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Spectrum of Chromosomal Aberrations in Peripheral Blood Lymphocytes of Gastrointestinal Tract (GIT) and Breast Cancer Patients

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KEYWORDS Peripheral Blood Lymphocytes. Gastrointestinal Cancer. Breast Cancer. Chromosomal Aberrations

ABSTRACT The aim of present study was to assess the spectrum of chromosomal aberrations in peripheral blood lymphocytes of sporadic Gastrointestinal tract (GIT) and Breast cancer patients. Ninety eight patients (56 GIT cancer and 42 breast cancer) and seventy seven unrelated healthy set of control individuals were investigated in the present study. Lymphocytes were cultured using standard protocol. In each case, 100 metaphases were screened for numerical as well as structural aberrations. Higher frequency of aberrant metaphases with chromosomal aberrations including gaps, breaks, terminal deletions, acentric fragments, double minutes, acrocentric associations, premature chromatid separations, pulverisations, polyploidy, loss and gain of chromosomes, ring chromosome and marker chromosomes were observed in cancer patients as compared to controls. A non-random involvement in aberrations of chromosomes harbouring genes implicated in tumorigenesis was observed in GIT as well as in breast cancer patients. Aberrations in peripheral blood lymphocytes (PBLs) can indicate the constitutional anomalies and understanding of molecular basis of chromosomal instability (CIN) phenotype can help in earlier diagnosis or prognosis.

INTRODUCTION

Genomic instability is a prerequisite for the onset of cancer. The majority of cancer cells are aneuploid, representing dynamic karyotypic changes, including gain or loss of whole chromosomes, chromosomal rearrangements and amplification or deletion of genetic material. There are two hypotheses namely the chromosomal instability hypothesis and the gene mutation hypothesis that differ in the type of genomic alterations necessary for a normal cell to become a cancerous cell (Marx 2002). Chromosomal instability (CIN) in cancer is driven by proceeding mutation in growth controlling oncogenes and tumor suppressor genes. Analysis of aneuploid cancer cells *in vitro* reveal that chromosome losses and gains occur at $>10^{-2}$ per chromosome per cycle, which is 10-100 times greater than in karyotypically stable diploid cancers of the same histological type (Lengauer et al. 1997). The elevated rate of chromosome missegregation in aneuploid tumors cells with CIN causes phenotypic changes that contribute to tumor cell evolution and pose therapeutic challenges (Gao et al. 2007). Defects in both bipolar spindle assembly and the spindle assembly checkpoint have been identified in some CIN tumor cell lines (Cahill et al. 1998; Lingle et al. 2002). The mechanism how the tumor cells acquire extra chromosomes and maintain during cell division is not clear.

The frequency of chromosomal aberrations (CAs) in human peripheral blood lymphocytes (PBLs) has routinely been used as a tool for the identification of occupational and environmental hazards (Carrano and Natarajan 1988; Rossner et al. 1995; Waters et al. 1999; Albertini et al. 2000; Sram and Binkova 2000; Bonassi et al. 2005). The association between CAs in peripheral lymphocytes and increased risk for cancer has been observed in a Nordic cohort (Hagmar et al. 1994, 1998, 2004), in an Italian cohort (Bonassi et al. 1995) and in a nested case-control study carried out in Taiwan (Liou et al. 1999). The association between frequency of CAs and risk of cancer was not modified by sex, age, cigarette smoking, occupational exposure, or time since the cytogenetic assay performed (Bonassi et al. 2005).

A positive association between the frequency of CAs in PBLs and the risk of cancer at different sites has been supported by numerous clinical observations, in particular, of patients suffering

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from hereditary chromosome breakage syndromes (Mathur et al. 2000) and several other precancerous conditions such as preleukemic states of adult T-cell leukemia (Nishino 1988), dysplastic nevus syndrome (Caporaso et al. 1987), or nevoid basal-cell syndrome (Shafei-Benaissa et al. 1998). Different case-control studies have reported a significant increase in the frequency of aberrant cells in PBLs of cancer patients (Barrios et al. 1988; Abarbanel et al. 1991; Barrios et al. 1991; Barletta et al. 1993; Gebhart et al. 1993; Dave et al. 1995; Dhillon et al. 1996; Patel et al. 1997; Dhillon and Dhillon 1998; Trivedi et al. 1998; Roy et al. 2000, 2001), but these studies have been subjected to criticism because of small sample size.

The aim of present study was to assess the spectrum of chromosomal aberrations in peripheral blood lymphocytes of Gastrointestinal tract (GIT) and Breast cancer patients and their diagnostic or prognostic utility. Frequency of sporadic GIT and Breast cancer is higher in areas adjoining Amritsar city of Punjab, India and is continuously increasing.

