Chromosome 1 Abnormalities in Cervical Carcinoma

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Abnormalities of chromosome 1 have been reported in a number of solid tumors and hematologic malignancies, indicating that this is a frequent event in neoplasia. Here we report our observations on aberrations of chromosome 1 in malignancies of the uterine cervix. Tumor material obtained from 148 patients with invasive carcinoma of the cervix and two cases of carcinoma *in situ* (CIS) was analyzed on direct preparations by G-banding. The results showed abnormalities of chromosome 1 to be one of the most common karyotypic changes, with 95% of the patients showing rearrangements of this chromosome. These changes were never seen as the sole abnormality but were always found in association with other chromosomal aberrations. Numerical rearrangements were present in 54% of the cases, with losses of unaltered chromosome 1 predominating. Consistent marker chromosomes included deletions of chromosome 1 at bands q32, p34, q42, p32, and p22, isochromosomes of both the "p" and "q" arms and translocations, particularly on the long arm. Specific regions on both arms of chromosome 1 (1p11–p13 and 1q21–q32) were preferentially overrepresented in changes involving this chromosome. Certain breakpoints were nonrandomly involved in the structural changes, particularly band 1q32 breaks occurring at this site in 88 instances. The presence of chromosome 1 aberrations in the two cases of CIS suggests that rearrangements of this chromosome are not always a secondary change contributing to the progression of the cancer, but also may represent an early cytogenetic event as in neuroblastoma, some leukemias, and myeloproliferative disorders.

***Cancer* 62:1317–1324, 1988.**

MARKER CHROMOSOMES involving chromosome 1 are a frequent phenomenon in diverse forms of cancer, including the hematologic malignancies. They have been associated more often with later stages of cancer and are postulated to represent a secondary genetic event capable of providing the cells with a proliferative advantage.[1–3] In certain malignancies, however, aberrations of chromosome 1 may represent specific initiating changes such as deletions of 1p in neuroblastomas[4–6] and melanomas,[7,8] and translocations involving chromosome 1 and chromosomes 3, 7, 17, and 19 in leukemias and myelodysplasia.[9–13]

Chromosome 1 aberrations have been observed in preinvasive lesions of the uterine cervix,[14,15] including the carcinoma *in situ* (CIS) stage that precedes stromal invasion, possibly suggesting an initiating role. Few banding analyses on invasive carcinmomas of the uterine cervix have appeared in the literature. Earlier reports[16,17] demonstrated the consistent involvement of chromosome 1 in cervical cancers, either as a relative excess of normal chromosome 1 (*i.e.*, trisomy) or in one or more structural changes. Subsequent studies with banding[18–21] have confirmed nonrandom changes involving this chromosome in cervical neoplasms.

In this report, various cytogenetic changes involving chromosome 1 in two cases of CIS and 148 cases of invasive carcinoma of the uterine cervix are described.

Materials and Methods

Chromosome preparations were made from biopsy material of primary untreated carcinomas of the cervix by a method described previously.[22] In brief, this consisted of disaggregation of the tissue by mincing, colchicine arrest (2 μg/ml) for 30 minutes, hypotonic treatment (0.075 mol/l of KCl) for 30 minutes more, and fixation in methanol and acetic acid (dilution, 3:1). Slides prepared the next day were G-banded by the method of Sumner *et al.*,[23] and karyotypes were expressed according to the standard nomenclature.[24] Although the tumors analyzed contained complex chromosome abnormalities involving almost all of the chromosomes in the complement, only those aberrations that involved all or part of chromosome 1 are considered here. Of the 150 cases, two or more cells were karyotypically assessed in 119 tumors. Considerable

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Supported by the Indian Council of Medical Research, New Delhi, India, vide Grant No. 3/1/1/41(525)/80–CAR–II.

The authors thank the staff of the Department of Gynecology, Kidwai Memorial Institute of Oncology, for the biopsy samples; Mr. M. N. Srinivas for photographic assistance; and Dr. Avery A. Sandberg for helpful comments on the manuscript.

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Accepted for publication February 29, 1988.

