ORIGINAL ARTICLE
DOI: 10.5327/Z2594539420170000194

ALTERATION OF BONE MINERAL DENSITY IN BREAST CANCER FEMALE SURVIVORS ON CHEMOTHERAPY TREATMENT: AN INTEGRATIVE REVIEW

Alteração da densidade mineral óssea em mulheres sobreviventes de câncer de mama tratadas com quimioterapia: revisão integrativa da literatura

Larissa Vaz Gonçalves[1,3]*, Sara Socorro Faria[3], Jordana Carolina Marques Godinho Mota[1,3], Karine Anusca Martins[2,3], Ruffo Freitas-Junior[1,3]

ABSTRACT

Introduction: Chemotherapy for treatment of patients with breast cancer has increased the survival of this population. However, it can significantly reduce bone mineral density (BMD). **Objective:** To verify bone mineral density modifications in women with breast cancer undergoing chemotherapy, as well as their clinical characteristics and risk factors. **Methods:** Integrative review of papers published from 2006 to 2016, carried out through specific terms in PubMed and SciELO databases. **Results:** In that period, 898 papers were identified (897 in PubMed and 1 in SciELO). Among the six papers recovered, there was a considerable reduction in lumbar spine and femoral bone mass. For women submitted to chemotherapy, the main regimens associated with the reduction were doxorubicin and cyclophosphamide (AC), cyclophosphamide, methotrexate and 5-fluorouracil (CMF) and cyclophosphamide, epirubicin and 5-fluorouracil (FEC). In addition, there was greater BMD reduction among women aged more than 50 years, Caucasian and who presented early ovarian failure induced by chemotherapy. **Conclusion:** The use of chemotherapy for breast cancer may lead to bone mass loss, especially when AC, CMF and FEC are used in women aged more than 50 years and among those with early menopause due to this treatment.

DESCRIPTORS: Breast neoplasms; Bone mineral density; Chemotherapy

RESUMO

Introdução: O uso de quimioterápicos para o tratamento de pacientes com câncer de mama tem aumentado a sobrevida dessa população. Entretanto, pode reduzir significativamente a densidade mineral óssea (DMO). **Objetivo:** Verificar a alteração da densidade mineral óssea em mulheres com câncer de mama submetidas a quimioterapia, assim como as características clínicas e os fatores de risco. **Métodos:** Revisão integrativa da literatura de artigos publicados no período de 2006 a 2016, realizada por meio de termos específicos nos bancos de dados da PubMed e da SciELO. **Resultados:** No período selecionado, foram identificados 898 artigos (897 na base PubMed e 1 na SciELO). Entre os seis artigos recuperados para leitura na íntegra, observou-se redução considerável na massa óssea na coluna lombar e no fêmur. Os principais tipos associados à redução foram os regimes doxorrubicina e ciclofosfamida (AC), ciclofosfamida, metotrexato e 5-fluorouracil (CMF) e ciclofosfamida, epirrubicina e 5-fluorouracil (FEC). Além disso, houve maior redução da DMO entre as mulheres com idade acima de 50 anos, caucasianas e que apresentaram falência ovariana precoce induzida pela quimioterapia. **Conclusão:** O uso de quimioterápicos para tratamento do câncer de mama pode acarretar perda de massa óssea, principalmente quando se utilizam os regimes AC, CMF e FEC em mulheres com idade acima de 50 anos e entre aquelas que apresentam menopausa precoce decorrente desse tratamento.

DESCRITORES: Neoplasias da mama; Densidade mineral óssea; Quimioterapia

Study carried out at the Advanced Center for Breast Diagnosis (CORA), *Hospital das Clínicas* (HC)/*Universidade Federal de Goiás* (UFG) – Goiânia (GO), Brazil.
[1]Graduation Program in Health Sciences, School of Medicine of UFG – Goiânia (GO), Brazil.
[2]Graduation Program in Nutrition and Health, School of Nutrition, UFG – Goiânia (GO), Brazil.
[3]Program of Mastology, CORA, HC/UFG – Goiânia (GO), Brazil.
***Correspondence address:** larivazg@hotmail.com
Conflict of interests: nothing to declare.
Received on: 01/17/2017. **Accepted on:** 06/01/2017

INTRODUCTION

Breast cancer is an important neoplasm that affects women all over the world. Chemotherapy (CT) is still one of the main types of treatment recommended to most of the women with a located disease, thus providing a recurrence reduction of around 30% and an increase of patients' survival[1]. However, this systemic treatment may include several side effects, such as modification of body composition with increase of total and abdominal body fat and loss of muscle mass; decrease of bone mineral density (BMD), which can result or intensify a preexisting condition of osteopenia and osteoporosis; and induction of premature ovarian failure (POF) in the pre-menopause period, among other comorbidities[1-3].

