Research Article

Serum Levels of Selenium and Zinc in Patients with Breast Cancer: A Case-Control Study

Seyed-Mehdi Hashemi,[1] Masoud Sadeghi,[2] Abdolbaset Vahedi Tabas,[3] Salehoddin Bouya,[1] Hosein Ali Danesh,[4] Alireza Khazaei,[4] and Abolghasem Allahyari[5,*]

[1]Clinical Immunology Research Center, Ali-ebne Abitaleb Hospital, Zahedan University of Medical Sciences, Zahedan, IR Iran
[2]Medical Biology Research Center, Kermanshah University of Medical Sciences, Kermanshah, IR Iran
[3]Student's Scientific Research Center, Zahedan University of Medical Sciences, Zahedan, IR Iran
[4]Department of Surgery, Zahedan University of Medical Sciences, Zahedan, IR Iran
[5]Department of Hematology and Medical Oncology, Mashhad University of Medical Sciences, Mashhad, IR Iran

[*] *Corresponding author*: Abolghasem Allahyari, Department of Hematology and Medical Oncology, Mashhad University of Medical Sciences, Mashhad, IR Iran. E-mail: allahyari.abolghasem@yahoo.com

Abstract

Background: Zinc (Zn) and Selenium (Se) are trace minerals that have high anti-cancer and chemopreventive properties.

Objectives: This study aimed at evaluating the serum levels of both elements in women with breast cancer (BC) compared with control group and the correlation of them with risk factors of BC.

Methods: In a case-control study, 142 women with BC and 158 healthy controls, aged 19 to 88 years, were selected. Both groups did not use any type of supplement 3 months before participation in the study; there was no history of chronic kidney or liver disease or malabsorption disorders among the participants and body mass index was between 18.5 and 30 based on Quetelet index. The Se by graphite furnace and Zn by flame were atomized and the amount of each of 2 elements was measured and recorded by the Absorption device.

Results: The mean Zn was 689.57 ± 146.13 mg/dL in the patient group and 874.85 ± 150.53 mg/dL in the control group ($P < 0.001$). Also, the mean Se was 101.24 ± 17.27 mg/dL in the patient group and 115.36 ± 13.31 mg/dL in the control group ($P < 0.001$). There was a significant difference between Se level with stage in patients; therefore, the Se level was lower in metastatic stage compared with 2 other stages ($P = 0.028$).

Conclusions: Decreasing the serum levels of Se and Zn may be the risk factors for BC. It seems that adding micronutrients of Zn and Se in patients with low serum levels may reduce the risk of BC.

Keywords: Breast Cancer, Zinc, Selenium, Serum

1. Background

Breast cancer (BC), as one of the most common causes of death in the world (1), has distinct pathological and histological characteristics and can be divided into several subtypes based on the presentation of hormone receptors (estrogen receptor (ER) and progesterone receptor (PR)) and the human epidermal growth factor receptor 2 (HER2) (2). Some risk factors including early menarche, late menopause occurred, body mass index (BMI) and obesity after menopause, estrogen intake, alcohol consumption and tobacco use, exposure to ionizing radiation, and eating habits (3), as well as genetic (4-6), environmental factors (5, 6), and ethnicity (7) can effect on the incidence of BC. In various studies, it was found that the serum levels of trace elements in patients with BC have changed and although their role is not fully understood, it may be asso-ciated with the risk of this disease (8). Zinc (Zn) is a vital mineral for the operation of numerous cellular processes and growth and may play an important role in malignancy etiology and outcome (9). This mineral has an excessive accumulation in BCs and malignant cell lines compared with normal mammary epithelium (10). Also, it plays a role on the cellular level, the function of transcription factors, and cell proliferation; it defends against radicals and deoxyribonucleic acid (DNA) repair (11). Zn has 4 general biological roles, including structural, signaling, catalytic, and regulatory functions (12). Selenium (Se) is another biotic mineral and a vital micronutrient that has high anti-cancer and chemopreventive properties (13). It is a micronutrient with an essential role in malignancy and has been widely studied as a chemopreventive factor in several experimental models of BC (14). Therefore, because of the importance

of Zn and Se in relation to BC and no adequate study in this field in Southeastern Iran, this study aimed at evaluating the serum levels of both elements in the women with BC compared with the control group and the correlation of them with risk factors of BC.

