

Review

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Review

# Low Bone Mineral Density and Bone Metastases—A Two-Way Street

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**Simple Summary:** Bone metastases (BM) have a deleterious effect on survival for patients with solid cancers. Due to the intertwined relationship between osteoporosis and bone metastasis development, we designed a systematic literature review with two main goals. Firstly, we investigated osteoporosis as a risk factor for bone metastasis development, and secondly, we investigated the risk factors for osteoporosis development in oncological patients.

**Abstract:** Background: Bone metastases (BM) have a detrimental effect on survival for patients with solid cancers. Materials and methods: This systematic review respected the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines. Results: When investigating OP as a risk factor for BM development, for breast cancer patients, some articles do not differentiate between intrinsic breast cancer subtypes. BMD does not seem to contribute in a significant manner when investigating Luminal A breast cancer. While researching breast cancer regardless of intrinsic subtype, untreated OP increases the risk of bone metastasis when compared to no OP group or treated OP group. In urological cancer cases, OP seems to predispose the patients to BM, especially early after diagnosis. Investigating risk factors for OP development in cancer patients resulted in the identification of 32 articles. Most articles identified risk factors for osteoporosis development in the context of breast cancer patients. Other commonly investigated solid cancers were prostate, other urological cancers, gynecological malignancies, and other less common subtypes of solid tumors. Discussion: While investigating OP as a risk factor for BM, it becomes clear that there is a high grade of heterogeneity in the behavior of each type of cancer in its dynamic concerning bone metastasis, and thus, OP might have different behaviors as a risk factor depending on the situation. Conclusion: There is a need for data regarding cancer subtypes that have not been explored concerning their interaction with the skeletal system in a low bone mineral density scenario.

**Keywords:** bone metastasis; osteoporosis; cancer; risk factors; solid cancers; low bone mineral density

## 1. Introduction

Bone metastases (BM) have a detrimental effect on survival for patients with solid cancers. Characteristics such as number of bone metastases, time from diagnostic to bone metastasis development [1], alkaline phosphatase levels [2], and others can be used as prognostic factors in survival estimation for patients with bone metastatic disease. The estimated time to develop bone metastasis is around 400 days [3] with a cumulative incidence of 5.6% at two years, 6.9% at five years, and 8.4% at ten years [3]. The tendency to develop bone metastasis varies widely between the cancer subtype and stage at diagnosis. Prostate cancer patients have the highest risk of developing bone disease followed by lung, renal, and breast [3]. While some cancers have a high tendency to develop bone metastasis in time, a combination of high survival with a high risk of developing bone metastasis

leads to high prevalence rates, some cancers have a very high risk of bone disease at diagnosis. At diagnosis lung – 18.05%, liver-6.63%, nasopharyngeal carcinoma – 6.33%, and renal cancer -5.45% had the highest rates of presenting themselves with bone metastasis [4]. The presence of BM increased the risk of mortality and decreased survival compared to previous stages, especially for patients with prostate cancer (aHR: 18,24) [4].

While survival rates for cancer patients have been improving, due to advancements in therapeutic options, the prevalence of metastatic bone disease has been on the rise. Due to the increased prevalence of BM, the complications of this bone disease are experienced by an increasing number of patients. Reports from 2004 from NIH estimated that in the US 1.5 million people suffer a fracture due to metastatic bone disease [5]. Other skeletal complications that impede the quality of life of patients with BM are hypercalcemia, bone pain, spinal cord compression due to BM, and cachexia [6]. All these complications require complex interventions such as surgical interventions, radiotherapy, systemic treatments, pain management, nutritional management, etc. Management of skeletal-related events (SREs) also imposes a significant economic burden on medical systems. The estimated lifetime SRE-related cost per lung cancer patient with bone metastatic disease was 11,979 USD (95% CI 10,193-13,766 USD) in a retrospective analysis performed on a large US health insurance claims database published in 2005 [7]. Radiotherapy accounted for the highest proportion of the cost. High costs of SRE management are also reported in Europe, with regards to costs involved in treating a prostate cancer patient with bone metastasis, a study from The Netherlands published in 2003 [8], reported an average cost of treatment per patient of €13,051 over 24 months with an average cost of €6973 per patient to treat SREs [8]. A systematic review of relevant economic analyses regarding the management of bone metastasis concluded that bisphosphonate treatments are cost-effective options, and denosumab has a less advantageous value proposition. Evidence concerning EBR and Sr89 is limited and less definitive [9].

