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Genetic Changes in Inherited and Sporadic Ovarian Carcinomas by Comparative Genomic Hybridization: Extensive Similarity Except for a Difference at Chromosome 2q24–q32[1]

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Abstract

Germ-line mutations in the *BRCA1* and *BRCA2* genes confer a predisposition to breast as well as ovarian carcinoma. Except for loss of the respective wild-type allele, somatic genetic changes needed for the progression of inherited ovarian tumors are unknown. A genome-wide search for such alterations was performed by comparative genomic hybridization analysis on *BRCA1* and *BRCA2* mutation-positive (n = 20) ovarian carcinoma specimens. Comparison with sporadic ovarian carcinomas (n = 20) revealed extensive genetic similarity between the inherited and sporadic carcinomas with the sole exception of a frequent gain of 2q24–q32 in the inherited group, suggesting the presence of an oncogene at 2q24–q32 operating in the absence of *BRCA1* function. The overall similarity of gains and losses by comparative genomic hybridization suggests a common main pathway in tumor progression of both inherited and sporadic ovarian carcinomas.

Introduction

A total of 5–10% of ovarian carcinomas are associated with inherited dominantly acting cancer-predisposing genes (1). A germ-line mutation of the *BRCA1* gene at chromosome 17q21 or the *BRCA2* gene at 13q12–13 confers a cumulative risk for ovarian carcinoma of up to 26–85 and 10%, respectively (Ref. 2 and references therein). Ovarian cancer risk may depend on the location of mutation in the *BRCA1* or *BRCA2* gene (3, 4), but little is known about other factors that modify the ovarian carcinoma risk of the mutation carriers (1).

Ovarian carcinoma originates from the epithelium of the ovary and takes many histological forms including serous, mucinous, and endometrioid subtypes with distinct genetic abnormalities as judged by molecular genetic karyotyping (5). For unknown reasons, virtually all *BRCA*-associated ovarian carcinomas (referred to henceforth as "inherited") are of the serous subtype (6). The inherited and sporadic ovarian carcinomas cannot be distinguished from each other by routine histopathology (7). Interestingly, patients with *BRCA1* mutation-associated ovarian carcinoma have a better survival rate compared with that of patients with sporadic disease (8). The possible molecular mechanisms underlying this difference are not known.

In sporadic ovarian carcinomas, somatic point mutations of the *BRCA1* and *BRCA2* genes are rare (1). In the inherited form, somatic loss of the wild-type allele of *BRCA1* or *BRCA2* takes place during tumor development (1). Additional genetic changes that are thus far unknown are required for the malignant phenotype to emerge. Knowledge of these events is of importance for developing strategies to intervene in the process of inherited carcinoma in the future.

CGH[3] allows screening of the entire genome for chromosomal aberrations (9). Regions showing an increased copy number (gain or amplification) may harbor dominant oncogenes, whereas regions with a decreased copy number (loss) may contain tumor suppressor genes. Genetic profiling by CGH analysis can serve as a fingerprint for tumors and the pathways of their development. We used CGH to identify DNA sequence copy number changes in tumor specimens from inherited *BRCA1* and *BRCA2* mutation-positive ovarian carcinomas and compared them with the changes observed in sporadic tumors of similar histology. Our aims were to discover whether the molecular karyotypes of these tumors are dissimilar, as suggested by their differences in clinical outcome, and to screen for somatically altered chromosomal regions in these tumors.

Materials and Methods

Tumor Samples. The study population comprised 20 hereditary ovarian cancer patients from different hospitals in Finland. They were members of breast-ovarian cancer families previously analyzed for *BRCA1* and *BRCA2* mutations (10, 11) or unselected mutation-positive ovarian cancer patients from the Department of Obstetrics and Gynecology, Helsinki University Central Hospital (Helsinki, Finland). Sixteen patients were *BRCA1* mutation-positive, and four patients were *BRCA2* mutation-positive. Histologically, 14 tumors of the *BRCA1* group were serous cystadenocarcinomas, 1 tumor was an endometrioid adenocarcinoma, and 1 tumor was a borderline mucinous cystadenoma. In the *BRCA2* group, three tumors were serous cystadenocarcinomas, one of which possibly originated from the fallopian tube, and one tumor was an endometrioid adenocarcinoma (Table 1). The sporadic group consisted of 20 serous ovarian cystadenocarcinomas of similar stage and grade. All of the patients with sporadic cancer were treated at the Department of Obstetrics and Gynecology, Helsinki University Central Hospital. The study was approved by the institutional review board of the department.