MATERIAL AND METHODS

The study was carried out under the guidelines of ethical committee constituted by Guru Nanak Dev University, Amritsar and tenets of declaration of Helsinki. Ninety eight patients (56 GIT cancer and 42 breast cancer) from Sri Guru Ram Das Rotary Cancer Hospital Amritsar and Government Medical College Amritsar, Punjab were investigated in the present study. The age of patients ranged from 25 to 95 years. Blood samples of 77 age and sex matched unrelated healthy control individuals were also investigated in this study. Relevant information including age, gender, occupation, personal and family medical history, habitat, habits and diet were recorded on a pre-tested structured questionnaire. Lymphocytes were cultured using standard protocol (Moorhead et al. 1960) with few modifications. GTG banding was done using Benn and Perle (1986) technique. In each case, 100 metaphases were examined for numerical as well as structural aberrations. Chromosomes were identified and classified according to Inter-

Table 1: Epidemiological profile of cancer patients and unrelated healthy control individuals

	Gastrointestinal cancers					
	Breast	*Oesophageal*	*Gastric*	*Intestinal**	*Others***	*Controls*
No. of subjects	42	34	3	13	6	77
Age in years						
(Range)	28-90	45-95	58-70	32-55	30-60	28-80
Gender						
Males	1	17	2	7	-	28
Females	41	17	1	6	6	49
Occupation						
Farmer	1	8	-	1	-	8
Labourer	1	8	-	2	-	-
Shopkeeper	-	1	-	2	-	3
Govt. Employee	-	-	1	3	-	21
Housewives	37	13	1	5	6	34
Teacher	3	2	-	-	-	5
Sweeper	-	1	1	-	-	1
Factory worker	-	1	-	-	-	-
Research student	-	-	-	-	-	5
Habitat						
Rural	21	27	-	7	4	32
Sub urban	5	1	-	-	1	5
Urban	16	6	3	6	1	40
Habits						
Smoker	-	3	2	1	-	-
Alcoholic	-	12	1	4	1	12
Drugs	2	-	-	1	-	-
Non-vegetarian	8	10	2	2	2	12

*Cecum, Colon, Colorectal, Rectal
**Pancreatic, Gall bladder

national system for human cytogenetic nomenclature (ISCN 2005).

RESULTS

Cancer patients and control individuals had similar epidemiological characteristics like habitat, habits and socioeconomic status (Table 1). Classical cytogenetic analysis revealed the presence of various types of chromosomal aberrations including gaps (Fig. 1), breaks (Fig. 2), terminal deletions (Fig. 2), acentric fragments (Fig. 1), double minutes (Fig. 3), acrocentric associations (Fig. 4), premature chromatid separations (Fig. 5), pulverisations (Fig. 6), polyploidy (Fig. 5), ring chromosome (Fig. 7), loss (Fig. 4 and 4K, Fig. 8 and 8K) and gain of chromosomes (Fig. 9) and marker chromosomes (Fig. 3) in PBLs of cancer patients (Table 2). Loss of all chromosomes except chromosome 13 and gain of chromosome 3, 4, 6, 7, 9, 10, 14, 16, 19, 22, terminal deletion on chromosome 2q, 3p, 7q, 12p, 15q, 16q, gaps on chromosome 1p, 2p, 3p, 3q, 4q, breaks on 1p, 1q, 2q, 4q, 5q, 10q, a Robertsonian translocation between chromosome 14 and 22 and dicentric chromosome 2 and 5 were observed in oesophageal cancer patients. In gastric cancer patients, loss of chromosome 21 and X, gain of chromosome 8, 15 and 19, chromatid gaps on 1p, 12p and breaks on 2q and 11q were seen. Intestinal cancer patients showed loss of chromosome 1, 5, 11, 12, 15, 16, 17, 18, 19, 21 and 22, gain of chromosome 7, 8, 15, 19, gaps on 1q, 2p, breaks on 1p, 2q, 6q and terminal deletion of 3p and 3q.