Regarding BMD damage, osteoporosis is characterized by the loss and deterioration of bone mass associated with the reduction of serum estrogen concentration with later deterioration of its microarchitecture and predisposal to risk of falls, injuries and fractures[4], with higher prevalence in Caucasian women[5].

Estrogen failure after menopause leads to misbalance of bone reabsorption and formation, and the increase of bone reabsorption exceeds that of formation[6]. This misbalance contributes to loss of bone quality, which increases the incidence of osteoporosis[7].

The decrease of estrogen endogenous production throughout the menopause transition has been associated with loss of BMD and skeleton muscle mass. In addition, aging per se promotes body composition modifications that result in a pattern of central fat accumulation or android distribution[8].

It is possible that CT causes damage to the female gonads, and the extent and/or evolution of this damage depends on the drug, prescribed dose, treatment period, and patient's age. Around 70% of the women develop POF associated with BMD decrease in the femoral shaft and lumbar spine[3]. Women whose menstrual cycle is not affected do not present significant bone loss; however, these cases are rare[9]. Postmenopausal women, on the other hand, have the protective role of body mass in the skeleton, especially regarding the risk of fractures and loss of bone mass during and immediately after menopause[10].

In recognizing the risk of CT treatment to bone health and its consequences to the quality of life of these patients, the aim of this study was to verify the BMD modification of breast cancer women who underwent CT, as well as the clinical characteristics and risk factors for low BMD.

METHODS

This is an integrative literature review of retrospective or prospective studies and clinical trials published in the last 10 years. The collection was carried out in September 2016, using primary and secondary search strategies in PubMed and SciELO computed databases.

The limits used for the bibliographic research were articles published between 2006 and 2016 in English and Portuguese, regarding humans and female sex.

The indexation terms for study collection were: breast cancer [Mesh], bone mineral density [Mesh] and chemotherapy [Mesh], which were used in combination and were based on Boolean operators.

The articles were evaluated following the inclusion and exclusion criteria illustrated in Chart 1.

Then, the texts were read in full and analyzed following the script that considered characteristics of the study (research type and outline, year and place of conduction, follow-up period, evaluation methods), participants (number of participants, inclusion criteria, age range, and anthropometric data), and the main clinical outcomes (Figure 1).

RESULTS

Eight hundred and ninety eight papers were identified (897 in PubMed base and 1 in SciELO base). After careful reading, six studies met all the inclusion criteria (Chart 1). The chosen papers were included in Table 1 in order to better describe and compare the different results obtained by the authors. Other documents were also mentioned throughout this review as the theoretical basis and discussion of the theme. Studies that showed BMD modification based on the CT regimen are found in Table 2.

The present review gathered data of 468 women with breast cancer at stages I–III that had been previously chosen in five different countries: Germany[11], Turkey[12], China[13], England[14], and the United States[15,16]. The follow-up duration in all studies comprised at least 12 months.

Chart 1. Inclusion and exclusion criteria for the literature review.

Inclusion criteria	Prospective, retrospective studies published in PubMed and SciELO databases between 2006 and 2016. English and Portuguese languages. Female breast cancer survivors treated with chemotherapy, aged ≥18 years in pre and postmenopausal periods. To analyze anthropometric data (weight, height) and measure densitometry (BMD) after CT treatment.
Exclusion criteria	Drug interventions (use of corticosteroids, vitamin supplements, biphosphates). Presence of diabetic intervention and physical exercises. Women who had been previously treated for other kind of cancer and/or metastatic women. Experiments with animals, in men and *in vitro*. Case reports, opinions, reviews, abstracts, editorials.

BMD: bone mineral density; CT: chemotherapy.

