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Letters

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Letters To The Editor: Comments on *The Role of Reproductive and Menstrual Factors in Cancer of the Breast Before and After Menopause,* Talamini *et al., Eur J Cancer,* 32A, No. 2, pp. 303–310, 1996

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LARGE BIRTH WEIGHT AND RISK OF POSTMENOPAUSAL BREAST CANCER

IN THE paper of R. Talamini and associates recently published in your journal [1], some differences were demonstrated in reproductive risk factors between pre- and postmenopausal breast cancer patients. Thus, premenopausal patients had a greater risk of breast cancer development associated with longer duration of menstrual bleeding, multiparity and high age at last birth. In both pre- and postmenopausal women, breast cancer risk was equally high for patients whose age at first birth was lower than 20 years.

We wish to add to this important list our observation on the incidence of large birth-weight babies (> 4000 g) in breast cancer patients. According to our data, the incidence of this sign of hormonal–metabolic disturbances is higher in postmenopausal than in premenopausal patients [2]. As most babies > 4000 g are born due to hyperglycaemia–hyperinsulinaemia during pregnancy [3] and are associated with early menarche [4, 5], large birth-weight may be considered both as a marker of predisposition to postmenopausal early breast cancer development as well as a possible indication for disease prevention strategies [2].

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Response from: S. Franceschi,[1] R. Talamini[1] and C. La Vecchia[2,3]

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L. BERSTEIN REPORTS an association between the frequency of large-baby births and breast cancer risk in postmenopausal women. Albeit we did not collect information on the weight at birth of the offspring of study women, we had data on history of diabetes mellitus which provides further evidence on the point he raised.

Postmenopausal women who reported history of diabetes had an odds ratio (OR) of 1.5 (95% confidence interval, CI: 1.1–2.0) (Table 1). Although this was strongly correlated with severe obesity (i.e. body mass index, BMI, $kg/m^2 > 28.8$), another risk factor for breast cancer in our study [1], diabetes seemed to enhance risk independently (Table 1). Conversely, among diabetic premenopausal women, there was no risk elevation (OR = 0.9; 95% CI: 0.4–2.1). With respect to age at onset of diabetes, an association emerged only for onset after 55 years of age, most likely to be type-2 non-insulin-dependent diabetes (not shown).

Thus, these data also lend support to the possibility that hyperinsulinaemia with insulin resistance may increase breast cancer in older women [2, 3]. Insulin and insulin-like growth factors (IGF) can act both directly on the growth of breast cancer cells and indirectly, as they are inversely correlated to sex-hormone binding globulins [2]. Since insulin and IGF levels are partly modifiable [4], these findings, if confirmed and better understood, can have implications on prevention

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Table 1. Combined effect of diabetes mellitus and obesity on postmenopausal breast cancer risk, Italy 1991–1994

	Diabetes mellitus				
	No		Yes		All
Severe obesity*	Cases:controls	OR (95% CI)†	Cases:controls	OR (95% CI)†	OR (95% CI)†
No	1117:1287	1‡	62:49	1.6 (1.1–2.4)	1‡
Yes	348:362	1.2 (1.0–1.4)	44:39	1.6 (1.0–2.5)	1.2 (1.0–1.4)
All	1465:1649	1‡	106:88	1.5 (1.1–2.0)	

* Women who belonged to the 5th highest quintile of body mass index ($kg/m^2 > 28.8$). † Odds ratios (OR) and 95% confidence intervals (CI) from unconditional multiple logistic regression equations including terms for study area, age, education, parity, menopausal status, plus diabetes and severe obesity, when required. ‡ Reference category.

(e.g. increase of physical activity [5]), as well as treatment (e.g. pharmacological inhibitors of IGF action [6]).

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p21^{WAF1} and p53 Immunohistochemical Expression in Breast Carcinoma may Predict Therapeutic Response to Adjuvant Treatment

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P53 GENE alterations may play a major role in determining cellular chemosensitivity [1, 2]. However, *in vivo* studies using p53 immunohistochemical overexpression as a marker of *P53* mutation provided conflicting results [3–5]. One problem with immunohistochemical studies is that p53 overexpression does not always reflects *P53* mutation and loss of function. A way to investigate the functional status of *P53* is to evaluate the expression of some of its downstream effectors, such as p21^{WAF1}, which acts by blocking cyclin-dependent kinases.

We investigated the immunohistochemical expression of p53 and p21 in 170 invasive breast carcinomas, treated with adjuvant systemic therapy. 140 patients were node-positive (N1/2) and 30 were node-negative (N0); median follow-up

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