

# Recent Progress in Treatment and Secondary Prevention of Breast Cancer With Supplements

Steve Austin, N.D.

## Abstract

This article discusses five naturally occurring agents that are currently being studied to evaluate their potential in the treatment and/or secondary prevention of breast cancer. Preliminary data have been published suggesting that high dose coenzyme Q10 may have anti-cancer activity in women with node-positive breast cancer. Low serum levels of dehydroepiandrosterone associate with increased risk of premenopausal breast cancer, but a reduced risk of postmenopausal breast cancer. The clinical implications remain unclear. Melatonin has antiestrogenic and antioxidant activity. Preliminary research suggests that high-dose melatonin may have anti-cancer activity particularly in women with estrogen receptor-positive breast cancer. Preliminary data show that vitamin D analogues and possibly vitamin D itself have anti-cancer activity in relation to human breast cancer. Blinded research using yeast-based selenium suggests powerful anti-cancer activity, though it does not yet appear that the protection extends to reduction in breast cancer risk specifically.

*(Alt Med Rev 1997;2(1):4-11)*

## Introduction

Small reductions in American breast cancer mortality rates are finally appearing after many decades showing no progress. Early detection may indirectly be the leading cause of these limited gains, but advances in allopathic treatment may also be partially responsible.<sup>1</sup> Nonetheless, in American women breast cancer remains both the most common invasive cancer and the second leading cause of cancer deaths.<sup>2</sup>

Many women choose to augment or in some cases replace parts of allopathic treatment with natural medicine. In the case of nutritional intervention for the purpose of secondary prevention, our basic understanding of the relationship between diet and breast cancer has not changed significantly in the last few years and has been reviewed elsewhere.<sup>3</sup> However, the picture is changing regarding the use of certain natural substances in the treatment of breast cancer. The purpose of this review is to describe these recent changes. Research regarding the relationship between breast cancer prevention or treatment and most standard nutritional antioxidants (vitamins E, C, and beta-carotene) and medicinal herbs (such as the Hoxsey formula) will not be included in this review.

## Coenzyme Q 10 (CoQ10) as a Treatment for Breast Cancer

Three preliminary reports by the same research group have recently concluded that coenzyme Q10 may play a role in the treatment and secondary prevention of breast cancer. All three have serious methodological shortcomings.

In 1994, Danish and American workers reported on the previously unpublished results<sup>4</sup> of treating 32 node-positive breast cancer patients for 18 months with a protocol of supplements plus conventional allopathic treatment.<sup>5</sup> The protocol included 2850 mg vitamin C, 2,500 IU vitamin E, 32.5 IU  $\beta$ -carotene (presumably synthetic), 387 mcg selenium, 1.2 g gamma-linolenic acid, 3.5 g omega-3 fatty acids from fish oil, 90 mg CoQ10 and a low-dose multi-vitamin/mineral per day. Only some of the 32 had evidence of metastatic disease at the start of the study but specifics were not given. It's remarkable that better data were not provided, as the staging of breast cancer is critical to prognosis, and expected prognoses are essential to the evaluation of the outcome of this study.

All 32 patients survived the 18 months. None showed further evidence of distal metastasis. As most node-positive patients would be expected to both survive and be metastasis-free after such a brief period, the chance of 18 months of metastasis-free survival in a group of 32 node-positive patients even without supplemental intervention is unclear without more staging detail and statistical analysis; neither was fully provided.

If many of the 32 patients actually had metastatic disease (stage IV), then a lack of progression after 18 months would be impressive indeed. By not listing how many patients were stage IV, proper evaluation of this study becomes impossible.

The authors reported no weight loss and a "reduced use of pain killers." However, stage II and III patients (some of whom were included in this study) would not be expected to lose weight and most do not take analgesics unless done so postsurgically. The use of postsurgical analgesics would naturally decline even in the absence of nutritional intervention. Again, the statements made by the authors cannot be properly evaluated.

Six of the 32 showed evidence of "partial remission." However, patients were also treated with tamoxifen and/or chemotherapy. The possibility of 18-month partial remissions from conventional treatment is quite real given the small sample size. As for typical stage II and III patients, most become temporarily disease-free as a result of conventional allopathic treatment, making "partial remission" resulting from the use of the supplements impossible to evaluate for such patients; they should already be in total remission.

