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Loss of heterozygosity at chromosome 1p in different solid human tumours: association with survival

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Summary The distal half of chromosome 1p was analysed with 15 polymorphic microsatellite markers in 683 human solid tumours at different locations. Loss of heterozygosity (LOH) was observed at least at one site in 369 cases or 54% of the tumours. LOHs detected ranged from 30–64%, depending on tumour location. The major results regarding LOH at different tumour locations were as follows: stomach, 20/38 (53%); colon and rectum, 60/109 (55%); lung, 38/63 (60%); breast, 145/238 (61%); endometrium, 18/25 (72%); ovary, 17/31 (55%); testis, 11/30 (37%); kidney, 22/73 (30%); thyroid, 4/14 (29%); and sarcomas, 9/14 (64%). High percentages of LOH were seen in the 1p36.3, 1p36.1, 1p35–p34.3, 1p32 and 1p31 regions, suggesting the presence of tumour-suppressor genes. All these regions on chromosome 1p show high LOH in more than one tumour type. However, distinct patterns of LOH were detected at different tumour locations. There was a significant separation of survival curves, with and without LOH at chromosome 1p, in the breast cancer patients. Multivariate analysis showed that LOH at 1p in breast tumours is a better indicator for prognosis than the other variables tested in our model, including nodal metastasis.

Keywords: cancer; chromosome 1p; loss of heterozygosity; survival statistics; tumour-suppressor gene

The majority of invasive human solid tumours are considered to be sporadic. Accumulation of multiple genetic alterations play a major part in tumorigenesis of these tumours. Mutations cause some genes (proto-oncogenes) to gain function while other genes [tumour-suppressor genes (TSG)] sustain loss of function (for review see Haber and Harlow, 1997). The localization of these genes to specific chromosome regions is currently a major area of study in cancer research. Loss or inactivation of TSG has been shown to be a major feature in the genesis of the solid cancers examined so far (Cavenee and White, 1995). As a full inactivation of a gene usually requires the silencing of both its alleles, the first inactivating mutation is, by inference, recessive. This first mutation can be somatic or passed through the germ line. The second mutation is somatic and proceeds through a chromosomal mechanism, which leads to loss of the wild-type allele (loss of heterozygosity) or replacement of the wild type allele by the mutant allele. The result is a complete absence of the normal protein product.

Loss of heterozygosity (LOH) on the short arm of chromosome 1 in solid human tumours has been reported in the following cancer types: breast cancer, neuroblastoma, mesothelioma, melanoma, testis cancer, liver cancer, stomach cancer, phaeochromocytoma, thyroid cancer, meningioma, colorectal cancer, endometrial cancer and Wilms tumour (Mathew et al, 1987; Dracopoli et al, 1989; Chen et al, 1992; Bardi et al, 1993; Taguchi et al, 1993; Bello et al, 1994; Bieche et al, 1994; Mathew et al, 1994; Stock et al, 1994; Yeh et al, 1994; Caron et al, 1995; Kuroki et al, 1995; Munn et al 1995; White et al, 1995; Di Vinci et al, 1996; Ezaki et al, 1996; Ragnarsson et al, 1996; Ogunbiyi et al, 1997; Vargas et al, 1997; Arlt et al, 1996; Steenman et al, 1997). All of these studies strongly indicate that TSGs may be located on the short arm of chromosome 1. A number of studies have shown a significant association between LOH at 1p and prognostic factors. The distal half of chromosome 1p from 1p31.1 to 1p36.3 is among the regions on 1p that have shown frequent LOH. At least two studies have shown an association between LOH at 1p and amplification of the N-*myc* proto-oncogene in breast tumours and neuroblastoma (Bieche et al, 1994; Caron et al, 1995). There seems to be an association between LOH at 1p and poor prognosis in patients with neuroblastoma (Caron et al, 1996), breast cancer (Ragnarsson et al, 1996) and colon cancer (Ogunbiyi et al, 1997). LOH at 1p was shown to be an early event in the carcinogenesis of breast cancer (Munn et al, 1995), liver cancer (Kuroki et al, 1995) and colorectal cancer (Di Vinci et al, 1996). One study indicates that LOH at 1p is a late event in melanomas (Dracopoli et al, 1989). Introduction of chromosome 1p36 into colon cancer cell line suppresses tumorigenic behaviour (Tanaka et al, 1993).

