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**REVIEW PAPER**

# THE ROLE OF SELENIUM IN THE RISK AND PREVENTION OF NEOPLASTIC DISEASES

**Monika Bojanowska[1], Marzena S. Brodowska[2], Izabella Jackowska[1]**

**[1]Department of Chemistry**
**[2]Department of Agricultural and Environment Chemistry**
**University of Life Sciences in Lublin, Poland**

**Abstract**

Neoplastic diseases, whose incidence is on the increase, rank the second among the diseases in which oxidative stress and disturbances in the organism's protective functions contribute to the development. The neoplastic process is a long-lasting and multi-level phenomenon. One of the main reasons for the initiation of carcinogenesis is DNA damage caused by mutagenic (genotoxic) factors, which include free radicals. This paper discusses the role of selenium in the risk and prevention of neoplastic diseases, based on a review of scientific reports and the results of studies conducted in different centers. The greatest biological significance of selenium is associated with its occurrence in enzymes and proteins. Moreover, it has been demonstrated that there is a strict correlation between the Se content in a diet and the incidence of neoplastic diseases and related mortality. Research evaluating medical applications of selenium has made significant progress, showing that the optimal level of selenium is correlated with a reduction in total mortality and cancer risk. Both excessively low and excessively high selenium concentrations are unfavourable. However, the optimal level of selenium varies and is population-dependent. This may be related to the contamination of the environment with different chemical compounds that are neutralized by selenium. Selenium decreases the risk of lung, urinary bladder, large intestine, liver, oesophagus, stomach and prostate neoplasms. A low selenium level in the blood, hair or nails may significantly increase the risk of neoplasms. It is possible to enhance the positive role of selenium in maintaining human health through the optimization of its content owing to research into genotypes.

**Keywords**: selenium, neoplasms, risk, prevention.

Monika Bojanowska, PhD, Department of Chemistry, University of Life Sciences in Lublin, Akademicka 15, 20-950 Lublin, Poland, e-mail: monika.bojanowska@up.lublin.pl

# INTRODUCTION

Neoplastic diseases, whose incidence is on the increase, rank the second among the diseases in which oxidative stress and disturbances in the organism's protective functions contribute to the development. The neoplastic process is a long-lasting and multi-level phenomenon. One of the main reasons for the initiation of carcinogenesis is DNA damage caused by mutagenic (genotoxic) factors, which include free radicals (Strzelczyk, Wiczkowski 2012). As shown by scientific research, antioxidants effectively neutralize the formation of free radicals and, when delivered to the organism, they support health and contribute to a reduced risk of diseases of affluence, including neoplasms (Olejnik et al. 2010, Zabłocka, Biernat 2010). Among many tested substances with such properties, selenium deserves special attention, although the results of clinical trials are not unambiguous (Vinceti et al. 2014).

## Selenium in the organism

The greatest biological significance of selenium is associated with its occurrence in enzymes and proteins. As selenocysteine, it is a necessary cofactor of selenium-dependent enzymes: glutathione peroxidases, thioredoxin reductases, iodothyronine deiodinases and other selenoproteins. The best known selenoenzymes occurring in mammals are as follows: glutathione peroxidase, selenoprotein P and tetraiodothyronine 5' deiodinase. Except for the latter one, all catalyze redox reactions (Brodowska et al. 2016, Klecha, Bukowska 2016). The main tasks of glutathione peroxidase include removal of organic peroxides and hydrogen peroxide, which are toxic to tissues, by reducing them to hydroxyl compounds – water or alcohol (Brigelius-Flohé, Maiorino 2013). In the case of selenium deficiency, it has been found that the level of this enzyme decreases, while reactive oxygen species production increases, and this raises the risk of neoplastic disease. Thioredoxin reductases, whose tasks include thioredoxin and protein disulfide reduction, are an important group of selenium-containing enzymes that participate in the prevention and repair of oxidative stress-induced damage. They also take part in DNA synthesis and influence apoptosis processes (Adbulah et al. 2005, Gromadzińska et al. 2008). As an antioxidant, selenium reduces the harmful processes of lipid, DNA and RNA peroxidation and thus protects cells against deformation and genetic damage (Tapiero et al. 2003). Selenium is very active in many selenoproteins that support the immune function and, through specific cellular pathways, may perform the preventive role in initiation and promotion of specific types of cancer.

## Selenium and cancers

Intensive research into the effect of selenium on the prevalence of different neoplasms has been pursued for more than 40 years now, demonstra-

ting *inter alia* an inverse relationship between selenium intake and cancer -related mortality (Schrauzer et al. 1977). The data from a meta-analysis conducted by Dennert et al. (2011) confirmed a 31% reduction in the incidence of new cases and a 45% decrease in cancer-related mortality in people with the optimal level of selenium. Moreover, a strict correlation has been demonstrated between the Se content in a diet and the incidence of neoplastic diseases and related mortality (Rayman 2005). The inclusion of sex as a distinguishing factor is very important for analyzing the role of Se in the prevention of neoplastic diseases. In a cohort study conducted in 5 countries, it turned out that the plasma selenium level was lower by up to 23% in people diagnosed with neoplastic diseases, particularly in men, than in healthy people (Waters et al. 2004). Selenium deficiency leads to the development of various types of cancer more frequently in men than in women. In a study group of men, a lower level of selenium was associated with a higher incidence of prostate cancer, whereas no such relationship was shown in the case of breast cancer in female patients.

