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*Review*

# Vibration Therapy for Cancer-Related Bone Diseases

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**Abstract:** Patients undergoing cancer treatments and/or suffering from metastatic bone lesions experience various skeletal-related events (SREs), substantially reducing functional independence and quality of life. Therefore, researchers are working towards developing new interventions by harnessing the bone's innate anabolic response to mechanical stimulations. Whole body vibration (WBV) has recently gained interest due to its nature of being safe, effective, and easy to perform. In this review, we will summarize the most cutting-edge vibration studies of cancer models and bone-cancer cell interactions. We will also discuss various parameters, including age, vibration settings, and differences between bone sites, which may affect vibration efficacy. Studies have shown that WBV improves bone mineral density (BMD) and bone volume in patients and mice with cancer. WBV also reduces tumor burden and normalizes bone vasculature in mice. At the cellular level, vibration promotes interactions between bone cells and cancer cells, which reduce osteoclastogenesis and inhibit cancer metastatic potential. Hence, WBV could potentially serve as a new intervention or adjuvant treatment to attenuate cancer progression while preserving bone health.

**Keywords:** vibration; bone; cancer; mechanobiology



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## 1. Cancers Affect Bone Health

Cancer is a leading cause of death and a critical public health issue. It is mainly driven by unstable genetic mutations in cells, resulting in uncontrolled cell proliferations and eventual metastases to other organs. The occurrence of metastases is the primary cause of treatment failure and cancer-related deaths [1–3]. Bones are a common secondary site for the metastases of breast and prostate cancer. Approximately 70% of advanced-stage breast and prostate cancer patients suffer from bone metastases, an unusually high occurrence rate for a secondary site of cancer [1,2]. Although less common, bone metastases can still occur in patients with thyroid, lung, or bladder cancer [3].

Bones provide a fertile "soil" for cancer cells throughout various stages of the metastatic cascade [4,5]. Briefly, bone marrow stromal cells and osteoblasts attract cancer cells to the bone via the secretion of chemokines [5]. Meanwhile, primary tumors secrete extracellular vesicles and growth factors to form a pre-metastatic niche, which primes the bone for colonization [4–8]. Metastatic cancer cells interact with osteoclasts and osteoblasts to establish a "vicious cycle", thereby altering bone homeostasis and fueling tumor growth. In cancer-induced osteolytic lesions (commonly found in multiple myeloma and breast cancer metastases), cancer cells stimulate osteoclastic bone resorption primarily through PTHrP (also known as PTHLH) or RANKL [9,10]. Bone degradation releases embedded growth factors (e.g., TGF-β, IGFs, VEGFs, BMPs, and FGFs), which, in turn, promote cancer proliferation [9,10]. In cancer-induced osteoblastic lesions (commonly found in prostate cancer metastases), tumor-derived factors (e.g., FGFs, IGFs, ET1, and BMPs) stimulate osteoblastic bone formation [8,9]. Osteoblasts subsequently support tumor progression by secreting growth factors (e.g., TGF-β, IL6, and VEGFs) [8]. Notably, recent studies have shown that osteocytes, the major regulators of bone homeostasis, also interact with cancer

cells [9,11–17]. For example, osteocytes could activate Notch signaling in myeloma cells, accelerating cancer cell proliferation [11]. Under mechanical stimulation, osteocytes directly and indirectly (via endothelial cells or osteoclasts) regulate breast cancer metastatic potential [12–14,16,17]. In addition to bone cells, tumor-derived factors (e.g., G-CSF) can remodel the bone marrow vasculature to support metastases [18,19]. The highly vascularized bone microenvironment further promotes and prolongs cancer survival [20].

Patients with hormone receptor-positive tumors may be administered anti-estrogen therapies for breast or ovarian cancer [21–24] or anti-androgen therapies for prostate cancer [25–27] to starve tumors of estrogens or androgens, respectively. However, estrogens protect against bone loss by reducing osteoclast formation [21–23]. During hormone treatment, lowered estrogen levels cause a disproportional increase in osteoclast activity, thus inducing substantial bone loss [21–23]. Similarly, prostate cancer patients who undergo anti-androgen therapy suffer from bone loss, as androgens enhance osteoblast activity and help to maintain bone mass [25–27]. Other common treatments for many cancer types (e.g., breast, prostate, ovarian, pediatric cancer, and multiple myeloma) involve chemotherapy, radiotherapy, or a combination of both. Although they are effective in shrinking tumors, these standard treatments have been demonstrated to impact bone health in cancer patients [28,29]. More specifically, recent studies indicate that chemotherapy and radiotherapy induce cell senescence. These senescent cells subsequently release molecular signals that disrupt bone remodeling [30,31]. Moreover, chemotherapy can attenuate osteogenic differentiation while promoting bone resorption, resulting in the dysregulation of bone homeostasis [32,33]. On the other hand, radiation decreases the number of osteoblasts and their differentiation, ultimately causing disturbances to bone growth and the incomplete healing of bone damage [34,35].

Ultimately, patients undergoing cancer treatments and/or suffering from metastatic bone lesions experience various skeletal-related events (SREs), including pain, bone fractures, spinal cord compression, loss of mobility, and hypercalcemia [10,28,29,36], resulting in substantially reduced functional independence and quality of life.

## 2. Mechanical Stimulation and Specifically Vibration

Current standard cancer treatments induce severe bone damage in cancer patients [28,29,36] who may already be at a high risk of bone loss due to bone metastases or hormonal fluctuations [10,28]. As such, cancer treatments are often accompanied by the administration of bisphosphonates or denosumab to ameliorate bone loss and fractures. However, long-term and high-dose usage increases bone brittleness and can induce rare but severe conditions, such as osteonecrosis of the jaw [37,38]. Therefore, researchers are working towards developing new interventions by harnessing the bone's innate anabolic response to mechanical stimulations.