Increased natural killer cell and total lymphocyte counts were recorded between months 3 and 12 of the intervention, but no baseline was provided. Thus, the increases in killer cell and lymphocyte count could have been due to cessation of chemotherapy.

Six cases were described more fully. One patient with bony metastases showed no progression of disease—an 18 month outcome which might have resulted from the tamoxifen she was taking. Another patient had pleural metastases which disappeared from her chest film, but she had also been treated with chemotherapy. Reports of the disappearance of local residual tumor and decrease in the size of recurrence to skin overlying the breast in two other patients were accompanied with no details about allopathic treatment. Another patient who did not have metastatic disease was in "excellent clinical condition" throughout the 18 months, but such an

outcome is common in the absence of the supplement protocol. The sixth case suffered a local recurrence during the intervention. Thus the outcome of this preliminary study proves very little.

A later report of the same trial describes two-year follow up.<sup>6</sup> At that time, all patients were still alive and evidence of further metastatic spread was not found. The authors report that six of the 32 were expected to be deceased at two years, but without staging information, this figure cannot be verified.

Higher dose CoQ10 were used in two of the 32 patients. In one case, after two years at 90 mg, the dose of CoQ10 was increased to 390 mg. Local recurrence apparently disappeared after one month on high-dose CoQ10. This case appears to be unverified, however, because apparent clinical recurrences need to be confirmed by biopsy; in this case the evidence of appearance and disappearance seem to have come from physical exam and mammography alone.

Another patient was given 300 mg of CoQ10. After four months, there was apparent disappearance of residual carcinoma not removed by the original surgery. Again, however, the evidence was from physical and mammographic findings apparently not confirmed by biopsy.

Like the initial report, the two-year follow-up claims tumor regression in “six” of the 32 patients. Two of the six cases of regression were discussed in the second report in more detail. However, neither is among the six discussed in the original report, suggesting that two of the original cases of regression must have suffered a relapse, though this is not stated. The second report goes on to review the data showing increased immune function in humans resulting from CoQ10 supplementation<sup>7</sup> and decreased blood levels of CoQ10 in cancer patients.<sup>8</sup>

A third report has more recently been published by the same group, describing three additional patients treated with 390 mg of CoQ10 for 3-5 years.<sup>9</sup> In one patient, multiple liver metastases disappeared after 11 months of high-dose CoQ10 administration. While the details are not completely clear, it seems that the disappearance of liver metastases did not happen during or shortly after chemotherapy, suggesting that the CoQ10 may have been responsible for the remarkable remission. This case is complicated by the fact that the diagnosis was apparently mislabeled “invasive intraductal” carcinoma (now called ductal carcinoma in situ [DCIS]). DCIS is by definition not invasive and does not progress directly to metastatic disease. Possibly, the patient had invasive ductal carcinoma, and the diagnosis was improperly stated.

In the second of the three cases, fluid in the right pleural cavity associated with proven metastasis disappeared during three years of CoQ10 administration (90 mg for one year and 390 for the last two years). In the absence of CoQ10, this durable remission would be extremely unlikely, even if chemotherapy or tamoxifen had been used.

The third patient described had lumpectomy with involved margins followed by mastectomy. While she remained disease-free during 39 months of CoQ10 therapy, no rationale is provided as to why this outcome would be unexpected in the absence of CoQ10. Many node-positive patients are disease-free at 39 months.

Most importantly in the evaluation of the last report, it is unclear whether the final three cases were consecutive or were selected because these patients fared particularly well. If the latter is true, then this report, as interesting as it is, would not tell us the likelihood that massive doses of CoQ10 would help late-stage patients.

While troubled by omissions and lack of important data in all three reports, I have nonetheless begun to suggest high-dose CoQ10 as part of the protocol I use with node-positive breast cancer patients with high risk of recurrence. A lack of serious CoQ10 toxicity, the hope of a therapeutic effect with CoQ10, and a lack of curative allopathic treatments for late-stage patients combines to form my rationale. Other doctors of natural medicine have done the same, but to date it appears that none of us has followed these patients long enough to evaluate the possible effects. While the preliminary results look both interesting and encouraging, the real effects of using high-dose CoQ10 in the treatment of breast cancer remain unknown.

