Selenium and oncology

**selenase®**

- high-dose sodium selenite to improve cancer therapy
- reduces side effects by protecting healthy cells
- selectively cytotoxic against tumor cells
- improves the body’s ability to destroy tumor cells
- for effective treatment of lymphedemas
- corrects selenium deficiency
What are the advantages of supportive therapy with sodium selenite?

- Reduction of side effects associated with cancer therapy
- Improvement of the immune status
- Reduction of chemotherapeutic resistance

How does high-dose sodium selenite work?

- Selective cytotoxicity against tumor cells
- Protection of healthy cells
  → improvement of cancer therapy

Prepared based on:
Olm E et al. Proc Natl Acad Sci U S A. 2009 Jul 7; 106(27): 11400-5. Extracellular thiol-assisted selenium uptake dependent on the x(c)- cystine transporter explains the cancer-specific cytotoxicity of selenite.


**Dosage selenium in oncology**

<table>
<thead>
<tr>
<th>Prevention</th>
<th>without genetic predisposition</th>
<th>up to 200 µg Se/day[^A,B]</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>with genetic predisposition</td>
<td>up to 300 µg Se/day[^C,D]</td>
</tr>
<tr>
<td>Therapy</td>
<td>before therapy**</td>
<td>up to 1,000 µg Se[^E–G]</td>
</tr>
<tr>
<td></td>
<td>on therapy-free days***</td>
<td>up to 500 µg Se/day[^H]</td>
</tr>
<tr>
<td>After cancer therapy</td>
<td></td>
<td>up to 300 µg Se/day[^I]</td>
</tr>
</tbody>
</table>

* according to dosage, regimes as presented in trials
** as therapy scheme[^H,J]
***regime of therapy and therapy-free days[^I]

Prepared based on:


[^E]: Holzhauer P. Dtsch. Z. für Onkol. 2002; 34; 14-6. Kann durch die prophylaktische Gabe von Natriumselenit die Inzidenz und der Schweregrad der durch Vinorelbine induzierten lokalen Phlebitis beeinflusst werden?


Why is high-dose sodium selenite selectively cytotoxic against tumor cells?

**Increased uptake of sodium selenite**
Due to changed metabolism of the tumor cell

**Reduces protection**
Sodium selenite binds the protecting glutathione

**Increases oxidative stress**
Reactive oxygen species result from breakdown of selenodiglutathione

**Apoptosis of the tumor cell**
Increased oxidative stress leads to DNA destabilization

Prepared based on:
Olm E et al. Proc Natl Acad Sci U S A. 2009 Jul 7; 106(27): 11400-5. Extracellular thiol-assisted selenium uptake dependent on the x(c)- cystine transporter explains the cancer-specific cytotoxicity of selenite.


How does high-dose sodium selenite protect healthy cells?

- Corrects selenium deficiency [A]
- Optimal activity of selenoproteins [B, C]
- DNA-stabilizing activity [D]
- Activates the immune system [E]
- Reduces oxidative stress [F, G]

Prepared based on:


When does high-dose sodium selenite work?

In prevention
(low selenium level, BRCA1 mutations)\(^{[A, B]}\)

During cancer therapy
(surgery, radiotherapy, chemotherapy, lymphedema)\(^{[C–J]}\)

After cancer therapy
(immune status, long-term side effects)\(^{[G, I, K–M]}\)

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<table>
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<th>Answer</th>
<th>References</th>
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### The tumor patient

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<th>Tumor diagnosis</th>
<th>Selenium measurement</th>
<th>Extent of selenium deficiencies</th>
</tr>
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<tr>
<td><strong>IMMEDIATELY:</strong> start selenase® treatment to correct selenium deficiency</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dosage: up to 300 µg selenium/day</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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**Surgery***

<table>
<thead>
<tr>
<th>Dosage:</th>
<th>Dosage:</th>
<th>Dosage:</th>
</tr>
</thead>
<tbody>
<tr>
<td>• 1,000 µg selenium before surgery^{[A–C]}</td>
<td>• 1,000 µg selenium before radiotherapy**^[E]</td>
<td>• 1,000 µg selenium before chemotherapy**^[H]</td>
</tr>
<tr>
<td>• 1,000 µg selenium intra- or postoperatively^[A,C]</td>
<td>• up to 500 µg selenium, 300 µg on therapy-free days**^[F,G]</td>
<td>• up to i.e. 500 µg selenium***</td>
</tr>
<tr>
<td>• Follow-up with up to 1,000 µg selenium^[A,C] for 2 weeks^[D]</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Dosage at increased risk of surgery-related lymphedema:**

| • 1,000 µg selenium pre-, intra- or postoperatively^[C] | • 1,000 µg selenium/ day for 1 week^[I] | • 1,000 µg selenium/ day for 1 week^[I] |
| • 1,000 µg selenium/ day for 3 weeks^[C] | • 500 µg selenium/day for up to 6 weeks^[I,K] | • 500 µg selenium/day for up to 6 weeks^[K] |

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**Radiotherapy***

<table>
<thead>
<tr>
<th>Dosage:</th>
</tr>
</thead>
<tbody>
<tr>
<td>• 1,000 µg selenium before radiotherapy**^[E]</td>
</tr>
<tr>
<td>• up to 500 µg selenium, 300 µg on therapy-free days**^[F,G]</td>
</tr>
</tbody>
</table>

**Dosage in radiotherapy-induced lymphedema:**

| • 1,000 µg selenium/ day for 1 week^[I] | • 500 µg selenium/day for up to 6 weeks^[I,K] |

---

**Chemotherapy***

<table>
<thead>
<tr>
<th>Dosage:</th>
</tr>
</thead>
<tbody>
<tr>
<td>• 1,000 µg selenium before chemotherapy**^[H]</td>
</tr>
<tr>
<td>• up to i.e. 500 µg selenium***</td>
</tr>
</tbody>
</table>

**Dosage in lymphedema (e.g. Mamma-Ca):**

| • 1,000 µg selenium/ day for 1 week^[I] |
| • 500 µg selenium/day for up to 6 weeks^[K] |

---

* * according to dosages, regimes as presented in trials
** ** reduction of side effects
*** *** based on properties of sodium selenite^[I], results from radiotherapy^[F] and current selenium status^[D]

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### After cancer therapy

<table>
<thead>
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</tr>
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<tr>
<td>up to 300 µg selenium/day continuously</td>
</tr>
</tbody>
</table>

### Chemotherapy resistance

<table>
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</tr>
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<tr>
<td>escalated up to 10.2 mg/m²/day for 2 weeks (5 days per week) as max. tolerable dosage (MTD)^<em>[M]</em></td>
</tr>
</tbody>
</table>
The tumor patient

Prepared based on:


[H] Holzhauer P, Dtsch. Z. Für Onkol. 2002; 34; 14-6. Kann durch die prophylaktische Gabe von Natriumselenit die Inzidenz und der Schweregrad der durch Vinorelbin induzierten lokalen Phlebitis beeinflusst werden?


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Selenium in cancer prevention

At a glance

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<td>Suboptimal selenium supply in Europe increases the risk of colon cancer $^{[10]}$</td>
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Optimal selenium supply

What is an optimal selenium supply? In the optimal selenium supply range, the maximum activity of selenoproteins and high DNA stability is achieved, and therefore the risk of cancer incidence or mortality is the least. Selenoproteins reach maximum activity at different selenium concentrations in the blood. For glutathione peroxidase, the value is 95 µg/l, for the selenium transport protein selenoprotein P it is 124 µg/l selenium in serum. $^{[12,13]}$ The highest DNA stability is shown at a selenium level of 120–160 µg/l selenium in serum. $^{[14]}$ The least risk for cancer mortality was on average at 140–160 µg/l selenium in serum. $^{[8]}$
Reference range defined by BfArM for selenium

In Germany, the reference range is between 80 – 120 µg/l selenium in serum. Therefore by definition all values under 80 µg/l indicate a selenium deficiency (Fig. 1). The most recent values show that the actual selenium status of Germans is 74.3 µg/l selenium in serum for men and 73.2 µg/l for women.

These numbers clearly demonstrate a selenium deficit in the majority of healthy Germans. Simultaneously, the German reference range does not cover the selenium levels in the blood where the greatest health benefit can be achieved, according to the latest state of scientific knowledge.

![Graph showing reference range and optimal selenium supply](image)

**Official reference range for selenium vs. optimal selenium supply**

- **Selenium deficiency**
- **Reference range of selenium in Germany**
- **Highest DNA stability**

- Average selenium concentration in Germany
- Optimal activity of glutathione peroxidase
- Optimal activity of selenoprotein P

**Serum selenium concentration [µg/l]**

60 80 100 120 140 160

---


Prescribing information selenase®, biosyn Arzneimittel GmbH, as of July 2017.

*Fig. 1*
Selenium deficiency increases the risk of cancer

Already in the 1970s, the American scientist Gerhard Schrauzer postulated a connection between low selenium levels and an increase in cancer mortality.\(^{[16]}\) Since then, numerous epidemiological trials have been able to confirm these findings.\(^{[8,9,17]}\) Among other things, it could be demonstrated that cancer mortality is the least in a range of about 140–160 µg/l selenium in serum (Fig. 2).\(^{[8]}\) The optimal selenium status for cancer prevention thus lies above the German reference range. Simultaneously, the average German has a serum selenium concentration of approx. 74 µg/l and therefore has an increased cancer risk due to a suboptimal selenium status.

Different impact of selenium status on various types of cancer

The impact of the selenium status on the risk of cancer is not linear. The statement that “a lot helps a lot” is not applicable for selenium. For many types of cancer, the following applies: the lower the selenium status, the higher the risk of cancer. However, this statement can also apply to an excessive selenium supply.

A U-shaped curve describes the risk of dying from lung cancer depending on the serum selenium concentration (Fig. 3).\(^{[8]}\)

Mortality from lung cancer significantly increases below and above the 140–160 µg/l level of selenium in serum. In contrast, the risk of dying from colon cancer detectably increases at low selenium levels, but not to such a great extent. From 120 µg/l selenium in serum, the risk declines linearly with increasing selenium status. The mortality curve for prostate cancer depending on the selenium status is between the two values: a steep increase in mortality risk at low selenium levels and risk stabilization at high selenium levels.

These differences could also explain the difficulties of same cancer prevention trials\(^{[18]}\) to demonstrate a significant reduction of cancer risk with selenium supplementation. In individual cases, the cancer risk even increased. This primarily concerns trials carried out on the American continent, since a high selenium level in the soil ensures a sufficient to high selenium supply in food across the country. A low selenium status in America is rather rare. However, a majority of Europeans show a suboptimal selenium status.

European soils are poor in selenium, and it is very difficult to receive an adequate selenium supply from the diet. Therefore, the likelihood that a person will benefit from selenium supplementation for cancer prevention is significantly higher in Europe.
Selenium status and cancer mortality correlate significantly

![Graph showing the correlation between serum selenium concentration and cancer mortality.](image)


**Fig. 2**

Differently pronounced correlations depending on type of cancer

![Graph showing different correlations for different types of cancer.](image)


**Fig. 3**
Suboptimal selenium supply in Europa increases risk of colon cancer

A prospective European trial (EPIC) from 2015 investigated the connection between selenium status and the risk of colon cancer.\[^{10}\] 966 cases of colon cancer were compared with 966 controls.

The trial yielded two important findings: first, the selenium supply in Europe is suboptimal with a significant gradient from North → South → Central Europe (Germany, Netherlands, Great Britain) (p < 0.001). Second, a low selenium level increased the risk of colon cancer. Primarily women were able to benefit from an improved selenium level (p\[^{trend}\] = 0.032; per 25 µg/l selenium in serum, IRR = 0.83, 95% CI: 0.70–0.97).\[^{10}\]

If the average serum selenium concentration of German women (73.2 µg/l) determined in the study is used as basis, a selenium status increase of 50 µg/l to 123.2 µg/l selenium in serum would decrease the risk of colon cancer by 34%.

Tenfold increased risk of liver cancer with a suboptimal selenium status

An additional result of the prospective EPIC trial is the considerably increased risk of liver cancer at suboptimal selenium levels (≤80.5 µg/l selenium in serum).\[^{11}\] A comparison between a serum selenium concentration ≤80.5 µg/l and ≥94.5 µg/l showed that the relative risk decreased by 82% (OR 0.18; 95% CI 0.05–0.66; p = 0.016).

An increase of the serum selenium status by 20 µg/l reduced the risk by 59% (OR 0.41; 95% CI 0.23–0.72). Even more significant was the association for the selenium transport protein selenoprotein P. A suboptimal selenoprotein P concentration increased the risk of liver cancer tenfold compared to an optimal selenoprotein P concentration (≤4.9 mg/l vs. ≥6.4 mg/l OR 0.09; 95% CI 0.03–0.32; p < 0.0001).
Issues of cancer prevention trials

Precondition for a preventive effect of selenium:

a) Low selenium status
b) Supplementation with sodium selenite
c) Dosage

Meanwhile, an entire series of cancer prevention trials using selenium was carried out. The results vary between a positive impact to no impact at all. A Cochrane analysis from 2014 concluded that on this basis, there is no convincing evidence for the preventive effect of selenium supplementation.\(^\text{[19]}\) This statement, however, is a matter of debate, elucidated in the following discussion.

No prevention trials conducted in Europe

Eight intervention trials were examined in the Cochrane analysis (Table 1).\(^\text{[16]}\) None of them were carried out in Europe. Sodium selenite was used in only one trial.\(^\text{[20]}\) All other trials used organic selenium, either selenomethionine or selenium yeast. In five trials, the participants displayed an adequate to optimal selenium status.\(^\text{[18, 21−24]}\) The other three trials were carried out in Qidong Province in China.\(^\text{[20, 25, 26]}\) The baseline selenium level in the Yu et al. trial was specified with 100 µg/l selenium in whole blood.\(^\text{[23]}\) There are no exact numbers available for the two other trials. But the average selenium concentration in whole blood in Qidong Province was 76 µg/l.\(^\text{[25]}\) It can therefore be assumed that the participants had a low selenium status.
<table>
<thead>
<tr>
<th>Trial</th>
<th>Serum selenium concentration</th>
<th>Trial design</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yu et al. 1991 [25]</td>
<td>80 µg/l*</td>
<td>N (selenium) = 1.444 N (placebo) = 1.030 200 µg selenium as selenium yeast for 2 years</td>
<td>Incidence of liver cancer: selenium: 30.8/100,000 placebo: 41.9/100,000 0.69% vs. 1.26% (p &lt; 0.05)</td>
</tr>
<tr>
<td>Yu et al. 1997 [26]</td>
<td>n.a.</td>
<td>N (selenium) = 113 N (placebo) = 113 200 µg selenium as selenium yeast for 4 years</td>
<td>Incidence of primary liver cancer: selenium: 27.2/100,000 placebo: 50.6/100,000 0.0% vs. 6.2% (p &lt; 0.05)</td>
</tr>
<tr>
<td>Li et al. 2000 [20]</td>
<td>n.a.</td>
<td>N (selenium) = 1.112 N (placebo) = 953 500 µg selenium as sodium selenite peroral for 3 years</td>
<td>Incidence of primary liver cancer: selenium: 3,057.6/100,000 placebo: 5,981.1/100,000 3.1% vs. 6.0% (p &lt; 0.01)</td>
</tr>
<tr>
<td>NPCT Duffield-Lillico et al. 2003 [22, 27]</td>
<td>115 µg/l</td>
<td>N (selenium) = 653 N (placebo) = 659 200 µg selenium as selenium yeast for 4.5 years</td>
<td>Cancer incidence total: HR = 0.75; 95 % CI, 0.58–0.97 p = 0.03 Cancer mortality: HR = 0.59; 95 % CI, 0.39–0.07 p = 0.008 Incidence of prostate cancer: HR = 0.48; 95 % CI, 0.28–0.80 p = 0.005</td>
</tr>
<tr>
<td>Reid et al. 2008 [23]</td>
<td>115 µg/l</td>
<td>N (selenium) = 210 N (placebo) = 213 400 µg selenium as selenium yeast for 3 years</td>
<td>Incidence of non-melanoma skin cancer: RR = 0.88; 95 % CI, 0.66–1.16 Incidence of basal cell carcinoma: RR = 0.90; 95 % CI, 0.65–1.24 Incidence of squamous cell carcinoma: RR = 1.05; 95 % CI, 0.71–1.56</td>
</tr>
<tr>
<td>SELECT Lippman et al. 2009 [18]</td>
<td>135 µg/l</td>
<td>N (selenium) = 8,752 N (placebo) = 8,696 200 µg selenium as selenomethionine for 3 years</td>
<td>Incidence of cancer total: HR = 1.01; 95 % CI, 0.89–1.15 Cancer mortality: HR = 1.02; 95 % CI, 0.74–1.41 Incidence of prostate cancer: HR = 1.04; 95 % CI, 0.90–1.18</td>
</tr>
<tr>
<td>Marshall et al. 2011 [21]</td>
<td>135 µg/l</td>
<td>N (selenium) = 227 N (placebo) = 225 200 µg selenium as selenium yeast for 3 years</td>
<td>Incidence of prostate cancer: selenium: RR = 0.82; 95 % CI, 0.40–1.69 35.6 % vs. 36.6 % (p = 0.73)</td>
</tr>
<tr>
<td>Algotar et al. 2013 [24]</td>
<td>126 µg/l</td>
<td>N (selenium 200) = 234 N (selenium 400) = 233 N (placebo) = 232 200/400 µg selenium as selenium yeast for 5 years</td>
<td>Incidence of prostate cancer: selenium 200: RR = 0.94; 95 % CI, 0.52–1.7 selenium 400: RR = 0.90; 95 % CI, 0.48–1.7 10.3 % vs. 9.9 % vs. 11.2 % (p = 0.88)</td>
</tr>
</tbody>
</table>

Highlighted trials showed a significantly positive effect of significantly positive effect of selenium supplementation.

