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Perspectives and Commentaries

Eicosanoids in Breast Cancer

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(A COMMENT ON: Watson J, Chuah S. Prostaglandins, steroids and human mammary cancer. *Eur J Cancer Clin Oncol*, 1985, **21**, 1051–1055.)

THE IMPETUS to investigate the relationship between eicosanoids and breast cancer came from two directions. First, Powles *et al.* [1] found that breast tumors from patients with bone metastases produced osteolysis *in vitro* which was reduced in the presence of acetylsalicylic acid, a prostaglandin synthetase inhibitor. These results suggested that a prostaglandin (PG)-like material was produced by the breast tumors and could be one of the caustive agents of bone resorption. Second, greater amounts of PGE_2 have been demonstrated in human and experimental mammary tumors, and it has been shown that other eicosanoids are also present in the biochemical environment of the normal and neoplastic mammary system [review—2].

In breast cancer, elevated levels of PG-like material or, specifically, PGE_2, have been associated with bone metastasis and hypercalcemia, shorter survival time, immunosuppression, degree of invasiveness and estrogen receptor status of the breast tumors [review—2]. There are numerous reports representing evidence that tumor-associated eicosanoids may exert physiologic and pathophysiologic effects in breast cancer patients. However, the decisive role of eicosanoids in breast cancer has remained unclear. This may be due, in part, to contradictions in research findings and a lack of standardization of procedures in different laboratories (Table 1).

A recent report by Watson and Chuah [3] described high levels of PGE_2 and $PGF_{2\alpha}$ secretion by malignant breast tumors compared with normal and benign breast tissue. Prostaglandin E_2 synthesis by estrogen positive (ER+) breast tumors was higher than by ER− breast tumors, a finding consistent with one study [4], but not with two previous reports [5, 6], Rolland *et al.* [5], stating that a lesion containing a steroid receptor tended to produce less PGE_2 than did a steroid receptor negative tumor. Exogenous estradiol (1 μg/ml) added to cultures of ER+ breast tumors significantly stimulated synthesis of both PGE_2 and $PGF_{2\alpha}$ [3], consistent with the hypothesis that ER+ breast tumors preferentially metastazising to bone are capable of producing high levels of PGE_2 equivalents [7].

In reviewing such results [3], a number of issues must be addressed in light of previous methodological variations which have been summarized in Table 1:

(1) Does storage of biopsy material in chilled medium for 1–2 hr offer an advantage over rapid freezing of the specimen in liquid nitrogen? A practical advantage of freezing may be that the specimens could be stored when immediate processing is not possible.

(2) What is the advantage of using 0.4 mm-thick tumor pieces over a microsomal preparation of prostaglandin synthetase? If the tumor pieces are used, what proportion of an eicosanoid measured in the medium is newly-synthesized and what level was already present in the tissue?

(3) Overall, new synthesis of eicosanoids is influenced by the concentration of the substrate fatty acid, arachidonate, and the availability of cofactors. Is it necessary to add these to obtain optimal conditions?

(4) Slices of tumor tissue may vary in cellular composition and histological characterization depending upon the section of the tumor biopsied. Would histological char-

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acterization provide useful information on tumor and inflammatory cells present and reflect the source of eicosanoids?

(5) Mechanical handling of tissue may result in stimulation of eicosanoid synthesis. This procedural error should be ruled out by including a sample treated with a prostaglandin synthetase inhibitor. Such a control would be useful in providing information on basal levels of eicosanoids present in tumor tissues.

Watson and Chuah [3] have introduced a simple procedure which may prove useful in studying the role of eicosanoids in relation to ER status in breast cancer. In developing future directions for such studies, it would be interesting to study the interaction of tamoxifen, a prostaglandin inhibitor [8] in relation to ER status. First, however, attention needs to be placed on standardizing the methodology in order to facilitate introduction of this test to a variety of cooperative groups.

Table 1

Reference	Groups (*n* patients)	Comments
1. Bennett *et al.* [9]	Benign neoplasms (5) Malignant neoplasms (23)	No bone metastases: almost entirely PGE-like material (180 ng/g). With bone metastases: 80–100% PGF-like material (70–1080 ng PGE_2 equivalents/g)
2. Bennett *et al.* [7]	Benign neoplasms (16) Carcinomas (66)	Tumors from patients with positive bone scan produced more prostaglandins than did those from scan-negative patients. Alkali hydrolysis failed to confirm PGF-like activity. Basal amounts of PG-like materials were higher in invasive tumors than in non-invasive tumors.
3. Bennett *et al.* [10]	Malignant (120)	Bone metastases and invasiveness were associated with highest amounts of PG-like material.
4. Ritchie [8]	Malignant (Stage I–II) (8)	PGE and PGF were present in malignant breast tissue and tamoxifen inhibited synthesis of both.
5. Wilson *et al.* [6]	StageI (16) Estrogen receptor (ER)+ (20)	No correlation between PG-like material, ER or axillary lymph node status.
6. Rolland *et al.* [5]	T1 (11) T2 (32) T3 (24) T4 (4)	(a) An inverse relationship between PGE_2 production and size of lesion—T1 +[2]T2 vs. T3 + T4. (b) PGE_2 production was proportional to cellularity in small-size tumours in which neoplastic cells were adherent. (c) PGE_2 production was higher in ER− than ER+[2] tumors.
7. Karmali *et al.* [4]	Malignant neoplasms (24)	(a) Tissue content of 5 eicosanoids was greater in neoplastic tissue than in noncancerous tissue. (b) There was no difference in the rate of eicosanoid production between cancerous and noncancerous tissue *in vitro*. (c) TXB_2 was associated with tumor size, axillary lymph node metastases and distant metastasis. (d) TXB_2 production was higher but PGE_2 and 6-keto-$PGF_{1\alpha}$ were lower in ER− tumors compared with ER+ tumors.
8. Watson *et al.* [11]	Breast carcinoma (100)	(a) A significant correlation between PGE_2 and $PGF_{2\alpha}$ in individual tumors. (b) No relation between $PGE_2/PGF_{2\alpha}$ and menopausal status of patients. (c) No relation between $PGE_2/PGF_{2\alpha}$ and estrogen/progesterone.
9. Watson *et al.* [3]	Normal (6) Benign (5) Malignant (20)	(a) Prostaglandin secretion was greater from malignant breast tumors than from normal or benign breast tissue. (b) PGE_2 synthesis by ER+ tumors was higher than ER− tumors. (c) Exogenous estradiol stimulated synthesis of PGE_2 and $PGF_{2\alpha}$ by ER+ tumors.

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