

Chapter 27

Heavy Metal Accumulation in Malignant Tumours as Basis for a New Integrative Therapy Model

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ABSTRACT

Increased levels of transition metals like iron, nickel, chromium, copper and lead are closely related to free radical generation, lipid peroxidation, formation of DNA-strand breaks, and tumour growth in cellular systems. In order to determine the correlation to malignant growth in humans, we investigated the accumulation of heavy metals in 8 healthy and 20 breast cancer biopsies by means of a standardized Atomic Absorption Spectrophotometry (AAS) methodology.

A highly significant accumulation of iron ($p < 0.0001$), nickel ($p < 0.00005$), chromium ($p < 0.00005$), zinc ($p < 0.00001$), cadmium ($p < 0.005$), mercury ($p < 0.005$), and lead ($p < 0.05$) was recorded in the cancer samples when compared to the control group. Copper and silver showed no significant differences to the control group whereas tin, gold, and palladium were not detectable in any biopsies.

As previously reported by us, the higher heavy metal concentration encountered in various tumours may be used for therapeutic intervention with ascorbic acid or substituted phenolic mixtures.

The autoxidation of vitamin C and phenolic compounds in the presence of heavy metals strongly increase superoxide and H_2O_2 generation at the tumour site, resulting in a fast depletion of the malignant cell reducing equivalents with oxidosis shift and apoptosis induction.

Our results suggest that the use of the above mentioned redox-active compounds devoid of side-effects should be seriously considered in the treatment of different malignancies and infections.

Keywords: Breast Cancer, Vitamin C, Substituted Phenols, Iron, Chromium, Nickel

INTRODUCTION

Reports in the last two decades are closely relating the presence of transition metals, such as iron or copper to free radical generation via Fenton / Haber-Weiss-reactions, ascorbate autoxidation, lipid peroxidation processes, and the formation of DNA strand breaks.¹⁻⁴ In turn, lipid peroxidation-induced malondialdehyde-DNA adducts can accumulate and reach high levels in the breast tissue of women with breast cancer leading to endogenous DNA modifications.⁵ Furthermore, ferric-EDDA- and -NTA-complexes have been proven to induce free radicals and renal carcinomas in Wistar rats demonstrating the key role of transition metals in the abnormal proliferation process.^{6,7}

As repeated mitochondrial and nuclear DNA mutations may lead to malignant growth, we investigated the heavy metal content in breast cancer biopsies supplied by the Institute of Pathophysiology of Charles University in Prague.

Based on these findings we have further investigated the behaviour of tumour cells following treatment with pharmacologically active doses of vitamin C or substituted redox-active phenols, respectively.

The use of vitamin C in different pathologies is based on its role in collagen synthesis, protein hydroxylation, drug detoxification, phagocytosis, and bactericidal activities.⁸ However, in view of its redox cycling associated with antioxidant and prooxidant activities,⁹⁻¹² the appropriate decision pro or contra the high dose vitamin C drip remains a permanent challenge for the physician.

Additionally, we have tested several substituted phenolic compounds acting against hypoxic and normoxic cancer cells through their semiquinonic intermediates and emerging reactive oxygen species. The phenolic mixtures in their activated forms are known to decrease the hypoxic mediated accumulation of reductive equivalents, to increase the oxygen consumption, and to restore normal redox potentials and functionality in hypoxic cells.

MATERIAL AND METHODS

Heavy metal analyses have been performed in 20 frozen breast cancer biopsies and in 8 frozen healthy breast tissue samples, supplied by the Department of Oncology, 1st Faculty of Medicine, Charles University, Prague, Czech Republic and by Caritas Hospital St. Josef, Regensburg, Germany. Biopsies in the patients group belong to women aged 23-49 years, and the control biopsies belong to healthy women aged 21-43 years. The basic histopathological characteristics of the investigated tumours are described in Table 1. None of our patients received cytostatic drugs before surgery.

The local ethic committee approved the study and all participants gave their informed written consent before enrolment in the study.

Table 1. Basic histopathological characteristics of breast tumours

Histological type	
Ductal carcinoma	12
Lobular carcinoma	4
Other	4
Grade	
I	5
II	12
III	1
unknown	2
Hormone receptor status	
ER+	13
ER-	7
ER unknown	0
PR+	17
PR-	1
PR unknown	2
HER2/ Neu staining intensity	
HERCEPTTEST 0	1
HERCEPTTEST 1	6
HERCEPTTEST 2	3
HERCEPTTEST 3	3
ND*	7