\* Calculated for the selenium concentration in whole blood

\** Average for 4 townships in Qidong
Preventive cancer effect depending on selenium status

The American prevention trial “Nutritional Prevention of Cancer” (NPC) could already demonstrate that a selenium supplementation primarily benefits persons with a low selenium status.\(^{[27]}\) The average plasma selenium concentration in the NPC trial was 115 µg/l. A classification of the trial participants based on their baseline selenium status in tertiles showed that only those in the lowest tertile (≤ 105.2 µg/l) had a significantly reduced cancer incidence (HR = 0.51; 95% CI, 0.32–0.81; \(p = 0.007\)) (Table 2).

The cut-off value of 105.2 µg/l selenium in plasma is in the middle of the German reference range (80–120 µg/l). One can therefore not only benefit from selenium supplementation in the event of a selenium deficiency (<80 µg/l).

### Preventive cancer effect depending on selenium status

<table>
<thead>
<tr>
<th>Plasma selenium concentration [µg/l]</th>
<th>Cases</th>
<th>Hazard Ratio (adjusted)</th>
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<tbody>
<tr>
<td></td>
<td>Selenium</td>
<td>Placebo</td>
</tr>
<tr>
<td>≤ 105.2</td>
<td>27</td>
<td>54</td>
</tr>
<tr>
<td>105.3–121.6</td>
<td>34</td>
<td>46</td>
</tr>
<tr>
<td>&gt; 121.6</td>
<td>44</td>
<td>37</td>
</tr>
</tbody>
</table>


*Table 2*
Risks of organic selenium forms for supplementation

The selenium form is crucial for maximizing the benefit of additional selenium supplementation and minimizing the risks. Selenium yeast primarily contains selenomethionine. This organic selenium form is in part incorporated non-specifically, since the body cannot differentiate between methionine (sulfur-containing) and selenomethionine (selenium-containing) compounds. The body can neither control nor regulate this process. Trials could show that the non-specifically-incorporated portion increases at increasing supplementation with selenomethionine. Only a part of the non-specifically incorporated selenium can later be specifically incorporated in selenoproteins. The body also cannot control this process. In addition, the non-specific incorporation of selenomethionine can result in an accumulation of selenium (Fig. 4).

In contrast to selenomethionine, sodium selenite does not accumulate in the body. The body eliminates excess sodium selenite via urine. Furthermore, sodium selenite is only specifically incorporated in selenoproteins. Sodium selenite is therefore dosable, in contrast to organic forms of selenium. As a consequence, only sodium selenite is approved as a medicinal product.
Two forms of selenium: selenomethionine and sodium selenite

Prepared based on:

Fig. 4
Successful cancer prevention with selenium

The following conclusions can be drawn from prevention trials conducted so far: a significant preventive effect for cancer by selenium supplementation primarily occurs in persons with low selenium status (Fig. 5). The safest selenium form is sodium selenite. The dosage can be adjusted by monitoring the selenium status in the blood. The risk of death from cancer is least at selenium levels between 140 – 160µg/l selenium in serum (see p. 14). This corresponds to a selenium concentration of 175 – 200µg/l in whole blood.

Prepared based on:
Reference range Germany: see Prescribing information selenase®, biosyn Arzneimittel GmbH, as of July 2017.
## Dosage recommendation

### Selenium in cancer prevention

<table>
<thead>
<tr>
<th>Low selenium status</th>
<th>Selenium deficit</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 100 µg/l selenium in serum</td>
<td>&lt; 80 µg/l selenium in serum</td>
</tr>
<tr>
<td>&lt; 120 µg/l selenium in whole blood</td>
<td>&lt; 100 µg/l selenium in whole blood</td>
</tr>
<tr>
<td>Continuously: up to 100 µg selenium per day (tablet or drinking ampoules)</td>
<td>Continuously: up to 200 µg selenium per day (tablet or drinking ampoules)</td>
</tr>
<tr>
<td>Costs: approx. €26 per months or €300 per year*</td>
<td>Costs: approx. €50 per months or €600 per year*</td>
</tr>
</tbody>
</table>

*calculation based on the marketed dosage forms indicated in parentheses

Prepared based on:
Selenium is important for DNA stability

At a glance

| Selenium reduces DNA damage<sup>[29]</sup> |
| Selenium improves DNA repair mechanisms<sup>[30]</sup> |
| Selenium supplementation improves DNA stability<sup>[14]</sup> |
| Highest DNA stability between 120–160 µg/l selenium in serum<sup>[14]</sup> |

Selenium reduces DNA damage

DNA damage occurs continuously. Every cell possesses an entire set of mechanisms to repair its DNA. If individual DNA damage cannot be repaired, a cell can destroy itself (programmed cell death or apoptosis). The body can also stop cell proliferation; the cell no longer divides and therefore does not pass on the DNA damage. If DNA repair mechanisms are impaired, the amount of permanent DNA damage as well as the risk of cancer increases.
More DNA damage at levels below 100 µg/l selenium in serum

In a New Zealand trial, 43 men with an increased risk for prostate cancer were examined. The serum selenium concentration varied between 59 – 128 µg/l. The average was 97.8 ± 16.6 µg/l selenium in serum. The DNA analysis from the leukocytes of the trial participants showed a significant inverse association between DNA damage and selenium status of less than 97.8 µg/l selenium in serum (Fig. 6). At a selenium level above 97.8 µg/l, this connection could not be established.

With respect to the German reference range, the results of this trial make it clear that more DNA damage can occur not only with a selenium deficit, but also with selenium levels in the lower reference range.

Selenium inhibits the development of DNA adducts

DNA adducts are modified DNA resulting from an exposure to carcinogens and are considered as biological markers for cancer risk. Carcinogens are chemicals that can trigger cancer. They include for instance acetaldehyde (in tobacco smoke), but also the chemotherapeutic agent Cisplatin. Animal experiments have shown that selenium inhibits the development of DNA adducts. In order to check the results in humans, a trial with 83 Inuit was conducted and the selenium status, PCB level, DNA adducts and 8-oxodG were measured. 8-oxodG is a biological marker for oxidative stress and the efficiency of the respective DNA repair system. Due to their traditional diet, the Inuit people incorporate high quantities of PCB and selenium. PCB is also carcinogenic.

The selenium status of the Inuits in the trial was very high, with a mean value of 673.9 ± 397.7 µg/l in plasma. The mean PCB level was 29.1 ± 26.7 µg/l. Based on the selenium/PCB ratio, there was a significant difference at an advanced age and in the PCB content. The group with a high selenium/PCB ratio was clearly younger and the PCB content was lower (Table 3). The determination of the DNA adducts and 8-oxodG showed that in the group with a high selenium/PCB ratio, both the quantity of DNA adducts as well as 8-oxodG declined with increasing selenium status (p = 0.0086 resp. p = 0.0137). Thus it can be concluded that selenium can attenuate the negative effects of PCB.
Inverse correlation of selenium status and DNA damage

Baseline serum selenium concentration [μg/l]

Average number of DNA damages


Different PCB burden with comparable selenium status

<table>
<thead>
<tr>
<th></th>
<th>Selenium/PCB ratio</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>high (n=41)</td>
<td>low (n=42)</td>
</tr>
<tr>
<td>Age [years]</td>
<td>35.6±1.5</td>
<td>53.7±2.0</td>
</tr>
<tr>
<td>Selenium [μg/l]</td>
<td>652.4±67.5</td>
<td>694.8±56.3</td>
</tr>
<tr>
<td>PCB [μg/l]</td>
<td>12.8±2.0</td>
<td>45.1±4.2</td>
</tr>
<tr>
<td>Selenium/PCB</td>
<td>75.5±7.9</td>
<td>18.0±1.1</td>
</tr>
</tbody>
</table>


Table 3

Fig. 6
Selenium improves DNA repair mechanisms

DNA damage is not a rarity. However, the human cell has several available mechanisms to repair DNA damage. These include the tumor suppressor and transcription factor p53. The gene of p53 is mutated in many tumor cells. Therefore, after DNA damage, p53 is no longer able to regulate the expression of genes involved in the control of the cell cycle, DNA repair, or the induction of apoptosis. The loss of the p53 function thus plays a critical role in the development of cancer.

Selenium improves DNA binding of p53

In cooperation with the protein Redox Factor 1 (Ref1), the sequence-specific DNA binding of p53 improves. BRCA1 is an additional protein required for DNA repair that is mediated by p53. Supplementation with selenium promotes the reduction of cysteine residues required for p53 to bind sequence-specifically to DNA. Ref1 is the mediator of this selenium-dependent pathway to activate p53. BRCA1 binds simultaneously with p53. Only when this triple complex is formed does selenium supplementation protect against DNA damage and improve the DNA repair (Fig. 7).

Selenium stabilizes transcription factor p53

Details on the effect of selenium on p53 could be demonstrated by an additional study conducted in 2013. The inactive form of p53 is not stable. If so-called negative regulators bind to p53, the conformation of p53 is modified and p53 is degraded by the proteasome. A negative regulator is c-JUN N-terminal Kinase-1 (JNK1). The study was able to demonstrate that selenium supplementation can inhibit the proteasome-dependent degradation of p53. Simultaneously, the Ref-1 activity increased. Ref1 modulates the redox status of proteins and is therefore able to influence the redox status of p53. The reduced form of p53 dissociates from JNK1 and p53 is stabilized (Fig. 8).
Selenium only improves the DNA binding of p53 with the participation of Ref1 and BRCA1

![Diagram showing the interaction between selenium, p53, BRCA1, and Ref1 in DNA protection and repair.]

**Fig. 7**

Selenium supplementation increases the stability of p53

![Diagram showing the impact of selenium on p53 stability, degradation, and stabilization.]

**Fig. 8**

---


Epigenetic effects of selenium

Epigenetic effects are mitotic-stable chromatin-based mechanisms that modulate gene expression without changing the genomic DNA sequence. They include the modification of DNA (methylation) and histones (acetylation and methylation) (Fig. 9). Changes in the epigenomes are associated with the occurrence and progression of cancer.\(^{[35]}\)

Sodium selenite inhibits DNA methyltransferases

The so-called DNA methyltransferases are responsible for DNA methylation. Several studies have meanwhile been able to show that sodium selenite inhibits the activity of DNA methyltransferases.\(^{[35]}\) In addition, the selenium status or selenium supplementation can influence global and gene-specific DNA methylation. In prostate tumors, the gene of the phase-II detoxification protein GSTP1 and the tumor suppressors APC and CSR1 are frequently “silenced” due to hypermethylation of their promoters. In prostate cancer cells, supplementation with sodium selenite led to demethylation and activation of these genes.\(^{[36]}\) In breast cancer cells, sodium selenite inhibits DNA methyltransferase 1 and increases the expression of the tumor suppressor RASSF1A.\(^{[37]}\)

The methylation status of colorectal cancer-associated genes in relation to selenium level was examined in a human trial.\(^{[38]}\) The plasma selenium concentration was associated with the methylation of several of these genes (WIF1, LINE1, PCA1, SFRP1/2 and APC). This conforms to the result of the EPIC trial, which could demonstrate an inverse association between selenium status and colorectal cancer risk.\(^{[10]}\)

Sodium selenite reactivates silenced genes

Histone acetylation occurs exclusively at the amino acid lysine and promotes transcription. The participating proteins are the histone acetyltransferases (HAT), and histone-deacetylases are responsible for the removal of the acetyl group.

Xiang et al. were able to show that sodium selenite reduces the activity of histone deacetylases (Fig. 10).\(^{[36]}\) Sodium selenite thereby increases the portion of acetylated H3-Lys\(^{[9]}\) and reduces the level of methylated H3-Lys.\(^{[9]}\) This favors the activation of genes (Fig. 10).
Sodium selenite reactivates silenced genes

Active gene

Demethylation by histones

+ sodium selenite

Inactive gene

Methylation by histones


Selenium improves DNA repair mechanisms and reduces DNA damage

Selenium leads to higher DNA stability and can thus possibly protect against cancer (Fig. 11). This effect of selenium is presumably mediated by selenium enhancing DNA repair mechanisms. The enhanced production of selenoproteins suppresses reactive oxygen species by anti-oxidation, so that no oxidative damage can occur at all. The selenoprotein effect does not act directly on the DNA, but rather via transduction pathways. An example for this is p53. In addition, selenium has epigenetic effects such as acetylation or phosphorylation, which directly influence DNA repair mechanisms.\(^{30}\)

Selenium improves DNA stability

In 2013 a trial was published that investigated the question whether targeted selenium supplementation can improve DNA stability in healthy people. A total of 14,503 men participated in the trial. The requirement was that no prior cancer disease existed and the serum selenium concentration was below 200 µg/l at trial start. The supplementation was 200 µg selenium in the form of selenium yeast for six months. Besides the activity of various selenoproteins, DNA damage was determined.

The mean serum selenium concentration was 111.5 µg/l. The selenium status of the trial participants was thus already adequate prior to start of the trial. Participants with a serum selenium level below 80 µg/l showed greater DNA damage compared to those whose selenium levels were between 100–120 µg/l.

Selenium supplementation had the greatest effect in the group with the most DNA damage at the start of the trial. Basal DNA damage and peroxide-induced DNA damage declined significantly (\(p < 0.0001\) or \(p < 0.000002\)).\(^{14}\) In contrast, basal and peroxide-induced DNA damage increased in the group with the least DNA damage as baseline value. Based on the trial results, the authors assume that the optimal benefit for DNA integrity is between 120–160 µg/l selenium in serum. At selenium levels above this value, the amount of DNA damage increases again.

A successful selenium supplementation to improve DNA stability therefore greatly depends on the selenium status. A low selenium level is associated with greater DNA damage. Selenium supplementation increases the selenium level and reduces the likelihood of increased DNA damage.
Selenium is important for DNA stability

- Selenium
  - Selenoprotein synthesis
    - Reactive oxygen species
    - Activation and stabilization of p53
      - Epigenetic effects
        - DNA damage
          - DNA repair
            - High DNA stability

Bera S et al. Mutagenesis. 2013 Mar; 28(2): 127-34. Does a role for selenium in DNA damage repair explain apparent controversies in its use in chemoprevention?

Fig. 11
Cancer prevention for patients with genetic disposition

BRCA1 mutations influence the number of chromosomal breakages

A clinical trial investigated the effect of a BRCA1 mutation on chromosomal breakages. An increased rate of chromosomal breakages is associated with an increased cancer risk. In the event of a BRCA1 mutation, the lifetime risk of breast cancer increases by about 80%, and about 40% for ovarian cancer. BRCA1 has various functions, including a participation in the response to DNA damage, nucleotide excision repair, and protection from oxidative stress.

The number of chromosomal breakages in 26 healthy female carriers with BRCA1 mutation was compared with a comparable healthy control group (siblings or other close relatives). The average number of chromosomal breakages of 0.58 per cell in the group with BRCA1 mutation was significantly higher compared to the control group with 0.39 per cell (p<0.0001) (Fig. 12).
Sodium selenite reduces the number of chromosomal breakages in women with BRCA1 mutation

Thirty-five healthy women with a BRCA1 mutation supplemented a daily dosage of 276µg selenium in the form of sodium selenite for an average of 1.5 months. The average serum selenium concentration increased from $56.7 \pm 12.7 \mu g/l$ to $90.2 \pm 17.6 \mu g/l$ ($p < 0.001$). The treatment with sodium selenite reduced the number of chromosomal breakages in every trial participant. The mean value declined significantly from $0.63 \ (0.42–0.81)$ to $0.40 \ (0.27–0.60)$ ($p < 0.001$) (Fig. 13).
Sodium selenite significantly reduces the number of chromosomal breakages in women with a BRCA1 mutation.


Fig. 13
Sodium selenite can decrease breast cancer risk of BRCA1 mutations

The results of the pilot study conducted by Kowalska et al. were checked in an elaborate, randomized, double-blind, placebo-controlled trial.\[^{39,40}\] A total of 260 women were divided into several groups. The control group was composed of healthy women without BRCA1 mutation (n = 91). Healthy BRCA1 mutation carriers were divided into a placebo group (n = 82) and a group treated with sodium selenite (n = 54), whereby both groups were respectively separated into two further groups: with and without adnexectomy. In the third large group, cancer patients with a BRCA1 mutation were divided into a placebo group (n = 38) and a group of women with adnexectomy who were treated with sodium selenite (n = 16). The daily selenium dosage was 300 µg in the form of sodium selenite.

Sodium selenite improves the selenium status in case of BRCA1 mutation

The selenium status significantly increased in all groups treated with sodium selenite compared to the respective placebo group (p < 0.05) (Table 4).\[^{40}\] The significantly greater positive effect of sodium selenite therapy on the selenium status of patients with adnexectomy was striking.

BRCA1 mutation significantly increases the 8-oxodG level

In contrast to the trial conducted by Kowalska et al., in the trial conducted by Dziawan et al. the number of chromosomal breakages was not examined, but rather the 8-oxo-7,8-dihydro-2’-deoxyguanosine level (8-oxodG) in leukocytes.\[^{39,40}\] 8-oxodG is an established biological marker for oxidative DNA damage and is associated with the potential mutagenicity of human cells.\[^{42}\] Compared to the healthy control group without BRCA1 mutation, both healthy as well as BRCA-1 carriers already diagnosed with cancer showed a significantly increased 8-oxodG level (p < 0.05).
Sodium selenite significantly increases the selenium status of carriers of BRCA1 mutation

<table>
<thead>
<tr>
<th></th>
<th>Plasma selenium concentration [µg/l]</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo</td>
<td>Sodium selenite</td>
</tr>
<tr>
<td>Healthy, BRCA1 mutation with adnexectomy</td>
<td>52.5</td>
<td>84.0</td>
</tr>
<tr>
<td>Healthy, BRCA1 mutation without adnexectomy</td>
<td>63.0</td>
<td>72.0</td>
</tr>
<tr>
<td>Cancer diagnosis, BRCA1 mutation with adnexectomy (placebo group without adnexectomy)</td>
<td>53.6</td>
<td>93.3</td>
</tr>
</tbody>
</table>

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

*Table 4*
Sodium selenite normalizes the 8-oxodG level after adnexectomy

In the trial conducted by Dziaman et al., the treatment with sodium selenite reduced the 8-oxodG level by about 25% in the group with BRCA1 mutation, cancer diagnosis and adnexectomy (Fig. 14). Despite a reduction in the 8-oxodG level by one fourth, the difference was not significant due to the small group size.