TABLE 1. Structural Rearrangements Involving Chromosome 1

Marker no.	Abnormality	No. of cases
Deletions		
M1	del(1)(p11)	22
M2	del(1)(p12)	2
M3	del(1)(p13)	16
M4	del(1)(p21)	4
M5	del(1)(p22)	29
M6	del(1)(p31)	3
M7	del(1)(p32)	32
M8	del(1)(p33)	3
M9	del(1)(p34)	45
M10	del(1)(p35)	2
M11	del(1)(q11)	6
M12	del(1)(q21)	4
M13	del(1)(q23)	4
M14	del(1)(q24)	4
M15	del(1)(q25)	3
M16	del(1)(q31)	2
M17	del(1)(q32)	58
M18	del(1)(q42)	42
M19	del(1)(:p13→q32:)	1
M20	del(1)(:p22→q41:)	2
M21	del(1)(:p32→q32:)	8
M22	del(1)(:p32→q42:)	2
M23	del(1)(:p34→q32:)	3
M24	del(1)(:p34→q42:)	3
M25	del(1)(:p35→q42:)	1
M26	del(1)(:p33→q41:)	1
M27	der(1)(qter→cen::q11→q31:)	2
M28	der(1)(qter→cen::q11→q32:)	1
M29	der(1)(qter→cen::q11→q41:)	2
Inversions		
M30	inv(1)(p11q21)	1
M31	inv(1)(p21q22)	1
M32	inv(1)(p13q21)	1
M33	inv(1)(p22q25)	1
M34	inv(1)(p22q42)	2
M35	inv(1)(p32q21)	1
M36	inv(1)(p32q23)	3
M37	inv(1)(p32q44)	1
M38	inv(1)(p34q32)	4
M39	inv(1)(p34q42)	1
M40	inv(1)(p34q44)	1
M41	inv(1)(p35q42)	1
M42	inv(1)(p36q21)	1
M43	inv(1)(p36q32)	9
M44	inv(1)(p36q42)	2
Insertions		
M45	?dir ins(1)(p13q32q43)	1
M46	?dir ins(1)(q21p11p32)	1
M47	?dir ins(1)(q21p32p35)	1
M48	?inv ins(1)(q21p32p11)	1
Duplications		
M49	dir dup(1)(q11→q21)	1
M50	dir dup(1)(q21→q44)	1
M51	dir dup(1)(q21→q32)	1
M52	dir dup(1)(q11→q42)	1
Isochromosomes		
M53	i(1p)	20
M54	i(1q)	34
Translocations		
M55	t(1;2)(p34;q37)	1
M56	t(1;2)(q21;p13)	1
M57	t(1;3)(p11;p11)	2
M58	t(1;3)(p11;q11)	5
M59	dic(1;3)(p34;q11)	1
M60	t(1;3)(q32;q39)	1
M61	t(1;3)(q44;q11)	1
M62	t(1;4)(q21;p16)	2
M63	t(1;5)(q21;p15)	1
M64	t(1;6)(p11;p11)	1
M65	t(1;10)(p21;q24)	1
M66	t(1;13)(q11;p11)	1
M67	t(1;13)(p11;p11)	1
M68	t(1;14)(p11;q11)	1
M69	t(1;15)(q11;q26)	1
M70	t(1;16)(q25;q24)	1
M71	t(1;17)(p32;q11)	1
M72	t(1;17)(p36;q11)	1
M73	t(1;17)(q42;q11)	
M74	dic(1;18)(q42;p11)	1
M76	t(1;?)(p32;?)	1
M75, M77–M84	t(1;?)(p36;?)	9
M85	? tri(1;?;?)(p22;?;?)	1
M86–M88	t(1;?)(q44;?)	3
M89	dic(1;1)(p32;p32)	1
M90	dic(1;1)(p22;q25)	1
M91	t(1;?)(p34;?)	1

karyotypic diversity was present in almost all of the 119 cases. Although a clonal change was evident by the presence of similar marker chromosomes in more than one cell in all the cases studied, extensive variation in karyotypes, both within and between cases, was common. In cases characterized by a number of marker chromosomes, they were observed in all of the cells or in only a portion of the cells, the remaining containing a combination of the markers. In 17 cases, only one cell could be analyzed in detail. In three cases, partial karyotypes were obtained. In the remaining 11 cases, only chromosome counts were possible.

