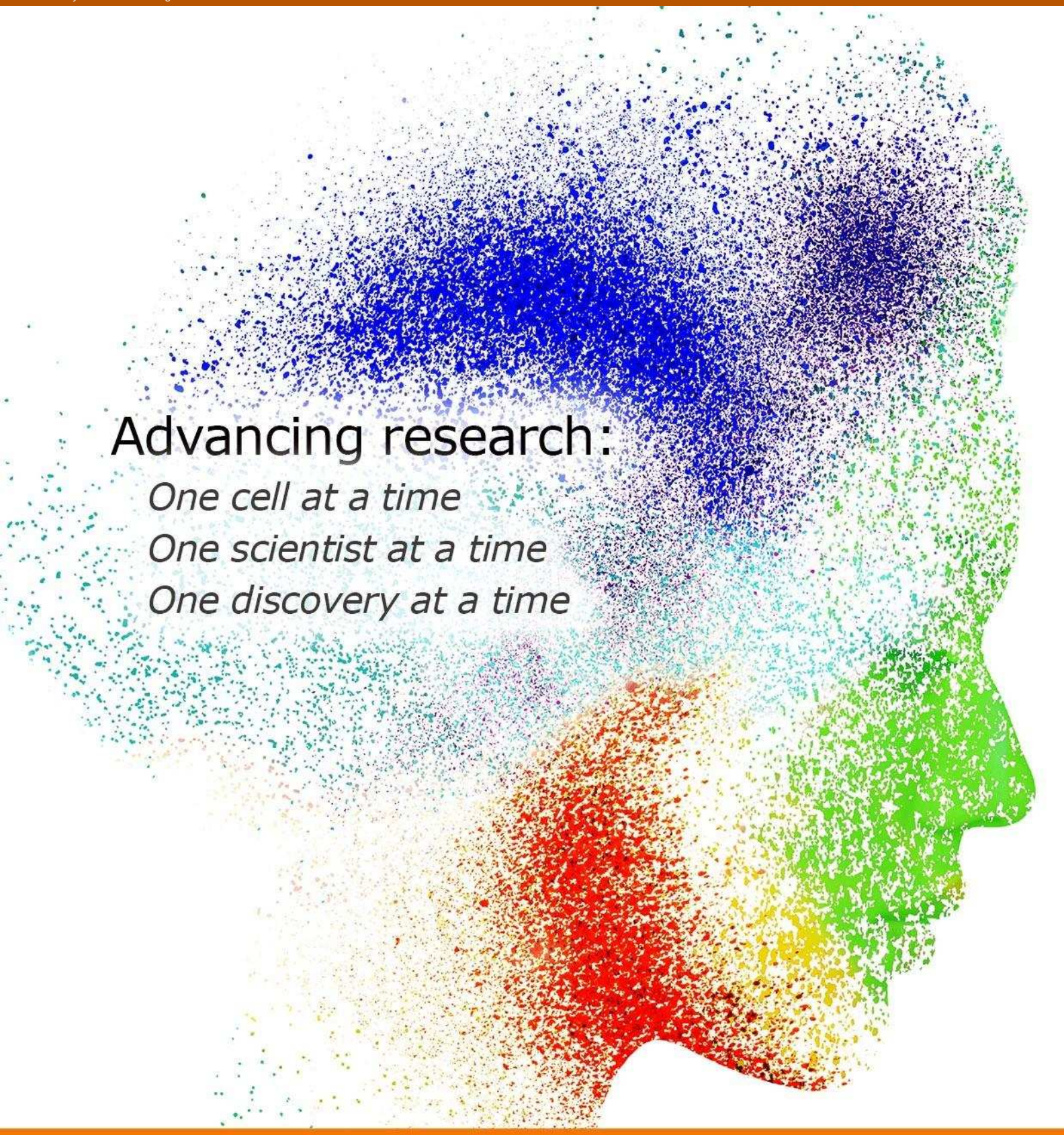

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LETTER TO THE EDITOR

Dear Sir,

Multiple births and breast cancer

Data from the Cancer and Steroid Hormone (CASH) study (Jacobson et al., *1989) suggested that having a multiple birth could be a reproductive correlate of breast cancer risk since mothers of multiple births were at reduced risk of subsequent breast cancer, after allowance for other reproductive variables. Since then, 3 studies on the issue have been published, one showing a non-significant increased risk (Hsieh* et al., *1993) and the other 2 (Nasca* et al., *1992; Dietz* et al., 1995) *no association.*