* not done

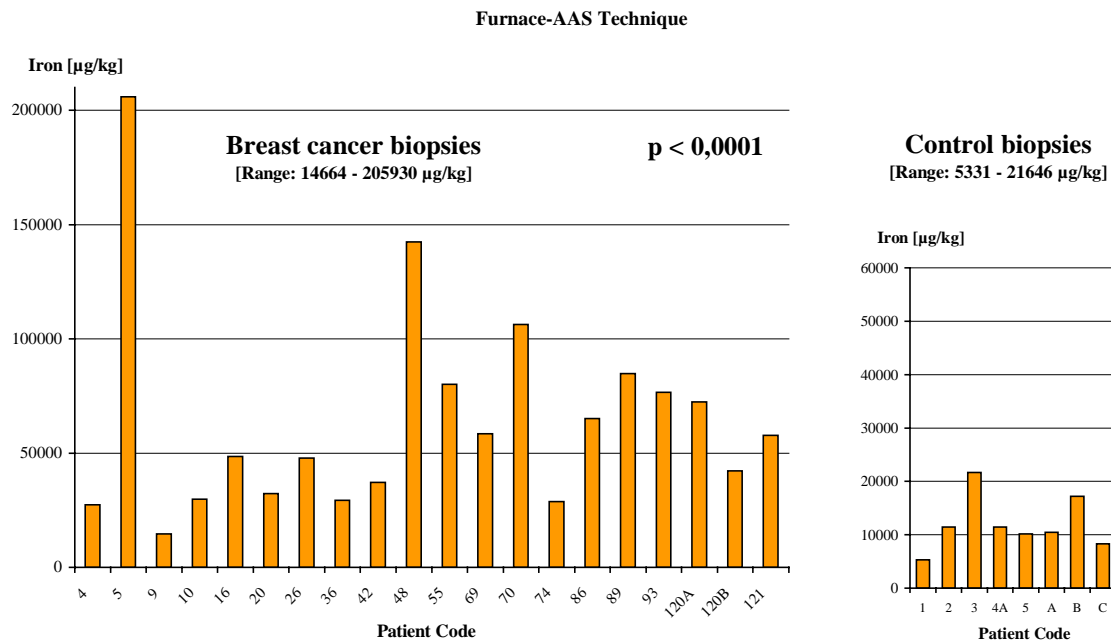
Tumour tissue probes of 1 g each were treated with 4 ml. Aqua regia (equal ratios of conc. HCl / conc. HNO₃) until complete mineralization and then completed to a final volume of 10 ml with distilled water. The concentrations of iron, cadmium, lead, chromium, tin, nickel, copper, silver, gold, palladium, and zinc in the final solution were measured by a standardized furnace-AAS-technique using a Perkin Elmer Sima 6000 AA-spectrophotometer and acidic hydrolysis as pulping procedure for sample preparation.¹³ The concentration of mercury was assessed by means of a Perkin-Elmer FIMS mercury analyzer. Additionally, heavy metal analysis in all control biopsies was done by using an ICP-MS technique in the Laboratory for Micro Trace Minerals, Hersbruck, Germany. All biopsies were taken from the center of the tumour nodules, and metal concentration in 1 g of tumour breast tissue was measured and compared to metal concentration in the same amount (1 g) of healthy breast tissue. All tests were performed three times and the final result per sample is expressed in µg/kg breast tissue, recording the mean value of three determinations. The Mann-Whitney U test was used for statistic analysis of the results.

RESULTS

Data analysis shows a highly significant accumulation of iron, nickel, chromium, cadmium, mercury, zinc and, at a lesser extend, of lead in malignant breast tissue, when compared to healthy breast tissue.

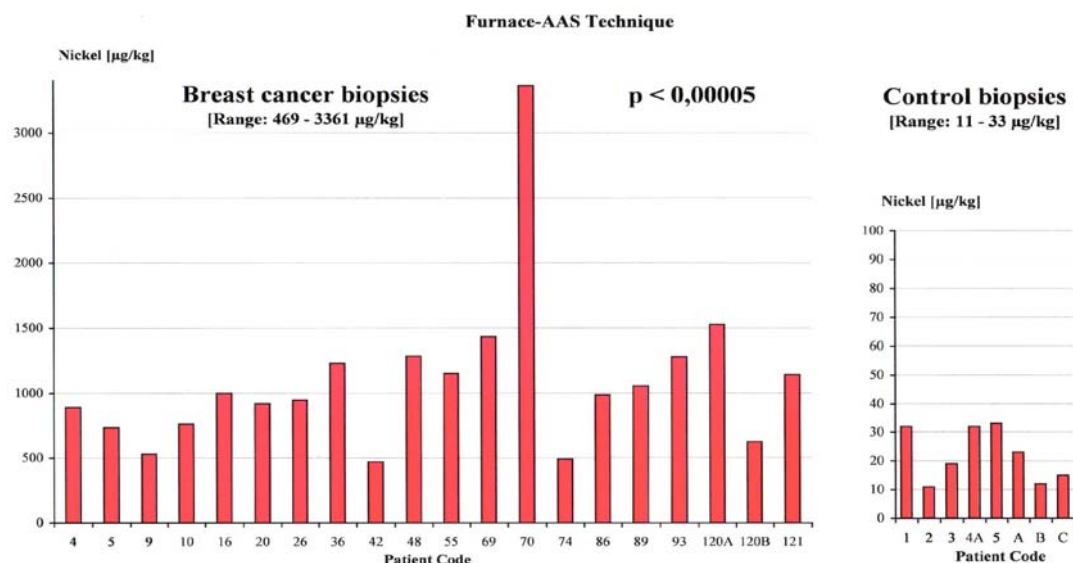
Iron levels were dramatically increased in the breast cancer biopsies (median: 53173.5 $\mu\text{g/kg}$, range: 14664 - 205930 $\mu\text{g/kg}$) when compared with the control group (median: 10937 $\mu\text{g/kg}$, range: 5331 - 21646 $\mu\text{g/kg}$) ($p < 0.0001$) [Fig. 1].

Fig. 1 Iron content of 20 breast cancer and 8 control human biopsies.



