Myanmar Health Sciences Research Journal, Vol. 29, No. 3, 2017

Assessment of Serum Selenium Levels in Breast Cancer Patients

Kyae Mhon Htwe[1], Aye Min Maw[1], Lei Lei Win[1], Khaing Khaing Mar[1], Khin Lay Sein[1], Aung Thura[1], Moe Kyaw Myint[2] & Yi Yi Myint[3]*

[1]Biochemistry Research Division
[2]Parasitology Research Division
Department of Medical Research (Pyin Oo Lwin Branch)
[3]Department of Traditional Medicine

Selenoproteins have roles that support immune function and, through specific cellular pathways, may play a preventive role in both the initiation and promotion of specific cancers. Selenium exerts its chemoprevention effect in different ways, such as a protective effect against oxidative damage by decreasing the amount of free radicals and increasing the synthesis of glutathione peroxidase. In Myanmar, breast cancer is annually increasing during these years. Therefore, the present study was taken up to assess serum selenium levels in breast cancer patients before the first cycle of chemotherapy and after the third cycle of chemotherapy. This hospital- and laboratory-based, cross-sectional comparative study was conducted at Cancer Unit in Mandalay General Hospital and Biochemistry Research Division, Department of Medical Research (Pyin Oo Lwin Branch). Study populations were 36 apparently healthy controls and 36 new cases of female breast cancer patients above 20 years of age who did not suffer from any major illness in the past. Serum selenium was measured by using the Atomic Absorption Spectrophotometer. The findings showed that the serum selenium level in breast cancer patients (34.1±16.8 µg/l) was significantly lower than that of controls (56.3±16 µg/l) and significantly lower when that measured after the third cycle of chemotherapy (26.9±17.5 µg/l). From the obtained results, it could be concluded that the deficiency of selenium may lead to increase in risk of the cancer incidence and the effect of chemotherapy may increase reactive oxygen species leading to more consumption of selenium.

Key words: Selenium, Breast cancer, AAS

INTRODUCTION

Cancer usually develops gradually over many years as the result of a complex mix of environmental, nutritional, behavioral and hereditary factors. Cancer, together with other non-communicable diseases are on the rise globally. According to WHO's report, non-communicable diseases including cancer rise throughout the world and are expected to be the cause of 54% of deaths in the year 2015. Cancer is the second most frequent cause of death in many developed countries. Breast cancer (BCA) is the most common cancer type in women worldwide, a major cause of morbidity in women, with 1.15 million new cases and 410,000 deaths in 2002.[1]

Selenium's unique role in human physiology has been found to include the prevention of atherosclerosis, specific cancers, arthritis, diseases of accelerated aging, central nervous system pathologies, male infertility, and

Kyae Mhon Htwe & Aye Min Maw contributed equally to this study and are joint first authors.

*To whom correspondence should be addressed.
Tel: +95-933021681
E-mail: kyaemhon.htwe.dr@gmail.com

altered immunological function.[2, 3] Selenium is a key component of a number of functional selenoproteins required for normal health.

The best known of these are the antioxidant glutathione peroxidase enzymes, which remove hydrogen peroxide and damaging lipid and phospholipids hydroperoxides generated *in vivo* by free radicals and other oxygen derived species. Antioxidant has been suggested to play a role in some physiological conditions and in many disease processes including carcinogenesis.[4]

Selenoproteins have roles that support immune function and, through specific cellular pathways, may play a preventive role in both the initiation and promotion of specific cancers. Erythrocyte, serum, plasma, and urine selenium levels have been found to be lower in a variety of cancer diagnosis compared to both matched and unmatched controls. The majority of epidemiological studies also provide evidence for selenium as a chemopreventive agent for specific cancers: prostate, lung, colorectal, stomach, and multiple cancers.[3, 5]

The chemopreventive effects of selenium may be due to its roles in cell cycle arrest, decreasing proliferation, inducing apoptosis, facilitating DNA repair by activation of p53, disruption of androgen receptor signalling, and being a key component of selenoenzymes, which incorporate selenium as selenocysteine, an infrequently occurring amino acid, into their active centre.[6]

The concept of the chemoprevention of cancer as originally proposed refers to prevention of cancer by use of pharmacological agents to inhibit or reverse the process of carcinogenesis. Experimental and clinical studies have shown that a major mechanism for cytotoxic activity of the numerous chemotherapeutic agents is through increased formation of the reactive oxygen species (ROS), including hydroxyl radicals (OH°), hydrogen peroxide (H_2O_2) and superoxide anion (°0^2-).[7-10]