Demographic and physical characteristics were obtained from structured interviews. Anatomopathological data were collected through the review of medical records. Some studies used evaluation of bone function serum markers, such as:

- osteoprotegerin (OPG), procollagen type 1 amino-terminal propeptide (P1NP), collagen type 1 c-terminal telopeptides (CTx); and
- Bone alkaline phosphatase (BAF).

All the studies analyzed the BMD before and after CT through the Dual-Energy X-Ray Absorptiometry (DXA), which is the gold standard for such purpose.

All studies with a control group presented samples divided into age, menopause status (as well as period of menopause), number of children, and body mass index (BMI).

Only two studies did not specify the kind of CT used[15,16]. The other papers found a significant reduction of the BMD in the lumbar spine, femoral shaft, and hip after the use of six cycles of doxorubicin and cyclophosphamide (AC)[11] and cyclophosphamide, epirubicin and 5-fluorouracil (FEC), with the onset of osteoporosis in patients aged more than 50 years[12]. It is worth noting that the studies were carried out in European countries, in the United States and in China, with high prevalence of Caucasian and postmenopausal women[11-16].

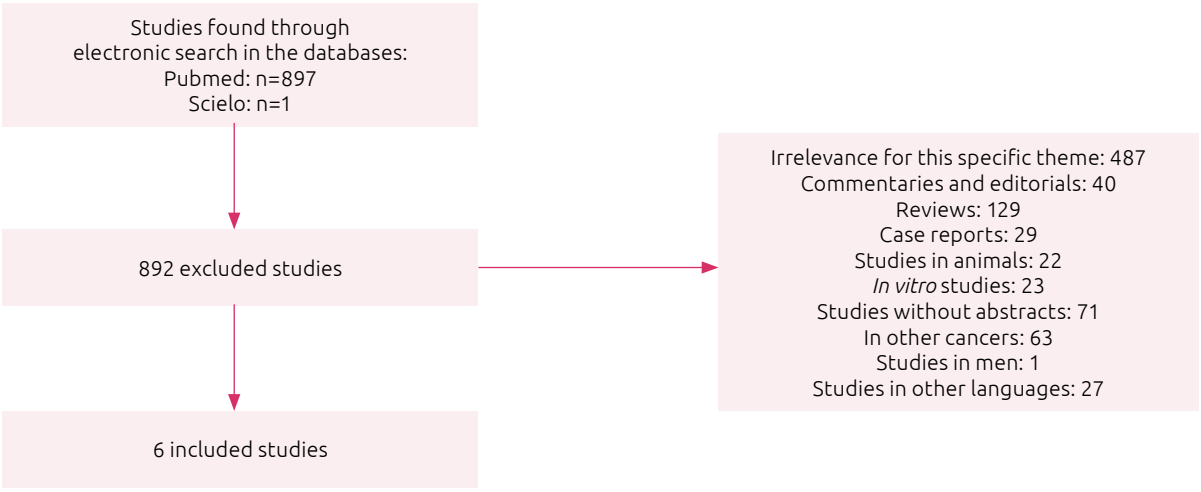

Figure 1. Flowchart of the study selection process, 2016.

Table 1. Selected articles.

Author, year, place	Population (n)	Study period	Study type	Mean age	Cancer staging
Hadji et al., 2009; Germany[11]	53 cases	12 months	Case-control	Cases 37.0 years old	I –III
	53 controls			Controls 38 years old	
Turan et al., 2009; Turkey[12]	26 cases	24 months	Case-control	Cases 49.0 years old	I–2
	21 controls			Controls 53.5 years old	II–19
					III–5
Loo et al. 2010; China[13]	120 cases	2001–2008	Case-control	66.9 years-old	I–11%
	118 controls				II–66%
					III–33%
Cameron et al., 2010; England[14]	41	2001–2003	Cohort	41.0 years-old	NR
Oostra et al.,2015; USA[15]	40	12 months	Cohort	42.0 years-old	I–II
Tabatabai et al., 2016; USA[16]	188	2006–2010	Randomized and controlled	45.9 years-old	NR

NR: non-reported.

Table 2. Modifications of the bone mineral density according to the chemotherapy regimen.