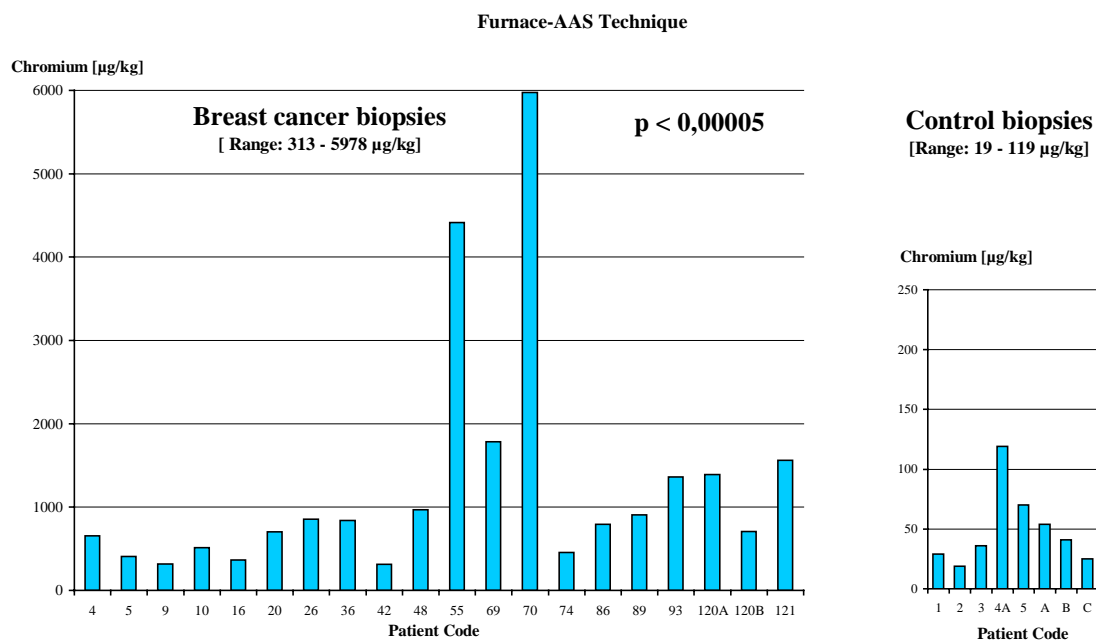
A strong nickel accumulation (median: 994.5 $\mu\text{g/kg}$, range: 469 - 3361 $\mu\text{g/kg}$) was recorded in the patient biopsies. Control biopsies showed measurable levels (median: 21 $\mu\text{g/kg}$, range: 11 - 33 $\mu\text{g/kg}$), but at more than one order of magnitude lower ($p < 0.00005$) [Fig. 2].

Fig. 2 Nickel content of 20 breast cancer and 8 control human biopsies.



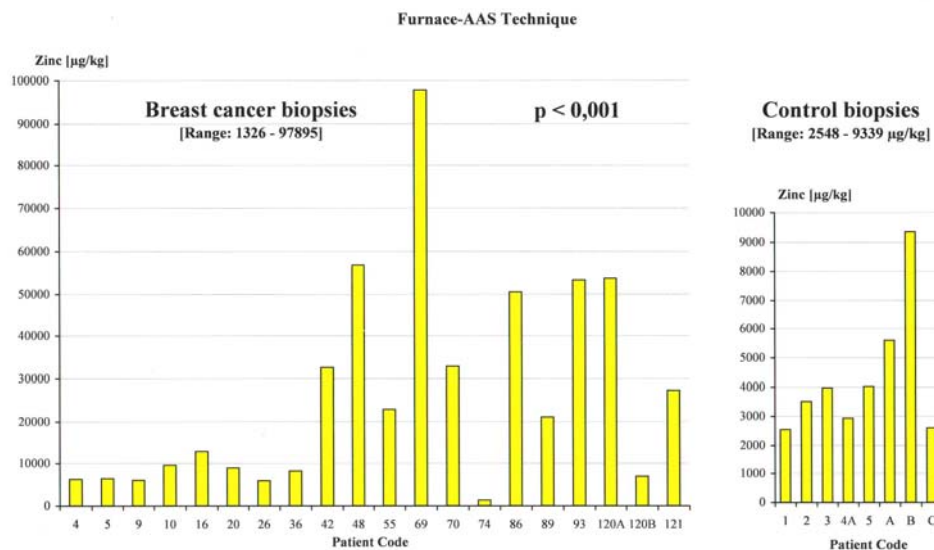
Similar results have been noticed for chromium (median: 815.5 µg/kg, range: 313 - 5978 µg/kg) when compared with the control group (median: 38.5 µg/kg, range: 19 - 119 µg/kg) ($p < 0.00005$) [Fig. 3].

Fig. 3 Chromium content of 20 breast cancer and 8 control human biopsies.



