Updates on clinical studies of selenium supplementation in radiotherapy

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Abstract
To establish guidelines for the selenium supplementation in radiotherapy we assessed the benefits and risks of selenium supplementation in radiotherapy. Clinical studies on the use of selenium in radiotherapy were searched in the PubMed electronic database in January 2013. Sixteen clinical studies were identified among the 167 articles selected in the initial search. Ten articles were observational studies, and the other 6 articles reported studies on the effects of selenium supplementation in patients with cancer who underwent radiotherapy. The studies were conducted worldwide including European, American and Asian countries between 1987 and 2012. Plasma, serum or whole blood selenium levels were common parameters used to assess the effects of radiotherapy and the selenium supplementation status. Selenium supplementation improved the general conditions of the patients, improved their quality of life and reduced the side effects of radiotherapy. At the dose of selenium used in these studies (200–500 μg/day), selenium supplementation did not reduce the effectiveness of radiotherapy, and no toxicities were reported. Selenium supplementation may offer specific benefits for several types of cancer patients who undergo radiotherapy. Because high-dose selenium and long-term supplementation may be unsafe due to selenium toxicity, more evidence-based information and additional research are needed to ensure the therapeutic benefits of selenium supplementation.

Keywords: Selenium, Supplementation, Clinical studies, Radiotherapy

Introduction
Radiotherapy is one of the most common and effective treatments for cancer [1]. Radiation damages cancer cells by direct ionization of DNA and by indirect effects caused by reactive oxygen species (ROS) [2]. Ionizing radiation consists of electromagnetic radiations, including X-rays and gamma rays, and particulate radiation such as electrons, protons and neutrons [2]. Exposure to ionizing radiation produces ROS in the tissue environment; including hydroxyl radicals (the most damaging), superoxide anion radicals and other oxidants such as hydrogen peroxide [2]. Although radiotherapy is effective in killing cancer cells, ROS produced in radiotherapy may threaten the integrity and survival of the surrounding normal cells and may cause late side effects of radiotherapy [1-3]. The administration of radioprotective agents, which are supposed to scavenge radiation-induced radicals and reduce the effects of radiation at an early stage, has been suggested as one approach for prophylaxis of radiation effects in normal tissues [4,5].

Selenium, a trace element, is an essential nutrient of fundamental importance in human biology [6] and as a preventive approach to ROS detoxification, which activates and stimulates the endogenous system [4,7,8]. Some of the most fundamental cellular processes, such as DNA synthesis, depend on the presence of selenium within the catalytic site of thioredoxin reductases (TrxR) [9,10]. A moderate deficiency of selenium has been linked to many conditions, such as an increased risk of cancer, infections and male infertility; a decrease in immune and thyroid function; and several neurological conditions [6,9]. A review paper reported that in prospective studies published in the 1980s and early 1990s involving 8,000 to 11,000 individuals, low selenium status was associated with significantly increased risks of cancer incidence and mortality [6].

A number of mechanisms have been suggested to explain the anti-cancer effects of selenium [11]. Selenium
in selenoproteins can reduce oxidative damage and can limit DNA damage, both of which are linked to cancer risk [11]. Other cellular processes and molecular pathways that may be involved in the anti-cancer effects of selenium are the induction of phase II conjugating enzymes that detoxify carcinogens, enhancement of the immune response, an increase in tumor-suppressor protein p53, inactivation of protein kinase C (PKC), alterations in DNA methylation, blockage of the cell cycle to allow DNA repair, induction of apoptosis in cancer cells and inhibition of angiogenesis [11]. In survey studies, selenium has been reported as a complementary alternative medicine (CAM) used in lung and prostate cancer patients undergoing radiotherapy [12,13].

