BJC

British Journal of Cancer (2015) 112, 1836 | doi: 10.1038/bjc.2014.613

Comment on: 'COUP-TFII regulates metastasis of colorectal adenocarcinoma cells by modulating Snail1'

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Sir,

We read with great interest the paper by Bao *et al* (2014) entitled 'COUP-TFII regulates metastasis of colorectal adenocarcinoma cells by modulating Snail1', showing upregulation of Snail and down-regulation of E-cadherin in the human epithelial intestinal cell line HIEC overexpressing COUP-TFII upon transfection (Bao *et al*, 2014; Figure 5) and converse effects in COUP-TFII-KO loVo cells (Bao *et al*, 2014; Figure 4). We previously explored the role of COUP-TFII as a regulator of E-cadherin expression because we also had noticed a correlation between abnormally high expression of COUP-TFII and lack of E-cadherin in a large panel of carcinoma cell lines of various origins including 22 colon cancer cell lines. We transfected several cell lines with an inducible COUP-TFII expression vector and, as shown in Figure 1, did not observe a pronounced effect on E-cadherin expression. In the human colon carcinoma line HCT116 in particular, E-cadherin remained perfectly stable. HCT116 cells are not invasive in Matrigel assays and invasion was not induced by COUP-TFII. Importantly, in the lung carcinoma line A549 that is invasive straightaway, E-cadherin expression was moderately increased together with, as previously reported (Navab *et al*, 2004), the invasion capacity of the cells. We also extinguished COUP-TFII expression in E-cadherin-negative cell lines (SW800, MDA-MB 231) using RNA interference and saw no E-cadherin switch-on. Together with the data from Bao *et al*, this shows that the effect of COUP-TFII is highly dependent on the cellular context. This is actually not very surprising since transcriptional regulation by COUP-TFII is quite complex, involving dimerisation and recruitment of cofactors, and can encompass not only activation but also direct and indirect repression (Park *et al*, 2003).

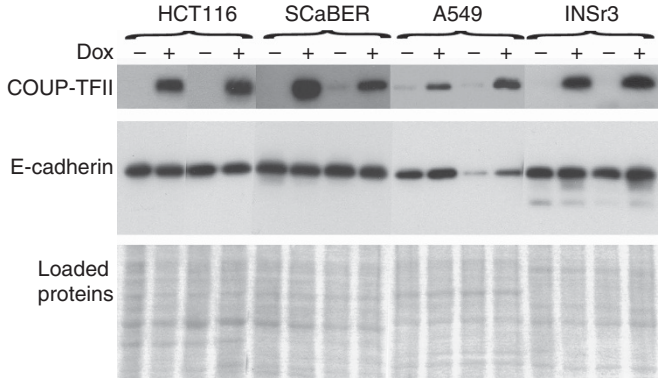

Figure 1. Expression of E-cadherin in cell lines overexpressing COUP-TFII upon transfection. HCT116 (human colon carcinoma), SCaBER (human bladder squamous carcinoma), A549 (human lung carcinoma) and INS (rat insulinoma) cell lines were treated with doxycyclin (+) to induce COUP-TFII expression. Two different clones are shown for each transfected cell line. COUP-TFII and E-cadherin expression was evaluated by western blotting using 20 μg of total protein extracts. Equal loading was checked by staining the membrane with amidoblack.

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Published online 9 December 2014

BJC

British Journal of Cancer (2015) 112, 1836–1837 | doi: 10.1038/bjc.2014.581

Comment on 'Updated investigations of cancer excesses in individuals born or resident in the vicinity of Sellafield and Dounreay': premature all-clear for nuclear power

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Sir,

Bunch *et al* (2014) report no increased leukaemia/cancer rates in children and young adults below age 25 in Seascale ward near the Sellafield nuclear site, during the period 1991–2006. But the case numbers are very small – 1 observed leukaemia case ($O=1$) *vs* 0.26 expected cases ($E=0.26$), which means a standardised incidence ratio (SIR) of 3.9 with a wide 90% confidence interval (90% CI: 0.28–33.8). Near the Dounreay nuclear installation, in the wards of Thurso and Reay, not a single leukaemia case was registered in 1991–2006, and also not in the respective control region, the rest of Caithness county. Thus, for 1991–2006, no meaningful conclusions about leukaemia risk near Sellafield and Dounreay can be drawn from these numbers.