In this study we made an attempt to discover whether LOH patterns were similar in different types of human solid cancers. We screened 682 human solid tumours from 20 different locations for loss of heterozygosity at chromosome 1p, using 15 highly polymorphic microsatellite markers focusing on 1p31-pter. Furthermore, we tested whether there was an association between LOH at 1p and overall patient survival and clinico-pathological variables.

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MATERIALS AND METHODS

Patients and tumour material

Fresh tumour samples from 683 primary solid tumours and normal tissue samples from the same patients were obtained on the day of surgery, immediately frozen and stored at – 70°C. The tumours were from the following locations (number of tumours investigated in parentheses): breast (238); colon and rectum (109); kidney (73); lung (63); stomach (38); ovary (31); testis (30); endometrium (25); thyroid (14); sarcoma (14); lymphoma (8);

Table 1 Information about the markers used in this study

Marker	Distance from D1S243 (cM)[a]	Location	Informative samples	Tumours with LOH	% LOH
D1S243	–	1p36.3	376	70	20
D1S468	6.4	1p36.3	340	86	25
D1S214	16.8	1p36.3	396	84	21
D1S228	33.2	1p36.1	333	65	20
D1S507	39.1	1p36.1	387	74	19
D1S436	43.6	1p36.1	258	59	23
D1S233	65.6	1p35	191	43	23
D1S201	66.7	1p35	246	53	22
D1S496	69.4	1p34.3	143	44	31
D1S209	98.8	1p32–p33	471	74	16
D1S216	110.1	1p32–p33	342	58	17
D1S207	120.5	1p32–p33	513	103	20
D1S488	121.0	1p32–p33	420	116	28
D1S167	128.4	1p31	426	104	24
D1S435	131.8	1p31	465	127	27

[a]The markers have been mapped by Genethon from D1S243.

Table 2 Multivariate analysis [proportional-hazard (Cox) regression] of survival in **A** 238 breast cancer patients and **B** 109 colorectal cancer patients

Parameter	Univariate *P*-value	Multivariate *P*-value	RR[a] 95% CI
A			
LOH at 1p	< 0.001	< 0.001	2.7 (1.5–4.9)
Axillary nodal involvement	0.024	0.015	1.8 (1.1–3.0)
Tumour size[b]	< 0.001	0.381	1.3 (0.73–2.3)
S-phase fraction[c]	0.020	0.071	1.6 (0.96–2.7)
Progesterone receptor[d]	0.040	0.371	1.3 (0.76–2.1)
B			
LOH at 1p	0.089	0.055	1.9 (0.99–3.6)
Dukes grade[e]	0.024	0.017	2.2 (1.2–4.4)
Differentiation[f]	0.348	0.287	1.5 (0.70–3.4)

[a]RR = relative risk of dying in the multivariate analysis. [b]Tumour size > 2 cm. [c]S-phase fraction > 7%. [d]Progesterone receptor < 25 fmol mg^{-1} protein. [e]Dukes grade C and D. [f]Differentiation grade III.