However, there are no guidelines on selenium supplementation in radiotherapy which should consist of inclusion and exclusion criteria for selenium supplementation, applicable cancer types, dose of supplementation, chemical form of selenium, duration of supplementation and the possible side effects of supplementation in radiotherapy. First, however, the benefits and risks of selenium use in radiotherapy should be clarified, as such information is still insufficient. Tabassum et al. [14] summarized the protective effect of selenium against prostate cancer and Fritz et al. [15] reviewed the relationship between selenium and lung cancer, suggesting positive effects of selenium in radiotherapy. Dennert and Horneber reviewed two clinical trials published in 2006 as a Cochrane database systematic review, and the review was revised in 2011 with the addition of one trial [16]. The subjects in the Cochrane database systematic reviews were limited to those included in randomized controlled trials; therefore, only 3 studies were reviewed, yielding no clear evidence that selenium supplements improve the side effects of cancer therapy [16]. In this paper, we summarized the clinical studies on selenium and radiotherapy to provide evidence-based information on the benefits and risks of selenium supplementation to aid in the establishment of guidelines for selenium supplementation in radiotherapy.

**Methodology**

The flowchart of our literature search is shown in Figure 1. Briefly, a PubMed electronic database search using medical subject headings (MeSH) terms and the keywords “selenium”, “radiation” and “therapy” in January 2013 yielded 167 articles, 16 of which were clinical studies on selenium and radiotherapy. The detailed keyword search was as follows: “selenium” [MeSH Terms] OR “selenium” [All Fields] AND (“radiotherapy” [Subheading] OR “radiotherapy” [All Fields] OR (“radiation” [All Fields] AND “therapy” [All Fields]) OR “radiation therapy” [All Fields] OR “radiotherapy” [MeSH Terms] OR (“radiation” [All Fields] AND “therapy” [All Fields]) OR “radiation therapy” [All Fields]).

**Clinical studies on selenium and radiotherapy**

Table 1 lists the 16 articles on selenium and radiotherapy in clinical studies. The studies were conducted worldwide, including European, American and Asian countries, between 1987 and 2012. A total of 1303 patients undergoing radiotherapy participated in the studies. Of the 16 articles, 10 articles were observational studies investigating patients’ selenium levels before, during and/or after radiotherapy, while the other 6 articles investigated the effects of selenium supplementation studies on cancer patients who underwent radiotherapy. The cancer types investigated were upper gastrointestinal, breast, lung, larynx, head and neck, non-Hodgkin lymphoma, brain, oral, prostate and gynecological cancers.
Among the 16 articles, only 7 articles mentioned the types of radiotherapy delivered to the patients, and in most cases, electromagnetic radiations was used.

**Observational studies**

Table 2 presents the observational studies investigating the selenium levels in patients who underwent radiotherapy without selenium supplementation. In addition to the 10 observational studies, 2 studies assessed selenium levels in patients who did not received selenium supplementation, who served as a placebo group and control group in the selenium supplementation studies. Thus, a total of 12 studies measured the selenium levels in patients who underwent radiotherapy without selenium supplementation.

**Selenium levels** Selenium levels were determined in the plasma, serum or whole blood using atomic absorption spectrometry (AAS) in 9 studies, inductively coupled plasma mass spectrometry (ICP-MS) in 2 studies and a fluorometric method in 1 study. The measurements were performed before radiotherapy, during radiotherapy, at the end of therapy and at specific time points.
Effect of radiotherapy on selenium levels

The results of selenium levels in patients who underwent radiotherapy without supplementation demonstrated that selenium levels had a tendency to decrease after radiotherapy. In 7 studies (study No. 2, 4, 5, 7, 10, 12, and 15), the selenium levels were not significantly different before and after therapy, but in 3 studies (study No. 1, 8, and 9), the selenium levels after therapy were significantly lower than those before therapy.

Effect of selenium supplementation on selenium levels

Table 3 shows the selenium levels in the patients who underwent radiotherapy with selenium supplementation.

