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Breast Cancer Chemoprevention

Alberto Costa

Cancer chemoprevention is a new challenging issue for oncology. For breast cancer, different strategies for risk avoidance, chemopreventive measures and chemosuppressive interventions are being investigated. Attention is presently focused on two compounds, the synthetic retinoid fenretinide (4-HPR) and the antioestrogen tamoxifen, and their possible synergism. More data are now available on the expression and regulation of retinoic acid receptors in human breast cancer cells and on the consequences of the interaction of retinoids with plasma retinol binding protein. Mechanistic relationships between retinoids and growth factors like transforming growth factor-β have been demonstrated in the frame of a central regulatory system of the state of differentiation and proliferation, in which tamoxifen is involved as well.

Recent data from different trials using tamoxifen as adjuvant treatment have shown a decrease in the incidence of contralateral new primaries and that it could soon become unethical not to prescribe this drug to all node-negative oestrogen receptor-positive postmenopausal patients.
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INTRODUCTION

IN CONCLUDING his Mühlbock Memorial Lecture in 1989, Sir Richard Doll affirmed that "we are, for the most part, winning the fight against cancer" and stressed the importance of a better application of the knowledge we already have to discover how new hazards can be avoided. In the same paper [1] he was basing his positive assessment mainly on the progress achieved in cancer control under 45 years of age. For tumours affecting the older population more effort needs to be made in order to improve curability rates.

Chemoprevention is currently proposed to develop and use new pharmacological agents to enhance the protective mechanisms which the human organism has to prevent the development of invasive cancer [2], which, in part, explains why it may be 20 years or more between the original mutagenic initiation of the carcinogenic process and the subsequent development of malignant cells.

Chemoprevention of cancer can be defined as the use of non-cytotoxic nutrients or pharmacological agents to enhance intrinsic physiological mechanisms that protect the organism against the development and progression of mutant clones of malignant cells [3]. In contrast to the cytotoxic approach of chemotherapy of invasive cancer, in which a deliberate attempt is made to kill cancer cells, chemoprevention attempts either to block the original initiation of the carcinogenic process (as with agents that prevent the activation of mutagenic agents or their subsequent binding to DNA) or to arrest or reverse the further progression of premalignant cells (before they become invasive or metastatic) during the very long latency period characteristic of most human cancers.

Indeed, there is already clinical evidence that chemoprevention can be useful in a human setting, as has been shown by the ability of synthetic retinoids to arrest or reverse the progression of leukoplakia (a presursor of oral carcinoma) [4, 5] and to reduce the occurrence of second primary carcinomas of the head and neck [6], as well as by the ability of tamoxifen to reduce the occurrence of second primaries in the contralateral gland of breast cancer patients [7].

Correspondence to A. Costa, European School of Oncology, Via Venezian, 18, 20133 Milano, Italy.
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Chemopreventive compounds

More than 600 potentially chemopreventive agents have been identified and approximately 30 of them are presently being tested in humans [8]. The great heterogeneity of these compounds (they belong to over 20 different classes of chemicals) might be a positive feature as it indicates that a variety of approaches is possible and that the options for selecting effective compounds will be numerous. Chemopreventive agents can be classified according to their mechanism into two broad categories [9], i.e. compounds effective against complete carcinogens and compounds effective against tumour promoters. Some compounds belong to both categories.

The inhibitors of carcinogen-induced tumours can be further divided into three major groups according to their different mechanisms of action. The first includes agents which interfere with the metabolic reactions changing precursor compounds into carcinogens. The second comprises agents capable of preventing carcinogens from reaching or reacting with target sites, such as by scavenging the reactive form of carcinogens. The third group includes molecules whose inhibitory action follows exposure to carcinogenic agents and which, for this reason, are called suppressing agents. The preventive activity of tumour promotion inhibitors has been tested mainly in models of epidermal mouse neoplasia induced by topical administration of phorbol esters (TPA). Modulators of calcium metabolism, polyamines and cyclic nucleotides strictly refer to this group, whereas other chemical classes (such as retinoids, phenols and protease inhibitors) also inhibit carcinogen-induced tumours [10].

Despite this large mass of available data and compounds, when focussing on the real potentially chemopreventive agents, we realise that the ones being extensively studied are mainly the retinoids and tamoxifen (Table 1). It is true, however, that research is continuing on other substances like other vitamins, micronutrients and common drugs like aspirin [11].