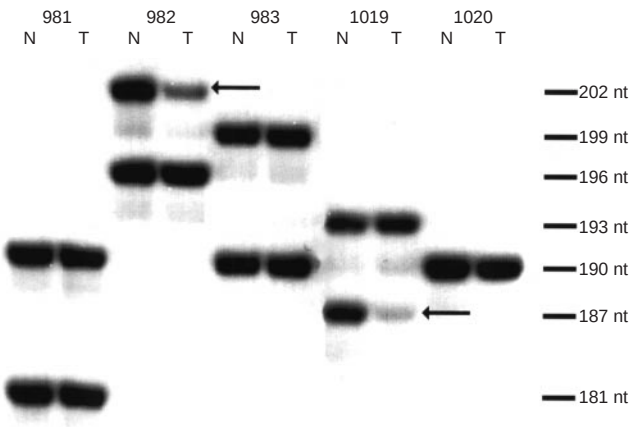

Figure 1 The picture demonstrates a trinucleotide repeat polymorphism in five matched normal (N) and tumour (T) tissues from breast cancer patients. The microsatellite marker D1S488 was used in PCR analysis and the amplified products separated by electrophoresis in a 6.5% polyacrylamide 8 *M* urea denaturing gel. Case numbers are shown at the top. Numbers to the right indicate the size (in nucleotides) of the PCR product. Deletion can be seen in tumours 982 and 1019. The fact that there is not a complete loss of allele in these tumours is most probably due to contamination from normal DNA in the tumour sample. The tumours 981 and 983 have normal heterozygous allele patterns and patient sample 1020 is a homozygote

oesophagus (6); liver (6); mouth (5); brain (5); pancreas (4); prostate (3); skin (3); adrenal gland (2); and unknown origin (6). In the case of the breast cancer patients, peripheral blood leukocytes were the source of normal DNA. Breast tumours were collected from the year 1987 to 1994 but other solid tumours from 1991 to 1997. All information about the tumours, e.g. size, type, age at diagnosis, histology and node status, was recorded at the Department of Pathology, University Hospital of Iceland.

DNA extraction and analysis

Tumour and normal DNA was extracted from the tissue samples with proteinase K using a method developed for paraffin-embedded tissue (Smith et al, 1992). In the case of the breast samples, normal DNA was extracted from peripheral blood leukocytes by a salting-out method (Miller et al, 1988) and tumour DNA was extracted according to standard protocols. Paired blood and tumour DNA was subjected to PCR analysis. DynaZyme™ polymerase (from Finnzymes Oy, Espoo, Finland) was used in the buffer solution provided by the manufacturer. Samples were subjected to 35 cycles of amplification, consisting of 30 s at 94°C, 40 s at 55°C and 30 s at 72°C, followed by 10 min at 72°C. The markers used (Table 1) were obtained from Research Genetics (Huntsville, AL, USA). Primers were elongated by terminal-transferase in 40 mM K-HEPES/1 mM $CoCl_2$ buffer at pH 7.2 and 37°C over night. PCR products were separated on 6.5% polyacrylamide 8 M urea sequencing gels and transferred to a Hybond-N^+ nylon film (Amersham, Aylesbury, UK). They were then hybridized for at least 2 h at 42°C with the elongated primers, covalently labelled with peroxidase (ECL kit, Amersham, Aylesbury, UK). The membranes were washed once in 3 × SSC/0.1% SDS at 39–42°C and then twice in 0.2 × SSC at 39–42°C. After washing, the membranes were bathed in a detection reagent containing H_2O_2, luminol and an enhancer (ECL kit, Amersham, Aylesbury, UK) for 1 min at room temperature and signals were detected on DUPONT Cronex-4 film. Any absence or significant decrease (more than 50%) in the intensity of one allele relative to the other was considered LOH (Figure 1).

Statistical analysis

A chi-squared test was used to assess the relationship between LOH at 1p and prognostic variables. In the breast tumours LOH at 1p was compared with node status, tumour size, histological type, age of diagnosis, steroid receptor content, S-phase fraction and tumour ploidy. In the other tumours LOH at 1p was compared with node status, tumour size and tumour differentiation. Survival curves were calculated according to the method of Kaplan and Meier (Kaplan and Meier, 1958). Tests of difference between curves were made with the log-rank test for censored survival data (Mantel, 1960). Multivariate analysis was performed with Cox's partially nonparametric regression model (Cox, 1972). The Survival Tools for Statview Package (Abacus Concepts, Inc., Berkeley, CA, USA) was used for the statistical analysis.