Osteoporosis (OP) is a pathological state of the skeletal system in which bone mineral density and bone mass decrease, many studies identify cancer patients as being at major risk for developing this bone disease [10]. Having certain kinds of cancer, such as cervical cancer [11], and cancer-specific treatments can predispose patients to osteoporosis [12]. Many modern treatments such as androgen deprivation therapy (ADT), aromatase inhibitors (AIs), selective estrogen receptor modulators (SERMs), chemotherapy regimens, high doses of corticosteroids usage over long periods, and other treatments used in cancer patient treatment can lead to early development of osteoporosis [12].

While an undeniable relationship exists between cancer patients during treatment and an increased risk of osteopenia and osteoporosis development, some argue that an inverse relationship also exists between patients with osteoporosis and an increased risk of developing bone metastases. The idea that metastatic cancer cells don't develop in random patterns dates to 1889 with the "seed and soil" hypothesis. Recent studies refined our understanding of specific microenvironment traits that can lead to the development of cancer cell colonies from a micro-metastasis state to macro-metastasis [13]. Some studies suggest the existence of a so-called "pre-metastatic niche" characterized by the presence of abnormal immune cells and a specific configuration of the extracellular matrix proteins [13]. This niche seems to be created by a combination of soluble factors produced by the primary tumor and other non-tumor-dependent factors such as endocrine or metabolic factors.

The endocrine system plays a key role in the development of osteoporosis and, some authors argue, in developing the premetastatic niches needed to develop bone metastases in certain subtypes of cancers [14]. Bone homeostasis is maintained by a fine-tuned balance between bone formation promoted by osteoblast activity, a cellular subset derived from mesenchymal stem cells, and bone removal performed by the osteoclasts, a cellular subset derived from hematopoietic stem cells [15]. The major endocrine promoters of high bone turnover found in malignant pathologies are PTH and PTH-like substances, which also have a key role in calcium-level regulation, high glucocorticoid levels, low progesterone, androgen, and estrogen levels. The osteoblasts and osteoclasts present on their surface estrogen receptors thus making estrogen levels especially important in osteoporosis pathogenesis and bone metastasis formation [16]. Antiresorptive agents such as bisphosphonates and anti-RANKL monoclonal antibodies are widely used in patients with metastatic bone disease

treatment regimens. These agents have a beneficial effect on bone density and reduce the fracture risk of these patients. While bone density increases predict a risk reduction for subsequent fractures, BMD increases and reductions do not fully explain fracture risk [17]. Bone architecture plays a major role alongside bone mass density (BMD) in the physical characteristics of the bone, for example, lumbar vertebrae murine models showed that two of the strongest correlations that predict the compressive strength of the bone are BMD and trabecular bone volume [18]. Some studies report that antiresorptive agents, such as risendronate and others, have a beneficial effect on bone architecture as well as BMD [19]. Due to the intertwined relationship between osteoporosis and bone metastasis development, we designed a systematic literature review with two main goals. Firstly, we investigated osteoporosis as a risk factor for bone metastasis development, and secondly, we investigated the risk factors for osteoporosis development in oncological patients.

## 2. Materials and Methods

### 2.1. Search Strategy and Study Selection

The systematic review respected the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines [20]. The identification of relevant studies was done by searching multiple online bibliographic databases such as Google Scholar, Cochrane Library, Embase, International Clinical Trials Registry Platform (ICTRP), and Cumulative Index to Nursing and Allied Health Literature (CINAHL) database. ClinicalTrials.gov was also included in the research to identify any ongoing trials concerning osteoporosis and bone metastases. The search was performed from inception until the date of the search, August 2024. Citations of the retrieved articles were also analyzed using a forward-backward search method. The publications selected this way were chosen using the same selection criteria as the rest of the articles. The search query included combinations of the terms: “osteoporosis”, “cancer patients”, “bone metastases/metastasis”, “risk factors”, and “solid cancers”. The selection process involved screening the title and abstract of the retrieved articles and extended reading of selected articles, any conflicts of selection between the first two authors were resolved by the third author. Two selection processes were performed, one in which the focus was on identifying OP as a risk factor for bone metastases development, and, for the secondary objective of the study a second selection was performed in which all risk factors for osteoporosis development in the context of cancer patients were identified.