Breast cancer chemoprevention with retinoids

Over the past few years retinoids have been shown to be effective inhibitors of chemical carcinogenesis in the skin, mammary gland, oesophagus, respiratory tract, pancreas and urinary bladder of experimental animals, particularly when administered shortly after carcinogenic insult. Modification of the basic retinoid structure has produced new molecules with

Table 1. Major areas of chemoprevention research

Compound	Site	Limitations
Retinoids	Lung, skin, head and neck, breast, bladder	Toxicity Teratogenity
Tamoxifen	Breast	Comorbidity Carcinogenicity
Other vitamins, NAC, selenium zinc, etc.	Oesophagus, stomach, colorectal, lung	Insufficient experimental and/or epidemiological data

enhanced target organ specificity, resulting in increased inhibitory activity with reduced systemic toxicity [12].

Additionally, retinoids can suppress tumour promotion and modify some properties of fully transformed malignant cells, restoring anchorage-dependent growth, increasing cellular adhesiveness and inducing multiple phenotypic changes [13].

The exact mechanism(s) of action of retinoids is still unclear, but it has been finally recognised that retinol and its metabolite retinoic acid exert their primary molecular action by activating and simultaneously repressing specific genes [14].

However, although all the encouraging data is arising from the laboratory on the chemopreventive properties of retinoids, the principal factor limiting their clinical use is toxicity, which can include liver toxicity, mucocutaneous drying (e.g. conjunctivitis, minor nose-bleeds, dry mouth), hair loss, palmoplantar desquamation, elevation of serum triglyceride and low-density lipoprotein levels, teratogenesis, arthralgias, bone rarefaction, and impaired dark adaptation.

Approximately 1500 different retinoids have been synthesised by modifying either the ring structure, the side chain or the terminal group of the molecule to obtain more efficacy and fewer side-effects. The most interesting vitamin A analogue presently studied for breast cancer chemoprevention is the synthetic retinoid fenretinide, *N*-(4-hydroxyphenyl)retinamide (4-HPR) [15].

4-HPR was synthesised in the United States of America in the late sixties by R. Gander, and its biological activity assayed by M. Sporn who also showed the preferential accumulation of this compound in breast instead of liver [16]. The inhibition of chemically induced mammary carcinoma in rats by 4-HPR was fully described by Moon *et al.* [17]. This compound has since been studied extensively and proved to be safer than many other retinoids [18].

4-HPR inhibition of carcinogenesis is enhanced by oophorectomy in rats with nitroso-methyl-urea-induced mammary cancers: this might suggest that 4-HPR is highly effective in inhibiting ovarian hormone-independent tumours and that its activity is not mediated via ovarian hormone action.

On the basis of all these data, 4-HPR has been proposed for chemopreventive evaluation in human breast cancer. No acute toxicity is found when administering the retinoid orally at the daily dose of 200 mg. Dermatological tolerability is good and no liver function abnormalities are observed: a 3-day drug holiday is suggested at the end of each month to avoid excessive lowering of serum retinol levels. This effect of 4-HPR has been shown both in rats and humans [19] and it has been related to the impaired dark adaptation side-effect [20, 21].

A large randomised clinical trial of brest cancer chemoprevention with 4-HPR was started at the Milan Cancer Institute in Italy in 1987, with the aim of evaluating the reduction of incidence of contralateral breast cancer in patients already operated on at one side.

The original idea of studying this population was developed by Veronesi *et al.* [20]. The concept was that a patient who has been treated for a small early cancer has a good prognosis (about 80–90% survival), but also has a known risk of developing a contralateral breast cancer. The first advantage of this model is that the incidence of contralateral breast cancer is about 0.8% per year, and that this figure remains stable for the first 10 years after surgery in patients who have experienced a primary in the breast. Secondly, as these patients are already under medical control with periodical follow-up, it is much easier to have them participate in the study for the required lengthy period of time. Thirdly, compliance in these patients is expected to be higher than in the general population.

If 4-HPR will succeed in preventing second primaries in breast cancer patients, it would possibly be useful for a wider group of high-risk subjects. The study has a randomised design with two arms: intervention group vs. no treatment. Treated and untreated patients have the same clinical and laboratory follow-up.

By 30 June 1992, 2713 patients had been randomised (1358 in 4-HPR group and 1355 in the control group). Compliance to protocol is high, and tolerability of the drug remains good. The first group of women who entered the phase I study in January 1986 have completed their 5-year intervention and started the 2-year follow-up. The incompleteness of accrual and the insufficient median follow-up do not allow at present the publication of any preliminary result of this trial. Additionally, as retinoids are not expected to have any effect on the already transformed cell, at least in breast cancer, contralateral primaries appearing in the first 3 years of intervention are thought to be already present at the baseline even if too small to be detected by physical examination and mammography. It is foreseen that the majority of treated patients will be at least in their fourth year of intervention by the summer of 1993, and that the first consistent analyses will be possible after that time.