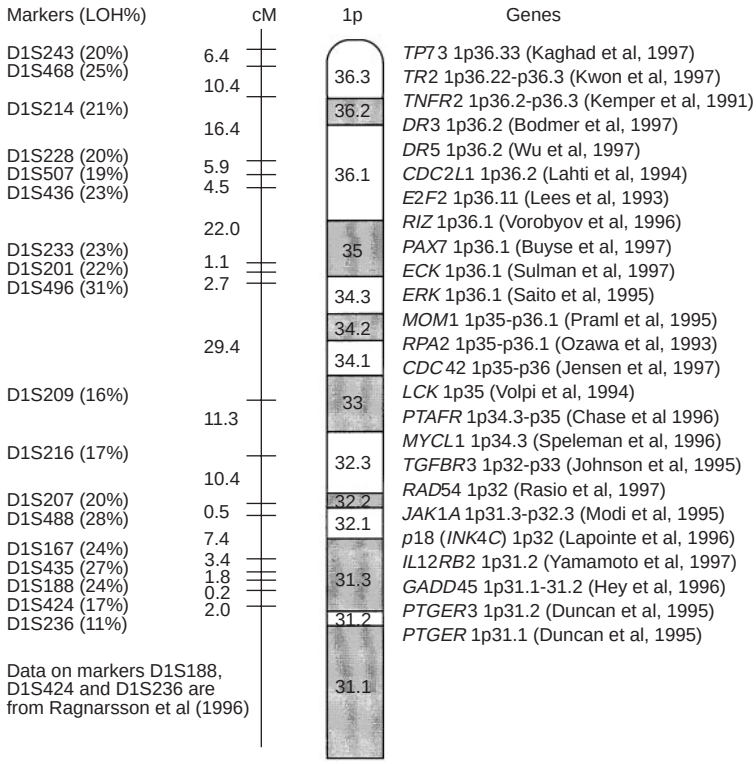

Figure 2 Information about individual markers used in the study, their localization and percentage of LOH in tumour samples tested. The information for markers D1S188, D1S424, and D1S236 is from our earlier work with breast cases. There is also information about possible TSG and their location on chromosome 1p

RESULTS

Loss of heterozygosity at chromosome 1p

Fifteen markers were used for the analysis of microsatellite polymorphism at the distal half of chromosome 1p in 683 primary tumours. Representative results are shown in Figure 1. LOH with at least one marker was detected in 369 (54%) while 46 tumours showed LOH at all informative markers, suggesting complete deletion of this region on chromosome 1p (132 cM). Figure 2 shows LOH at different markers for all tumour samples tested, location of the markers and possible TSGs. There was a difference in LOH frequency between tumours of different locations. The types where LOH was detected in over 50% of the tumours were: endometrium, 18/25 (72%); sarcoma, 9/14 (64%); breast, 146/238 (61%); lung, 38/63 (60%); colon and rectum, 60/109 (55%); ovary, 17/31 (55%); and stomach, 20/38 (53%). The LOH frequency detected in thyroid, kidney and testis tumours was lower, i.e. 4/14 (29%), 22/73 (30%), and 11/30 (37%) respectively. There were less than 10 samples of each of the following tumour types, so the LOH frequency is of little reliability: mouth (2/5); oesophagus (2/6); liver (3/6); pancreas (2/4); prostate (2/3); melanoma (3/3); brain (2/5); phaeochromocytoma (1/1); adrenocortical cancer (1/1); lymphoma (5/8); and unknown origin (2/6).