In the group with healthy BRCA1 carriers, a difference could also be established after treatment with sodium selenite. Those with adnexectomy had a significantly lower 8-oxodG level (vs. without adnexectomy; 4.67 vs. 5.34 per 106 dG; p < 0.05). Since no significant difference could be determined between healthy BRCA1 carriers with or without adnexectomy in the respective placebo group, the results indicate that DNA damage induced by oxidative stress in patients with a BRCA1 mutation and an adnexectomy can be normalized.

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

### Selenium in cancer prevention for patients with genetic predisposition

<table>
<thead>
<tr>
<th>Low selenium status</th>
<th>Selenium deficit</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;100 µg/l selenium in serum</td>
<td>&lt;80 µg/l selenium in serum</td>
</tr>
<tr>
<td>&lt;120 µg/l selenium in whole blood</td>
<td>&lt;100 µg/l selenium in whole blood</td>
</tr>
</tbody>
</table>

**Continuously:**
- up to 200 µg selenium per day (tablet or drinking ampoules)
- up to 300 µg selenium per day (tablet or drinking ampoules)

**Costs:**
- approx. €17 per months or €200 per year*
- approx. €50 per months or €600 per year*

* calculation based on the marketed dosage forms indicated in parentheses

Prepared based on:
*Increased rates of chromosome breakage in BRCA1 carriers are normalized by oral selenium supplementation.*
*Selenium supplementation reduced oxidative DNA damage in adnexectomized BRCA1 mutations carriers.*
Selenium deficiency in cancer patients

At a glance

- Reduced selenium status at diagnosis [43–48]
- Low selenium status worsens prognosis [49,50]

Reduced selenium status at diagnosis

The natural selenium supply differs widely around the world. Nevertheless, all cancer patients have one thing in common: at cancer diagnosis, most of them have a significantly reduced selenium status compared to healthy persons (p < 0.05). The selenium deficiency accompanying cancer already exists before the start of cancer therapy. [43–48] A possible cause is the increased selenium requirements of the body. For instance, cancer increases oxidative stress, since it benefits cancer cells. In order to protect itself against oxidative stress, the body needs selenoproteins. The immune system also attempts to combat cancer cells. This activity of the required natural killer cells is influenced by selenium-dependent pathways. [51,52]

Reduced selenium levels appear at different tumor localizations (Fig. 15). [43–48] The extent depends on the localization: particularly patients with liver, gastric or breast cancer show a massive decline in selenium status. If a selenium deficiency already existed before the cancer diagnosis, the negative effects are more serious. [49,50] In countries with a known suboptimal selenium supply such as in Europe, one can assume a definite selenium deficit at diagnosis that cannot be compensated by diet, and which therefore requires treatment with high-dose selenium medication.
Reduced selenium status in cancer patients at diagnosis

![Graph showing reduced selenium status with liver cancer](image)

Selenium status with liver cancer starting with a:
* suboptimal selenium status
** adequate selenium status

Charalabopoulos K et al. Br J Cancer. 2006 Sep 18; 95(6): 674-6. [Selenium in serum and neoplastic tissue in breast cancer: correlation with CEA](https://doi.org/10.1038/sj.bjc.6603534).


Muecke R et al. Acta Oncol. 2009; 48(3): 452-6. [Whole blood selenium levels (WBSL) in patients with prostate cancer (PC), benign prostatic hyperplasia (BPH) and healthy male inhabitants (HMI) and prostatic tissue selenium levels (PTSL) in patients with PC and BPH](https://doi.org/10.2340/03007995-0882).


Fig. 15
Low selenium level worsens the prognosis

A low selenium level in cancer patients is not a negligible trace element deficiency. Two trials were able to demonstrate the negative effect of low selenium status on various cancer types.

Hematological cancer

In a trial composed of 430 patients with different hematological cancers, Stevens et al. showed that a low serum selenium concentration at cancer diagnosis is associated with an inferior outcome. The observation period was up to 20 years.

The trial defined serum selenium levels below 70.3 µg/l as a low selenium status. A low status significantly reduced the total survival rate of patients with Hodgkin’s disease and follicular lymphoma \((p = 0.05 \text{ resp. } p = 0.002)\) (Fig. 16). Hodgkin’s/lymphoma patients with a low selenium status primarily died in the first six years. With follicular lymphoma, fewer than 25 % of the patients with low selenium levels were still alive after 15 years, while the percentage of those with normal or high selenium levels was greater than 50 %.

For patients with follicular lymphoma, the Cox analysis resulted in a significantly increased mortality risk \((HR = 2.3; 95 \% \text{ CI } 1.4–4.0; \ p = 0.002)\) \(\text{(Table 5)}\). Acute myeloid leukemia showed a trend towards increased risk \((HR = 1.4; 95 \% \text{ CI } 0.9–4.0; \ p = 0.002)\). Due to the non-proportional risk distribution for Hodgkin’s lymphoma patients with low vs. normal selenium status, a Cox analysis was not possible.

### Increased mortality risk at low selenium status (<70.3 µg/l selenium in serum) for hematological cancer patients

<table>
<thead>
<tr>
<th></th>
<th>Number of patients</th>
<th>Hazard Ratio 95 % CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute myeloid leukemia</td>
<td>163</td>
<td>1.43</td>
<td>0.08</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.96 – 2.13</td>
<td></td>
</tr>
<tr>
<td>Hodgkin’s lymphoma</td>
<td>156</td>
<td>Could not be interpreted due to non-proportional risks in the selenium groups</td>
<td></td>
</tr>
<tr>
<td>Follicular lymphoma</td>
<td>111</td>
<td>2.3</td>
<td>0.002</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1.4 – 4.0</td>
<td></td>
</tr>
</tbody>
</table>

A low selenium status reduces the overall survival of hematological cancer patients


Fig. 16
Renal cell carcinoma

One year later, a trial on the impact of selenium status on the prognosis for renal cell carcinoma patients was able to corroborate the result of Stevens et al.\textsuperscript{[48, 50]} In this trial (n = 41), the selenium status was determined using the selenium transport protein selenoprotein P. For suboptimal selenium levels, selenoprotein P correlates with the concentration of selenium in the blood and is therefore a reliable marker for selenium status in Europe. The five-year survival rate declined from over 80\% at a selenium level in the top third to below 20\% in patients with selenium levels in the lowest third (Fig. 17).

Low selenium status at diagnosis worsens overall survival of renal cell carcinoma patients

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{fig17.png}
\caption{Selenoprotein P status correlates to cancer-specific mortality in renal cancer patients.}
\end{figure}

\textit{Fig. 17}

\begin{flushright}
\end{flushright}
**Dosage recommendation**

<table>
<thead>
<tr>
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</tr>
</thead>
<tbody>
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<td>&lt; 100 µg/l selenium in serum</td>
<td>&lt; 80 µg/l selenium in serum</td>
</tr>
<tr>
<td>&lt; 120 µg/l selenium in whole blood</td>
<td>&lt; 100 µg/l selenium in whole blood</td>
</tr>
<tr>
<td>Until start of cancer therapy up to 200 µg selenium per day (tablet or drinking ampoules)</td>
<td>Until start of cancer therapy up to 300 µg selenium per day (tablet)</td>
</tr>
<tr>
<td>Costs: approx. € 17 per month or € 200 per year*</td>
<td>Costs: approx. € 50 per month or € 600 per year*</td>
</tr>
</tbody>
</table>

*calculation based on the marketed dosage forms indicated in parentheses

Sodium selenite at tumor surgery

At a glance

<table>
<thead>
<tr>
<th>Surgical interventions result in a significant decrease in selenium levels $^{[53,54]}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>A small increase of the inflammation marker CRP already significantly reduces selenium status $^{[55]}$</td>
</tr>
<tr>
<td>Negative effect of surgery-induced systemic inflammatory response to therapy success $^{[56,57]}$</td>
</tr>
<tr>
<td>Supranutritive dosage of sodium selenite promotes TH1 differentiation $^{[58]}$</td>
</tr>
<tr>
<td>Peri- and post-operative administration of selenase® improves selenium status $^{[59]}$</td>
</tr>
</tbody>
</table>
Surgical interventions result in a significant decrease in selenium levels

Both major and minor operations result in a reduction in selenium levels on the day after surgery. Already in 1998, Nichol et al. were able to demonstrate that a minor elective surgery, in this case a hernia operation, significantly reduces the selenium status by about 10% (p < 0.01).\[53\]

The concentration of the C-reactive protein (CRP), an inflammation marker, simultaneously increased slightly (p < 0.01). Major operations such as elective heart surgery result in a significantly greater decrease in the selenium status by more than 20%, whereby this was associated with post-operative multi-organ failure as an independent factor (p = 0.0026).\[54\]

Even a slight increase in the inflammation marker CRP already significantly reduces selenium levels

Surgery is connected with ischemia or reperfusion, which in turn results in the release of reactive oxygen species. Simultaneously, surgery triggers a systemic inflammatory response. A trial published in 2012 shows the close correlation between the extent of a systemic inflammatory response (marker: CRP) and the decline in the selenium level.\[55\] At a CRP increase of 5–10 mg/l, the plasma selenium concentration already declines significantly (p < 0.001) (Table 6).
Association between systemic inflammatory response (marker: CRP) and reduction in selenium level

<table>
<thead>
<tr>
<th>CRP concentration [mg/l]</th>
<th>Number of samples</th>
<th>Plasma selenium concentration, median in [µg/l] (range: 25 – 75 %)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤5</td>
<td>1,132</td>
<td>72.6 (58.4 – 89.2)</td>
<td>–</td>
</tr>
<tr>
<td>&gt;5 – 10</td>
<td>311</td>
<td>65.5 (52.9 – 79.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>&gt;10 – 20</td>
<td>227</td>
<td>61.6 (43.4 – 77.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>&gt;20 – 40</td>
<td>174</td>
<td>56.9 (41.1 – 75.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>&gt;40 – 80</td>
<td>144</td>
<td>47.4 (34.0 – 63.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>&gt;80</td>
<td>190</td>
<td>37.9 (25.3 – 54.5)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>


Table 6
Negative impact of surgery-induced systemic inflammatory response on the therapy success

For various cancer types, especially colorectal carcinoma, it could meanwhile be shown that the inflammation significantly influences the prognosis of recurrence and survival probability.\textsuperscript{[60,61]} Surgery creates a non-specific shift of the TH1/TH2 balance of the immune system in the TH2 direction.\textsuperscript{[56]} This results in non-specific activation of the congenital immune response and restricted cell-mediated immunity. Cell-mediated immunity is important for the body’s ability to destroy tumor cell with the help of cytotoxic lymphocytes. The peri-operative time period is therefore one of immunological susceptibility for cancer patients (\textit{Fig. 18}).\textsuperscript{[57]} An intact and coordinated cell-mediated immune response, however, is associated with improved tumor therapy success.\textsuperscript{[62]}
Surgery-induced shift of the TH1/TH2 balance negatively influences the therapy success

Healthy

Cancer

Cancer + surgery


Fig. 18
SODIUM SELENITE AT TUMOR SURGERY

High-dose sodium selenite increases the expression of high-affinity interleukin-2 receptors

Cytokine interleukin-2 (IL-2) plays a central role in the body’s immune response. IL-2 is a growth factor for T-cells and promotes the cytolytic activity of CD8⁺-T cells and natural killer cells. In addition, IL-2 modulates the differentiation of naive CD4⁺-T cells into T-helper cells 1 (TH1) and T-helper cells 2 (TH2). To forward signals, IL-2 binds at the interleukin-2 receptor (IL-2R) that occurs in various combinations of three subunits. IL-2Rα (CD25) is the so-called low-affinity IL-2R (Kd ~ 1 nM), which is only expressed after stimulation of the T-cells. The two subunits IL-2Rβ (CD122) and IL-2Rγ (CD132) together form the intermediate-affinity IL-2R (Kd ~ 0.1 nM). The high-affinity IL-2R (Kd ~ 10 pM) consists of three subunits. Both the intermediate- as well as the high-affinity IL-2R are functional. While the intermediate-affinity IL-R2 is expressed on dormant T-cells and natural killer cells, the high-affinity IL-2R are found on activated lymphocytes. After T-cell activation, IL-2Rα is rapidly induced and high-affinity IL-2R is formed, which increases the responsiveness compared to IL-2.

It was already demonstrated in 1992 that a high-dose therapy with sodium selenite could significantly increase the expression of high-affinity interleukin-2 receptors (IL-2R) compared to an adequate or deficit selenium status (p < 0.05 resp. p < 0.005) (Fig. 19). An additional trial provided a detailed picture of the effect of high-dose sodium selenite. The expression of IL-2Rα and high-affinity IL-2R increased significantly in vitro as well as in vivo compared to an adequate selenium supply. These results were confirmed in a trial conducted in 2010. In this in vivo trial, a deficit was compared to an adequate selenium supply as well as to a high-dose sodium selenite supplementation. Both the expression of IL-2 as well as IL-2Rα significantly increased at high-dose sodium selenite supplementation (p < 0.05) (Fig. 20). IL-2 and IL-2R incite the proliferation of T-cells. Consequently the results showed that the proliferation of CD4⁺ cells significantly increased with increasing selenium intake.
Increased proliferation of CD4\(^{+}\) cells at increased selenium intake


Fig. 19

High-dose sodium selenite significantly increases the expression of IL-2R\(\alpha\)


Fig. 20
Supranutritive dose of sodium selenite promotes TH1 differentiation

Certain cytokines are characteristic for T-cell differentiation, interferon gamma (IFNγ) for TH1 and interleukin-4 (IL-4) for TH2. A supranutritive dose of sodium selenite significantly increases the expression of IFNγ compared to a low or adequate selenium status (p < 0.05). Simultaneously, IL-4 was significantly increased in the group with a low selenium supply (p < 0.05). The expression of CD154, which plays a key role in the differentiation of T-cells, also increased significantly when high-dose sodium selenite was supplemented (p < 0.05).

In summary, these results show that a supranutritive dose of sodium selenite shifts the TH1/TH2 equilibrium towards TH1 differentiation (Fig. 21). This effect of high-dose sodium selenite can restore the balance in the TH1/TH2 relationship that was disturbed by surgery. However, a low selenium level reinforces the shift towards TH2 differentiation and hence the inhibition of cell-mediated immunity.
High-dose sodium selenite enhances TH1 differentiation


Fig. 21

Peri- and postoperative administration of selenase® improves the selenium status of tumor patients


Fig. 22
Peri- and postoperative administration of selenase® improves selenium status

Winnefeld et al. investigated the effect of selenase® in cases of major surgery already in 1995.[59] Nine patients who underwent gastrectomy due to cancer were divided into two groups. Aside from parenteral nutrition, five patients were treated with high-dose selenase® (average of 2,034.4 µg sodium selenite), whereas the control group only received parenteral nutrition after surgery.

At the beginning of parenteral nutrition, all participants showed low selenium levels. In the control group, the selenium status significantly declined after surgery, and did not regain its initial value during the observation period of ten days. In the selenase® therapy regime group, the selenium status increased after eight days into the lower reference range (Fig. 22).[59]

Moreover, this trial also simultaneously determined the selenium status in serum and in whole blood. The results support the latest state of scientific knowledge that a serum selenium measurement reflects the short-term status and that whole blood better indicates the long-term supply with selenium (Fig. 22).

Too few patients participated in the trial in order to make significant statements about the reduction of surgical complications due to selenase®. However, three-fifths of the patients in the selenase® group showed no complications, while only one-fourth of the participants in the control group were likewise without complications. In total, the trial could demonstrate that the peri- and postoperative administration of selenase® significantly improved the selenium status of the tumor patients. In contrast, surgery worsened the selenium level in the control group.
# Dosage recommendation

## Dosage* and costs of selenium in tumor surgery

To reduce surgery-related oxidative stress and improve the immune status*:

<table>
<thead>
<tr>
<th>Before surgery**[(A–C)](i. v. or drinking ampoules)</th>
<th>Intra- or post-operative**[(A, C)](i. v.)</th>
<th>Per day for 2 weeks**[(D)](i. v. or drinking ampoules)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1,000 µg selenium</td>
<td>1,000 µg selenium</td>
<td>up to 1,000 µg selenium**[(A, C)](i. v. or drinking ampoules)</td>
</tr>
</tbody>
</table>

Costs: approx. € 185**

## Dosage* and costs of selenium in lymphedema

At increased risk of surgery-related lymphedema*:

<table>
<thead>
<tr>
<th>Before surgery**[(C)](i. v. or drinking ampoules)</th>
<th>Intra- or post-operative**[(C)](i. v.)</th>
<th>Per day for 3 weeks**[(C)](i. v. or drinking ampoules)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1,000 µg selenium</td>
<td>1,000 µg selenium</td>
<td>1,000 µg selenium</td>
</tr>
</tbody>
</table>

Costs: approx. € 265**

* according to dosages, regimes as presented in trials
** calculation based on the marketed dosage forms of selenase® indicated in parentheses

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Selenium and cancer-related lymphedema

At a glance

Especially affected: breast cancer patients and patients with head and neck tumors

Only half of those affected obtain therapy\textsuperscript{[67]}

The selenium status declines with increasing degree of severity of lymphedema\textsuperscript{[68]}

Sodium selenite produces both biological as well as pharmacological effects\textsuperscript{[68]}

\textbf{selenase}\textsuperscript{®}

– reduces lymphedema volume\textsuperscript{[66, 69]}
– increases the effectiveness of physical therapy\textsuperscript{[69]}
– reduces the risk of erysipelas\textsuperscript{[69, 70]}
– improves quality of life scores\textsuperscript{[71]}
– reduces side effects
New therapy option for lymphedema

Secondary lymphedema is a frequent side effect of cancer therapy. The incident rate varies highly, since no uniform diagnostic criteria exist up to now.\(^7\) Most data comes from breast cancer patients, whose incidence rate ranges between 13\% and 65\%.\(^7\)

There is no curative therapy for lymphedema. The standard treatment (complex physical therapy) aims at reducing and maintaining the size of the extremities in the long term, protecting from complications, and improving the function of the extremities as well as the overall well-being of the patient. Up to now, pharmacotherapy has only played a limited role, since many medicinal products are either not effective or only produce a short-term effect. The only exception here is sodium selenite. Paskett et al. mention sodium selenite as the only effective medicinal product in their review of cancer-related lymphedema.\(^7\)

Gap in knowledge about lymphedema

In a large-scale US-American trial, 1,287 women who had survived breast cancer were examined with respect to the occurrence of lymphedema.\(^6\) Lymphedema was diagnosed in 8.1\% of the women. An additional 37.2\% reported arm symptoms without the diagnosis of lymphedema. However, both the group with diagnosed lymphedema as well as the group with arm symptoms showed lower values with respect to their physical and mental quality of life.