Results

Abnormalities of chromosome 1, both numerical and structural, represented the most frequent karyotypic change among the cervical carcinomas analyzed. All of the chromosomes in the set were involved in rearrangements to varying extents. In addition to chromosome 1, those showing nonrandom involvement in marker formation were chromosomes 6, 11, 3, 5, and 17 (in order of frequency). Although abnormalities of chromosome 10 were uncommon, a marker involving this chromosome, del(10)(q24), along with del(1)(q32) constituted the

two most common markers in the series. Numerical rearrangements involved nonrandom losses of chromosomes 1, 2, and 11, and specific gains of chromosomes 5, 7, 9, 12, 16, 18, 19, 20, and X. Only five of 139 cases in which karyotypic data were available did not show either a numerical or structural change of chromosome 1. Two other cases had no structural aberrations of chromosome 1, but were monosomic for chromosome 1.

Numerical changes (loss or gain of an unaltered chromosome) were present in 54% of the cases, with losses predominating. In most instances, the resulting monosomy or nullisomy of chromosome 1 with respect to the normal unaltered chromosome 1 was partial due to its involvement in structural rearrangements. Up to 11 different markers of chromosome 1 were present in some cases.

The structural changes included deletions (resulting in the formation of 307 markers), isochromosome formations (20 of the p arm and 34 of the q arm), 42 translocations, 30 inversions, four cases of duplication, and four tumors with insertions. Ninety one different markers were formed by the above mechanisms (Table 1). Sixty percent of these marker chromosomes (55 of 91) were apparently unique (*i.e.*, present in one case only), whereas a number of the others were nonrandom changes.

Deletions

All were terminal deletions and represented the most frequent type of aberration. The 307 deletions involved either the short or long arms or both along their entire length. The most consistent marker was a deletion of the long arm at band q32 in 58 cases (41%) (Fig. 1, part g). The other specific marker of the long arm was del(1)(q42) in 42 cases (Fig. 1, part h). On the short arm, deletions nonrandomly occurred in bands p34 (n = 45), p32 (n = 32), p22 (n = 29), p11 (n = 22), and p13 (n = 16) (Figs. 1, parts a through e). The other bands were deleted in lower frequencies. Deletions involving both arms simultaneously were present in 26 cases, the most common being del(1)(:p32→q32:) in eight cases (Fig. 1, part i).

Inversions

Fifteen types of pericentric inversions were recorded in 30 cases. The most common was an inversion involving bands p36 and q32 (inv(1)(p36q32)) in nine cases (Fig. 1, part j). The origin of four markers (M45 to M48; Table 1) was tentatively identified as being due to insertions within chromosome 1 itself.

Duplications

Duplications were present in five cases and involved variable segments of the long arm (Table 1).