Author, year, place	CT regimen	BMD g/cm²	Δ	p-value	BMI kg/m²	Methods – interventions	Main outcomes
Hadji et al., 2009; Germany[11]	AC	NR	NR	<.0010	Control±25.0	Serum dosage: bone turnover markers; BMD through the DXA: lumbar spine, femoral shaft, and hip	Levels of bone markers increased as the BMD decreased
					Cases±25.0		In the case group, osteopenia increased from 23.5 to 39.2% after 12 months of CT
Turan et al., 2009; Turkey[12]	FEC	Mean of lumbar spine cases: 0.9380	NR	=0.010	Cases ±28.1 Controls ±28.5	BMD through DXA: lumbar spine, femoral shaft, trochanter and Ward's triangle	The spine BMD was lower in the case group (p=0.01);
		Mean of lumbar spine controls: 1.0660					The OP was higher in patients <50 years old during the CT
Loo et al. 2010; China[13]	CMF	Means of cases: mandible:	0.290	<0.050	NR	Serum dosage: hormones (estradiol, progesterone, luteinizing hormone, FSH), minerals (calcium, phosphate and magnesium) and bone turnover markers; BMD through the DXA: mandible and left hip	Menopause was marked by estrogen failure, which was more seen in the first 5 years in the G1 Patients receiving CT had a decrease of the mandible BMD in the left hip
		before CT: 1.11					
		After 48 months of CT: 0.87					
		After 60 months of CT: 0.82					
		Mean of controls: mandible	0.170				
		before CT: 1.28					
		After 48 months of CT: 1.15					
		After 60 months of CT: 1.11					
		Mean of cases: left hip	0.271				
		before CT: 0.8080					
		After 48 months of CT: 0.5912					
		After 60 months of CT: 0.5370					
		Mean of controls: left hip	0.172				
		before CT: 0.8510					
		After 48 months of CT: 0.7134					
		After 60 months of CT: 0.6790					
Cameron et al., 2010; England[14]	3 CMF	Lumbar spine	0.050	<0.001	NR	Serum dosage: estrogen and FSH – bone turnover markers; BMD through the DXA: lumbar spine and hip	Decrease of BMD in the lumbar spine and hip in 6 and 12 months after CT (p<0.001); Increase of serum markers of bone turnover after 1 year of CT No significant relation between the levels of FSH and BMD
		before CT: 1.05					
		After 6 months of CT: 1.01					
	27 AC	After 12 months of CT: 1.00					
		Total hip					
	11 AT	before CT: 0.95					
		After 6 months of CT: 0.91					
		After 12 months of CT: 0.90					

Continue...

Tabela 2. Continuation.

Author, year, place	CT regimen	BMD g/cm²	Δ	p-value	BMI kg/m²	Methods – interventions	Main outcomes
Oostra et al.,2015; USA[15]	NR	NR	NR	NR	23	Serum dosage: FSH, ionized Ca+, osteocalcin and osteoprotegerin BMD through DXA: lumbar spine and femur	Multivariate statistical analysis with ovarian failure induced by CT decreased the BMD of the lumbar spine and femur, 6 and 12 m. Osteoprotegerin decreased after 6 m (without significance after 12 m). Osteocalcin increased after 6 and 12 m
Tabatabai et al., 2016; USA[16]	NR	NR	NR	NR	26.1±6.4	Serum dosage: FSH; DXA: hip, lumbar spine and femur	Bone loss in the femoral shaft and lumbar spine; Less than 20% of the women continued menstruating after CT Amenorrhea was associated with decrease of the BMD, both in the femoral shaft and in the spine

CT: chemotherapy; BMD: bone mineral density; BMI: body mass index; AC: doxorubicin and cyclophosphamide; NR: non-reported; DXA: Dual-Energy X-Ray Absorptiometry; FEC: cyclophosphamide, epirubicin and 5-fluorouracil; OP: osteoporosis; POF: premature ovarian failure; CMF: cyclophosphamide, methotrexate and 5-fluorouracil; FSH: follicle-stimulating hormone; G1: case group (breast cancer patients); AT: anthracyclines and taxanes.

An investigation carried out in England evaluated the impact of CT in the BMD of three groups of postmenopausal women that used cyclophosphamide, methotrexate and 5-fluorouracil (CMF), followed by doxorubicin (A-CMF) or FEC, followed by docetaxel (FEC-T). There was no significant reduction of the lumbar spine and hip BMD regardless of age, BMI, estradiol levels, and CT regimen. When the group of women presenting with amenorrhea was compared with those that did not develop it, the authors found a significant decrease of the BMD in the first group ($p<0.001$)[14].