The histology of all tumor specimens was evaluated by the same investigator (R. B.). Tissue specimens containing more than 50% tumor cells were selected for DNA extraction, which was performed using standard protocols from either paraffin-embedded blocks or frozen sections.

CGH. The protocol regarding directly fluorochrome-conjugated nucleotides (12) was followed with some modifications. Briefly, 1 μg of tumor DNA was labeled with FITC-12dUTP (DuPont New England Nuclear, Boston, MA) or with FITC-12dUTP and FITC-12dCTP (1:1; DuPont New England Nuclear), and 1 μg of normal DNA was labeled with Texas Red-5dUTP (DuPont New England Nuclear) or with Texas Red-5dUTP and Texas Red-5dCTP (1:1; DuPont New England Nuclear) in standard nick translation. Equal amounts of labeled test and reference DNA were hybridized to normal metaphase spreads. The slides were counterstained with 4′,6-diamidino-2-phenylindole (Sigma, St. Louis, MO) for the identification of the chromosomes.

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[3] The abbreviation used is: CGH, comparative genomic hybridization.

Table 1 *Clinical features and mutation characteristics of the BRCA1- and BRCA2-associated and sporadic ovarian carcinomas*

Case no.	Age (yr)	Stage	Grade	Mutation
BRCA1				
87	58	II	2	446C-T
661	16	I	1	1924delA
671	52	III	1	2803delAA
654	44	III	2	3604delA
677	48	III	2	3604delA
911	42	III	3	3604delA
816	43	III	2	3744delT
659	58	III	3	3904C-T
660	66	III	3	3904C-T
667	50	III	3	3904C-T
673	47	III	3	4153delA
723	59	III	3	4216(−2)A-G
851	70	III	2	4216(−2)A-G
883	58	III	3	4216(−2)A-G
656	41	I	3	4446C-T
655	57	III	3	5370C-T
BRCA2				
676	57	III	3	999del5
672	50	II	NA[a]	9346(−2)A-G
95	55	III	1	9346(−2)A-G
657	66	I	3	9346(−2)A-G
Sporadic				
91	38	III	2	
215	43	III	3	
226	57	I	3	
102	66	I	3	
243	47	III	3	
424	47	III	3	
261	39	I	1	
428	48	III	3	
250	51	III	1	
228	55	IV	3	
473	47	III	3	
101	72	III	3	
402	43	III	2	
125	68	II	2	
83	31	III	1	
484	51	II	2	
108	47	III	3	
405	51	III	2	
440	58	III	2	
431	47	IV	3	

[a] NA, not available.

In one sample, the amount of DNA was insufficient for CGH. This sample was treated using degenerate oligonucleotide-primed PCR, performed as described by Kuukasjarvi *et al.* (13), with some modifications. Briefly, six cycles were used in the preamplification step, and Thermosequenase enzyme (Amersham, Cleveland, OH) was used in both amplification steps. The product was labeled using a standard random priming method.

The results were analyzed using an Olympus fluorescence microscope and an ISIS digital image analysis system (MetaSystems GmbH, Altlussheim, Germany). Three-color images (green for tumor DNA, red for normal reference DNA, and blue for DNA counterstain) were acquired from 6–10 metaphases/sample. Green:red ratio profiles along the chromosome axis were displayed. Chromosomal regions with a green:red ratio exceeding 1.17 were considered to be overrepresented (gains), whereas regions with a ratio below 0.85 were considered underrepresented (losses). These values were set on the basis of the results of negative control experiments in which two differently labeled normal DNAs were hybridized together. In the negative controls, the ratios varied within these limits. Tumor DNA with the known copy number alterations was used in positive control experiments. Reverse-labeling CGH was performed on selected cases (cases 671, 673, and 883), which confirmed the alterations detected by the standard technique (14). All findings were confirmed using a confidence interval of 99%. The cutoff level for high-level amplification was 1.5. Telomeric and heterochromatic areas were discarded from the analysis.

Statistical Analyses. Differences in the frequency of copy number changes between *BRCA1* and sporadic groups were tested by using Fisher's exact test with two-tailed *P*s.