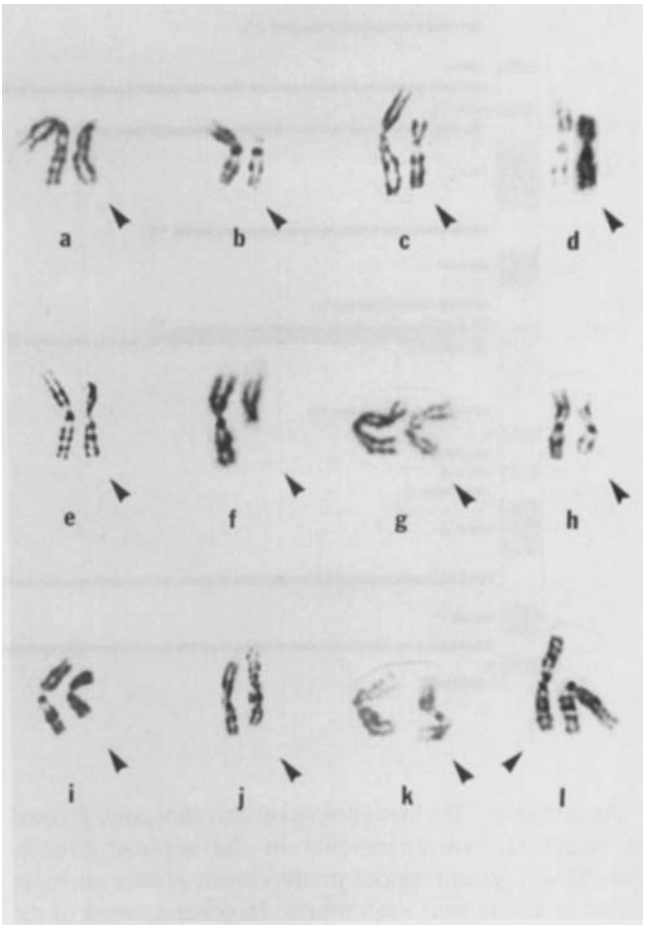

FIG. 1. G-banded partial karyotypes of consistent marker chromosomes involving chromosome 1. Arrows indicate the rearranged chromosomes. (a) del(1)(p11); (b) del(1)(p13); (c) del(1)(p22); (d) del(1)(p32); (e) del(1)(p34); (f) del(1)(q11); (g) del(1)(q32); (h) del(1)(q42); (i) del(1)(:p32→q32:); (j) inv(1)(p36q32); (k) i(1p); and (l) i(1q).

Isochromosomes

Short arm isochromosomes, i(1p) (Fig. 1, part k), were present in 20 cases. Long arm isochromosomes, i(1q) (Fig. 1, part l), were present in 34 cases.

Translocations

Forty-two cases showed translocations of chromosome 1 (Table 1). The participating chromosomes were chromosomes 2, 3, 4, 5, 6, 10, 13, 14, 15, 16, 17, and 18 with variable breakpoints. The most common translocation partner was chromosome 3. Translocations between chromosomes 1 and 3 occurred in ten cases, with breaks at 1p11 in seven cases and at 3q11 in six cases. Translocations of unidentified material were present on the short arm in 11 cases and on the long arm in three cases. Dicentric chromosomes formed by translocations between chromosomes 1 were observed in two cases.

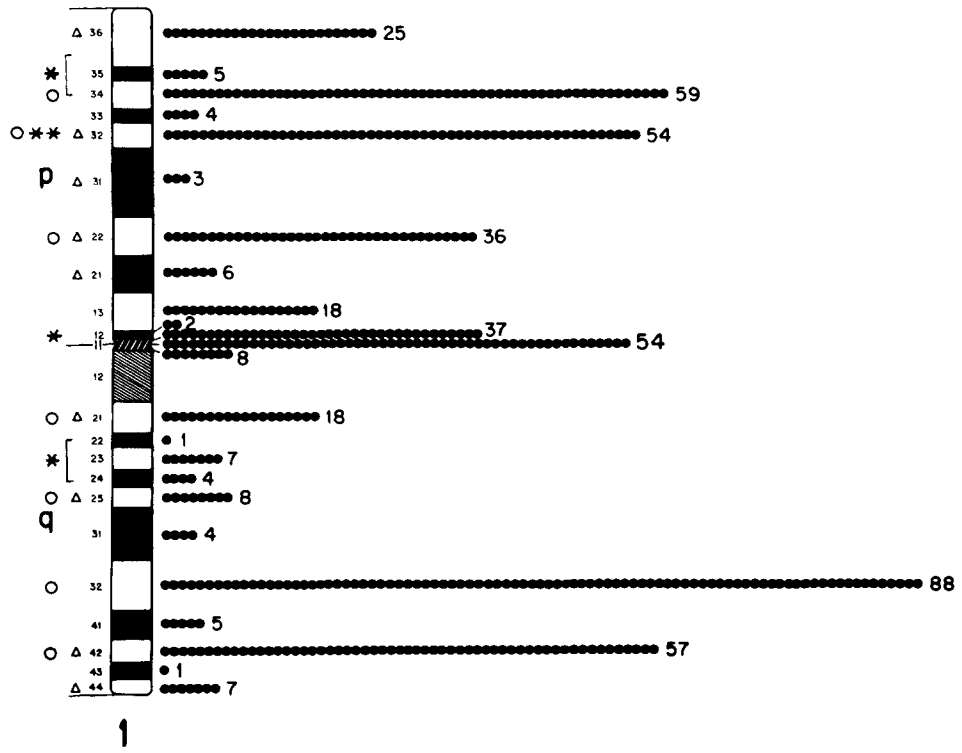

FIG. 2. Schematic illustration of the sites and frequency of breaks due to rearrangements of chromosome 1. The location of the five oncogenes (*), the nine fragile sites (△), and the seven nonrandom sites of breakage induced by HSV (○) also are indicated.