Figure 3 shows the frequency of LOH detected in 10 different solid tumour locations, where the highest number of samples was available. The pattern of LOH is similar but several differences can be detected. Four peaks of LOH are detected with markers D1S468, D1S507, D1S488 and D1S435 in stomach tumours (Figure 3A). The two latter markers also show elevated LOH in tumours of other tissues, e.g. colorectum, lung and breast, as well as in sarcomas (Figure 3B, C, J, I). Furthermore, the D1S488 marker shows the highest detected LOH for an individual marker in this study in sarcomas at 63% (Figure 3I). Markers D1S243 and D1S436 also show high LOH in sarcoma, 50% and 60%, respectively (Figure 3I). Interestingly, the highest detected LOH in ovarian cancer is also by the D1S436 marker (Figure 3E). The D1S468 marker also has a high LOH in endometrial cancer, together with an elevation of LOH at markers D1S201 and D1S167 (Figure 3D). There is an interesting difference in the LOH pattern of markers D1S488, D1S167 and D1S435 in endometrial cancer compared with most of the other tumours. Low frequency was detected with all markers in testis, renal, and thyroid cancer, with the exception of an elevation of LOH detected by marker D1S216 in thyroid cancer (Figure 3F, G, H). The pattern of microdeletions in breast and colorectal tumours is consistent with the smallest region of overlap (SRO) in five regions: 1p36.3, 1p36.1, 1p35, 1p32 and 1p31 (Figure 4). A low number of microdeletions and the complex pattern of LOH in lung tumours makes mapping of SRO difficult. A complex pattern of LOH and loss of all markers analysed is more frequently detected in lung and colorectal tumours than tumours of breast and kidney. The fraction of complete loss of chromosome 1p31-pter (all informative markers with LOH) was as following: testis, 0/30 (0%); breast, 6/238 (2.5%); kidney, 3/73 (4.1%); stomach, 2/38 (5.3%); thyroid, 1/14 (7.1%); colon/rectum, 14/109 (13%); lung, 9/63 (14%); ovaries, 5/31 (16%); endometrium, 5/25 (20%); and sarcoma, 3/14 (21%). The mapping of the renal tumour samples indicates two SROs in the 1p36.3–p36.1 region, distinct from the

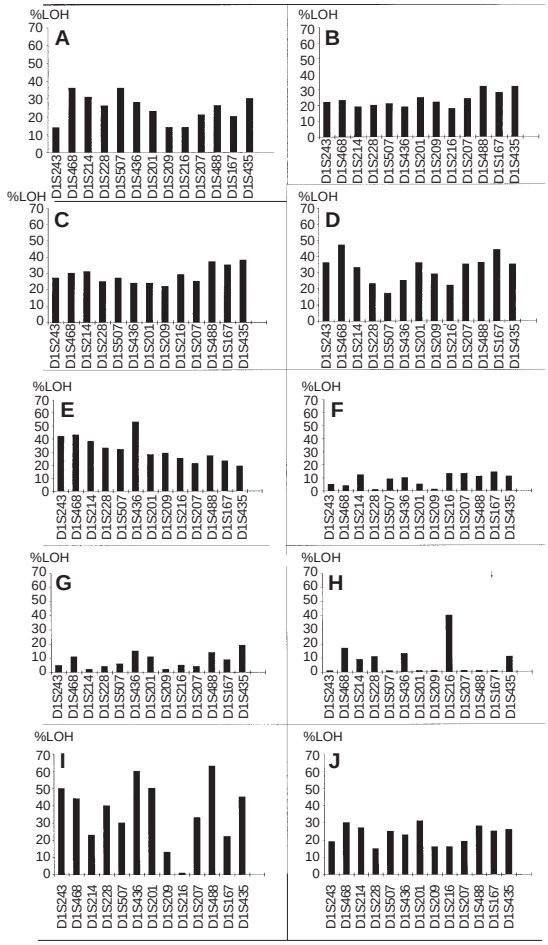

Figure 3 Graphic illustrations of % LOH at 1p for individual markers in 10 different solid human cancer types: **A**, stomach (n = 38); **B**, colorectal (n = 10a) **C**, lung (n = 63); **D**, endometrial (n = 25); **E**, ovarian (n = 31) **F**, testis (n = 30); **G**, renal (n = 73); **H**, thyroid (n = 14); **I**, sarcoma (n = 14); and **J**, breast (n = 238)

SROs detected in the other three tumour types (Figure 4). A difference is also detected between the renal tumours and the other tumour types in the 1p32 region. In the 1p31 region the same SRO are detected, located between markers D1S435 and D1S167, in all four tumour types (Figure 4).

