

## Tabular literature survey: Selenium in oncology

### Selenium / selenite in cancer prevention, therapy, and aftercare

Second version

Date of literature search: 6<sup>th</sup> June, 2014

Database: PubMed ([www.ncbi.nlm.nih.gov/pubmed](http://www.ncbi.nlm.nih.gov/pubmed))

Abbreviations:        Se                Selenium (includes all types of Se compounds)  
                          SoSel            Selenite (usually sodium selenite)

#### Pharmakodynamics of selenite (API: sodium selenite pentahydrate)

##### *Primary pharmacodynamics*

The selenite anion (oxidation state +4) functions as an antioxidative substance and radical scavenger.

##### *Secondary pharmacodynamics*

Selenite is specifically and effectively incorporated in selenoenzymes (via the intermediate selenide). As a functional component of selenoenzymes selenite is

1. an efficient antioxidant (glutathione peroxidases, thioredoxin reductases)
2. an anti-inflammatory substance (e.g. downregulation of the proinflammatory transcription factor NF- $\kappa$ B)
3. an immunoactivator (e.g. upregulation of the high-affinity interleukin-2 receptor)
4. a crucial component of the DNA repair system (e.g. activation of impaired tumor suppressor gene p53, even in malignant tissues)

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Search phrase	Pre-clin. / Clin. / RCT	Type of cancer	Literature reference	Comments
Cancer AND Se 4,232 SoSel 713				
Cancer AND prevention Se 1,418 SoSel 195		<b>Prospective studies:</b> beneficial effect on risk of lung, bladder, colorectal, liver, oesophageal, gastric-cardia, thyroid and prostate cancers. <b>Meta-analyses:</b> lung, bladder, prostate cancer.	Overview see Rayman 2012, Bera et al. 2013  Lippman et al. 2009 Tsavachidou et al. 2009 Klein et al. 2011  Directive 2008/100/EU	Preventive use makes sense in Se-deficient persons. Two mechanisms under discussion: 1. Se is essential component of DNA repair, 2. Se as antioxidative protection against DNA damage.  Risk of Se-promoted diabetes type 2 (SELECT trial) proved to be an artifact.  <b>European RDA 55 mcg/d</b>  <b>Dosage in trials 200 mcg/d</b>
Cancer AND surgery Se 337 SoSel 42  Relevant addition: Sakr, Y., et al.: Crit. Care 18: R68 (2014): Retrospective analysis of 1047 sepsis patients, no effect of selenium on mortality and length of ICU stay.	21 / 29 / 10	Head and neck Head and neck, gynecol. Gynecol. (uterus) Breast Oral / lymphedema Head and neck / lymphedema Radiation-associated edema Head and neck / immunocompetence Secondary lymphedema Brain	Büntzel et al. 2010 (1) Büntzel et al. 2010 (2) Mücke et al. 2010 Dziaman et al. 2009 Zimmermann et al. 2005 Bruns et al. 2004 Micke et al. 2003 Kiremidjan-Schumacher 2000 Kasseroller 1998 Pakdaman 1998	Best data from elective heart surgery (Stoppe et al. 2011, 2013): 1. Intraoperative decrease of whole blood Se 2. Independent predictor of postoperative multi-organ failure 3. Severe Se decrease on 1 <sup>st</sup> day post-op  Dosages used: 200 – 2,000 mcg/d

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				<b>Recommendation: &gt; 2,000 mcg/d</b>
<p>Cancer AND radiotherapy  Se 92  SoSel 24</p> <p>Relevant addition:  Puspitasari, I., et al.: Updates on clinical studies of selenium supplementation in radiotherapy. Radiation Oncology 9: 125 (2014)</p>	7 / 20 / 9	<p><b>Gynecol. (uterus)</b>  Head and neck  Head and neck, gynecol.  Gynecol. (uterus)  Oral  Head and neck / lymphedema  Radiation-associated edema  Head and neck  Breast</p>	<p><b>Mücke et al. 2013</b>  Büntzel et al. 2010 (1)  Büntzel et al. 2010 (2)  Mücke et al. 2010  Elango et al. 2006  Bruns et al. 2004  Micke et al. 2003  Büntzel 1999  Schumacher 1999</p>	<p>Puspitasari et al. 2014: Se supplementation may offer specific benefits for several types of cancer patients who undergo radiotherapy.</p> <p>500 mcg/d during RT:  1. Reduction of side effects (radiogenic diarrhea)  2. No reduction of efficacy of radiation therapy  3. Patients do not reach lower limit of Se reference range – dosage still too low  4. Se blood levels drop after end of supplementation</p> <p><b>Recommendation: 1,000 mcg/d during RT, 200 mcg/d after end of RT</b></p>
<p>Cancer AND chemotherapy  Se 865  SoSel 186</p> <p>Relevant addition:  Harvie, M.: Nutritional supplements and cancer: Potential benefits and proven harm. ASCO Educ. Book 34:</p>	84 / 135 / 13	<p>Breast  Head and neck  Head and neck, gynecol.  Non-Hodgkin’s lymphoma  Oral  Oral / lymphedema  Head and neck / lymphedema  Radiation-associated edema</p>	<p>Uhlenbruck et al. 2010  Büntzel et al. 2010 (1)  Büntzel et al. 2010 (2)  Asfour et al. 2006, 2007, 2009  Elango et al. 2006  Zimmermann et al. 2005  Bruns et al. 2004  Micke et al. 2003</p>	<p>Dosages used: 200 – 500 mcg/d</p> <p>Highest dosages used by Asfour et al.: CHOP protocol in treatment of high-grade NHL. Se 0.2 mg/kg/d for 5 – 30 days (person with 70 kg BW: 14 mg/d!)</p> <p>1. Reduction in infection rate</p>