### 2.2. Data Extraction

Data was extracted from the articles by the authors and two databases were created in Microsoft Excel spreadsheet application. In the first database studies that investigated OP as a risk factor for BM were selected. An ID was attributed to each study with an appropriate identification tied to the study reference, year of publication, country of publication, study type, number of patients included, controls, groups that were compared, and statistical analysis measures were extracted from the main text and summarized in the database. In the second database, data from studies that investigated risk factors for OP development in cancer patients was selected. An ID was attributed to each study with an appropriate identification tied to the study reference, year of publication, country of publication, number of patients investigated, cancer subtype investigated, specified risk or protective factor, type of effect of the said factor, and statistical analysis measures of the effect.

### 2.3. Inclusion and Exclusion Criteria

Studies that were peer-reviewed with available texts in English were included. Types of studies evaluated for inclusion have consisted of randomized controlled trials, cross-sectional, cohort studies, case-control, systematic analyses, and meta-analyses. When analyzing studies exploring OP as a risk factor for BM the following inclusion criteria were used: (1) Randomised control trials, cross-sectional, cohort studies, and case-controls; (2) Studies that explored OP as a risk factor for BM; (3) Studies that included adult patients, defined as above 18 years of age. Exclusion criteria (1) Language of publication – not English; (2) Studies that included pediatric patients; (3) Articles that explored only animal models/cell lines. When exploring the risk and protective factors involved in OP

development in oncological contexts, the same inclusion and exclusion criteria were applied with the mention that the included study types were extended to include systematic analyses and meta-analyses.

#### *2.4. Quality Assessment*

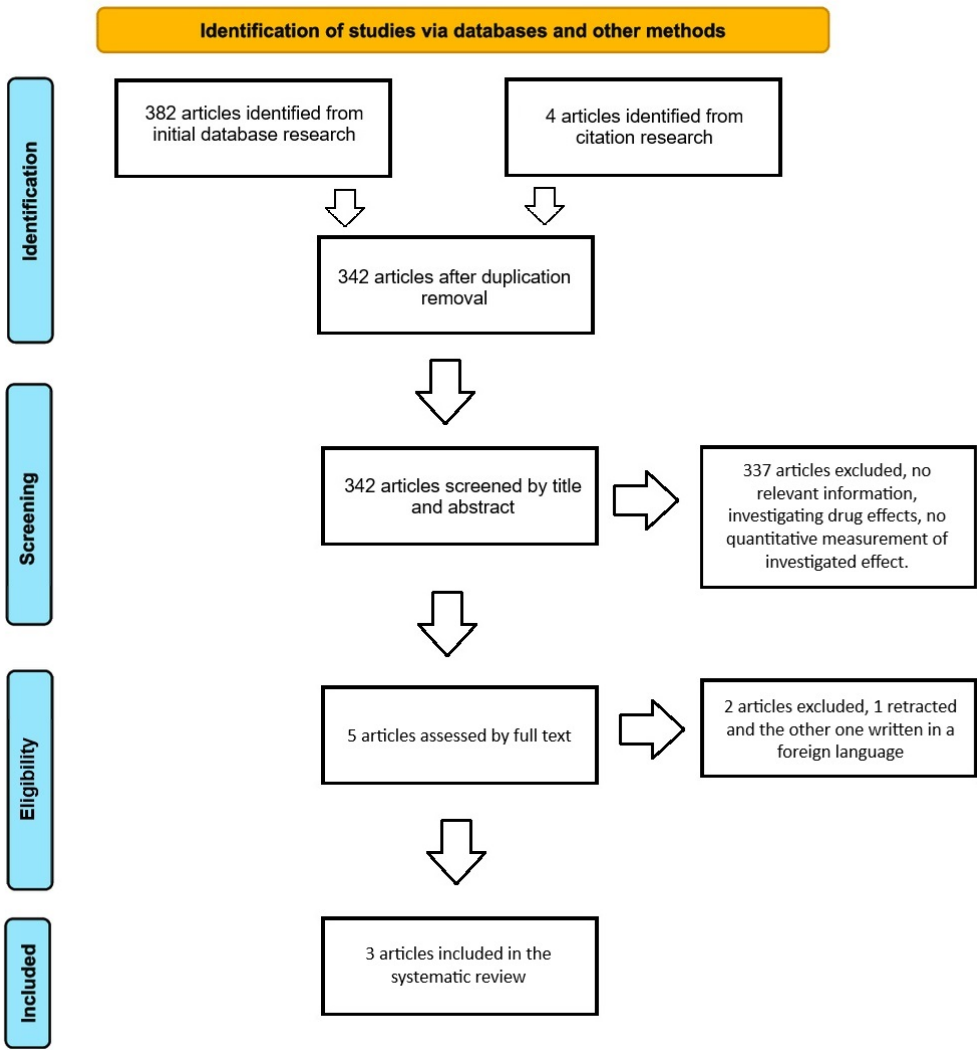
Quality assessment for the studies that analyzed the main objective of the study was performed using the NIH Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies [21]. This tool includes a 14-item questionnaire in which a total score of 14 points can be obtained. Each question can be answered in one of 3 ways: Yes (1 point); No (0 points); or CD, cannot be determined (0 points)/NA, not applicable (0 points)/NR, not reported (0 points). The questions evaluate how the research was done; study population; groups recruited from the same population and uniform eligibility criteria; sample size justification; exposure assessed before outcome measurement; sufficient timeframe to see an effect; different levels of the exposure of interest; exposure measures and assessment; repeated exposure assessment; outcome measures; blinding of outcome assessors; follow up rate and, lastly statistical analyses. A quality rating of good, fair, or poor can be attributed to each evaluated study as a conclusion to the assessment.