The bone is an active and dynamic tissue with the ability to continuously adapt to mechanical stimulation. Physical activity or exercise not only maintains bone homeostasis but also reduces the risk of developing cancer [39]. Moreover, it is beneficial both during and after cancer treatments. Studies have shown that high levels of physical activity can reduce cancer progression and the patient's mortality [40–42]. Moderate-to-vigorous exercise can mitigate adverse side effects of cancer treatments and decreases the risk of SREs in cancer patients [42,43]. In murine cancer models, exercise reduces bone lesions and tumor formations [44,45]. Nevertheless, exercise is often physically challenging for bedridden or elderly patients. This physical inactivity further accelerates the rate of bone degradation, exacerbating cancer progressions. As an alternative to exercise, whole body vibration (WBV) has recently gained attention due to its safety, effectiveness, and ease of performance. Notably, WBV has been shown to be effective in improving bone mineral density (BMD) and reducing fracture risks in patients [46–48]. Even for bedridden patients, vibration therapy can potentially preserve bone integrity with or without the condition of weight bearing [49,50].

In this review paper, we will summarize vibration studies involving cancer models (Figure 1) in clinical trials (Table 1) [51–56], in animal studies (Table 2) [57–59], and in vitro studies examining bone-cancer cell interactions (Table 3) [16,17,60]. We will also discuss various parameters that may affect vibration efficacy, including age, vibration settings, and differences between bone sites.

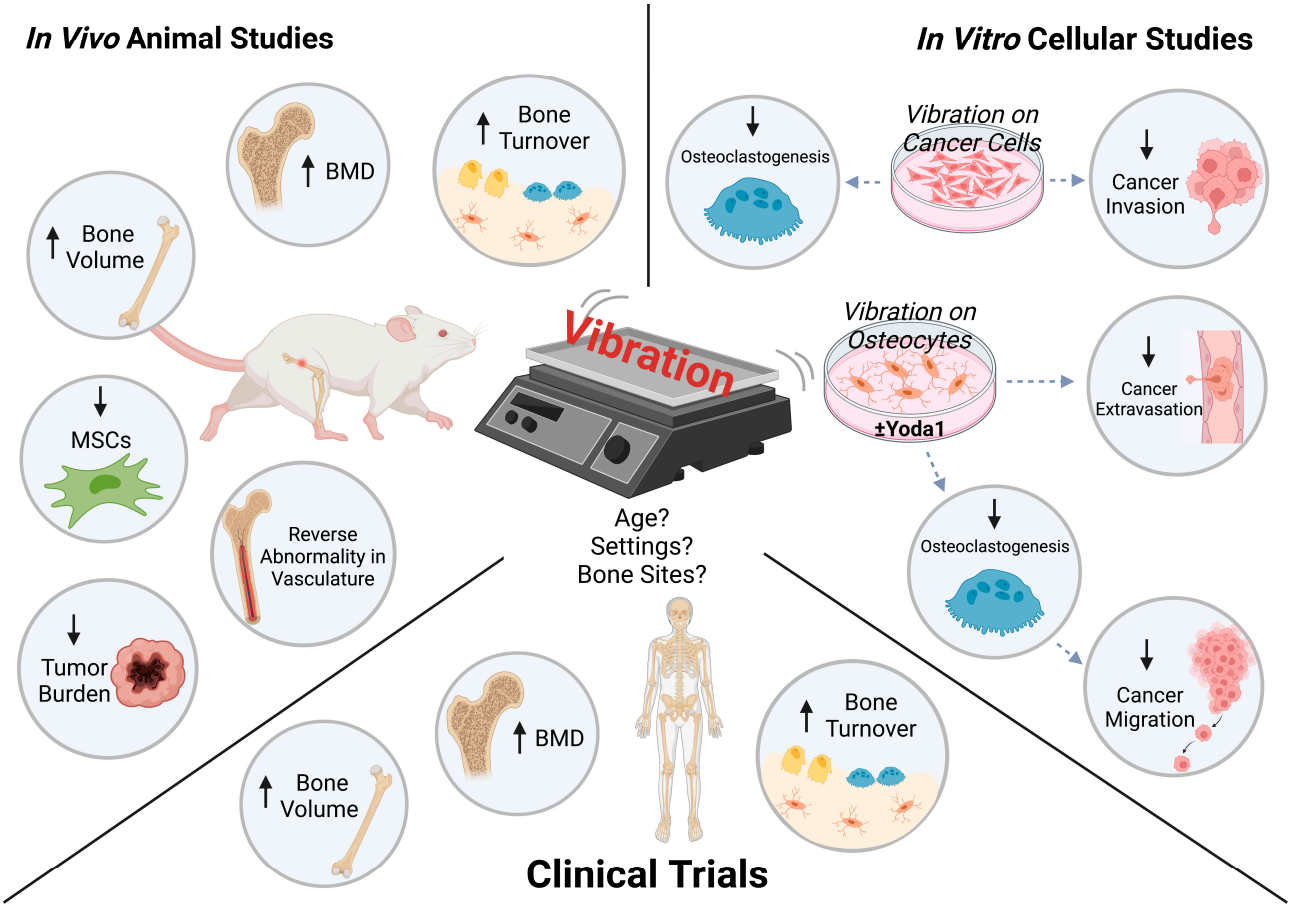


**Figure 1.** Effects of mechanical vibration on cancer patients, murine cancer models, and bone-cancer cell interactions. Created with BioRender.com.