Results

***BRCA1* Mutation-positive Patients.** DNA copy number changes were observed in 13 of the 16 patients (average, 6 changes/tumor; SD, 4.9; Fig. 1*A*). Gains were three times more common than losses. The most common gains were at 2q24–q32, 3q25–q26.3, 7q31, and 8q22–qter, each of which occurred in 8 of the 16 (50%) patients. Chromosomal regions 6p21.1–pter and 11q21 revealed gains in five tumors. High-level amplification (cutoff value, 1.5) was observed at 8q in five cases in which the common subregion narrowed down to 8q23–q24.1, twice at 6p22–p24, and once at 5p, 12p, and 12q13–q21. The most common region of loss was at 8p (6 of 16 cases, 38%), with a common minimum region of 8p22–pter.

***BRCA2* Mutation-positive Patients.** All four cases in this group had DNA copy number changes. Again, gains were more common than losses. Gains were most frequent at 6p21.1–pter and 8q22–qter (three of the four tumors). High-level amplification was found twice at 1q32–qter and 3q26.1 and once at 6q21–q22 and 8q23–qter. The losses affected 8p21–pter and Xq.

Sporadic Cancers. CGH revealed changes in 17 of 20 patients (average, 7.5 changes/tumor; SD, 6.2; Fig. 1*B*). Gains were more frequent than losses, with the gains:losses ratio being 2.3:1. The most common gain was observed at 8q (14 of 20 tumors, 70%), with a common minimum region of 8q23–q24. The other frequent gains were detected at 3q26.1–q26.3 (40%) and 7q32-q33 (35%). High-level amplification was found four times at 8q22–qter, three times at 3q25–q26.1, twice at 1q32 and 12p12, and once at 2q22–q24, 6q13–qter, 12q14–q24.1, 13q32–qter, and 17q21–qter. The most frequent losses were found at 8p22–pter and 17p (both in 5 of the 20 cases, 25%).

Difference at 2q. A significant difference between *BRCA1* mutation-positive tumors and sporadic tumors was found at 2q24–q32, where gains were more common in the *BRCA1* group (57 *versus* 15%; $P = 0.03$; only serous *BRCA1* tumors included; Table 2).

Discussion

Genetic alterations in serous ovarian carcinoma turned out to be complex. In sporadic carcinomas, our findings expand those obtained by allele analysis (15, 16), cytogenetic karyotyping (17), and previous CGH studies (5, 18, 19). It was remarkable that the frequency of gross genetic abnormalities was similar in both the inherited and sporadic carcinomas. Also, qualitatively, the changes were strikingly similar. This is different from breast cancer, in which there are several significant differences between *BRCA1/BRCA2* mutation-positive and sporadic carcinomas (20). Thus, our results suggest that unlike ductal carcinoma of the breast, serous carcinoma of the ovary may progress along a relatively narrow pathway, irrespective of its background. In fact, this may hold true for serous tumors of the extended Müllerian tract in general, because uterine papillary serous carcinomas show a basically similar profile of genetic abnormalities as that now reported for both inherited and sporadic serous ovarian carcinomas (21).

Gains were found in several chromosomal regions in both the inherited and sporadic carcinomas. One way of validating these findings and the value of CGH in mapping relevant oncogenes is to compare the amplicons with the chromosomal localization of oncogenes known to be involved in ovarian carcinoma. Oncogenes and growth factors like *CMYC* (8q24.12–q24.13), *INT2* (11q13), *CMET* (7q31), *VEGFA* (6p21.3), and *VEGFB* (11q13) are all within the most prominently gained regions found in this study, demonstrating the applicability of CGH as a screening method for oncogenic chromosomal regions. The similarity of gains in the inherited and sporadic groups suggests that the genes listed above may be involved in the