### **Dehydroepiandrosterone (DHEA) as a Treatment for Breast Cancer**

Animal studies show that DHEA can inhibit mammary cancer.<sup>10</sup> An association has been reported between low serum DHEA levels and premenopausal breast cancer risk in humans.<sup>11</sup> Those in the highest tertile (third) of serum DHEA had a 60% decreased risk compared with those in the lowest tertile. DHEA sulfate, on the other hand, did not correlate with risk in this or other reports.<sup>12</sup>

However, while DHEA appears to be low in patients with premenopausal breast cancer, higher levels of both DHEA and DHEAS have been reported in postmenopausal patients.<sup>13</sup> The meaning of this discrepancy remains unclear, though high doses of DHEA in postmenopausal women can increase estrogen levels<sup>14</sup> while DHEA is thought to be a potential estrogen antagonist in premenopausal women.<sup>15</sup> Under certain circumstances, DHEA appears to cause cancer in animals.<sup>16,17</sup>

In the absence of intervention trials in humans, the typical interpretation of these data

is that DHEA supplementation may have anti-cancer effects for premenopausal women but may be dangerous for postmenopausal women.<sup>18</sup> While this hypothesis fits with the available data, we still don't know the usefulness or danger in using DHEA in the treatment of breast cancer, nor is an appropriate dose of DHEA for premenopausal women clear. As a result of these uncertainties, the noted author Alan Gaby, M.D., has said in this journal "Until those questions can be answered, DHEA therapy should be approached with caution in patients who are at risk for developing hormone-dependent cancers."<sup>19</sup>

At present there is reason to tell postmenopausal breast cancer patients to avoid DHEA supplementation until more is known. It does not seem unreasonable, however, in the presence of low serum DHEA (as opposed to DHEAS) in a premenopausal woman to consider low-dose DHEA supplementation to restore age-specific normal serum levels.

### **Melatonin as a Treatment for Breast Cancer**

Melatonin is a free-radical scavenger, known to inhibit cellular replication of human breast cancer cells.<sup>20</sup> Melatonin protects against the promotional phase of mammary cancer in animals.<sup>21</sup> Melatonin may indirectly lower estrogen levels.<sup>22</sup> As a result, melatonin delays puberty and suppresses ovulation in mammals.<sup>23</sup> Estrogen-receptor (ER) positive breast cancer patients have been reported to have low melatonin levels (though the opposite was found in ER negative patients).<sup>24</sup>

Some researchers have therefore suggested that melatonin may help protect against breast cancer.<sup>25</sup> Melatonin is also being investigated as a possible treatment for late-stage disease. In a study with 14 stage IV breast cancer patients previously non-responsive to

tamoxifen, 20 mg of melatonin per evening plus tamoxifen led to objective partial remission (median duration eight months) in 4/14 patients (28%).<sup>26</sup> A reduction in anxiety was reported in these patients, perhaps because they might have slept better—a known effect of this hormone.

Some late-stage cancer patients with other primary sites have been reported to stabilize (6/14) or go into partial remission (1/14) as a result of high dose melatonin.<sup>27</sup> Prolongation of life has been reported for lung cancer patients in a trial using 10 mg per evening.<sup>28</sup> Patients lived an average of 7.9 months vs 4.1 without melatonin. Remarkable results have also been reported for patients with metastatic renal cell carcinoma.<sup>29</sup>

The life-and-death nature of metastatic cancer and the absence of any known common serious side effects make melatonin an attractive therapy despite the lack of long-term safety data. It's critical to not take melatonin during the day. Animal data suggest that AM administration stimulates cancer growth in the same species in which PM administration of melatonin inhibits such growth.<sup>30</sup> The known circadian effects of this pineal hormone probably have something to do with these effects which would be viewed as paradoxical in relation to most other hormones.

