# Die Rolle des Selens in der Behandlung des Mammakarzinoms

# Was sagt die Theorie und was die Praxis über diese Therapieoption?

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# Warum sind freie Radikale so reaktiv ?



# Wichtige freie Radikale in biologischen Systemen



VE = Valenzelektronen

## Wie entstehen freie Radikale ?

In jeder Zelle entstehen täglich über 10.000 freie Radikale, in erster Linie aus endogenen Quellen in *natürlichen* Prozessen

Stoffwechselprozesse in den Mitochondrien: ca. 1 % des eingeatmeten Sauerstoffs wird durch Elektronentransfer zu **Superoxid** umgesetzt

Gezielte enzymatische Bildung von **Superoxid** als Signalmolekül und in der Immunabwehr (Makrophagen)



 $NAD^+ + H^+$ 

 $+20_{2}$ 

NADH-Oxidase



NADH

 $+20_{2}$ 

## Bildung freier Radikale und ROS durch exogene Faktoren



## Zellschädigende Wirkungen freier Radikale

Schädigung der DNA besonders durch Oxidation der Nucleobase Guanin



## **Nichtenzymatische Antioxidantien**



Baut u.a. Wasserstoffperoxid H<sub>2</sub>O<sub>2</sub> ab, v.a. in den roten Blutkörperchen und in der Leber



### Who can the human body synthetizes Selene-proteins



Abb. 1 Die Biosynthese von Selenoproteinen ist ungewöhnlich. Die Aminosäure Selenocystein wird enzymatisch durch Selenocysteinsynthase (SEPSECS) aus Serin-tRNA<sup>Sec</sup> und Selenophosphat gebildet und als Sec-tRNA<sup>Sec</sup> von einem eigenen Translationsfaktor (EFSEC) zum Ribosom gebracht. Dazu ist eine Interaktion von EFSEC mit dem SECIS-bindenden Protein (SECISBP2) notwendig, welches die Selenocystein-Insertionssequenz (SECIS) der mRNA bindet. Kommt diese Interaktion nicht zustande, wird das UGA Codon in der mRNA als STOPP gelesen und die Proteinbiosynthese frühzeitig abgebrochen.

## Human lymphocytes cell lines exhibit different baseline and selenium-induced GPx enzyme activity



Cancer Res. 2009 Oct 15;

Molecular Consequences of Genetic Variations in the Glutathione Peroxidase 1 Selenoenzyme; Pin Zhuo et al.

### Int J Cancer. 2015 May 1;136(9):2178-86..

# Total dietary antioxidant capacity, individual antioxidant intake and breast cancer risk: the Rotterdam Study.

Pantavos A1, Ruiter R, Feskens EF, de Keyser CE, Hofman A, Stricker BH, Franco OH, Kiefte-de Jong JC.

### Abstract

Some studies suggest a favorable role of antioxidants on breast cancer risk but this is still inconclusive. The aim of this study was to assess whether overall dietary antioxidant capacity, as assessed by dietary ferric reducing antioxidant potential (FRAP), and individual dietary antioxidant intake were associated with breast cancer risk. Data was used from women participating in the Rotterdam Study, a prospective cohort study among subjects aged 55 years and older (**N = 3,209**). FRAP scores and antioxidant intake (i.e., vitamin A, C, E, **selenium**, flavonoids and carotenoids) was assessed at baseline by a food frequency questionnaire. Incident cases of breast cancer were confirmed through medical reports. During a median follow-up of 17 years, 199 cases with breast cancer were identified. High dietary FRAP score was associated with a lower risk of breast cancer [hazard ratio (HR): 0.68; 95% confidence intervals (CI): 0.49, 0.96]. No overall association between individual antioxidant intake and breast cancer risk was found. However, low intake of alpha carotene and beta carotene was associated with a higher risk of breast cancer among smokers (HR: 2.48; 95% CI: 1.21, 5.12 and HR: 2.31; 95% CI: 1.12, 4.76 for alpha and beta carotene, respectively) and low intake of flavonoids was associated with breast cancer risk in women over the age of 70 (HR: 1.80; 95% CI: 1.09, 2.99). These results suggest that high overall dietary antioxidant capacity is associated with a lower risk of breast cancer. Individual effects of dietary carotenoids and dietary flavonoids may be restricted to subgroups such as smokers and elderly.