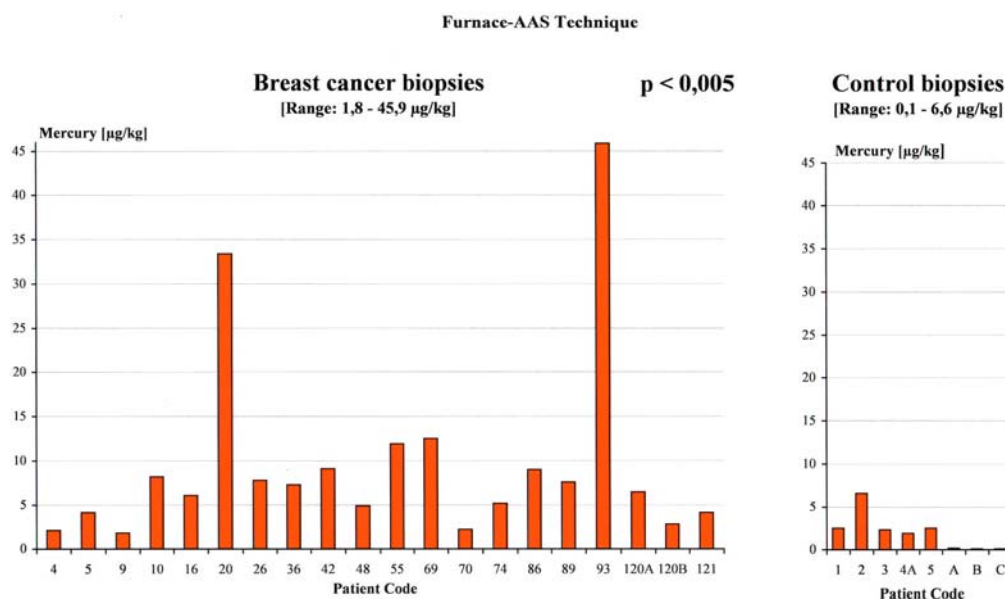
A surprisingly high accumulation of zinc (median: 17075 µg/kg, range: 1326 - 97895 µg/kg) was recorded in the cancer biopsies; the difference to the control group (median: 3741 µg/kg, range: 2548 - 9339 µg/kg) was again highly significant ($p < 0.001$) [Fig. 4].

Fig. 4 Zinc content of 20 breast cancer and 8 control human biopsies.



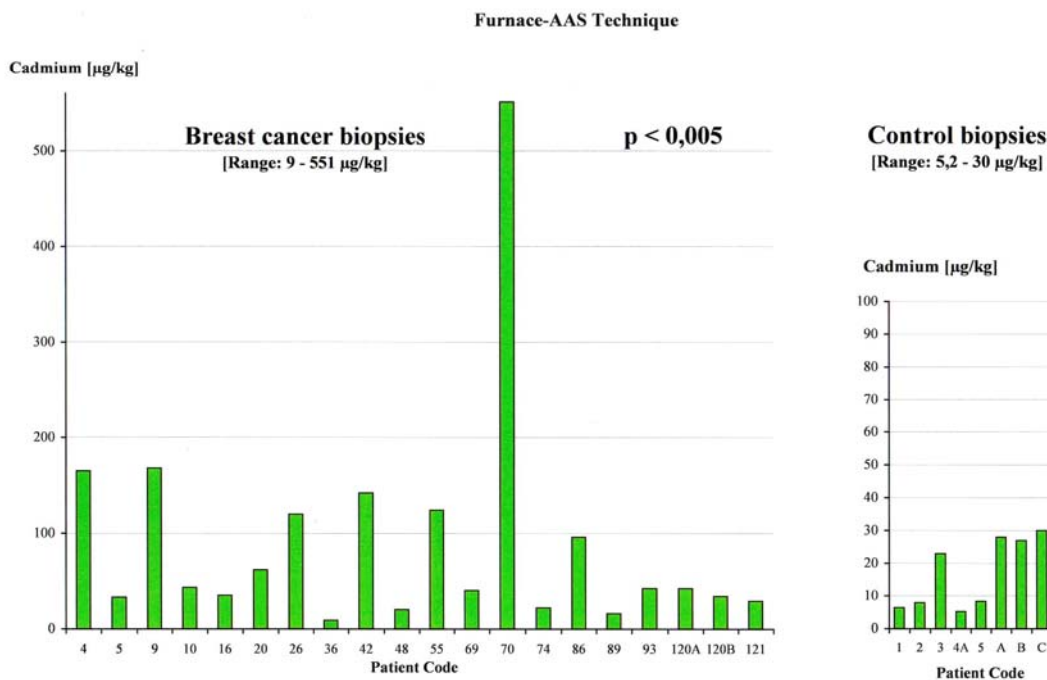
Mercury was found to be moderately increased in 11 out of 20 cancer samples (median: 6.9 µg/kg, range: 1.8 - 45.9 µg/kg), a highly significant difference was recorded when compared to the control group (median: 2.1 µg/kg, range: 0.1 - 6.6 µg/kg) ($p < 0.005$) [Fig. 5].

Fig. 5 Mercury content of 20 breast cancer and 8 control human biopsies.



Increased cadmium concentrations were found in 18 out of 20 cancer biopsies (median: 42 µg/kg, range: 9 - 551 µg/kg), again, the difference to the control group (median: 15,6 µg/kg, median: 5,2 - 30 µg/kg) was highly significant ($p < 0.005$) [Fig. 6].

Fig. 6 Cadmium content of 20 breast cancer and 8 control human biopsies.



Lead was also increased in 12 out of 20 tumour biopsies (median: 104.5 µg/kg, range: 9 - 976 µg/kg). The statistical difference to the control group (median: 63.5, range: 1 - 92 µg/kg) was still significant ($p < 0.05$).