Breast cancer chemoprevention with tamoxifen

In his recently published overview of new treatments for breast cancer [22], Hortobagy stresses the importance of the new data showing the capability of tamoxifen to reduce the

Table 2. Chemoprevention with tamoxifen. Cumulative frequency of contralateral breast cancers in clinical trials with adjuvant tamoxifen therapy

	Tamoxifen treated patients		Controls	
Clinical trial	No. of patients	No. of tumours	No. of patients	No. of tumours
NATO	564	15	567	17
Scottish	661	9	651	12
Stockholm	931	18	915	32
Copenhagen	164	3	153	4
Toronto-Edmonton	198	3	202	3
ECOG 1178	91	1	90	3
NSABP B-14	1419	23	1428	32
CRC	947	7	965	18
Peto overview	9128	122	9135	184

Modified from S.G. Nayfield, *et al. JNCI* 1991, **83**, 1450–1459.

Table 3. Breast cancer chemoprevention with tamoxifen ongoing studies in healthy women

Study coordinators	Target population	Dosage	Length of intervention
M. Baum, J. Cuzick, T. Powles from the U.K.	Candidate to have three of the following five characteristics: (a) nulliparity of first childbirth after age of 28; (b) serum sex hormone-binding globulin levels below the population median; (c) Wolfe grades (P2 or DY) at mammography; (d) family history of breast cancer (mother or sister); (e) previous benign "fibrocystic" disease	20 mg/daily vs. placebo	5 years
U. Veronesi, C. Maltoni from Italy	Hysterectomised women between 45 and 65 years of age. Multiparous (> 4 pregnancies) and early primiparous (< 20 years of age) are excluded	20 mg/daily vs. placebo	5 years
B. Fisher, NSABP, from the U.S.A.	60 years old or older. Women between ages 35 and 59 at risk for breast cancer (close relatives with the disease, previous breast biopsies, early menarche, etc.)	20 mg/daily vs. placebo	5 years

occurrence of new primaries in the contralateral mammary gland of breast cancer patients receiving the antioestrogen as adjuvant treatment.

This data is reported by the great majority of authors involved in adjuvant tamoxifen clinical trials (Table 2).

However, it should be recalled that these clinical observations [23] are subsequent in time to a number of important laboratory data on the efficacy of tamoxifen to prevent chemically induced mammary carcinomas [24] as well as spontaneous tumour in rats [25].

On the basis of these data three studies have been designed in the U.K., the U.S.A. and Italy on different target populations (Table 3), to evaluate the efficacy of tamoxifen in preventing breast cancer. From recent evaluation of adjuvant studies with tamoxifen [26] one would expect to see greater results mainly in postmenopausal women. However, some of the ongoing studies will try to address also the issue of the efficacy of tamoxifen in younger subjects, as well of the capability of this agent to reduce cardiovascular risk factors [27] and decrease in bone density [28] in postmenopausal women.

Future prospects

Although it will certainly take more than 10 years to have solid results from the three chemoprevention trials with tamoxifen in healthy women, clinicians should always continue to pay attention to new data coming from the laboratory. There is a growing mass of knowledge, for example, on the nuclear retinoic acid receptors (RAR) which are believed to be the mediators of the mammary carcinogenesis inhibition induced by retinoic acid. In fact, the potential chemopreventive effect of retinoids in breast cancer raises the question of whether breast cancers express RAR [29], and whether this expression is the biomolecular basis for the increased ability of retinoids and antioestrogens to inhibit breast cancer cell growth in combination. Preliminary studies in Sprague–Dawley rats, for example, showed that combined treatment with 4-HPR plus tamoxifen is superior to that of either agent alone in blocking progression of incipient neoplastic lesions [30]. The tolerability of the same two agents (tamoxifen at 20 mg, in combination with fenretinide at 100–400 mg/daily with drug holiday) has recently been assessed in previously untreated metastatic breast cancer patients at Rush-Presbiterian-St. Luke's Medical Center in Chicago by M.A. Cobleigh *et al.* (paper in preparation). No significant adverse effects on renal, hepatic, haematological or lipid values were recorded, also myctalopia, photophobia, cheilitis and pruritus were not observed.

The perspective of the availability of different agents separately capable of inhibiting tumour occurrence and/or progression in hormone dependent and independent breast cancers seems very intriguing. The hypothesis that tamoxifen could prevent oestrogen receptor-positive tumours and retinoids the oestrogen receptor negatives is at present purely theoretical but the great similarities among the different members of the so-called steroid receptor superfamily, including retinoids, make it worthy of further investigation.