A study assessed the quality of life of 26 Turkish women with breast cancer who underwent six cycles of CT (CMF). The authors used the SF-36 questionnaire as an instrument. Postmenopausal women showed worse quality of life compared with the control group due to the higher physical limitation in daily activities. There were no alterations in the mental domain; however, the pain score had mean of 70.8 (±32.7), considering the patients presented osteoporosis and osteopenia[12].

DISCUSSION

CT seems to induce the reduction of BMD in the lumbar spine and femoral shaft segments, the decrease of femoral cortical porosity, and the decrease of femoral bone endurance, thus increasing the risk of fractures[14]. In studies reporting chemotherapeutical agents, the most vulnerable groups were those receiving treatments with AC, CMF and FEC, women aged more than 50 years and who developed POF[11-14]. Furthermore, these chemotherapeutical agents are myotoxic to musculoskeletal, which leads to dose-dependent myofibrillar loss.

This alteration is possibly associated with the action of alkylates originated from the CT that cause gonadal toxicity, which is commonly associated with the POF. The alterations seen in the bone mass, according to different studies, are influenced by the patient's age, type, dose of chemotherapeutical agent, and treatment period. These factors are found interconnected; therefore, they influence concomitantly the loss of bone mass[17]. The loss of cortical bone mass is related to estrogen failure, which contributes to age-related bone loss[18].

There is a relation between chemotherapy treatment, POF in pre-menopause, weight gain and bone mass loss due to the reduction of estrogens[11]. This effect seems to have a direct correlation with the chemotherapeutical agent dose, in addition to damaging vascularization and ovarian stroma, which, regardless of the loss of oocytes and cells of

granulosa, are related to the gonadotoxic effect of CT. The authors pointed out that ovarian aging after CT seems to develop due to a series of factors, such as apoptosis, alterations in the DNA of oocytes and in the granulosa cells, as well as vascular changes[11].

Women with osteoporosis diagnosed before the diagnosis of breast cancer, who underwent CT treatment, present an expressive risk of intensifying bone loss due to the toxic action of CT, regardless of their menopausal status. Furthermore, the risk is even higher among pre-menopausal women due to POF[9]. On the other hand, a reduction in breast cancer incidence in women with POF is known, when compared with those in the menopause at a habitual age (OR=0.59; 95%CI 0.38–0.91)[19].

A cohort study with North-American patients in the premenopausal period aged around 45.9 years aimed to assess the relationship between the level of follicle-stimulating hormone (FSH) in the baseline and the BMD modification after CT treatment. After the regression analysis adjusted by age, ethnicity, physical activity practice, initial BMD and quantity of C-reactive protein, the authors found that the lowest levels of FSH were associated with bone loss in the lumbar and femoral shaft segments after 12 months of follow-up ($p<0.001$). Amenorrhea was also associated with decreasing BMD in both evaluated sites[16], which does not occur in breast cancer patients whose neoplasm cells present positive estrogen receptors, and the absence of menstrual flow – if early diagnosed – may determine better prognosis[20].

A cohort research carried out with 40 American women in the premenopausal period aiming at evaluating the relation between OPG and bone loss in women with CT-induced POF found a reduction of the BMD in the lumbar spine and femoral shaft when they were evaluated 6 and 12 months after the beginning of the systemic treatment ($p<0.001$). The authors found a suppression of the ovarian function in both assessed periods, whereas the OPG was significantly high only in the first six months. The authors pointed out that such increase would be a compensatory attempt of the organism to stop the quick bone loss during the treatment, considering that the OPG has an inhibitory activity on the osteoclasts[15].

In addition, women with cancer and hypergonadotropic amenorrhea show a significant reduction of the bone mineral mass in the lumbar spine compared with the hypogonadotropic women; therefore, the negative correlation between the levels of FSH and BMD in this anatomical site calls our attention, which signalizes the follicle reserve depletion. This may also be explained by the fact that the lumbar spine has a larger surface and is more metabolically active; thus, it is more prone to mineral balance modifications[15].

