REFERENCES

- Adélaïde J, Penault-Llorca F, Dib A, Yarden Y, Jacquemier J, Birnbaum D (1994) The Heregulin gene can be included in the 8p12 amplification unit in breast cancer. *Genes Chromosomes Cancer* **11**: 66–69
- Adélaïde J, Chaffanet M, Imbert A, Allione F, Geneix J, Popovici C, van Alewijk D, Trapman R, Zeillinger R, Borresen-Dale AL, Liderau R, Birnbaum D, Pébusque M-J (1998) Chromosome 8p11-p12 region: refined mapping and molecular alterations in breast cancer. *Genes Chromosomes Cancer* **22**: 186–199
- Adélaïde J, Chaffanet M, Mozziconacci M-J, Popovici C, Conte N, Fernández F, Sobol H, Jacquemier J, Pébusque M-J, Ron D, Lafage-Pochitaloff M, Birnbaum D (2000) Translocation and coamplification of loci from chromosome arms 8p and 11q in the MDA-MB-175 mammary carcinoma cell line. *Int J Oncol* **16**: 683–688
- Burden S, Yarden Y (1997) Neuregulins and their receptors: a versatile signalling module in organogenesis and oncogenesis. *Neuron* **18**: 847–855
- Carraway KL, Carraway CA, Carraway KL (1997) Roles of ErbB3 and ErbB4 in the physiology and pathology of the mammary gland. *J Mammary Gland Biol Neoplasia* **2**: 187–198
- Courtay-Cahen C, Morris JS, Edwards PAW (2000) Chromosome translocations in breast cancer with breakpoints at 8p12. *Genomics* **66**: 15–25
- Holmes WE, Sliwkowski MX, Akita RW, Henzel WJ, Lee J, Park JW, Yansura D, Abadi N, Raab H, Lewis GD, Shepard HM, Kuang W-J, Wood WI, Goeddel DV, Vandlen RL (1992) Identification of Heregulin, a specific activator of p185^{erbB2}. *Science* **256**: 1205–1210
- Le X-F, McWatters A, Wiener J, Wu J-Y, Mills GB, Bast Jr RC (2000) Anti-HER2 antibody and heregulin suppress growth of HER2-overexpressing human breast cancer cells through different mechanisms. *Clin Cancer Res* **6**: 260–270
- Lee J, Wood WI (1993) Assignment of heregulin (HGL) to human chromosome 8p22-p11 by PCR analysis of somatic cell hybrid DNA. *Genomics* **16**: 790–791
- Lewis GD, Figari I, Fendly B, Wong WL, Carter P, Gorman C, Shepard HM (1993) Differential responses of human tumor cell lines to anti-p185HER2 monoclonal antibodies. *Cancer Immunol Immunother* **37**: 255–263
- Liu X, Baker E, Eyre HJ, Sutherland GR, Zhou M (1999) γ -Heregulin: a fusion gene of DOC-4 and neuregulin-1 derived from a chromosome translocation. *Oncogene* **18**: 7110–7114
- Lupu R, Cardillo M, Cho C, Harris L, Hijazi M, Perez C, Resenberg K, Yang D, Tang C (1996) The significance of heregulin in breast cancer tumor progression and drug resistance. *Breast Cancer Res Treat* **38**: 57–66
- Morris J, Carter N, Ferguson-Smith M, Edwards P (1997) Cytogenetic analysis of three breast carcinoma cell lines using reverse chromosome painting. *Genes Chromosomes Cancer* **20**: 120–139
- Peles E, Yarden Y (1993) Neu and its ligands: from an oncogene to neural factors. *Bioessays* **15**: 815–824
- Ram TG, Kokeny KE, Dilts CA, Ethier SP (1995) Mitogenic activity of neu differentiation factor/hergulin mimics that of epidermal growth factor and insulin-like growth factor-I in human mammary epithelial cells. *J Cell Physiol* **163**: 589–596
- Schaefer G, Fitzpatrick VD, Sliwkowski MX (1997) γ -Heregulin: a novel heregulin isoform that is an autocrine growth factor for the human breast cancer cell line, MDA-MB-175. *Oncogene* **15**: 1385–1394
- Sánchez I, San Miguel JF, Corral J, Martín C, Pérez R, González M, Cañizo MC, Orfao A, González-Sarmiento R (1995) Gene rearrangement in Acute non-lymphoblastic leukemia. Correlation with morphological and immunophenotypic characteristics of blast cells. *Br J Haematol* **89**: 104–109
- Utada Y, Haga S, Kajiura T, Kasumi F, Sakamoto G, Nakamura Y, Emi M (2000) Allelic loss at the 8p22 region as a prognostic factor in large and estrogen receptor negative breast carcinoma. *Cancer* **88**: 1410–1416
- Wang X-Z, Jolicoeur EM, Conte N, Chaffanet M, Zhang Y, Mozziconacci M-J, Feiner H, Birnbaum D, Pébusque M-J, Ron D (1999) γ -heregulin is the product of a chromosomal translocation fusing the DOC4 and HGL/ NRG1 genes in the MDA-MB-175 breast cancer cell line. *Oncogene* **18**: 5718–5721
- Weinstein EJ, Grimm S, Leder P (1998) The oncogene heregulin induces apoptosis in breast epithelial cells and tumors. *Oncogene* **17**: 2107–2113
- Yokota T, Yoshimoto M, Kasumi F, Sakamoto G, Nakamura Y, Emi M (1999) Localization of a tumor suppressor gene associated with the progression of human breast carcinoma within a 1-cM interval of 8p22-p23.1. *Cancer* **85**: 447–452