The reactive oxygen species play an effective role in pathogenesis of different pathological diseases including cancer. Free radical induced lipid peroxidation causes a loss of cell homeostasis by modifying the structure and functions of cell membrane. The most important characteristic of lipid peroxidation is to cause a considerable DNA-MDA adducts by interaction with cellular DNA. However, mammalian cells possess elaborate antioxidant defence mechanisms to neutralize the deleterious effects of free radical induced lipid peroxidation.[10]

Selenium (Se) is a very important component of antioxidative protective mechanism which belongs to every cell, and there is evidence that this essential trace element have anticancer properties. Selenium exerts its chemopreventive effect in different ways, such as a protective effect against oxidative damage by decreasing the amount of free radicals and increasing the synthesis of glutathione peroxidase.[3, 10-13]

In Myanmar, breast cancer is annually increasing during these years. Therefore, the present study was aimed to assess and compare serum selenium levels in breast cancer patients before the first cycle and after the third cycle of chemotherapy, and those in the controls.

MATERIALS AND METHODS

This hospital- and laboratory-based, comparative study was conducted at Oncology Unit, Mandalay General Hospital from October, 2014 to May, 2015. Study populations were 36 new cases of breast cancer patients.

Inclusion criteria:

- Above 20 years of age
- New cases of biopsy proved female breast cancer patients attended at Out-patient Department of Cancer Unit in Mandalay General Hospital
- Female patients who had not undergone any treatment, i.e. chemotherapy or radiotherapy
- Female patients who did not suffer from any major illness in the past

- Female patients who had not taken long-course of any mineral supplement containing selenium during last six months

Exclusion criteria:

- Patients either with pregnancy or metastasis or other diseases
- Thirty-six apparently healthy age-matched women were used as controls

Sample size

It was assumed that the risk factor of biomedical profile of cancer patients to be as common as 70% among cases and 35% among controls with the power of 80% and 95% confidence, so, the required sample size was 74.

Data collection and determination

After explaining the purpose, risks and benefits of the research and after getting informed consents from the participants, five millilitres of venous blood was collected under aseptic precautions. Serum was obtained by spinning at 3000 rpm centrifuge for 10 minutes and stored at -20°C until analysis. After collecting required samples, serum selenium was measured by using the Atomic Absorption Spectrophotometer at the Department of Medical Research (Pyin Oo Lwin Branch).[14]

Data analysis

Data analysis was done by using SPSS software 20.0 version in the calculation of arithmetic means (X), standard deviation (SD). The comparison of serum selenium levels within patients were analysed by using paired 't' test whereas Student 't' test was used to compare those of patients and controls. $p<0.05$ was considered as significant.

Ethical consideration

This study was permitted by the Ethics Review Committee on Medical Research involving Human Subjects, Department of Medical Research (Pyin Oo Lwin Branch).

RESULTS

Among a total of 36 patients, 32(88.9%) patients were stage 2A and 4(11.1%) patients were stage 2B. Among 72 female subjects (36 Ca breast patients and 36 normal subjects), mean age was 42.5±13.1 years. The youngest was 20 and the oldest was 73 in years. Mean systolic and diastolic blood pressure in cases were 114.4±8.4 mmHg and 74.4±6.9 mmHg, respectively. In controls, these were 120±13.3 mmHg and 79.6±8.8 mmHg.

Mean±SD value of serum selenium level in cases before the first cycle of chemotherapy was 34.1±16.8 µg/l and that of the control group was 56.3±16 µg/l. It was significantly lower in cases than the control group ($p<0.00$). The association of serum selenium levels in Ca breast patients before the first cycle of chemotherapy and control subjects is shown in Fig. 1.