Only about half of the women diagnosed with lymphedema received specific treatment for the disease.\(^6\) Even more dramatic were the numbers concerning the available knowledge about lymphedema. Only 39.8\% of the women with arm symptoms had ever heard anything about lymphedema. This knowledge gap is probably partially responsible for the fact that only 10.3\% of the women had ever spoken with their physician about the changes in their arms.
Only half of those affected received therapy

A large-scale prospective trial conducted over 5 years (n = 631) examined the incidence of lymphedema, extent, therapy and symptoms in breast cancer patients after tumor resection. The cumulative incidence of lymphedema after five years was 42 per 100 women, with the incidence in women under 50 years significantly higher compared to women over 80 years (50% vs. 26%) (Fig. 23).

In the first three years, 23% of the trial participants reported mild lymphedema, an additional 12% reported moderate and 2% severe forms of lymphedema. In this trial as well, only about half of the affected women received any lymphedema therapy, whereby the percentage of those treated with a severe form was significantly higher than those with a mild form (68% vs. 37%).

Early signs of lymphedema

Specific symptoms are associated with a significantly higher risk of subsequent lymphedema. The lymphedema risk increased more than sevenfold when jewelry suddenly became too tight (Hazard Ratio [HR] 7.37; 95% CI, 4.26 – 12.76) (Table 7). When clothing became too tight, the risk increased by 5.5-fold (HR 5.47; 95% CI, 1.98 – 15.10).

Until now, however, no trial has yet examined whether immediate treatment of such early symptoms can protect the patient from developing lymphedema or prevent a progression from a mild to a moderate or severe form of the disease.
Lymphedema incidence in breast cancer patients

Percentage of breast cancer patients with secondary lymphedema

- **42%** of all patients
- **50%** of patients under 50 years
- **26%** of patients above 80 years


**Fig. 23**

Symptoms associated with the development of lymphedema

<table>
<thead>
<tr>
<th>Suddenly too tight jewelry</th>
<th>Suddenly too tight clothing</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR 7.37; 95% CI, 4.26–12.76</td>
<td>HR 5.47; 95% CI, 1.98–15.10</td>
</tr>
<tr>
<td>7-fold increased risk</td>
<td>5.5-fold increased risk</td>
</tr>
</tbody>
</table>


**Table 7**
Decreasing selenium levels with increasing degree of severity of lymphedema

The selenium level in whole blood of 234 lymphedema patients and/or lipidema patients was examined in a new German trial. The average selenium concentration in whole blood was 102.4 ± 19.8 µg and thus barely within the reference range (100–140 µg/l selenium in whole blood). 44% of the patients had a selenium deficit. The percentage increased to 78% (p = 0.001) in stage III lymphedema patients (Fig. 24).

Almost 80 percent of patients with stage III lymphedema show a selenium deficit


Fig. 24
The degree of severity of the lymphedema correlated with the selenium status. Patients with stage III lymphedema showed significantly low selenium levels compared to patients with grade I and grade II lymphedema (91.5 ± 14.4 vs. 106.5 ± 23.9 vs. 109.1 ± 17.9; p = 0.0109 resp. p = 0.0002) (Fig. 25).

These results show that lymphedema patients have an increased selenium requirement. The cause could be increased oxidative stress and increased inflammatory activity.

**Declining selenium status with increasing severity of lymphedema**


*Fig. 25*
Mechanism of action of sodium selenite in lymphedema patients

Sodium selenite has both a biological as well as a pharmacological effect on lymphedema patients. In its inorganic form, selenium selenite supplies the body with essential selenium for the important selenoproteins. Simultaneously, high-dose sodium selenite has a direct anti-inflammatory effect.

Increased formation of metabolites 4-HNE and MDA

Increased concentrations of reactive oxygen species were found in patients with lymphedema. The resulting high oxidative stress induces an inflammatory reaction. As a consequence, the affected lymphatic duct is flooded with phagocytes and other activated leukocytes. Subsequently the so-called “respiratory burst” triggers an entire cascade of peroxidative reactions. Among other things, increasing numbers of 4-hydroxynonenal (4-HNE) and malondialdehyde (MDA) are formed. These metabolites exhibit a whole series of negative properties. They are pro-inflammatory, vasoconstrictive, cytotoxic and potentially carcinogenic (Fig. 26).

Increased consumption of glutathione is compensated by administering sodium selenite

In order to eliminate the lymphedema created by metabolites, large quantities of glutathione (GSH) are oxidized (GSSG). Siems et al. could demonstrate this procedure in lymphedema patients. Whereas the serum concentration of MDA and 4-HNE increased three-fold or two-fold, the GSH level declined and the GSSG levels increased (Fig. 27). Treatment with oral sodium selenite led to a rapid increase of GSH and thus to an improved relationship of reduced and oxidized glutathione. As a component of the selenoproteins glutathione peroxidase and thioredoxin reductase, selenium is essential for redox reactions such as GSH–GSSG. Sodium selenite therapy increases the activity of these selenoproteins, which increases the GSH concentration and decreases the GSSG level. Aside from the availability of selenium, the function of glutathione peroxidase is influenced by glutathione availability. The reduction in the GSH concentration impairs the activity of glutathione peroxidase. If sufficient GSH is available, this negative effect is nullified.
Metabolites with negative characteristics occur in lymphedema

Respiratory burst → Peroxidative reactions → Metabolites among others: MDA + 4-HNE

- Inflammatory
- Vasoconstructive
- Cytotoxic
- Potentially carcinogenic


Fig. 26

Biological effects of sodium selenite in lymphedema

Sodium selenite

↓

Glutathione peroxidase (selenoprotein)

↑

↓

ROS (Reactive Oxygen Species)

MDA 4-HNE

↓

↑

GSH/GSSG (glutathione reduced / glutathione oxidized)


Fig. 27
Direct pharmacological effect of sodium selenite

The first indication that sodium selenite has a positive effect on lymphedema was observed in 1991. [69] A patient with acute inflamed lymphedema was treated with 800 µg selenium in the form of oral sodium selenite. After 15 minutes, the inflammation and edema was visibly reduced. This quick effect cannot be explained by a biological process, but rather indicates a direct pharmacological effect of sodium selenite.

Disturbed immune communication in lymphoid tissue

Disturbed immune communication plays an important role in the pathogenesis of lymphedema. [76] Phagocytes and lymphocytes normally reach the afferent lymphatic ducts and lymph nodes in order to trigger a primary immune response. In chronic lymphedema, this communication between tissue and regional lymph nodes is restricted (Fig. 28), resulting in an inefficient elimination of foreign antigens, the basis for chronic inflammatory changes. [76] The risk of inflammation from lymphedema significantly increases.

Due to the malfunctioning immune communication, lymphedema patients are prone to infections
Disturbed immune communication in lymphatic tissue

Lymphatic capillaries with flap valves

In the lymphedema
Immune cells with adhesion proteins on the cell surface
attaches to the walls of the lymphatic capillaries

Disturbed immune communication

Lymphatic ducts with lymphatic valves

Lymph node

Immune cells Fluid and macromolecules Lymph flow

Based on:

*Fig. 28*
Sodium selenite inhibits the expression of adhesion proteins

Latest research findings could show that adhesion proteins are decisively involved in the pathogenesis of the lymphatic system. So-called adhesion proteins are located on the cell surface of phagocytes and activated leukocytes, which immune cells require in order to be able to immigrate to the inflamed tissue.\(^{[77]}\) The immune cells can attach to the walls of the lymphatic capillaries, thus reinforcing the venous lymphatic insufficiency.\(^{[69]}\)

Sodium selenite can inhibit several adhesion proteins that occur on the cell surface of immune cells.\(^{[68]}\) Among other things, L-selectin is inhibited, which in turn reduces the mobility of monocytes and their adhesion capacity.\(^{[78]}\) Immune communication is improved and the venous lymphatic insufficiency reduced due to the decreased adhesiveness of the immune cells. The lymph volume declines and the risk of infection decreases.

Sodium selenite inhibits NFκB

The transcriptions factor NFκB is necessary for the expression of adhesion proteins. Sodium selenite can directly inhibit NFκB via the production of adducts with essential thiols.\(^{[79]}\) This inhibition depends on the dosage.

Simultaneously, NFκB plays an important role in inflammation. Proinflammatory cytokines activate NFκB. In turn, NFκB induces the expression of cytokines, chemokines, and adhesion proteins.\(^{[80]}\) The inhibition of NFκB by sodium selenite is therefore a possible cause for its anti-inflammatory effect in lymphedema patients.

Aside from the direct inhibition of NFκB by sodium selenite, the two selenoproteins glutathione peroxidase 1 and 4 are able to inhibit NFκB. Thus sodium selenite reduces the effect of NFκB on two levels (Fig. 29).
Direct pharmacological effect of sodium selenite apart from biological effects

Sodium selenite

↓

Biological effects

↓

Pharmacological effects

GPx-1 ↑

GPx-4 ↑

ROS ↓

NFKB ↓

Adhesion proteins ↓

↓

Decreased lymphedema volume

Reduced risk of infection

Improved efficiency of complex physical therapy


Fig. 29
Surgery-related lymphedema

Primarily patients with head and neck tumors are affected by surgery-related lymphedema. Three-quarters of all patients develop lymphedema after tumor resection. Approximately half of them showed a combination of internal and external lymphedema in trials.

Lower surgery-related lymphedema volume with simultaneous selenase® therapy

In a prospective, randomized, placebo-controlled, double-blind trial, Zimmermann et al. investigated the effect of pre-, intra- and post-operative administration (for a total of 3 weeks) of high-dose selenase® (1,000 µg selenium per day) on the development of lymphedema in patients with head and neck tumors. The follow-up time period was one year in total.

The lymphedema volume in the head and neck area was measured post-operatively after one or two weeks, and compared to the pre-operative measurements. The extent of the lymphedema volume was significantly lower in the group treated with sodium selenite, both after one as well as after two weeks (p = 0.009 resp. p = 0.029) (Fig. 30). Simultaneously, the volume of the lymphedema in the intervention group declined significantly faster. In the placebo group, the volume only decreased in the second post-operative week, whereas the lymphedema already subsided in the first week after tumor resection in the group treated with sodium selenite.

Development of selenium status in patients with head and neck tumors in Germany

Zimmermann et al. conducted the trial in Germany. They documented the selenium status of the tumor patients at the start of the trial and the effect of high-dose selenase® therapy for 3 weeks (1,000 µg sodium selenite per day) over a follow-up period of one year after tumor resection.

On average, all participants in the trial showed a massive selenium deficit. In the placebo group, the selenium concentration in whole blood continued to decline after tumor resection and increased slightly after one week, and then persisted at a similarly low level over the course of the year. In contrast, the selenium concentration in the group treated with selenase® already increased significantly at the post-operative measurement (p = 0.001). This increase in the selenium status continued during the entire selenase® therapy, so that after two weeks these patients had selenium levels in the upper reference range (Fig. 31).

The steep decline in the selenium status after one month clearly shows that terminating the selenase® therapy only one week earlier already had a negative effect on the selenium level. The simultaneous measurement of the activity of the selenoprotein glutathione peroxidase showed a course parallel to the selenium concentration in whole blood with significantly greater activity in the intervention group after one resp. two weeks (p = 0.03).
Treatment with high-dose selenase® significantly reduces the volume of surgery-related lymphedema


Fig. 30

Development of the selenium status with high-dose selenase® therapy for head and neck tumors


Fig. 31
Secondary lymphedema in breast cancer patients

Breast cancer patients are particularly often affected by lymphedema, frequently even years after cancer therapy. 42 of 100 breast cancer patients are affected within 5 years (cumulative lymphedema incidence of 42%). In a placebo-controlled, double-blind trial, a total of 179 breast cancer patients with lymphedema were treated either with high-dose selenase® (1,000 µg selenium per day, 2nd + 3rd week: 300 µg selenium per day) or a placebo for three weeks in addition to combined physical decongestive therapy. A dosage of 100 µg selenium per day was given during the follow-up period of three months.

At the beginning of the trial, the average selenium concentration in whole blood was 69 ± 8 µg/l. In the group treated with selenase® the selenium status increased to 112 ± 24 µg/l selenium in whole blood, whereas no change could be detected in the placebo group.

High-dose selenase® therapy significantly reduces lymphedema volume

The lymphedema volume significantly decreased in the group treated with selenase® during the entire 3-week therapy. In contrast, in the placebo group the volume only decreased with every subsequent standard treatment. After three weeks the lymphedema volume in the group treated with selenase® significantly declined by 52 ± 18% compared to the placebo group (43 ± 16%; p < 0.01), after correction for weight and size (Fig. 32).

High-dose selenase® therapy effectively prevents erysipelas

The anti-inflammatory effect of high-dose selenase® in lymphedema patients is especially powerful. A trial investigated 60 cancer patients with erysipelas treated with combined physical decongestive therapy over the course of 3 weeks. In addition, half of the participants received high-dose selenase® (1st week: 1,000 µg selenium per day, 2nd + 3rd week: 300 µg selenium per day) and the other half received a placebo. During the 3-month follow-up phase, the intervention group received 100 µg (<70 kg body weight) resp. 200 µg (>70 kg body weight) selenium per day.

In the placebo group, 50% of the patients developed erysipelas during the course of the trial. However, the incidence of erysipelas in the group treated with selenase® was 0% (Fig. 33). Lymphedema patients requiring long-term antibacterial treatment did not develop any additional erysipelas after the antibiotic treatment ceased and continued high-dose selenase® therapy.
High-dose selenase® therapy significantly reduces lymphedema volume


Fig. 32

High-dose selenase® therapy effectively prevents erysipelas

Prepared based on:

Fig. 33
Radiotherapy-induced lymphedema

Radiotherapy can cause secondary lymphedema. Patients with head and neck tumors and breast cancer are particularly affected, with an additional aggravation being that lymphedema impairs breathing and can therefore make a tracheotomy necessary.

High-dose selenase® reduces the number of necessary tracheotomies

In a trial conducted by Bruns et al., 36 patients with head and neck tumors who had developed persistent, extensive and progressive lymphedema after radiotherapy were treated with high-dose selenase® (500 µg sodium selenite per day for 4–6 weeks, peroral).[71]

Different scoring systems were used to evaluate the lymphedema. Using the 5-point Miller scoring system improved the evaluation for 75% of the patients by one degree or more. Applying the Földi scoring system resulted in 63% of the patients showing improvement by one degree or more. 65% of the trial participants showed a substantial reduction in endolaryngal swelling, so that the endolaryngal respiratory tract normalized and no tracheotomy became necessary. Moreover, none of the trial participants developed erysipelas during the trial.

Improved quality of life after high-dose selenase® therapy

This trial also examined the quality of life as well.[71] For this purpose, the so-called visual analog scale (VAS) was used, where higher values mean a worse quality of life. After selenase® therapy the VAS value declined significantly by 4.4 points from 7.9±2.3 to 3.5±2.4 (p<0.05) (Fig. 34).
Positive effects of high-dose selenase® therapy on radiotherapy-induced lymphedema for neck and head tumors


Fig. 34
Positive effects of high-dose selenase® therapy in breast cancer patients

In an additional trial, breast cancer patients with radiotherapy-induced lymphedema (n = 12) were treated with high-dose selenase® (500 µg selenium per day for 4 – 6 weeks, peroral). The size of the affected arm decreased in 83% of the trial participants (Fig. 35). For all participants, the lymphedema improved by at least one degree according to the Földi scoring system. The measurement of the skinfold thickness using the skinfold index resulted in a reduction of 68.4 ± 18.3 points to 45.1 ± 18.5 points (Fig. 36). This difference was not significant due to the low number of trial participants.