The estrogen level required to maintain a relative regular bone remodeling in postmenopausal women is lower than that required to stimulate the classical target tissues, such as those of breast and uterus. Furthermore, the risk of fractures is inversely related to the levels of estrogen in the postmenopausal period, and one fourth of the estrogen dose, which would stimulate uterus and breast, would be sufficient to decrease bone reabsorption and increase bone mass in elderly women[21].

The BMI effects on fractures at a certain level of the BMD remain controversial due to the different effects on several fracture locations. In a cross-sectional study including 48 women with mammary neoplasms, a high percentage of body fat was verified in all the patients in the android area obtained through the DXA[22]. After analyzing the association between the risk of fractures and the BMI in healthy women aged around 63 years, a recent meta-analysis showed that the hazard ratio (HR) for osteoporotic fractures was 0.87 (0.85–0.90), when a BMI of 25 kg/m^2 was under analysis. However, when it was adjusted for the BMD, the same analysis showed an increase of the HR for osteoporotic fractures (HR=1.16; 95%CI 1.09–1.23). This investigation included prospective studies conducted in more than 25 countries. Obesity (BMI≥30 kg/m^2) was present in 22% of these subjects, and there were 30,280 osteoporotic fractures in the follow-up period. The authors concluded that the association between BMI and fractures is complex, different between the skeletal sites and modified due to the interaction between the BMI and the BMD[23].

The studies developed to assess the relationship between BMD and CT in breast cancer both agree to attribute the worst clinical outcome to CT. However, based on the populations and designs of different studies, most of these papers are observational and sometimes have conflicting results.

In association with the development of bisphosphonate, of the estrogen receptor selective modulators and vitamin D supplementation, the early identification of the high risk presented by the breast cancer population of having osteoporotic fractures is considered an effective strategy to reduce this condition. Hence, substantial efforts have been made to identify clinical risk factors, in addition to the BMD, and to integrate them to risk assessment tools or to predicting models, such as the Fracture Risk Assessment Tool (FRAX) and the Garvan Fracture Risk Calculator. In addition, vitamin D has been used in cancer patients due to its effect on the prevention of growth of tumor cells possibly reducing tumor metastases[24]. New studies establishing such relation should be carried out, especially regarding bone metastasis.

Besides the aspects directly related with the decrease of BMD and health risks, this alteration can directly affect the patients' perception of their quality of life. We also found, among breast cancer women treated with CT, that those presenting a reduction of the BMD had a worse evaluation of quality of life, especially in the physical functionality aspect[12].

Therefore, in the light of current knowledge on mammary neoplasm follow-up protocol, the following should be included: incentive to food reeducation and physical exercises, to proper vitamin supplementation, to bone mass monitoring, and to customized multidisciplinary service in order to promote early therapeutic intervention and improve the quality and survival of these patients in the pre and postmenopausal periods.

CONCLUSION

We found that CT might have different influences on the BMD of breast cancer patients, with significant reductions in the lumbar spine and femoral shaft, which can lead to the increase of fracture risk and worse quality of life perception. In addition, the main regimens associated with decrease of BMD were AC, CMF and FEC, especially in women aged more than 50 years and with POF.

