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Skeletal sequelae of cancer and cancer treatment

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Abstract
Introduction Survivors of cancer may experience lingering adverse skeletal effects such as osteoporosis and osteomalacia. Skeletal disorders are often associated with advancing age, but these effects can be exacerbated by exposure to cancer and its treatment. This review will explore the cancer and cancer treatment-related causes of skeletal disorders.
Methods We performed a comprehensive search, using various Internet-based medical search engines such as PubMed, Medline Plus, Scopus, and Google Scholar, for published articles on the skeletal effects of cancer and cancer therapies.
Results One-hundred-forty-two publications, including journal articles, books, and book chapters, met the inclusion criteria. They included case reports, literature reviews, systematic analyses, and cohort reports. Skeletal effects resulting from cancer and cancer therapies, including hypogonadism, androgen deprivation therapy, estrogen suppression, glucocorticoids/corticosteroids, methotrexate, megestrol acetate, platinum compounds, cyclophosphamide, doxorubicin, interferon-alpha, valproic acid, cyclosporine, vitamin A, NSAIDS, estramustine, ifosfamide, radiotherapy, and combined chemotherapeutic regimens, were identified and described. Skeletal effects of hyperparathyroidism, vitamin D deficiency, gastrectomy, hypophosphatemia, and hyperprolactinemia resulting from cancer therapies were also described.
Discussion/Conclusions The publications researched during this review both highlight and emphasize the association between cancer therapies, including chemotherapy and radiotherapy, and skeletal dysfunction.
Implications for cancer survivors These studies confirm that cancer survivors experience a more rapid acceleration of bone loss than their age-matched peers who were never diagnosed with cancer. Further studies are needed to better address the skeletal needs of cancer survivors.

Keywords Osteoporosis · Cancer survivorship · Skeletal effects · Drug-induced bone loss

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Introduction

Cancer survivors have become an important component of mainstream society, as nearly 4% of the United States population has been diagnosed with cancer and survived [1]. Following great innovations in therapy and detection, the number of cancer survivors has grown to more than 10.8 million individuals. Therapy regimens used to treat cancer have undergone tremendous change over the past four decades, and adjuvant chemotherapy and hormone therapy have become more widely used. Toxic chemotherapeutic drugs, radiotherapy, surgery, hormone therapy, and tumor activity itself may result in undesired long-term effects, including cardiovascular, neurologic, integumentary, pulmonary, musculoskeletal, gastrointestinal, and endocrinologic problems.

In recognition of the challenges facing cancer survivors, the Institute of Medicine and the National Research Council released recommendations for long-term follow-up care and research in this field [2]. The Life After Cancer Care (LACC) program at The University of Texas M. D. Anderson Cancer Center was established to study the long-term health profiles of cancer survivors and to develop recommendations for

their health care. Several studies on the long-term health effects of cancer survivors have been published by the LACC team [3–12].

One of the most prevalent long-term health effects in cancer survivors is bone loss, including osteoporosis and osteomalacia. Osteoporosis is a systemic skeletal disorder defined by low bone mineral density and deterioration of the bone tissue microarchitecture, which may result in an increased propensity to fracture [13, 14]. It has been recognized as a major health threat for an estimated 44 million Americans, or 55% of people 50 years of age and older. In the United States, at least 10 million people have osteoporosis, and an additional 34 million are estimated to have low bone mass, placing them at increased risk for osteoporosis [15, 16] . Of the 10 million people estimated to have osteoporosis, 80% are women. Osteopenia is defined as bone mineral density (BMD) values between 1 and 2.5 standard deviations (SD) below the young adult mean value. Osteoporosis reflects BMD values more than 2.5 SD below the young adult mean value, and severe osteoporosis includes BMD values more than 2.5 SD below the young adult mean value in the presence of one or more fragility fractures [17].

Osteomalacia is a condition defined by incomplete mineralization of bone structure [13], otherwise known as softening of the bones. There are several groups of survivors who have been recognized to be at particularly high risk for osteoporosis. Women with breast cancer treated with cytotoxic chemotherapy frequently experience early menopause and cannot receive estrogen replacement therapy. Men with prostate cancer who are on antiandrogenic therapy and become hypogonadal are at equivalent risk for developing osteoporosis. A third group at risk for bone loss is patients with lymphoma, myeloma, or leukemia. The common mechanisms shared by these groups include the production of bone-resorbing cytokines secreted by neoplastic cells and the use of high-dose glucocorticoids in treatment regimens [18]. A number of other drugs can induce osteoporosis, including methotrexate and various cytotoxic drugs that cause renal loss of calcium, magnesium, or phosphorous (e.g., platinum compounds, cyclophosphamide, and ifosfamide). These agents can have significant impact on bone density, especially at high dosages [18]. In most cases, it is undetermined whether bone loss in cancer survivors stems directly from the therapy itself, from the underlying disease process (including the impact of cachexia, malnutrition, and poor calcium and vitamin D intake), or from a combination of the two [19]. In addition to hormone therapy and cytotoxic drugs, radiation therapy and surgical castration can lead to loss of bone density [20].