Association with clinical and pathological variables

Chi-squared analysis comparing tumours with LOH at chromosome 1p with clinical and pathological variables showed a weak association between LOH at 1p and high S-phase fraction (P = 0.021) in the breast tumours. There was also an association between LOH at 1p and poor tumour differentiation (grade III) in the colorectal cancer cases (P = 0.047), but association was not found in other cancers (lung, stomach, endometrium, ovary, kidney or testis). There was no significant association between LOH at 1p and node status or tumour size in any cancer types (breast, lung, colorectum, stomach, endometrium, ovary, kidney or testis). There was no association between LOH at 1p in the breast tumours and parameters such as histological type, age at diagnosis, ploidy, or steroid receptor content. Furthermore, there was no association between LOH at 1p and Duke's grade in colorectal cancer cases (data not shown).

Survival analysis

Breast cancer patients showed significant association between LOH at chromosome 1p and overall survival as tested with a log-rank test ($P < 0.001$). There was a significant separation of survival curves (Figure 5A). Median follow-up time is 5.0 years. When individual markers were analysed separately, with respect to association with breast cancer patients' overall survival, only one marker showed significance with a long-rank test (P = 0.022) – the D1S435 marker, located at the chromosome region 1p31.1. Colorectal cancer patients showed a trend between LOH at 1p and survival (P = 0.085) but the median follow-up time was only 2.1 years. Figure 5A shows the graphic representation of the survival statistics in the breast cancer patients and Figure 5B shows the survival statistics in colorectal cancer patients. Only 66 of the 146 breast cancer patients with LOH at 1p had metastasis in lymph nodes but 80 were lymph node-negative. Multivariate analysis was undertaken to evaluate the possible clinical relevance of LOH at 1p as a prognostic factor in breast cancer patients. The analysis showed that breast cancer patients with tumours with LOH at 1p had nearly a three-fold increase in relative mortality rate compared with patients with tumours without LOH at 1p. The RR (relative risk of dying in the multivariate analysis) was 2.7 (95% confidence interval: 1.5–4.9) and $P < 0.001$. The only other factor of prognostic value in the multivariate analysis was axillary nodal involvement with RR = 1.8 (95% CI: 1.1–3.0) and P = 0.015 (Table 2A). A multivariate analysis in colorectal cancer patients showed that patients with LOH at 1p had a nearly twofold increase in relative mortality rate compared with patients with tumours without LOH at 1p. The 95% confidence interval of the multivariate analysis was 0.99–3.6 and P = 0.055 (Table 2B).

DISCUSSION

In this study LOH at chromosome 1p was detected with at least one marker in 54% of the tumours examined. The elevated frequency of LOH with certain markers suggests five regions of deletion indicating locations of putative TSGs. Known genes, located in these regions, that could possibly play a role in tumorigenesis are shown in Figure 2. The p*53* homologue p*73* on 1p36.33 (Kaghad et al, 1997) is one of these genes. A modifier gene of colon tumorigenesis (Mom1) in the mouse, which encodes secretory type II phospholipase A_2, affects the numbers of polyps developing as the consequence of a mutation in the *Apc* gene (Min mouse). A human homologue of the candidate for the *Mom*1 locus has been mapped to 1p35–p36.1 (Praml et al, 1995). Other genes or homologues to genes involved in cell growth and fidelity are: transcription factors, *E2F*2 on 1p36.11 (Lees et al, 1993), *PAX*7 on 1p36.1 (Vorobyov et al, 1997) and L-*myc* on 1p34.3 (Speleman et al, 1996); replication protein gene *RPA*2 on 1p35 (Ozawa et al, 1993); death receptor genes, *TR*2 (Kwon et al, 1997), *TNFR*2 (Kemper et al, 1991), *DR*3 (Bodmer et al, 1997) and *DR*5 (Wu et al, 1997), all on 1p36; other receptor genes, *PTAFR* on 1p34.3–p35 (Chase et al, 1996), *TGFβR*3 on 1p32–p33 (Johnson et al, 1995) and *IL*12*Rβ*2 on 1p31.2 (Yamamoto et al, 1997); prostaglandin receptors, *PTGER*3 on 1p31.2 and *PTGFR* on 1p31.1 (Duncan et al, 1995); tyrosine kinases, *ECK* on 1p36.1 (Sulman et al, 1997), *LCK* on 1p35 (Volpi et al, 1994) and *JAK*1 on 1p31.3–p32.3 (Modi et al, 1995); dual specific kinase *ERK* (Saito et al, 1995) on 1p36.1; repair protein genes, *RAD*54 on 1p32 (Rasio et al, 1997); and *GADD*45 on 1p31.1–p31.2 (Hey et al, 1996); cell cycle control proteins,