The available results of prospective studies have provided evidence of the effect of Se on the incidence of lung, urinary bladder, large intestine, liver, oesophagus, stomach and prostate neoplasms (Wei et al. 2004, Zhuo et al. 2004, Brinkman et al. 2006, Peters, Takata 2008, Amaral et al. 2010, Rayman 2012, Fakhiri et al. 2016). A low selenium level in the blood, hair or nails may significantly increase the risk of neoplasms, e.g. in the case of thyroid cancer the risk can be 8 times higher (Glattre et al. 1989). Selenium's protective role is confirmed by numerous studies carried out in many countries (El-Bayoumy 2001, Brozmanova 2011), but not all analyses investigating this issue are coherent. A Chinese study found a statistically significant increase in the incidence of oesophagus and stomach cancer in a population with a low selenium content, but no such relationship was found in the case of lung cancer (Chen et al. 1992). A review of the epidemiological study concerning lung cancer and selenium concentration in biological material undertaken by Zhuo et al. (2004) shows that Se has a certain protective effect, but only in populations where its low level is noted. A team of scientists from Szczecin also demonstrated a strong correlation between the level of selenium and cancer. In patients with lung cancer, the average serum selenium concentration was 63.2 μg $dm^{-3}$, while in healthy people it reached 74.6 μg $dm^{-3}$. A ten-fold lower risk of lung cancer was also observed in persons with the serum selenium level >80 μg $dm^{-3}$ compared to patients whose Se concentration was <60 μg $dm^{-3}$ (Jaworska et al. 2013). An increased risk of lung and/or larynx cancer in people with a low blood selenium level has been presented in several publications (Jabłońska et al. 2008, Borawska et al. 2009). Prospective studies have also revealed a reverse correlation between selenium concentration and lung cancer risk. Moreover, a reduced risk of lung cancer was found in a study on selenium supplementation, which led to a nearly 3-fold decrease in the risk of these neoplasms, provided that the initial serum selenium concentration was no more than 106 μg $dm^{-3}$ (Schrauzer et al. 1977).

In people with a significantly increased content of Se, its supplementation was associated with up to a 25% increase in lung cancer risk. The above results are confirmed by the data obtained in Polish research centers (Jabłońska et al. 2008, Jaworska et al. 2011).

The effect of selenium on the prostate cancer incidence is analyzed most frequently. Many studies show the existence of a relationship between a high Se level in the organism and a reduced risk of the development and growth of this neoplasm (Brinkman et al. 2006, Allen et al. 2016). In a Dutch cohort study, which lasted 6 years, a high nail selenium concentration was associated with a much reduced risk of prostate cancer (van den Brandt et al. 2003). In two large studies relating to the male population in the United Kingdom and Canada, no such relationship was found based on the evaluation of nail selenium content (Allen et al. 2016, Ghadirian et al. 2000). The study SELECT (Selenium and Vitamin E Cancer Prevention Trial), conducted in the USA over the years 2001-2009 and designed to evaluate the effect of selenium and/or vitamin E supplementation on prostate cancer risk, proved to be of key importance (Lippman et al. 2009). This study did not prove the efficacy of selenium supplementation in chemoprevention of this cancer nor did it confirm a decrease in the incidence of neoplasms in the selenium--supplemented groups compared to the placebo group. However, the results of the SELECT trial confirm the observations from the NPC (Nutritional Prevention of Cancer) trial (Duffield et al. 2003*a*) that supplementation with selenium depends on its initial concentration and is beneficial only for people with its low serum level (<106 μg $dm^{-3}$) – in men participating in the SELECT trial, the initial Se concentration was ~137 μg $dm^{-3}$, that is, it was much too high to observe the protective effect of its administration. Supplementation with selenium in men with non-metastatic prostate cancer at an amount of 140 μg per day or more may increase the risk of mortality (Kenfield et al. 2015). The relationships between selenium and prostate gland cancer are complicated, as shown by the analyses published in 2014. In an American study, the study group comprised 1739 men with prostate cancer, while the control group consisted of 3117 people in the same age range. Selenium supplementation had no effect on the increased prostate cancer growth in people with a low initial selenium content. However, the study showed a 91% increase in the incidence of advanced prostate cancer in people with a high initial content of selenium who were additionally supplemented with this element (Kristal et al. 2014). The results of a Dutch study, which comprised 817 men with advanced prostate cancer and 1048 healthy persons, suggest that a low selenium content in the body is associated with an increased risk of the advanced form of this tumor, regardless of the genetic variability for glutathione peroxidase 1 and *selenoprotein P plasma 1* (Geybels et al. 2014).