In breast cancer patients loss of all chromosomes except 6, 8 and 9, gain of chromosome 1q, 2q, 5, 13, 15, 19 and 20, terminal deletion on chromosome 1p, 3p, 3q, 4p, 16q, 17q, dicentric chromosome 2 and 4, ring chromosome 1 and 3 and a translocation between chromosome

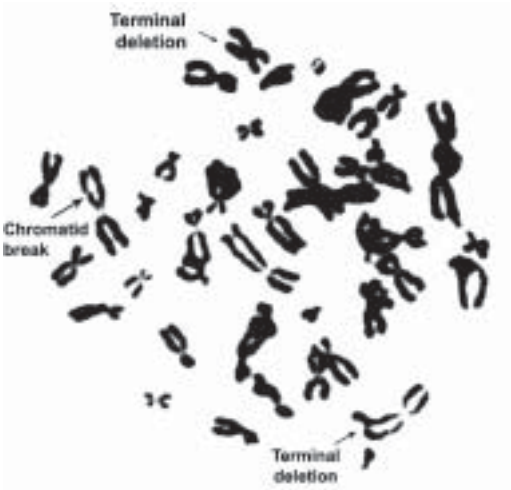

Fig. 2. Metaphase spread of Breast cancer patient showing chromatid break and terminal deletions

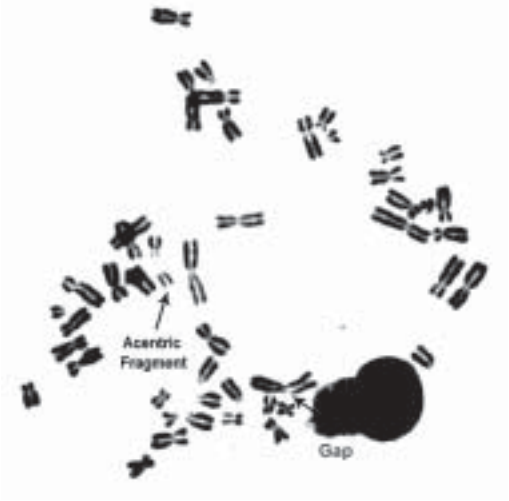

Fig. 1. Metaphase spread of Breast cancer patient showing acentric fragment and chromatid gap

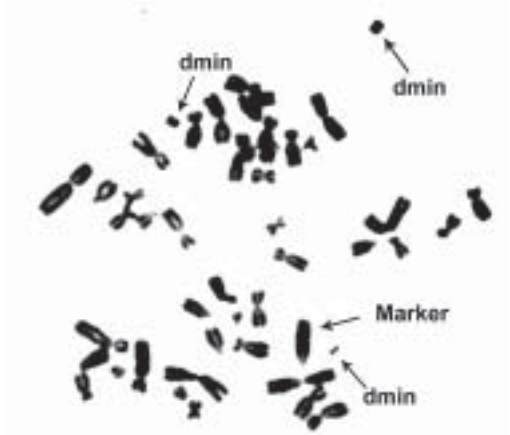

Fig. 3. Metaphase spread of GIT cancer patient showing three double minutes and a marker chromosome

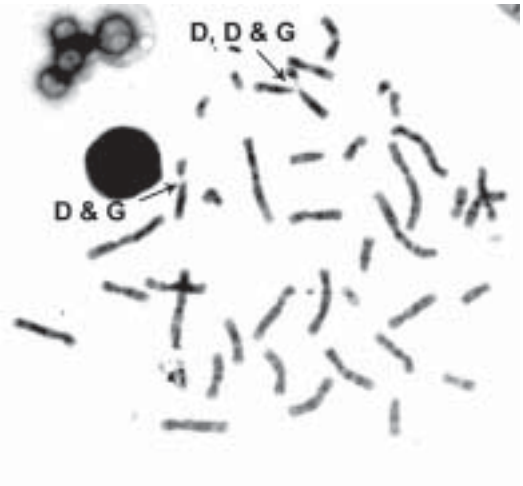

Fig. 4. Metaphase spread of GIT cancer patient showing D, D & G and D & G acrocentric associations and loss of chromosomes