2. Methods

This study was approved by the ethics committee of Zahedan University of Medical Sciences, Zahedan, Iran. Informed consent was taken from the participants. During 2015 to 2016, 142 women with BC (the diagnosis is based on pathology) were referred to the clinic of hematology and medical oncology, Ali Ebne Abitaleb hospital, Zahedan, Iran; they did not have any treatment or it passed more than 6 months from their last treatment. Also, 158 healthy controls, aged 19 to 88 years, were selected for the present study. The participants in both groups did not use any the type of supplement 3 months before the study and they had no history of chronic kidney or liver disease or malabsorption disorders (such as Crohn's or celiac disease). The BMI was between 18.5 and 30 kg/m² based on the Quetelet index (15) in 2 groups. After recording the demographic and pathology data (according to their medical records), blood samples were collected from both groups. Then, the serum was separated by centrifugation and by maintaining the cold chain and for the assessment of the levels of Zn and Se, it was transferred to the laboratory of Razavi Hospital in Mashhad (Khorasan province in Eastern Iran). Natural menopause was defined as the permanent cessation of menstrual periods, determined retrospectively after a patient had experienced 12 months of amenorrhea without any another obvious pathological or physiological cause, otherwise considered as premenopausal state. Stage was divided to 3 parts based on TNM staging including early stage (stage [T1N0M0], A [T0N1M0, T1N1M0 or T2N0M0] or B [T2N1M0 or T3N0M0]), locally advanced (stage A [T0N2M0, T1N2M0, T2N2M0, T3N1M0 or T3N2M0] to B [T4, any N except N3M0], or C [Any T, N3, M0]) and metastatic (V [Any T, any N, M1]) (16).

The Se was atomized by graphite furnace, in 2300°C and the wavelength of 194 nm. Consumption standard (Se standard Art No: Hc946651, Merck Co., Germany) was used in concentrations of 50 to 500 μg/mL. Also, we used the standard edition method and the palladium chloride as a Matrix Modifier. Zn was atomized by flame, heated up to 800°C and at a wavelength of 314 nm. Consumption standard (Zn standard Art No: Hc62775, Merck Co., Germany) was used in concentrations of 250 to 2000 μg/mL. The amount of these elements was measured and recorded by the atomic absorption device 240 (AA240, Varian Co., Australia). The ER, PR, and HER2 statuses were evaluated

by immunohistochemistry (IHC); ER and PR were positive, if they had > 10% positive in tumor cells. For the patients with HER2 2+, chromogenic in situ hybridization (CISH) test was done if the result was 3+ (HER2 positivity) and 2+ (HER2 negativity).

The data was analyzed by SPSS version 11.0; t test was used to compare the mean elements in 2-way variables and One-way ANOVA test was used for 3-way variables (grade and stage). P value < 0.05 was considered to be statistically significant.

3. Results

The mean age at diagnosis of the patient group was 48.71 ± 1.87 years and the control group was 46.86 ± 13.59 years. The mean Zn was 689.57 ± 146.13 mg/dL in the patient group and 874.85 ± 150.53 mg/dL in the control group; the mean was significantly more in the control group compared with the patient group (P < 0.001) (Table 1). Also, the mean Se was 101.24 ± 17.27 mg/dL in the patient group and 115.36 ± 13.31 mg/dL in the control group; the mean was significantly more in the control group compared with the patient group (P < 0.001).

Table 1. Comparison of the Means of Zn and Se Among the Patient and Control Groups

Variables	Patient Group (n = 142)	Control Group (n = 158)	P Value
Zn, mg/dL	689.57 ± 146.13	874.85 ± 150.53	< 0.001
Se, mg/dL	101.24 ± 17.27	115.36 ± 13.31	< 0.001

Table 2 shows the prevalence of several clinicopathological variables in the patient group. Out of 142 patients, 92 (64.8%), 84 (59.2%), and 45 (31.7%) had ER-, PR-, and HER2-positive, respectively. Also, 90 (63.4%) patients were postmenopausal and 13 (9.2%) had a familial history of BC. Thirty-four (23.9%) patients had early stage, 86 (60.66%) locally advanced, and 22 (15.5%) metastatic stage. Fifteen (10.5%) patients had grade I, 82 (57.8%) grade II, and 45 (31.7%) grade III.