Selenium toxicity symptoms (nail deformation, hair loss, nausea, irritation of airways, vertigo, and metallic aftertaste in the mouth) reduce doses

used in chemoprevention. Administration of 400 µg per day and reaching a concentration of 1000 ng $cm^{-3}$ in the blood plasma did not cause adverse effects. A study by Reid et al. (2004) presented blood plasma selenium levels and reports on selenium toxicity in 24 men suffering from biopsy-confirmed prostate cancer. Over a period of one year, the patients were given 1600 or 3200 µg of selenium-enriched yeasts, reaching an Se concentration of 492.2 and 639.7 ng $cm^{-3}$, respectively. The performed analysis of the haematological parameters showed that these parameters were within the normal range in both groups. No significant toxicity symptoms were observed at the selenium doses administered, while monitoring the functioning of the kidneys and liver as well as the condition of the hair and nails. Dietary supplementation with selenium may be used to prevent changes related to benign prostatic hyperplasia without neoplastic changes, which is very common in men after 40 years of age. As shown by the results of an analysis performed by American scientists, in more than 2400 men over 60 years of age a high plasma selenium content (>126 µg $dm^{-3}$) was associated with a less frequent incidence, by even 50%, of adverse symptoms of prostatic hyperplasia in relation to men with a lower content of this element (Rohrmann et al. 2004).

The results of a study conducted among a group of people suffering from oesophageal and cardiac cancer as well as from bladder cancer showed a significant relationship between higher serum selenium concentrations and a decreased risk of these neoplasms (Mark et al. 2000, Zeegers et al. 2002). A Polish-Estonian study that evaluated a similar relationship found an over 13-fold higher probability of colorectal cancer in people with a Se concentration <40 µg $dm^{-3}$ compared to those where it was >72 µg $dm^{-3}$ (Lener et al. 2013). The results obtained by Jacobs et al. (2004) and Ou et al. (2012) also indicated that a higher level of selenium may be associated with a lower risk of colorectal cancer. On the other hand, the study by Takata et al. (2011) and Sobiecki (2017) found no such relationship.

Existing research into the correlation between selenium concentrations and breast cancer risk is not unambiguous (Ghadirian et al. 2000, Susana et al. 2009). In the study conducted by scientists from Szczecin on a group of women without the BRCA1 gene mutation, the blood serum selenium concentration >100 µg $dm^{-3}$ was associated with an increased risk of breast cancer incidence. Also in this group, at a low blood serum selenium concentration (<73 µg $dm^{-3}$), an increased risk of neoplasms of different organ localization was observed (Lener et al. 2016). As shown in the NPC trial, effective cancer prevention through supplementation of selenium depends not only on its initial concentration in the organism but also on the localization of an organ affected by cancer, and it was associated with a reduced risk of prostate, colon and lung cancer, but a trend towards an increased risk of breast cancer was observed.

Thus far, the scientific studies have not clearly confirmed the effect of selenium on the risk of various types of skin cancer. Researchers point to

many different factors determining the development of cancer (Payette et al. 2010, Bronsnick et al. 2014, Murzaku et al. 2014, Katta, Brown 2015, Vinceti et al. 2017). Melanoma and nonmelanoma skin cancers arise from normal cells in the epithelial layer of the skin. In animal studies, oral selenium supplementation resulted in decreased melanoma tumor growth (Cassidy et al. 2013). The relationship between selenium and NMSC (nonmelonomena skin cancer) clinically is less certain. The studies have found a potentially protective role of selenium for NMSC. In a case control study, the mean plasma selenium level was significantly lower amongst NMSC cases than controls (Clark et al. 1984). Similarly, in an 8-year-long prospective study, participants with the highest selenium concentrations had an approximately 60% lower incidence of BCCs (basal cell carcinoma) and SCCs (squamous cell carcinoma) than participants with the lowest concentrations (van der Pols et al. 2009). Duffield-Lillico et al. (2003*b*) investigated the impact of oral selenium supplementation on NMSC and found no significant association with the risk of BCC, but elevated risks of SCC and total NMSC. Other studies found no significant relationship between selenium levels and melanoma risk (Bergomi et al. 2005, Heinen et al. 2007, Asgari et al. 2009).

Risk factors responsible for skin cancers are complex and involve many inherited, environmental, and biological factors, including selenoproteins which participate in the response of the skin to UV-induced oxidative stress (Hercberg et.al. 2007, Leiter, Garbe 2008, Cassidy et. al. 2013). *In vitro* studies suggest that selenium may protect cells from UVB-induced damage by inducing DNA repair enzymes and transactivating p53, a tumor suppressor protein that is involved in cell growth arrest and apoptosis in response to DNA and other cellular damage (Traynor et al. 2006). The studies on mice have shown that topical L-selenomethionine (SeMet) can prevent UVB-induced skin cancer when applied continuously before, during and after the radiation exposure. Results obtained by Burke et al. (2014) suggest that even beginning SeMet supplementation late in the process of tumorigenesis can help protect from UV-induced photodamage and skin cancer.

The correlations between a low selenium concentration and increased cancer incidence are confirmed by the results of many studies (El-Bayoumy 2001, Gromadzińska et al. 2008, Rayman 2012). Doubts may arise from the fact that the optimal serum selenium concentration is different in individual populations. An American study demonstrated that in people with the serum selenium concentration at a level of about 120 μg $dm^{-3}$, there is a several-fold decrease in the total (regardless of the localization) cancer incidence and cancer-related mortality (Rayman 2005), while the serum Se concentration associated with the lowest risk of intestinal polyps is >150 μg $dm^{-3}$. The differences between Europe and America may be related to the genetic and environmental factors, including the exposure to chemical compounds (Ou et al. 2012).