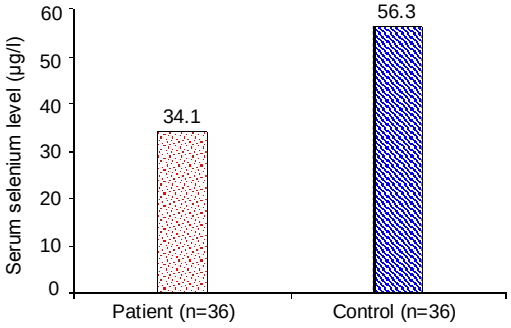

Fig. 1. Mean serum selenium levels in breast cancer patients before the first cycle of chemotherapy and control subjects

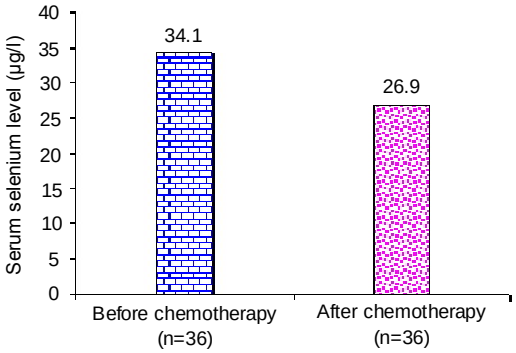

Fig. 2. Mean serum selenium levels in Ca breast patients before the first cycle of chemotherapy and after the third cycle of chemotherapy

Mean±SD value of serum selenium levels in cases before the first cycle of chemotherapy was 34.1±16.8 µg/l and that of patients after the third cycle of chemotherapy was 26.9±17.5 µg/l. It was significantly lower in cases after the third cycle of chemotherapy when compared with that before chemotherapy ($p<0.02$).

The association of serum selenium levels in Ca breast patients before the first cycle of chemotherapy and after third cycle of chemotherapy is shown in Fig. 2.

DISCUSSION

Prevention of a number of degenerative conditions including cancers, inflammatory diseases, thyroid functions, cardiovascular diseases, neurological diseases, aging, infertility, and infections, has been established by laboratory experiments, clinical trials, and epidemiological data. Most of the effects in these conditions are related to the function of selenium in antioxidant enzyme systems. Replenishing selenium in deficiency conditions appears to have immune-stimulating effects, particularly in patients undergoing chemotherapy. However, increasing the levels of selenoprotein antioxidant enzymes (glutathione peroxidase, thioredoxin reductase, etc.) appears to be only one of many ways in which selenium-based metabolites contribute to normal cellular growth and function. Animal data, epidemiological data, and intervention trials have shown a clear role for selenium compounds in both prevention of specific cancers and antitumorigenic effects in post-initiation phases of cancer.[3]

Chemotherapy involves administration of cytotoxic drugs that prevents growth and proliferation of cells, and it's especially used in cancer treatment in order to destroy neoplastic cells that show uncontrolled growth. Due to toxicity of drugs, chemotherapy delivered in any setting is usually associated with a number of distressing side effects for the patient.[15] Some investigations showed that chemotherapeutic agents routinely used in cancers increase free oxygen radicals that leads to a damage also of normal tissue.[8, 16] Selenium behaves as an antioxidant agent and as its antioxidant role, notably glutathione peroxidase, can reduce hydrogen peroxide, lipid and phospholipids hydroperoxides, thereby dampening the propagation of free radicals and reactive oxygen species.[12]

In the present study, mean serum selenium level was 56.3 µg/l in apparently healthy women. One study from Myanmar found that mean serum selenium level in female young age group was 104.16 µg/l and that of elderly group was 91.5 µg/l.[14] Even though the two studies were determined by the same procedure, the results from the present study were lower than those of the previous study. This might be due to the following reasons: different geographic situations, underlying social determinants of populations, wide age range (20-73 years) and small sample size. However, one study from New Zealand found that the mean selenium level in apparently healthy females of age above 60 was 37 µg/l and that of age under 60 was 48 µg/l.[17]

The result of the present study showed that the mean selenium level in breast cancer patients before chemotherapy was significantly lower than that of controls and the mean serum selenium level in these patients after third cycle of chemotherapy also significantly decreased than that measured before chemotherapy. In the study of Goyal, *et al*.[2] they also found that mean serum selenium level in cancer patients was significantly lower than that of controls. It was suggested that selenium protects cell by inhibiting free oxygen radical production. The results of the present study also agreed with Hassanein and co-investigators who found that the differences between the mean serum selenium concentrations of breast cancer patients were found to be significant. They claimed that the finding of the deficiency of antioxidant enzymes and their cofactors (selenium for gluthathione peroxidase and zinc for superoxide dismutase) may increase the risk factor of cancer incidence in women.[18]