The comparison of Zn and Se levels with a number of variables in the patient group has been shown in Table 3. There was no a significant difference between elements levels with variables, except for the correlation between stage and Se level in patients; therefore, Se level was lower compared with 2 other stages (P = 0.028).

4. Discussion

It has been suggested that oxidative stress produced through either increased free radical generation and/or a

Table 2. Clinicopathological Variables in the Patient Group (n = 142)

Variables	No. (%)
ER	
Positive	92 (64.8)
Negative	50 (35.2)
PR	
Positive	84 (59.2)
Negative	58 (40.8)
HER2	
Positive	45 (31.7)
Negative	97 (68.3)
Menopausal Status	
Postmenopausal	90 (63.4)
Premenopausal	52 (36.6)
Familial history	
Positive	13 (9.2)
Negative	129 (90.8)
Stage	
Early	34 (23.9)
Locally advanced	86 (60.6)
Metastatic	22 (15.5)
Grade	
I	15 (10.5)
II	82 (57.8)
III	45 (31.7)

Table 3. Comparison of Zn and Se Levels with Variables in the Patient Group (n = 142)

Variables	Zn	P Value	Se	P Value
ER		0.736		0.600
Positive	694.21 ± 147.04		101.81 ± 16.63	
Negative	685.42 ± 154.09		100.20 ± 18.62	
PR		0.870		0.909
Positive	692.83 ± 146.22		101.39 ± 17.08	
Negative	688.68 ± 148.19		101.05 ± 17.77	
HER2		0.481		0.106
Positive	678.18 ± 153.53		97.75 ± 15.88	
Negative	697.08 ± 143.08		102.85 ± 17.77	
Menopausal Status		0.547		0.689
Postmenopausal	684.78 ± 141.39		100.44 ± 17.20	
Premenopausal	700.56 ± 156.94		101.65 ± 16.77	
Familial history		0.784		0.939
Positive	678.92 ± 90.77		100.90 ± 16.88	
Negative	690.65 ± 150.79		101.28 ± 17.37	
Stage		0.219		0.028
Early	710.44 ± 147.52		104.91 ± 19.98	
Locally advanced	693.39 ± 148.79		101.98 ± 16.59	
Metastatic	642.40 ± 128.33		92.70 ± 12.67	
Grade		0.350		0.674
I	748.69 ± 191.46		104.78 ± 18.32	
II	683.84 ± 130.95		101.38 ± 15.69	
III	698.90 ± 164.14		99.91 ± 19.45	

reduced antioxidant level in the target cells and tissues may play a main role in carcinogenesis ([17]). The vital elements such as copper, Zn, and Se are connected together in cytosolic defense against reactive oxygen and nitrogen species ([18]). Human and laboratory studies have been conducted on the role of these 2 elements in preventing carcinogenesis process and tumor cell growth ([19-22]). On the other hand, epidemiological studies have shown that differences in dietary habits or diet ([23], [24]) and air pollution ([25]) can effect on risk of BC, in line with genetics ([26]). In Ku's study, it was suggested that change the vital elements in serum and tissue might be beneficial and considerable biomarkers in BC ([27]). Also, Wu et al. ([28]) reported that there was a significant difference in concentrations of 13 elements in serum between patients with BC and controls, the most important of which were Cadmium, Manganese, Iron, Chromium, and Zn. In this study, the serum levels of Zn and Se was significantly lower in patients with BC compared with the control group; regarding Zn, the results of this study were in line with the results of studies conducted by Pavithra et al. ([29]) in India and Yucel et al. ([30]) in Ankara, Turkey; also, regarding Se, result of this study were in line with the results of the studies in Iran ([31]), Spain ([32]), India ([33]), Greece ([34]), and Nigeria ([35]).