### **Vitamin D in the Treatment of Breast Cancer**

Vitamin D is needed for normal cell replication. Activated vitamin D suppresses cancer cell growth.<sup>31</sup> Vitamin D may have antiestrogenic activity.<sup>32</sup> Some breast cancer cells have receptors for vitamin D.<sup>33</sup> In some,<sup>34</sup> but not all studies, 35 patients with higher levels of vitamin D receptors have been reported to have longer disease-free survival compared with those lacking such receptors. Sunlight exposure (leading to increased levels of

vitamin D) correlates with reduced risk of breast cancer.<sup>36,37</sup> Non-Hodgkin's lymphoma patients with high levels of receptors for vitamin D have responded to activated (1,25 dihydroxycholecalciferol) vitamin D in a small Scottish trial.<sup>38</sup> To date, intervention trials have not been published with breast cancer, however.

Recently, it was reported that white (but not black) breast cancer patients have low levels of activated vitamin D.<sup>39</sup> Some vitamin D analogues inhibit breast cancer cell growth, a process dramatically facilitated by addition of tamoxifen.<sup>40</sup> New analogues of vitamin D have prevented mammary cancer in rats.<sup>41</sup> A topical vitamin D analogue has led to 50% reduction in locally advanced or cutaneous metastatic breast cancer in 3 of 14 patients.<sup>42</sup> As with the non-Hodgkin's patients, responders had higher levels of vitamin D receptors.

Dietary vitamin D has correlated with increased risk of breast cancer.<sup>43</sup> However, such a finding should be expected because most dietary sources of vitamin D are high in saturated animal fat linked to increased breast cancer risk.

Activated vitamin D is both expensive and potentially quite toxic. Small amounts (1000 IU/day) of vitamin D<sub>3</sub>, more equivalent to the effects of sun exposure associated with protection, can be safely added to the protocol for the treatment of breast cancer in most patients who do not have hypercalcemia. In practice in the Pacific Northwest, accurately noted for its lack of sunshine. Until more is known, I recommend 800-1000 IU of supplemental vitamin D<sub>3</sub> per day to most breast cancer patients.

### **Selenium in the Treatment of Breast Cancer**

Selenium (Se) activates glutathione peroxidase, an enzyme with significant

antioxidant activity. Soil Se (and therefore the level of Se in produce grown in that soil) correlates inversely with cancer.<sup>44</sup>

In the past, prospective and nested case-control studies looking at toenail selenium (Se) levels have not been able to find a correlation between Se and protection from breast cancer.<sup>45-47</sup> There is evidence, however, that dietary Se intake may not correlate with toenail levels.<sup>48</sup>

Conversely, studies evaluating the relationship between serum Se and breast cancer risk have found that higher Se does associate with a significant protective effect.<sup>49-51</sup> In animal studies, supplemental Se helps protect against chemically induced mammary cancer.<sup>52,53</sup> In short, the relationship between Se and breast cancer prevention remains in dispute.

Recently, results from the first double-blinded, randomized cancer prevention trial supplementing Se were published.<sup>54</sup> High-selenium yeast (200 mcg/day Se), or placebo was administered for 4.5 years to 1,312 patients with a past history of non-melanoma skin cancers. These patients were followed for an average of 6.4 years. Recurrence of squamous and basal cell skin cancers was not reduced in the Se group. However, there was a 50% reduction in total cancer mortality ( $p=0.0009$ ), a 45% reduction in total carcinoma incidence ( $p=0.001$ ), a 63% drop in prostate cancer incidence ( $p=0.002$ ), a 58% decrease in colorectal cancer incidence, and a 46% decrease in lung cancer incidence ( $p=0.04$ ). The results were so dramatic that the researchers ended the blinded phase of the trial before the study was completed.

Only 12 people developed breast cancer during the study. Despite the decrease in overall cancer incidence, 9 in the Se group but only 3 in the placebo group developed breast cancer. These numbers did not reach

statistical significance, but the trend clearly does not suggest that Se was protective.

Were Se a patentable drug, a randomized blinded trial showing 50% reduction in total cancer mortality would be followed by a flood of research dollars. We can only hope that further investigation will sort out the true efficacy of Se in preventing cancer and answer three other critical questions: Does the form of Se make a difference? Can Se influence the course of established cancer? Were the paradoxical results regarding breast cancer risk merely a statistical fluke due to small sample size or is the effect of Se on breast cancer risk different from that of other cancers? Until that final question is answered, there is insufficient reason for breast cancer patients to supplement Se.