A group of researchers from Iraq determined the erythrocyte glutathione peroxidase activity and serum selenium level in patients with breast cancer. They found that all investigated breast cancer patients had significantly lower mean serum selenium level as compared with the values of healthy controls. They suggested that it may be a result of a protective mechanism that develops in breast cancer patients against free radical damage.[4] Some human epidemiologic studies showed that a low selenium concentration in serum increase the risk of human cancer (cancer of the stomach, oesophagus, colon, lung, prostate and breast).[12, 19] These observations suggested that low antioxidant status may be associated with neoplastic activity and subsequent poor health and support the idea that antioxidant supplementation could benefit cancer patients.[20]

In addition, Moradi and co-workers also found that the mean serum selenium level in these patients after third cycle of chemotherapy also decreased than that measured before chemotherapy.[10] However, the results found in the study of Breedlove and co-workers revealed that Se status was within the normal range before and following adjuvant chemotherapy, and was not affected by chemotherapy-induced ovarian failure.[21] In another study, Faber showed that the plasma selenium level in cancer patients was decreased, but not further modified by chemotherapy.[22]

A number of chemotherapy toxicities and adverse effects have been linked to the formation of free radicals by cytostatics.[7] Surveys in Canada, UK, Austria and Germany found that 4-12% of breast cancer and prostate cancer patients used selenium supplements during and after cancer therapy to alleviate adverse effects of conventional therapy and to improve quality of life. Concerning with the efficacy of selenium supplements against radio-/chemotherapy associated side effect, selenium supplements are frequently recommended for this indication in secondary publications and claimed that "a protective effect against chemotherapy toxicities" has been proven in clinical studies and observations. They also suggested that selenium is a trace element (one required at quantities of less than one milligram per day) that is important in the regulation of detoxification enzyme activity in the liver and other cells of the body. Supplements of 50-200 micrograms per day can prevent any potential deficiencies that may occur with certain chemotherapy agents.[23]

Conclusion

These findings showed that mean serum selenium level in breast cancer patients was significantly lower than that of controls and significantly lower when that measured after the third cycle of chemotherapy. From the obtained results, it can be concluded that the deficiency of selenium may increase the risk of cancer incidence and the effect of chemotherapy may increase reactive oxygen species leading to more consumption of selenium. Further studies need to be conducted for the role of selenium supplementation in treatment of breast cancer and the effect of dietary changes on bioavailability of selenium.

ACKNOWLEDGEMENT

We would like to express our grateful thanks to Dr. Kyaw Zin Thant, Director-General, and Dr. Win Aung, Deputy Director-General for their thoughtful help and encouragement. We must also express our profound gratitude to Dr. Tin Moe Win (Consultant Oncologist), Dr. Soe Thiha and staff from Oncology Unit, MGH for their help in sample collection. We must also express our profound thanks to Dr. May Pyone Kyaw, Professor and Head, Biochemistry Department, University of Medicine (Mandalay) for her precious guidance. We also thank Dr. Phyu Phyu Thin Zaw and Dr. Kyaw Ko Ko Htet, Research Officers, Epidemiology Research Division, DMR (POL Branch) for their help and suggestions. Finally, we must not fail to mention our sincere thanks to all participants who gave their consent to participate in this study.