The determination of quality of life based on the visual analog scale (VAS) showed a significant reduction from 5.7 ± 1.5 points to 2.1 ± 1.1 points (p<0.05) and thus an improvement in the quality of life (Fig. 37).
High-dose selenase® reduces the skinfold index of radiation-associated lymphedema in breast cancer patients

![Bar chart showing skinfold index (SFA) before and after selenase® therapy]


Fig. 36

High-dose selenase® therapy improves the quality of life

![Bar chart showing quality of life (visual analog scale) before and after selenase® therapy]


Fig. 37
Dosage recommendation

### Dosage* and costs of selenium in lymphedema patients

#### At increased risk of surgery-related lymphedema*

<table>
<thead>
<tr>
<th>Before surgery[A] (i. v. or peroral)</th>
<th>Intra- or post-operative[A] (i. v.)</th>
<th>For 3 weeks[A] (i. v. or peroral)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1,000 µg selenium</td>
<td>1,000 µg selenium</td>
<td>1,000 µg selenium per day</td>
</tr>
</tbody>
</table>

Costs: approx. €265**

#### In radiotherapy-induced lymphedema patients*

<table>
<thead>
<tr>
<th>For 1 week[B] (i. v. or peroral)</th>
<th>For up to 6 weeks[C,D] (peroral)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1,000 µg selenium per day</td>
<td>500 µg selenium per day</td>
</tr>
</tbody>
</table>

Costs: approx. €320**

#### In breast cancer patients with secondary lymphedema*

<table>
<thead>
<tr>
<th>For 1 week[B] (i. v. or peroral)</th>
<th>For 2 weeks[D] (peroral)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1,000 µg selenium per day</td>
<td>500 µg selenium per day</td>
</tr>
</tbody>
</table>

Costs: approx. €160**

* according to dosages, regimes as presented in trials
** calculation based on the marketed dosage forms of selenase® indicated in parentheses

SODIUM SELENITE IN RADIOTHERAPY
Sodium selenite in radiotherapy

At a glance

<table>
<thead>
<tr>
<th>Negative effect of radiotherapy on the selenium status[^84]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium selenite therapy reduces radiotherapy-induced side effects[^85]</td>
</tr>
<tr>
<td>Phase III trial[^1,3]:</td>
</tr>
<tr>
<td>– selenase® reduces radiotherapy-induced diarrhea</td>
</tr>
<tr>
<td>– selenase® significantly increases the selenium status</td>
</tr>
<tr>
<td>– selenase® does not reduce the effectiveness of radiotherapy during treatment</td>
</tr>
</tbody>
</table>

Negative effect of radiotherapy on selenium status

Numerous clinical trials, including two prospective trials on breast cancer and lung cancer, were able to demonstrate that radiotherapy can have a massively negative impact on selenium status.[^84,86] In both trials, the average selenium level prior to the start of radiotherapy was in the normal range. After radiotherapy, almost 90% of the participants showed a selenium deficiency, over 60% even a critical selenium status.
Breast cancer

A prospective trial examined the selenium status in 209 breast cancer patients before and after radiotherapy. The mean plasma selenium concentration prior to radiotherapy was 86.4 µg/l. After radiotherapy, the average selenium status had declined to 47.8 µg/l selenium in plasma. Whereas before radiotherapy not a single patient had a critical selenium level under 40 µg/l, the percentage after radiotherapy increased to 63%. In fact, 86% of the breast cancer patients showed a low selenium status or selenium deficiency after radiotherapy (Fig. 38).

Lung cancer

The selenium status before and after radiotherapy was examined in 95 lung cancer patients in a prospective trial. The mean plasma selenium concentration was 90.4 µg/l prior to radiotherapy. The selenium determination after radiotherapy showed a decline to 56.3 µg/l selenium in plasma. Before radiotherapy, no patient had a critical selenium status (<45 µg/l). After radiotherapy, 70 % of the trial participants had critical selenium levels. The percentage of lung cancer patients with selenium deficiency increased from 29 % to 88 % (Fig. 39).


Fig. 39
Which patients are especially at risk?

Two prospective trials examined not only the selenium status before and after radiotherapy in patients with breast cancer or lung cancer patients, but other parameters as well, in order to determine the impact of age, weight, negative eating habits, previous chemotherapy and tumor subtype on the selenium level (Fig. 40).[84,86]

Age

The selenium status before radiotherapy was significantly higher in the under-60 age group than the over-60 age group.[84,86] The younger participants among breast cancer as well as lung cancer patients showed higher selenium levels (breast cancer: 102 µg/l vs. 65 µg/l; lung cancer: 110 µg/l vs. 70 µg/l selenium in plasma; p < 0.001). The reduction in selenium status by 43–48% due to radiotherapy was comparable in both groups (breast cancer: 58 µg/l vs. 34 µg/l; lung cancer: 60 µg/l vs. 40 µg/l selenium in plasma). In all patients over 60 years of age, the low selenium levels at the start led to a critical selenium status after radiotherapy (<40 µg/l).

Weight

Cancer patients with a BMI below 24.9 had lower selenium levels before beginning radiotherapy than cancer patients with a BMI ≥25 (breast cancer: 67 µg/l vs. 92 µg/l; lung cancer: 70 µg/l vs. 98 µg/l selenium in plasma; p < 0.001). In both groups, the selenium status decreased after radiotherapy to the same extent between 41–45% (breast cancer: 39 µg/l vs. 50 µg/l, lung cancer: 55 µg/l vs. 40 µg/l selenium in plasma). Almost all patients with normal weight showed critical selenium levels after radiotherapy.
Cancer patients with higher risk of critical selenium status

- Smoking
- Alcohol abuse
- BMI $\leq 24.9$
- Age $> 60$ years
- Prior chemotherapy

Higher risk of critical selenium status


Fig. 40
Smoking and alcohol

The baseline values of smokers and alcoholics among lung cancer patients were not significantly different than non-smokers and non-alcoholics. Among the breast cancer patients, smoking and alcohol abuse were associated with lower selenium levels ($p < 0.001$). The negative effect of radiotherapy on the selenium status was especially aggravated in lung cancer patients by both factors (smoker vs. non-smoker: -51% vs. -29%; alcoholic vs. non-alcoholic: -43% vs. -30%; $p < 0.05$) (Fig. 41 + 42).

Smoking reinforces the reduction of selenium status caused by radiotherapy


Fig. 41
Previous chemotherapy

Previous chemotherapy was associated with a significantly reduced selenium status (p < 0.001), especially in breast cancer patients.\(^{[84]}\) 47% of the participants had had previous chemotherapy. This group exhibited an average plasma selenium concentration of 73 µg/l. The average selenium status of breast cancer patients without chemotherapy was 104 µg/l. After radiotherapy, the level of selenium in chemotherapy-treated patients declined to 37.5 µg/l selenium in plasma and thus to the critical range, and to 62 µg/l selenium in plasma in the group without chemotherapy.

![Graph showing reduction in selenium status caused by radiotherapy](image)

**Fig. 42**


Sodium selenite therapy increases selenium status

Three trials investigated the effect of sodium selenite therapy on selenium status during radiotherapy. In all studies, the selenium level could be increased by supplementation (Table 8). However, a selenium dose of less than 1,000 µg per day was too low to correct the selenium deficiency. After discontinuation of sodium selenite therapy, the selenium status decreased to the baseline level before the start of radiotherapy.

Sodium selenite therapy reduces radiotherapy-induced side effects

Six trials investigated sodium selenite therapy during radiotherapy for various types of tumors (Table 9). None of the trials demonstrated any reduction in the effectiveness of radiotherapy. Side effects due to sodium selenite therapy did not occur. The daily selenium dose varied between 200 µg and 1,000 µg. The duration of therapy was between four weeks and six months. Sodium selenite treatment during radiotherapy reduced various side effects, improved the cell-mediated immune response and antioxidative defense mechanisms, and reduced lymphedema.
Sodium selenite therapy increases selenium status during radiotherapy

<table>
<thead>
<tr>
<th>Study</th>
<th>Mean Selenium Concentration [µg/l]</th>
<th>Reference Range in Germany [100–140 µg/l]</th>
<th>Before Radiotherapy</th>
<th>At End of Radiotherapy</th>
<th>After Radiotherapy (without supplementation)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pakdaman et al. [A]</td>
<td>63</td>
<td></td>
<td></td>
<td>120</td>
<td>n.a.</td>
</tr>
<tr>
<td>Kiremidjian-Schumacher et al.* [B]</td>
<td>114.1**</td>
<td></td>
<td></td>
<td>131.6**</td>
<td>After 8 weeks 110.9**</td>
</tr>
<tr>
<td>Muecke et al. [C]</td>
<td>65.3</td>
<td></td>
<td></td>
<td>90.9</td>
<td>After 6 weeks 73.2</td>
</tr>
</tbody>
</table>

* Single case

** Plasma selenium values converted into whole blood values


Table 8
### Intervention trials with sodium selenite during radiotherapy

<table>
<thead>
<tr>
<th>Trial</th>
<th>Trial type</th>
<th>Tumor type</th>
<th>Selenium dose per day</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pakdaman et al. [A]</td>
<td>n. a.</td>
<td>Brain tumor</td>
<td>1,000 µg (4–8 weeks)</td>
<td>Reduction of intracranial pressure in 76% of patients</td>
</tr>
<tr>
<td>Kiremidjian-Schumacher et al.</td>
<td>Randomized, double-blind, placebo-controlled trial</td>
<td>Head and neck tumor</td>
<td>200 µg (8 week)</td>
<td>Significantly improved cell-mediated immune response</td>
</tr>
<tr>
<td>Micke et al. [C]</td>
<td>n. a.</td>
<td>Secondary lymphedema</td>
<td>500 µg (4–6 weeks)</td>
<td>Improvement by one or more degrees at 78% (Foldi and Miller score)</td>
</tr>
<tr>
<td>Elango et al. [D]</td>
<td>n. a.</td>
<td>Oral cancer</td>
<td>400 µg (6 months)</td>
<td>Improvement of enzymatic and non-enzymatic antioxidant defense mechanisms</td>
</tr>
<tr>
<td>Büntzel et al. [E]</td>
<td>Randomized phase II trial</td>
<td>Head and neck tumor</td>
<td>500 µg or 300 µg (6 weeks)</td>
<td>Reduced occurrence of dysphagia</td>
</tr>
<tr>
<td>Muecke et al. [F]</td>
<td>Multicentric phase III trial</td>
<td>Uterine cancer, cervical cancer</td>
<td>500 µg or 300 µg (6 weeks)</td>
<td>Statistically significant reduction of frequency and severity of diarrhea</td>
</tr>
</tbody>
</table>


*Table 9*
Phase III trial: selenase® reduces radiotherapy-induced diarrhea

A multicenter phase III trial examined the effect of selenase® therapy on radiotherapy-induced diarrhea in 81 patients with gynecological tumors.\textsuperscript{[1]} The selenium status in whole blood was measured after surgery. The participants were randomized at a value below 84 µg/l selenium in whole blood, and 39 participants were treated with 500 µg selenium (selenase® T peroral) on therapy days and with 300 µg selenium on therapy-free days during the entire course of radiotherapy (6 weeks). The control group (n = 42) did not receive selenase® therapy.

selenase® therapy significantly increases selenium status

The primary objective of the trial was to correct selenium deficiency in patients receiving radiotherapy of the pelvis.\textsuperscript{[1]} The selenium status in whole blood was measured before, halfway through, after termination, and six weeks after radiotherapy. Prior to radiotherapy, both trial groups showed a selenium deficiency (65.3 ± 13.6 µg/l vs. 63.2 ± 12.7 µg/l selenium in whole blood; p = 0.49). Halfway through radiotherapy, the selenium status in the selenase®-group increased significantly to 93.2 ± 26.0 µg/l (vs. 67.3 ± 16.6 µg/l; p < 0.001). At the end of radiotherapy, the difference between the group treated with selenase® and the control group was comparable (90.0 ± 19.9 µg/l vs. 61.4 ± 15.5 µg/l; p < 0.001). The measurement six weeks after radiotherapy and after the end of selenase® therapy showed that the selenium status had decreased to the originally low selenium level in the intervention group (73.2 ± 18.6 µg/l vs. 69.0 ± 16.3 µg/l; p = 0.32). During selenase® therapy there were no side effects due to selenium.

The authors concluded from the results that although the dosage used was able to improve the selenium status, it was too low to correct the selenium deficiency (Fig. 43).\textsuperscript{[1]}
selenase® therapy significantly increases selenium status


Fig. 43
Significant reduction of radiotherapy-induced diarrhea

Diarrhea is the most common side effect of pelvic irradiation. Therefore, the effect of selenase® therapy on radiotherapy-induced diarrhea was investigated in a multicenter phase III trial. After four weeks of radiotherapy, the frequency of CTC (Common Toxicity Criteria) grade 1–3 diarrhea in the selenase®-group was significantly lower (p = 0.01). The actuarial incidence of radiotherapy-induced diarrhea with a CTC grade of at least 2 was significantly lower in the selenase®-group (p = 0.04) than in the control group (20.5% vs. 44.5%) (Fig. 44).

selenase® therapy during radiotherapy does not reduce its effectiveness

Sodium selenite reduces the side effects of radiotherapy by protecting healthy cells from oxidative stress and stabilizing DNA. At the same time, radiotherapy increases oxidative stress to a level that causes the tumor cells to die. The use of cell-protective substances in cancer patients raises the question of whether the success of radiotherapy itself could be impaired by “protection” of cancer cells. In a 12-year follow-up period, a multicenter phase III trial demonstrated that selenase® does not interfere with radiotherapy. The survival rate after five years was 91.9% in the selenase®-group and 83.1% (p = 0.34) in the control group. After 10 years, there was even a tendency towards a higher survival rate with selenase® therapy (55.3% vs. 42.7%; p = 0.09) (Fig. 45).
**SODIUM SELENITE IN RADIOTHERAPY**

**selenase® reduces radiation-associated diarrhea**

![Graph showing the incidence of diarrhea, at least CTC degree 2, over weeks of radiotherapy. The graph compares the incidence between control and selenase® groups. There is a statistically significant difference (p = 0.04) in favor of selenase®.](image)


*Fig. 44*

**selenase® did not impair effectiveness of radiotherapy during treatment**

![Graph showing total survival after 12 years over months. The graph compares the survival rates between control and selenase® groups. There is no statistically significant difference (p = 0.09).](image)


*Fig. 45*
Long-term positive effect of selenase® therapy on overall survival?

Mücke et al. were able to demonstrate in a phase III trial that supplementation with selenase® during radiotherapy did not impair the radiotherapy effectiveness.\(^3\) In a 12-year follow-up period, the trial simultaneously also showed that a trend towards a higher survival rate in the selenase®-group only developed after several years. The total survival rate five years after selenase® treatment in addition to radiotherapy was higher by 8.8 % (\(p=0.34\)), the percentage of survivors who had obtained selenase® therapy during radiotherapy further increased (55.3 % vs. 42.7 %; \(p=0.09\)) (Fig. 46). This trend towards a higher total survival rate many years after the end of selenase® therapy raises the question of “why”.

As possible reasons, the authors cite the protective effect due to the increased antioxidative capacity and DNA repair activation on healthy cells.\(^3\) Another cause is the selective cytotoxicity of selenase® on tumor cells. This would not only reduce the side effects of selenase® therapy during radiotherapy, but also reduce long-term damage, some of which only manifests itself many years after cancer therapy. There is still no clear answer to this question.

**Possible long-term positive effect of selenase® therapy on total survival rate?**

![Graph showing survival rates](image)


*Fig. 46*
Dosage recommendation

<table>
<thead>
<tr>
<th>Dosage* and costs of selenium during radiotherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>For the reduction of radiotherapy-induced side effects*</td>
</tr>
<tr>
<td>before radiation**[A](i. v. or drinking ampoules)</td>
</tr>
<tr>
<td>up to 1,000 µg selenium</td>
</tr>
</tbody>
</table>

Costs: approx. €405
(calculation based on example of radiotherapy for 5 days/week for 6 weeks and on the marketed dosage forms of selenase® indicated in parentheses)

* according to dosages, regimes as presented in trials
** regime of therapy and therapy-free days


Sodium selenite in chemotherapy

### At a glance

<table>
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<th>Benefit</th>
<th>Reference</th>
</tr>
</thead>
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<td>Sodium selenite is selectively cytotoxic for tumor cells</td>
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</tr>
<tr>
<td>Nephroprotective effect of sodium selenite on platinum-based chemotherapeutics</td>
<td>[4]</td>
</tr>
<tr>
<td>Reduction of anthracycline-induced cardiotoxicity</td>
<td>[5]</td>
</tr>
<tr>
<td>selenase® reduces vinorelbine-induced phlebitis</td>
<td>[7]</td>
</tr>
<tr>
<td>Sodium selenite reduces side effects due to adjuvant hormone therapy in breast cancer patients</td>
<td>[90]</td>
</tr>
<tr>
<td>High-dose sodium selenite (&gt; 10,000 µg/day):</td>
<td></td>
</tr>
<tr>
<td>– Reduction of infection rate</td>
<td>[6]</td>
</tr>
<tr>
<td>– Cardioprotective effect</td>
<td>[91]</td>
</tr>
</tbody>
</table>
Oxidative stress – tumor cell vs. healthy cell

Oxidative stress occurs when the balance between the formation and degradation of reactive oxygen species is disturbed. The increase of oxidative stress in a cell can cause cell damage. After a certain degree of oxidative stress, the repair mechanisms of a cell are no longer sufficient and the cell dies. The human body tries to avoid this from happening in healthy cells.

On the other hand, an increased degree of oxidative stress works to the advantage of a tumor cell, because cell processes are set in motion that promote the growth and proliferation of a tumor. But oxidative stress can also become cytotoxic for tumor cells (Fig. 47). This situation is used in both radio- and chemotherapy. The tumor reacts by increasing endogenous antioxidants. For this reason, oncologists often recommend avoiding antioxidants during cancer therapy in order to avoid reducing the effect of the therapy.


Fig. 47
Sodium selenite selectively increases oxidative stress in tumor cells

Selenium is an antioxidant. Nevertheless, the drug sodium selenite is of great advantage during cancer therapy and demonstrably does not reduce its effectiveness. Why?

The answer lies in the differences between a healthy cell and a tumor cell. A tumor cell alters the processes in a cell to ensure tumor cell proliferation and growth. At the same time, the tumor cell protects itself from negative influences. Among other processes, this works by enriching glutathione.

Sodium selenite reduces the protection of tumor cells

High-dose sodium selenite reacts with the enriched glutathione to form selenium glutathione. First, the glutathione content of tumor cells decreases, along with its protection capacity. Secondly, hyperoxide anions result from the degradation of selenodiglutathione, leading to increased DNA breakages and cell death (Fig. 48). However, this effect occurs only at high doses. Only high-dose sodium selenite therefore increases oxidative stress in tumor cells to cytotoxic levels.
High-dose sodium selenite leads to oxidative stress in tumor cells at cytotoxic level

High glutathione concentration

Glutathione-induced protection = chemotherapy resistance

High-dose sodium selenite

Abrogation of chemotherapy resistance

Seleno-diglutathione

Reactive oxygen species

Apoptosis

“Apoptotic bodies”


Fig. 48
Selective toxicity of sodium selenite

Why does sodium selenite not also damage healthy cells? The intake and concentration of sodium selenite in the cell is crucial for the cytotoxic effect. Sodium selenite must be reduced before being absorbed into the cell. This reduction is mediated by cysteine. How much reduced sodium selenite, probably in the form of hydrogen selenide, is incorporated in the cell depends on the xC-cysteine transporter and the extracellular concentration of cysteine. The reason for the increased extracellular cysteine level of tumor cells are the multi-drug resistance proteins. Both the xC-cysteine transporter and multi-drug resistance proteins are overexpressed by resistant tumor cells. Resistant tumor cells are therefore particularly sensitive to sodium selenite (Fig. 49).