Early life exposure to oestrogen and testicular cancer risk: evidence against an aetiological hypothesis

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Sir

Testicular cancer has a peak incidence among men aged 25 to 44 years, suggesting early life influences (Akre *et al*, 1996). The hypothesis that exposure to endogenous or environmental oestrogenic compounds affects embryonic testis and increases the risk of testicular cancer has been put forth (Sharpe and Skakkeback, 1993). This intriguing hypothesis has acquired momentum and,

in fact, was invoked as the main aetiological mechanism in a recent major review (Dearnaley *et al*, 2001). If prenatal exposure to oestrogens were indeed important, one would expect that populations with higher levels of pregnancy oestrogens would experience a higher rate of testicular cancer. We have studied pregnancy hormone levels, including oestrogen levels, in two populations with very different rates of testicular cancer (Lipworth *et al*, 1999).

Adult pregnant women were recruited from maternity clinics of Beth Israel Hospital in Boston, MA, USA, and from hospitals

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affiliated with the Shanghai Medical University in Shanghai, China. Pregnant women were enrolled during their first prenatal visit to the collaborating maternity clinic. Eligibility requirements included that the pregnant women had to be less than 40 years old, had no more than one previous stillborn or liveborn child, took no hormonal medication during the index pregnancy and had no prior diagnosis of diabetes mellitus or thyroid disease. Three hundred and four Caucasian women in Boston and 335 Chinese women in Shanghai were studied. Pregnancy serum concentrations of oestradiol-17 β (E2) and unconjugated oestriol (E3) were measured in maternal blood at weeks 16 and 27 of gestation. Details of the study have been published in this journal (Lipworth *et al*, 1999). Levels of E2 and E3 were consistently and significantly higher among Chinese women at both sample 1 and sample 2 (Table 1). The age-standardised rate as well as age-specific incidence rates of testicular cancer during the period of 1988–1992 for white and Chinese males (aged 15–49) were obtained from the Connecticut and the Shanghai Cancer Registries, respectively

(Parkin *et al*, 1997). The rates for Chinese males in Shanghai at all ages were much lower than those for white males in Connecticut, despite evidence of exposure to higher levels of oestrogens *in utero*.

While the hypothesis linking high oestrogen exposure with testicular cancer and other disorders of the male reproductive system is ingenious, empirical support so far has been limited. Our data are incompatible with this hypothesis and, although they do not conclusively refute it, tend to reduce its plausibility.

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Table 1 Pregnancy serum concentrations of oestradiol (E2), and oestriol (E3) in Chinese women (Shanghai, China) and Caucasian women (Boston, USA) (upper panel); age standardised and age-specific rates of testicular cancer for Chinese and US males during 1988–1992 (lower panel)

	Pregnancy oestrogen concentrations (nmol l ⁻¹ , mean $\pm$ s.d.), 1994–1995 (Lipworth <i>et al</i> , 1999)			
	Samples at 16th weeks of gestation		Samples at 27th weeks of gestation	
	E2	E3	E2	E3
Shanghai, China	20.7 $\pm$ 9.7	6.3 $\pm$ 3.9	48.2 $\pm$ 18.3	21.9 $\pm$ 9.5
Boston, US	14.0 $\pm$ 6.4	3.9 $\pm$ 1.7	39.1 $\pm$ 16.6	14.0 $\pm$ 4.4

	Age-specific incidence rate of testicular cancer (per 100 000), 1988–1992 (Parkin <i>et al</i> , 1997)							
	ASR	15–19	20–24	25–29	30–34	35–39	40–44	45–49
Shanghai, China	0.74	0.24	0.63	0.39	1.71	1.53	1.44	0.56
Connecticut, US, Whites	5.29	3.60	9.68	14.36	14.87	12.28	9.14	5.81

ASR: age standardised rate, adjusting all the age-specific rates in 5 year category (0–4, 5–9, ..., 80–84, 85+) to standard world population (Parkin *et al*, 1997)

REFERENCES

- Akre O, Ekblom A, Hsieh CC, Trichopoulos D, Adami H-O (1996) Testicular nonseminoma and seminoma in relation to perinatal characteristics. *J Natl Cancer Inst* **88**: 883–889
- Dearnaley DP, Huddart RA, Horwich A (2001) Managing testicular cancer. *BMJ* **322**: 1583–1588
- Lipworth L, Hsieh CC, Wide L, Ekblom A, Yu SZ, Yu GP, Xu B, Hellerstein S, Carlstrom K, Trichopoulos D, Adami H-O (1999) Maternal pregnancy hormone levels in an area with a high incidence (Boston, USA) and in an area with a low incidence (Shanghai, China) of breast cancer. *Br J Cancer* **79**: 7–12
- Parkin DK, Whelan SL, Ferlay J, Raymond L, Young J (1997) Cancer incidence in five continents. Volume VII, IARC Scientific Publications No. 143, Lyon: IARC
- Sharpe RM, Skakkeback NE (1993) Are oestrogens involved in falling sperm counts and disorders of the male reproductive tract?. *Lancet* **341**: 1392–1395