Selenium Deficiency and Thyroid Cancer

Subjects: Oncology

Contributor: Latifa Sarra Kazi Tani , Nouria Dennouni-Medjati , Benoit Toubhans , Laurent Charlet , kazi tani sarra latifa

Selenium (Se) is an essential micronutrient present in all tissues of the human body. It is incorporated into selenoproteins as selenocysteine (Se-Cys), the 21st amino acid. Se is present in high concentration in thyroid and plays an important role in the elimination of reactive oxygen species (ROS), and hydrogen peroxide produced during the iodination of thyroid hormones. Therefore, a fluctuation in its level could affect the expression of antioxidant selenoproteins. Indeed, Se deficiency in various diseases, including cancer, could be related to a high level of free radicals caused by oxidative stress.

The relationship between Se and cancer risk is not fully understood and still debated worldwide. Most studies indicate a low Se levels in the patients with thyroid cancer. However, some selenoproteins have been reported to fight tumor cell growth, while others support it, highlighting the fact that the role of Se in the mechanisms of thyroid tumor carcinogenesis is far from clear.

Selenium deficiency selenoproteins cancer

1. Introduction

Selenium (Se) is an essential trace element for human body. It is required at all stages of embryological development of the thyroid gland [1][2]. In humans, Se is integrated into 25 selenoproteins in the form of the amino acid Se-Cys. Some of them such as glutathione peroxidases (GPx), iodothyronine deiodinases (DIO) and thioredoxine reductases (TRx) play an important role in the metabolism of the thyroid gland [3] and are essential for biosynthesis of thyroid hormones [4]. Se is present at higher concentrations in thyroid than in other organs and it is considered to be the second most important element in thyroid metabolism after iodine [5]. Deficiency of Se can aggravate the abnormalities induced by iodine deficiency [6]. Hence, the influence of Se on thyroid function is closely related to the state of iodine.

2. Selenoproteins of thyroid gland

During biosynthesis of thyroid hormones, high concentrations of hydrogen peroxide (H_2O_2) are generated in order to oxidize iodide (I^-). The iodination of tyrosyl residues on thyroglobulin give rise to the iodine-containing thyroid hormones; thyroxine (T4) and triiodothyronine (T3) [7]. The DIO selenoprotein family plays an important role in activation or inactivation of thyroid hormones [8]. Excess H_2O_2 could be a major source of free radicals and reactive oxygen species (ROS). These molecules can significantly damage the cell and DNA. Indeed, a greater amount of DNA modified by oxidation was observed in follicular cells of the thyroid compared to the spleen, lung

and liver [9]. The role of the GPx and TRx families is to reduce H_2O_2 and organic hydroperoxides to protect cells from the effects of ROS [10].

Others selenoproteins are involved in the function of thyroid gland including Selenoprotein P (SePP), Selenoprotein S and K provide quality control in endoplasmic reticulum [10]. Table 1 summarizes the main functions of selenoproteins in thyroid gland.

Table 1. Main selenoproteins in thyroid and their functions.

Selenoproteines	Localization	Functions	References
Deiodinases (DIO)			[8]
DIO1	Liver, kidney, thyroid gland, lung, eyes, pituitary, CNS	Conversion of T4 into T3and rT3 and T3 into rT3 or T2	
DIO2	Thyroid gland, pituitary gland, skeletal, heart muscles , brain, fat tissue, spinal cord, placenta	Conversion of T4 into T3 and of rT3 into T2	
DIO3	Gravid uterus, placenta, fetus liver, fetal and neonatal brain, skin	Conversion of T4 into T3 and of rT3 into T2	
Gluthatione peroxidases (GPx)			[10][11]

GPx1	Cytoplasm, ubiquitous	Cytosol antioxidant	
GPx3	Plasma and thyroid follicle	Plasma and extracellular antioxidant	
GPx4	Mitochondrial membrane	Membrane antioxidant	
Thioredoxin reductase (TRx)			[10][12]
TRx1	Principally cytosolic, ubiquitous	Inhibition of apoptosis, redox state of transcription factors	
TRx2	Mitochondrial, ubiquitous	Reduce basal oxidative stress,	
TRx3	Principally mitochondrial, ubiquitous	Regulation of apoptosis and signaling pathway	
Selenoprotein P (SePP)	Blood and thyroid	Transportation of selenium and storage, endothelial antioxidant	[13]

DIO = iodothyronine deiodinase, T2 = diiodothyronine, T3 = triiodothyronine, rT3 = reverse T3, T4 = thyroxine, GPx = glutathione peroxydase, TRx = Thioredoxin reductase, SePP = selenoprotein P.