Prerequisites for the cytotoxicity of sodium selenite

- High-dose sodium selenite
- \( x_c \) cysteine transporter
- Multidrug-resistance proteins
- Cytotoxicity

Olm E et al. Proc Natl Acad Sci U S A. 2009 Jul 7; 106(27): 11400-5. Extracellular thiol-assisted selenium uptake dependent on the \( x(c) \)-cystine transporter explains the cancer-specific cytotoxicity of selenite.

Fig. 49
Sodium selenite protects healthy cells and is cytotoxic for tumor cells

In summary: tumor cells, in particular resistant tumor cells, fulfill the prerequisite for cytotoxicity of high-dose sodium selenite, whereas healthy cells do not. Healthy cells, on the other hand, benefit from an adequate selenium supply. While high-dose sodium selenite selectively increases oxidative stress in tumor cells, radio- and/or chemotherapy is not so specific. This leads to side effects. Increased oxidative stress in healthy cells results in an increased selenium requirement that in turn can be met by high-dose sodium selenite therapy. Oxidative stress in healthy cells can be decreased, also reducing the side effects of cancer therapy (Fig. 50).

Based on:
Olm E et al. Proc Natl Acad Sci U S A. 2009 Jul 7; 106(27): 11400-5. Extracellular thiol-assisted selenium uptake dependent on the x(c)- cystine transporter explains the cancer-specific cytotoxicity of selenite.

Fig. 50
Nephroprotective effect of sodium selenite in platinum-based chemotherapeutics

Platinum-based chemotherapeutics are used to treat many tumor types. A serious side effect of these therapies is kidney damage that can lead to renal failure. After cisplatin injection, some kidney involvement results in 30–50 % of cases. Kidney damage can have different manifestations and symptoms, including hematuria, proteinuria, glucosuria, hypomagnesemia and, above all, acute renal failure.

Sodium selenite protects against cisplatin and carboplatin-induced resistance

The nephroprotective effect of sodium selenite on cisplatin-induced side effects could already be demonstrated in the early 1990s. At the same time, sodium selenite does not affect the systemic bioavailability of cisplatin or platinum.

Tumor cells develop resistance to both cisplatin and carboplatin, which means that these chemotherapeutic agents lose their effect. Two in vivo trials have shown that sodium selenite effectively protects against the development of resistance to cisplatin and carboplatin. The mechanism of action is based on sodium selenite preventing the cisplatin-induced increase in glutathione concentration (Fig. 51).

No acute kidney damage with selenium co-therapy

A double-blind, randomized, controlled trial (n = 122) examined the effect of 400 µg selenium per day on the nephrotoxicity of cisplatin for various tumor types. The most common type of cancer was stomach cancer. The average cisplatin dose (203.72 mg) in the intervention and placebo group was comparable. Acute kidney damage was defined as the increase in plasma creatinine concentration above 1.5 mg/dl in men or 1.4 mg/dl in women, or an increase of more than 50 % over the baseline. Another parameter was a urine flow rate of less than 0.5 ml/kg after the cisplatin infusion. In addition, all trial participants received three liters of saline solution and 40 mg of furosemide (i.v.) on the first day.

Acute kidney failure occurred in 12 % of the patients (7/61) in the placebo group. In contrast, none of the participants in the intervention group suffered kidney damage (Fig. 52). The nephroprotective effect of selenium was significant (p = 0.013).
Sodium selenite prevents the increase in concentration of protective glutathione

Glutathione in tumor cells [nmol/10⁶]

Control  Cisplatin only  Cisplatin + sodium selenite


Fig. 51

Renoprotective effect of selenium with cisplatin

Percentage of patients with acute renal failure

Placebo: 12%  Selenium: 0%


Fig. 52
Reduction of anthracycline-induced cardiac toxicity

Anthracyclines, in particular doxorubicin, are key chemotherapeutics in cancer treatment. However, their effect is associated with acute and chronic toxicity. Anthracyclines are cardiotoxic and can cause dosage-dependent cardiomyopathy.\(^\text{[99]}\)

The impact and toxic effects of doxorubicin are based on two fundamental molecular mechanisms: first, the production of free radicals, and second, the modification of DNA.\(^\text{[99]}\)

Selenium deficiency is associated with an increased risk of cardiovascular diseases

It has been known since the 1970s that a massive selenium deficiency can trigger cardiomyopathy (Keshan disease). Prevention is possible through the prophylactic administration of sodium selenite. Both animal experiments and clinical trials have shown an inverse correlation between selenium status and cardiovascular diseases. A meta-analysis of 25 observational trials showed that a 50% increase in selenium concentration is associated with a 24% reduction in the risk of coronary heart disease.\(^\text{[100]}\)
Selenium deficiency reinforces the cardiotoxicity of doxorubicin

Other important results were provided by an animal trial comparing the effects of doxorubicin on the heart with the effects of selenium-deficient diets.[101]

The comparison of BNP concentration, a marker of cardiac insufficiency, showed that a selenium deficiency caused a deterioration in the BNP levels to the same extent as doxorubicin therapy. The combination of selenium deficit and doxorubicin led to a further significant increase in BNP concentration (p < 0.01). In contrast, the BNP value decreased significantly in high-dose sodium selenite levels during doxorubicin therapy compared to the chemotherapeutic agent alone (p < 0.05) (Fig. 53). The measurement of glutathione peroxidase activity showed significantly reduced values in the selenium deficiency and doxorubicin-treated groups (p < 0.01 and p < 0.001, respectively).[101]

In the combination of selenium deficiency and doxorubicin therapy, glutathione peroxidase activity decreased significantly compared to the individual groups (p < 0.001 or p < 0.05). The high-dose sodium selenite content restored glutathione peroxidase activity (Fig. 54). This is most likely responsible for the reduction of cardiotoxicity by sodium selenite, as glutathione peroxidase is an important ROS scavenger.
A selenium deficiency reinforces the cardiac toxicity of doxorubicin (Dox)


Optimal activity of selenium proteins reduces cardiac toxicity

Fig. 53
Reconstitution of glutathione peroxidase activity with doxorubicin therapy by high-dose sodium selenite

![Graph showing glutathione peroxidase activity comparison between control, selenium deficit, doxorubicin (Dox), doxorubicin + selenium deficit, and doxorubicin + sodium selenite.](image)


Fig. 54
Low selenium status correlates with high pro-BNP values

Anthracycline-induced cardiotoxicity was analyzed depending on selenium status in 67 pediatric cancer patients. Those patients with high pro-BNP values, a marker for cardiac insufficiency and/or heart failure, showed significantly lower selenium values (p<0.001) (Fig. 55).

Selenium protects against anthracycline-induced cardiac toxicity

Treatment of children with elevated pro-BNP values and a low selenium status with 100 µg selenium per day for 4–33 months (median: 6 months) improved the pro-BNP concentration ($p=0.018$) and/or the results of echocardiography. The concentration of selenium increased significantly ($p=0.028$). After reaching normal selenium and pro-BNP values, the selenium therapy was discontinued.

An additional measurement of selenium status and pro-BNP concentration 2–6 months later showed significantly lower selenium levels ($p=0.068$) and increased pro-BNP concentration ($p=0.109$) (Fig. 56). The authors of the clinical trial therefore recommend to continue the selenium treatment for a much longer period in order to protect against anthracycline-induced cardiotoxicity or reduce the risk.

---

**Selenium reduces anthracycline-induced cardiac toxicity**

![Graph showing pro-BNP and serum selenium concentrations before, during, and after therapy with selenium.](image)

**Pro-BNP concentration** $[^*]$ [pg/ml]

- Before therapy
- During therapy
- After therapy

**Serum selenium concentration** $[^*]$ [µg/l]

- Before therapy
- During therapy
- After therapy

$p=0.028$

$p=0.018$

*Median


Fig. 56
selenase® reduces vinorelbine-induced phlebitis

The plant alkaloid vinorelbine is approved for treating certain types of malignant tumors, since vinorelbine is particularly effective on cells with a high mitotic rate. It is primarily used to treat metastatic breast cancer and non-small cell lung cancer. A characteristic side effect of vinorelbine is local phlebitis after infusion. The incidence is between 10 – 26%. Phlebitides of grade 2 or higher are regarded as a complication and frequently impair the quality of life and compliance of affected patients.

The effect of prophylactic administration of selenase® on the incidence of phlebitis was investigated in a prospective trial with 69 participants. Phlebitis of grade 2 or higher was observed in 29% (20/69) of patients. Prior to the next infusions with vinorelbine, these patients received 1,000 µg selenium (selenase®) as a rapid infusion. In 80% of the affected participants (16/20) no more phlebitis developed in the further course of therapy (Fig. 57).

The author of the trial points out that the prophylactic administration of selenase® is an effective supportive treatment option free of side effects that can improve the quality of life of patients as well as their compliance. Especially in comparison with human blood derivatives such as human albumin, selenase® is an inexpensive alternative.
selenase® reduces vinorelbine-induced phlebitis

29% (20/69) phlebitis incidence after vinorelbine injection

80% (16/20) no reoccurrence of phlebitis with prophylactic selenase® therapy

Low-priced and reliable supportive precaution to improve compliance

Prepared based on: Holzhauer P. Dtsch. Z. Für Onkol. 2002; 34; 14-6. Kann durch die prophylaktische Gabe von Natriumselenit die Inzidenz und der Schweregrad der durch Vinorelbine induzierten lokalen Phlebitis beeinflusst werden?

Fig. 57
Sodium selenite reduces side effects caused by adjuvant anti-hormone therapy in breast cancer patients

The side effects of anti-hormone therapy are usually better-tolerated than chemotherapy. However, the duration of anti-hormone treatment of five years, in some cases even ten years, is considerably longer. This means that comparatively minor side effects are also gaining in importance for the affected women. Two common side effects are arthralgia and mucositis.

A large-scale trial included a total of 1,561 breast cancer patients receiving adjuvant anti-hormone therapy. \[^{99}\] 1,165 of the participants suffered from severe side effects (symptom evaluation \(> 3\) on a scale of \(1–6\)). The incidence of severe arthralgia was 63\% (729/1,165). The mucositis incidence was even higher at 72\% (520/725).

Treatment with 300 \(\mu\)g selenium in the form of sodium selenite as part of a combination with proteolytic plant enzymes significantly reduced the severity of arthralgia and dehydration of the mucous membranes after four weeks of therapy (\(p < 0.001\)). Values decreased from 4.83 to 3.23 for arthralgia and from 4.72 to 2.99 for mucositis (Fig. 58).

The tolerance of anti-hormone therapy determines its optimal administration. Supportive treatment with sodium selenite can improve tolerance by reducing the side effects and thus contribute to a successful therapy.
Sodium selenite reduces side effects due to adjuvant anti-hormone therapy in breast cancer patients


Fig. 58
Positive effect of sodium selenite in non-Hodgkin’s lymphoma patients

The effect of very high-dose sodium selenite (0.2 mg/kg selenium per day) was studied in a controlled trial with 30 newly diagnosed non-Hodgkin’s lymphoma patients.\cite{6,91,103}

All trial participants received CHOP chemotherapy (cyclophosphamide, doxorubicin, vincristine, prednisone). Half of the patients were treated with 0.2 mg/kg selenium per day for an additional five days (from day 3 – 7 of the chemotherapy cycle). With a body weight of 70 kg, this corresponds to a daily selenium dose of 14,000 µg or 14 mg.

High-dose sodium selenite reduces infection rate

After treatment with high-dose sodium selenite, the number of apoptotic lymphoma cells on day 8 increased significantly (78.9 ± 13.3 % vs. 58.9 ± 18.9 %; p < 0.001) compared to the control group.\cite{103} The percentage of cervical and axillary lymphadenopathies decreased significantly (p = 0.04).\cite{103}

Sodium selenite therapy also reduced spleen size (p < 0.05) and reduced the number of lymphoma cells that had infiltrated the bone marrow (p < 0.001).\cite{103}

The infection rate decreased significantly to 20 % in the group treated with sodium selenite compared to 67 % in the control group (p < 0.05) (Fig. 59).\cite{6}
High-dose sodium selenite reduces the infection rate in non-Hodgkin’s lymphoma patients


Fig. 59
Cardioprotective effects of sodium selenite during CHOP therapy

Cardiotoxicity is primarily known as a serious side effect of anthracyclines, such as doxorubicin. Anthracyclines are part of CHOP therapy. Therefore, the cardiac ejection fraction was measured before and after sodium selenite treatment.[103]

At baseline, there was no significant difference in the cardiac ejection fraction between the two groups. In the control group, CHOP therapy led to a deterioration of the cardiac ejection fraction, while in the sodium selenite group it remained unchanged. Sodium selenite had a significant cardioprotective effect during CHOP therapy (p = 0.04) (Fig. 60).


Fig. 60
Significantly longer survival time for patients treated with sodium selenite with complete remission

Treatment with high-dose sodium selenite in addition to chemotherapy resulted in a higher rate of complete remissions (60% vs. 40%) and a lower relapse rate compared to the control group (12% vs. 20%).\[91\]

Total survival time improved significantly in the sodium selenite treated group (21.8 ± 1.4 months vs. 19.7 ± 1.9 months; p = 0.01) (Fig. 61).\[91\]


Fig. 61
No known interactions between sodium selenite and chemotherapeutics

So far, no interactions between sodium selenite and chemotherapeutic drugs have been found that would have led to a deterioration in the effectiveness of chemotherapy. In vitro experiments with different tumor types showed no interaction with cisplatin, docetaxel, doxorubicin, mitomycin C, paclitaxel or etoposide.\(^\text{[104]}\) For irinotecan, 5-fluorouracil and oxaliplatin, sodium selenite was able to potentiate their effect.\(^\text{[105]}\) The combination of sodium selenite and imatinib led to a synergistic effect, in which sodium selenite increased the cytotoxicity of imatinib in colorectal cancer cells.\(^\text{[106]}\)

In intervention trials with simultaneous administration of sodium selenite and chemotherapeutic drugs (CHOP therapy, cisplatin, doxorubicin, anti-hormone therapy), no harmful effects of sodium selenite were observed.\(^\text{[4–6,90,91,107]}\)

Hardly any side effects at daily dosages up to 3 mg/m\(^2\) selenium

What are the side effects of a high-dose sodium selenite therapy? How long may sodium selenite be used in the recommended dosage? Both are frequently asked questions in connection with high-dose sodium selenite treatment.

Clinical trials have used a wide range of sodium selenite dosages. A dose escalation trial with sodium selenite has investigated the side effect spectrum in the range of 0.5 to 15.3 mg/m\(^2\) in oncological patients.\(^\text{[2]}\) For a body size of 1.70 m and 70 kg, this corresponds to a daily dosage of 910 µg to 27,846 µg selenium per day. At a dosage of less than 3.0 mg/m\(^2\) (5,460 µg per day selenium (1.70 m and 70 kg)), virtually no side effects occurred in this trial. From 4.5 mg/m\(^2\) (8,190 µg per day selenium (1.70 m and 70 kg or higher) mostly fatigue, nausea and vomiting occurred (Fig. 62).
<table>
<thead>
<tr>
<th>Side Effect</th>
<th>Frequency [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatigue</td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td></td>
</tr>
<tr>
<td>Vomiting</td>
<td></td>
</tr>
<tr>
<td>Cramps in legs / fingers</td>
<td></td>
</tr>
<tr>
<td>Garlic breath</td>
<td></td>
</tr>
<tr>
<td>Anorexia</td>
<td></td>
</tr>
<tr>
<td>Arthralgia</td>
<td></td>
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<tr>
<td>Alopecia</td>
<td></td>
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<tr>
<td>Acute respiratory distress</td>
<td></td>
</tr>
<tr>
<td>Pain at the infusion site</td>
<td></td>
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<tr>
<td>Breast pain</td>
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<tr>
<td>Gastritis</td>
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<tr>
<td>Stomach pain</td>
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<tr>
<td>Stomach swelling</td>
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<tr>
<td>Hot flashes</td>
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<tr>
<td>Dizziness</td>
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<tr>
<td>Peripheral neuropathy</td>
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<tr>
<td>Itching on the legs</td>
<td></td>
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<tr>
<td>Thrombopenia</td>
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</tbody>
</table>

Brodin O et al. Nutrients. 2015 Jun 19; 7(6): 4978-94. Pharmacokinetics and Toxicity of Sodium Selenite in the Treatment of Patients with Carcinoma in a Phase I Clinical Trial: The SECAR Study.

Fig. 62
Maximum tolerable daily dose for sodium selenite: 10.2 mg/m\(^2\) selenium

Side effects greater than CTC grade 3 occurred only at a dosage of > 12.8 mg/m\(^2\) of selenium. The maximum tolerable daily dose was defined as 10.2 mg/m\(^2\) selenium (18,564 µg per day selenium (1.70 m and 70 kg)), as there were no dose-limiting toxicities up to this dose (Fig. 63).

No critical systemic toxicity

Dose-limiting toxicities due to sodium selenite were acute, of short duration, and reversible within 1–2 days. Various biomarkers for organ function showed no critical systemic toxicity. The authors concluded that a dosage of up to 10.2 mg/m\(^2\) selenium per day for 2 weeks is safe and tolerable. Betamethasone and omeprazole were routinely administered as pre-treatment at a dose of 10.2 mg/m\(^2\) of selenium and above.