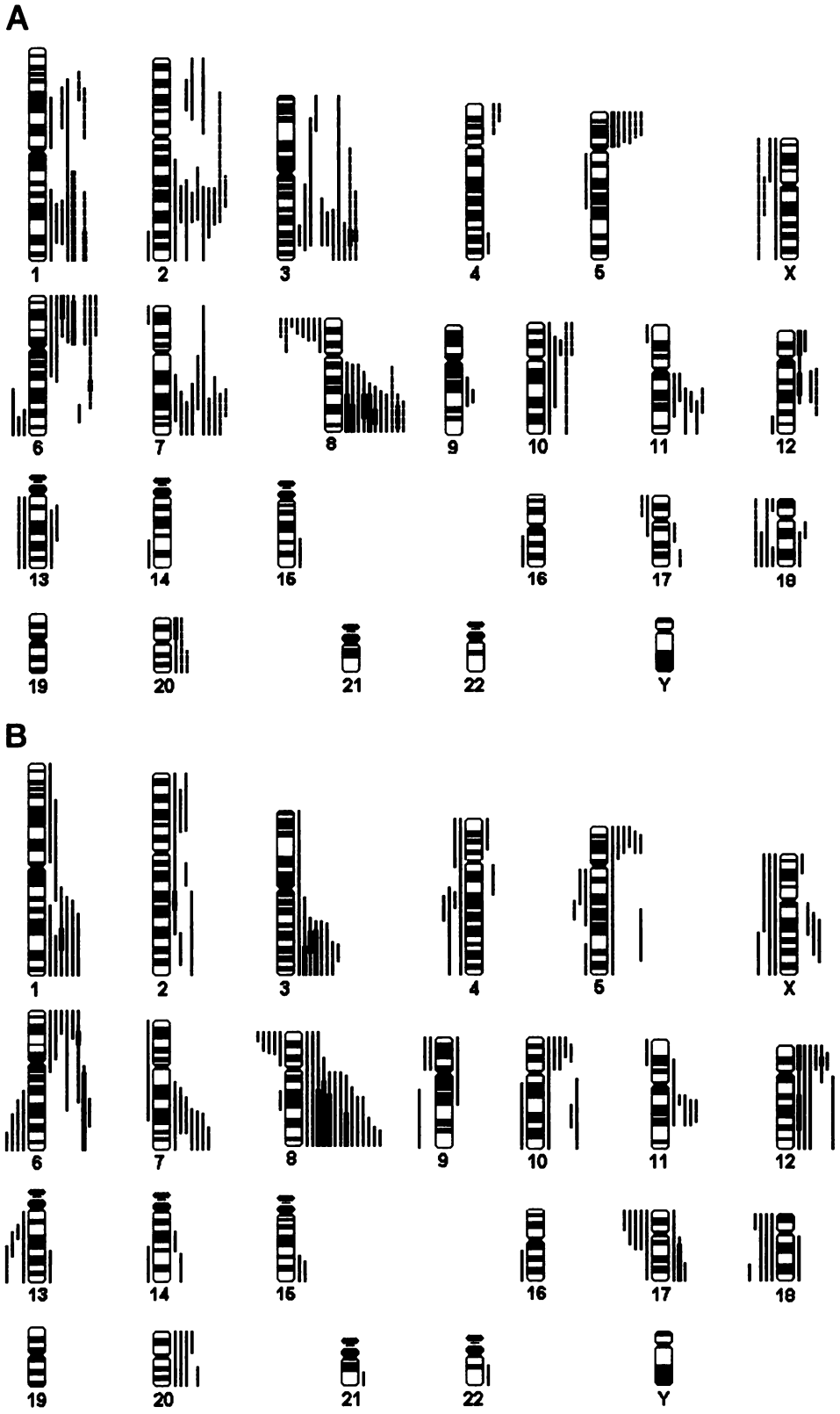

Fig. 1. *A*, DNA copy number changes in 16 *BRCA1*-associated and 4 *BRCA2*-associated ovarian carcinomas evaluated by CGH. Losses are shown on the *left* of the chromosome, and gains are shown on the *right* of the chromosome. High-level amplifications are displayed in *bold*. *BRCA1*-associated carcinomas are marked with a *continuous line*, and *BRCA2*-associated tumors are marked with a *broken line*. *B*, DNA copy number changes in 20 sporadic ovarian carcinomas evaluated by CGH.

inherited carcinomas as well. In addition, we identified new chromosomal regions, such as 3q26, 5p, 6p, 7q (distal to *CMET*), and 8q (proximal to *CMYC*), that are likely to be important in both inherited and sporadic serous ovarian carcinomas.