Table 2 Observational studies investigating the selenium levels in patients who underwent radiotherapy without selenium supplementation

| Study no. | Reference | Sample | Measurement method | Mean selenium levels (μg/l) |
|-----------|-----------|--------|--------------------|---------------------------|
| 1         | Pothier et al. [17] | Plasma | AAS (at stable stage) | 61.8↓ |
| 2         | Antila et al. [18] | Serum | AAS | 130.7* Middle of therapy 124.4* 128.3* 2 weeks 126.7* 2 months 121.2* |
| 3         | Piccinini et al. [19] | Plasma | Fluorometric method | Breast cancer: 71.81 Lung cancer: 69.59 |
| 4         | Rostkowska-Nadolska et al. [20] | Serum | AAS | 253.8** |
| 5         | Yadav et al. [21] | Serum | AAS | 62.7 - - 61.0 1 year Cured: 91.5 Residual disease: 61.8 |
| 6         | Last et al. [22] | Serum | ICP-MS | 72.44* |
| 7         | Fraunholz et al. [23] | Whole blood | AAS | 75.64 - - 75.88 6 weeks 81.28 |
| 8         | Franca et al. [24] | Plasma | AAS | ≤60 years: 101.8 - - ≤60 years: 58.1↓ >60 years: 65.2 >60 years: 33.7↓ |
| 9         | Zeng YC et al. [25] | Whole blood | AAS | 90.4 - - 56.3↓ - - |
| 10        | Eroglu C et al. [26] | Serum | ICP-MS | 58.09 - - 56.34 - - |
| 12        | Kiremidjian-Schumacher et al. [28] | Plasma (placebo group) | Graphite-furnace AAS | 94.38 - - 88.73 8 weeks: 91.8 |
| 15        | Muecke et al. [31] | Whole blood (control group) | AAS | 63.2 50% of therapy 67.3 61.4 6 weeks 69 |

*1 μmol/l = 1 μg/l x 0.0127 [33].
**1 ppm = 1,000 μg/l.

Table 3 Selenium levels in patients who underwent radiotherapy with selenium supplementation

| Study no. | Reference | Sample | Measurement method | Mean selenium levels (μg/L) |
|-----------|-----------|--------|--------------------|---------------------------|
| 9         | Pakdaman, [27] | Not mentioned | Not mentioned | 63 - - 120↑ - - |
| 12        | Kiremidjian-Schumacher et al. [28] | Plasma | Graphite-furnace AAS | 91.29 - - 88.73 8 weeks (without supplementation) |
| 15        | Muecke et al. [31] | Whole blood | AAS | 65.3 50% of therapy 93.2↑ 90.9↑ 6 weeks (without supplementation) 73.2 |

† = significant decrease.

Puspitasari et al. Radiation Oncology 2014, 9:125
http://www.ro-journal.com/content/9/1/125

Page 4 of 9
The selenium levels in patients who received selenium supplementation had a tendency to increase after radiotherapy. However, the selenium levels decreased again at 8 weeks (study No.12) and 6 weeks (study No.15) after the completion of radiotherapy without selenium supplementation.

**Selenium supplementation studies**

Table 4 provides a summary of selenium supplementation studies. The selenium supplementation studies in patients who underwent radiotherapy were conducted from 1998 to 2010. Different types of studies were conducted, including a randomized double-blind placebo-controlled study (study No. 12), a multicenter phase 3 trial (study No. 15), and a randomized phase 2 study (study No.16).

**Therapeutic form of selenium, dose and administration**

All of the studies used sodium selenite as the form of selenium for supplementation. Sodium selenite was administered orally in most studies (study No. 12–16) and in physiological saline in another report. The dose of supplementation by oral administration ranged from 200 to 500 μg daily, or 1,000 μg daily by infusion in physiological saline.

**Parameters observed or measured**

To assess the effectiveness of selenium supplementation in radiotherapy, the parameters measured or observed in the studies were selenium levels in the serum, plasma or whole blood; mineral elements in the blood and other blood parameters (aspartate amino transferase (AST), alanine amino transferase (ALT), gamma glutamyl transeptidase (γ-GTP) and erythrocyte sedimentation rate (ESR)) [27]; immune function [28]; quality of life [29]; enzymatic and non-enzymatic antioxidants [30]; and side effects [31,32].

**Effects of selenium supplementation on therapy**

Most of the studies revealed positive effects of selenium supplementation on the general condition of the patients and their quality of life. The effects of supplementation were different depending on cancer type. No reduction in effectiveness of radiotherapy [31] and no selenium toxicities or complications were reported in any of the supplementation studies.