Fig. 5. Polyploid metaphase showing premature chromatid separations

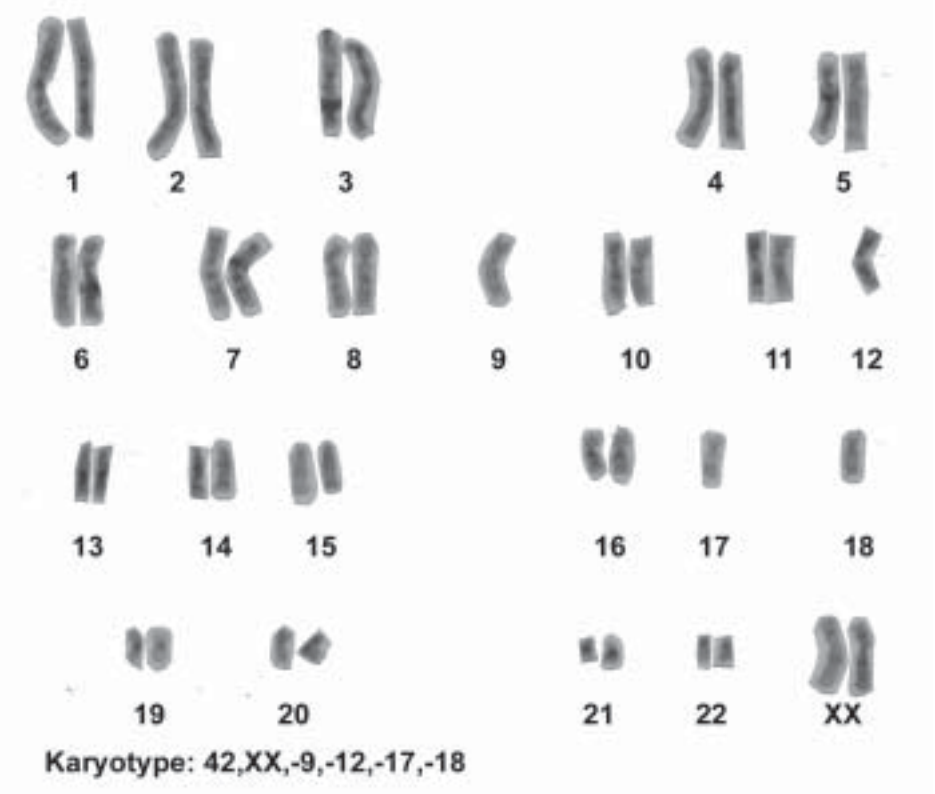

Fig. 4 K. Karyotype of the metaphase spread showing D, D & G and D & G acrocentric associations and loss of chromosomes

Fig. 6. Metaphase spread of GIT cancer patient showing pulverized chromosomes

4 and 10 were seen. Gaps on 1p, 2p, 2q, 3p, 3q, 4q, 5q, 6q, 11p, 14q and 18q and breaks on chromosome 2p, 2q, 3p, 4q, 5q, 6q, 14, 16q were also observed.

In lymphocytes of healthy unrelated controls, majority of metaphases had normal karyotypes. Gross aberrations including aneuploidy, gaps, breaks, diplo chromosomes, pulverization, double minutes, acentric fragments, terminal deletions, premature chromatid separations and acrocentric associations were seen in few cells.

DISCUSSION

In the present study, the chromosomal aberrations in PBLs of 98 cancer patients (56 GIT cancer and 42 breast cancer) who had not received any preoperative treatment, such as chemotherapy or irradiation were analyzed. High frequency of chromosomal aberrations in cancer patients as compared to controls was observed.

Fig. 7. Metaphase spread of GIT cancer patient showing ring chromosome

In most of GIT cancer patients, aberrations of chromosome 1, 2, 3, 4, 12, 17 and 21 were observed (Table 2). Thirteen patients had chromosomal aberrations of chromosome 1 and 2 while 8 patients had aberrations of chromosome 3. These chromosomes harbour a number of tumor suppressor genes that may contribute to the pathogenesis or susceptibility to cancer e.g. *GDB2* (1p34.3), *IBD7*(1p36), *BCL10*(1p22), *PLA2G2A* (1p35), *MUTYH*(1p32.1), *NRAS* (1p13.2), *MSH2*(2p21), *MSH6*(2p16), *IL1RN* (2q14), *BUB1*(2q14), *CASP10*(2q34), *DLEC1* (3p22), *ARMET*(3p21), *MLH1*(3p21.3), *ST11*(3p25), *TGFBR2*(3p22), *CTNNB1*(3p21.3), *PTEN* (10q23.3), *BUB1B*(15q15), *CRCA1*(15q13), *CASC4*(15q15.3), *MMP15*(16q13) and *TFF1*, *TFF2*, *TFF3*(21q22.2) (Table 2). Structural and numerical aberrations in chromosome 1, 2, 5, 7, 12, 14, 17, 18 and 21 have been reported earlier in lymphocytes of GIT cancer patients (Barletta et al. 1993; Dave et al. 1995; Sokova et al. 1997). Chromosome loss associated with 1p, 3p, chromosome 4, 11q and 12q, and gain of chromosome 12q, 17 and 19 have been reported to be involved in either genesis or progression of the malignancy in esophageal cancers (Pack et al. 1999). Aneuploidy of chromosomes 3, 8, 10, 20 and Y has been reported in esophageal squamous cell carcinoma (Kang et al. 2009). Aberrations of chromosomes 8, 11 and 13 have been observed previously in lymphocytes of GIT cancer patients, suggesting possible cancer predisposition (Jude et al. 2005). Recurrent losses, including 1p, 14q, 10q, 13q, 15q, 18q and 22q, and gain of 5p, 12q, 17q and 20q have been reported as genetic markers with prognostic potential in gastrointestinal stromal tumors (Chen et al. 2004). Loss of genetic information from 1p is considered as an early primary premalignant event in intestinal tumorigenesis (Bardi et al. 1993). In nine GIT cancer patients, there was loss of chromosome 21. The tumor-suppressor genes *RUNX1*, *ETS2*, *TFF1*, *TFF2*, *TFF3* and *ERG* implicated in cancers are localized on chromosome 21. The functions of *TFF1*, *TFF2* and *TFF3* genes are not fully defined, but they may protect the mucosa from insults, stabilize the mucus layer, and affect healing of epithelium. Loss of this gene