Surprisingly, lower copper levels were found in 11 out of 20 patient biopsies (median: 919 µg/kg, range 320 - 44687 µg/kg), when compared to the control samples (median: 1279.5 µg/kg, range: 261 - 3049). The other 9 cancer samples showed 7 increased values and 2 in the normal range documenting a different accumulation pattern possibly related to the tumour etiology or growth stage. All in all, no significant difference was recorded between the cancer group and the controls ($p = 0.65$).

Just 4 out of 20 cancer samples showed detectable levels of silver (range: 34.4 - 90.9 µg/kg), however none of the control biopsies had detectable levels of silver.

Tin, gold, and palladium were not detectable in either the cancer or the control biopsies.

When compared by two different techniques (AAS and ICP-MS), there was no statistical difference in the heavy metal content of the control biopsies (data not shown here).

DISCUSSION

In biological systems, the concentration of redox-active transition metals capable of catalysing and/or generating free radicals such as superoxide, hydrogen peroxide, and the hydroxyl radical appears to be relatively low. However, under certain pathological conditions (hemochromatosis, Wilson disease, collagenoses and different malignancies), transition metals and their transport proteins may accumulate in different target organs and induce cellular lipid peroxidation and DNA-attack.

In this respect, the ability of excess iron in mediating the formation of hydroxyl radicals, suppressing cellular immune functions, and promoting tumour growth is well established^{2, 6, 7, 14} and increased copper concentrations have also been found in human lung cancer biopsies¹⁵ and in other tumours.¹⁶

Nickel, chromium, and cadmium have been recognized as mutagens and carcinogens through their ability to inhibit the repair of damaged DNA. Furthermore, they also have the ability to enhance the mutagenicity and carcinogenicity of directly acting genotoxic agents.¹⁷ At the same time, carcinogenic effects of nickel, directly or in association with organic compounds, have been described in the literature^{18, 19} and, recently, slightly increased concentrations of iron and nickel have been found in the malign human prostate.²⁰

Inhaled particulate forms of hexavalent chromium cause lung cancer and at cellular levels, chromium exposure may lead to cell cycle arrest, apoptosis, or neoplastic transformation.²¹ Occupational exposure to cadmium is associated with lung cancer in humans and high cadmium concentrations have been found in proliferative prostate lesions.²² Interestingly, zinc as an essential element has been shown to mediate and increase tumour growth and zinc depletion has been shown to suppress tumour growth in mice and rats.²³⁻²⁵ Macromolecular compounds (dextrans) substituted with mercury containing side-chains have been reported to promote fibrosarcoma growth in mice.²⁶

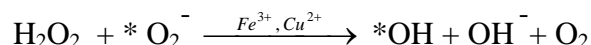
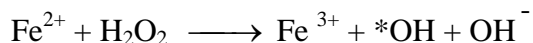
The etiology of the majority of human breast cancers is still controversial; however, hormonal influences and environmental toxic compounds inducing oxidative stress and lipid peroxidation have been suggested to play a role in breast carcinogenesis.

Although the patients came from both rural and industrial areas of the Czech Republic, none of them was occupationally exposed to metals. However, all of them were in contact to metals through dental restorations such as amalgam fillings (mercury, zinc), metallic bridges, or retainers. Other sources of metal exposure are crockery, cutlery (chromium, nickel, iron) and cigarette smoke (cadmium). Approximately half of our patients were smokers and virtually all of them have been exposed passively to cigarette smoke.

Our data describe for the first time a major accumulation of iron and other transition metals, such as nickel, chromium, cadmium, zinc, mercury, and lead in the breast cancer tissue with implications in the pathogenesis of the disease.

Environmental exposure as mentioned above and genetic polymorphisms associated with a deficient Phase II- detoxification process and alterations of metal transfer proteins or their receptors may be responsible for this phenomenon. A study of such correlations is ongoing in our facility as previous research demonstrates high levels of transferrin receptors and of ferritin accumulation in breast cancer tissue.²⁷