REFERENCES

1. Silva BB, Fernandes RC, Martins KA, Machado MG. Influência da quimioterapia no peso corporal de mulheres com câncer de mama. Ciênc Saúde. 2010 Dec;21(3):245-52.
2. Georges SO, Braga CC, Martins KA. Variação ponderal e quimioterapia em mulheres com câncer de mama atendidas em serviço público. Mundo Saúde. 2014;38(3):260-8.
3. Chang CH, Chen SJ, Liu CY. Fracture Risk and Adjuvant Therapies in Young Breast Cancer Patients: A Population-Based Study. PLoS ONE. 2015;10(6):e0130725.
4. Pan K, Chlebowski RT, Simon MS, Ray RM, Livaudais-Toman J, Sullivan SD, et al. Medication use trajectories of portmenopausal breast cancer survivors and matched cancer-free controls. Breast Cancer Res Treat. 2016 Apr;156(3)567-76.
5. Harvey NC, Biver E, Kaufman JM, Bauer J, Branco J, Brandi ML, et al. The role of calcium supplementation in healthy musculoskeletal ageing: An expert consensus meeting of the European Society for Clinical and Economic Aspects of Osteoporosis, Osteoarthritis and Musculoskeletal Diseases (ESCEO) and the International Foundation for Osteoporosis (IOF). Osteoporos Int. 2016.
6. Feng X, McDonald JM. Disorders of bone remodeling. Annu Rev Pathol. 2011 Feb;6:121-45.
7. Klein-Nulend J, Bacabac RG. Bone adaptation and regeneration – New developments. Int J Mod Phys Conf Ser. 2012;17:34-43.
8. Zhu K, Hunter M, James A, Lim EM, Walsh JP. Associations between body mass index, lean and fat body mass and bone mineral density in middle-aged Australians: The Busselton Healthy Ageing Study. Bone. 2015;74:146-52.
9. Conde DM, Costa-Paiva L, Martinez EZ, Pinto-Neto AM. Bone mineral density in postmenopausal women with and without breast cancer. Rev Assoc Med Bras. 2012;58(6):673-8.
10. Islam M. Postmenopausal osteoporosis in obese women. J Biom Pharmacol Res. 2014;3(6).
11. Hadji P, Ziller M, Maskow C, Albert U, Kalder M. The influence of chemotherapy on bone mineral density, quantitative ultrasonometry and bone turn over in pre-menopausal women with breast cancer. Eur J Cancer. 2009;45(18):3205-12.
12. Turan Y, Kocaaga Z, Karakoyun-Celik O, Gurgan A, Duransoy A. Osteoporosis in women with breast cancer and its effect on quality of life: a pilot study. J BUON. 2009;14(2):239-43.
13. Loo WTY, Jin LJ, Cheung MNB, Chow LWC, Wang M. Combination of radiological and biochemical methods to assess bone mineral density of mandible in fullyedentulous patients after chemotherapy: a 5-year prospective study. Expert Opin Investig Drugs. 2010;19(Suppl. I):S109-15.
14. Cameron DA, Douglas S, Brown JE, Anderson RA. Bone mineral density loss during adjuvant chemotherapy in pre-menopausal women with early breast cancer: is it dependent on oestrogen deficiency? Breast Cancer Res Treat. 2010;123(3):805-14.
15. Oostra DR, Lusterberg MB, Reinbolt RE, Pan X, Wesolowski R, Shaoiro CL. Association of osteoprotegerin and bone loss after adjuvant chemotherapy in early-stage breast cancer. Mol Cell Endocrinol. 2015;402:51-6.
16. Tabatabai LS, Bloom J, Stewart S, Sellmeyer DE. FSH Levels Predict Bone Loss in Premenopausal Women Treated for Breast Cancer More Than One Year Treatment. J Clin Endocrinol Metab. 2016;101(3):1257-62.
17. Maclaran K, Panay N. Current concepts in premature ovarian insufficiency. Womens Health (LondEngl). 2015;11(2):169-82.
18. Khosla S, Melton LJ, Riggs BL. The unitary model for estrogen deficiency and the pathogenesis of osteoporosis: is a revision needed? J Bone Miner Res. 2011;26(3):441-51.
19. Wu X, Cai H, Kallianpur A, Li H, Yang G, Gao J, et al. Impact of Premature Ovarian Failure on Mortality and Morbidity among Chinese Women. PLoS ONE. 2014;9(3):e89597.
20. Sheri A, Dowsett M. Predicting response to cytotoxic drugs-the endocrine part of the story. Breast. 2011 Oct;20(Suppl. 3):S28-30.
21. Fabian CJ, Kimler BF, Zalles CM, Phillips TA, Metheny T, Petroff BK, et al. Clinical Trial of Acolbifene in Premenopausal Women at High Risk for Breast Cancer. Cancer Prev Res (Philadelphia, Pa). 2015;8(12):1146-55.
22. Godinho Mota JCM, Martins KA, Mota JF, Freitas-Junior R. Excesso de peso e de gordura androide em mulheres goianas recém-diagnosticadas com câncer de mama. RBM. 2016;26(2):50-5.
23. Johansson H, Kanis J, Oden A, Mccloskeye, Chapurlat R, Christiansen C, et al. A meta-analysis of the association of fracture risk and body mass index in women. J Bone Mineral Res. 2014;29(1):223-33.
24. Jacobs ET, Kohler LN, Kunihiro AG, Jurutka PW. Vitamin D and Colorectal, Breast, and Prostate Cancers: A Review of the Epidemiological Evidence. J Cancer. 2016;7(3):232-40.