Recent research (Borawska et al. 2009, Jaworska et al. 2013, Lener et al. 2013) has shown that the Polish population is characterized by a low serum/

plasma selenium level, about 70 μg $dm^{-3}$. The results indicate a significant reduction in the risk of neoplasms (by as much as ten times) at higher selenium levels in the case of cancer of the lung, larynx, large intestine, stomach, thyroid and prostate. Based on many years of observations by the Szczecin-based scientists, it can be agreed that the optimal serum/plasma selenium concentration is 85-120 for men and about 75-85 μg $dm^{-3}$ for females, which correlates well with the results of the NPC trial, according to which the optimal selenium level is similar and is 100-120 μg $dm^{-3}$ in the serum/plasma. In the case of people whose threshold concentration is <60 μg $dm^{-3}$, there is an increased risk of cancer and selenium supplementation is necessary (Lener et al. 2016). Supplements containing selenium in an easily absorbed form can be a source of selenium in supplementation. According to the literature data on the metabolism of different forms of selenium, selenates (IV) at a dose of about 25-50 μg of selenium per day would be the best. The effect of selenium on the risk and course of cancer may be dependent not only on its concentration, but also on the molecular basis of inheritance. Selenoprotein-coding genes are genes that are significantly associated with selenium activity. As regards the need of selenium supplementation, women from a high risk group of breast/ovarian cancer are an exception here. According to the data, about 40% of them have selenoprotein genotypes that require a selenium level above 100 μg $dm^{-3}$, while for the other ones the optimal level is lower (Lippman et al. 2009).

Being part of numerous enzymes with protective activity against the effects of oxidative stress, which is associated with an increased risk of neoplasm, selenium may affect this by blocking DNA synthesis in neoplastic cells, enhancing the immunological cellular response, inhibiting lipid peroxidation and oxidative DNA damage as well as by removing peroxides and free oxygen radicals (Zabłocka, Biernat 2010, Rayman 2012, Varlamova et al. 2017). It exhibits antiproliferative activity towards neoplastic cells as well as having an inhibitory effect on neoplasm growth and an antiangiogenic effect. It is noted more and more frequently that some chemical forms of selenium are responsible for ROS (reactive oxygen species) production in cells. The prooxidant activity of selenium takes advantage of the fact that neoplastic cells have disturbed antioxidant-prooxidant balance because many reactive oxygen species are produced in them as a result of intense glycolysis and the pentose cycle. The mechanism of selenium action on neoplastic cells is comprehensive and includes, among others, the production of reactive oxygen species, the modification of thiol groups in proteins, and chromatin remodeling. Selenium contributes to cellular apoptosis by modifying proteins and inactivating the transcription factors as well as it may inhibit the cell cycle (Drake 2006, Fernandes 2015).

**Selenium and its potential therapeutic usage**

Experimental research has shown that selenium availability is strictly dependent on the chemical form of this element, which affects its intracellular distribution in the organism. Supplied to the organism with food or diet supplements, selenium occurs both in organic forms, such as selenomethionine (Se-Met) and selenocysteine (Se-Cys), and inorganic forms – selenates(IV) or (VI). The biological activity of selenium in living organisms and its anticancerogenic or toxic effects depend on how it is metabolized in the body. Combination with antioxidant vitamins (e.g. vitamin E) and zinc increases the absorption of selenium from the alimentary canal and enhances the antioxidant activity of this element. In tumor prevention, sodium selenate(IV), L-selenomethionine and Se-methyl-L-selenocysteine deserve attention. L-selenomethionine is absorbed better than sodium selenate(IV), but the latter more effectively increases the gene expression of the main antioxidant selenium-containing enzyme – glutathione peroxidase. These compounds complement each other, influencing the expression of essential proteins related to tumor prevention and suppression. Moreover, they all induce the death of different types of neoplastic cells. L-selenomethionine increases the death of neoplastic cells through apoptosis only in cells with the intact p53 gene, whereas Se-methyl-L-selenocysteine induces apoptosis in mutated cells that do not have this important control mechanism (Suzuki et al. 2010).

Some studies suggest that selenium may be useful in treating already developed tumors through its cytotoxic activity that destroys tumor cells. Selenate(IV) is used to support treatment of cancer of various organs, among others: lung, prostate and uterus, and moreover its application may enhance the action of radiation on well-developed hormone-independent prostate tumors (Fernandes et al. 2015).

A study by Flis-Borsuk et al. (2016) shows the possibility of applying Selol ($Se^{+4}$ containing selenite-triglycerides) in tumor control. Initially, Selol has prooxidant and antineoplastic effects, while during the second phase it exhibits strong antioxidant and repair properties. The advantage of this agent over sodium selenate(IV), which is used in treatment, is its low toxicity that allows higher selenium doses to be taken.

## SUMMARY

Research evaluating medical applications of selenium has made significant progress, showing that the optimal level of selenium is correlated with a reduction in total mortality and cancer risk. Both excessively low and excessively high selenium concentrations are unfavourable (Varlamova et al. 2017). However, the optimal level of selenium varies and is population-dependent. This may be related to the contamination of the environment with

different chemical compounds that are neutralized by selenium. The role of selenium in human health can be even greater if its optimal concentration is customized for each person by studying individual genotypes.