**Table 1.** Effects of mechanical vibration on cancer patients.

| | Treatment | Vibration Magnitude and Frequency | Vibration Duration | Age | Cancer | Major Findings |
|---|---|---|---|---|---|---|
| Mogil et al. 2016 [51] | WBV | 0.3 g; 32–37 Hz | 10 min/session; 2 sessions/day; 7 days/week for 1 year | Mean 14 | Pediatric cancer | - Total-body BMD ↑<br>- Tibial trabecular bone ↑<br>- Osteocalcin, P1NP, BSAP ↑ (trend)<br>- RANKL ↑<br>- Circulating osteocalcin correlated with change in total-body BMD |
| Almstedt et al. 2016 [52] | Resistance cardio training + WBV | 20–25 Hz | 30–45 s/day; 3 days/week for 26 weeks | Mean 63 | Breast cancer | - BMD at spine, hips, and whole body ↑<br>- P1NP ↓<br>- CTX ↓ (trend) |

**Table 1.** *Cont.*

| | Treatment | Vibration Magnitude and Frequency | Vibration Duration | Age | Cancer | Major Findings |
|---|---|---|---|---|---|---|
| Baker et al. 2018 [53] | WBV | 0.3 g; 27–32 Hz | 20 min/session; 3 sessions/ week for 12 weeks | Mean 62 | Breast cancer | - No differences for markers of bone formation/resorption, physical functioning, body composition<br>- No changes in BMD |
| Seefried et al. 2020 [54] | WBV | 1.5–3 mm; 7–30 Hz | 30 min/session; 2 sessions/ week for 3 or 6 months | Median 62 | Precancer | - Physical functioning ↑<br>- No differences in tibial BMD<br>- Sclerostin, NTX of collagen type 1, TRACP5b ↑ (trend)<br>- DKK1, P1NP ↓ (trend)<br>- Total ALP ↓ |
| de Sire et al. 2021 [55] | Exercise + WBV | 20.44 m/s$^2$ (2.1 g with g = 9.81 m/s$^2$); 30 Hz | 50–60 min/ session; 3 sessions/week for 4 weeks | Mean 52 | Breast cancer | - Physical performance ↑<br>- Muscle strength ↑<br>- Pain ↓ |

Note: trend: non-significant difference with $p > 0.05$. ↑: increased. ↓: decreased.

**Table 2.** Effects of mechanical vibration on cancer animal models.

| | Vibration Magnitude and Frequency | Vibration Duration | Age | Cancer | Major Findings |
|---|---|---|---|---|---|
| Pagnotti et al. 2012 [57] | 0.3 g; 90 Hz | 15 min/day; 5 days/week for a year | 3 months | Ovarian cancer | - Trabecular bone volume of proximal tibia and L5 vertebrae ↑<br>- L5 vertebrae was more plate-like<br>- Marrow-derived MSCs ↓<br>- Overall tumor incidence and metastatic lesions ↓ (trend) |
| Pagnotti et al. 2016 [58] | | 15 min/day; 5 days/week for 8 weeks | 7 weeks | Multiple myeloma | - Trabecular bone volume in the femur ↑ but not in the tibia<br>- Cortical bone volume in the femur ↑<br>- Transcortical perforations in the femur ↓<br>- Trabecular bone volume and trabecular connectivity density in the L5 vertebrae ↑<br>- Serum TRACP5b ↓<br>- Tumor expansion and myeloma cells ↓<br>- Necrotic tumor of tibial marrow ↓ |
| Matsumoto et al. 2022 [59] | | 20 min/day; 5 days/week for 3 weeks | 8 weeks | Breast cancer | - Osteolytic bone loss ↓<br>- BMD of cortical and trabecular bones ↑<br>- Serum osteocalcin ↑ (trend)<br>- Vessel diameter ↓, vessel number density ↑ (trend), and vessel diameter heterogeneity ↓ |

Note: trend: non-significant difference with $p > 0.05$. ↑: increased. ↓: decreased.

**Table 3.** Effects of mechanical vibration on bone-cancer cell interactions.

| | Vibration Magnitude and Frequency | Vibration Duration | Cells Exposed to Vibration | Cancer | Experimental Set-Up | Major Findings |
|---|---|---|---|---|---|---|
| Yi et al. 2020 [60] | 0.3 g; 90 Hz | 20 min/bout; 1 or 2 bouts/day for 3 days | MDA-MB-231, MCF-7 breast cancer | | Conventional cell cultures | - PTHLH, IL11, RANKL ↓<br>- Osteoclastogenesis ↓<br>- FASL-mediated cancer apoptosis ↑<br>- Cancer invasion ↓ more with twice-daily vibration<br>- Cancer cell stiffness ↑ |
| Lin et al. 2022 [16] | 0.3 g; 60 Hz | 1 h | MLO-Y4 osteocytes; MDA-MB-231 breast cancer | MDA-MB-231 breast cancer | | - Nuclear translocation of YAP ↑<br>- Vibration + Yoda1: nuclear translocation of YAP ↑↑<br>- Vibration ± Yoda1: osteoclastogenesis ↓<br>- Vibration + Yoda1: cancer migration ↓ |
| Song et al. 2022 [17] | | 1 h/day for 3 days | MLO-Y4 osteocytes; HUVECs; MDA-MB-231 breast cancer | | Microfluidic platform | - COX-2, Piezo1 ↑<br>- RANKL and RANKL/OPG ↓<br>- Piezo1 knockdown in osteocytes: vibration-stimulation of COX-2, OPG ↓<br>- Cancer extravasation ↓<br>- Vibration + Yoda1: cancer extravasation ↓↓ on Day 2 but no on Day 4 |

Note: ↑: increased. ↓: decreased. ↑↑: more increased. ↓↓: more decreased.