Region 17q12–q21 harboring *ERBB2*, which is frequently amplified in ovarian carcinomas (22), failed to arise as a candidate region in CGH screening. In the *BRCA1* mutation-associated tumors, we found only one loss at 17q, probably reflecting loss of the wild-type allele of the *BRCA1* gene. The rarity of changes is in keeping with the results of a previous study on *BRCA1* mutation-positive breast cancer in which no losses were detected in the *BRCA1* region by CGH (20). The most likely explanation for these

Table 2 *Summary and comparison of the frequency of particular aberrations by CGH in the BRCA1-associated and sporadic ovarian carcinomas (Fisher's exact test with two-tailed Ps)*

Region	*BRCA1*	Sporadic	Significance of the difference
+1q32–q41	25%	30%	P = 1.00, NS[a]
+2q32	50%	15%	P = 0.03
+3q25–q26.3	50%	40%	P = 0.74, NS
−4q21–q24	0%	20%	P = 0.11, NS
+5p14–p15.2	19%	30%	P = 0.70, NS
+6p22–pter	31%	35%	P = 1.00, NS
−6q25–qter	19%	20%	P = 1.00, NS
+7q	50%	35%	P = 0.50, NS
−8p23	38%	25%	P = 0.48, NS
+8q24.1–qter	50%	70%	P = 0.31, NS
+11q	31%	25%	P = 0.72, NS
+12p11.2–p13	13%	30%	P = 0.26, NS
−17p	6%	25%	P = 0.20, NS
−18p11.2–pter	13%	20%	P = 0.70, NS
−18q22–qter	19%	20%	P = 1.00, NS

[a] NS, not significant.

discordances is the fact that CGH is a whole-genome screening method, and its resolution is not sufficient to detect small amplifications and deletions.

Chromosome 8p was the region of most frequent loss of genetic material in inherited and sporadic tumors. The presence of a tumor suppressor gene here involved in ovarian carcinoma is supported by a frequent loss of heterozygosity at 8p (15, 16). Interestingly, the loci frequently deleted in many other tumors, including carcinoma of the prostate (23), are inside the deletion unit at 8p22–pter identified in this study. Also, a third breast cancer susceptibility locus has been suggested to reside at 8p12–p22 (24). We observed that in inherited tumors, loss at 8p is commonly combined with a partial or total gain at 8q. At least some of these changes could be interpreted as an isochromosome formation.

In the present study, the clustering of gains and losses appeared at the same chromosomal region (3q, 6p, 8q, and 12p and 8p, 13q, 17p, and 18q, respectively) as it did in the two earlier studies (18, 19), with one exception. We did not detect losses at 16q. The explanation for this difference is unclear, but it may be due to the fact that only serous carcinomas were analyzed in our study, whereas other histological subtypes were also included in the previous studies. Compared to the CGH results of *BRCA1/BRCA2* mutation-positive ductal breast cancer (20), the pattern of gains and losses is different in *BRCA1/BRCA2* mutation-positive ovarian cancer. This suggests that there is no universal BRCA mutation-associated pathway of tumor progression.

Our finding that *BRCA1* mutation-positive ovarian cancers show gains at 2q24–q32 more frequently than do sporadic cancers is interesting, because this region contains several genes with potential oncogenic properties. These include nine homeo box genes,[4] a serine-threonine kinase receptor (25), *I-TRAF* (tumor necrosis factor receptor-associated factor; Ref. 26), and the gene for FRZB-1, a secreted antagonist of WNT signaling (27). None of these genes has been directly linked to ovarian carcinoma. Of particular interest is the gene for BARD1 (*BRCA1*-associated RING domain 1), which also localized to the 2q region. BARD1 protein interacts with BRCA1 protein and shares homology with the two most conserved regions of BRCA1 (28). A previous study has suggested that oncogenic mutations in the *BARD1* gene could occur in sporadic breast and ovarian cancers (28). Obviously, our results give an impetus to targeted molecular investigation of the 2q24–q32 region, especially in inherited ovarian carcinomas.

[4] M. Rebhan, V. Chalifa-Caspi, J. Prilusky, and D. Lancet. Gene Cards: Encyclopedia for Genes, Proteins and Diseases. Rehovot, Israel: Weizmann Institute of Science, Bioinformatics Unit and Genome Center, 1998. http://bioinfo.weizmann.ac.il/cards.