Accelerated loss of bone mineral density, with consequential complications of pain, risk of compression, and pathological and traumatic fractures, becomes more important with increased duration of survival [21]. Disease-related skeletal complications are associated with shorter overall survival and a decreased quality of life [22].

The health effects reported by cancer survivors are numerous, but medical research and published literature on the topic are scarce, especially for adult survivors. Published literature on the risk, incidence, and detection of cancer treatment-induced bone loss in survivors of cancers other than breast or prostate cancer remains limited [16]. Most studies of cancer treatment-induced bone loss focused on survivors of childhood cancers. Those studies show varied, sometimes conflicting, results, and it is, therefore, challenging for researchers to reach explicit conclusions.

This review focuses on the skeletal sequelae of cancer and cancer treatments in survivors of pediatric and adult cancers. We conducted an intensive and current search using several medical Internet search engines, including PubMed, Medline Plus, Scopus, and Google Scholar. Since we wanted to focus on skeletal effects of cancer and cancer therapies, our criteria included search terms such as osteoporosis, osteomalacia, effects of cancer therapies, drug-induced skeletal disorders, effects of hormone replacement therapies, and skeletal effects of endocrine disorders. We excluded effects of bone metastases and skeletal effects of endocrine disorders not attributed to cancer therapies.

One-hundred-forty-two publications, mostly journal articles, met the inclusion criteria and were used for this review. The following analysis chronicles the many skeletal complications experienced by cancer survivors and observed in clinical studies.

Hypogonadism

The primary cause of cancer treatment-induced bone loss in both men and women survivors is hypogonadism induced by chemotherapy, irradiation, hormone therapy, or surgical castration [20]. Osteoporosis stemming from hypogonadism is frequently seen in survivors of breast and prostate cancer, as therapeutic hypogonadism is an important strategy for controlling these hormone-dependent tumors [23]. The risk of osteoporosis induced by hypogonadism is not limited to survivors of these cancers, however. Bone loss has been observed in lymphoma survivors who received therapy regimens including corticosteroids, alkylating agents, and radiation therapy, all of which can cause hypogonadism [13, 16]. Bone loss was also observed in patients made hypogonadic by cytotoxic drugs used in hematopoietic stem cell transplantations as part of their treatment regimens for certain cancers [24].

Researchers began highlighting the association between estrogen deficiency and lower bone mass in postmenopausal

women as early as 1941 [25]. Estrogen deficiency, either due to menopause or surgical castration, can lead to increased osteoclastic bone resorption resulting in significant bone loss [13, 26]. The association between hypogonadism and osteoporosis has been more extensively studied in women than in men. Approximately 20% of men with spinal osteoporosis have hypogonadism [27], but the exact mechanism by which hypogonadism causes bone loss in men treated for prostate cancer is less clear. However, in hypogonadal prostate cancer patients, decreased circulating testosterone and estrogen levels cause a decrease in osteoblastic bone formation and an increase in osteoclastic bone resorption, resulting in accelerated bone loss [16]. (Table 1)

Chemotherapy-induced menopause and hypogonadism

Chemotherapy-induced menopause has been determined to be a more important cause of osteoporosis than the direct effects of cytotoxic agents and glucocorticoids [19]. Cytotoxic drugs used as adjuvant therapy for breast cancer may induce ovarian failure, which can ultimately hasten loss of bone mineral density in postmenopausal patients. Permanent ovarian failure was observed following individual therapeutic doses of cyclophosphamide, L-phenylalanine mustard, busulfan, chlorambucil, and mitomycin-C. Bines et al. reported that cyclophosphamide is the most common agent implicated in chemotherapy-related amenorrhea and that premature menopause was dependent on its cumulative dose [28].

The use of chemotherapy for prostate cancer is usually reserved in cases of advanced or recurring prostate cancer and studies on its effect on bone density are limited. However, chlorambucil and cyclophosphamide taken individually have been observed to cause prolonged azoospermia in male patients [29]. In addition, gonadal toxicity was evident in patients, especially those with testicular cancer, receiving a cumulative dose of cisplatinum greater than 400 mg/m^2 [30]. The effects of cyclophosphamide and cisplatinum on bone will be discussed later in this review.