Bunch *et al* fail to discuss the leukaemia increases over the full period, 1963–2006. A highly significant increase is found in Seascale ward ($O=6$, $E=0.91$, SIR = 6.67, 90% CI: 2.9, 13.0). The ratio of the SIR in Seascale (SIR = 6.67) to the SIR in Copeland and Allerdale County excluding Seascale (SIR = 0.90) yields a relative risk (RR) of RR = 6.67/0.90 = 7.4 ($P=0.0002$). Near Dounreay the increase in leukaemia risk is not significant (RR = 1.64, $P=0.227$). For all malignancies and over the whole study period 1963–2006 a significantly increased risk is found near Sellafield (RR = 3.3, $P=0.0004$), but the increase is not statistically significant near Dounreay (RR = 1.22, $P=0.274$).

Pooled data from Sellafield, Dounreay, and La Hague: Guizard *et al* (2001) reported on leukaemia around the La Hague reprocessing plant in France between 1978 and 1998. Leukaemia rates in the 10-km zone were compared with rates in the 10–35-km zone. During the 21-year study period, four leukaemia cases were found among children in the 10-km

Table 1. Leukaemias in children and young adults aged under 24 in the vicinities of Sellafeld, Dounreay, and La Hague

	Study region			Control region				
Site	***O***	***E***	**SIR**	***O***	***E***	**SIR**	**RR**	***P*-value**
Sellafield	6	0.90	6.67	68	75.93	0.90	7.44	0.0002
Dounreay	8	5.46	1.47	8	8.88	0.90	1.63	0.2317
La Hague	5	2.30	2.17	33	34.63	0.95	2.28	0.0852
Pooled data	19	8.66	2.19	109	119.4	0.91	2.40	0.0010

Abbreviations: *E* = expected; *O* = observed; RR = relative risk; SIR = standardised incidence ratio.

zone: all were between 1 year and 6 years old. A relative risk of RR = 3.4 was found, which was not statistically significant using a two-sided test. However, with the one-sided test, which we use here as we test for an increase, the increase of childhood leukaemia near La Hague is statistically significant ($P = 0.042$).

We have pooled the data for leukaemia in children and young adults aged under 24 in the vicinities of Sellafeld, Dounreay, and La Hague (study areas: the wards Seascale, Thurso/Reay, and Beaumont-Hague). We compared the leukaemia rates in the combined study areas with the rates in the combined respective control areas and found a significantly increased relative risk of 2.40 ($P = 0.0010$). The results are shown in Table 1.

In 2012, we analysed the pooled data of leukaemia cases near nuclear power stations in Germany, Great Britain, Switzerland, and France, and found a 37% increased risk in young children living near them (Koerblein and Fairlie, 2012). Since radiation exposures near nuclear reprocessing plants are likely to be greater than those near nuclear power stations, higher leukaemia risks would also be expected. The result in Table 1 is in line with this expectation.

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Published online 20 December 2014

BJC

British Journal of Cancer (2015) 112, 1837 | doi: 10.1038/bjc.2014.582

Response to: Comment on 'Updated investigations of cancer excesses in individuals born or resident in the vicinity of Sellafield and Dounreay'

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Sir,

We thank Drs Fairlie and Korblein for their comments on our paper that reported a lack of recent excesses of childhood or young adult cancer in individuals born or resident in the vicinity of Sellafield or Dounreay (Bunch *et al*, 2014). They stress that the analyses presented were based on small numbers; we have already acknowledged that this was a limitation of our study. However, although there was a statistically significant excess of leukaemia in Seascale ward over the whole study period, this was entirely attributable to an excess in the earliest time period. Four cases were diagnosed during 1963–1983, with only one case diagnosed during 1984–1990 and another during 1991–2006. In contrast to Drs Fairlie and Korblein, we would argue that it is misleading to consider the whole time period (a duration of 44 years) without recourse to subdivision. This would imply that any putative environmental agent related to aetiology was temporally invariant during this prolonged time span. Furthermore, Drs Fairlie and Korblein state that 'radiation exposures near nuclear reprocessing plants are likely to be greater than those near nuclear power stations', but do not provide any evidence for this assertion. Indeed we would dispute their implicit inference that any excesses in leukaemia risk during the earlier time periods are necessarily linked to potential exposures from the nuclear facilities. As we have stated in our paper, there are a number of alternative hypotheses. The most plausible, especially for childhood leukaemia, proposes that increased risk is linked with an infectious aetiology, especially in situations of unusual population mixing, such as those that occurred in the localities around the nuclear facilities (Kinlen, 1988, 1995, 2012). While potential exposure to radiation has not changed over the years, the scale and nature of population mixing has substantively altered. This would be consistent with the observed pattern of excess in the earlier period that was not present in more recent times. We suggest that future research should further consider non-radiation putative risk factors such as changes in population mixing.

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Published online 20 November 2014