## REFERENCES


Abdulah R., Miyazaki K., Nakazawa M., Koyama H. 2005. *Chemical forms of selenium for cancer prevention*. J. Trace Elem. Med. Biol., 19: 141-150. DOI: 10.1016/j.jtemb.2005.09.003

Allen N.E., Travis R.C., Appleby P.N., Albanes D., Barnett M.J., Black A., Bueno-de-Mesquita H.B., Deschasaux M., Galan P., Goodman G.E., Goodman P.J., Gunter M.J., Heliövaara M., Helzlsouer K.J., Henderson B.E., Hercberg S., Knekt P., Kolonel L.N., Lasheras C., Linseisen .J, Metter E.J., Neuhouser M.L., Olsen A., Pala V., Platz E.A., Rissanen H., Reid M.E., Schenk J.M., Stampfer M.J., Stattin P., Tangen C.M., Touvier M., Trichopoulou A., van den Brandt P.A., Key T.J. 2016. *Selenium and prostate cancer: Analysis of individual participant data from fifteen prospective studies*. J. Natl. Cancer Inst., 108(11): djw153. DOI: 10.1093/jnci/djw153

Amaral A.F., Cantor K.P., Silverman D.T., Malats N. 2010. *Selenium and bladder cancer risk: A meta-analysis*. Cancer Epidemiol. Biomarkers Prev., 19: 2407-2415. DOI: 10.1158/1055--9965.EPI-10-0544

Asgari M.M., Maruti S.S., Kushi L.H., White E. 2009. *Antioxidant supplementation and risk of incident melanomas: Results from a large prospective cohort study*. Arch. Dermatol. 145:879-82. DOI: 10.1001/archdermatol.2009.176

Bergomi M., Pellacani G., Vinceti M., Bassissi S., Malagoli C., Alber D., Sieri S., Vescovi L., Seidenari S., Vivoli R. 2005. *Trace elements and melanoma*. J. Trace Elem. Med. Biol., 19:69-73. DOI: 10.1016/j.jtemb.2005.06.002

Borawska M.H., Socha K., Łazarczyk B., Czyżewska E., Markiewicz R., Darewicz B. 2009. *The effects of diet on selenium concentration in serum in patients with cancer*. Nutr. Cancer, 61: 629-633. http://dx.doi.org/10.1080/01635580902825555

Brigelius-Flohé R., Maiorino M. 2013. *Glutathione peroxidases*. Biochim. Biophys. Acta, 1830(5): 3289-3303. DOI: 10.1016/j.bbagen.2012.11.020

Brinkman M., Reulen R.C., Kellen E., Buntinx F., Zeegers M.P. 2006. *Are men with low selenium levels at increased risk of prostate cancer?* Eur. J. Cancer, 42: 2463-2471. DOI: 10.1016/j.ejca.2006.02.027

Brodowska M.S., Kurzyna-Szklarek M., Haliniarz M. 2016. *Selenium in the environment*. J. Elem., 21(4): 1173-1185. DOI: 10.5601/jelem.2016.21.2.1148

Bronsnick T., Murzaku E.C., Rao B.K. 2014. *Diet in dermatology: Part I. Atopic dermatitis, acne, and nonmelanoma skin cancer*. J. Am. Acad. Dermatol., 71(6): 1039.e1-1039.e12. DOI: 10.1016/j.jaad.2014.06.015

Brozmanova J. 2011. *Selenium and cancer: from prevention to treatment*. Klin. Onkol., 24(3): 171-179.

Burke K.E., Zhou X., Wang Y., Commisso J., Keen C.L., Nakamura R.M., Combs G.F., Wei H. 2014. *The effects of topical L-selenomethionine on protection against UVB-induced skin cancer when given before, during, and after UVB exposure*. J. Drugs Dermatol., 13(10): 1214-1223.

Cassidy P.B., Fain H.D., James P. Cassidy J.P., Tran S.M., Moos P.J., Boucher K.M., Gerads R., Florell S.R., Grossman D., Sancy A. Leachman S.A. 2013. *Selenium for the prevention of cutaneous melanoma*. Nutrients, 5(3): 725-749. DOI: 10.3390/nu5030725

Chen J., Geissler C., Parpia B., Li J., Campbell T.C. 1992. *Antioxidant status and cancer mortality in China*. Int. J. Epidemiol., 21: 625-635. https://doi.org/10.1093/ije/21.4.625

Clark L.C., Graham G.F., Crounse R.G., Grimson R., Hulka B., Shy C.M. 1984. *Plasma selenium and skin neoplasms: A case-control study*. Nutr. Cancer, 6: 13-21.

Drake E.N. 2006. *Cancer chemoprevention: Selenium as a prooxidant, not an antioxidant*. Med. Hypotheses, 67(2): 318-322. DOI: 10.1016/j.mehy.2006.01.058

Duffield-Lillico A.J., Dalkin B.L., Reid M.E., Turnbull B.W., Slate E.H., Jacobs E.T., Marshall J.R., Clark L.C. 2003*a*. *Selenium supplementation, baseline plasma selenium status and incidence of prostate cancer: An analysis of the complete treatment period of the Nutritional Prevention of Cancer Trial*. BJU Int., 91(7): 608-612.