Table 1 Cancer treatment regimens directly and indirectly associated with bone loss

Osteoporosis	Osteomalacia
Direct effects:	Direct effects:
Androgen Deprivation Therapy	Estramustine
Estrogen Suppression	Ifosfamide
Glucocorticoids/Corticosteroids	Valproic Acid
Methotrexate	
Megestrol Acetate	
Platinum Compounds	
Cyclophosphamide	
Doxorubicin	
Interferon-alpha	
Valproic Acid	
Cyclosporine	
Vitamin A	
NSAIDS	
Estramustine	
Ifosfamide	
Radiotherapy	
Combination Chemotherapy Regimens	
Indirect effects:	Indirect effects:
Hypogonadism	Hypophosphatemia
Hyperparathyroidism	Gastrectomy
Vitamin D Deficiency	
Gastrectomy	
Hyperprolactinemia	

Radiation-induced hypogonadism

Both female and male cancer survivors who received irradiation to the cranium [29, 31], ovaries, or testes have displayed hypogonadism [20, 27, 32–35]. Daniell et al. highlighted the association between male hypogonadism and osteoporosis through reports of fractures occurring after external-beam radiation therapy to the prostate bed for prostate cancer [27, 34]. An older report by Grigsby et al. also demonstrated hypogonadism following radiation to the prostate bed [36].

Hormone treatment-induced hypogonadism

Treatment regimens for metastatic or locally advanced non-metastatic prostate cancer increasingly involve the use of hormone therapy such as androgen deprivation therapies (ADT; i.e., bilateral orchiectomy, leuprolide, and other GnRH analogues). ADT induces severe hypogonadism characterized by loss of libido, impotence, gynecomastia, reduction of muscle mass, and loss of bone mineral density [23]. The most common type of ADT is the use of gonadotropin-releasing hormone (GnRH) agonists [37, 38]. The use of ADTs, particularly GnRH agonists, instead of surgical castration as part of the treatment regimen for cancer has been and is preferred by a large number of patients, especially those with prostate cancer [39–43].

Direct effects of cancer therapies

Androgen deprivation therapy (ADT)

Like many hormone replacement therapies, ADT is used as a palliative agent rather than as a treatment to cure the cancer itself and is taken over an extended period of time. Numerous studies, including retrospective audits, have

demonstrated the association between ADT and osteoporosis [14, 40, 43–47].

The rate of BMD loss that occurs with ADT is significantly greater (as much as 10-fold higher) than that due to normal aging or female menopause [16, 39]. Kiratli et al. reported a trend towards decreased hip BMD with increasing years of ADT; this increase was more dramatic in patients who had undergone surgical castration than in those receiving medical ADT [47].

GnRH analogues were reported in a study by Smith et al. [48] to be an independent risk factor for fracture and were associated with an increased risk of any clinical fractures, with an odds ratio of 1.13 (95% CI, 1.02–2.26, p=0.024). Maillefert et al. reported reductions in bone density from 3% to as high as 10% after 18 months of therapy with GnRH agonists [49].

Homes-Walker et al. demonstrated that the frequency of fractures in prostate cancer patients was dependent on the number of doses of gonadotropin-releasing hormone received during the first 12 months after diagnosis of cancer and on the age of the patient [50]. GnRH analogues suppress the secretion of follicle-stimulating hormone (FSH) and luteinizing hormone (LH) by the pituitary gland. These effects and hypoestrogenemia may result in decreased BMD and osteoporosis [51]. However, the review by McLeod et al. demonstrates that the mechanism of bone loss due to ADT in male survivors of cancer is not well understood. Theories include the absence of circulating testosterone, which bonds to androgen receptors on osteoblasts, mediating their proliferation, and reduced substrate for the peripheral conversion of testosterone to estrogen, which positively maintains bone mass [52].

Estrogen suppression

Aromatase inhibitors (AIs)

The most common estrogen suppressors used in the treatment of cancer are aromatase inhibitors (AIs). AIs do not exert estrogen agonist or antagonist activity; they can, however, cause bone loss by suppressing aromatase activity and interfering with the conversion of adrenal and other androgens to estrogen, thereby reducing both circulating and tissue levels of estrogen [16, 53]. A retrospective longitudinal analysis of a large cohort of patients with breast cancer determined that AIs were independently associated with a 27% increase in risk of bone loss and a 21% increase in clinical fractures, after controlling for age, comorbidities, income, geographic location, and health plan type [54].

Nonsteroidal (anastrozole and letrozole) and steroidal (exemestane) AIs may have different effects on bone. Exemestane has a structure similar to androstenedione, an androgen precursor. It is presumed to have more bone-protective qualities than anastrozole or letrozole because of the increased bone formation seen with androgen excess [23]. However, both types of AIs may result in similar degrees of bone loss regardless of whether they are steroidal or nonsteroidal. The overall effects of nonsteroidal versus steroidal AIs on bone health are controversial [55]. Osteoporosis was more frequent in patients receiving exemestane, but the fracture rate was only slightly higher than in those taking tamoxifen, and the difference did not reach statistical significance. A British study also found no statistically significant differences between the three agents in terms of effects on bone turnover markers in postmenopausal women [56].