Holtkamp et al. ([36]) reported that plasma Zn in pa-

tients with BC was decreased according to the stage of the disease and, therefore, in patients with metastatic disease, plasma Zn concentrations were in the lower region of the normal range (mean ± SD: 84.9 ± 21.6 μg/dL), whereas patients with no metastatic BC had normal Zn levels (mean ± SD: 126.0 ± 27.7 μg/dL), and the difference between 2 groups was highly significant (P = 0.001). Zhang et al. ([37]) reported that low Se-binding protein 1 (SELENBP1) expression in ER-positive patients with BC was significantly associated with a poor survival, and SELENBP1 levels progressively reduced with advancing clinical stages of BC. There was a trend towards the decreased expression of SELENBP1 from stage II (5.62 ± 2.48) to stage III (5.06 ± 2.34), but it did not reach the statistical significance due to limited sample size. One study ([13]) suggested that organic Se supplementation may reduce/delay BC metastasis. In this study, with increasing the stage, mean Se and Zn was reduced, but this correlation has been just significant for Se. Riesop et al. ([38]) showed that Zn levels in carcinomatous tissues had a direct correlation with the histological malignancy grade that was almost similar to the result of this study, but the correlation was not significant. Kowalska et al. ([39]) reported that oral Se was a good candidate for chemoprevention in women, who had BRCA1 gene mutation. One study demonstrated that the Se was as a chemopreventive factor

for high-risk BC women or as a therapeutic strategy for ER-positive BC (40). Therefore, differences in the levels of Se and Zn in patients with BC can be because of the prevalence of tumor markers or risk factors as well as genetics and ethnicity.

In conclusion, decreasing the serum levels of Se and Zn may be the risk factors for BC. It seems that adding micronutrients of Zn and Se in patients with serum low levels may reduce the risk of BC. In addition, the role of pathological and genetic factors and their relationship with these 2 elements in the process of treatment may be considered.

Acknowledgments

None declared.

Footnotes

Authors' Contribution: None.

Conflict of Interests: None.

Financial Disclosure: None.

References

1. Rezaei M, Hashemi M, Hashemi SM, Mashhadi MA, Taheri M. APOBEC3 Deletion is Associated with Breast Cancer Risk in a Sample of Southeast Iranian Population. *Int J Mol Cell Med.* 2015;**4**(2):103–8. [PubMed: 26261799].

2. Payandeh M, Shazad B, Madani S, Ramezani M, Sadeghi M. Androgen Receptor Expression and its Correlation with Other Risk Factors in Triple Negative Breast Cancers: a Report from Western Iran. *Asian Pac J Cancer Prev.* 2016;**17**(7):3321–4. [PubMed: 27509970].

3. Key TJ, Verkasalo PK, Banks E. Epidemiology of breast cancer. *Lancet Oncol.* 2001;**2**(3):133–40. doi: 10.1016/S1470-2045(00)00254-0. [PubMed: 11902563].

4. Moheb Afzali F, Tahmasebi Fard Z, Akbari ME. The Effect of Polymorphisms on the Ala 119 Ser Gene Cytochrome P450 1B1*2 on the Susceptibility of Iranian Women to Develop Breast Cancer. *Int J Cancer Manag.* 2017;**10**(3). doi: 10.5812/ijcp.4042.

5. Hashemi M, Amininia S, Ebrahimi M, Hashemi SM, Taheri M, Ghavami S. Association between hTERT polymorphisms and the risk of breast cancer in a sample of Southeast Iranian population. *BMC Res Notes.* 2014;**7**:895. doi: 10.1186/1756-0500-7-895. [PubMed: 25491902].

6. Hashemi M, Yousefi J, Hashemi SM, Amininia S, Ebrahimi M, Taheri M, et al. Association between Programmed Cell Death 6 Interacting Protein Insertion/Deletion Polymorphism and the Risk of Breast Cancer in a Sample of Iranian Population. *Dis Markers.* 2015;**2015**:854621. doi: 10.1155/2015/854621. [PubMed: 26063962].

7. Hashemi SM, Arbabi N, Hashemi M, Mashhadi MA, Allahyari A, Sadeghi M. Association between VDR Gene Polymorphisms (rs 1544410, rs 7975232, rs 2228570, rs 731236 and rs 11568820) and Susceptibility to Breast Cancer in a Sample of Southeastern Iranian Population. *Int J Cancer Manag.* 2017;**10**(3). doi: 10.5812/ijcm.8807.

8. Ding X, Jiang M, Jing H, Sheng W, Wang X, Han J, et al. Analysis of serum levels of 15 trace elements in breast cancer patients in Shandong, China. *Environ Sci Pollut Res Int.* 2015;**22**(10):7930–5. doi: 10.1007/s11356-014-3970-9. [PubMed: 25520207].

9. Grattan BJ, Freake HC. Zinc and cancer: implications for LIV-1 in breast cancer. *Nutrients.* 2012;**4**(7):648–75. doi: 10.3390/nu4070648. [PubMed: 22852056].