### **Cancer Treat Res**. 2014;159:145-66. doi: 10.1007/978-3-642-38007-5\_9. Selenium and cancer: a story that should not be forgotten-insights from genomics. Méplan C, Hesketh J

#### Abstract

Selenium (Se) is an essential micronutrient that is incorporated into selenoproteins. Although epidemiological studies suggest that low Se intake is associated with increased risk of various cancers, the results of supplementation trials have been confusing. These conflicting results may be due to different baseline Se status and/or genetic factors. In addition, mechanistic links between Se intake, selenoproteins and carcinogenesis are not clear. In this article, we discuss the functional significance of single-nucleotide polymorphisms (SNP) in selenoprotein genes and the evidence as to whether or not they influence risk of colorectal, prostate, lung or breast cancers. Both in vitro and in vivo studies have shown that a small number of SNPs in genes encoding glutathione peroxidases 1 and 4, selenoprotein P, selenoprotein S and 15-kDa selenoprotein have functional consequences. Data from casecontrol studies suggest that a variant at codon 198 in glutathione peroxidase 1 influences the effect of Se status on prostate cancer and risk, and it has also been associated with **breast cancer** and lung cancer risk, whereas variants in glutathione peroxidase 4, selenoprotein P and selenoprotein S may influence the risk of colorectal cancer. In addition, the results of gene microarray (transcriptomic) studies have identified novel selenoprotein biomarkers of Se status and novel downstream Se-targeted pathways. The work highlights the need to take baseline Se status and genetic factors into account in the design of future intervention trials

## Cell Proliferation is Inhibited in SELENBP1 High Expression Cell Lines but not in SELENBP1 Low Expression Cell Lines upon MSA Treatment.



Zhang et al.,

# GPx-1 allelic variation influences thermostability of the protein



Cancer Res. 2009 Oct 15; Molecular Consequences of Genetic Variations in the Glutathione Peroxidase 1 Selenoenzyme; Pin Zhuo et al. Int J Cancer. 2013 Nov;133(9):2054-64. doi: 10.1002/ijc.28224. Epub 2013 Jul 6. Dietary selenium supplementation modifies breast tumor growth and metastasis. Chen YC, Prabhu KS, Das A, Mastro AM Abstract

The survival rate for breast cancer drops dramatically once the disease progresses to the metastatic stage. Selenium (Se) is an essential micronutrient credited with having high anticancer and chemopreventive properties. In our study, we investigated if dietary Se supplementation modified breast cancer development in vivo. Three diets supplemented with sodium selenite, methylseleninic acid (MSA) or selenomethionine (SeMet), as well as a Se-deficient and a Se-adequate diet were fed to mice before mammary gland inoculation of 4T1.2 cells. The primary tumor growth, the numbers of cancer cells present in lungs, hearts, livers, kidneys and femurs and several proinflammatory cytokines were measured. We found that inorganic selenite supplementation provided only short-term delay of tumor growth, whereas the two organic SeMet and MSA supplements provided more potent growth inhibition. These diets also affected cancer metastasis differently. Mice fed selenite developed the most extensive metastasis and had an increased incidence of kidney and bone metastasis. On the other hand, mice fed the SeMet diet showed the least amount of cancer growth at metastatic sites. The MSA diet also provided some protection against breast cancer metastasis although the effects were less significant than those of SeMet. The cytokine profiles indicated that serum levels of interlukin-2, interleukin-6, interferon y and vascular endothelial growth factor were elevated in SeMet-supplemented mice. There was no significant difference in tumor growth and the patterns of metastasis between the Se-deficient and Se-adequate groups. Our data suggest that organic Se supplementation may reduce/ delay breast cancer metastasis, while selenite may exacerbate it.