3. Selenium and Thyroid Cancer

Thyroid cancer is the most common endocrine tumor, responsible for more than half a million new cases per year, ranking 9th place in cancers prevalence worldwide [14][15]. It remains rare in children and adolescent, the median age of diagnostic is 45 to 50 years old [16], it is diagnosed three times more often in women than in men [17]. Thyroid cancer includes three main types of tumors: medullary thyroid carcinoma, anaplastic thyroid carcinoma and differentiated thyroid carcinoma [18]. Differentiated carcinoma alone accounts for about 90% of thyroid cancers. It is derived from the follicular cells of the thyroid, which are responsible for the production of thyroid hormones [17].

The relationship between Se status and cancer has been debated for a long time. Observational studies and randomized controlled trials have shown conflicting results. In a meta-analysis and meta-regression conducted by Cai et al. [19], the results were in favor of a significant association between Se and cancer. High Se exposure may reduce risk of cancer, especially those of: lung, breast, esophagus, stomach and prostate [19]**.** On the other hand, Vinceti et al. [20] and Jablonska and Vinceti [21] published a review that reports the results of various trials suggesting dramatic effects of Se on cancer development.

The Selenium and Vitamin E Cancer Prevention Trial (SELECT) is one of the largest intervention studies, launched in 2001 and involving more than 32,000 American males. The trial investigated the effect of vitamin E and/or L-selenomethionine supplementations, primarily against the development of prostate cancer and other type of cancers, that is, colorectal cancer, lung cancer and bladder cancer [22]. The results of SELECT showed an increase in prostate cancer risk for patients supplemented with the highest Se levels [23]. However, the results of this study should be interpreted taking into account certain limitations. The possibility that the supplements given to men exceeded the adequate doses to prevent prostate cancer and on the other hand, men selected were characterized by a relatively high baseline selenium status, which suggests that selenium only reduces the risk of prostate cancer in selenium-deficient men and not in the general population [22].This may explain why certain clinical trials have not shown any side effects in cancer patients after intravenous administration of sodium selenite [24].

In a review of Murdolo et al., different information was collected to explain the divergence concerning the role of Se in the pathophysiology of cancer [25]. First: the effects of Se may be more effective against the progression of cancer, at advanced stages of the disease rather than at early stages. Its role could therefore be more important in preventing cancer progression than in its development. Second: the effects of Se are observed at concentrations lower or higher than the required concentrations to optimize selenoprotein activities especially GPx and SePP. The effects of selenium status on cancer show a U-shape curve. Third: genetic variability could also be of importance. Several single nucleotide polymorphisms (SNP) of certain selenoprotein genes have been linked to different types of cancer.

Most studies indicate low Se levels in the patients with thyroid cancer. Se deficiency in various diseases, including cancer, could be related to a high level of free radicals caused by oxidative stress [17]. Significant increase in production of ROS is observed in thyroid tumor tissue samples vs. healthy tissue [9][26]. Se is present in high concentrations in the thyroid and plays an important role in the elimination of ROS. Therefore, a fluctuation in its level could affect the expression of antioxidant selenoproteins, sensitive to the intake of Se in the thyroid (GPx1 and GPx3). In the review by Olivera et al., studies corroborate the reduction in the activity of selenoproteins in thyroid cancer, in case of Se deficiency [17].

In primary papillary thyroid carcinoma (PTC) samples, reduced or even absent expression of GPx3 has been found in patients and it has been correlated with lymph node metastasis and increased tumor size [27]. In thyroid cancer cell lines TPC-1 and FTC133, GPx3 could inhibit Wnt/β-catenin signaling and thereby suppress metastasis of thyroid cancer [27]. The anticarcinogenic effect of Se during the initiation phase of tumor development is the increased expression of antioxidant selenoproteins. Numerous cohort studies have shown that individuals with plasma selenium levels below 100–120 µg/L might benefit by increasing their selenium intake. This concentration is the amount needed to reach a plateau in SePP level and beyond, an increase of selenium concentrations no longer provides protective effects on the development of cancer [14].