Tamoxifen

Tamoxifen, a selective estrogen receptor modulator (SERM), has been shown to both cause and prevent bone loss, depending on the menopausal status of the woman. In premenopausal women with high estrogen levels, it works as a bone antagonist, whereas in postmenopausal women with low estrogen levels, it works as a bone agonist and seemingly protects against bone loss [57, 58].

Powles et al. determined that while tamoxifen treatment has been associated with a significant loss of BMD in premenopausal women, the effects of tamoxifen on bone actually have not been adequately studied in these women [59]. Many treatment regimens for breast cancer involve adjuvant therapy with aromatase inhibitors after two or three years of tamoxifen therapy, and measuring the effect of both therapies on bone health has posed challenges for researchers studying bone turnover because prior, or concurrent, administration of tamoxifen exerts a protective effect on bone in postmenopausal women treated with AIs.

Glucocorticoids, cytotoxic chemotherapy, and other agents

Glucocorticoids

The majority of therapeutic regimens for many hematopoietic based malignancies involve high-dose glucocorticoids, usually administered over extended periods of time. Glucocorticoids, which are often used as a pain adjuvant, palliative agent, antiemetic, or as part of the treatment, suppress the activity of osteoblasts and, therefore, reduce bone formation [20]. Prolonged exposure to corticosteroids is the third leading cause of osteoporosis, after loss of sex steroids and old age in the normal population [60]. Osteoporosis develops in approximately half of the patients on long-term treatment with glucocorticoids [13, 60]. In fact, the risk of fracture increases by 50–100% in recipients of oral corticosteroids [61, 62].

The mechanisms underlying the negative effects of glucocorticoids on bone include (i) direct inhibitory effects on osteoblast function, (ii) reduction in the production of

estrogen and testosterone along with the inhibition of anabolic action of sex steroids, and (iii) enhanced effects of parathyroid hormone [62].

There appears to be a defined relationship between the rate of bone loss and the dose of corticosteroid drug. The risk of corticosteroid-induced osteoporosis increases as the cumulative corticosteroid dose increases [63].

Methotrexate

The association between methotrexate and bone loss was reported as early as 1970 in a study of children on long-term methotrexate therapy for acute leukemia [64], and several publications have since confirmed the association [65, 66]. The review by Pfeilschifter et al. documented incidences of skeletal fractures in leukemic children ranging from 12% to 45% [13]. Methotrexate increases bone resorption and suppresses matrix mineralization, which reduces bone formation [20, 67].

Megestrol acetate

Megestrol acetate, a progestational agent used to treat metastatic breast cancer and endometrial carcinoma, has been implicated in osteoporosis and fractures in some patients. Its glucocorticoid-like activity may lead to the development of osteoporosis as well as other comorbidities. Wermers et al. documented the first possible association between megestrol and osteoporosis in two patients. This finding suggested that megestrol, especially at higher doses, may negatively affect bone density and potentially be associated with bone loss and the development of fractures [68].

Platinum-based therapy regimens

Published literature on the effects of platinum-based therapy regimens on bone is limited and primarily focused on animal studies. Platinum compounds are often administered in conjunction with other cytotoxic agents, so it has been challenging for researchers to differentiate between their effects on bone turnover and those of other agents. Cisplatinum is known for its hypomagnesemic effects, which include cessation of bone growth with suppressed osteoblast activity, inhibited bone formation, and osteopenia [18, 69, 70]. A Welsh study concluded that exposure to 6-mercaptopurine and cisplatin was associated with a reduction in hip bone mineral content in children treated for acute lymphoblastic leukemia [71].

Cyclophosphamide

Besides its role in hypogonadism, cyclophosphamide suppresses bone formation and resorption by directly arresting the cell division of preosteoblasts and osteoclasts, which in turn, results in fewer osteoblasts and osteoclasts on the bone surface [13, 16, 20]. This mechanism was also observed in an older study involving rats [72]. At the time of Wang's writing (1986), the long-term effects of cyclophosphamide on the human skeleton had not yet been determined [72]. While adjuvant taxane-containing regimens (e.g., AC [doxorubicin/cyclophosphamide] followed by paclitaxel) may elicit menopause, it remains unknown whether cyclophosphamide or the combination of a taxane and alkylating agent causes the loss of bone density [16].

Doxorubicin

Both *in vitro* studies and animal studies of doxorubicin have demonstrated that the agent inhibits the proliferation and differentiation of osteoblasts and selectively reduces the rate of bone formation by altering the interaction of parathyroid hormone with the osteoblast receptor [16, 20, 73, 74]. Studies demonstrating doxorubicin's effect on bone's biomechanical properties are limited [69].