# **Breast Cancer Res Treat.** 2012 Aug;134(3):1269-77. doi: 10.1007/s10549-012-2139-9. Epub 2012 Jun 27.

Selenium intake and breast cancer mortality in a cohort of Swedish women.

Harris HR, Bergkvist L, Wolk A.

#### Abstract

Selenium is an important cofactor in the production of antioxidant enzymes that may influence cancer progression. Selenium intake and cancer survival has not been extensively studied; however, selenium supplementation has been demonstrated to reduce cancer mortality in nutritional intervention trials. We investigated whether dietary selenium intake was associated with survival among 3,146 women diagnosed with invasive breast cancer in the population-based Swedish Mammography Cohort. Selenium intake before breast cancer diagnosis was estimated using a food frequency questionnaire completed in 1987. Cox proportional hazard models were used to calculate hazard ratios (HRs) and 95 % confidence intervals (95 % CIs) for death from breast cancer, non-breast cancer death, and death from any cause. During 28,172 **person-years of follow-up** from 1987 to 2009, there were 416 breast cancer-specific deaths and 964 total deaths. Dietary selenium intake was inversely associated with breast cancerspecific mortality and overall mortality. Women in the highest quartile of selenium intake had a multivariable HR (95 % CI) of death from breast cancer of 0.69 (0.52-0.92) compared with those in the lowest quartile (P (trend) = 0.009). The inverse association between **dietary** selenium intake and breast cancer death appeared strongest among women who had ever **smoked** (HR = 0.34; 95 % CI 0.14-0.83; P (trend) = 0.01) comparing the highest to lowest quartile. Our findings suggest that selenium intake before breast cancer diagnosis may improve breast cancer-specific survival and overall survival. However, these results may be limited to populations with low intakes of selenium.

Biol Trace Elem Res. 2011 Oct;143(1):261-73. doi: 10.1007/s12011-010-8839-2. Comparison of different forms of dietary selenium supplementation on growth performance, meat quality, selenium deposition, and antioxidant property in broilers. Wang Y, Zhan X, Zhang X, Wu R, Yuan D. Abstract

.... These three groups received the same basal diet containing 0.04 mg Se/kg, supplemented with 0.15 mg Se/kg from sodium selenite (SS) or from L-selenomethionine (L-Se-methionine (Met)) or from D-selenomethionine (D-Se-Met). The experiment lasted 42 days. Both Se source and time significantly influenced (p < 0.01) drip loss of breast muscle..... The SS-supplemented diet increased more (p < 0.05) liver, kidney, and pancreas glutathione peroxidase (GSH-Px) activities than the D-Se-Met-supplemented diet. In addition, L-Se-Met increased more (p < 0.01) liver and pancreas GSH-Px activities than D-Se-Met. The antioxidant status was greatly improved in broilers of L-Se-Met-treated group in comparison with the SStreated group and was illuminated by the increased glutathione (GSH) concentration in serum, liver, and breast muscle (p < 0.05); superoxide dismutase (SOD) activity in liver (p < 0.01); total antioxidant capability (T-AOC) in kidney, pancreas, and breast muscle (p < 0.05) and decreased malondialdehyde (MDA) concentration in kidney and breast muscle (p < 0.05) of broilers. Besides, supplementation with D-Se-Met was more effective (p < 0.01) in increasing serum GSH concentration and decreasing breast muscle MDA concentration than SS. L-Selenomethionine supplementation significantly increased GSH concentration in liver and breast muscle (p < 0.05); SOD activity in liver (p < 0.01); and T-AOC in liver, pancreas, and breast muscle (p < 0.05) of broilers, compared with broilers fed D-Se-Met diet. . Therefore, dietary L-Se-Met and D-Se-Met supplementation could improve antioxidant capability and Se deposition in serum and tissues and reduce drip loss of breast muscle in broilers compared with SS. Besides, L-Se-Met is more effective than D-Se-Met in improving antioxidant status in broilers.