In cancer cells, abnormal redox regulation is observed at different stage of tumor progression [24]. Tumor cells require antioxidant molecules such as selenoproteins to maintain the redox balance [14]. The expression of antioxidant proteins increases in many types of cancer and decreases in others [24]. Indeed, tumor cells present major differences in their selenoprotein expression pattern such as the GPx gene [14]. In colorectal cancer, 15 selenoprotein genes were analyzed in two cohorts. Both selenoproteins TRx3 and GPx2 were upregulated in adenoma and carcinoma, while SePP and selenoprotein S were down regulated [28]. The increased gene expression of GPx2 and TRx3 can be explained by the fact that both are target genes for Wnt signaling. This signaling pathway is activated in most colorectal cancer tissues [29]. However, there are not many studies regarding the overall changes in selenoprotein genes in thyroid cancer. Selenoproteins GPx1 and TRx1 in thyroid cancer tissue are lower in patients versus controls, while DIO3 mRNA levels and activity were increased in PTC [30][31]. This increase in DIO3 mRNA levels was correlated with distant metastasis or lymph nodes. Thus, it appears that some selenoproteins fight the growth of tumor cells, while others support it, which underlines the fact that the carcinogenesis mechanisms linked to the Se status are far from being elucidated [31].

Experiments have suggested that selenoproteins can act to modulate the susceptibility of the malignancy by acting on tumor suppressor gene pathways. It has been observed in breast and prostate cancer that selenoproteins carry on, for example, control in the checkpoint kinase-2 (CHEK2) gene, a suppressor tumor gene which is involved in the signal transduction in cellular response to DNA damage who is associated with thyroid malignancy [32]. Different mutations in the tumor suppressor gene CHEK2, such as 1100delC, IVS2 1 1G > A, del5395 and I157T, are associated with multi-organ cancers including breast and papillary thyroid cancer [33]. In addition, Se could act as an anti-mutagenic agent with toxicity against cancer cells [34]. Se acts by inducing cell death by production of superoxide radicals thus triggering the mitochondrial pathway of apoptosis, while sparing healthy cells [34]. It is clear that Se has anticarcinogenic properties, linked to its valence states. Selenite has the

capacity to intervene in redox reactions, while selenate is completely devoid of this ability [35]. It is reported in a review by Kieliszek et al. that only selenite ions react with the –SH groups of proteins and prevent the formation of protein polymers rich in disulfides [35]. Indeed, a barrier made up of blood proteins with fibrin properties, protects the membranes of cancer cells from recognition by the immune system. Sodium selenite inhibits the protein disulfide exchange on the surface of cancer cell membranes and thus makes the tumor sensitive to the destructive activity of phagocytic cells [35].

Selenium supplementation has positive results in autoimmune thyroid disease and may improve thyroid cancer outcome, however the results are not conclusive in the majority of cases [17]. The question that remains is whether a deficiency in this micronutrient is a consequence of thyroid cancer or a risk factor. The example of hypoxia, which can influence selenoproteins biosynthesis, the expression of SePP is reduced noting a decrease in the distribution of Se by hepatocytes causing a general decline in selenoproteins expression [36][37][38]

To conclude, several studies have highlighted a Se deficiency in thyroid cancer patients. However, in the lack of evidence to this relationship, many studies are needed to confirm and to explain this hypothesis.

4. Conclusion

More than two centuries after the discovery of the trace element selenium, the roles of this mineral in human health and disease have not been fully elucidated. The relationship between Se status and cancer has been debated for a long time and the results of epidemiological studies are contradictory. In thyroid cancer, most studies indicate a significant association between Se deficiency and the risk of this cancer. However, recent studies have shown that certain selenoproteins fight the growth of tumor cells, while others support it, which underlines the fact that the carcinogenesis mechanisms linked to Se status are not completely understood in thyroid cancer. Different approaches are still needed to clarify the link between Se status and thyroid cancer; genetic association studies, large-scale population-based studies and other omics-based analysis.

References

1. [1] A. Valea et C. E. Georgescu, « Selenoproteins in human body: focus on thyroid pathophysiology », Hormones, vol. 17, no 2, p. 183-196, juin 2018, doi: 10.1007/s42000-018-0033-5.
2. [2] K. Lacka et A. Szeliga, « Significance of selenium in thyroid physiology and pathology », Pol. Merkur. Lekarski, vol. 38, no 228, p. 348-353, juin 2015.
3. [3] L. H. Duntas et S. Benvenga, « Selenium: an element for life », Endocrine, vol. 48, no 3, p. 756-775, avr. 2015, doi: 10.1007/s12020-014-0477-6.