## Discussion

Allopathic medicine would no doubt argue that using any of the natural therapies discussed in this review for the purpose of treatment or secondary prevention when even primary prevention remains unproved is “unscientific.” In fact this is not so. The data speak for themselves, and in them lie the science or what little we know of it. Deciding how to use those data to effect clinical practice, however, is a function of philosophy (if not ideology)—not a scientific call. The idea that there is no cost in telling women to avoid CoQ10 or melatonin is a philosophical position that may be appropriate in a legal setting but feels both unethical and unreasonable to many doctors of natural medicine.

Stem cell replacement/high dose chemotherapy regimens for breast cancer patients at high risk of recurrence are widely accepted by oncologists. This therapy also remains unproven in the treatment of breast cancer, however, and induces severe

morbidity.<sup>55</sup> The double standard of accepting toxic and partially proven therapies but discrediting harmless and partially proven natural treatments reveals that the unwillingness to seriously consider natural medicine stems from ideology, not science.

## References

1. Chu KC, Tarone RE, Kessler LG. Recent trends in U.S. breast cancer incidence, survival, and mortality rates. *J Natl Cancer Inst* 1996;88:1571-1579.
2. Parker SL, Tong T, Bolden S, Wingo PA. Cancer statistics 1996. *CA Cancer J Clin* 1996;46:5-27.
3. Austin S, Hitchcock C. *Breast Cancer: What You Should Know (But May Not be Told) About Prevention, Diagnosis, and Treatment*. Rocklin, California: Prima Publishing; 1994.
4. Lockwood K, Moesgaard S, Hanioka T, Folkers K. Apparent partial remission of breast cancer in "high risk" patients supplemented with nutritional antioxidants, essential fatty acids and CoQ10. *Eighth International Symposium on the Biomedical and Clinical Aspects of Coenzyme Q10*; Stockholm, Sweden, November, 1993.
5. Lockwood K, Moesgaard S, Hanioka T, Folkers K. Apparent partial remission of breast cancer in 'high risk' patients supplemented with nutritional antioxidants, essential fatty acids and coenzyme Q10. *Molec Aspects Med* 1994;15(Suppl):s231-240.
6. Lockwood K, Moesgaard S, Folkers K. Partial and complete regression of breast cancer in patients in relation to dosage of coenzyme Q10. *Biochem Biophys Res Comm* 1994;199:1504-1508.
7. Folkers K, Shizukuishi S, Takemura K, et al. Increase in levels of IgG in serum of patients treated with coenzyme Q10. *Res Comm Pathol Pharmacol* 1982;38:335-338.
8. Folkers K, Ellis JM, Yang O, et al. In: *Vitamins and Cancer Prevention*. New York: Wiley-Liss; 1991:103-111.
9. Lockwood K, Moesgaard S, Yamamoto T, Folkers K. Progress on therapy of breast cancer with vitamin Q10 and the regression of metastases. *Biochem Biophys Res Comm* 1995;212:172-177.