1. Doll R. Are we winning the fight against cancer? An epidemiological assessment. EACR-Mühlbock Memorial Lecture. *Eur J Cancer* 1990, **26**, 500–508.
2. Sporn MB, Roberts AB, Glick AB, Luckert PH, Pollard M. Interaction of retinoids and transforming growth factor-β in the chemoprevention of cancer. In Sporn MB, ed. *Control of Growth Factors and Prevention of Cancer. ESO Monograph*. Berlin, Springer 1992, 37–49.
3. Sporn MB. Carcinogenesis and cancer: different perspectives on the same disease. *Cancer Res* 1991, **51**, 6215–6218.
4. Hong WK, Endicott J, Itri LM, *et al.* 13-*cis*-retinoic acid in the treatment of oral leukoplakia. *N Engl J Med* 1986, **315**, 1501–1505.
5. Chiesa F, Tradati N, Marazza M, *et al.* Prevention of local relapses and new localization of oral leukoplakias with synthetic retinoid fenretinide (4-HPR). *Oral Oncol Eur J Cancer* 1992, **28B**, 97–102.
6. Hong WK, Lippman SM, Itri LM, *et al.* Prevention of second primary tumours in squamous cell carcinoma of the head and neck with 13-*cis*-retinoic acid. *N Engl J Med* 1990, **323**, 795–801.
7. Early Breast Cancer Trialists' Collaborative Group. Systemic treatment of eary breast cancer by hormonal, cytotoxic, or immune therapy: 133 randomised trials involving 31,000 recurrences and 24,000 deaths among 75,000 women. *Lancet* 1992, **339**, 1–15.
8. Malone WF, Kelloff GJ, Pierson H, Greenwald P. Chemoprevention of bladder cancer. *Cancer* 1987, **60**, 650–657.
9. Wattemberg LW. Chemoprevention of cancer. *Cancer Res* 1985, **45**, 1–8.
10. Costa A. Chemoprevention of cancer: experimental and clinical aspects. *Forum* 1991, **1**, 331–337.
11. Baron JA, Greenberg ER. Could aspirin really prevent colon cancer? *N Engl J Med* 1991, **325**, 1644–1645.
12. Costa A, De Palo G, Formelli F, Veronesi U. Breast cancer chemoprevention with retinoids. In Livrea, Packer, eds. *Retinoids: Progress in Research and Clinical Applications*. New York, Marcel Dekker Inc. 1992, 453–464.
13. Moon RC, McCormick DL, Metha RG. Inhibition of carcinogenesis by retinoids. *Cancer Res* 1983, **43**, 2469s–2475s.
14. Glick AB, Flanders KC, Danielpour D, Yuspa SH, Sporn MB. Retinoic acid induces transforming growth factor-β2 in cultured keratinocytes and mouse epidermis. *Cell Reg* 1989, **1**, 87–97.
15. Costa A. Biological approaches to breast cancer prevention. *The Breast* 1992, **1**, 119–123.
16. Sporn MB, Newton DL. Chemoprevention of cancer with retinoids. *Fed Proc* 1979, **38**, 2528–2534.