Interferon-alpha

Interferon-alpha (INF-α), one of the earliest known cytokine agents, is used to treat certain cancers such as hematologic malignancies, especially hairy cell leukemia, and solid tumors. Treatment with this agent may suppress bone formation; however, the consequences of its effects on bone mass remain undetermined. The review by Pfeischifter et al. described that recombinant INF-α transformed the cellular functions of both osteoblastic and osteoclastic lineages [13]. Beresford et al. suggested that INF-α suppressed proliferation of normal human bone-derived cells but did not appear to enhance differentiation [75]. The majority of studies demonstrating interferon's effects on bone were conducted in *in vitro* models, and the exact mechanism remains incompletely understood [76, 77]. However, some of the *in vitro* studies suggest that INF-α causes decreased bone turnover, with decreased resorption by osteoclasts but increased differentiation of osteoblasts [77].

Solis-Herruzo et al. observed severe osteoporosis in a patient treated with ribavirin plus interferon for a year. This was the first published report of the effect of this therapy on bone mineral metabolism [78]. Another study concluded that male patients treated with interferon for multiple sclerosis demonstrated a decrease in bone mineral density [79]. In contrast, Lehmann et al. reported a case in which INF-α was instrumental in reversing some of the osteoporotic effects brought about by systemic mast cell disease [80] whereas it was suggested that INF-α inhibited the accretion of mast cells in bone marrow.

Valproic acid

In addition to its role as a mood stabilizer and anticonvulsant, the role of valproic acid (valproate) as a histone-deacetylase inhibitor renders it cytotoxic to many different types of cancer, including multiple myeloma, glioma, and melanoma. Osteopenia and osteoporosis were often reported in patients with chronic mental illness treated with long-term valproate therapy [81]. Sato et al. found that 37% of patients on valproate for epilepsy displayed osteopenia [82]. Sixty-eight percent of patients receiving chronic treatment with valproate in a study showed either osteoporosis or osteopenia compared to 22% in the control group. Furthermore, the longer an individual was on valproate, the worse the bone health; at 6-month follow-up, all lumbar spine and femoral bone density measures had worsened [81].

The mechanism behind how valproate adversely affects bone microarchitecture remains unidentified [83]. Valproate has, however, been associated with reversible Fanconi syndrome, suggesting that valproate may cause renal tubular dysfunction with increased urinary loss of calcium and phosphorus, leading to decreased mineral substrates for bone formation [84].

Cyclosporine

The immunosuppressant cyclosporine has been shown to stimulate osteoclasts, suppress osteoblasts, and inhibit mineral apposition and bone formation rates [85]. It has been hard to pinpoint the actual role of cyclosporine in bone density because it is almost always used in conjunction with other agents, such as corticosteroids, that are known to induce bone loss. Severe bone loss is often experienced by patients who undergo allogeneic or autologous hematopoietic stem cell transplantation. While post-transplantation osteopenia was brought about in part by hypogonadism, which can be prevented by hormone replacement, glucocorticoids and cyclosporine appear to be major components of bone loss in recipients, as bone loss was shown to be dependent on both the glucocorticoid dose and duration of cyclosporine therapy [86, 87].

Furthermore, in renal transplant patients, histomorphometric studies demonstrated increased bone turnover and delayed repair of renal osteodystrophy, suggesting that the effect of cyclosporine on bone turnover is independent of corticosteroids [88]. In addition, a follow-up study of patients more than six years after allogeneic bone marrow transplantation demonstrated that increased bone turnover was mainly present in patients who took cyclosporine during treatment [89].

Vitamin A

Excessive intake of vitamin A or retinoic acid was shown to be effective in the treatment of certain cancers and is suspected of inducing osteoporosis in humans [90, 91], but data are limited. In multivariate analysis, retinol intake was negatively associated with bone mineral density. For every 1-mg increase in daily intake of retinol, risk for hip fracture increased by 68% [92].

Nonsteroidal anti-inflammatory drugs

There are conflicting reports on the effect of nonsteroidal anti-inflammatory drugs (NSAIDs) on bone health. NSAIDs, which are used in various cancer therapies, inhibit the production of prostaglandins that modulate bone metabolism. Most published studies on NSAIDs' effects on bone were performed in uncontrolled settings or in animals. A study of ovariectomized rats on long-term indomethacin treatment demonstrated reduced lumbar vertebral bone mass and compressive strength [93]. In another study, Goodman et al. [94] reported that NSAIDs were associated with delayed fracture healing and bone growth in humans; however, these effects may be reversible after discontinuation of treatment. Van Staa et al. showed that regular NSAID users experienced a higher risk of fracture compared with non-NSAID controls [95]. A Japanese study demonstrated that 60% of women taking NSAIDs had BMD scores less than 80% of the nation's age-matched mean values [96].

In contrast to most data highlighting the negative effect of NSAIDs on bone health, a cohort study suggested that the use of COX-2-selective NSAIDs with aspirin was associated with higher BMD levels in various skeletal sites in both men and women [97]. Likewise, Bauer et al. found that regular use of aspirin or NSAIDs may exert a modest but beneficial effect on BMD in postmenopausal women [98].