10. Schwartz AG, Whitcomb JM, Nyce JW, et al. Dehydroepiandrosterone and structural analogs: a new class of cancer chemopreventive agents. *Adv Cancer Res* 1988;51:391-424.
11. Helzlsouer KJ, Gordon GB, Alberg AH, et al. Relationship of prediagnostic serum levels of dehydroepiandrosterone and dehydroepiandrosterone sulfate to the risk of developing premenopausal breast cancer. *Cancer Res* 1992;52:1-4.
12. Barrett-Connor E, Friedlander NJ, Khaw K-T. Dehydroepiandrosterone sulfate and breast cancer risk. *Cancer Res* 1990;50:6571-6574.
13. Zumoff B, Levin J, Rosenfeld RS, et al. Abnormal 24 hour mean plasma concentrations of dehydroepiandrosterone and dehydroepiandrosterone sulfate in women with primary operable breast cancer. *Cancer Res* 1981;41:3360-3363.
14. Mortola JF, Yen SS. The effects of oral dehydroepiandrosterone on endocrine-metabolic parameters in postmenopausal women. *J Clin Endocrinol Metabol* 1990;71:696-704.
15. Ebeling P, Koivisto VA. Physiological importance of dehydroepiandrosterone. *Lancet* 1994;343:1479-1481.
16. Orner GA, Mathews C, Hendricks JD, et al. Dehydroepiandrosterone is a complete hepatocarcinogen and potent tumor promoter in the absence of peroxisome proliferation in rainbow trout. *Carcinogenesis* 1995;16:2893-2898.
17. Shibata M, Hasegawa R. Chemoprevention by dehydroepiandrosterone and indomethacin in a rat multiorgan carcinogenesis model. *Cancer Res* 1995;55:4870-4874.
18. Ebeling P, Koivisto VA. Physiological importance of dehydroepiandrosterone. *Lancet* 1994;343:1479-1481.
19. Gaby AR. Dehydroepiandrosterone: biological effects and clinical significance. *Alt Med Rev* 1996;1:60-69.
20. Cos S, Sanchez-Barcelo EJ. Differences between pulsatile or continuous exposure to melatonin on MCF-7 human breast cancer cell proliferation. *Cancer Lett* 1994;85:105-109.
21. Kothari LS. Influence of chronic melatonin on 9,10-dimethyl-1,2-benzanthracene-induced mammary tumors in female Holtzman rats exposed to continuous light. *Oncology* 1987;44:64-66.
22. Tamarkin L, Baird CJ, Almeida OFX. Melatonin: a coordinating signal for mammalian reproduction? *Science* 1985;227:714-720.
23. Reiter JR. The pineal and its hormones in the control of reproduction in mammals. *Endocrine Rev* 1980;1:109-130.
24. Tamarkin L, Danforth D, Lichter A, et al. Decreased nocturnal plasma melatonin peak in patients with estrogen receptor positive breast cancer. *Science* 1982;216:1003-1005.
25. Cohen M, Lippman M, Chabner B. Role of pineal gland in aetiology and treatment of breast cancer. *Lancet* 1978;ii:814-816.
26. Lissoni P, Barni S, Meregalli S, et al. Modulation of cancer endocrine therapy by melatonin: a phase II study of tamoxifen plus melatonin in metastatic breast cancer patients progression under tamoxifen alone. *Brit J Cancer* 1995;71:854-856.