## Cancer Epidemiol Biomarkers Prev. 2009 Nov;18(11):2923-8. doi:

10.1158/1055-9965.EPI-09-0529. Epub 2009 Oct 20.

Selenium supplementation reduced oxidative DNA damage in adnexectomized BRCA1 mutations carriers.

Dziaman T, Huzarski T Gackowski D, et al.

Abstract

Some experimental evidence suggests that BRCA1 plays a role in repair of oxidative DNA damage. Selenium has anticancer properties that are linked with protection against oxidative stress. To assess whether supplementation of BRCA1 mutation carriers with selenium have a beneficial effect concerning oxidative stress/DNA damage in the present double-blinded placebo control study, we determined 8-oxodG level in cellular DNA and urinary excretion of 8oxodG and 8-oxoGua in the mutation carriers. We found that 8-oxodG level in leukocytes **DNA is significantly higher in BRCA1 mutation carriers**. In the distinct subpopulation of BRCA1 mutation carriers without symptoms of cancer who underwent adnexectomy and were supplemented with selenium, the level of 8-oxodG in DNA decreased significantly in comparison with the subgroup without supplementation. Simultaneously in the same group, an increase of urinary 8-oxoGua, the product of base excision repair (hOGG1 glycosylase), was observed. Therefore, it is likely that the selenium supplementation of the patients is responsible for the increase of BER enzymes activities, which in turn may result in reduction of oxidative DNA damage. Importantly, in a double-blinded placebo control prospective study, it was shown that in the same patient groups, reduction in cancer incidents was observed. Altogether, these results suggest that BRCA1 deficiency contributes to 8-oxodG accumulation in cellular DNA, which in turn may be a factor responsible for cancer development in women with mutations, and that the risk to developed breast cancer in BRCA1 mutation carriers may be reduced in selenium-supplemented patients who underwent adnexectomy.

### **Crit Rev Biotechnol**. 2009;29(1):10-7. doi: 10.1080/07388550802658048. Selenium and selenium-antagonistic elements in nutritional cancer prevention. Schrauzer GN.

#### Abstract

Selenium is an essential trace element with antioxidative, antimutagenic, antiviral and anticarcinogenic properties. There is **increasing evidence that the dietary selenium intakes** are sub-optimal in the populations of many countries and that human cancer mortalities would significantly decline if additional selenium was made available either through supplementation or the fortification of certain foods. An important property of selenium is its interaction with other elements that may be present in foods, the water, the workplace and the environment, e.g. As, Cu, Ni, Co, Cr, Mn, Zn, Cd, Sn, Pb, Hg, Bi, Mo, Ag, Au, etc. The sequestration of elements by selenium represents an efficient natural detoxification mechanism for some of these elements but also results in the physiological inactivation of selenium. Animal experiments confirm that the chronic exposure to low levels of these elements abolishes the cancer-protective effect of selenium. Human cancer is likewise significantly determined by the interactions of selenium with other elements, as evidenced by epidemiological, ecological and case-control studies. Cadmium, for example, is a key risk-increasing element for prostate cancer: for breast cancer. Cd. Cr. Zn are mainly contributing; for bronchial cancer (in smelter workers), Cd, As, Cr, Sb, Co, La, all these elements are in a reciprocal relationship with Se. While selenium remains the key cancer-protective trace element, the interpretation of its mode of action necessitates consideration of the effects of selenium antagonistic elements

## The Expression of SELENBP1 in Normal and Tumor Breast Tissues.





PLoS One. 2013; 8(5): e63702.

Reduced Selenium-Binding Protein 1 in Breast Cancer Correlates with Poor Survival and Resistance to the Anti-Proliferative Effects of Selenium, Zhang S. et al.

