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Letters to the Editor

TP53 intron 6 polymorphism and the risk of ovarian and breast cancer

Sir

Germline mutations in the coding and splice junction regions of *TP53* that directly alter the amino acid sequence are rare but are generally highly penetrant and predispose such individuals to a variety of malignancies. Recently, there has been speculation that some common sequence variants of *TP53*, which either result in conservative amino acid substitutions or lie in intronic regions outside of splice junction regions, may represent low penetrance mutations (Peller et al, 1995; Avigad et al, 1997). The biological significant of these sequence variants needs to be carefully assessed as conflicting associations with cancer predisposition have been reported. For example, Runnenbaum et al (1995) reported an eightfold relative risk of ovarian cancer in women harbouring a 16-bp polymorphism in intron 3 of *TP53*. However, we (Campbell et al, 1996) and Lancaster et al (1995) found no evidence of a significant association of this allele in larger groups of ovarian cancer patients, suggesting that the association reported by Runnenbaum et al (1995) was spurious.

Recently, Peller et al (1995) reported an association between an intron 6 polymorphism and predisposition to breast and colon cancer in a small number of cases from Israel. The polymorphism is a G to A transition located 61 nucleotides from the end of exon 6 and abolishes an *MspI* restriction endonuclease site (CCGG to CCAG). We investigated the frequency of the CCGG (N) and CCAG (N′) alleles in 224 women with ovarian and 224 women with breast cancer treated in the UK, and in 254 control subjects without cancer by polymerase chain reaction amplification over the polymorphic region and analysis on sequencing acrylamide gels (Table 1). All cancer patients and non-cancer controls were caucasians from southern England.

Statistical analysis using the chi-square test revealed a significant increase in the prevalence of the N′ allele in those patients with ovarian cancer when compared with controls ($P = 0.01$). In contrast to Pellers' (1995) study, there was no difference seen in those patients with breast cancer against the control ($P = 0.88$).

Sequencing of the polymorphic region confirmed the presence of a G to A transition at position 61 in the N′ individuals (Figure 1) but there was a discrepancy between the N allele sequence reported by Peller et al (1995) (TGG–CTGCCGGGTG) and that deposited in the GenBank sequence database (5′ TGG**C-CCTCCGGG**TG). This discrepancy is probably due to a sequencing artefact caused by the profound compression of the triplet of cytosines. Interestingly, the compression is absent in the N′ allele sequence and it is possible that the G to A transition disrupts a 'hairpin-like' structure formed by the annealing of the cytosine and guanine triplets in the N allele (shown in bold in Figure 1). The disruption of this secondary structure in the N′ allele may provide a mechanism for the impact of this polymorphism on *TP53* function.

Although the association of the N′ allele with ovarian cancer reaches formal significance, it will be important to confirm this in other populations, particularly in the light of previous spurious associations of *TP53* polymorphism and cancer risk.

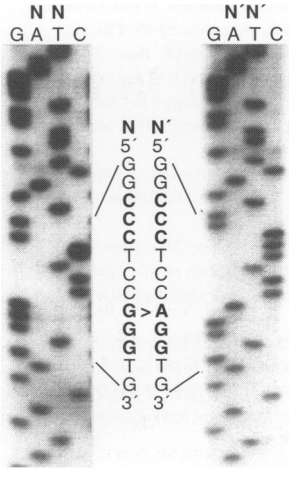

Figure 1 DNA sequence across the intron 6 polymorphism. The DNA sequence of individuals homozygous for the **NN** and **N′N′** alleles are shown. A compression of the cytosine triplet is observed in the **NN** individual but a normal spacing of the bands is observed in the **N′N′** individual. The triplet of cytosines and guanines which are postulated to form a 'hairpin-like' structure are shown in bold

Table 1 Frequency of *TP53* intron 6 polymorphism alleles in control, ovarian, and breast cancer groups

	Genotype		
	N/N	**NN′**	**N′N′**
Controls ($n = 254$)	208 (81.9%)	42 (16.5%)	4 (1.6%)
Ovarian cancer ($n = 225$)	157 (69.8%)	62 (27.5%)	6 (2.7%)
Breast cancer ($n = 224$)	184 (82.1%)	39 (17.4%)	1 (0.5%)

P(control/ovarian) = 0.01; P(control/breast) = 0.88

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Seasonality in the presentation of acute lymphoid leukaemia

Sir

A recent report by Badrinath et al (1997) observed a seasonal distribution in the diagnosis of cases of acute lymphocytic leukaemia as recorded by the East Anglian Cancer Registry in the period 1971–94. This took the form of a 40% excess of cases diagnosed in the summer months (May–October), and was seen in children (aged 0–14 years, summer–winter cases 158:113) and adults (aged 15+ years, 142:102). Shown below are observations obtained from a much larger dataset of both childhood leukaemias and solid cancers, namely the Oxford Survey of Childhood Cancers (OSCC), a national case–control study of childhood cancer (Stewart et al, 1958; Knox et al, 1987), as well as data on acute lymphoblastic leukaemia registrations from the West Midlands region.

Table 1 shows the monthly pattern of onsets, divided into summer (May–October) and winter (November–April) for all childhood leukaemias and childhood lymphatic leukaemias in the period 1953–81. (Onset date is the date when the survey child was last perfectly well, obtained from the mother's description of the fatal disease and any preceding illnesses.) For neither of the diagnostic groups was there a 40% summer–winter excess of onsets, although a significant ratio of 1.05 was found for all childhood leukaemias. The summer–winter ratio was even less marked for date of diagnosis: all leukaemias 1.03 (0.99–1.07); lymphatic leukaemias 1.02 (0.97–1.08). In addition, these data did not show a more prominent summer excess of lymphatic leukaemia among children less than 6 years of age (ratio 1.03, 95% confidence interval 0.97–1.10, date of diagnosis), as was reported by Badrinath et al (1997).

Table 1 also shows data from the West Midlands Cancer Intelligence Unit on acute lymphoblastic leukaemia registrations

Table 1 Monthly distribution of presentation of lymphoid leukaemias

	Onsets in children who died from cancer aged 0–15 years, Great Britain, 1953–81		Registrations, West Midlands residents 1971–94	
	All leukaemias	Lymphatic leukaemias only	Acute lymphoblastic leukaemia	
Month	Children (0–15 years)		Children (0–14 years)	Adults (15 + years)
May	775	449	65	47
June	820	495	71	62
July	808	425	78	48
August	757	444	74	45
September	756	425	75	48
October	794	481	69	42
Summer total	4710	2719	432	292
November	657	383	63	47
December	894	527	59	33
January	783	440	84	45
February	673	393	64	30
March	756	433	48	31
April	734	417	55	57
Winter total	4497	2593	373	243
Summer–Winter ratio	1.05	1.05	1.16	1.20
95% confidence limits	1.01, 1.09	1.00, 1.10	1.02, 1.30	1.03, 1.37