4. [4] J. Köhrle, « The trace element selenium and the thyroid gland », Biochimie, vol. 81, no 5, p. 527-533, mai 1999, doi: 10.1016/S0300-9084(99)80105-9.
5. [5] D. Sakız, A. Kaya, et M. Kulaksizoglu, « Serum Selenium Levels in Euthyroid Nodular Thyroid Diseases », Biol Trace Elem Res, vol. 174, no 1, p. 21-26, nov. 2016, doi: 10.1007/s12011-016-0688-1.
6. [6] J. Köhrle, « Selenium and the thyroid »:, Current Opinion in Endocrinology & Diabetes and Obesity, vol. 22, no 5, p. 392-401, oct. 2015, doi: 10.1097/MED.0000000000000190.
7. [7] S. Mehl et al., « Cross-sectional analysis of trace element status in thyroid disease », Journal of Trace Elements in Medicine and Biology, vol. 58, p. 126430, mars 2020, doi: 10.1016/j.jtemb.2019.126430.
8. [8] A. Orozco, C. Valverde-R, A. Olvera, et C. García-G, « Iodothyronine deiodinases: a functional and evolutionary perspective », Journal of Endocrinology, vol. 215, no 2, p. 207-219, nov. 2012, doi: 10.1530/JOE-12-0258.
9. [9] K. Krohn, J. Maier, et R. Paschke, « Mechanisms of Disease: hydrogen peroxide, DNA damage and mutagenesis in the development of thyroid tumors », Nat Rev Endocrinol, vol. 3, no 10, p. 713-720, oct. 2007, doi: 10.1038/ncpendmet0621.
10. [10] L. Schomburg, « Selenium, selenoproteins and the thyroid gland: interactions in health and disease », Nat Rev Endocrinol, vol. 8, no 3, p. 160-171, mars 2012, doi: 10.1038/nrendo.2011.174.
11. [11] O. M. Guillin, C. Vindry, T. Ohlmann, et L. Chavatte, « Selenium, Selenoproteins and Viral Infection », Nutrients, vol. 11, no 9, p. 2101, sept. 2019, doi: 10.3390/nu11092101.
12. [12] S. Hu et M. P. Rayman, « Multiple Nutritional Factors and the Risk of Hashimoto’s Thyroiditis », Thyroid, vol. 27, no 5, p. 597-610, mai 2017, doi: 10.1089/thy.2016.0635.
13. [13] S. Kurokawa, M. J. Berry « Role of the Essential Metalloid in Health», Met. Ions Life Sci.2013, 13, 499-610.
14. [14] A. P. Kipp, « Selenium in colorectal and differentiated thyroid cancer », Hormones, vol. 19, no 1, p. 41-46, mars 2020, doi: 10.1007/s42000-019-00118-4.
15. [15] J. Ferlay et al., « Cancer incidence and mortality worldwide: Sources, methods and major patterns in GLOBOCAN 2012: Globocan 2012 », Int. J. Cancer, vol. 136, no 5, p. E359-E386, mars 2015, doi: 10.1002/ijc.29210.
16. [16] M. Schlumberger, « Cancer papillaire et folliculaire de la thyroïde », Annales d’Endocrinologie, vol. 68, no 2-3, p. 120-128, juin 2007, doi: 10.1016/j.ando.2007.04.004.
17. [17] M. de Oliveira Maia, B. A. M. Batista, M. P. Sousa, L. M. de Souza, et C. S. C. Maia, « Selenium and thyroid cancer: a systematic review », Nutrition and Cancer, p. 1-9, oct. 2019, doi:

10.1080/01635581.2019.1679194.

