical expression of *p53* and HER2/*neu* in carcinoma of the ovary and of the breast

	p53 gene product	HER2/*neu* gene product
Ovarian carcinoma	38/84 (45%)	6/84 (7%)
Breast carcinoma	10/42 (24%)	3/42 (7%)

Immunohistochemical expression of HER2/*neu* was observed in 6/84 (7%) ovarian and 3/42 (7%) breast carcinomas, as illustrated in Fig. 3 and summarized in Table 4. Immunoreactivity was significantly more prevalent among mucinous tumours of the ovary than papillary serous, endometrioid and clear cell carcinomas. There was no relationship between HER2/*neu* immunoreactivity and LOH seen in ovarian or breast carcinomas.

Discussion

As inherited mutations in *BRCA1* predispose to both breast and ovarian carcinoma, it was hoped that investigation of this gene would increase our understanding of the biological link between these malignancies. Studies conducted before the discovery of *BRCA1* demonstrated frequent LOH of 17q21 in sporadic breast [7] and ovarian [23] carcinomas, which was thought to indicate frequent involvement of *BRCA1* in the development of these tumours. Subsequently, however, it was determined that somatic mutations in *BRCA1* are substantially less frequent in sporadic ovarian [20] and breast [12] cancers than is LOH of 17q21. This is illustrated by the subgroup analysed in this study previously analysed for mutations in *BRCA1* [20]. All four tumours in the earlier study with mutations in *BRCA1* demonstrated LOH of 17q21, but 15 other tumours with LOH of 17q21 lacked mutations (including 5 tumours in which LOH was confined to 17q21). Other tumour suppressor genes on 17q21 have been implicated in the development of breast and ovarian carcinoma [1].

Patterns of allelic loss in ovarian [13, 14, 29] and breast [6, 17] carcinoma suggest the presence of other tumour suppressor genes on 17q, distal to 17q21, but the genes involved may differ between these tumours. LOH analysis of ovarian carcinomas indicates that GH on 17q23 is part of a minimum deletion unit on 17q [13, 14]. In contrast, studies of breast cancer have found that loss of a region closer to the telomeric end was more common than loss of GH itself [6, 17]. Our observation of LOH of GH in 56% of ovarian cancers as opposed to 7% of breast cancers suggests that the presence of a tumour suppressor gene near GH is more likely to be altered in carcinomas of the ovary than of the breast.

A putative tumour suppressor gene elsewhere in 17q, however, has been implicated in the development of sporadic carcinomas of both ovary and breast [6, 17, 29]. LOH of a 3-cM portion of 17q25 (distal to the marker D17S1330 analysed in this study) was originally identified in breast cancers [16] and subsequently also in ovarian carcinomas (using several of the ovarian tumours analysed in this study) [15]. It thus appears likely that while some genes on 17q may be important in the development of both breast and ovarian cancer, others may be significant principally in the development of one or the other.

We found that a greater proportion of ovarian than of breast cancers demonstrated immunoreactivity with the *p53* gene product. Immunohistochemical staining with monoclonal antibody Pab1801 has been performed in paraffin-embedded breast [5] and ovarian [18] carcinoma and found to correlate well with *p53* missense mutations, which comprise the majority of *p53* mutations in human neoplasia. Our finding of diffuse nuclear staining in 45% of ovarian tumours as opposed to 24% of breast carcinomas is quite similar to the findings recorded in studies in which frozen tissue sections of ovarian [19] and breast [4] cancers were used.

In contrast to immunoreactivity for the *p53* gene product, we saw no difference in HER2/*neu* staining between ovarian and breast carcinomas. While amplification of HER2/*neu* has been reported in up to 25–30% of breast cancers [27], other studies have estimated that only 15% of infiltrating ductal carcinomas demonstrate either amplification of the HER2/*neu* gene [17] or overexpression of its gene product [2]. Immunoreactivity with the HER2/*neu* protein was observed in 7% of the infiltrating ductal carcinomas in this study. Some differences between studies may result from differences in methodologies. For this reason we utilized a monoclonal antibody (TAB-250) that has been shown to be among the most sensitive and specific in paraffin-embedded tissue for the detection of HER2/*neu* overexpression [26]. Furthermore, because cytoplasmic staining has been shown to represent cross-reactivity with a mitochondrial protein [8], we did not count tumours as positive unless diffuse cells demonstrated distinct and strong staining of the cell membrane.

In summary, studies have indicated that tumour suppressor genes on 17q21 and 17q25 may be involved in the development of sporadic carcinomas of both breast and ovary. Despite these similarities, our data indicate that LOH on 17q and p53 protein immunoreactivity are more common in ovarian carcinomas. Our data further indicate the presence of a tumour suppressor gene in the central portion of 17q that is more important in the development of ovarian than of breast cancer.

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