## 3. Vibration Effects on Cancer Models and Bone-Cancer Cell Interactions

The effects of vibration on cancer patients (Table 1) [51–56], cancer animal models (Table 2) [57–59], and bone-cancer cell interactions (Table 3) [16,17,60] are summarized below (Figure 1). Specifically, we examine vibration safety, summarize vibration effects on bone health (i.e., BMD, bone volume, bone remodeling, and bone turnovers), and elucidate the impacts of vibration on tumor burden and progression, bone vascularization, and mesenchymal stem cells (MSCs).

### *3.1. Safe to Perform*

In studies examining WBV effects on cancer patients, no adverse effects were reported for children, adolescents [51,56], adults, or the elderly [52–55]. However, in an exploratory feasibility study, it was proposed that while no WBV-related adverse events were reported, there were two incidents of bleeding in patients with low platelets (<30,000/μL) [56]. When a 30,000 platelets/μL of blood threshold was established, no additional incidents occurred [56]. While Baker et al. reported that vibration was well tolerated, one patient experienced syncope, and another reported increased arm swelling [53]. These events were classified as minor, and all participants were able to continue with the vibration intervention.

In animal studies, mice with ovarian cancer underwent long-term (1 year) WBV (0.3 g, 90 Hz), but the longevity was unperturbed by WBV [57]. In general, WBV has been reported as safe for cancer patients and animals.

### *3.2. Bone Mineral Density (BMD) and Bone Volume*

Current clinical studies report varying effects of WBV on BMD and bone volume (Table 1). WBV did not change BMD or bone volume in aged cancer patients (~62 years old) [53,54]. However, in young cancer survivors (~14 years old), WBV (0.3 g, 32–37 Hz) was found to increase their BMD and tibial trabecular bone by 11.2% [51]. In a study examining the effects of combined aerobic and resistance training on bone health, the authors reported significant improvements in BMD at the spine, hip, and whole body in postmenopausal cancer survivors [52]. Specifically, WBV (20–25 Hz) was included as two stations in a circuit-style resistance training regimen [52]. While the authors concluded that the observed osteogenic effects may be due to the vibration, it is more likely that improvements in BMD were attributed to the combined effects of both exercise and vibration. These results were further supported by a pilot study demonstrating that the combination of exercise and

WBV significantly reduced pain and improved muscle strength and physical performance in breast cancer patients [55].

More beneficial effects can be observed in animal studies (Table 2). In a murine model of ovarian cancer, WBV (0.3 g, 90 Hz) improved trabecular bone volume in the proximal tibia and the L5 vertebrae [57]. Moreover, vibration made the L5 vertebrae more plate-like, which is more resilient and stronger than rod-like structures [57]. In mice with multiple myeloma, WBV (0.3 g, 90 Hz) increased trabecular and cortical bone volume and reduced transcortical perforations caused by myeloma-induced osteolysis in the femur [58]. Trabecular bone volume and trabecular connectivity density in the L5 vertebrae were also higher in the WBV group [58]. Furthermore, WBV (0.3 g, 90 Hz) reduced osteolytic bone loss and elevated the mean BMD of cortical and trabecular bones in mice with breast cancer [59]. These studies suggest that WBV improves both bone mass and structural quality in young cancer patients and in murine cancer models.

### *3.3. Bone Remodeling and Turnover Markers*

Several studies have examined the effects of WBV on bone turnover in clinical trials (Table 1) [51,53,54]. In postmenopausal women with breast cancer, WBV (0.3 g, 27–32 Hz) did not alter the expression of bone turnover markers [53]. However, in childhood cancer survivors, WBV (0.3 g, 32–37 Hz) promoted the expression of bone formation markers (i.e., osteocalcin, P1NP, and BSAP), which matched the increases in BMD and trabecular bone percentages [51]. Notably, vibration also increased the level of bone resorption markers (i.e., mean RANKL), indicating enhanced osteoclast activity and bone turnover [51]. Seefried et al. also reported that WBV (1.5–3 mm, 7–30 Hz) increased the levels of sclerostin and bone resorption markers (i.e., NTX of collagen type 1 and TRACP5b) while reducing the levels of total ALP, DKK1, and P1NP [54]. The reduced level of P1NP were also observed in breast cancer survivors under combined exercise and vibration (20–25 Hz) treatment [52]. These changes in biomarkers indicate that WBV indeed induces adaptive and anabolic responses by promoting bone turnover.

Bone anabolic responses stimulated by WBV have been reported in animal studies as well (Table 2). In myeloma-injected mice, elevated serum-bound TRACP5b induced by myeloma was suppressed by vibration (0.3 g, 90 Hz) [58], indicating that WBV can reduce bone resorption and potentially normalize bone remodeling in the face of cancer-specific perturbations. Additionally, Matsumoto et al. measured the level of serum osteocalcin, a marker of bone turnover, in mice with breast cancer [59]. The authors reported a higher level of osteocalcin in the vibration group (0.3 g, 90 Hz) [59], suggesting the potential contribution of WBV in inducing bone anabolic responses while regulating cancer-induced bone loss.

At the cellular level, vibration can directly regulate bone effector cells involved in bone remodeling. Vibration has been shown to modulate osteogenic markers in osteoblastic cells by upregulating ALP, RUNX2, and OPG while downregulating RANKL [61–65]. However, the literature presents mixed results regarding RANKL expression in osteocytes. In studies conducted by Song et al. and Lau et al., vibration (0.3 g, 60 Hz) decreased the levels of transcriptional and secreted RANKL in osteocytes (Table 3) [17,66]. In contrast, Sakamoto et al. (0.5 g, 48.3 Hz) reported a significant increase in RANKL expression, and Thompson et al. (0.7 g, 90 Hz) did not observe a difference in RANKL expression [67,68]. These inconsistent findings may be attributed to variations in vibration settings, cell models, and the incubation period after vibration exposure. In addition to directly regulating bone cells, vibration can promote cellular interactions involved in bone remodeling. Several studies applied vibration (0.3 g, 60 Hz) to osteocytes to investigate their role in regulating osteoclastogenesis (Table 3) [16,66]. The authors found that vibration-stimulated osteocytes reduced osteoclast formation [16,66]. Moreover, Yi et al. applied vibration (0.3 g, 90 Hz) to breast cancer cells and studied cancer cell regulation of osteoclastogenesis (Table 3) [60]. The authors observed that vibration reduced osteoclast formation through

cancer cell signaling [60]. Taken together, these studies indicate that vibration can suppress osteoclastogenesis through both cancer cell and osteocyte signaling.