18. [18] M. E. Cabanillas, D. G. McFadden, et C. Durante, « Thyroid cancer », The Lancet, vol. 388, no 10061, p. 2783-2795, déc. 2016, doi: 10.1016/S0140-6736(16)30172-6.
19. [19] X. Cai et al., « Selenium Exposure and Cancer Risk: an Updated Meta-analysis and Meta-regression », Sci Rep, vol. 6, no 1, p. 19213, mai 2016, doi: 10.1038/srep19213.
20. [20] M. Vinceti et al., « Health risk assessment of environmental selenium: Emerging evidence and challenges », Molecular Medicine Reports, vol. 15, no 5, p. 3323-3335, mai 2017, doi: 10.3892/mmr.2017.6377.
21. [21] E. Jablonska et M. Vinceti, « Selenium and Human Health: Witnessing a Copernican Revolution? », Journal of Environmental Science and Health, Part C, vol. 33, no 3, p. 328-368, juill. 2015, doi: 10.1080/10590501.2015.1055163.
22. [22] M. Vinceti et al., « Selenium for preventing cancer », Cochrane Database of Systematic Reviews, janv. 2018, doi: 10.1002/14651858.CD005195.pub4.
23. [23] A. R. Kristal et al., « Baseline Selenium Status and Effects of Selenium and Vitamin E Supplementation on Prostate Cancer Risk », JNCI: Journal of the National Cancer Institute, vol. 106, no 3, mars 2014, doi: 10.1093/jnci/djt456.
24. [24] M. Wallenberg, S. Misra, et M. Björnstedt, « Selenium Cytotoxicity in Cancer », Basic Clin Pharmacol Toxicol, vol. 114, no 5, p. 377-386, mai 2014, doi: 10.1111/bcpt.12207.
25. [25] G. Murdolo, D. Bartolini, C. Tortoioli, M. Piroddi, P. Torquato, et F. Galli, « Selenium and Cancer Stem Cells », in Advances in Cancer Research, vol. 136, Elsevier, 2017, p. 235-257.
26. [26] A. K. Baltaci, T. K. Dundar, F. Aksoy, et R. Mogulkoc, « Changes in the Serum Levels of Trace Elements Before and After the Operation in Thyroid Cancer Patients », Biol Trace Elem Res, vol. 175, no 1, p. 57-64, janv. 2017, doi: 10.1007/s12011-016-0768-2.
27. [27] H. Zhao et al., « Silencing GPX3 Expression Promotes Tumor Metastasis in Human Thyroid Cancer », CPPS, vol. 16, no 4, p. 316-321, avr. 2015, doi: 10.2174/1389203716041504291548 40.
28. [28] D. Hughes, T. Kunická, L. Schomburg, V. Liška, N. Swan, et P. Souček, « Expression of Selenoprotein Genes and Association with Selenium Status in Colorectal Adenoma and Colorectal Cancer », Nutrients, vol. 10, no 11, p. 1812, nov. 2018, doi: 10.3390/nu10111812.
29. [29] A. P. Kipp, M. F. Müller, E. M. Göken, S. Deubel, et R. Brigelius-Flohé, « The selenoproteins GPx2, TrxR2 and TrxR3 are regulated by Wnt signalling in the intestinal epithelium », Biochimica et Biophysica Acta (BBA) - General Subjects, vol. 1820, no 10, p. 1588-1596, oct. 2012, doi: 10.1016/j.bbagen.2012.05.016.
30. [30] A. Metere et al., « A possible role for selenoprotein glutathione peroxidase (GPx1) and thioredoxin reductases (TrxR1) in thyroid cancer: our experience in thyroid surgery », Cancer Cell

Int, vol. 18, no 1, p. 7, déc. 2018, doi: 10.1186/s12935-018-0504-4.

31. [31] M. Romitti et al., « Increased Type 3 Deiodinase Expression in Papillary Thyroid Carcinoma », Thyroid, vol. 22, no 9, p. 897-904, sept. 2012, doi: 10.1089/thy.2012.0031.
32. [32] S. Gupta, K. Jaworska-Bieniek, J. Lubinski, et A. Jakubowska, « Can selenium be a modifier of cancer risk in CHEK2 mutation carriers? », Mutagenesis, vol. 28, no 6, p. 625-629, nov. 2013, doi: 10.1093/mutage/get050.
33. [33] M. Siołek et al., « CHEK 2 mutations and the risk of papillary thyroid cancer: Genetic association between thyroid and breast cancer », Int. J. Cancer, vol. 137, no 3, p. 548-552, août 2015, doi: 10.1002/ijc.29426.
34. [34] C. M. Weekley et al., « Selenite-mediated production of superoxide radical anions in A549 cancer cells is accompanied by a selective increase in SOD1 concentration, enhanced apoptosis and Se–Cu bonding », J Biol Inorg Chem, vol. 19, no 6, p. 813-828, août 2014, doi: 10.1007/s00775-014-1113-x.
35. [35] M. Kieliszek, B. Lipinski, et S. Błażejak, « Application of Sodium Selenite in the Prevention and Treatment of Cancers », Cells, vol. 6, no 4, p. 39, oct. 2017, doi: 10.3390/cells6040039.
36. [36] N.-P. Becker et al., « Hypoxia reduces and redirects selenoprotein biosynthesis », Metallomics, vol. 6, no 5, p. 1079-1086, 2014, doi: 10.1039/C4MT00004H.
37. [37] I. Dreher, T. C. Jakobs, et J. Köhrle, « Cloning and Characterization of the Human Selenoprotein P Promoter: RESPONSE OF SELENOPROTEIN P EXPRESSION TO CYTOKINES IN LIVER CELLS », J. Biol. Chem., vol. 272, no 46, p. 29364-29371, nov. 1997, doi: 10.1074/jbc.272.46.29364.
38. [38] K. Renko et al., « Down-regulation of the hepatic selenoprotein biosynthesis machinery impairs selenium metabolism during the acute phase response in mice », FASEB j., vol. 23, no 6, p. 1758-1765, juin 2009, doi: 10.1096/fj.08-119370.