Fig. 8. Metaphase spread of Breast cancer patient showing loss of chromosomes

Fig. 9. Metaphase spread of Breast cancer patient showing gain of chromosome (47,XX,+3)

cluster has been previously reported in human GIT tumors (Katoh 2003).

Aberrations of chromosome 1, 2, 3, 13, 19 and 22 were seen in most of the breast cancer patients. Seven breast cancer patients had abnormalities of chromosome 1, ten had of chromosome 2 and eleven patients had aberrations of chromosome 3. These chromosomes harbour many putative oncogenes that play an important role in pathogenesis e.g. *BRCD2*(1p36), *RAD54L*(1p32),

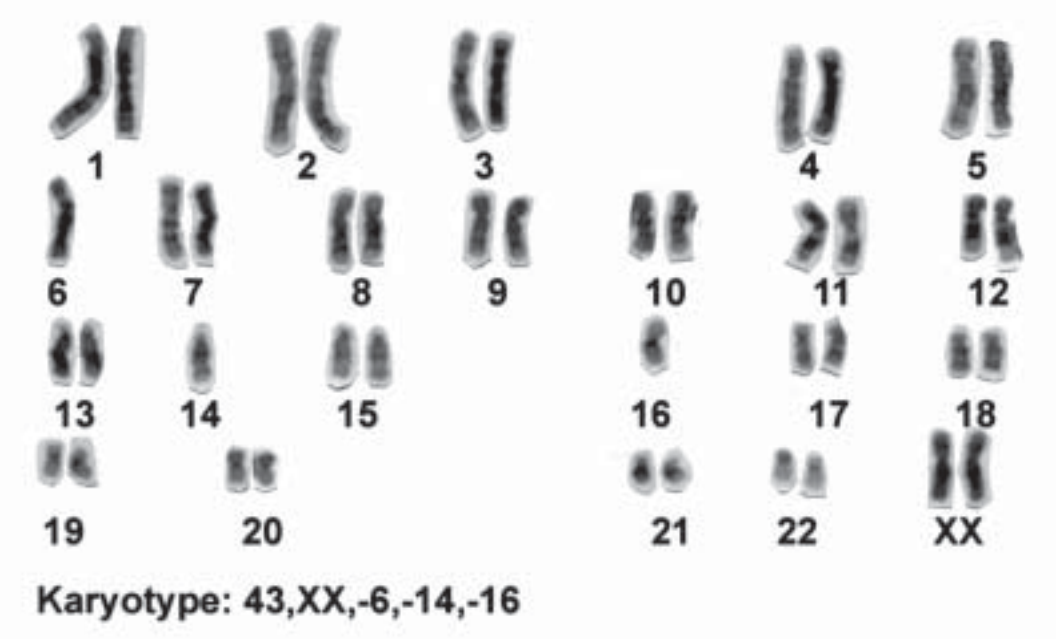

Fig. 8 K. Karyotype of the metaphase spread showing loss of chromosomes

Table 2: Detailed cytogenetic profiles of cancer patients and unrelated healthy controls individuals