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References

1. Boyd, J., and Rubin, S. C. Hereditary ovarian cancer: molecular genetics and clinical implications. Gynecol. Oncol., *64:* 196–206, 1997.
2. Burke, W., Daly, M., Garber, J., Botkin, J., Kahn, M. J., Lynch, P., McTiernan, A., Offit, K., Perlman, J., Petersen, G., Thomson, E., and Varricchio, C. Recommendations for follow-up care of individuals with an inherited predisposition to cancer. II. BRCA1 and BRCA2. Cancer Genetics Studies Consortium. J. Am. Med. Assoc., *277:* 997–1003, 1997.
3. Gayther, S. A., Warren, W., Mazoyer, S., Russell, P. A., Harrington, P. A., Chiano, M., Seal, S., Hamoudi, R., van Rensburg, E. J., Dunning, A. M., Love, R., Evans, G., Easton, D., Clayton, D., Stratton, M. R., and Ponder, B. A. J. Germline mutations of the BRCA1 gene in breast and ovarian cancer families provide evidence for a genotype-phenotype correlation. Nat. Genet., *11:* 428–433, 1995.
4. Gayther, S. A., Mangion, J., Russell, P., Seal, S., Barfoot, R., Ponder, B. A., Stratton, M. R., and Easton, D. Variation of risks of breast and ovarian cancer associated with different germline mutations of the BRCA2 gene. Nat. Genet., *15:* 103–105, 1997.
5. Tapper, J., Butzow, R., Wahlstrom, T., Seppälä, M., and Knuutila, S. Evidence for divergence of DNA copy number changes in serous, mucinous and endometrioid ovarian carcinomas. Br. J. Cancer, *75:* 1782–1787, 1997.
6. Bewtra, C., Watson, P., Conway, T., Read, H. C., and Lynch, H. T. Hereditary ovarian cancer: a clinicopathological study. Int. J. Gynecol. Pathol., *11:* 180–187, 1992.
7. Auranen, A., Grenman, S., and Klemi, P. J. Immunohistochemically detected p53 and HER-2/neu expression and nuclear DNA content in familial epithelial ovarian carcinomas. Cancer (Phila.), *79:* 2147–2153, 1997.
8. Rubin, S. C., Benjamin, I., Behbakht, K., Takahashi, H., Morgan, M. A., LiVolsi, V. A., Berchuck, A., Muto, M. G., Garber, J. E., Weber, B. L., Lynch, H. T., and Boyd, J. Clinical and pathological features of ovarian cancer in women with germ-line mutations of. BRCA1. N. Engl. J. Med., *335:* 1413–1416, 1996.
9. Kallioniemi, A., Kallioniemi, O-P., Sudar, D., Rutovitz, D., Gray, J. W., Waldman, F., and Pinkel, D. Comparative genomic hybridization for molecular cytogenetic analysis of solid tumors. Science (Washington DC), *258:* 818–821, 1992.
10. Vehmanen, P., Friedman, L. S., Eerola, H., Sarantaus, L., Pyrhonen, S., Ponder, B. A., Muhonen, T., and Nevanlinna, H. A low proportion of BRCA2 mutations in Finnish breast cancer families. Am. J. Hum. Genet., *60:* 1050–1058, 1997.
11. Vehmanen, P., Friedman, L. S., Eerola, H., McClure, M., Ward, B., Sarantaus, L., Kainu, T., Syrjakoski, K., Pyrhonen, S., Kallioniemi, O-P., Muhonen, T., Frank, T. S., and Nevanlinna, H. Low proportion of *BRCA1* and *BRCA2* mutations in Finnish breast cancer families: evidence for additional susceptibility genes. Hum. Mol. Genet., *6:* 2309–2315, 1997.
12. El Rifai, W., Larramendy, M. L., Bjorkqvist, A-M., Hemmer, S., and Knuutila, S. Optimization of comparative genomic hybridization using fluorochrome conjugated to dCTP and dUTP nucleotides. Lab. Invest., *77:* 699–700, 1998.
13. Kuukasjarvi, T., Tanner, M., Pennanen, S., Karhu, R., Visakorpi, T., and Isola, J. Optimizing DOP-PCR for universal amplification of small DNA samples in comparative genomic hybridization. Genes Chromosomes Cancer, *18:* 94–101, 1997.
14. Larramendy, M. L., El Rifai, W., and Knuutila, S. Comparison of fluorescein isothiocyanate- and Texas Red-conjugated nucleotides for direct labeling in comparative genomic hybridization. Cytometry, *31:* 174–179, 1998.
15. Cliby, W., Ritland, S., Hartmann, L., Dodson, M., Halling, K. C., Keeney, G., Podratz, K. C., and Jenkins, R. B. Human epithelial ovarian cancer allelotype. Cancer Res., *53:* 2393–2398, 1993.
16. Dodson, M. K., Hartmann, L. C., Cliby, W. A., DeLacey, K. A., Keeney, G. L., Ritland, S. R., Su, J. Q., Podratz, K. C., and Jenkins, R. B. Comparison of loss of heterozygosity patterns in invasive low-grade and high-grade epithelial ovarian carcinomas. Cancer Res., *53:* 4456–4460, 1993.
17. Pejovic, T., Heim, S., Mandahl, N., Baldetorp, B., Elmfors, B., Floderus, U-M., Furgyik, S., Helm, G., Himmelmann, A., Willen, H., and Mitelman, F. Chromosome aberrations in 35 primary ovarian carcinomas. Genes Chromosomes Cancer, *4:* 58–68, 1992.
18. Iwabuchi, H., Sakamoto, M., Sakunaga, H., Ma, Y. Y., Carcangiu, M. L., Pinkel, D., Yang, F. T., and Gray, J. W. Genetic analysis of benign, low-grade, and high-grade ovarian tumors. Cancer Res., *55:* 6172–6180, 1995.
19. Arnold, N., Hägele, L., Walz, L., Schempp, W., Pfisterer, J., Bauknecht, T., and Kiechle, M. Overrepresentation of 3q and 8q material and loss of 18q material are recurrent findings in advanced human ovarian cancer. Genes Chromosomes Cancer, *16:* 46–54, 1996.
20. Tirkkonen, M., Johannsson, O., Agnarsson, B. A., Olsson, H., Ingvarsson, S., Karhu, R., Tanner, M., Isola, J., Barkardottir, R. B., Borg, A., and Kallioniemi, O-P. Distinct somatic genetic changes associated with tumor progression in carriers of BRCA1 and BRCA2 germ-line mutations. Cancer Res., *57:* 1222–1227, 1997.
21. Pere, H., Tapper, J., Wahlstrom, T., Knuutila, S., and Butzow, R. Distinct chromosomal imbalances in uterine serous and endometrioid carcinomas. Cancer Res., *58:* 892–895, 1998.