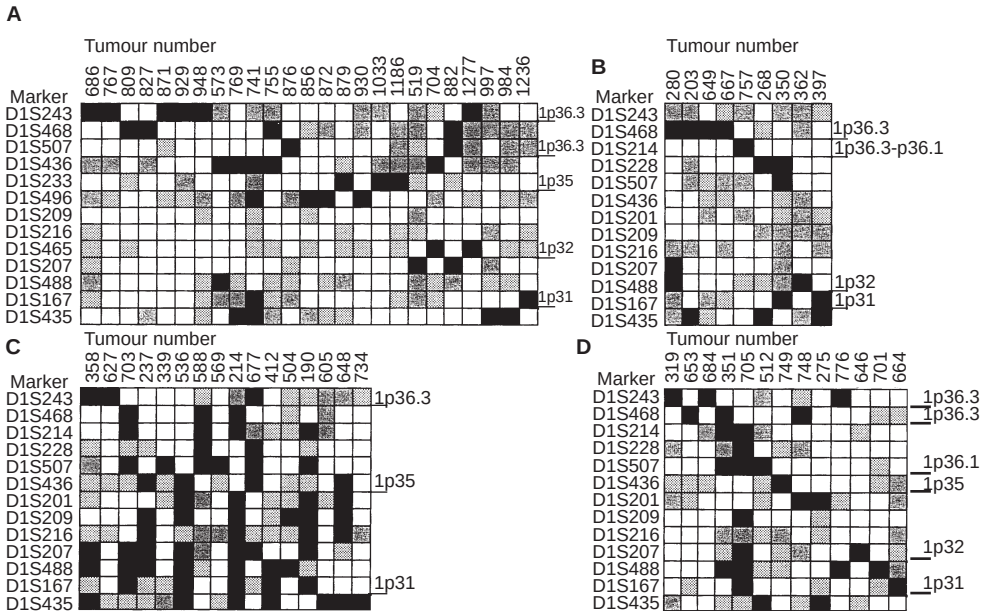

Figure 4 Patterns of LOH in selected samples of (**A**) breast, (**B**) renal, (**C**) lung and (**D**) colorectal tumours. Black, LOH; white, ROH (retention of heterozygosity); gridline, homozygous; grey, not informative. These are selected tumours with partial and interstitial deletions on chromosome 1p. The complex pattern of LOH could be consistent with the smallest regions of overlap (SROs), in colorectal and lung tumours, in regions 1p36.3 (6.4 cM), 1p36.1 (4.5 cM), 1p35–p34.3 (23.1 cM), 1p32 (0.5 cM) and 1p31 (3.4 cM). In breast tumours microdeletions are consistent with SRO at the same regions. In renal tumours the deletion pattern is different to other tumour types in the distal as well as the more proximal regions. The SRO at the 1p31 region is located between the same markers in renal tumours as in the other tumour types but other SROs map differently; the SROs in the renal tumours are located in the 1p36.3 region between markers D1S468 and D1S214 (10.4 cM), in the 1p36.3–1p36.1 region between markers D1S214 and D1S228 (16.4 cM), and in the 1p32–p31.3 region between markers D1S488 and D1S167 (7.4 cM)