### **3. Results**

#### *3.1. Search Results*

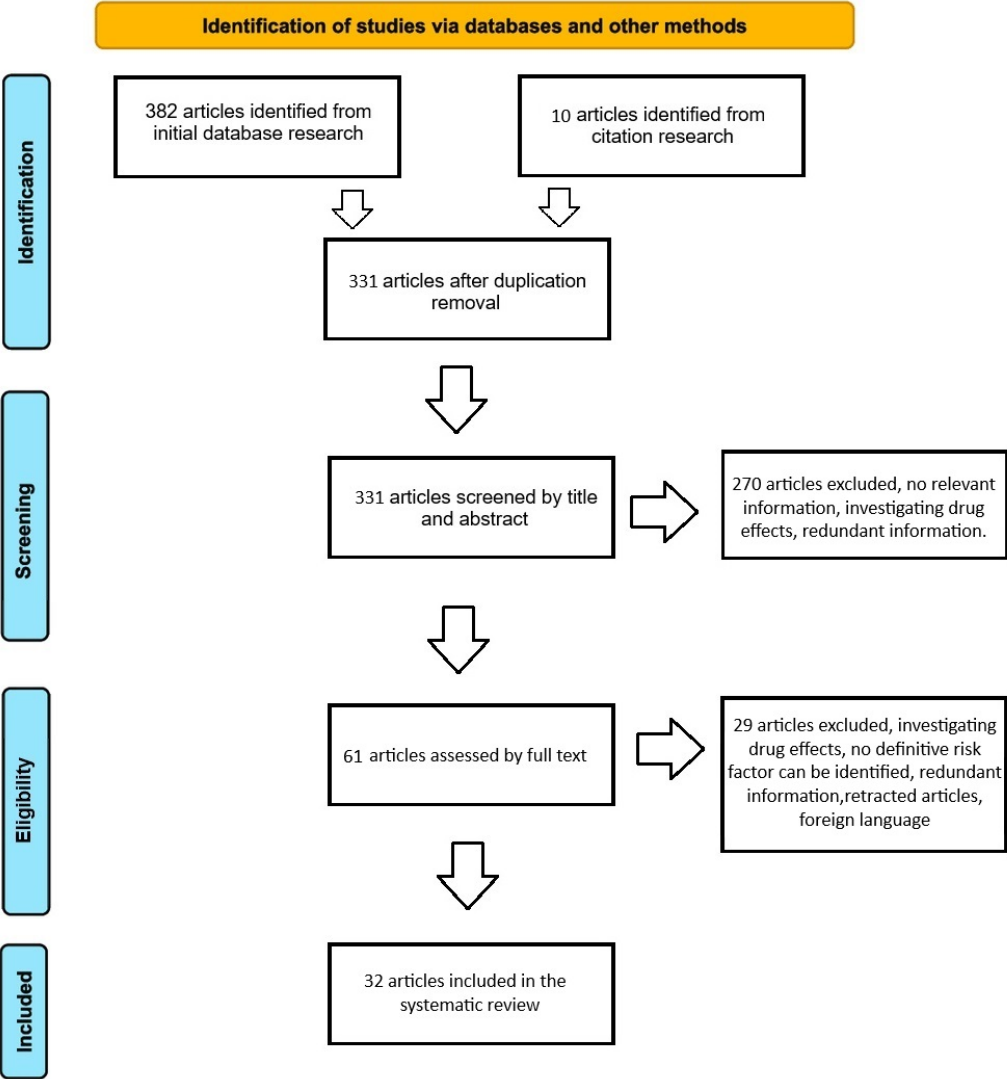
The online database searches, with multiple search combinations of the keywords, as mentioned earlier led to the identification of 382 articles of interest and 4 articles identified through citation research. The databases were searched from the date of inception until June 2024. For the main objective of this review only studies that reported a statistical analysis of the risk OP represents for BM development were selected, the selection process is detailed in Figure 1. Only 3 studies respected the inclusion criteria and were included in the final analysis.