Estramustine

Estramustine, an estrogen derivative used in prostate cancer therapy regimens, has been reported to increase bone resorption and at the same time induce hypocalcemia, hypophosphatemia, secondary hyperparathyroidism, and osteomalacia [18, 99]. It has been suggested that estramustine owes part of its therapeutic action and toxicity to a high-dose estrogen effect. Citrin et al. confirmed that estramustine was associated with significant changes in calcium and phosphate metabolism similar to those previously observed with high-dose estrogen therapy [100]. It was suggested that castration resulted in increased bone turnover and decreased BMD, but these changes may be exacerbated by using estramustine phosphate rather than bicalutamide [101].

Ifosfamide

Ifosfamide, used in many different cancer therapeutic regimens, including those for solid tumors in children, induces more sex-hormone-independent negative effects on the skeletal system than any other alkylating agent [13]. The effects of ifosfamide on the skeletal and renal systems have been well studied in the pediatric population, but a dearth of literature exists on its effects in adults [102]. Toxic effects of ifosfamide include tubular damage (e.g., Fanconi syndrome) that leads to renal phosphate wasting, hypophosphatemia, and rickets/osteomalacia [18, 103, 104]. Other associations between hypophosphatemia and Fanconi syndrome resulting from cancer therapies and bone health will be discussed later in this review.

Radiotherapy

Skeletal effects of radiation therapy may include altered bone growth and damaged or necrotic osteoblasts, which can result in secondary or uncontrolled resorption of the bone matrix [105, 106]. Bone alterations or damages caused by radiation are called radiation osteitis and radiation osteonecrosis, or osteoradionecrosis [106]. The study by Williams et al., conducted in Britain [106], suggests that radiation damage to bone in children usually involves altered bone growth patterns, wherein radiation affects the immature skeleton by disrupting the chondrogenesis and reabsorption of calcified cartilage. The authors of that study also reported that in adult skeletons, radiation may result in decreased matrix formation resulting from affected osteoblasts. However, Hopewell did not find a direct association between local radiotherapy to bone and reduced bone density in childhood cancer patients, even though the review documented other investigations that suggested reduced bone mineral density and increased fragility in mature bone [107].

Risk factors for developing radiation-associated fractures include radiation doses higher than 3,000 cGy, high-energy radiation beams, and underlying osteoporosis, especially in postmenopausal patients [105]. The effect of radiation therapy is dependent on the field of radiation, as cranial, rib, and pelvic irradiation each may result in different lingering effects.

Cranial irradiation has been studied as a prominent cause of osteopenia [13], and osteopenia was observed amongst 26 long-term survivors of cancer who were treated with cranial irradiation [108]. Therapy for tumors requiring radiation to the cranium, including acute lymphoblastic leukemia and nasopharyngeal carcinomas, can often inhibit the secretion of growth hormone and gonadotropins, which may result in hypogonadism. However, depending on the age at which treatment was received, hypopituitarism brought about by radiation can result in lack of skeletal growth and reduced BMD [109]. The mandible is particularly vulnerable to the effects of radiation, and osteoradionecrosis may occur within a year of treatment [106, 110]. As mentioned in this review, gonadotropin deficiency has been observed in patients treated with cranial irradiation, and subsequent hypogonadism may affect bone mineral density.

The literature suggests that radiation to the chest area for breast cancer and other cancers, including Hodgkin's lymphoma, can result in radiation osteotitis involving the ribs, clavicles, and scapulae [107, 111, 112]. Pierce et al. determined that among a cohort of 1624 patients treated with irradiation for early-stage breast cancer, 1.8% experienced rib fractures an average of 12 months after treatment [113]. However, a Danish study demonstrated that 19% of post-mastectomy patients treated with a large dose per fraction of radiation experienced bone damage between one and six years after treatment [114].

Pelvic irradiation for ovarian/cervical cancer and prostate cancer is a common predisposing factor for sacral and femoral neck fractures [110, 115]. Bonfiglio [115] reported back in 1953 that femoral neck fractures were observed in 2% of cervical cancer patients who received orthovoltage radiation therapy. Another study published in 1981 reported several cases of slipped upper femoral epiphysis among childhood cancer patients treated with pelvic irradiation [116]. The effects of pelvic irradiation on bones, including demineralization and osteopenia, may develop following one year after therapy, and the effects may be progressive [117]. Bone changes resulting from pelvic irradiation may not be a direct consequence of the radiation itself but rather an indirect effect of radiation-induced hypogonadism.

Combination regimens

Combination therapy regimens can also exert negative effects on bone. As mentioned previously, it has been a challenge for researchers to study the toxicity of individual agents because most cancer treatments are administered as multi-agent regimens. Determining the actual incidences of skeletal damage for individual cancer therapies is often not possible because most protocols contain multiple agents and are subject to frequent revisions, and studies involving large numbers of patients and long-term follow-up remain scarce. In childhood cancer patients, van Leeuwen et al. concluded that it was difficult to distinguish the effect of one single agent on the growing skeleton [118]. However, some combination adjuvant chemotherapy regimens (including regimens with 5-fluorouracil, cyclophosphamide, and doxorubicin or methotrexate) have been associated with low bone mass [18].