### *3.4. Tumor Burden and Progression*

Animal studies have shown that vibration could directly affect tumor burden and progression in bone (Table 2). Primary lesions caused by ovarian cancer and peripheral metastases were apparent in both vibration (0.3 g, 90 Hz) and static groups. However, the overall tumor incidence and metastatic lesions were reduced by WBV [57]. WBV (0.3 g, 90 Hz) also decreased the myeloma cell population, suppressed tumor expansion, and reduced the presence of necrotic tumor in the tibial marrow [58].

At the cellular level, vibration (0.3 g, 90 Hz) suppressed breast cancer invasion and the expression of osteolytic factors (i.e., PTHLH, IL11, and RANKL) (Table 3) [60]. Vibration also enhanced cancer cell stiffness by upregulating the production of LINC complex components, thereby reducing cancer metastatic potential [60]. On the contrary, another study demonstrated that vibration (0.15 g, 90 Hz) did not affect breast cancer migration [69]. Moreover, Song et al. used a microfluidic co-culture platform to mimic the bone-cancer microenvironment and apply vibration (0.3 g, 60 Hz) to multiple cell types, including osteocytes, human umbilical vein endothelial cells (HUVECs), and breast cancer cells (Table 3) [17]. While vibration did not significantly impact cancer invasion under monoculture conditions, breast cancer extravasation (i.e., transendothelial cancer invasion) was reduced in co-culture with osteocytes. These results suggest that osteocytes play a critical role in regulating endothelial cancer cell interactions under vibration [17].

### *3.5. Vascularization*

The structure of the bone marrow vasculature has a vital role in the tumor microenvironment. An abnormal and heterogeneous vasculature caused by cancer metastasis promotes tumor progression and affects the delivery of antitumor drugs [70,71]. The heterogeneous vasculature can also result in heterogeneous perfusion, leading to localized tissue hypoxia. The hypoxia environment makes tumors more aggressive and metastatic [72,73]. Matsumoto et al. demonstrated that WBV (0.3 g, 90 Hz) could reverse the abnormal changes in the marrow vasculature in a murine model of breast cancer bone metastasis [59]. Specifically, WBV decreased vessel diameter and reduced diameter heterogeneity, thereby improving tumor perfusion and oxygenation (Table 2) [59].

In vitro, mechanical stimulations can modulate endothelial cell functions through osteocyte signaling. For example, one study showed that flow-stimulated osteocytes reduced endothelial permeability and cancer adhesion onto endothelial monolayers [13]. Recently, Song et al. studied osteocyte regulation of breast cancer invasion with and without endothelial cells under vibration (0.3 g, 60 Hz) using a microfluidic co-culture platform [17]. The inclusion of a 3D monolayer of endothelial cells not only improved the physiological relevance of the cancer tissue model but also further inhibited cancer invasion [17]. This result suggests that vibration may affect endothelial cells, leading to cellular crosstalk that alters cancer cell behaviors. As endothelial cells closely interact with both cancer and bone cells [13,74,75], future studies are needed to investigate their functions under vibration.

### *3.6. Mesenchymal Stem Cell (MSC) Population*

The MSC population serves as a double-edged sword in the tumor microenvironment, both promoting [76] and suppressing [77] tumor growth. In mice with multiple myeloma, increased tumor burden was associated with an elevated MSC population, which could be lowered by WBV (0.3 g, 90 Hz) (Table 2) [57]. These data suggest that vibration reduces the MSC population by driving MSCs towards the formation of bone tissue. This speculation was supported by another mice study, in which MSCs showed a tendency to differentiate into connective tissues such as bones rather than adipose and neoplastic tissues under vibration [78]. In vitro studies have also shown that vibration induces osteogenic differ-

entiation of MSCs by upregulating the expression of osteogenic markers, such as RUNX2, osterix, type 1 collagen, osteocalcin, and ALP [79–82].

## 4. Parameters Contributing towards Vibration Efficacy

Although vibration has been shown to potentially preserve bone health and suppress tumor progression, mixed results are presented in the literature. In the following sections, we discuss various parameters, including age, vibration settings (i.e., magnitude, frequency, and rest periods), and differences between bone sites, which may affect vibration efficacy.

### *4.1. Age*

Postmenopausal women encounter a reduction in estrogen levels, which can result in the development of osteoporosis and a considerable elevation in fracture risk. Encouragingly, emerging research suggests that vibration therapy holds promise in mitigating bone deterioration in this population. Specifically, significant improvements in bone turnover [83], BMD [46–48], and bone stiffness [84] were observed in postmenopausal women exposed to WBV. Studies have shown that the involvement of estrogen receptor $\alpha$-signaling under estrogen deficiency could potentially enhance bone sensitivity to vibration [85,86]. Conversely, young and healthy adults (19–38 years old) exposed to WBV (2–8 g, 25–45 Hz) demonstrated no effects on bone mass, bone structure, and overall strength [87]. Furthermore, the beneficial effects of vibration have also been reflected in aged bone cells [88–90]. For instance, vibration (0.3 g, 90 Hz) stimulated the expression of osteogenic genes in aged rat-derived bone marrow MSCs [88]. Vibration (0.7 g, 90 Hz) also increased cell proliferation, restored oxidoreductase activity (i.e., G6PD and NADP-ME1 proteins), and reduced senescence-associated beta-galactosidase (SA-βgal) activity in late passage (P60) primary MSCs [89]. Despite differences in vibration settings, aged participants or cells exhibit greater improvements under vibration interventions, whereas their younger and healthier counterparts may not benefit from vibration, as they have no need to adapt to vibration [91].