These apparent inconsistencies are not surprising, since epidemiological inference is based on only about 500 cases with multiple births; hence, besides differences in population characteristics, calendar periods and methods of analysis, the play of chance may explain at least part of the apparent differences across various studies.

To provide further information on the issue, we have therefore considered data from a large case-control study conducted between June 1991 and April 1994 in 6 Italian areas: the provinces of Pordenone and Gorizia, the greater Milan area, the urban area of Genoa, and the province of Forlì, in northern Italy; the province of Latina, in central Italy; and the urban area of Naples, in southern Italy (La Vecchia et al., *1995).*

Briefly, cases were 2,569 women admitted to the major teaching and general hospitals of the study areas, with incident, histologically confirmed breast cancer. The age range was 23–74 years and the median age 55 years. Controls were 2,588 women, with no history of cancer, admitted to hospitals in the same catchment areas as cases for acute, non-neoplastic, non-gynaecological conditions (22% traumas, 33% non-traumatic orthopaedic diseases, 15% surgical conditions, 18% eye diseases and 12% miscellaneous other diseases). The age range was 20–74 years and the median age 56 years. The distributions of cases and controls were similar in terms of age and area of residence.

Information on reproductive factors included number of births (singleton and multiple), abortions and stillbirths and age at each pregnancy or birth.

Odds ratios (OR) for multiple births and the corresponding 95% confidence intervals (CI) were computed using multiple logistic regression models (Breslow and Day, 1980). All regression equations included terms for age in quinquennia and area of residence. Further models included years of education, parity, age at menarche, age at first birth, menopausal status/age at menopause, history of benign breast disease, family history of breast cancer, oral contraceptive use and body mass index. A total of 38 (1.5%) cases and 58 (2.2%) controls had ever had multiple births. Only one control had had more than one multiple birth.

Compared with parous women with only singleton births, the OR for women with multiple birth was 0.66 (of borderline significance), after allowance for age and centre only, and 0.74 (not significant) after multivariate analysis. No appreciable heterogeneity was evident according to whether the multiple birth was first, subsequent or last. The multivariate OR was 0.50 when the first multiple birth occurred below age 25 years and rose to 0.98 at age 35 years or over. No linear trend emerged with reference to time since last multiple birth, but only 4 cases and 5 controls reported a multiple birth within the last 15 years (Table I).

Our findings confirm that multiple births do not appear to influence subsequent breast cancer risk, and indicate that women with multiple births are not at increased risk to any substantial extent, independently from birth order or other time factors. The point estimate was below unity in univariate analysis, but the apparent inverse relationship decreased after allowance for a number of relevant co-variates.

Multiple births were comparatively rare in our data set. Apart from the baseline characteristics of the population, this

TABLE I – DISTRIBUTION OF 2,569 CASES OF BREAST CANCER AND 2,588 CONTROLS ACCORDING TO TYPE OF BIRTH (SINGLETON ONLY OR MULTIPLE), ITALY, 1991–1994