17. Moon RC, Thompson HJ, Becci PL, *et al.* *N*-(4-hydroxyphenyl)retinamide, a new retinoid for prevention of breast cancer. *Cancer Res* 1979, **39**, 1339–1346.
18. Paulson JD, Oldham JW, Preston RF, *et al.* Lack of genotoxicity of the cancer chemopreventive agent *N*-(4-hydroxyphenyl)retinamide. *Fundam Appl Toxicol* 1985, 5, 144–150.
19. Formelli F, Carsana R, Costa A, *et al.* Plasma retinol level reduction by the synthetic retinoid fenretinide: a one year follow-up study of breast cancer patients. *Cancer Res* 1989, **48**, 6149–6152.
20. Veronesi U, De Palo G, Costa A, *et al.* Chemoprevention of breast cancer with retinoids. *INCI Monographs* 1992, **12**, 93–97.
21. Berni R, Formelli F. The interaction of fenretinide with plasma retinol-binding protein and its functional consequences. In press.
22. Hortobagyi GN. Overview of new treatments for breast cancer. *Breast Cancer Res Treat* 1992, **21**, 3–13.
23. Fisher B, Costantino J, Redmond C, *et al.* A randomized clinical trial evaluating tamoxifen in the treatment of patients with node-negative breast cancer who have estrogen-receptor-positive tumours. *N Engl J Med* 1989, **320**, 479–484.
24. Jordan VC. Effect of tamoxifen on initiation and growth of DMBA-induced rat mammary carcinomata. *Eur J Cancer* 1976, 12, 419–424.
25. Maltoni C, Pinto C, Paladini G. Project of experimental bioassays on chemoprevention agents performed at the Bologna Institute of Oncology: report on tamoxifen control of spontaneous mammary tumours on Sprague–Dawley rats. *Cancer Invest* 1988, **6**, 643–658.
26. Cancer Research Campaign Breast Cancer Trials Group. The effect of adjuvant tamoxifen: the latest results from the Cancer Research Campaign Adjuvant Breast Trial. *Eur J Cancer* 1992, **28A**, 904–907.
27. Love RR, Wiebe DA, Newcomb PA, *et al.* Effects of tamoxifen on cardiovascular risk factors in postmenopausal women. *Ann Int Med* 1991, **115**, 860–864.
28. Love RR, Mazess RB, Barden HS, *et al.* Effects of tamoxifen on bone mineral density in postmenopausal women with breast cancer. *N Engl J Med* 1992, **326**, 852–856.
29. Roman SD, Clarke CL, Hall RE, Alexander IE, Sutherland RL. Expression and regulation of retinoic acid receptors in human breast cancer cells. *Cancer Res* 1992, 52, 2236–2242.
30. Ratko TA, Detrisac CJ, Dinger MN, Thomas CF, Kelloff GJ, Moon RC. Chemopreventive efficacy of combined retinoid and tamoxifen treatment following surgical excision of a primary mammary cancer in female rats. *Cancer Res* 1989, **49**, 4472–4476.

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****** IMPORTANT NOTICE ******

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Primary Medical (Neo-adjuvant) Chemotherapy for Operable Breast Cancer by Ian A Smith, Alison L Jones, Mary E R O'Brien, J A McKinna, Nigel Sacks and Michael Baum.

THIS ARTICLE CONTAINS ERRORS AND HAS BEEN WITHDRAWN. A CORRECTED VERSION WILL BE PUBLISHED IN A LATER ISSUE OF VOLUME 29 OF THE *EUROPEAN JOURNAL OF CANCER*.

84 patients with large operable breast cancer have been treated with primary medical chemotherapy rather than mastectomy in three sequential studies. 86% had tumours greater than 4 cm in diameter; median diameter was 6 cm (range 1–12). Median age was 46 years (range 23–66). In the first two studies 64 patients were treated with either CMF [cyclophosphamide 100 mg orally days 1–14, methotrexate 50 mg intravenously (i.v.) days 1 and 8, and 5-fluorouracil 1 g i.v. days 1 and 8, repeating at 28-day intervals for six courses] or MMM (mitozantrone 8 mg/m² i.v. three times a week, methotrexate 50 mg i.v. three times a week, mitomycin C 8 mg/m² six times a week, for 8 courses). 69% achieved an overall response including 17% complete remissions. 27% have had local relapse but only 3% uncontrolled local relapse. Only 14% have required mastectomy. In the third study which is ongoing, 19 patients have been treated with infusional FEC (5-fluorouracil 200 mg/m² i.v. 24 hourly by continuous infusion via a Hickman line for 6 months, epirubicin 50 mg/m² i.v. bolus three times a week for 6 months, cisplatin 60 mg/m² i.v. three times a week for 6 months with appropriate intravenous hydration). Overall response rate so far is 84% with 58% complete remissions. There have been no local relapses and no patient has required mastectomy. This study demonstrates that primary medical chemotherapy can be used to avoid mastectomy in the great majority of patients presenting with large operable primary breast cancer. Infusional FEC may be more active than conventional chemotherapy in terms of overall response and complete remission rate, and infusional FEC chemotherapy now needs to be compared with conventional chemotherapy. The concept of primary medical therapy should also be compared with conventional mastectomy followed by adjuvant chemotherapy.
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INTRODUCTION

THE CONVENTIONAL approach to the systemic management of early breast cancer is to give adjuvant chemotherapy or endocrine therapy postoperatively, after surgical excision of the primary tumour. In primary medical therapy (also called neo-adjuvant therapy) the roles are reversed, and chemotherapy and/or endocrine therapy is given as first-line treatment to try to achieve tumour regression before surgery. The origins of primary medical therapy lie in experience gained in the management of locally advanced inoperable breast cancer; here medical treatment has been used increasingly in recent years prior to local radiotherapy to try to improve local control and prolong survival [1].