Duffield-Lillico A.J., Slate E.H., Reid M.E., Turnbull B.W., Wilkins P.A., Combs G.F., Park H.K., Gross E.G., Graham G.F., Stratton M.S., Marshall J.R., Clark L.C. 2003b. *Selenium supplementation and secondary prevention of nonmelanoma skin cancer in a randomized trial*. J. Natl. Cancer Inst., 95(19): 1477-1481.

El-Bayoumy K. 2001. *The protective role of selenium on genetic damage and on cancer*. Mutat. Res., 475:123–139.

Fakhri Y., Ghahremanfard F., Avazpour M., Moradi M., Amanidaz N., Zandsalimi Y., Moradi B., Amirhajeloo L.R., Keramati H. 2016. *Selenium and lung cancer: A systematic review, meta-analysis and meta-regression*. Int. J. Pharm. Technol., 8(2): 13038-13056.

Fernandes A.P., Gandin V. 2015. *Selenium compounds as therapeutic agents in cancer*. Biochim. Biophys. Acta, 1850(8): 1642-1660. DOI: 10.1016/j.bbagen.2014.10.008

Flis-Borsuk A., Śliwka L., Suchocka Z., Borsuk J., Fijałek Z., Lubelska K., Suchocki P. 2016. *Selenitetriglycerides and their promise in cancer treatment*. Biul. Wydz. Farm. WUM, 3: 17-24. (in Polish)

Geybels M.S., van den Brandt P.A., Schouten L.J., van Schooten F.J., van Breda S.G., Rayman M.P., Green F.R., Verhage B.A. 2014. *Selenoprotein gene variants, toenail selenium levels, and risk for advanced prostate cancer*. J. Natl. Cancer Inst., 106(3):dju003. DOI: 10.1093/jnci/dju003

Ghadirian P., Maisonneuve P., Perret C., Kennedy G., Boyle P., Krewski D., Lacroix A. 2000. *A case-control study of toenail selenium and cancer of the breast, colon, and prostate*. Cancer Detect. Prev., 24(4): 305-313.

Glattre E., Thomassen Y., Thoresen S.Ø., Haldorsen T., Lund-Larsen P.G., Theodorsen L., Aaseth J.P. 1989. *Prediagnostic serum selenium in a case-control study of thyroid cancer*. Int. J. Epidemiol., 18: 45-49. https://doi.org/10.1093/ije/18.1.45

Gromadzińska J., Reszka E., Bruzelius K., Wasowicz W., Akesson B. 2008. *Selenium and cancer: Biomarkers of selenium status and molecular action of selenium supplements*. Eur. J. Nutr., 47(2): 29-50. DOI: 10.1007/s00394-008-2005-z

Heinen M.M., Hughes M.C., Ibiebele T.I., Marks G.C., Green A.C., van der Pols J.C. 2007. *Intake of antioxidant nutrients and the risk of skin cancer*. Eur. J. Cancer, 43: 2707-16. DOI: 10.1016/j.ejca.2007.09.005

Hercberg S., Ezzedine K, Guinot C, Preziosi P, Galan P, Bertrais S, Estaquio C, Briançon S, Favier A, Latreille J, Malvy D. 2007. *Antioxidant supplementation increases the risk of skin cancers in women but not in men*. J. Nutr. 137(9): 2098-2105.

Jabłońska E., Gromadzińska J., Sobala W., Reszka E., Wąsowicz W. 2008. *Lung cancer risk associated with selenium status is modified in smoking individuals by Sep15 polymorphism*. Eur. J. Nutr., 47: 47-54. DOI: 10.1007/s00394-008-0696-9

Jacobs E.T., Jiang R., Alberts D.S., Greenberg E.R., Gunter E.W., Karagas M.R., Lanza E., Ratnasinghe L., Reid M.E., Schatzkin A., Smith-Warner S.A., Wallace K., Martínez M.E. 2004. *Selenium and colorectal adenoma: Results of a pooled analysis*. J. Natl. Cancer Inst., 96(22): 1669-1675. DOI: 10.1093/jnci/djh310

Jaworska K., Durda K., Gupta S., Muszyńska M., Sukiennicki G., Grodzki T., Waloszczyk P., Jaworowska E., Lubiński J., Kładny J., Wilk G., Górecka B., Sikorski A., Gołąb A., Wokołorczyk D., Cybulski C., Tołoczko-Grabarek A., Huzarski T., Jakubowska A., Lubiński J. 2011. *Selenoprotein genotypes as well as selenium levels in organisms are critical features of human cancer risk*. Wspolczesna Onkol., 15: 39-43.