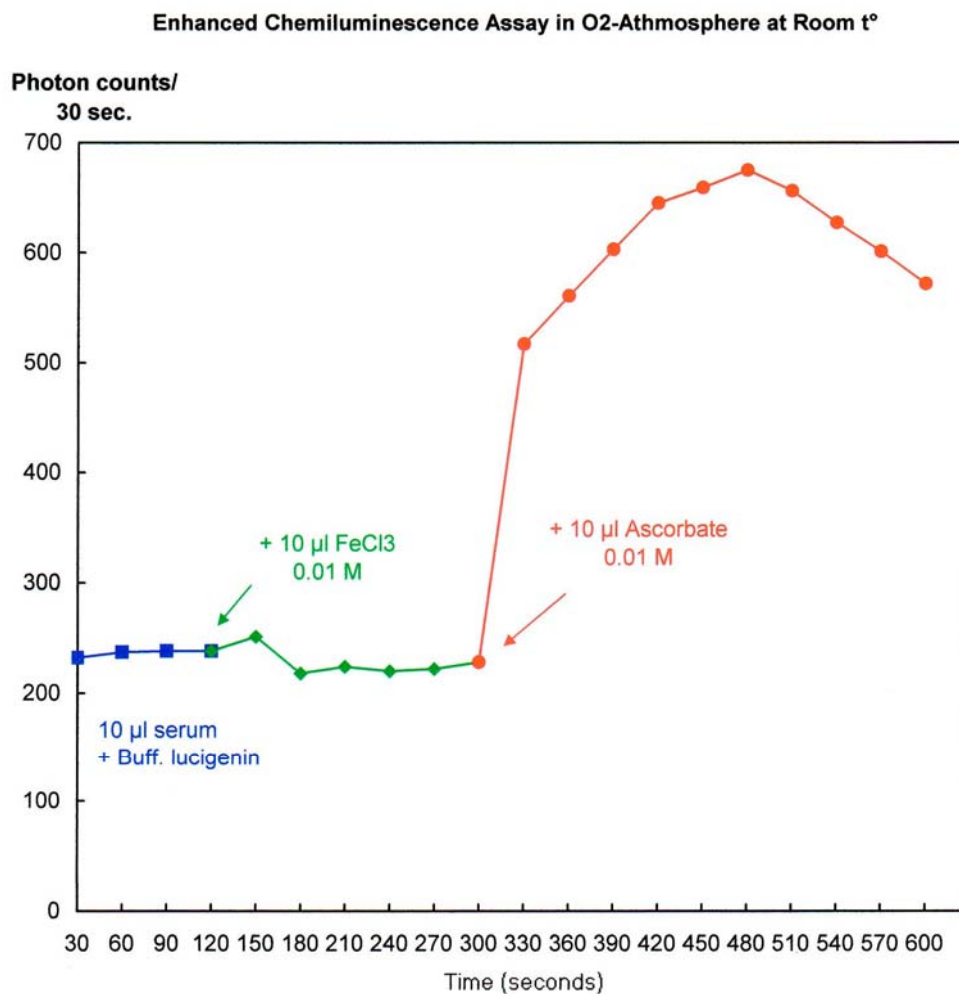
On the other hand, the higher heavy metal concentration encountered in various tumour cells may be used for therapeutic interventions with ascorbic acid or phenolic compounds as already reported.²⁸⁻³² Reduction and mobilization of transition metals from their storage or transport proteins renders them extremely reactive in catalysing free radical reactions according to the equations:



The described Fenton and Haber-Weiss-reactions are strong generators of the hydroxyl radical, leading to lipid peroxidation, DNA strand breaks, and apoptosis.^{2, 7, 28} The autoxidation of vitamin C with superoxide generation in the presence of transition metals like Fe^{3+} , Cu^{2+} or Hg^{2+} can be easily demonstrated with the chemiluminescence methodology in human serum [Fig. 7]. In an acidic milieu (H^+ excess) the superoxide radical is further converted to H_2O_2 . We therefore believe that the clinical improvement in cancer patients treated with high doses of ascorbate³²⁻³⁵ is based on the mechanism described above.

In turn, bioactivation of phenolic / quinonic compounds at the tumour site may lead to a significant generation of superoxide and semiquinone radicals with deleterious effects for the metal rich malignant cells.^{29, 30} As previously demonstrated in the presence of heavy metals, mixtures of substituted phenols oxidize to quinonic compounds, thus significantly increasing their redox potential [Fig. 8] with induction of an apoptotic cascade in metal-rich tumours.²⁹ The anti-tumour activity of the phenol / quinone containing drugs largely depends on the activity of microsomal NADPH: quinone oxidoreductase conferring such compounds increased tumour selectivity through the overexpressed enzyme in various tumour types.^{36, 37}

Fig. 7 Iron (III) and ascorbate induced superoxide radical generation in human serum

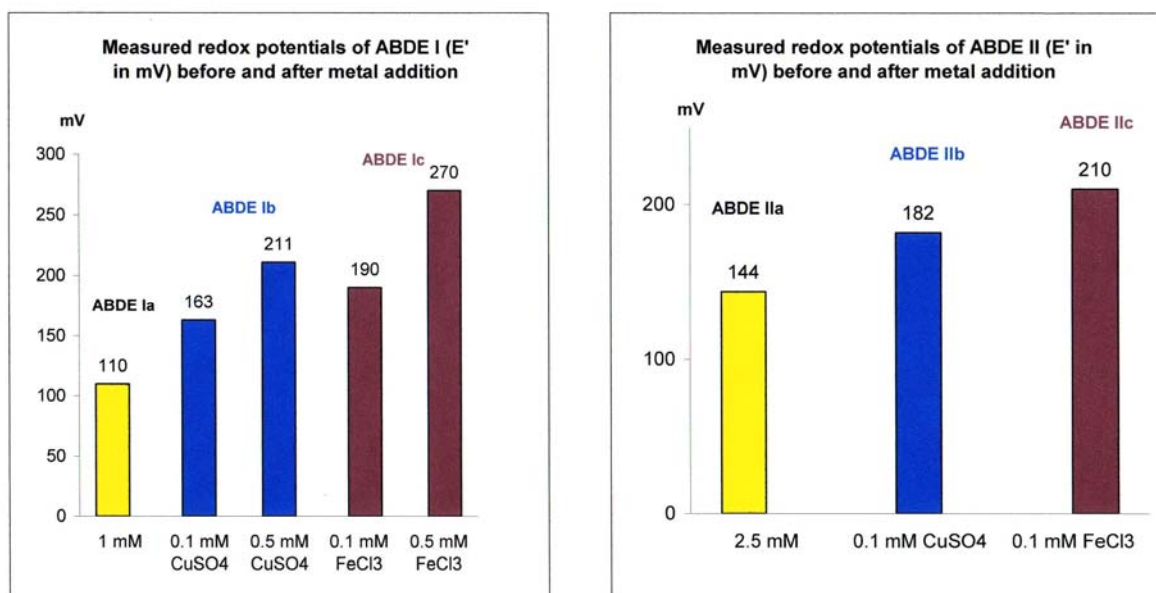


BJL Chemiluminescence Analyzer

Voltage: 860 V. Calibration: 14C source/ 10000 c/ sec.