Pakdaman (study No.11) reported that treatment with sodium selenite in patients with brain tumors was well tolerated by all patients and increased blood selenium levels [27]. A significant diminution of symptoms of intracranial pressure was achieved in 76% of patients after sodium selenite treatment [27]. In the study by Kiremidjian-Schumacher et al. (study No. 12), sodium selenite treatment was shown to significantly enhance cell-mediated immune responsiveness in head and neck cancer patients [28]. This outcome related to the ability of selenium to enhance the expression of both the α- (p55) and β- (p70/75) subunits of the interleukin-2 receptor (IL2-R), which resulted in a greater number of high-affinity IL2-R/cells and enhanced proliferation and differentiation in cytotoxic effector cells [28,34,35].

Miecke et al. (study No. 13) demonstrated, using the visual analogue scale, that the self-assessment of the quality of life of patients suffering from head and neck cancer with lymphedema significantly improved after selenium supplementation [29].

Elanga et al. (study No. 14) found that supplementation with selenium in oral cancer patients for 6 months may help to increase the enzymatic (superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx), Glutathione reductase (GRx), Glucose-6-phosphate dehydrogenase (G6PDH)) and non-enzymatic (glutathione (GSH), vitamin E, vitamin C, vitamin A and ceruloplasmin) defense systems. The mechanism of the increase in the activity of the enzymatic defense system is due to increased GPx synthesis as a result of the enhanced de novo synthesis of this enzyme in the erythroid precursors of red blood cells [30].

Muecke et al. (study No. 15) reported that selenium supplementation in cervical and uterine cancer patients yielded significant prevention of diarrhea and thus improved the quality of life [31]. The increased activity of the protective intestinal GPx isoenzymes may be responsible for these effects due to the enhanced neutralization of radiation-induced hydroperoxides and free radicals in the small intestinal mucosa included in the radiation volume [31]. In the study by Büntzel et al. (study No.16) selenium supplementation reduced the radiation-associated side-effects of dysphagia developments in patients with head and neck cancer patients [32].

**Parameters used to assess the effect of radiotherapy on selenium status**

We found that the plasma, serum or whole blood selenium levels were common parameters used to assess the effect of radiotherapy on selenium status and the effectiveness of selenium supplementation. Selenium levels had a tendency to decrease after radiotherapy and to increase with selenium supplementation. The mechanism of this decrease is still unclear [24,25]. Pothier et al. suggested that poor dietary intake due to anorexia, nausea, and obstruction, compounded by selenium loss from vomiting, diarrhea, and malabsorption, probably played a role in the decrease [17]. Radiotherapy and chemotherapy, combined with the suboptimal nutrition of cancer patients, may further aggravate the selenium deficiency [24,31]. Muecke et al. highlighted that patients with higher blood selenium levels had a better radiation tolerance, without any effect on the survival data [31]. Therefore,
| Study no. | Reference | Type of cancer/disease | Type of study | Form of Se used for supplementation | Dose (μg) | Administration | Items observed/measured | Result |
|-----------|-----------|------------------------|---------------|-------------------------------------|-----------|----------------|--------------------------|--------|
| 11        | Pakdaman, [27] | Brain tumor | Not mentioned | Sodium selenite | 1000/day (4–8 weeks) | Infusion (during radiotherapy) | Mineral elements, Se and other blood parameters (AST, ALT, γ-GTP, ESR) | A significant diminution of symptoms of intracranial pressure was achieved in 76% of patients. |
| 12        | Kiremidjian-Schumacher et al. [28] | Head and neck cancer | Randomized double-blind placebo-controlled study | Sodium selenite | 200/day (8 weeks) | Oral (during radiotherapy) | Se in plasma, CTL, MLR, PHA | Significantly enhanced cell-mediated immune responsiveness |
| 13        | Micke et al. [29] | Secondary Lymphedema | Not mentioned | Sodium selenite | 500/day (4–6 weeks) | Oral (4 or 10 months after radiotherapy) | Foldi and Miller scoring and quality of life | Foldi and Miller score: more than 78% showed an improvement of one stage or more |
| 14        | Elango et al. [30] | Oral cancer | Not mentioned | Sodium selenite | 400/day (6 months) | Oral (during radiotherapy) | Plasma Se, enzymatic (GPx and others) and non-enzymatic antioxidants | Supplementation increased the enzymatic and non enzymatic defense systems |
| 15        | Muecke et al. [31] | Cervical cancer (n = 11); Uterin cancer (n = 70) | Multicenter, phase 3 trial | Sodium selenite | 500 or 300/day | Oral (during radiotherapy) | Whole blood Se | Statistically significant in reducing the number of episode and severity of RT-induced diarrhea |
| 16        | Buntzel et al. [32] | Head and neck (n = 39) | Randomized phase II study | Sodium selenite | 500 or 300/day | Oral (during radiotherapy) | Side effect evaluation | Reduced the development of dysphagia due to radiotherapy |
Muecke et al. and Franca et al. strongly recommended that physicians take the selenium status into account before prescribing any anticancer therapy to their patients or consider additional supplementation before therapy when the current selenium status appears insufficient [24,31].