Occurrence of side effects depending on sodium selenite dosage

Brodin O et al. Nutrients. 2015 Jun 19; 7(6): 4978-94. Pharmacokinetics and Toxicity of Sodium Selenite in the Treatment of Patients with Carcinoma in a Phase I Clinical Trial: The SECAR Study.
## Dosage recommendation

### Sodium selenite during chemotherapy

**To reduce chemotherapy-induced adverse reactions***

<table>
<thead>
<tr>
<th>before chemotherapy**[A]** (i. v. or drinking ampoules)</th>
<th>therapy-free days*** (drinking ampoules)</th>
</tr>
</thead>
<tbody>
<tr>
<td>up to 1.000 µg selenium</td>
<td>up to 500 µg selenium per day</td>
</tr>
</tbody>
</table>

**Costs: approx. €575**

(calculation based on the example of chemotherapy 6x every 21 days and on the marketed dosage forms of selenase® indicated in parentheses)

* according to dosages, regimes as presented in trials

** reduction of side effects

*** based on properties of sodium selenite®[B], results from radiotherapy[C] and current selenium status[D]

---


Future prospects of high-dose sodium selenite as monotherapy

### At a glance

<p>| | |</p>
<table>
<thead>
<tr>
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<tbody>
<tr>
<td>Abrogation of resistance to chemotherapeutics[^2]</td>
<td>Stabilization of more than one third of therapy-resistant tumor patients[^2]</td>
</tr>
<tr>
<td>No negative impact of high-dose sodium selenite therapy on survival[^2]</td>
<td></td>
</tr>
</tbody>
</table>
SECAR trial: Phase I dose-escalation trial

The SECAR trial was an open-label phase I dose-escalation trial with intravenously administered sodium selenite as a single active substance. The trial included 34 patients with various therapy-resistant tumors, primarily lung carcinomas (71%). The second most common type of tumor was colon carcinoma (12%).

The primary endpoint of the study was safety, dose-limiting toxic effects, and the maximum tolerable dose of sodium selenite. The secondary endpoint was the evaluation of the primary response to sodium selenite.

Sodium selenite abrogates chemotherapeutic resistance

Resistant tumor cells are particularly sensitive to sodium selenite. The SECAR trial showed that high-dose sodium selenite is capable of attacking certain types of tumors. This effect was further enhanced by subsequent chemotherapy. It was particularly interesting that many of the patients again responded to their first-line chemotherapy. The therapy with high-dose sodium selenite was able to abrogate the chemotherapeutic resistance in these patients.
High-dose sodium selenite stabilizes more than one third of therapy-resistant tumor patients

The results regarding the anti-tumoral effect of sodium selenite were promising, but need to be reviewed in further trials due to the low number of patients. Sodium selenite showed no consistent effect on tumor size. But after sodium selenite treatment, 13 patients (38%) showed a stable disease. 16 patients (47%) were stable after the subsequent chemotherapy (Fig. 64).

High-dose sodium selenite had no negative effect on survival

In total, sodium selenite therapy did not lead to a significantly higher overall survival rate. This was primarily due to the low number of patients in the trial. However, therapy with high-dose sodium selenite and a following chemotherapy had no negative impact on survival.

The median survival time after sodium selenite treatment was 6.5 months. Since the trial participants had advanced, treatment-resistant cancer, this was a comparatively long survival period, according to the authors. The stable disease in 38% of the participants after sodium selenite therapy, or 47% with subsequent chemotherapy, is a clear sign that further trials with high-dose sodium selenite as monotherapy should be carried out.
Stabilization in more than one third of the therapy-resistant tumor patients

Brodin O et al. Nutrients. 2015 Jun 19; 7(6): 4978-94. Pharmacokinetics and Toxicity of Sodium Selenite in the Treatment of Patients with Carcinoma in a Phase I Clinical Trial: The SECAR Study.

Fig. 64
Sodium selenite after cancer therapy

At a glance

<table>
<thead>
<tr>
<th>Long-term deterioration of the immune status after chemotherapy[^{108}]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium selenite to improve the immune status[^{51}]</td>
</tr>
<tr>
<td>Long-term side effects[^{109}]: lymphedema, cardiotoxicity, osteoporosis, secondary tumors</td>
</tr>
<tr>
<td>selenase(^\text{®}) for prophylaxis and treatment of lymphedema[^{69}]</td>
</tr>
<tr>
<td>Sodium selenite for protection against increased cardiotoxicity[^{5}] and risk of osteoporosis[^{110,111}]</td>
</tr>
</tbody>
</table>

Immune system

It is generally known that cancer therapy affects the immune system. However, it has scarcely been investigated how severe the effect is after different kinds of cancer treatment, and how long the impairment lasts. This is precisely the question addressed by a clinical trial published in 2016 involving 88 breast cancer patients\[^{111}\].
Chemotherapy significantly reduces lymphocyte levels

The level of different lymphocyte subgroups in the trial participants prior to chemotherapy was normal and did not differ from those of healthy people. Two weeks after the end of chemotherapy, the values of all four subgroups had decreased significantly (p < 0.001). The B-lymphocytes in particular declined to a median of 5.4% compared to the values before chemotherapy (Fig. 65).[108]

Long-term deterioration of immune status after chemotherapy

Lymphocyte levels gradually recovered over the nine-month observation period.[108] While the values of CD8+ cells and natural killer cells approached the baseline after six months, B-cells and CD4+ cells showed only a partial recovery with 69% and 60% of baseline values respectively (p < 0.001) (Fig. 65). In addition, there was no further improvement in lymphocyte levels after six and nine months.
Differently pronounced negative effect of various chemotherapy regimes

The chemotherapy regime also influences the immune system differently.\textsuperscript{[108]} Chemotherapy with epirubicin and cyclophosphamide (EC) or in combination with 5-flourouracil (FEC) resulted in a significantly higher reduction of B-cells compared to the combination EC and taxanes (docetaxel) (3\% vs. 8\%; \(p<0.001\)). In contrast, the EC/FEC group showed a significantly faster recovery of B-cell levels (after 6 months: \(p=0.04\), after 9 months \(p=0.03\)) (Fig. 66). In the EC+Tax group, B-cells remained permanently below the initial level (64\%; \(p<0.001\)). In CD4\(^+\) cells, EC/FEC therapy also had a significantly stronger suppressive effect (37\% vs. 59\%; \(p=0.002\)). However, there was no recovery of the levels in either group.

Long-term deterioration of vaccination protection due to chemotherapy

The clinical trial examined the number of circulating antibodies against pneumococci and tetanus, which are routinely vaccinated, in order to check the immune status after chemotherapy.\textsuperscript{[108]}

The antibody titer was already relatively low in the participants at the beginning of the trial. In 15\% of patients, the antibody titer against pneumococcal infections was classified as suboptimal, and in 2\% as inadequate, with both groups having insufficient protection against infection. Anti-tetanus titer was suboptimal in 21\% of patients.

After chemotherapy, the two antibody titers were significantly lower compared to the baseline values (\(p<0.001\)). This difference was still evident after nine months (\(p<0.001\) or \(p<0.05\)) (Fig. 67). At that time, the proportion of trial participants with suboptimal or inadequate antibody titers against pneumococci had increased to 19\% and 6\% respectively.
Differently pronounced negative effect of various chemotherapy regimens on the immune status


Fig. 66

Long-term deterioration of vaccination protection against pneumococci due to chemotherapy


Fig. 67
Sodium selenite improves the immune status

A randomized, double-blind, placebo-controlled trial (n = 33) investigated the effect of sodium selenite therapy on the immune status of patients with head and neck tumors. \[51\] For eight weeks, 17 trial participants received 200 µg of selenium per day in the form of sodium selenite.

The mean plasma selenium concentration was significantly lower in tumor patients compared to healthy patients (91.29 ± 4.41 µg/l vs. 127.6 ± 2.4 µg/l; p < 0.005). Patients with grade 3 or 4 tumors also showed a significant reduction in selenium status (87.7 ± 3.86 µg/l vs. 105.55 ± 6.59 µg/l; p < 0.03). After eight weeks of sodium selenite therapy, the mean selenium level increased to 105.29 ± 6.38 µg/l selenium in plasma.

Ten-fold increase in cytotoxic T-cells

The immune system is able to recognize and destroy tumor cells. The cytotoxic T-cells (or CD8+ cells) are responsible for this process as part of the cellular immune response. After eight weeks, the concentration of cytotoxic T-cells had increased significantly from 7.1% to 78.5% (p < 0.001) (Fig. 68).\[51\]

However, this effect took several weeks. The comparison between the initial value and the status after four weeks showed no significant difference (p = 0.29). After eight weeks, the concentration of cytotoxic T-cells was significantly higher (p < 0.049 or p < 0.005) compared to four weeks and the baseline value (Fig. 69).
10-fold increase in cytotoxic T-cells with sodium selenite therapy


Fig. 68

Time-delayed effect of sodium selenite therapy


Fig. 69
SODIUM SELENITE AFTER CANCER THERAPY
Improved immune status in connection with risk of recurrence and susceptibility to infection

The result of the clinical trial by Kiremidjian-Schumacher et al. clearly shows that long-term sodium selenite therapy with 200 μg selenium per day leads to a highly significant increase in the immune response.[51] The improved ability to form cytotoxic T-cells capable of destroying tumor cells is based on the increased expression of the high-affinity interleukin-2 receptor (see p. 54). Thus sodium selenite could help to reduce the frequency of infections after cancer therapy and also reduce the risk of recurrence (Fig. 70).


Fig. 70
Short- and long-term side effects of cancer therapy

Follow-up care is an important part of supporting tumor patients. On the one hand, the aim is to improve long-term negative effects of the disease or its treatment in order to achieve the highest possible quality of life. On the other hand, frequent follow-up exams make it possible to detect recurrences at an early stage.

Cancer therapy can cause short-term and/or long-term side effects. The side effects depend on the therapy used. Generally speaking, it can be said that the combination of different treatments or medications can exacerbate side effects.

Long-term side effects of cancer therapy

An increasing number of people survive after cancer diagnosis thanks to improved therapy options. Therefore, the long-term consequences of cancer therapy are also becoming increasingly important. The medical consequences of breast cancer have been best studied years after breast cancer diagnosis.

Due to increasing survival rates, the long-term side effects of cancer therapy are coming to the fore
Breast cancer

More than 12% of women are diagnosed with breast cancer during their lifetime. Up to 78% of them survive the diagnosis for at least 15 years. At the same time, about 90% of survivors have physical problems. In addition to the immediate side effects of cancer therapy, some negative effects of the treatment occur years later and are often not associated with cancer therapy.

Lymphedema is a common side effect of irradiation of the chest area in breast cancer patients. In contrast, some frequently used chemotherapeutic drugs have a high cardiotoxicity (e.g. anthracyclines, cyclophosphamide, taxanes or trastuzumab). The bones can also be damaged and increase the risk of osteoporosis (e.g. aromatase inhibitors, tamoxifen) (Fig. 71).

Another problem facing long-term survivors is the development of secondary tumors, which now make up one-sixth of tumors. Since nearly a quarter of long-term survivors had breast cancer, this group is particularly affected by the risk of secondary tumors.
Lymphedema

Lymphedema caused by breast cancer is a common, serious, chronic and debilitating consequence of breast cancer therapy. Many fear the diagnosis of lymphedema almost more than the cancer diagnosis itself or mastectomy. One in five breast cancer patients is affected by this irreversible, lifelong disease. The increased risk of lymphedema is elevated throughout the lifetime of breast cancer patients.

Risk factors

There are many risk factors for breast cancer-related lymphedema, which can be divided into disease-specific and lifestyle-related risk factors (Fig. 72). The patient cannot influence the disease-specific risk factors. Surgical-related therapy has the greatest influence on the risk of lymphedema.

Increased lymphedema incidence in mastectomy and axillary dissection patients

A mastectomy increases the risk of lymphedema two to six times compared to a lymphectomy. The extent of axillary dissection and the proportion of affected lymph nodes pose further risk factors. Compared to axillary dissection, sentinel lymph node biopsy significantly reduces the risk of lymphedema. Nevertheless, lymphedema incidence in the first six months after biopsy is 7 %. Anthracycline-based treatments are specifically associated with increased lymphedema incidence. The risk of lymphedema increases by almost 50 % (HR 1.46; 95 % CI 1.04 – 2.04) and for moderate or severe lymphedema by as much as 276 % (HR 3.76; 95 % CI 2.01 – 7.04).

Chemotherapy increases lymphedema risk

The correlation between chemotherapy and lymphedema has so far been poorly documented, which is mainly due to the outpatient treatment of chemotherapy. Shih et al. showed in a trial with 1,877 breast cancer patients that chemotherapy increased the risk of lymphedema by almost 60 % after two years (HR 1.59; 95 % CI 1.12 – 2.27) and after three or four years by more than 80 % (HR 1.76; 95 % CI 1.26 – 2.77 or HR 1.95 % CI 1.26 – 2.77 or HR 1.77). Anthracycline-based treatments are specifically associated with increased lymphedema incidence. The risk of lymphedema increases by almost 50 % (HR 1.46; 95 % CI 1.04 – 2.04) and for moderate or severe lymphedema by as much as 276 % (HR 3.76; 95 % CI 2.01 – 7.04).
Risk factors for lymphedema caused by breast cancer

- Number of removed lymph nodes
- Post-operative infections
- Adjuvant chemotherapy
- Adjuvant radiotherapy
- Adiposity
- Breast trauma after therapy
- Diabetes, high blood pressure
- Cancer stage
- Age
- Lymphedema risk


Fig. 72
Breast trauma as risk factor

A large number of trials has shown the correlation between increased lymphedema risk and radiotherapy in the chest area.\textsuperscript{[109]} In a trial published in 2014 with 1,476 participants, irradiation of the regional lymph nodes significantly increased lymphedema incidence (HR 1.7; 95% CI 1.07 – 2.70; \(p = 0.025\)).\textsuperscript{[116]} Other risk factors for lymphedema are postoperative infections or formation of seroma.\textsuperscript{[109]}

Overweight as risk factor

Overweight (BMI > 30) increases the risk of lymphedema by almost 200% (HR 2.93; 95% CI 1.03 – 8.31 \(p = 0.003\)) compared to people with normal weight (BMI < 25).\textsuperscript{[117]} The extent of the increase in arm volume also depends on the BMI (Fig. 73). Further trials have shown that sport not only reduces BMI, but also the incidence of lymphatic edema.\textsuperscript{[109]} At the same time, two diseases associated with an elevated BMI, diabetes and hypertension, are associated with an increased risk of lymphedema.\textsuperscript{[109]}
Extent of increase in arm volume depends on BMI

<table>
<thead>
<tr>
<th>BMI Range</th>
<th>Volume Increase [%]</th>
</tr>
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<tbody>
<tr>
<td>&lt; 18.5</td>
<td>2</td>
</tr>
<tr>
<td>18.5–24.9</td>
<td>4</td>
</tr>
<tr>
<td>25–29.9</td>
<td>6</td>
</tr>
<tr>
<td>&gt; 30</td>
<td>10</td>
</tr>
</tbody>
</table>

Helyer LK et al. Breast J. 2010 Jan-Feb; 16(1): 48-54. *Obesity is a risk factor for developing postoperative lymphedema in breast cancer patients.*

Fig. 73
Lymphedema as cost factor

In addition to the physical and psychological strain on the patient, there are also significantly higher costs for breast cancer related lymphedema. A US American trial showed that the total adjusted therapy costs for two years for a breast cancer patient with lymphedema are higher by $23,167 (€20,799). The difference in adjusted costs not related to cancer therapy alone was $14,877 (€13,354). [114]

These significantly higher costs consisted mainly of outpatient treatment ($9,463; p < 0.001), outpatient medication ($2,403; p = 0.0063) and physical therapy or medical supplies such as compression clothing ($769; p = 0.0035) (Fig. 74).

Comparatively low costs of selenase® therapy

In contrast, the costs for a high-dose selenase® therapy are negligible at €268 for the prevention of lymphedema after surgery (therapy duration 3 weeks) and €218 for treatment (therapy duration 4 months), whereby the duration and scope of treatment should be specified depending on the severity of lymphedema. Especially in a selenium-deficient country like Germany, long-term support of selenium status with an increased risk of lymphedema is recommended (Fig. 75). According to the EU, a sustained intake of 300 µg selenium per day is safe.
Increased costs in 2-year timeframe for breast cancer patients with lymphedema


Fig. 74

selenase® therapy for lymphedema in a country with selenium deficiency such as Germany


Prescribing information selenase®, biosyn Arzneimittel GmbH, as of July 2017.

Fig. 75
selenase® in lymphedema

Sodium selenite is the only pharmacologically active substance currently available with an effective and long-term effect for treating lymphedema. Several trials have shown that high-dose selenase® therapy (active ingredient: sodium selenite pentahydrate) is effective in treating cancer-related lymphedema. In addition to reducing lymphedema volume, selenase® reduces the frequency of erysipelas. selenase® can also have a positive influence on the development of lymphedema.

High-dose selenase® therapy significantly reduces lymphedema volume

In a placebo-controlled, double-blind trial, a total of 179 breast cancer patients with lymphedema were treated with either high-dose selenase® (1st week: 1,000 µg selenium per day, 2nd + 3rd week: 300 µg selenium per day) or a placebo for three weeks in addition to combined physical, decongestive therapy. In the three-month follow-up period, 100 µg of selenium was given per day.

In the selenase®-treated group, lymphedema volume decreased significantly during the entire three-week therapy. In the placebo group, however, volume reduction decreased with each subsequent standard treatment. After three weeks, the volume of lymphedema was significantly reduced by 52 ± 18% in the selenase®-treated group after correction in terms of size and weight compared to the placebo group (43 ± 16%; p < 0.01) (Fig. 76).
High-dose selenase® therapy significantly reduces lymphedema volume


Fig. 76
High-dose selenase® therapy effectively prevents erysipelas

The anti-inflammatory effect of selenase® in lymphedema is particularly effective. In one trial, 60 cancer patients with erysipelas were treated with a three-week combined physical, decongestive therapy. In addition, half of the participants received high-dose selenase® (1st week: 1,000 µg selenium per day, 2nd + 3rd week: 300 µg selenium per day) and the other half received a placebo. During the three-month follow-up phase, the intervention group received 100 µg (< 70 kg body weight) or 200 µg (> 70 kg body weight) of selenium per day.