Type	*Types of aberrations (% of aberrant metaphases)*	*Representative aberrant karyotype*	*Aberrant chromo-some*	*No. of subjects*	*Genes involved in tumorigenesis (Chromosomal location)*
	Aneuploidy	44,XY,-4,-15,+ace	1	13	*MYCL1*(1p34.2), *GDB2*(1p34.3), *TP73*(1p36.3),
	Gaps	46,XY,+10,-12			*SKI*(1q22), *IBD7*(1p36), *BCL10*(1p22), *PLA2G2A*
	Breaks	45,XY,+3,-11,-12,-17,+22			(1p35), *MUTYH*(1p32.1), *DJ1*(1p36), *NRAS*(1p13.2)
	Acentric fragments	43,XY,-10,-11,-19,+ace	2	13	*TP53I3*(2p23.3), *MSH2*(2p21), *MSH6*(2p16),
	Ring	46,XX,+19,-21			*PMS1*(2q33), *IL1RN*(2q14), *BUB1*(2q14), *CASP10*(2q34)
	Marker	42,XY,-14,-15,-17,-22	3	8	DLEC1(3p22), *ARMET*(3p21), *TUSC2*(3p21.3),
	Terminal deletions	46,XX,+4,+9,+16,-18,-19,-20			*TUSC4*(3p21.3), *MLH1*(3p21.3), *RAF1*(3p25),
	Double minutes	43,XX,-6,-14,-16			*VHL*(3p26), *ST11*(3p25), *TGFBR2*(3p22), *CTNNB1*(3p21.3)
	Dicentric chromosomes	42,X, -Y, -6,-11,-12	4	6	*RAB28*(4q15), *RAB23B*(4q28)
	Premature chromatid separations				
	Translocations	46,XY,+4,terdel(15q),-16	5	3	*HMMR*(5q33), *MCC*(5q21), *APC*(5q21),
	Acrocentric associations	43,XY,terdel(2p),-10,-11,-12			*RAB3C*(5q13), *XRCC4*(5q13)
		46,XY,chtb(1q),chtb(3q)	10	5	*RAB18*(10p12), *SNCG*(10q23.2), *LZT52*(10q24),
	(41%)	42,XY,-9,-11,-12,-21			*PTEN*(10q23.3)
GIT		44,Y,-5,-X,terdel(15q),terdel(16q)	11	5	*TP53I11*(11p11), *HRAS*(11p15.5),
		46,XY,chtb(1p)			*PTPRT*(11p11.2), *CCND1*(11q13)
		45,XY,-1,+7,+14,-21,-22	12	6	*TNFRSF1A*(12p13.2), *BCL2L14*(12p13),
		46,XY,+6,-21			*KRAS*(12p12.1), *SSPN*(12p11.2), *CDK2*(12q13),
		42,XX,-9,-12,-17,-18			*RAB5B*(12q13), *ERBB3*(12q13), *RAP1B*(12q14),
		42,X,-6,-11,-12,-7			*MDM2*(12q14), *CASC1*(12p12.1), *ETV6*(12p13)
		45,XY,rob(14;22)	14	3	*AKT1*(14q32), *RAB2B*(14q11), *HIF1A*(14q12),
		46, X, -X,11q-, + mar			*MAX*(14q23), *MLH3*(14p24)
		45,XY,-21,chtb(2q),chtg(12p)	15	4	*BUB1B*(15q15), *RAD51A*(15q15.1), *BMF*(15q14),
		45,XY,-1,-12,+19			*CRCA1*(15q13), *CASC4*(15q15.3)
		46,XY,-1,+8,+15,-17,chtb(6q)	16	4	*RAB40C*(16p13), *RAB26* (16q13), *MMP15*(16q13),
		46,XY,g(2p), terdel(3q),chtb(2q)			*NQO1*(16q22), *MYH11*(16p13)
		46,XY,terdel(6q)	17	6	*TP53*(17p13), *CASC3*(17q11), *TP53I13*(17q11.2),
		45,XY,-17,isochtb(2q),isochtg(3q)			*HIC1*(17p13), *TUSC5*(17p13.3)
		46, XX, 8q-, +ace	19	4	*TGFB*(19q13), *APC2*(19p13.3), *RAB11B*(19p13.2),
		45,XX,-14,-22,t(14;22),3p-,+ace			*STK11*(19p13)
		46,XY,g(2p), terdel(3q),chtb(2q)	21	9	*RUNX1*(21q22.3), *ETS2*(21q22.2), *TFF1*, *TFF2*,
					TFF3(21q22.2), *ERG*(21q22.3)

Table 2: Contd ....