For cancer patients with a poor baseline of bone health (Table 1), WBV appears to have a greater impact on bones in children [51] than in postmenopausal women [53]. In cancer studies, WBV increased BMD and tibial trabecular bone percentage in young cancer survivors (~14 years old; WBV: 0.3 g, 32–37 Hz) [51] but not in postmenopausal breast cancer patients (~62 years old; WBV: 0.3 g, 27–32 Hz) receiving aromatase inhibitors [53]. Notably, the lack of beneficial effects in postmenopausal women may be attributed to ongoing aromatase inhibitor therapy or the short duration of exposure to vibration [53]. Alternatively, it is more likely that there is a decline in bone mechanosensitivity with increasing age.

Age dependency is more prominent in animal studies. The beneficial effects of vibration on bone health were observed in young and adult animals, including sheep [92–94], rats [95,96], and mice [97,98]. In addition, several studies compared vibration efficacy in young adult animals to aged animals. WBV (0.3/1 g, 90 Hz) increased bone mineral content (BMC) in 7-month-old but not 22-month-old mice [98]. In another study involving 9-month-old rats, WBV (0.3 g, 35 Hz) promoted fracture healing in osteoporotic bones only in week 2 and week 3 [96]. As the rats became more advanced in age, the beneficial effects of vibration were not observed in week 8 [96]. These data suggest that vibration does not demonstrate similar beneficial effects in aged animal models compared to young adult animal models.

Inconsistencies in the effects of vibration due to age can also be observed in vitro. For example, vibration (0.7 g, 90 Hz) only demonstrated an upregulation of transcriptional ALP in the early passage (P12–15) primary MSCs but not in the late passage cells (P60) [89], suggesting passage-dependent effects of vibration. Aged osteocytes and osteoblasts are less responsive to fluid flow, implying that their mechanosensitivity is altered over time [99,100]. It is possible that age-related degeneration of the intricate lacunocanalicular network (LCN) changes the LCN architecture and impairs fluid dynamics [101], thereby affecting its

ability to transmit mechanical signals. Alternatively, aging could induce changes in the morphology of osteocytes [102], which are the major mechanosensing bone cells [103,104], resulting in impaired osteocyte mechanotransduction and subsequent biological responses.

To overcome the mechanosensing barrier for the elderly, Yoda1 has recently gained attention. Yoda1 is an activator of Piezo1, a mechanosensitive ion channel highly expressed in bone cells [105–107]. Studies have revealed that the loss of Piezo1 in mice makes bones small and weak and impairs their response to fluid flow [106,107]. At the cellular level, Piezo1 knockdown in osteocytes blunted their response to vibration by reducing the expression of mechanosensitive genes (i.e., COX2 and OPG) [17]. On the other hand, the chemical activation of Piezo1 by Yoda1 stimulated the expression of mechanosensitive genes and increased intracellular calcium concentration [106]. Therefore, researchers believe that Yoda1 can potentially enhance the effects of vibration (Table 3). A recent study showed that Yoda1 further enhanced the effects of vibration (0.3 g, 60 Hz) on YAP translocation in osteocytes [16]. With the help of Yoda1, vibration-stimulated osteocytes decreased osteoclastogenesis and further reduced breast cancer migration [16]. The Yoda1 enhancement effect was further validated by a microfluidic study, which demonstrated that Yoda1 accelerated the effects of vibration (0.3 g, 60 Hz), reducing breast cancer extravasation at early time points [17]. These studies provide evidence that Yoda1 can enhance the vibration-induced inhibition of osteoclastogenesis and breast cancer metastatic potential, paving the way to elevate bone mechanosensitivity for the elderly.

### *4.2. Vibration Settings*

#### 4.2.1. Magnitude and Frequency

When considering theory alone, Wolff's law states that bone remodeling is triggered wherever load is placed [108,109]. For vibration, the beneficial effects are dependent on the selected settings. Clinical studies have shown that low-magnitude vibration can increase BMD [47,84,110]. Notably, low-magnitude (LM, $\leq$1 g) high-frequency (HF, $\geq$30 Hz) vibration was found to be optimal for patients with compromised bone quality [84] but not for those with healthy bones [111]. Pre-osteoporotic postmenopausal women displayed improvements in tibial stiffness and increases in trabecular BMD following exposure to LMHF vibration (0.3 g, 30 Hz) [84]. In contrast, healthy postmenopausal women exhibited no changes under LMHF vibration (0.3 g, 30–90 Hz) [111]. In addition to WBV with LMHF, other settings, including low-magnitude low-frequency (LMLF) vibration and high-magnitude low-frequency (HMLF) vibration, have also been shown to promote bone health [83,110]. For instance, LMLF vibration (0.3 g, 12 Hz) significantly reduced bone resorption by decreasing NTx/Cr levels [83]. A meta-analysis revealed that HMLF vibration could improve BMD of the lumbar spine similar to LMHF vibration [110].