In the placebo group, 50% of patients developed erysipelas during the trial. In contrast, erysipelas incidence in the selenase®-treated group was 0% (Fig. 77). Lymphedema patients who needed long-term antibiotic therapy did not develop any further erysipelas after discontinuing antibiotic treatment and using high-dose selenase® therapy.

Lower volume of lymphedema in selenase® therapy

In a prospective, randomized, placebo-controlled, double-blind trial, Zimmermann et al. investigated the effect of pre-, intra- and postoperative administration (totally 3 weeks) of high-dose selenase® (1,000 µg selenium per day) on the development of lymphedema in patients with head and neck tumors.

The lymphedema volume in the head and neck area was measured postoperatively as well as after one or two weeks, and compared with the preoperative measurements. The volume of lymphedema in the selenase®-treated group was significantly lower after one as well as after two weeks (p = 0.009 resp. p = 0.029).
High-dose selenase® therapy effectively prevents erysipelas

Prepared based on:

Fig. 77
Chemotherapy

Anthracyclines (doxorubicin, epirubicin) increase the incidence of heart failure and cardiomyopathy by 2%. The combination of anthracycline with trastuzumab or sequential therapy leads to a doubling of the incidence to 4%.\[109\]

Cyclophosphamide can cause heart damage, which is why almost 30% of the patients treated with cyclophosphamide develop heart failure.\[109\] As with other cardiotoxic chemotherapeutics, the risk is dose-dependent. The cardiotoxic risk increases if there has been prior therapy with anthracyclines or the patient is elderly.

The most common side effects of taxane therapy (paclitaxel, docetaxel) are associated with cardiovascular diseases. The incidence of paclitaxel is between 0.5–5% for paclitaxel and 2% for docetaxel. Docetaxel-induced heart failure occurs in 2.3–8% of cases.

Radiotherapy

Breast-conserving therapy has become the standard therapy, especially for early-stage breast cancer. An integral part of this therapy is adjuvant radiotherapy. It has been known for a long time that radiation of the thorax leads to cardiac damage.\[108\] But only the large number of long-term survivors has made this long-term side effect a subject of increased attention.

The mortality risk due to heart disorders increases by 3% per Gray radiation exposure.\[118,119\] However, this long-term side effect only manifests one to two decades later, so that the radiotherapy-induced mortality rate begins to increase ten years after treatment.\[119\]

Targeted biological therapy

Approximately 15–30% of breast cancer cases are HER2-positive.\[100\] The inhibition of the HER2 signal pathway with trastuzumab is therefore an important therapy in breast cancer. The most serious side effect of trastuzumab therapy is cardiotoxicity, which further increases with additional risk factors for cardiovascular diseases.\[119\] Lapatinib has a lower incidence of cardiotoxicity than trastuzumab.\[109\]
Cardiotoxicity

Cancer is not the number one cause of death in women, but rather cardiovascular diseases. Whoever has survived breast cancer often has a significantly increased risk of dying from cardiovascular disease.\(^{[109]}\) This risk is significantly higher than that of the original breast cancer disease or recurrence.\(^{[109]}\)

Both old and new chemotherapeutic agents can cause acute and chronic cardiovascular complications. The spectrum of cardiovascular diseases triggered by chemotherapy includes cardiac insufficiency, myocardial ischemia, hypertension, arrhythmias, prolongation of the QT interval, bradycardia, pericarditis, acute coronary syndrome and thromboembolic events. But also the irradiation of the chest area, tamoxifen and targeted biological therapy with for instance trastuzumab increases the risk of cardiovascular disease (Fig. 78).

Sodium for protection against cardiotoxicity

Several points speak for the screening of selenium status and sodium selenite therapy in follow-up care to protect against cancer therapy-induced cardiotoxicity.

Selenium deficiency is a risk factor for cardiovascular diseases

On the one hand, selenium deficiency increases the incidence of cardiovascular diseases. A meta-analysis of 25 observational trials showed that a 50% increase in selenium concentration is associated with a 24% reduction in the risk of coronary heart disease.\textsuperscript{[100]}

A selenium deficit increases cardiotoxicity of anthracyclines

On the other hand, a selenium deficiency increases the cardiotoxicity of anthracyclines.\textsuperscript{[101]} In contrast, the BNP value decreased significantly in vivo at high-dose sodium selenite levels during doxorubicin therapy compared to the chemotherapeutic agent alone (p < 0.05) (\textit{Fig. 53, see p. 112}). This data has been confirmed by a pediatric trial.\textsuperscript{[5]} The pediatric patients with high pro-BNP values, a marker for cardiac insufficiency and/or heart failure, showed significantly lower selenium values (p < 0.001) (\textit{Fig. 55, see p. 114}).
Selenium therapy reduces anthracycline-induced cardiotoxicity

The treatment of children with elevated pro-BNP values and low selenium status with 100 µg selenium per day for 4 to 33 months (median: 6 months) improved the pro-BNP concentration (p = 0.018) and/or the results of echocardiography. After reaching the normal range of selenium, selenium therapy was discontinued. However, significantly lower selenium levels (p = 0.068) and increased pro-BNP concentrations (p = 0.109) were detected (Fig. 56, see p. 115). Therefore, long-term treatment with selenium in follow-up care is recommended.
Secondary tumors

Secondary tumors now make up one-sixth of all tumors. Long-term survivors of breast cancer form the largest group of survivors and are therefore particularly affected by the risk of secondary tumors.

50 % higher incidence rate compared to the general population

In a large-scale trial with 100,915 female and 578 male breast cancer patients, 3,153 cases of secondary tumors occurred. The standardized incidence rate (SIR) was about 50 % higher than the general population (SIR 1.51; 95 % CI 1.46 – 1.56). Breast cancer patients not over 40 years of age at the time of diagnosis (SIR 3.39; 95 % CI 2.80 – 4.07) were particularly affected (Fig. 79). Risk factors for a secondary tumor are increased age (per 10 years: HR 1.45; 95 % CI 1.40 – 1.49; p < 0.001), chemotherapy (HR 1.26; 95 % CI 1.16 – 1.36; p < 0.001), cirrhosis of the liver (HR 2.84; 95 % CI 2.32 – 3.47; p < 0.001), and male gender (HR 3.01; 95 % CI 2.38 – 3.80; p < 0.001).

Secondary tumor impairs survival probability

European trials support the results of the major Taiwanese trial. In a Dutch trial with 58,068 participants, 2,578 secondary tumors occurred. This corresponded to an increased SIR (standardized incidence rate) of 1.22 (95 % CI 1.17 – 1.27). The absolute additional risk was 13.6 (95 % CI 9.7 – 17.6) per 10,000 person-years. The cumulative incidence increased after 10 years to 5.4 % (95 % CI 5.18 – 5.64). A secondary tumor significantly impaired the survival probability (HR 3.98; 95 % CI 3.77 – 4.20).
Standardized Incidence Rate (SIR) of a secondary tumor in breast cancer survivors is dependent on age.


Fig. 79
Selenium deficiency as risk factor for secondary tumors

Selenium deficiency increases cancer risk.\(^{[8,9,17]}\) This correlation is especially relevant for cancer survivors. The negative effects of selenium deficiency on DNA stability\(^{[29]}\), the immune system\(^{[77]}\) or the activity of the tumor suppressor p53\(^{[123]}\) suggest that a selenium deficiency poses another risk factor for the development of secondary tumors (Fig. 80).

**Risk factors for secondary tumors in breast cancer survivors**

- Family history
- Genetics
- Chemo-therapy
- Radio-therapy
- Age
- Selenium deficiency
- G-CSF (Granulocytes-Colony Stimulating Factor)
- Antiestrogens


Fig. 80
Osteoporosis

Adjuvant breast cancer therapies increase the risk of osteoporosis. The problem with osteoporosis is its usually unnoticed course, since it is often only recognized when a bone fracture occurs. Aromatase inhibitors in particular significantly and often very rapidly reduce bone mineral density and increase the risk of fracture. Tamoxifen has a positive effect on bone strength in post-menopausal women. However, post-menopausal women may experience what is known as “estrogen deprivation syndrome” after discontinuing tamoxifen. This increases the risk of fracture.

In addition, medications that are often prescribed for cancer patients also increase the risk of osteoporosis. These include proton pump inhibitors, glucocorticoids, L-thyroxine or antidepressants (Table 10). Thyroid diseases in particular occur as comorbidities in patients with breast cancer. Both hyperthyroidism and the treatment of hypothyroidism (L-thyroxine) increase the risk of osteoporosis.

### Risk factors for osteoporosis

<table>
<thead>
<tr>
<th>Cannot be influenced</th>
<th>Can be influenced</th>
<th>Medications</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 50 years of age</td>
<td>Sedentary life-style</td>
<td>Aromatase inhibitors</td>
</tr>
<tr>
<td>Family predisposition</td>
<td>Poor nutrition:</td>
<td>Glucocorticoids</td>
</tr>
<tr>
<td>Small, thin physique</td>
<td>- excessive protein,</td>
<td>Proton pump inhibitors</td>
</tr>
<tr>
<td>Prior broken bones</td>
<td>sodium and sugar</td>
<td>Psychotropic agents</td>
</tr>
<tr>
<td>Early menopause</td>
<td>Inadequate intake</td>
<td>Antidepressants</td>
</tr>
<tr>
<td></td>
<td>of calcium, vita-</td>
<td>L-thyroxine</td>
</tr>
<tr>
<td></td>
<td>min D3 and selenium</td>
<td>Anticoagulants</td>
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<tr>
<td></td>
<td>Smoking</td>
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<td></td>
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</tr>
</tbody>
</table>


Selenium for bone health

A known selenium deficiency disorder is Kashin-Beck disease, an osteo-arthropathy. Additional trials have detected a correlation between selenium deficiency and growth inhibition or altered bone metabolism.\textsuperscript{[127, 128]}

Selenium deficiency is associated with lower bone mineral density

Both the serum selenium and selenoprotein P concentration are associated with bone mineral density.\textsuperscript{[110, 111]} The higher the selenium status, the higher the bone density of the hip ($p=0.004$ (selenium in serum); $p<0.001$ (selenoprotein P)) at the beginning of the trial and after six years (Fig. 81).\textsuperscript{[110]} At the same time, bone turnover was lower at a high selenium level ($p<0.001$ (osteocalcin level)). High bone turnover increases not only the risk of osteoporosis, but also the risk of bone metastases in advanced breast cancer patients.\textsuperscript{[129]} A high selenium status was also associated with a higher pulse rate and better grip strength ($p=0.003$ or $p=0.011$).

![Graph showing the relationship between serum selenium concentration and bone mineral density](image-url)


Fig. 81
Dosage recommendation

**Dosage** and costs of selenium after cancer therapy

<table>
<thead>
<tr>
<th>To improve the immune status[A], for prophylaxis in case of lymphedema[B, C], for elevated cardiotoxicity[D] and osteoporosis risk[E, F]</th>
<th>continuously up to 300 µg selenium per day[G]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Costs: approx. € 17 per month or € 200 per year (calculation based on the marketed dosage forms of selenase[G])</td>
<td></td>
</tr>
</tbody>
</table>

**For secondary lymphedema in breast cancer patients** *

<table>
<thead>
<tr>
<th>for 1 week[C] (i.v. or drinking ampoules)</th>
<th>for 2 weeks[H] (drinking ampoules)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1,000 µg selenium per day</td>
<td>500 µg selenium per day</td>
</tr>
<tr>
<td>Costs: approx. € 160 (calculation based on the marketed dosage forms of selenase[G] indicated in parentheses)</td>
<td></td>
</tr>
</tbody>
</table>

\* according to dosages, regimes as presented in trials


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**selenase® drug products: prescription only**

<table>
<thead>
<tr>
<th>selenase® 300 RP</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Active substance:</strong> Sodium selenite pentahydrate. 300 µg selenium per tablet</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>selenase® 100 µg peroral</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Active substance:</strong> Sodium selenite pentahydrate. 100 µg selenium in 2 ml oral solution</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>selenase® T peroral</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Active substance:</strong> Sodium selenite pentahydrate. 500 µg selenium in 10 ml oral solution</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>selenase® 100 µg pro injectione/selenase® T pro injectione</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Active substance:</strong> Sodium selenite pentahydrate. 100 µg selenium in 2 ml, 500 µg selenium in 10 ml and 1,000 µg selenium in 20 ml injection solution</td>
</tr>
</tbody>
</table>
selenase®

**Active substance:** Sodium selenite pentahydrate. *selenase® 100 µg pro injectione, selenase® T pro injectione, selenase® 100 µg peroral, selenase® T peroral:* 50 µg selenium per ml. *selenase® 300 RP:* 300 µg selenium per tablet. **Indications:** *selenase® 100 µg pro injectione, selenase® T pro injectione, selenase® 100 µg peroral, selenase® T peroral:* Proven selenium deficiency that cannot be offset from food sources. Selenium deficiencies may occur as a result of states of maldigestion and malabsorption, as well as in malnutrition (e.g., due to complete parenteral nutrition). *selenase® 300 RP:* Proven selenium deficiency that cannot be offset from food sources. Selenium deficiencies may occur as a result of states of maldigestion and malabsorption, as well as in malnutrition.

**Composition:**
- *selenase® 100 µg pro injectione:* 1 ampoule of 2 ml solution for injection contains: 0.333 mg sodium selenite pentahydrate, corresponding to 100 µg (micrograms) selenium.
- *selenase® T pro injectione:* 1 injection vial of 10 ml/20 ml solution for injection contains: 1.67 mg/3.33 mg sodium selenite pentahydrate, corresponding to 500 µg/1,000 µg (micrograms) selenium. *selenase® 100 µg peroral:* 1 drinking ampoule of 2 ml oral solution contains: 0.333 mg sodium selenite pentahydrate, corresponding to 100 µg (micrograms) selenium.
- *selenase® T peroral:* 1 ml oral solution contains: 0.167 mg sodium selenite pentahydrate, corresponding to 50 µg (micrograms) selenium. Excipients: Sodium chloride, hydrochloric acid, water for injections. *selenase® 300 RP:* 1 tablet contains 0.999 mg sodium selenite pentahydrate (corresponding to 300 µg selenium). Excipients: magnesium stearate (Ph. Eur.), maize starch, povidone K25, sucrose, talcum.

**Contra-indications:** Selenium poisoning.

**Undesirable effects:** None known to date if the medicinal product is administered according to prescription. For *selenase® 100 µg pro injectione, selenase® T pro injectione:* General disorders and administration site conditions: Frequency not known (cannot be estimated from the available data): After intramuscular administration local pain at the site of administration has been reported. Form of administration, size of packages: *selenase® 100 µg pro injectione,* 10 or 50 ampoules of 2 ml solution for injection. *selenase® T pro injectione:* 2 or 10 injection vials of 10 ml solution for injection, hospital-size pack 30 (3 × 10) or 50 (5 × 10) injection vials of 10 ml solution for injection, 2 or 10 injection vials of 20 ml solution for injection, hospital-size pack 30 (3 × 10) or 50 (5 × 10) injection vials of 20 ml solution for injection. *selenase® 100 µg peroral:* 20, 60, 90 or 100 ampoules of 2 ml oral solution. *selenase® T peroral:* 10 drinking bottles of 10 ml oral solution plus one measuring cup. *selenase® 300 RP:* 20, 50, 100 tablets. *selenase® 100 µg pro injectione, selenase® T pro injectione, selenase® 100 µg peroral, selenase® T peroral, selenase® 300 RP:* Subject to prescription.
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- Selenium is essential for human health. A selenium deficiency impairs the body's ability to destroy tumor cells, and it eliminates selenium deficiency.

- Selenium improves cancer therapy, protects healthy cells, is selectively cytotoxic for tumor cells, and improves the body's ability to destroy tumor cells. It also improves the effective treatment of lymphedemas.

- Selenium reduces side effects by protecting healthy cells, selectively cytotoxic for tumor cells, improves cancer therapy, and improves the body's ability to destroy tumor cells.

- Selenium supports the body in coping with cancer therapy, optimizes scientifically-based oncological therapy, alleviates tumor-associated symptoms and side effects, and improves quality of life.

- Selenium is important for the thyroid gland, especially for pregnant women. A selenium deficiency impairs the thyroid gland and increases the prevalence of thyroiditis (inflammation of the thyroid).

- Selenium requirements in patients with chronic thyroiditis are increased. Germany is a selenium-deficient country. Selenium and iodine are an essential duo for the thyroid gland.

- Selenium reduces the lymphedema volume, raises the effectiveness of physical therapy, reduces the risk of erysipelas, improves quality of life scores, and reduces adverse reactions.

- Selenium is essential for the thyroid gland, especially for pregnant women. A selenium deficiency impairs the thyroid gland and increases the prevalence of thyroiditis (inflammation of the thyroid).

- Selenium requirements in patients with chronic thyroiditis are increased. Germany is a selenium-deficient country. Selenium and iodine are an essential duo for the thyroid gland.

- Selenium reduces nosocomial infections, shortens the hospital stay, and corrects selenium deficiency.

- Selenium is critical in many aspects of general health and medicine, such as oxidative stress, an active immune system, and the thyroid gland. It is important for people who are sensitive to pesticides and those with limited access to the food supply.
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World market leader for high-dose selenium injections

 biosyn Arzneimittel GmbH is a pharmaceutical and biotech company based in Fellbach, Germany. It specializes in trace elements, is a world market leader for high-dose selenium injections, developer and operator of two unique GMP manufacturing operations for producing active ingredients, and in the biotech sector, is actively involved in the production of glycoprotein isolated from the Megathura crenulata, a sea snail found in California. 70 percent of our sales turnover is realized outside of Germany – in 26 countries all around the world.

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Selenium and oncology

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