Jaworska K., Gupta S., Durda K., Muszyńska M., Sukiennicki G., Jaworowska E., Grodzki T., Sulikowski M., Woloszczyk P., Wójcik J., Lubiński J., Cybulski C., Dębniak T., Lener M., Morawski A.W., Krzystolik K., Narod S.A., Sun P., Lubiński J., Jakubowska A. 2013. *A low selenium level is associated with lung and laryngeal cancers*. PLoS One, 8: e59051. DOI: 10.1371/journal.pone.0059051

Katta R., Brown D.N. 2015. *Diet and skin cancer: The potential role of dietary antioxidants in nonmelanoma skin cancer prevention*. J Skin Cancer, (2015), Article ID 893149, 1-10. http://dx.doi.org/10.1155/2015/893149

Klecha B., Bukowska B. 2016. *Selenium in human organism – Characteristics of the element and its potential therapeutic application* Bromat. Chem. Toksykol., 49(4): 818-829. (in Polish)

Kristal A.R., Darke A.K., Morris J.S., Tangen C.M., Goodman P.J., Thompson I.M., Meyskens F.L., Goodman G.E., Minasian L.M., Parnes H.L., Lippman S.M., Klein E.A. 2014. *Baseline selenium status and effects of selenium and vitamin E supplementation on prostate cancer risk*. J. Natl. Cancer Inst., 106(3):djt456. DOI: 10.1093/jnci/djt456

Leiter U., Garbe C. 2008. *Epidemiology of melanoma and nonmelanoma skin cancer - The role of sunlight*. Adv. Exp. Med. Biol., 624:89-103. DOI: 10.1007/978-0-387-77574-6_8

Lener M., Jaworska-Bieniek K., Jakubowska A., Sukiennicki G., Marciniak W., Muszyńska M., Durda K., Kaczmarek K., Lubiński J. 2016. *Selenium (Se) in cancers*. In: *Clinical genetics of cancers*. (Ed. J. Lubiński), Szczecin, 377-387. (in Polish)

Lener M.R., Gupta S., Scott R.J., Tootsi M., Kulp M., Tammesoo M.L., Viitak A., Metspalu A., Serrano-Fernández P., Kładny J., Jaworska-Bieniek K., Durda K., Muszyńska M., Sukiennicki G., Jakubowska A., Lubiński J. 2013. *Can selenium levels act as a marker of colorectal cancer risk?* BMC Cancer, 13: 214. DOI: 10.1186/1471-2407-13-214

Lippman S.M., Klein E.A., Goodman P.J., Lucia M.S., Thompson I.M., Ford L.G., Parnes H.L., Minasian L.M., Gaziano J.M., Hartline J.A., Parsons J.K., Bearden J.D., Crawford E.D., Goodman G.E., Claudio J., Winquist E., Cook E.D., Karp D.D., Walther P., Lieber M.M., Kristal A.R., Darke A.K., Arnold K.B., Ganz P.A., Santella R.M., Albanes D., Taylor P.R., Probstfield J.L., Jagpal T.J., Crowley J.J., Meyskens F.L., Baker L.H., Coltman C.A. 2009. *Effect of selenium and vitamin E on risk of prostate cancer and other cancers: the selenium and vitamin E cancer prevention trial (SELECT)*. JAMA, 301(1): 39-51. DOI: 10.1001/jama.2008.864

Mark S.D., Qiao Y.L., Dawsey S.M., Wu Y.P., Katki H., Gunter E.W., Fraumeni J.F., Blot W.J., Dong Z.W., Taylor P.R. 2000. *Prospective study of serum selenium levels and incident esophageal and gastric cancers*. J. Natl. Cancer Inst., 92: 1753-1763.

Murzaku E.C., Bronsnick T., Rao B.K. 2014. *Diet in dermatology*. Part II. *Melanoma, chronic urticaria, and psoriasis*. J. Am. Acad. Dermatol., 71(6): 1053.e1-1053.e16. DOI: 10.1016/j.jaad.2014.06.016

Olejnik A., Tomczyk J., Kowalska K., Grajek W. 2010. *The role of natural dietary compounds in colorectal cancer chemoprevention*. Post. Hig. Med. Dośw., 64: 175-187. (in Polish)

Ou, Y., Jiang, B., Wang, X., Ma, W., Guo, J. 2012. *Selenium and colorectal adenomas risk: A meta-analysis*. Nutr. Cancer, 64: 1153-1159. DOI: 10.1080/01635581.2012.722248

Payette M.J., Whalen J., Grant-Kels J.M. 2010. *Nutrition and nonmelanoma skin cancers*. Clin. Dermatol., 28(6):650-62. DOI: 10.1016/j.clindermatol.2010.03.033

Peters U., Takata Y. 2008. *Selenium and the prevention of prostate and colorectal cancer*. Mol. Nutr. Food Res., 52: 1261-1272. DOI: 10.1002/mnfr.200800103

Rayman M.P. 2005. *Selenium in cancer prevention: A review of the evidence and mechanism of action*. Proc. Nutr. Soc., 64(4): 527-542.

Rayman M.P. 2012. *Selenium and human health*. Lancet 379: 1256-1268. DOI: 10.1016/S0140-6736(11)61452-9

Reid M., Stratton M.S., Lillico A.J., Fakih M., Natarajan R., Clark L.C., Marshall J.R. 2004.

*A report of high-dose selenium supplementation: Response and toxicities*. J. Trace Elem. Med. Biol., 18: 69-74. DOI: 10.1016/j.jtemb.2004.03.004

Rohrmann S., Smit E., Giovannucci E., Platz E.A. 2004. *Association between serum concentrations of micronutrients and lower urinary tract symptoms in older men in the Third National Health and Nutrition Examination Survey*. Urology, 64(3):504-509. DOI: 10.1016/j.urology.2004.04.012

Schrauzer G.N., White D.A., Schneider C.J. 1977. *Cancer mortality correlation studies*. III. *Statistical association with dietary selenium intakes*. Bioinorg. Chem., 7: 35-56.