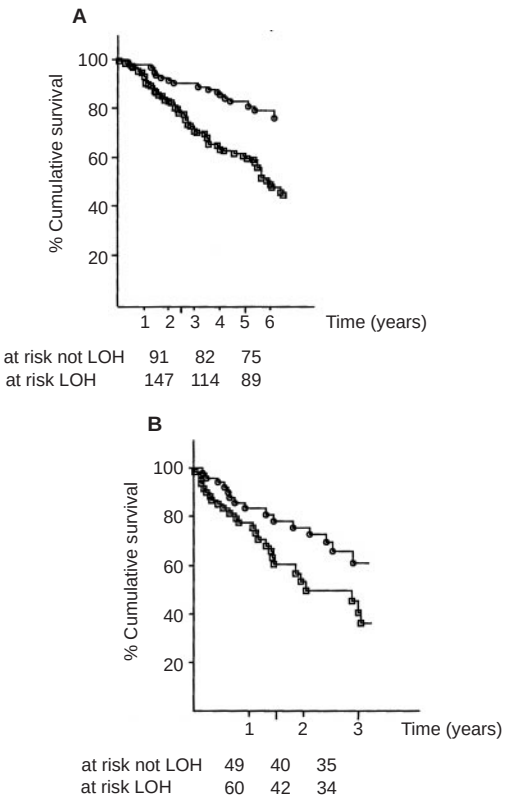

Figure 5 Cumulative percent surviving at different time intervals for (**A**) breast cancer patients and (**B**) colorectal cancer patients. Time intervals are given in years. The median follow-up time is (**A**) 5.0 years and (**B**) 2.1 years. The upper line shows patients without LOH on 1p but the lower line shows patients with LOH on 1p. The number of patients at risk at (**A**) time 0, 2, 5 years, and (**B**) 0, 1.5 and 3 years, are shown for both categories

CDC2L1 (Lahti et al, 1994) on 1p36.2, *RIZ* on 1p36.1 (Buyse et al, 1996) and *p18* (*INK4C*) on 1p32 (Lapointe et al, 1996).

A difference in LOH was detected between different tumour types. Some tumour types, testis and renal cancer, show low frequency of LOH while other tumour types have a high frequency of LOH, the highest in sarcomas and endometrial cancers. A subset of markers show elevated frequency of LOH in a number of different tumour types, suggesting that loss of a given TSG might be involved in pathogenesis of tumour growth in different tissues. Otherwise, a distinct pattern of LOH was detected in individual tumour types, reflecting multiple TSGs, that could be differentially inactivated in tumorigenesis. Furthermore, the study shows that LOH at 1p can be detected in tumours of the mouth, oesophagus, liver, pancreas, prostate, brain and adrenal gland, as well as melanoma and lymphoma.

There was a weak significant association between LOH at 1p and high S-phase fraction in breast tumours and between LOH and poor tumour differentiation in colorectal tumours. In breast cancer patients, there seems to be no association between LOH at 1p and age of onset, tumour ploidy or steroid receptor content. Furthermore, no association was detected between LOH at 1p and tumour size or nodal metastasis in tumours of the breast, stomach, colorectum, lung, endometrium, ovary, kidney or testis. LOH at 1p does not appear to be associated with the nodal metastasis step in carcinogenesis. LOH at 1p is an independent prognostic factor for the breast cancer patients and is in line with our earlier finding with less patient material and a shorter follow-up time (Ragnarsson et al, 1996). Furthermore, LOH at 1p seems to be a prognostic factor in colorectal cancer also, though in this study the association is not significant probably due to the short follow-up time. In a different study it was concluded that allelic loss in the

1p36 and 1p32 regions of chromosome 1 appears to be an independent predictor of poor prognosis in patients with adenocarcinoma of the colon (Ogunbiyi et al, 1997).

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