An analysis of the breakpoints on chromosomes formed by structural rearrangements in the cervical cancers showed that certain regions on the chromosomes are more prone to aberrations than others. In general, most of the breakpoints listed could be grouped into the following three areas: (1) 1p32–p34 with 117 breaks; (2) 1p11–p13 with 57 breaks; and (3) 1q32–q34 with 150 breakpoints. A schematic illustration of breakpoints involved in chromosome 1 aberrations is depicted in Figure 2. A high degree of specificity was apparent for a number of bands along both the long and short arms. Band 1q32 was the most frequently involved breakpoint in deletions, inversions, translocations, and duplications. Breaks occurred at this site 88 times. Fifty-nine breaks at band 1p34, 57 breaks at band 1q42, and 54 breaks at band 1p32 occurred predominantly due to deletions. Thirty-seven breaks at 1p11, 36 breaks at 1p22, and 25 breaks at 1p36 were a consequence of deletions, inversions, and translocations. Smaller clusters of breaks were observed for bands 1p13 and 1q21 (18 times each), 1q11 and 1q25 (eight times each), and 1q23 and 1q44 (seven times each). Of the 119 breaks in the centromeric region (1p12–1q21), 54 were involved in the formation of isochromosomes.

Specific regions of chromosome 1, on both the short arm and long arm, were present consistently in the marker chromosomes formed. Region 1p11–1p13 was retained in 84% of the rearrangements and region 1q21–1q32 in 94% of the changes. This is illustrated in Figure 3. Each vertical line of Figure 3 represents the abnormalities of chromosome 1 (markers M1 to M91; Table 1). The inversions and insertions are represented as lines running the length of the chromosome because no loss of chromosome 1 material occurred in these abnormalities, and in some cases, they were present in addition to the normal chromosomes 1 or other aberrations of chromosome 1. The dashed horizontal lines enclose the specific segments.

Discussion

Chromosome 1 is the chromosome most frequently involved in human cancer and leukemia. Its association with the malignant process has been stressed repeatedly. Aberrations of this chromosome have been reported in a variety of malignancies, including lung, bladder, breast, testes, prostate, kidney, colorectum, neuroblastomas, malignant melanomas, soft tissue sarcomas, gynecologic malignancies, and those of hematologic origin.[25] From our data and the published literature, numerical and structural changes of chromosome 1 constitute the most common karyotypic alteration in carcinoma of the cervix uterus. Before the introduction of banding, abnormalities of chromosome 1 were reported as isochromosomes, terminal deletions, and translocations of either or both arms.[16,17] With banding, Atkin and Baker reported consistent involvement of chromosome 1 in structural and numerical changes in six of nine near-diploid tumors[19]