**Sodium selenite supplementation**

In the studies reviewed, sodium selenite was the only form of selenium used for supplementation. In nature, selenium exists in many forms. The most well studied forms are selenomethionine (SeMet), sodium selenite, selenium methylselenocysteine, 1,4-phenylenebis (methylene) selenocyanate (p-XSC), and methylseleninic acid (MSA) [15]. Selenomethionine and selenocysteine (SeCys) are found predominantly in foods such as bread, cereals, nuts, meat, fish, and other seafood [36]. In human antioxidant systems, selenium participates in the form of SeCys incorporated into the various selenoproteins [11,15]. There are at least 25 known selenoproteins, including GPx, TrxR, iodothyroninedeiodinase, and the selenoproteins P, W and R [37]. The most abundant selenoproteins in the blood are selenoprotein P, which accounts for approximately 50% of plasma selenium [36,38,39], and GPx, which accounts for 10–30% of plasma selenium [36,39].

Sodium selenite, an inorganic form of selenium, was used for supplementation because it can primarily improve the expression of selenoproteins after specific incorporation as SeCys [31]. Sodium selenite also has high biological activity and availability in the body [28] and is known to easily pass the blood–brain barrier [27]. It does not raise the concentrations of nonspecific selenium-containing proteins (e.g., selenium-albumin), which is in contrast to other widely used organic selenium supplements (e.g., selenomethionine) [31].

**Selenium toxicity**

The Food and Nutrition Board, Institute of Medicine, suggested a recommended dietary allowance (RDA) of selenium for both men and women of 55 μg (0.7 μmol)/day [40]. The tolerable upper intake level (UL) of selenium in adults is set at 400 μg (5.1 μmol)/day based on the adverse effect of selenosis [40]. The results of our review of supplementation studies revealed that selenium supplementation doses ranging from 200–500 μg/day by oral administration was well tolerated by all patients, and no toxicities were reported. Selenium supplementation increased the blood selenium level, improved the general condition of patients, improved quality of life and prevented or reduced the side effects of radiotherapy. Muecke et al. [31] also implied that supplementation with selenium neither interferes with the biological effects of ionizing radiation nor protects tumor cells.

The Nutritional Prevention of Cancer (NPC) trial reported that selenium supplementation in subjects, with histories of non-melanoma skin cancers significantly decreased the incidence of lung cancer in patients with low baseline selenium concentrations, but supplementation did not significantly decrease this incidence among individuals in the overall population [41]. Therefore, selenium supplementation may have benefits if the selenium is administered to patients with low selenium levels.

High-dose selenium and long-term supplementation may be ineffective and unsafe because selenium can be toxic at high concentrations. The NPC trial also reported an association between long-term selenium supplementation and an increased risk of diabetes [42]. A review paper in 2006 [43] revealed that serum selenium levels ranging from 400–30,000 μg/l were associated with acute toxicity and that levels ranging from 500–1,400 μg/l were associated with chronic toxicity (mean normal serum selenium level is 125 μg/l [44]).