Effect of age

While bone loss and osteoporosis are common signs of advancing age, survivors of cancer may experience bone loss at a more accelerated rate than their age-matched controls. Estrogen and androgen production decreases with age, and most anti-cancer therapeutic regimens leave cancer patients with little or no remaining estrogen and/or androgen. If these levels are not increased by ongoing estrogen replacement therapy, the patient's rate of bone loss will rapidly accelerate with age. The Women's Health Initiative Observational Study showed that female survivors of breast cancer had a 15% higher rate of all fractures, regardless of treatment received, than age-matched women without any history of cancer [119]. The rate of bone loss in a study of prostate cancer survivors was nearly 10-fold greater than that reported for a group of age-matched healthy elderly men [39].

Indirect effects of cancer therapies

It has been noted in this review that chemotherapy, irradiation, and hormone therapy may indirectly affect the skeleton through the mechanism of hypogonadism. There are, however, other indirect effects on bone health that result from cancer therapies. These effects include hyperparathyroidism, hypovitaminosis D, hypophosphatemia/Fanconi syndrome, gastrointestinal complications, and hyperprolactinemia.

Hyperparathyroidism

Hyperparathyroidism has long been associated with osteoporosis in which the parathyroid hormone (PTH) activates osteoblasts, which in turn matures the osteoclasts. Osteoclasts release hydrochloric acid, which dissolves bone mineral, causing osteopenia and osteoporosis [120, 121]. Incidences of secondary hyperparathyroidism associated with glucocorticoid intake have been demonstrated variably in both human and animal studies. The review by Reid showed that in some studies, patients receiving long-term glucocorticoid therapy exhibited PTH levels 50–100% higher than those of control subjects [122]. On the other hand, Pearce et al. [63] could not determine an effect of hyperparathyroidism on bone amongst a cohort of men treated with prednisolone to reduce antisperm antibodies.

Nonetheless, the role of hyperparathyroidism on bone mineral density in patients who have undergone organ transplantation, including autologous stem cell transplantation, has not been fully studied [123]. Heaf et al. concluded that ongoing hyperparathyroidism was a major cause of bone loss after renal transplantation [124]. In the review by Conde et al. [14] corticosteroid-related hypocalcemia directly stimulates PTH secretion, which can lead to increased osteoclastic bone resorption. Immunosuppressive therapy involving cyclosporine and tacrolimus can both directly and indirectly influence bone health, resulting in secondary hyperparathyroidism and increased bone resorption [125].

Radiotherapy has been associated with hyperparathyroidism, but few studies have been published on its effect on bone density [126–128]. In a study of patients with radiation-associated hyperparathyroidism, mean lumbar spine bone mineral density was found to be lower in women whose hyperparathyroidism was induced by radiation than in women with no history of radiation exposure [129].

Vitamin D deficiency

Hypovitaminosis D, or vitamin D deficiency, can lead to alterations in calcium intake and phosphorous homeostasis, secondary hyperparathyroidism, osteomalacia, and osteoporosis, as well as an increase in fracture risk [43, 50, 79, 130–133]. The association between hypovitaminosis D and high-dose or long-term glucocorticoid therapy has been pointed out in recent studies [134, 135]. Fifteen percent of a cohort of patients treated with bone marrow transplantation displayed hypovitaminosis D more than five years after treatment [87], and associated secondary hyperparathyroidism leading to increased bone turnover was evident in these patients.

Hypophosphatemia

Varying degrees of hypophosphatemia, with associated changes in bone and mineral metabolism, have been observed in up to 45% of patients taking tyrosine kinase inhibitors such as imatinib, sunitinib, and sorafenib [136–140]. However, Grey et al. suggested that hypophosphatemia from imatinib use resulted from secondary hyperparathyroidism [137]. One suggested explanation for the abnormalities in bone and mineral metabolism seen in patients taking imatinib is that the drug itself affects the formation and resorption of bone by inhibiting the platelet-derived growth factor receptor [138].

Hypophosphatemia, due to vitamin D deficiency and secondary hyperparathyroidism or primary renal tubular defects with phosphate wasting, is the most common cause of osteomalacia [103]. Hypophosphatemic osteomalacia has been reported among prostate cancer patients, which suggests that prostate cancer itself may be a cause of tumor-induced osteomalacia [100].

Osteomalacia resulting from hypophosphatemia associated with Fanconi syndrome has been observed in patients [103], and that study suggested that cisplatin and ifosfamide were well-recognized etiologies of the syndrome. Ifosfamide

has been a well-recognized risk factor for Fanconi syndrome, and tubular damage was most commonly associated with doses of ifosfamide greater than 50 g/m^2 and with concurrent use of cisplatin [19, 102, 103].