27. Lissoni P, Barni S, Crispino S, et al. Endocrine and immune effects of melatonin therapy in metastatic cancer patients. *Eur J Cancer Clin Oncol* 1989;25:789-795.
28. Lissoni P, Barni S, Ardizzoia A, et al. Randomized study with the pineal hormone melatonin versus supportive care alone in advanced small cell lung cancer resistant to a first-line chemotherapy containing cisplatin. *Oncology* 1992;49:336-339.
29. Neri B, Fiorelli C, Moroni F, et al. Modulation of human lymphoblastoid interferon activity by melatonin in metastatic renal cell carcinoma. *Cancer* 1994;73:3015-3019.
30. Bartsch H, Bartsch C. Effect of melatonin on experimental tumors under different photoperiods and times of administration. *J Neural Transm* 1981;52:269-279.
31. Eisman JA, Barkla DH, Tutton PJM. Suppression of in vivo growth of human cancer solid tumor xenografts by 1,25-dihydroxyvitamin D<sub>3</sub>. *Cancer Res* 1987;47:21-25.
32. Demirpense E, Balaguer P, Trousse F, et al. Antiestrogenic effects of all-trans-retinoic acid and 1,25-dihydroxyvitamin D<sub>3</sub> in breast cancer cells occur at the estrogen response element level but through different molecular mechanisms. *Cancer Res* 1994;54:1458-1464.
33. Eisman JA, Suva LJ, Martin TJ. Significance of 1,25-dihydroxyvitamin D<sub>3</sub> receptor in primary breast cancers. *Cancer Res* 1986;46:5406-5408.
34. Colston KW, Berger U, Coombes RC. Possible role for vitamin D in controlling breast cancer cell proliferation. *Lancet* 1989;i:188-191.
35. Freake HC, Abeyasekera G, Iwasaki J, et al. Measurement of 1,25-dihydroxyvitamin D<sub>3</sub> receptors in breast cancer and their relationship to biochemical and clinical indices. *Cancer Res* 1984;44:1677-1681.
36. Garland FC, Garland CF, Gorham ED. Geographic variation in breast cancer mortality in the United States: a hypothesis involving exposure to solar radiation. *Prev Med* 1990;19:614-622.
37. Gorham ED, Garland F, Garland CF. Sunlight and breast cancer incidence in the USSR. *Int J Epidemiol* 1990;19:820-824.
38. Cunningham D, Gilchrist NL, Cowan RA, et al. Vitamin D as a modulator of tumour growth in low grade lymphoma. *Scottish Med J* 1985;30:193 [abstr].
39. Janowsky E, Lester G, Hulka B. Vitamin D and breast cancer. *Am J Epidemiol* 1996;143 (11 suppl):S37 [abstr#146].
40. Wijngaarden T V-v, Pols HAP, Buurman CJ, et al. Inhibition of breast cancer cell growth by combined treatment with vitamin D<sub>3</sub> analogues and tamoxifen. *Cancer Res* 1994;54:5711-5717.
41. Anzano MA, Smith JM, Uskokovic MR, et al. 1a,25-dihydroxy-16-ene-23-yne-26,27-hexafluorocholecalciferol (Ro24-5531), a new deltanoid (vitamin D analogue) for prevention of breast cancer in the rat. *Cancer Res* 1994;54:1653-1656.
42. Bower M, Colston KW, Stein RC, et al. Topical calcipotriol treatment in advanced breast cancer. *Lancet* 1991;337:701-702.
43. Simard A, Vobecky J, Vobecky JS. Vitamin D deficiency and cancer of the breast: an unprovocative ecological hypothesis. *Canadian J Public Health* 1991;82:300-303.
44. Foster HD. Reducing cancer mortality: a geographical perspective, Western geographical series, vol 23, University of Victoria, Victoria, BC.
45. Van den Brandt PA, Goldbohm A, van 't Veer P, et al. Toenail selenium levels and the risk of breast cancer. *Am J Epidemiol* 1994;140:20-14026.
46. Van Noord PAH, Collett HJA, Maas MJ, de Waard F. Selenium levels in nails of premenopausal breast cancer patients assessed pre-diagnostically in a cohort-nested case-referent study among women screened in the DOM project. *Int J Epidemiol* 1987;16 (Suppl):318-322.
47. Hunter DJ, Morris JS, Stampfer MJ, et al. A prospective study of selenium status and breast cancer risk. *JAMA* 1990;264:1128-1131.
48. Mannisto S, Virtanen M, Mikkonen T, Pietinen P. Reproducibility and validity of a food frequency questionnaire in a case-control study on breast cancer. *J Clin Epidemiol* 1996;49:401-409.
49. McConnell KP, Jager RM, Bland KI, Blotchky AJ. The relationship of dietary selenium and breast cancer. *J Surg Oncology* 1980;15:67-70.
50. Shamberger RJ. Relationship of selenium to cancer. Inhibitory effect of selenium on carcinogenesis. *J Natl Cancer Inst* 1970;44:931-941.
51. Schrauzer GN, Molenaar T, Mead S, et al. Selenium in the blood of Japanese and American women with and without breast cancer and fibrocystic disease. *Jpn J Cancer Res* 1985;76:374-377.
52. Schrauzer GN, Ishmael D. Effects of selenium and of arsenic on the genesis of spontaneous mammary tumors in inbred C3H mice. *Ann Clin Lab Sci* 1974;4:441-447.
53. Thompson HJ, Meeker LD, Becci PJ, Kokoska S. Effect of short-term feeding of sodium selenite on 7,12-dimethylbenz(a)anthracene-induced mammary carcinogenesis in the rat. *Cancer Res* 1982;42:4954-4958.
54. Clark LC, Combs GF, Turnbull BW, et al. Effects of selenium supplementation for cancer prevention in patients with carcinoma of the skin. *JAMA* 1996; 276:1957-1963.
55. Gradishar WJ, Tallman MS, Abrams JS. High-dose chemotherapy for breast cancer. *Ann Intern Med* 1996;125:599-604.