Conflicting results have been also observed in cancer patients (Table 1). While LMHF vibration was effective for childhood cancer survivors [51], it was insufficient to generate an osteogenic stimulus in postmenopausal breast cancer survivors receiving aromatase inhibitors [53]. In addition to the age difference, aromatase inhibitors are known to greatly reduce bone quality [21–23], to the extent that even physical activity did not result in significant improvements in bone health [112]. As such, the intensity and duration of WBV may need to be much higher and longer to overcome the significant bone loss induced by aromatase inhibitors. Of note, a precancer study highlighted the potential benefits of increasing magnitude (1.5–3 mm) and frequency (7–30 Hz) over time [54]. Improvements in physical functioning and bone metabolism may be due to the gradual adaptation to mechanical stimulation, thereby enhancing the biochemical and structural bone properties. In summary, an effective regimen of WBV treatment in clinical trials is not well established. This lack of knowledge may be primarily attributed to various factors, such as age and disease conditions, which are hard to control in patients.

Unlike clinical trials, it is well established that LMHF vibration promotes bone health in animals with (Table 2) [57–59] and without cancer [98,113–115]. However, these beneficial effects may depend on the specific magnitude and frequency. A study in turkeys

demonstrated a linear dose–response in labeled bone surface expansion with increasing magnitude from 0.1 g to 0.9 g (at 30 Hz) [113], whereas another study showed a non-dose-dependent phenomenon [114]. In this study, mice exposed to 0.1 g and 1 g WBV had significant improvements in trabecular bone volume compared to those exposed to 0.3 g (at 45 Hz) [114]. In contrast, Lynch et al. did not find that 1 g WBV produced more anabolic effects than 0.3 g (at 90 Hz), as both magnitudes effectively improved BMC in mice [98]. In terms of frequency, Judex et al. reported that 90 Hz WBV effectively stimulated bone formation, increased trabecular bone volume, and thickened trabeculae compared to 45 Hz (at 0.15 g) in rats [115]. There are mixed results regarding magnitude dependency, and only a few are focused on finding the optimal frequency; hence, more studies are needed.

At the cellular level, selecting an optimal magnitude and frequency depends on the cell types and desired outcomes. In rat-derived bone marrow MSCs, vibration promoted the expression of osteogenic genes (i.e., RUNX2 and osteocalcin) most significantly at 0.3 g and 90 Hz among all tested settings [88]. In MLO-Y4 osteocytes, RANKL levels for osteoclast formation were most significantly reduced at 60 Hz compared to 30 Hz or 90 Hz (at 0.3 g) [66]. Another study demonstrated that vibration at 5.0 $m/s^2$ (0.51 g, where g = 9.81 $m/s^2$) and 60 Hz was the most effective setting for osteogenesis by upregulating RUNX2, type 1 collagen, and ALP expressions in MC3T3-E1 osteoblasts [61]. In cancer cells, vibration at 0.3 g and 90 Hz decreased breast cancer invasion [60]. However, Song et al. (0.3 g, 60 Hz) and Olcum et al. (0.15 g, 90 Hz) reported no negative impacts of vibration on breast cancer invasion (in mono-culture conditions) and migration, respectively [17,69]. These seemingly contradictory observations were possibly due to variations in vibration settings, durations, and experimental assays.

#### 4.2.2. Rest Periods

Zhang et al. demonstrated that a 7-day insertion, in which vibration (0.25 g, 35 Hz, 15 min/day) for 7 days was followed by a 7-day rest, significantly increased the rate of bone formation and improved micromechanical properties in rats [116]. However, in a recent rat study, three bouts of daily vibration (0.25 g, 35 Hz, 5 min/bout) separated by 4 h between each bout more effectively promoted fracture healing than the aforementioned 7-day rest insertion, indicating that osteogenic accumulation may be weakened by the long period of rest [117].

The benefits of inserting rest periods also can be observed at the cellular level. Twice-daily vibration (0.3 g, 90 Hz, 20 min/bout) separated by 3 h of rest decreased breast cancer invasion more than once-daily vibration treatment (Table 3) [60]. Therefore, including rest periods between vibration treatments could improve vibration efficacy.

### *4.3. Bone Site-Specific*

The transmissibility of vibration mainly depends on the participant's posture on the platform. An upright, erect posture enhances the effects on the lumbar spine [46,51], whereas a semi-squat stance with flexed knees reduces transmission through the spine to the head and concentrates the effects of vibration at the hip [48]. Lai et al. reported a significant increase in the BMD of the lumbar spine in participants following vibration exposure (3.2 g, 30 Hz) in a fully standing posture [46]. In contrast, Gusi et al. instructed participants to stand on the platform with a 60-degree angle of flexion [48]. Vibration (12.6 Hz) increased BMD at the femoral neck, but no changes were reported in the lumbar spine [48]. Despite differences in vibration settings, both studies involved postmenopausal women with similar age ranges and selection criteria, further emphasizing the impact of posture on the effects of vibration. Generally, more positive effects can be found in appendicular skeletons, which are closer to the site of vibration than axial skeletons. However, in a murine cancer model, beneficial effects of vibration (0.3 g, 90 Hz) were also found in axial skeletons (i.e., L5 vertebrae) [57,58], suggesting a significant contribution from circulatory factors.

The anabolic effects of vibration are specific to the region of the skeleton. For example, sheep exposed to WBV (0.3 g, 30 Hz) exhibited a higher rate of bone formation and a greater

mineralizing surface in the trabecular bone but not in the cortical bone [93,94]. Similarly, in rats exposed to WBV (90 Hz), more significant effects were observed in the trabecular bone compared to the cortical bone [118]. These findings can be attributed to the characteristics of the trabecular bone, which has a larger surface area exposed to bone marrow and blood flow and contains a greater number of bone cells, leading to a higher metabolic activity and a faster bone remodeling rate [119,120]. Hence, the trabecular bone is more responsive and malleable to mechanical stimulation than the cortical bone [93,94].