10. Chandler P, Kochupurakkal BS, Alam S, Richardson AL, Soybel DI, Kelleher SL. Subtype-specific accumulation of intracellular zinc pools is associated with the malignant phenotype in breast cancer. *Mol Cancer.* 2016;**15**:2. doi: 10.1186/s12943-015-0486-y. [PubMed: 26728511].

11. Ho E. Zinc deficiency, DNA damage and cancer risk. *J Nutr Biochem.* 2004;**15**(10):572–8. doi: 10.1016/j.jnutbio.2004.07.005. [PubMed: 15542347].

12. Stipanuk MH. *Biochemical, Physiological, and Molecular Aspects of Human Nutrition.* 2006.

13. Chen YC, Prabhu KS, Das A, Mastro AM. Dietary selenium supplementation modifies breast tumor growth and metastasis. *Int J Cancer.* 2013;**133**(9):2054–64. doi: 10.1002/ijc.28224. [PubMed: 23613334].

14. Guido LN, Fontelles CC, Rosim MP, Pires VC, Cozzolino SM, Castro IA, et al. Paternal selenium deficiency but not supplementation during preconception alters mammary gland development and 7,12-dimethylbenz[a]anthracene-induced mammary carcinogenesis in female rat offspring. *Int J Cancer.* 2016;**139**(8):1873–82. doi: 10.1002/ijc.30223. [PubMed: 27270969].

15. Pasco JA, Nicholson GC, Brennan SL, Kotowicz MA. Prevalence of obesity and the relationship between the body mass index and body fat: cross-sectional, population-based data. *PLoS One.* 2012;**7**(1). e29580. doi: 10.1371/journal.pone.0029580. [PubMed: 22253741].

16. Atoum MF, Hourani HM, Shoter A, Al-Raheem SN, Al Muhrib TK. TNM staging and classification (familial and nonfamilial) of breast cancer in Jordanian females. *Indian J Cancer.* 2010;**47**(2):194–8. doi: 10.4103/0019-509X.63022. [PubMed: 20448386].

17. Rice-Evans C, Burdon R. Free radical-lipid interactions and their pathological consequences. *Prog Lipid Res.* 1993;**32**(1):71–110. [PubMed: 8415800].

18. Klotz LO, Kroncke KD, Buchczyk DP, Sies H. Role of copper, zinc, selenium and tellurium in the cellular defense against oxidative and nitrosative stress. *J Nutr.* 2003;**133**(5 Suppl 1):1448S–51S. [PubMed: 12730440].

19. Hoang BX, Han B, Shaw DG, Nimni M. Zinc as a possible preventive and therapeutic agent in pancreatic, prostate, and breast cancer. *Eur J Cancer Prev.* 2016;**25**(5):457–61. doi: 10.1097/CEJ.0000000000000194. [PubMed: 26317381].

20. Platz EA, Helzlsouer KJ. Selenium, zinc, and prostate cancer. *Epidemiol Rev.* 2001;**23**(1):93–101. [PubMed: 11588860].

21. Whanger PD. Selenium and its relationship to cancer: an update. *Br J Nutr.* 2004;**91**(1):11–28. [PubMed: 14748935].

22. Wallenberg M, Misra S, Bjornstedt M. Selenium cytotoxicity in cancer. *Basic Clin Pharmacol Toxicol.* 2014;**114**(5):377–86. doi: 10.1111/bcpt.12207. [PubMed: 24529300].

23. Hankinson SE, Colditz GA, Willett WC. Towards an integrated model for breast cancer etiology: the lifelong interplay of genes, lifestyle, and hormones. *Breast Cancer Res.* 2004;**6**(5):213–8. doi: 10.1186/bcr921. [PubMed: 15318928].

24. Greenlee H, White E, Patterson RE, Kristal AR, Lifestyle Study C.Vitamins. Supplement use among cancer survivors in the Vitamins and Lifestyle (VITAL) study cohort. *J Altern Complement Med.* 2004;**10**(4):660–6. doi: 10.1089/acm.2004.10.660. [PubMed: 15353022].

25. Garcia E, Hurley S, Nelson DO, Hertz A, Reynolds P. Hazardous air pollutants and breast cancer risk in California teachers: a cohort study. *Environ Health.* 2015;**14**:14. doi: 10.1186/1476-069X-14-14. [PubMed: 25636809].