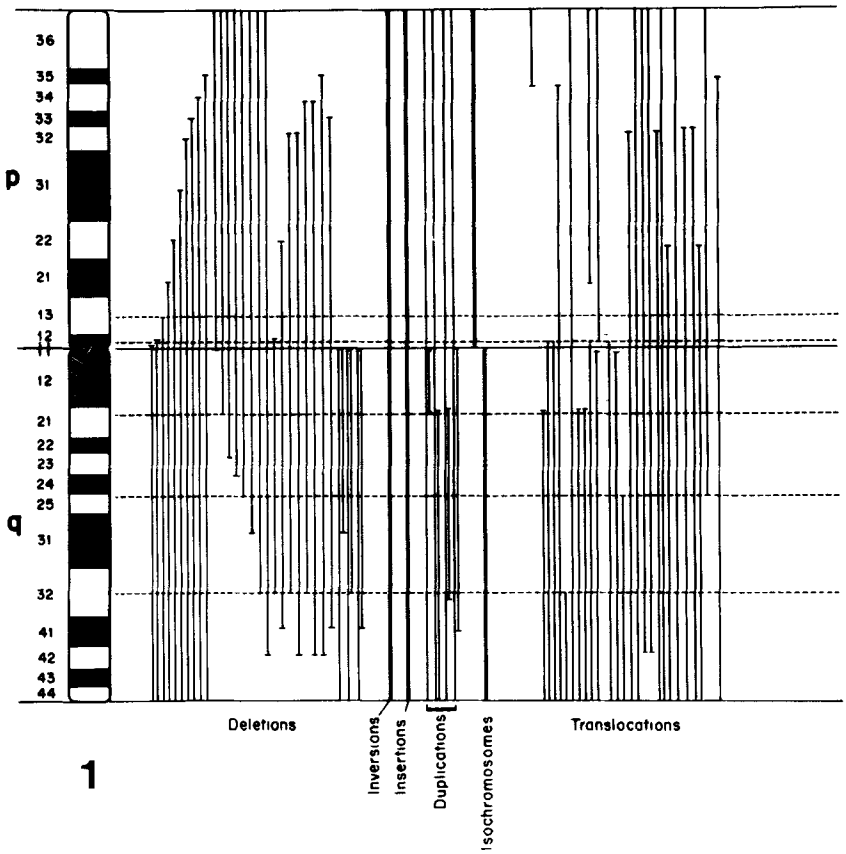

FIG. 3. Diagrammatic representation of the various abnormalities (vertical lines) and the specific regions consistently retained in structural aberrations of chromosome 1 (enclosed by the dashed horizontal lines). Region 1p11–1p13 was involved in 84% of the rearrangements and region 1q21–1q32 in 94%.

and seven of ten in the triploid–tetraploid range.[20] Isochromosome of the long arm, deletions of the short arm, and translocations with various chromosomes were the changes observed. In their analysis, van der Riet-Fox *et al.*[18] observed structural aberrations of chromosome 1 in two of six cervical carcinomas studied. In both instances, duplication of the long arm (region q21–q32) was noticed. One other case had a translocation between chromosomes 1 and 5,[21] with the break on chromosome 1 at q25.

In this series, deletions of chromosome 1 at various bands constituted the most common markers. The most frequent marker, del(1)(q32), present in 58 cases (41%), also has been reported in both hematologic and solid malignancies.[26] The other specific marker on the long arm, del(1)(q42), found in 42 cases, was seen in primary and metastatic cancers of other sites.[18,27,28] Markers of the short arm, del(1)(p34), del(1)(p32), del(1)(p22), and del(1)(p11), were common to neuroblastomas, lung cancers, lymphomas, and leukemias.[25,26,29,30] The del(1)(p13) marker present in 16 cases was reported by Kakati *et al.*[31] in cells obtained from the pleural effusion of a breast cancer and the ascitic fluid of a patient with ovarian carcinoma.

Translocations to other chromosomes appear to have occurred at random, except to chromosome 3 in ten cases. In cervical cancer, translocations have been reported between chromosome 1 and chromosomes 3, 4, 11 (two cases each), 17, and 19 (one case each),[19,20] and 5.[21] The other translocations mentioned as 1p+ or 1q+[16,17] probably represent translocations of unidentified material onto the arms.

Isochromosomes of both the long and short arms were observed commonly in 34 and 20 cases, respectively. Both markers have been reported in cervical cancer, isochromosomes of the long arm being more frequent.[16,17,19,20] In other tumors, short arm isochromosomes are relatively rare. In contrast, i(1q) is a common nonrandom karyotypic change in solid tumors[32] and also has been observed in leukemia.[29] Among solid tumors, i(1q) was common to tumors of the breast,[32] colon,[32–34] ovary,[31,35–37] bladder,[38,39] and melanomas.[40] The other markers also were observed in other malignancies, but in lower frequencies.[26]

In a number of cases, more than one chromosome 1 marker was present. Up to 11 markers were observed in some cases. In 21 cases, at least one of the markers was present in duplicate. Interestingly, 15 of these cases were hyperploid, indicating that in these cases chromosomal doubling had probably taken place after the tumor stemline evolved with subsequent loss of some of the other duplicated markers. In a majority of the tumors, however, the marker chromosomes seem to have appeared after the

neoplastic stemline had undergone polyploidization. The coexistence of two normal chromosomes 1 with the marker chromosomes in some cases also suggests that the markers were formed after chromosomal doubling or cell replication in late S-phase or G2-phase. Selective endoreduplication after establishment of the clone also may account for multiple copies of the same marker.

The specificity with which certain bands and regions on chromosome 1 were involved in the structural aberrations suggests that these sites contain genes whose loss or amplification is of importance in tumor development and/or maintenance. Although the number of published cases of cervical carcinoma is small,[19–21] taken together, the bands affected more than once are p32 in two cases and q21 (n = 7), q12 (n = 3), q32 (n = 3), q25 (n = 2), q31 (n = 2) on the long arm, and the centromeric region (n = 2). All of these bands were the site of nonrandom breaks in our cases (Fig. 2). In addition, they correlate well with the survey of breakpoints on chromosome 1 by Brito-Babapulle and Atkin[30] in various other malignancies in which the centromeric region was primarily affected with smaller clusters of breaks at bands 1q31–32, 1p22–p32, and p36. This again stresses the instability of particular regions on chromosome 1 and their predisposition to rearrangement.