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e478 – 486 (2014)		Head and neck Breast Brain	Büntzel 1999 Schumacher 1999 Pakdaman 1998	2. Improvement in cardiac ejection (cardioprotection) 3. Increase in tumor cell apoptosis 3. Better complete response 4. Better overall survival  Safety: Only low-grade gastrointestinal side-effects (nausea, occasional vomiting)  <b>Recommendation: 1,000 – 2,000 mcg/d during CTx, 200 mcg/d after end of CTx</b>
Cancer AND chemotherapy AND <b>5-fluorouracil</b> Se 11 SoSel 4		Cancer cells  Radiation-associated edema	Thant et al. 2008 Schroeder et al. 2004 Micke et al. 2003	Se as a strategy to overcome the 5-FU resistance of some cancer cell lines
Cancer AND chemotherapy AND <b>carboplatin</b> Se 7 SoSel 3		Mouse model	Caffrey and Frenkel 2013	Prevention of carboplatin-induced drug resistance
Cancer AND chemotherapy AND <b>cetuximab</b> Se 1 SoSel 0		Medical hypothesis	Altundag et al. 2005	Increase of efficacy of cetuximab by down-regulation of prostaglandin synthesis
Cancer AND chemotherapy AND <b>cisplatin</b> Se 49 SoSel 26	24 / 28 / 9 18 / 13 / 1	Different cancer types Different cancer types Ovarian cancer Radiation-associated edema Different cancer types Different cancer types	Ghorbani et al. 2013 Weijl et al. 2004 Sieja and Talercyk 2004 Micke et al. 2003 Eisendoorn et al. 2001 Hu et al. 1997	<b>Reduction of nephrotoxicity</b> Reduction of ototoxicity Reduction of gastrointestinal side-effects Reduction of bone marrow suppression Reduction of mucositis

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				Reduction of hair loss  Dosages used: 100 – 4.000 mcg/d  <b>Recommendation: at least 1.000 mcg/d, 200 mcg/d after end of CTx</b>
Cancer AND chemotherapy AND <b>cyclophosphamide</b> Se 15 SoSel 1		Ovarian cancer Non-Hodgkin's lymphoma	Sieja and Talercyk 2004 Asfour et al. 2007 Last et al. 2003	Reduction of gastrointestinal side-effects Reduction of bone marrow suppression Reduction of hair loss
Cancer AND chemotherapy AND <b>docetaxel</b> Se 3 SoSel 2		Cancer cell lines	Freitas et al. 2011 Schroeder et al. 2004	Synergistic effect of selenite and docetaxel on prostate cancer cells
Cancer AND chemotherapy AND <b>doxorubicin</b> Se 29 SoSel 9		Rat	Liu et al. 2013 Taskin and Dursun 2012	Protection against mitochondrial damage Protection against cardiac dysfunction
Cancer AND chemotherapy AND <b>etoposide</b> Se 4 SoSel 4		Cancer cell lines	Jülicher et al. 2007	Enhancement of apoptosis induction via NF-KB pathways
Cancer AND chemotherapy AND <b>gemcitabine</b> Se 1 SoSel 2		Cancer cell lines	Szulkin et al. 2013	Combination of selenite and conventional drugs shows superior activity
Cancer AND chemotherapy AND <b>irinotecan</b> Se 7 SoSel 1		Cancer cell lines	Schroeder et al. 2004	Enhancement of cytotoxicity of irinotecan

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Cancer AND chemotherapy AND <b>methotrexate</b> Se 5 SoSel 3		Cancer cell lines  Non-Hodgkin's lymphoma	Schroeder et al. 2004  Last et al. 2003	Enhancement of cytotoxicity of methotrexate Better therapy response under higher Se levels
Cancer AND chemotherapy AND <b>oxaliplatin</b> Se 2 SoSel 2		Cancer cell lines	Schroeder et al. 2004	Enhancement of cytotoxicity of oxaliplatin
Cancer AND chemotherapy AND <b>paclitaxel</b> Se 8 SoSel 3		Cancer cell lines	Qi et al. 2011	MSA enhances caspase- mediated apoptosis in triple- negative breast cancer
Cancer AND chemotherapy AND <b>prednisone / prednisolone</b> Se 2 SoSel 1		Non-Hodgkin's lymphoma	Asfour et al. 2007 Last et al. 2003	Reduction of gastrointestinal side-effects Reduction of bone marrow suppression Reduction of hair loss
Cancer AND chemotherapy AND <b>topotecan</b> Se 2 SoSel 0		Cancer cell lines	Saifo et al. 2010	$\beta$ -Catenin as a drug resistance molecule is a target of MSA
Cancer AND chemotherapy AND <b>vincristine</b> Se 3 SoSel 1		Non-Hodgkin's lymphoma	Asfour et al. 2007 Last et al. 2003	Reduction of gastrointestinal side-effects Reduction of bone marrow suppression
Cancer AND <b>tamoxifen</b> Se 34 SoSel 5		Cancer cell lines	Li et al. 2008	MSA increases the growth- inhibitory effect of tamoxifen and reverses tamoxifen resistance in breast cancer cells
Cancer AND <b>tumor aftercare</b> Se 0				No relevant data

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SoSel	0				
Cancer AND <b>fatigue</b>					No relevant data
Se	4				
SoSel	0				
<b>Immune system</b>					
Se	1,128	12	Breast cancer	Dziaman et al. 2009	Se reduces oxidative DNA damage in BRCA1 carriers
SoSel	221		Head- & neck cancer	Kiremidjian-Schumacher 2000	Se improves T-cell cytotoxicity against cancer cells
					<b>Dosage in trials 200 mcg/d</b>