Another high-dose selenium case consisting of the use of a liquid dietary supplement containing 200 times the labeled concentration of selenium was reported in the United States [44]. Of the 201 cases identified in 10 states, 1 person was hospitalized. The median estimated dose of selenium consumed was 41,749 μg/day. The frequently reported symptoms included diarrhea (78%), fatigue (75%), hair loss (72%), joint pain (70%), nail discoloration (61%) and nausea (58%). The symptoms persisting 90 days or longer included fingernail discoloration and loss (52%), fatigue (35%), and hair loss (29%) [44].

**Conclusion**

This paper summarized 16 clinical studies on selenium and radiotherapy conducted from 1987 to 2012. The studies included 1303 cancer patients. To assess the selenium status in patients before and after radiotherapy, the plasma, serum or whole blood selenium level was a common parameter used to assess the effect of radiotherapy on selenium status and the effectiveness of selenium supplementation. Selenium supplementation increased the blood selenium level, improved the general condition of patients, improved quality of life, prevented or reduced the side effects of radiotherapy and did not reduce the effectiveness of radiotherapy or cause any toxicity.

The results of our summary suggest that selenium supplementation in the form of sodium selenite at doses ranging from 200–500 μg daily by oral administration may offer benefits for head and neck cancer; head and neck cancer with lymphedema; and oral, cervical and uterine cancer patients who undergo radiotherapy and have low selenium levels. In the future, further research and additional evidence of the benefits of selenium supplementation in patients during radiotherapy are required to clarify optimal dosing strategies in specific types of cancer and the associated risks, to ensure therapeutic efficacy before it can be recommended for broad clinical use.
Abbreviations
ROS: Reactive oxygen species; TrxR: Thioredoxin reductase; PKC: Protein kinase C; CAM: Complementary alternative medicine; MeSH: Medical subject headings; AAS: Absorption spectrometry; ICP-MS: Inductively coupled plasma mass spectrometry; AST: Aspartate amino transferase; ALT: Alanine amino transferase; γ-GTP: Gamma glutamyl transpeptidase; ESR: Erythrocyte sedimentation rate; IL-2R: Interleukin-2 receptor; SOD: Superoxide dismutase; CAT: Catalase; G6PDH: Glucose-6-phosphate dehydrogenase; GSH: Glutathione; SeMet: Selenomethionine; p-XSC: 1,4-phenylenebis (methylene) selenocyanate; MSA: Methylseleninic acid; SeCys: Selenocysteine; NDA: Recommended dietary allowance; UL: Upper intake level; NPC: Nutritional prevention of cancer.

Competing interests
The authors have no competing interests to declare.

Authors’ contributions
IMP, TN and HK were responsible for supervising the study. All authors participated in the drafting SK were responsible for articles collections and analysis. TN and HK were responsible for the study design. IMP, RA, CY and Puspitasari were responsible for the article. IMP, TA, CY and Puspitasari were responsible for the article.