Certain segments on the chromosome were retained or present in excess, and this may vary for different neoplasms. For instance, Rowley[41] observed consistent duplication of bands 1q25–q32 in a series of patients with various hematologic disorders. However, Gahrton *et al.*,[42] summarizing abnormalities of chromosome 1 in myeloproliferative disorders, noticed duplication of region 1q23–q25. Kakati *et al.*,[40] and Kovacs[32] each reported over-representation of bands 1q21–q25 in various solid tumors. In our analysis, we observed that region 1q21–q32 was present consistently in 94% of the structural rearrangements involving chromosome 1 (Fig. 3), either as short arm deletions, translocations, or isochromosomes. In addition, a specific region on the short arm (1p11–p13 in 84%) was present nonrandomly. The delineation of these critical regions and bands specifically rearranged may enhance the possibility of localizing oncogenes associated with cervical cancer.

The nonrandomness of chromosome 1 involvement in human cervical carcinoma is of special importance because five oncogenes have been mapped to this chromosome. The oncogenes B-Lym-1 and L-*myc* have been localized to band 1p32,[43,44] N-*ras* has been assigned to band 1p11–p12,[45] c-*src* to 1p34–p36,[46] and c-*ski* to 1q22–q24.[47] Nine fragile sites also have been located on chromosome 1 (1p36, 1p32, 1p31.2, 1p22, 1p21.2, 1q21.3, 1q25.1, 1q42, and 1q44.1).[48] In addition, genes for nucleic acid synthesis are localized on 1q.[49] All of the above oncogene sites and fragile sites are located at bands or regions frequently involved in the aberrations (Fig. 2). However, whether or not these oncogenes have a role in the transformation and progression of cervical carcinoma remains to be determined. A correlative study of oncogene activity at the molecular level might help to verify the role of nonrandom structural chromosome changes in neoplasia.

Much evidence has accumulated for an association between herpes simplex virus (HSV) and carcinoma of the cervix.[50–54] HSV have been known to induce chromosome damage.[55,56] A study by Mincheva *et al.*,[57] on the effects of HSV strains on human fibroblast and lymphocyte chromosomes by banding showed that the most frequent aberrations were localized in bands p32, p34, q21, and q32 of chromosome 1 and band q21 of chromosome 3. This is of interest because all four bands on chromosome 1 represent sites specifically altered in structural aberrations, particularly band 1q32 that was involved in 88 rearrangements. A subsequent report by the same authors[58] showed additional damage at bands 1p22, 1q25, and 1q42 by a temperature-sensitive mutant. These bands are again nonrandom sites of breakage. Studies on the effect of adenovirus 12 on cultured human cells led to recognition of the same bands 1p32, 1p36, 1q42, and 1q12 as sites of chromosome damage.[59] The preferential damage of these sites suggest that these areas are susceptible to aberration or that they are of etiologic significance.

To summarize, cancer is a multistep process and cancer progression is a complex secondary phenomenon that may involve a multitude of genes located in different chromosomes.[60] Cytogenetically, this may manifest as increased chromosomal heterogeneity, and although these secondary changes may be extensive, the involvement of certain chromosomes or segments of chromosomes may be nonrandom. The fact that chromosome 1 is reported to be affected in a variety of tumors suggests that chromosome 1 changes may play a role in the evolution of all types of malignancy[25] by conferring the tumor with a proliferative advantage, aiding in the maintenance of the tumor, or contributing to its resistance to therapy. In our study, the superimposition of other chromosomal alterations in all of the cases makes it difficult to ascertain whether they represent the initial cytogenetic event. The presence of chromosome 1 aberrations in early malignancy or premalignant lesions as in cervical cancers,[14,15] however, suggests that this might constitute an initiating event with maintenance of the premalignant state and subsequent progression to the invasive form of the cancer. Analysis of more cases of CIS with banding may clarify the role of chromosomes in early malignancy, as may also the blending of results obtained with molecular biologic techniques and cytogenetic methods. The use of DNA probes and restriction enzymes for gene mapping may

soon provide more information to define the precise contribution of specific chromosome abnormalities to oncogenesis and tumor growth.[61]

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