Finally, there is evidence of spatial and volume differences in bone marrow not only within a specific bone but also between different bones [121,122]. These variations may influence cancer progression and the efficacy of vibration. For instance, in mice with myeloma, tumor necrosis was observed in the tibia but not in the femur [58]. This dissimilarity may be because the volume of marrow in the femur is approximately twice that of the tibia, and tumor necrosis begins after crowding out the bone marrow, resulting in varying rates of cancer progression [58]. Encouragingly, WBV (0.3 g, 90 Hz) was found to reduce the tumor necrosis in the tibia marrow, demonstrating its potential in delaying cancer progression (Table 2) [58]. However, in terms of overall bone health, vibration improved trabecular bone volume in the femur but not in the tibia (Table 2) [58]. One plausible explanation is the comparatively lower volume of bone marrow in the tibia, which potentially leads to greater cancer progression but with a limited number of MSCs available for osteogenic differentiation and bone reformation [58,122]. Alternatively, structural and morphological differences between the femur and the tibia can also lead to distinct responses to vibration [58,122]. Consequently, skeletal adaptation to vibration is bone-site specific.

## 5. Conclusions

For cancer patients, the cumulative effects of diseases, standard treatments (i.e., hormone therapy, chemotherapy, and radiotherapy), and physical inactivity are detrimental to bones [10,28,29,36]. While cancer-associated SREs could be alleviated by exercise [39–43], it is often physically challenging for bedridden or elderly patients. This paper highlights existing evidence on how vibration, an exercise surrogate, benefits cancer-related bone diseases (Figure 1). WBV has been shown to improve bone quality and quantity as well as enhance bone turnover in patients (Table 1) [51,52,54] and mice (Table 2) [57–59] with cancer. Additionally, WBV has demonstrated the ability to reduce tumor burden and normalize bone vasculature altered by cancer metastases in mice (Table 2) [57–59]. LMHF vibration has also been shown to promote interactions between bone cells and cancer cells, which ultimately reduce osteoclastogenesis and inhibit cancer metastatic potential (Table 3) [16,17,60].

To date, it has been observed that LMHF vibration promotes bone health in animal cancer models (Table 2) [57–59], whereas clinical trials yield mixed results (Table 1) [51–56]. The divergence in findings could be attributed to differences in vibration settings and, most importantly, inherent biological dissimilarities, such as variations in size and bone properties, which affect vibration transmissibility. Furthermore, animal studies have examined several factors, such as tumor burden [57,58], bone vascularization [59], and MSC population [57] as outcome measures alongside bone health, whereas clinical cancer studies focus solely on bone health. Hence, more clinical trials are needed to investigate vibration effects on cancer progression. Moreover, there has been a predominant emphasis in vibration research on osteolytic bone metastases, particularly those arising from breast cancer. It is imperative to conduct investigations encompassing diverse cancer types and their associated bone metastases. Additionally, several studies have shown that vibration influences muscle cytokines by increasing irisin [123] while decreasing myostatin [124]. Therefore, it would be valuable for future cancer studies to delve into the impact of vibration on muscle cytokines and explore their relationship with cancer. In this review paper, we expounded upon various parameters, including magnitude, frequency, age, and differences between bone sites, which may affect vibration efficacy. Nevertheless, the extent to which these parameters alter vibration efficacy remains unknown. More in-depth studies are

needed to determine the optimal magnitude and frequency of vibration for inhibiting cancer progression and maintaining bone health.

Research on vibration is still ongoing and growing. In an effort to further elucidate vibration efficacy, several clinical trials are actively recruiting participants to investigate vibration effects on vertebral BMD [125], bone rigidity [126], and overall joint motility following cancer treatments [127]. Additionally, further studies are being conducted to explore the cellular mechanisms and interactions under vibration, as well as the effects of WBV on murine cancer models. Due to its nature of being safe, effective, and easy to perform, WBV can potentially serve as a new intervention or adjuvant therapy to combat cancer-associated bone diseases.

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## Abbreviations

| | |
|---|---|
| 3D | Three-dimensional |
| ALP | Alkaline phosphatase |
| BMC | Bone mineral content |
| BMD | Bone mineral density |
| BMPs | Bone morphogenetic proteins |
| BSAP | Bone-specific alkaline phosphatase |
| COX2 | Cyclooxygenase 2 |
| CTX | C-terminal telopeptide |
| DKK1 | Dickkopf-related protein 1 |
| ET1 | Endothelin 1 |
| FASL | First apoptosis signal ligand |
| FGFs | Fibroblast growth factors |
| G-CSF | Granulocyte colony-stimulating factor |
| G6PD | Glucose-6-phosphate dehydrogenase |
| HMLF | High-magnitude low-frequency |
| HUVECs | Human umbilical vein endothelial cells |
| IGFs | Insulin-like growth factors |
| IL11 | Interleukin 11 |
| IL6 | Interleukin 6 |
| LCN | Lacunocanalicular network |
| LINC | Linker of nucleoskeleton and cytoskeleton |
| LMHF | Low-magnitude high-frequency |
| LMLF | Low-magnitude low-frequency |
| MSCs | Mesenchymal stem cells |
| NADP-ME1 | Nicotinamide adenine dinucleotide phosphate-dependent malic enzyme 1 |
| NTX | N-terminal telopeptide |
| OPG | Osteoprotegerin |
| P1NP | Procollagen type 1 N-terminal propeptide |
| PTHrP/PTHLH | Parathyroid hormone-related protein/hormone-like hormone |
| RANKL | Receptor activator of nuclear factor kappa-B ligand |
| RUNX2 | Runt-related transcription factor 2 |
| SA-βgal | Senescence-associated beta-galactosidase |

| | |
|---|---|
| SREs | Skeletal-related events |
| TGF-β | Transforming growth factor-beta |
| TRACP5b | Tartrate-resistant acid phosphatase 5b |
| VEGFs | Vascular endothelial growth factors |
| WBV | Whole body vibration |
| YAP | Yes-associated protein |

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