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References
1. Shiraz A, Ghobadi G, Ghazi-Khansari M: A radiobiological review on selenium: a novel radioprotector. J Radiat Res 2007, 48:263–272.
2. Borek C: Antioxidants and radiation therapy. J Nutr 2004, 134:3207–3209.
3. Bentzen SM: From selenium to selenoproteins: Enzymatic and non-enzymatic antioxidative mechanisms in cells and tissue. Strahlenther Onkol 2006, 182:693–695.
4. Weiss JF, Landauer MR: Radioprotection by antioxidants. Annu N Y Acad Sci 2000, 908:46–66.
5. Rayman MP: The importance of selenium to human health. Lancet 2000, 356:233–241.
6. Persson L, Engqvist LK, Hansson R, Sillanaukee P, Stahelin HB: Selenium and cancer: Evidence from epidemiological studies. Am J Clin Nutr 1992, 55:1141–1151.
7. Rayman MP: Selenium in the treatment of radiation-associated secondary lymphedema. J Cancer Res Clin Oncol 2007, 133:187–196.
8. Rayman MP: Selenium in the treatment of radiation-associated secondary lymphedema. J Cancer Res Clin Oncol 2007, 133:187–196.
9. Papp LV, Lu J, Holmgren A, Khanna KK: Selenium and lung cancer: a systematic review and meta analysis. PLoS One 2012, 7:e44571.
10. Arner ES, Holmgren A: Selenium for alleviating the side effects of chemotherapy, radiotherapy and surgery in cancer patients. Cochrane Database Syst Rev 2006, 3:CD005937.
11. Pothen L, Patel A, Michelson C, Douglass HO Jr: Plasma selenium levels in patients with advanced upper gastrointestinal cancer. Cancer 1987, 60:2251–2260.
12. Antilla HM, Salo MS, Niittymäki V, Nikkuniemi V, Kivelä O: The effect of postoperative radiotherapy on leukocyte zinc, serum trace elements and nutritional status of breast cancer patients. Acta Oncol 1992, 31:569–572.
13. Piccinni L, Borella P, Bargellini A, Medici O, Zoboli A: A case–control study on selenium, zinc, and copper in plasma and hair of subjects affected by breast and lung cancer. Biol Trace Elem Res 1996, 51:23–30.
14. Tabassum A, Bristow RG, Venkateswaran V: Effects of selenium on radiation responses of tumor cells and tissue. Strahlenther Onkol 2000, 176:695–700.
15. Fritz H, Kennedy D, Ferguson D, Fernandes R, Cooley K, Seely A, Sagar S, Wong R, Seely D: Selenium and lung cancer: a systematic review and meta analysis. PLoS One 2011, 6:e26259.
36. Ashton K, Hooper L, Harvey LJ, Hurst R, Casgrain A, Fairweather-Tait SJ: Methods of assessment of selenium status in humans: a systematic review. Am J Clin Nutr 2009, 89:2025S–2039S.

37. Abdulah R, Miyazaki K, Nakazawa M, Koyama H: Chemical forms of selenium for cancer prevention. J Trace Elem Med Biol 2005, 19:141–150.

38. Akesson B, Bellew T, Burf RK: Purification of selenoprotein P from human plasma. Biochim Biophys Acta 1994, 1204:243–249.

39. Deagen JT, Butler JA, Zachara BA, Whanger PD: Determination of the distribution of selenium between glutathione peroxidase, selenoprotein P, and albumin in plasma. Anal Biochem 1993, 208:176–181.

40. Panel on Dietary Antioxidants and Related Compounds, Subcommittees on Upper Reference Levels of Nutrients and Interpretation and Uses of DRIs, Standing Committee on the Scientific Evaluation of Dietary Reference Intakes, Food and Nutrition Board, Institute of Medicine: DRI Dietary Reference Intakes for Vitamin C, Vitamin E, Selenium, and Carotenoids. Washington D.C: National Academy Press; 2000.

41. Reid ME, Duffield-Lillico AJ, Garland L, Turnbull BW, Clark LC, Marshall JR: Selenium supplementation and lung cancer incidence: an update of the nutritional prevention of cancer trial. Cancer Epidemiol Biomarkers Prev 2002, 11:1285–1291.

42. Stranges S, Marshall JR, Natarajan R, Donahue RP, Trevisan M, Combs GF, Cappuccio FP, Ceriello A, Reid ME: Effects of long-term selenium supplementation on the incidence of type 2 diabetes: a randomized trial. Ann Intern Med 2007, 147:217–223.

43. Nuttall KL: Evaluating selenium poisoning. Ann Clin Lab Sci 2006, 36:409–420.

44. MacFarquhar JK, Broussard DL, Melstrom P, Hutchinson R, Wolkin A, Martin C, Burk RF, Dunn Jr, Green AL, Hammond R, Schaffner W, Jones TF: Acute selenium toxicity associated with a dietary supplement. Arch Intern Med 2010, 170:256–261.

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