**Figure 1.** PRISMA flow diagram of the study selection process for the main objective – osteoporosis as a risk factor for bone metastasis development.

For the second objective of the study, investigating risk factors reported in studies as being risk factors for OP development in the context of cancer patients, to the 382 articles found through databases research 10 more articles were added through citation research. A total of 61 articles were assessed in full text, which led to the identification of 32 articles that met the inclusion criteria as detailed in Figure 2. For the secondary objective, the inclusion criteria have been expanded to include not only studies that reported a statistical analysis of the identified risk factor for OP development but also systematic reviews and meta-analyses that concluded concerning said risk factor. The reasoning behind this decision was supported by the intent of the secondary objective, which is the identification of said risk factors. A meta-analysis of the data reported in this systematic analysis was excluded as the lack of uniformity of data reporting and the lack of data with regards to specific subgroup analyses such as cancer types, cancer stages, pre-postmenopausal female patients, and others, led to a high heterogeneity of data which in turn made a meta-analysis of this statistical data undue at the time of analysis.



**Figure 2.** PRISMA flow diagram of the study selection process for the secondary objective – risk factors for osteoporosis development in cancer patients.

3.2. Characteristics of the Studies and Participants – OP a Risk Factor for BM Development?

Only limited data regarding this topic is available. All 3 studies identified were large retrospective studies, the first two studies [22,23], one from Taiwan and the other from South Korea, investigated breast cancer patients. In the first study, data was extracted from a nationwide database, the intrinsic subtype of breast cancer was not specified. This study concluded that even if precancer osteoporosis was not associated with a difference in BM incidence, in the context of breast cancer patients, those who had precancer osteoporosis had a shorter time for BM development. This predisposition was mitigated by treating OP as seen in Table 1. To sum up, OP does not increase the incidence of de novo BM, but it leads to accelerated BM progression when it occurs if left untreated.

In the second study [23], 348 patients with Luminal A breast cancer subtype were investigated. In this retrospective study, the patients were grouped into 2 categories, normal BMD vs low BMD (the authors included osteoporosis and osteopenia in this category). No statistically significant link between BMD and BM was found. Based on the trend of BMD after surgery, the subgroup analysis showed that upward trends, downward trends, and stable BMD did not show any significant differences either.

The last articles explored the relationship between OP and BM in the context of urologic cancers. Published in 2024 in the USA [24], it investigated a large, matched control cohort from a pool of 685066 urological cancer patients, as seen in Table 1. The article concluded that there is a strong correlation between precancer deficit of bone mineral density and BM apparition, especially in the first week after diagnosis for all investigated cancer subtypes. Bisphosphonate administration reduces the risk of BM for kidney, bladder, and prostate cancers.