26. Kholousi Adab F, Tahmasebi Fard Z, Esmaeil Akbari M. Association Between Cytochrome 1B1*3 Polymorphism and the Breast Cancer in a Group of Iranian Women. *Iran J Cancer Prevent.* 2017;**In Press**(In Press). doi: 10.17795/ijcp-6428.

27. Kuo HW, Chen SF, Wu CC, Chen DR, Lee JH. Serum and tissue trace elements in patients with breast cancer in Taiwan. *Biol Trace Elem Res.* 2002;**89**(1):1–11. doi: 10.1385/BTER:89:1:1. [PubMed: 12413046].

28. Wu HD, Chou SY, Chen DR, Kuo HW. Differentiation of serum levels of trace elements in normal and malignant breast patients. *Biol Trace Elem Res.* 2006;**113**(1):9–18. doi: 10.1385/BTER:113:1:19. [PubMed: 17114811].

29. Pavithra V, Sathisha TG, Kasturi K, Mallika DS, Amos SJ, Ragunatha S. Serum levels of metal ions in female patients with breast cancer. *J Clin Diagn Res.* 2015;**9**(1):BC25–c27. doi: 10.7860/JCDR/2015/11627.5476. [PubMed: 25737978].

30. Yucel I, Arpaci F, Ozet A, Doner B, Karayilanoglu T, Sayar A, et al. Serum copper and zinc levels and copper/zinc ratio in patients with breast cancer. *Biol Trace Elem Res.* 1994;**40**(1):31–8. [PubMed: 7511919].

31. Mir M, Mir P, Elmi S, Maleki M. Comparison of Serum Selenium Levels in Breast Cancer Patients and Healthy People at a Cancer Institute in 2004. *SSUJ.* 2007;**14**(4):2–8.

32. Lopez-Saez JB, Senra-Varela A, Pousa-Estevez L. Selenium in breast cancer. *Oncology.* 2003;**64**(3):227–31. doi: 10.1159/000069312. [PubMed: 12697962].

33. Singh P, Kapil U, Shukla NK, Deo S, Dwivedi SN. Association between breast cancer and vitamin C, vitamin E and selenium levels: results of a case-control study in India. *Asian Pac J Cancer Prev.* 2005;**6**(2):177–80. [PubMed: 16101329].

34. Bratakos MS, Vouterakos TP, Ioannou PV. Selenium status of cancer patients in Greece. *Sci Total Environ.* 1990;**92**:207–22. [PubMed: 2326622].

35. Alatise OI, Babalola OO, Omoniyi-Esan GO, Lawal OO, Adesunkanmi AR, Agbakwuru EA. Selenium levels in neoplastic breast lesions. *Niger Postgrad Med J.* 2013;**20**(2):91–7. [PubMed: 23959347].

36. Holtkamp W, Thiery J, Rauschecker H, Nagel GA, Reis HE. [Decreased plasma zinc levels in metastatic breast cancer]. *Onkologie.* 1990;**13**(3):207–9. [PubMed: 2204008].

37. Zhang S, Li F, Younes M, Liu H, Chen C, Yao Q. Reduced selenium-binding protein 1 in breast cancer correlates with poor survival and resistance to the anti-proliferative effects of selenium. *PLoS One.* 2013;**8**(5). e63702. doi: 10.1371/journal.pone.0063702. [PubMed: 23704933].

38. Riesop D, Hirner AV, Rusch P, Bankfalvi A. Zinc distribution within breast cancer tissue: A possible marker for histological grading?. *J Cancer Res Clin Oncol.* 2015;**141**(7):1321–31. doi: 10.1007/s00432-015-1932-3. [PubMed: 25672953].

39. Kowalska E, Narod SA, Huzarski T, Zajaczek S, Huzarska J, Gorski B, et al. Increased rates of chromosome breakage in BRCA1 carriers are normalized by oral selenium supplementation. *Cancer Epidemiol Biomarkers Prev.* 2005;**14**(5):1302–6. doi: 10.1158/1055-9965.EPI-03-0448. [PubMed: 15894690].

40. Shah YM, Kaul A, Dong Y, Ip C, Rowan BG. Attenuation of estrogen receptor alpha (ERalpha) signaling by selenium in breast cancer cells via downregulation of ERalpha gene expression. *Breast Cancer Res Treat.* 2005;**92**(3):239–50. doi: 10.1007/s10549-005-3203-5. [PubMed: 16155795].