Sobiecki J.G. 2017. *Vegetarianism and colorectal cancer risk in a low-selenium environment: effect modification by selenium status? A possible factor contributing to the null results in British vegetarians*. Eur. J. Nutr., 56(5): 1819-1832. DOI: 10.1007/s00394-016-1364-0

Strzelczyk J.K., Wiczkowski A. 2012. *Oxidative damage and carcinogenesis*. Wspolczesna Onkol., 16(3): 230-233. DOI: 10.5114/wo.2012.29290

Suzana S., Cham B.G., Ahmad Rohi G., Mohd Rizal R., Fairulnizal M.N., Normah H., Fatimah A. 2009. *Relationship between selenium and breast cancer: A case-control study in the Klang Valley*. Singapore Med. J., 50(3): 265-269.

Suzuki M., Endo M., Shinohara F., Echigo S., Rikiishi H. 2010. *Differential apoptotic response of human cancer cells to organoselenium compounds*. Cancer Chemother. Pharmacol., 66(3): 475-484.

Takata Y., Kristal A.R., King I.B., Song X., Diamond A.M., Foster C.B., Hutter C.M., Hsu L., Duggan D.J., Langer R.D., Petrovitch H., Shikany J.M., Vaughan T.L., Lampe J.W., Prentice R.L., Peters U. 2011. *Serum selenium, genetic variation in selenoenzymes, and risk of colorectal cancer: primary analysis from the Women's Health Initiative Observational Study and meta-analysis*. Cancer Epidemiol. Biomarkers Prev., 20(9):1822-1830. DOI: 10.1158/1055-9965.EPI-11-0364

Tapiero H., Townsend D.M., Tew K.D. 2003. *The antioxidant role of selenium and seleno-compounds*. Biomed. Pharmacother., 57(3-4): 134-144.

Traynor N.J., McKenzie R.C., Beckett G.J., Gibbs N.K. 2006. *Selenomethionine inhibits ultraviolet radiation-induced p53 transactivation*. Photodermatol. Photoimmunol. Photomed., 22:297-303. DOI: 10.1111/j.1600-0781.2006.00256.x

van den Brandt P.A, Zeegers M.P, Bode P., Goldbohm R.A. 2003. *Toenail selenium levels and the subsequent risk of prostate cancer: A prospective cohort study*. Cancer Epidemiol. Biomarkers Prev., 12: 866-871.

van der Pols J.C., Heinen M.M., Hughes M.C., Ibiebele T.I., Marks G.C., Green A.C. 2009. *Serum antioxidants and skin cancer risk: An 8-year community-based follow-up study*. Cancer Epidemiol. Biomarkers Prev., 18(4): 1167-73. DOI: 10.1158/1055-9965.EPI-08-1211

Varlamova E.G., Cheremushkina I.V. 2017. *Contribution of mammalian selenocysteine-containing proteins to carcinogenesis*. J. Trace Elem. Med Biol., 39:76-85. DOI: 10.1016/j.jtemb.2016.08.004

Vinceti M., Dennert G., Crespi C.M., Zwahlen M., Brinkman M., Zeegers M.P.A., Horneber M., D'Amico R., Del Giovane C. 2014. *Selenium for preventing cancer*. Cochrane Database Syst. Rev., 3: CD005195. DOI: 10.1002/14651858.CD005195.pub3

Vinceti M., Filippini T., Cilloni S., Bargellini A., Vergoni A.V., Tsatsakis A., Ferrante M. 2017. *Health risk assessment of environmental selenium: Emerging evidence and challenges (*review*)*. Mol. Med. Rep., 15(5): 3323-3335. DOI: 10.3892/mmr.2017.6377

Waters D.J., Chiang E.C., Cooley D.M., Morris J.S. 2004. *Making sense of sex and supplements: Differences in the anticarcinogenic effects of selenium in men and women*. Mutation Res., 551: 91-107. DOI: 10.1016/j.mrfmmm.2004.02.019

Wei W.Q., Abnet C.C., Qiao Y.L., Dawsey S.M., Dong Z.W., Sun X.D., Fan J.H., Gunter E.W., Taylor P.R., Mark S.D. 2004. *Prospective study of serum selenium concentrations and*

*esophageal and gastric cardia cancer, heart disease, stroke, and total death*. Am. J. Clin. Nutr., 79: 80-85.

Zabłocka K, Biernat J. 2010. *The influence of selected nutritional components in lung cancer risk - unsaturated fatty acids, isothiocyanates, selenium*. Wspolczesna Onkol., 14(1): 54-58. (in Polish) https://doi.org/10.5114/wo.2010.979

Zeegers M.P, Goldbohm R.A, Bode P., van den Brandt P.A. 2002. *Prediagnostic toenail selenium and risk of bladder cancer*. Cancer Epidemiol. Biomarkers Prev., 11: 1292-1297.

Zhuo H., Smith A.H., Steinmaus C. 2004. *Selenium and lung cancer: a quantitative analysis of heterogeneity the current epidemiological literature*. Cancer Epidemiol. Biomarkers Prev., 13: 771-778.