REFERENCES

1. Nwozo SO, Solomon O, Abimbola O & Kikelomo DO. Comparative study of bio-chemical and nutritional status of breast cancer patients on chemotherapy/radiotherapy in ibadan. *American Journal of Cancer Science* 2013; 1: 23-32.
2. Goyal MM, Kalwar AK, Vyas RK & Bhati A. A study of serum zinc, selenium and copper levels in carcinoma of esophagus patients. *Indian Journal of Clinical Biochemistry* 2006; 21(1): 208-210.
3. Lyn Patrick ND. Selenium biochemistry & cancer. A review of the literature. *Alternative Medicine Review* 2004; 9(3): 239-258.
4. Basma TJ. Determination the erythrocyte glutathione peroxidase activity and serum selenium level in patients with breast cancer. *Tikrit Journal of Pure Science* 2011; 16(2): 4.
5. Duffield-Lillico AJ, Reid ME, Turnbull BW, Combs GF Jr, Slate EH, Fischbach LA, *et al.* Baseline characteristics and the effect of selenium supplementation on cancer incidence in a randomized clinical trial. *Cancer Epidemiology, Biomarkers & Prevention* 2002; 11: 630.
6. Peters U, Foster CB, Chatterjee N, Schatzkin A, Reding D, Gerald L, *et al.* Serum selenium and risk of prostate cancer-a nested case-control study. *American Journal of Clinical Nutrition* 2007; 85(1): 209-217.
7. Weijl NI, Cleton FJ & Osanto S. Free radicals and antioxidants in chemotherapy-induced toxicity. *Cancer Treatment Reviews* 1997; 23(4): 209-240.
8. Sangeetha P, Das UN, Koratkar R & Suryaprabha P. Increase in free radical generation and lipid peroxidation following chemotherapy in patient with cancer. *Free Radical Biology & Medicne* 1990; 8(1): 15-19.
9. Clemens MR, Ladner C, Schmidt H, Ehninger G, Einsele H, Buhler E, *et al.* Decreased essential antioxidant and increased lipid hydroperoxides following high-dose radiochemotherapy. *Free Radical Research Communications* 1989; 7(3-6): 227-232.
10. Moradi M, Eftekhari MH & Talei A. Plasma selenium concentration and glutathione per-oxidase activity in breast cancer patients before and after chemotherapy. *Iranian Journal of Cancer Prevention* 2008; 1(3): 119-122.
11. Howard EG. Selenium metabolism, seleno-proteins and mechanisms of cancer prevention: Complexities with thioredoxin reductase. *Carcinogenesis* 1999; 20(9): 657-1666.
12. Rayman MP. The importance of selenium to human health. *The Lancet* 2000; 356: 233-41.
13. Clement IP. Lessons from basic research in selenium and cancer prevention. *Journal of Nutrition* 1998; 128: 845-1854.
14. May Pyone Kyaw. Effects of antioxidant vitamins on age-related changes in markers of oxidative stress in apparently healthy elderly individuals: Determination of serum selenium by Atomic Absorption Spectrophotometer. [PhD *thesis*]. University of Medicine 2: Yangon; 2005.
15. Ambrosone CB, Ahn J & Schoenenberger V. Antioxidant supplements, genetics and chemo-therapy outcomes. *Current Cancer Therapy Reviews* 2005; 1: 251-258.
16. Schumacher K. Effect of selenium on the side effect profile of adjuvant chemotherapy/ radiotherapy in patients with breast cancer carcinoma. Design for clinical study. *Medizinische Klinik* 1999; 94(Suppl 3): 45-8.
17. Robinson MF, Thomson CD & Van Rij AM. Blood serum and gluthathione peroxidase activity in normal subjects and in surgical patients with and without cancer in New Zealand. *The American Journal of Clinical Nutrition* 1979; 32: 1477-1485.
18. Hassanein MRR, Mahfouz MKM, Abou Zied OAR, Mostafa RMA & Rafaat MRG. Biochemical study on the activities of glutathione peroxidase, superoxide dismutase and catalase in women breast cancer. *Abstract of the 1st Annual Conference; Facutly of Veterinary Medicine (FVM), Moshtohor* 2004; 92-107.
19. Miyamoto H, Araya Y, Ito M, Isobe H, Dosaka H, Shimizu T, *et al*. Serum selenium and Vitamin E concentration in families of lung cancer patients. *Cancer* 1987; 60: 1159-1162.
20. Ladas EJ. Antioxidants and cancer therapy: A systematic review. *Journal of Clinical Oncology* 2004; 22(3): 517-528.
21. Breedlove HA, Smith AM, Burk RF, Hill KE & Shapiro CL. Serum selenium measurements in women with early-stage breast cancer with and without chemotherapy-induced ovarian failure. *Breast Cancer Research & Treatment* 2006; 97(3): 225-230.
22. Faber M, Coudray C, Hida H, Mousseau M & Favier A. Lipid peroxidation products, and vitamin and trace element status in patients with cancer before and after chemotherapy, including adriamycin: A preliminary study. *Biological Trace Element Research* 1995; 47(1-3): 117-23.
23. Dennert G & Horneber M. Selenium for alleviating the side effects of chemotherapy, radiotherapy and surgery in cancer patients (Review). *The Cochrane Database of Systematic Reviews.* The Cochrane Collaboration, John Wiley and Sons, Ltd, 2011; 8-9. Available from: http://www.thecochranelibrary.com