22. Slamon, D. J., Godolphin, W., Jones, L. A., Holt, J. A., Wong S. G., Keith, D. E., Levin, W. J., Stuart, S. G., Udove, J., Ullrich, A., and Press, M. F. Studies of the HER-2/*neu* proto-oncogene in human breast and ovarian cancer. Science (Washington DC), *244:* 707–712, 1989.
23. Vocke, C. D., Pozzatti, R. O., Bostwick, D. G., Florence, C. D., Jennings, S. B., Strup, S. E., Duray, P. H., Liotta, L. A., Emmert-Buck, M. R., and Linehan, W. M. Analysis of 99 microdissected prostate carcinomas reveals a high frequency of allelic loss on chromosome 8p12–21. Cancer Res., *56:* 2411–2416, 1996.
24. Seitz, S., Rohde, K., Bender, E., Nothnagel, A., Kolble, K., Schlag, P. M., and Scherneck, S. Strong indication for a breast cancer susceptibility gene on chromosome 8p12–p22: linkage analysis in German breast cancer families. Oncogene, *14:* 741–743, 1997.
25. ten Dijke, P., Ichijo, H., Franzen, P., Schulz, P., Saras, J., Toyoshima, H., Heldin, C. H., and Miyazono, K. Activin receptor-like kinases: a novel subclass of cell-surface receptors with predicted serine/threonine kinase activity. Oncogene, *8:* 2879–2887, 1993.
26. Rothe, M., Xiong, J., Shu, H. B., Williamson, K., Goddard, A., and Goeddel, D. V. I-TRAF is a novel TRAF-interacting protein that regulates TRAF-mediated signal transduction. Proc. Natl. Acad. Sci. USA, *93:* 8241–8246, 1996.
27. Leyns, L., Bouwmeester, T., Kim, S. H., Piccolo, S., and De, R. E. Frzb-1 is a secreted antagonist of Wnt signaling expressed in the Spemann organizer. Cell, *88:* 747–756, 1997.
28. Wu, L. C., Wang, Z. W., Tsan, J. T., Spillman, M. A., Phung, A., Xu, X. L., Yang, M. C., Hwang, L. Y., Bowcock, A. M., and Baer, R. Identification of a RING protein that can interact *in vivo* with the BRCA1 gene product. Nat. Genet., *14:* 430–440, 1996.

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