Type	*Types of aberrations (% of aberrant metaphases)*	*Representative aberrant karyotype*	*Aberrant chromo-some*	*No. of subjects*	*Genes involved in tumorigenesis (Chromosomal location)*
	Aneuploidy	42,XX,-3,-4,-21,-22	1	7	*MYCL1*(1p34.2), *TP73*(1p36.3), *SKI*(1q22), *BRCD2*(1p36),
	Gaps	43,XX,-13,-19,-22			*RAD54L*(1p32), *DJ1*(1p36), *NRAS*(1p13.2)
	Breaks	44,XX,-20,-22	2	10	*REL*(2p13), *TP53I3*(2p23.3), *MSH2*(2p21), *MSH6*(2p16),
	Acentric fragments	36,X,-X,-1,-5,-10, -11,-12,			*PMS1*(2q33), *CASP8*(2q33), *BARD1*(2q35)
		-13,-15,-16,-18,-22,+ mar	3	11	*BAP1*(3p21), *ARMET*(3p21), *TUSC2*(3p21.3), *TUSC4*(3p21.3),
	Ring	42,XX,-1,-2,-4,-18			*RAF1*(3p25), *VHL*(3p26), *ST11*(3p25), *PIK3CA*(3q26.3),
	Marker	42,XX,-3,-4,-21,-22			*TGFBR2*(3p22), *CTNNB1*(3p21.3)
	Terminal deletions	42,XX,-13,-14,-20,-22	4	5	*RAB28*(4q15), *RAB23B*(4q28)
	Double minutes	46,X,-X,+5	5	4	*HMMR*(5q33), *RAB3C*(5q13), *XRCC4*(5q13)
	Dicentric chromosomes	47,XX,+13	11	5	*TP53I11*(11p11), *HRAS*(11p15.5), *SLC22A1L*(11p15.5),
	Premature chromatid separations				*TSG101*(11p15.1), *ATM*(11q22.3), *BRCATA*(11q23)
	Translocations	47,XX,+3			
	Acrocentric associations	43,XX,-3,-4,-16	13	6	*GER*(13q14), *EPSTI1*(13q13), *BRCA2*(13q12.3), *B*
Breast		46,XX,t(4q;10q),10q-			*RCA3*(13q21), *TNFSF11*(13q14), *TPTI*(13q12)
	(44%)	49,XX,-2,-7,+16,+20,	14	3	*AKT1*(14q32), *RAB2B*(14q11), *HIF1A*(14q12),
		+ mar1,mar2,mar3			*MAX*(14q23), *BRMS1L*(14q13.2)
		46, XX,r(1),r(3)	16	4	*PABL2*(16q12), *RAB40C*(16p13), *RAB26*(16q13),
					MMP15(16q13), *NQO1*(16q22)
		44,XY,-19,-20/43,XY,-13,	17	3	*BRCA1*(17q21), *PPMID*(17q22), *TP53*(17p13),
		-17,-20/43,Y,-X,-4,-20			*BRIP1*(17q22), *ERBB2*(17q21.1), *CASC3*(17q11),
					TP53I13(17q11.2), *TUSC5*(17p13.3), *BCPR*(17p13.3),
					AXIN2(17q24), *TOP2A*(17q21)
			19	6	*TGFB*(19q13), *RAB11B*(19p13.2), *STK11*(19p13)
			22	11	*CHEK2*(22q12), *BCRL*(22q11), *CRKL*(22q11.2),
					MAFF(22q13.1), *ST13*(22q13.2), *GSTT1*(22q11)
	Aneuploidy, Gaps, Breaks	46,XY/46,XY,chtg(1),+ace			
	Diplo chromosome	46,XY/46,XY,terdel(2)			
	Pulverization	46,XY/46,XY,chtb(2)			
	Double minutes	46,XX/44,XX,-3,-12			
Controls	Acentric fragments	46,XX/45,XX,-19			
	Terminal deletions	46,XY/45,XY,-2			
	Premature chromatid separations	46,XY/44,XY,-8,-11, -17,+18			
	Acrocentric associations	46,XY			
	(8.57%)	46,XX			

BAP1(3p21), *PIK3CA*(3q26.3), *EPSTI1*(13q13), *BRCA2*(13q12.3), *BRCA3*(13q21), *RAB11B* (19p13.2), *STK11*(19p13), *CHEK2*(22q12) and *BCRL*(22q11) (Table 2). Significantly higher frequency of aberrant metaphases in PBLs of breast cancer patients as compared to controls has also been reported earlier (Barrios et al. 1991; Cecener et al. 1998). Non-random involvement of chromosomes 1, 3, 11, 13, 16 and 17 (Pathak 1986) and of chromosome 5, 12, 16 and 17 have been reported in breast cancer patients (Trivedi et al. 1998). In PBLs of benign breast cancer patients increased frequency of aneusomy of chromosome 1 as compared to controls has been observed (Verdoodt et al. 1994). Aneusomy of chromosome 1, 11 and 17 has been reported in Japanese breast cancer patients (Takehisa et al. 2007). Gaps and breaks have also been reported in peripheral blood leucocytes of breast cancer patients (Ochi et al. 1988). Loss of chromosomes 1, 3 and r(11) has also been reported in PBLs of breast cancer patient (Mirfakhraie et al. 2002). In PBLs of breast cancer patients, frequent involvement of chromosomes 1, 2 and B, D and E group chromosomes has also been reported (Patel et al. 1997; Roy et al 2000). In a male breast cancer patient there was a loss of chromosome 19 and 20. Loss of chromosome 19 has also been reported in a male breast cancer patient (Udayakumar and Bhargava 1994). Comparative Genomic Hybridization (CGH) analysis revealed gain of +1q, +8q, +17q and loss of -13q in Iranian breast carcinomas patients (Ghaffari et al. 2008). CGH analysis also observed frequent losses at 7q11, 14q24.3-q31 and 17q22-q24 in lymph node metastasis patients and losses at 5p15, 12q24 and 17q22-q24 in distant metastasis breast cancer patients (Friedrich et al. 2008). In 11 breast cancer patients, there was loss of chromosome 22. The genes, *CHEK2* (22q12), *BCRL* (22q11), *CRKL* (22q11.21), *GSTT1* (22q11) and *MAFF* (22q13.1) implicated in cancers are localized on chromosome 22. *CHEK2* is a putative tumor suppressor gene and encodes a protein involved in cell cycle checkpoint regulation. Mutations in *CHEK2* are associated with a two-fold increase in breast cancer risk (Meijers-Heijbour et al. 2002; Shaag et al. 2005).

