



LETTERS TO THE EDITOR

The sex ratios of offspring and sibs of patients with cancer

Sir – Hawkins *et al.* (1995) present data on the sexes of offspring of survivors of childhood leukaemia and non-Hodgkin lymphomas. They are reproduced here in Table I together with other data on the sexes of offspring of cancer patients. The impression is given that illness is associated with variation in the sex ratio (proportion male) of offspring of patients. Two points are worth making:

(1) The association depends on the timing of the illness vis-a-vis the conception of the offspring. In the data of Olsson and Brandt (1982), the sex ratio of offspring of male non-Hodgkin lymphoma patients is strongly associated with the time of initiation of the disease (before or after age 50) ($\chi^2 = 12.9$, $P < 0.0005$). So it seems that children sired before the onset of the illness in men have a normal sex ratio, whereas those sired after it contain a significant excess of daughters.

(2) Inspection of the Table suggests that—at least in some sets of data—male patients are more likely to produce female offspring, and female patients male offspring. Such a suggestion is reminiscent of data on the sex ratios of offspring of patients with multiple sclerosis (MS). Before disease onset, patients of both sexes produce children with normal sex ratios. But after disease onset, male patients produce a significant excess of daughters, and female patients an excess of sons (James, 1994a).

Both points may be important in assessing the implications of sex ratio disturbances in the offspring of cancer patients.

If (as in MS), the offspring sex ratio biases occur only after disease onset, one may infer that these disturbances are merely a (possibly hormonal) consequence of the disease (or its treatment) and so probably throw no light on the cause of the disease. In contrast, offspring sex ratio bias occurring before disease onset suggests hormonal imbalance that is causally associated with the disease. The point is illustrated by the offspring sex ratio of patients who later develop prostatic cancer. These men apparently sire an excess of sons (James, 1990). This suggests that they already have high androgen levels at the time of conception (James, 1987), i.e. before disease onset. These high androgen levels are thought to be causally associated with the disease.

In contrast, one might suspect that the excess of daughters sired by men after contracting non-Hodgkin lymphoma is merely a hormonal consequence of the disease. This suggestion is supported by the low testosterone and high LH levels reported by Olsson (1984) in men with non-Hodgkin lymphoma.

Regardless of the timing of conceptions as regards disease onset, a pattern in which men produce excess daughters may be indicative of pathology. There are several male occupations in which low offspring sex ratios are thought to reflect reproductive hazard e.g. divers, carbon setters and pesticide sprayers (James, 1994b). Moreover men with one other disease (besides MS and non-Hodgkin lymphoma), otosclerosis, reportedly sire an excess of daughters (James, 1989). All of this may be explained simply by the observation that men react to many (non-endocrine) illnesses by diminished secretion of testosterone and/or increased gonadotrophins (Semple, 1986).

I have noted that sex ratios of sibs (as well as of offspring) of patients may throw light on possible hormonal imbalance in the mother (James, 1991). In particular, sib sex ratios may test those hypotheses suggesting that diseases are related to hormone levels experienced by the patient when *in utero*, namely cancers of the ovarian germ cell (Walker *et al.*, 1988) and breast (Trichopoulos, 1990).

Meanwhile it should be emphasised that for offspring sex ratios to be usefully exploited, the sexes of offspring must be categorised simultaneously by (i) sex of parent and (ii) whether the children were conceived before or after disease onset.

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Table I The sexes of offspring of patients with cancer

	Male patients		Female patients		Status of parent
	M	F	M	F	
Hawkins <i>et al.</i> (1995)	78	79	130	95	Survivors of childhood leukaemia and non-Hodgkin lymphoma
Moe <i>et al.</i> (1979)	0	1	5	2	Survivors of acute lymphocytic leukaemia
Olsson and Brandt (1982)	21	49	15	24	Non-Hodgkin lymphoma onset age 30–49
	84	63	64	55	Non-Hodgkin lymphoma onset age > 50

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Tenascin and oncofetal fibronectin – oncofetal markers or indicators of extracellular matrix remodelling?

Sir – We read with interest the study on ‘Immunohistochemical expression of tenascin in normal stomach tissue, gastric carcinomas and gastric carcinoma in lymph nodes’ recently published in *British Journal of Cancer* (Ikeda *et al.*, 1995). In this study Ikeda *et al.* observed that tenascin, which is not expressed in the adult mucosal and submucosal connective tissue of the stomach, is expressed in the fibrous stroma surrounding foci of cancer in 41% of primary tumours and 32% of lymph node metastases (Ikeda *et al.*, 1995). They also observed that tenascin expression did not correlate with any of the parameters evaluated in the study, namely the degree of differentiation, abundance of fibrous stroma, depth of invasion, lymph node metastasis and prognosis.

We concur that their results show that ‘tenascin appears during the process of either malignant transformation or tumour progression’ (Ikeda *et al.*, 1995). This does not mean, however, that one can assume that tenascin expression is strictly associated to the neoplastic condition *per se*. Moreover, we think Ikeda *et al.* have not obtained sufficient evidence to substantiate the assumption that ‘the positive expression of tenascin may be useful as a stromal marker for the early detection of gastric cancer’ (Ikeda *et al.*, 1995). Firstly, they did not study precursor lesions of gastric carcinoma, either as isolated lesions or as lesions in the periphery of carcinomas, and thus missed the first steps of gastric carcinogenesis. Secondly, they did not include in their study the analysis of non-cancerous conditions that may induce the expression of tenascin (e.g. peptic ulcers with granulation tissue and marked remodelling of the connective tissue).

We raise these issues because we found that the aforementioned conditions may cause false-positive results when dealing with markers with oncofetal potential, such as the so-called oncofetal fibronectin (onf-FN), an isoform of fibronectin that some authors claim to be specifically associated with malignant transformation (Matsuura and Hakomori, 1989; Loidon-Rosa *et al.*, 1990; Mandel *et al.*, 1992). At variance with fibronectin, which is widely distributed in normal tissues and particularly prominent in the granulation tissue of ulcerated areas of gastric carcinomas (David *et al.*, 1994), onf-FN was thought to appear exclusively in the stroma of cancers, thus leading to the possibility of using its detection in the diagnosis of the initial steps of carcinogenesis (Loidon-Rosa *et al.*, 1990; Mandel *et al.*, 1992). This is not the case because, apart from its presence in gastric carcinoma, we observed strong immunostaining for onf-FN at the base of the three peptic ulcers included in our study (David *et al.*, 1993). Our findings thus show that the production of onf-FN is not strictly associated with malignancy, being dependent on a variety of conditions having in common the capacity to induce deposition and/or remodelling of extracellular matrix. We wonder whether this is also the case for the expression of tenascin.

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