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Fig. 8 Oxidation patterns of phenolic mixtures ABDE (I) and ABDE (II) in the presence of Cu^{2+} and Fe^{3+} in vitro



These effects have been noticed both in tumour-bearing C57B1 mice treated with phenolic mixtures in the Medical School of Prague University (Prof. Dr. Sevc) according to a NIH protocol [Fig. 9], as well as in cancer patients (preliminary data) taking similar mixtures orally for 2-3 months on a daily basis [Fig. 10, Fig. 11].

Fig. 9 Survival curves in tumour bearing mice treated with phenolic mixtures

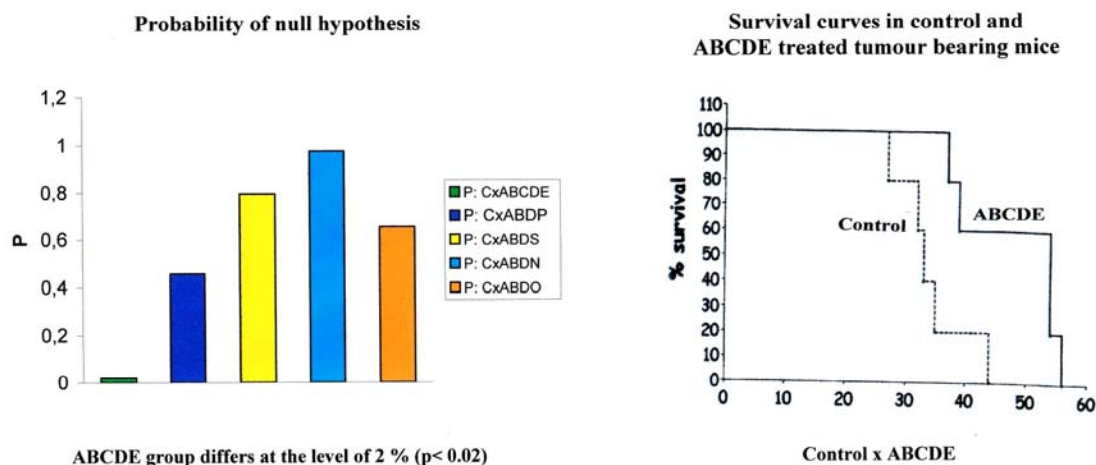


Figure 10. RX pictures of pulmonary adenocarcinoma before and after 12 weeks treatment with substituted phenolic compounds