Gastrectomy

Patients who undergo gastrectomy for gastric carcinoma may develop osteoporosis or osteomalacia [141–144]. A German study documented that the overall rate of vertebral fractures or osteopenia in a cohort of post-gastrectomy patients was as high as 55% [142]. It has been suggested that patients who undergo gastrectomy may experience hypocalcemia and low vitamin D levels because their intake of dairy products is limited and essential nutrients are malabsorbed as a result of the adverse effects of the surgery, which may result in bone loss, and ultimately, fracture [142, 144, 145]. A recently published study conducted in Korea confirmed a high rate of osteoporosis amongst patients with gastric adenocarcinoma following gastrectomy [146].

Hyperprolactinemia

Hyperprolactinemia and subsequent central hypogonadism have been associated with the development of osteoporosis [147–150]. Hyperprolactinemia caused by prolactinomia in women influences bone metabolism unfavorably, primarily owing to the impact on the activity of bone turnover markers [151].

Cranial irradiation for brain malignancies may result in hyperprolactinemia, as dopamine released from the cellular damage and degeneration of the hypothalamus is unable to inhibit prolactin secretion from the pituitary gland. Hyperprolactinemia can be observed following radiotherapy doses of greater than 40 Gy [150] and is more common in young women [152, 153]. In one study, seven of eight patients who received chemotherapy including carmustine, vincristine, and methotrexate concurrent with radiotherapy for brain malignancies exhibited hyperprolactinemia [150].

Conclusions

This is a descriptive and inclusive review of scientific literature on bone and mineral metabolic disorders to which cancer survivors are prone. This review demonstrates that dysfunctions of the skeletal system are amongst the adverse effects of anti-cancer therapy. Some effects may not develop immediately after completion of therapy, and may be compounded with advancing age. Bone loss that occurs with cancer therapy is generally more rapid and severe than postmenopausal bone loss in women or normal age-related osteoporosis in men.

Bone recovery is poor once bone loss has occurred. Therefore early intervention is crucial to improving outcomes as osteoporosis therapy, or bone maintenance therapy, is most effective at preventing deterioration of bone.

The American Society of Clinical Oncology (ASCO) in 2003 established evidence-based guidelines for clinicians for the treatment of cancer-treatment-induced bone loss in patients with breast cancer. However, guidelines still do not exist for survivors of other cancers who are experiencing bone loss, including men who survived prostate cancer. At the time of this writing, no consensus statement or societal recommendation exists advising clinicians which men should receive therapy. The lack of guidelines for survivors of cancers other than breast cancer is due, in part, to the dearth of published evidence on cancer survivorship and its follow-up strategies [2]. As of 2004, there have been 374 PubMed citations on adult cancer survivorship research compared to 23,736 citations on adult cancer treatment research [2]. However, there has been a recent surge in published studies on bone loss caused by anti-cancer therapies, and it is with hope that successful follow-up strategies will encourage more guidelines on treatment-induced bone loss in survivors of other cancers such as prostate and ovarian cancer, multiple myeloma, and other hematologic malignancies. One of the recommendations issued by the Institute of Medicine in 2005 was to refine existing guidelines on the late effects of cancer and its treatment, and to develop new ones [154]. In fact, in 2005, one of the topics that ASCO assigned several panel subgroups was to study osteoporosis in long-term cancer survivorship. Hopefully the findings from the subgroups will be published in the near future [154].

As indicated in this review, further studies on cancer treatment-induced bone loss to answer these questions and to help clinicians better address the skeletal needs of cancer survivors are highly encouraged. Studies that isolate the effects of cancer and its treatments from the effects of normal aging on bone will be extremely useful. Hopefully with new cancer survivorship programs established at various referral cancer centers, researchers will be able to follow survivors over even longer periods of time. In the meantime until appropriate guidelines are developed, clinicians and other health care providers who treat cancer survivors should: (1) be aware of the patient's full treatment history and exposure to cytotoxic agents, (2) identify the potential side effects of treatment agents/regimens, (3) identify other common risk factors not related to their treatments such as aging, family history of osteoporosis, lack of estrogen replacement therapy, a previous history of fractures, and others that may suggests an increased risk for bone loss, (4) provide diligent surveillance of patients' bone density evaluation and measurements of kidney, liver, and thyroid function studies, a complete evaluation of mineral

metabolism including serum measurements of parathyroid hormone, vitamin D metabolites, calcium, phosphate, albumin, and markers of bone turnover, and other hormones such as testosterone in men, (5) educate the individual patient on how to prevent bone loss and fractures by having adequate dietary calcium and vitamin D intake, sun exposure, exercise, prevention of falls, and the elimination of important risk factors for osteoporosis such as alcohol abuse and smoking, and (6) finally, if necessary, refer the patient to a cancer survivorship clinic.

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