Type of birth	Cases	Controls	OR[1] (95% CI)	OR[2] (95% CI)
Nulliparae	401	381	1.15 (0.98–1.34)	1.16 (0.94–1.43)
Singleton only	2,130	2,149	1[3]	1[3]
Multiple, all	38	58	0.66 (0.44–1.00)	0.74 (0.51–1.06)
First birth multiple	12	21	0.58 (0.29–1.19)	0.59 (0.23–1.41)
Subsequent birth multiple	26	37	0.70 (0.42–1.16)	0.85 (0.50–1.44)
Last birth multiple	26	40	0.67 (0.32–1.38)	0.79 (0.37–1.67)
Age at first multiple (yr)				
<25	5	12	0.42 (0.14–1.23)	0.50 (0.17–1.47)
25–29	17	22	0.75 (0.40–1.40)	0.88 (0.46–1.64)
30–34	10	17	0.59 (0.27–1.29)	0.70 (0.32–1.53)
≥35	6	7	0.95 (0.32–2.83)	0.98 (0.36–2.85)
Time since last multiple (yr)				
<15	4	5	0.88 (0.23–3.34)	0.90 (0.27–3.12)
15–29	19	29	0.60 (0.33–1.07)	0.62 (0.35–1.13)
≥30	15	24	0.69 (0.36–1.33)	0.78 (0.40–1.53)

[1]Estimates from multiple logistic regression equations, including terms for age and center.–[2]Estimates from multiple logistic regression equations including terms for age, centre, parity, age at menarche, age at first birth, menopausal status, age at menopause, history of benign breast disease, familial history of breast cancer, oral contraceptive use and body mass index.–[3]Reference category.

indicates that ovulation-inducing drugs were not common in Italy in the generations of women included in our study.

Twin pregnancies are associated with higher levels of alpha-foeto-protein (Jacobson et al., *1989; Johnson* et al., *1990), whose action on mammary tissue may reduce subsequent breast cancer risk, but also of oestrogens, which may increase breast cancer risk (Trichopoulos, 1990). On the basis of available epidemiological data, however, it is unclear whether these mechanisms have any practical influence on breast cancer risk following multiple births or whether reciprocal interactions of both factors or thresholds in their effects on breast tissue led to the absence of association (of practical relevance) between multiple births and breast cancer risk.*

Yours sincerely,

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REFERENCES

BRESLOW, N. E. and DAY, N. E., *Statistical methods in cancer research, Vol. 1, The analysis of case-control studies,* IARC Scientific Publication, **32,** IARC, Lyon (1980).

DIETZ, A.T., NEWCOMB, P.A., STORER, B.E., LONGNECKER, M.P., and MITTENDORF, R., Multiple births and risk of breast cancer. *Int. J. Cancer,* **62,** 162–164 (1995).

HSIEH, C., GOLDMAN, M., PAVIA, M., EKBOM, A., PETRIDOU, E., ADAMI, H. and TRICHOPOULOS, D., Breast cancer risk in mothers of multiple births. *Int. J. Cancer,* **54,** 81–84 (1993).

JACOBSON, H.I., THOMPSON, W.D. and JANERICH, D.T., Multiple births and maternal risk of breast cancer. *Amer. J. Epidemiol.,* **129,** 865–873 (1989).

JOHNSON, J.M., HARMAN, C.R., EVANS, J.A., MACDONALD, K. and MANNING, F.A., Maternal serum alpha-fetoprotein in twin pregnancy. *Amer. J. Obstet. Gynecol.,* **162,** 1020–1025 (1990).

LA VECCHIA, C., NEGRI, E., FRANCESCHI, S., FAVERO, A., NANNI, O., FILIBERTI, R., CONTI, E., MONTELLA, M., VERONESI, A., FERRARONI, M. and DECARLI, A., Hormone replacement treatment and breast cancer risk: a cooperative Italian study. *Brit. J. Cancer,* **72,** 244–248 (1995).

NASCA, P.C., WENSTEIN, A., BAPTISTE, M. and MAHONEY, M., The relation between multiple births and maternal risk of breast cancer. *Amer. J. Epidemiol.,* **136,** 1316–1320 (1992).

TRICHOPOULOS, D., Hypothesis: does breast cancer originate *in utero? Lancet,* **335,** 939–940 (1990).