Double minutes and premature chromatid separations were seen in GIT as well as in breast cancer patients. Premature chromosomal condensation and double minutes have been reported in the lymphocytes and tumor tissue of the breast cancer patients (Udayakumar and Bhargava 1994, 1995). In present study acentric fragments were observed in both categories of cancer patients. The losses of chromosome or chromosome segments harbour tumor suppressor genes and dominantly acting growth regulatory genes. Polyploidy has also been seen in PBLs of cancer patients. Polyploidy is an indicator of fast growing tumors. Ploidy status is associated with the advancing stage of tumor but not statistically associated with the differentiation of tumor (Blant et al. 2001). Higher frequency of satellite associations were seen in cancer patients as compared to controls. Acrocentric associations are considered an indicator of acrocentic chromosomes to be involved in Robertsonion translocation.

In the present study, trisomies of chromosome 3, 4, 6, 7, 8, 9, 10, 14, 15, 16, 19 and 22 in GIT cancers patients and of chromosome 1, 2, 5, 13, 15, 19 and 20 in breast cancer patients were seen. The associations between several genes on the same chromosome may represent a general mechanism by which trisomies affect development and cancer. Elevated and significant variable expression of multiple genes on trisomic chromosomes has been reported (Taub et al. 1999; Hertzberg et al. 2007). Aneusomies of specific chromosomes as observed in cancer patients in the present study, indicate that these chromosomes may contain gene (s) that are important for neoplastic progression when their dosage is imbalanced. Aneuploidy is not only a very early event but also increases with aggressiveness of the tumor and is proportional to the degree of malignancy (Han et al. 1996; Sugai et al. 1999; Reid et al. 2000; Doak et al. 2003; Williams et al. 2005). From animal model studies it has been concluded that aneoploidy reduces cellular fitness by repressing cell proliferation, alters their properties and influences their immortalizing capabilities (Baker et al. 2004; Weaver et al. 2007).

In the present study, cancer patients and control individuals had similar epidemiological characteristics like habitat, habits and socio-economic status (Table 1). However, the cancer patients had higher frequency of chromosomal aberrations as compared to controls. High frequency of aberrations in PBLs of cancer patients similar to those seen in tumor tissue indicated that defective genetic mechanisms expressed in tumor tissue are also manifested in similar manner in circulating lymphocytes of

patients. Aberrations of chromosome 1, 2, 3, 4, 5, 11, 14, 16, 17 and 19 were observed in both GIT and breast cancer patients in current study (Table 2). The involvement of these chromosomes / chromosomal regions implicated in tumorigenesis has already been reported in tumor tissue. These chromosomes harbour genes involved in tumorigenesis including many low penetrance genes which may also contribute to the cancer pathogenesis in the studied patients. Low penetrance gene products affect the pathways like detoxification of environmental carcinogens steroid hormone metabolism, DNA damage repair and immune surveillance involved in carcinogenesis. Recurrent chromosomal aberrations in solid tumors can reveal the genetic pathways involved in the evolution of malignancy and in some cases predict biological behaviour. However, the role of individual's genetic background in shaping karyotypes of sporadic tumors is unknown. Aberrations in PBLs indicate the constitutional anomalies and understanding of molecular basis of CIN phenotype can help in earlier diagnosis or prognosis. A part of study has already been published (Guleria and Sambyal 2003; Guleria et al. 2005; Kaur and Sambyal 2008; Kaur et al. 2009).

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