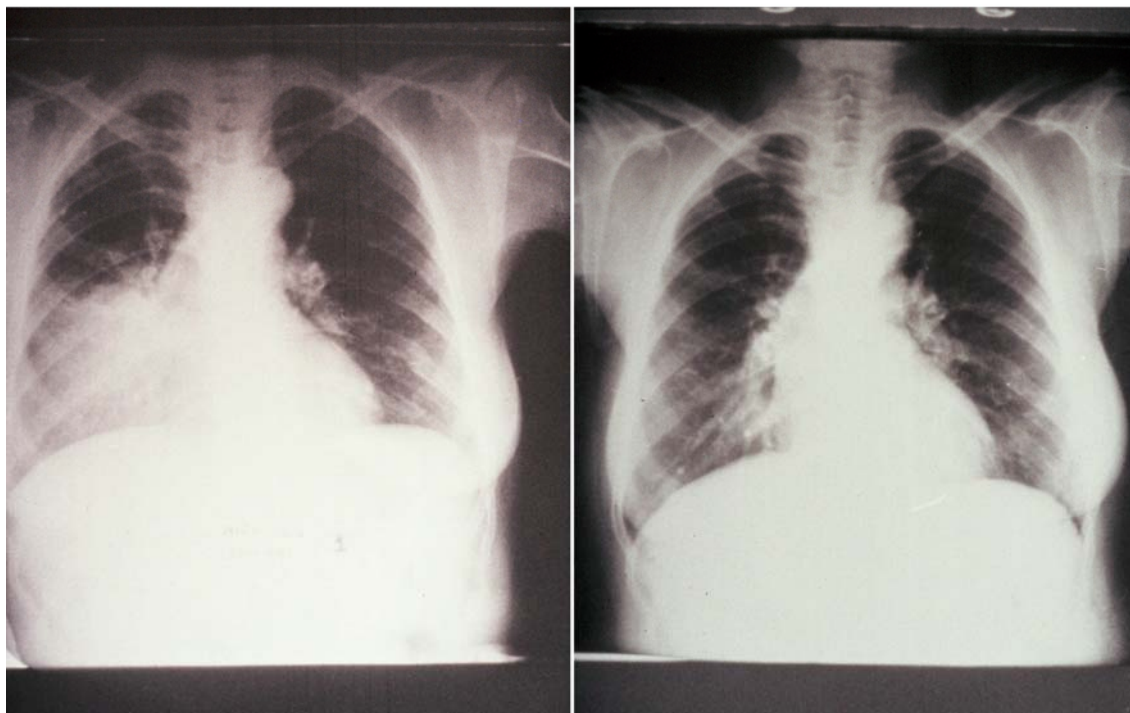
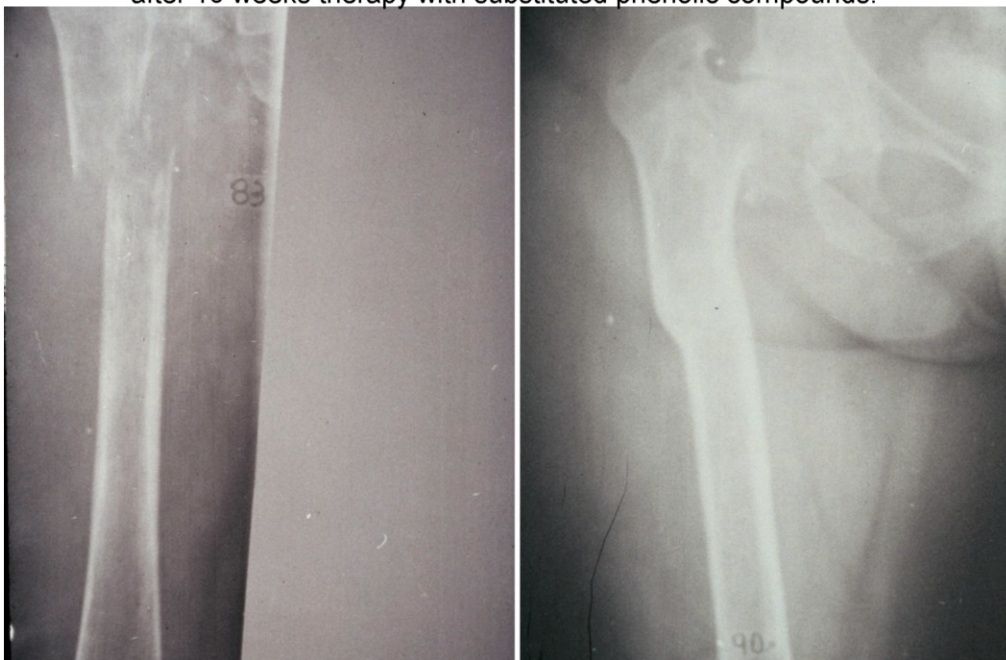


Figure 11. Prostate tumour with bone metastases (femoral fracture) before and after 15 weeks therapy with substituted phenolic compounds.



We therefore suggest that future utilisation of high dose vitamin C with prooxidant character and / or combinations of substituted phenolic compounds devoid of side-effects should be seriously considered in the treatment of different malignancies. Both vitamin C and the phenolic compounds are taking advantage of the diminished capability of tumour cells to handle free radicals. Whereas free radicals are

quickly scavenged in normoxic (healthy) tissues, hypoxic tumour cells are expressing low levels of ROS protective enzymes, such as superoxide dismutase, catalase, and GSH-peroxidase (GPx). Therefore, the tumour cells are much more vulnerable to free radical attack than normal cells.³⁸⁻⁴⁰

Preventive diagnostic procedures for breast cancer should include (besides medical imaging and current tumours markers): 2 / 16-OH-estrogen ratio, Phase II detoxification assessment, and the MELISA test ®⁴¹ for metal specific lymphocytes.

CONCLUDING REMARKS

The above data suggest that unphysiological accumulation of transition metals in tumour tissue may be closely related to the malignant growth process, and allow the consideration of a new therapy concept with prooxidant vitamin C or phenolic compounds.

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Prof. Ionescu founded in 1986 in Bavaria the Spezialklinik Neukirchen (www.spezialklinik-neukirchen.de) for the treatment of allergic, skin and environmental diseases according to the principles of the nutritional and environmental medicine. The 160 bed facility is fully integrated in the official hospital system and the treatment fees are reimbursed by all German and Austrian health insurances.

The original diagnostic and therapeutic approaches of his cortisone-, cytostatic- and radiation-free concept have been reported in more than 170 scientific publications in Germany, Europe and USA. Current work involves the investigation of biological redox and free radical reactions in skin, environmental and cancer patients. His research results are subjects of new methods for the rapid free radical and redox potential assessment in human blood samples, new dermatological formulations for the diseased and aging skin, patented anti-cancer drugs and original integrative protocols for the treatment of MCS, CFS and chronic dermatoses like atopic eczema and psoriasis.

Prof. Ionescu is member of the European Academy for Allergology and Clinical Immunology, of the British Society for Allergy and Environmental Medicine, of the American Academy of Environmental Medicine and of the American Academy of Anti-Aging Medicine. Between 1998 and 2006, he served as Professor for Applied Laboratory Medicine and Oxidology at the Capital University of Integrative Medicine, Washington, D.C. (USA). Since May 2006, Dr. Ionescu was appointed as Associate Professor for Gerontology at the University of Medicine and Pharmacy, Carol Davila, Bucharest. Since April 2007, he was nominated as Visiting Professor for Nutritional Medicine at the Donau University, Krems/Vienna.

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