## The Expression of SELENBP1 under E2 treatment.



Zhang et al.,

SELENBP1 Expression is Progressively Reduced in Advancing Clinical Stages in Breast Cancer Tissues.



Zhang et al.,

The Correlation of SELENBP1 Expression with ER, PR, and TP53 in Breast Cancer Tissues.



## Metabolic pathway of dietary selenium (Se) in humans.



SeMet, selenomethionine; SeCys, selenocysteine; GSSeSG, selenodiglutathione;  $\gamma$ -glutamyl-CH3SeCys,  $\gamma$ -glutamyl-Se-methyl-selenocysteine; H<sub>2</sub>Se, hydrogen selenide; HSePO<sub>3</sub><sup>2-</sup>, selenophosphate; CH3SeCys, Se-methylselenocysteine; CH3SeH, methylselenol; (CH3)<sub>2</sub>Se, dimethyl selenide; SeO<sub>2</sub>, selenium dioxide; (CH3)<sub>3</sub>Set, trimethyl selenonium ion.

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EINGELADENER ÜBERSICHTSARTIKEL

## Supplementieren oder nicht? Das Spurenelement Selen

Ulrich Schweizer<sup>1,\*</sup>, Josef Köhrle<sup>2</sup>, Stefanie Schweizer<sup>3</sup>

Dosierempfehlung		[µg/Tag]	Anwendungsdauer
Tumorprävention	bei Nichtrisikogruppen	50 - 100	unbegrenzt
	bei Risikogruppen	100	unbegrenzt
Operation	präoperativ	300	1 — 2 Tage
	OP-Tag	900	1 Tag
	postoperativ	300	-
Chemotherapie	vor 1. Chemotherapie	900	1 – 2 Tage
	behandlungsfreie Tage	300	ab 6. Behandlungstag
Strahlentherapie	vor 1. Bestrahlung	900	1 — 2 Tage
	während Behandlung	300	
	behandlungsfreie Tage	300	
Tumornachsorge	ohne od. bei stabilem Resttumor	100	unbegrenzt
	bei fortgeschrittenen Tumoren od. Metastasierung	200	unbegrenzt

Quelle: Cefak KG "Selen- ein essentielles Spurenelement"; Kempten



Kein Anspruch auf Vollständigkeit. Stand: April 2013.

Tabelle 4

4.1. Arzneimittel bei nachgewiesenem Selenmangel angewendet, der ernährungsmäßig nicht behoben werden kann.

Name des Präparates	Wirkstoff, Wirkstoffmenge pro Einheit	Firma, Darreichungsformen
Cefasel	Natriumselenit 5 H2O	Cefak
50 μg AP	50 $\mu$ g Selen	Tabletten
100 μg RP	100 µg Selen	Tabletten, Tropfen, Ampullen
		zur Injektion, Trinkampullen
300 μg RP	300 µg Selen	Tabletten, Ampullen
Selenase	Natriumselenit 5 H2O	Biosyn
50 AP	50 $\mu$ g Selen	Tabletten, Trinkampullen
Selenase RP	79 $\mu$ g Selen	Tabletten
100 RP	100 µg Selen	Ampullen, Trinkampullen
300 RP	300 µg Selen	Tabletten
Selen-loges	Natriumselenit 5 H2O	Dr. Loges
300 RP	300 µg Selen	Tabletten



## Warum Selentherapie bei Tumorpatienten

- •Stabilisierung des Immunsystems;
- •Reduktion von Nebenwirkungen der Zytostatika, Verringerung der Zytostatika-Resistenz;
- •Reduktion von Nebenwirkungen der Strahlentherapie;
- •Reduktion der Tumorneubildung;
- •Reduktion des Ödemvolumens sowie der Erysipelinzidenz beim Lymphödem.
- Unterstützung antioxidativer Enzyme
- •Beeinflussung des Stoffwechsels der Tumorzelle Unterstützung des DNA-Reparaturmechanismus
- •Unterstützung des programmierten Zelltods

# **Thanks for your attention!**

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