To sum up the findings, for breast cancer a better investigation of OP as a risk factor for BM is required as many articles do not differentiate between intrinsic breast cancer subtypes [22]. Up to this point, BMD does not seem to contribute in a significant manner when investigating Luminal A breast cancer [23] - defined as estrogenic receptor (ER) and progesterone receptor (PR) positive, HER 2 negative, ki67 low [25]. When investigating breast cancer regardless of intrinsic subtype, untreated OP seems to increase the risk of bone metastasis after diagnosis when compared to no OP group or treated OP group. In contrast to breast cancer, which appears to be a heterogeneous group due to the different behavior that it has due to the intrinsic subtypes of cancer that it encompasses, in all urological cancer cases, OP seems to predispose the patients to BM, especially early after diagnosis.

3.3. Characteristics of the Studies and Participants – Risk Factors for OP Development in Cancer Patients

Out of the 32 articles identified, as seen in Figure 2, most articles identified risk factors for osteoporosis development in the context of breast cancer patients. 19 articles contained data regarding breast cancer patients [26–38,44,47,49,51–52,54,57], most common deleterious factors for bone mass density identified were treatments that led to ovarian failure and a low estrogenic bone environment. The most notable examples are chemotherapy that resulted in ovarian insufficiency/ovarian failure, an analog of luteinizing hormone-releasing hormone usage, aromatase inhibitors usage, steroidal inhibitor- exemestane, SERM usage when used in the pre-menopausal setting, oophorectomy, high dose glucocorticoids and lastly but not least breast cancer in of itself can serve as a risk factor for OP, articles findings summarized in Figure 2. Protective factors identified in this setting include weight/high BMI (body mass index), high levels of gonadal inhibin of the transforming (TGF)-B superfamily levels, SERM usage in the postmenopausal/low estrogen context, statin usage, melatonin supplementation, and mixed-mode exercises.

**Table 1.** Studies that investigate osteoporosis as a risk factor for bone metastasis. PBMD (precancer-poor bone mineral density) - defined as osteopenia or osteoporosis.

ID	Yea r	Cou ntry	No. of Patient s	No. of Control s	Study type	Cancer subtype	Comparison	Reported value
Hsiu- Man Chen [22]	2019	Taiwan	9104 - breast cancer 14020 - precan cer osteop orosis	NA	Nation wide retrospe ctive cohort study	Breast cancer - subtype not specified	Breast cancer group – precancer osteoporosis vs without	No additional risk of bone metastasis (aHR, 0.87; 95% CI, 0.58-1.30; P = .49)



							Precancer osteoporosis group – osteoporosis therapy vs NUL	No association with risk of bone metastasis (bisphosphonates: aHR, 1.47; 95% CI, 1.00-2.17; P = .05; non-bisphosphonate drugs: aHR, 1.00; 95% CI, 0.72-1.39; P > .99)
							Breast cancer group – no precancer osteoporosis vs untreated osteoporosis vs treated osteoporosis	Median time to develop bone metastasis was shorter in the untreated group vs the other two groups. (no precancer osteoporosis 2.87 years; IQR, 1.34-4.86 years) vs (untreated 1.74 years; IQR, 0.58-3.60 years; P < .001) vs (bisphosphonates: 2.34 years; IQR, 1.23-3.13 years; non-bisphosphonate drugs: 2.08 years; IQR, 0.92-4.95 years)
Seungju Lee [23]	2023	South Korea	348 - breast cancer	129 – normal bone density	Retrospective study	Breast cancer – Luminal A	Breast cancer – low BMD vs normal BMD	BMD not statistically significant on five-year DFS (98.2% - low BMD group vs 95.0% - normal BMD group, P=0.33), metastases (5 y - 4 in the normal BMD group vs 2 in the low BMD group) or incidence of contralateral breast cancer
							Breast cancer – no change in BMD over time vs improvement vs worsening BMD	DFS at 5 y was 97.0% for - no change in the BMD group, 94.6% for the BMD improvement group, and 98.4% for the BMD degradation group (P=0.79).

Gartre Il C. Bowling [24]	2024	USA	69,721 - kidney cancer, 84,755 - bladder cancer, 184,855 - prostate cancer, 3202 - testicular cancer.	Matched PearlDiver Database - retrospective, propensity-score matched cohort analysis.	Kidney, bladder, prostate, and testicular cancer groups – PBMD vs matched control group	Strong association at 1 week of cancer diagnosis (kidney: adjusted odds ratio [aOR], 2.37, P <.001; bladder: [aOR], 2.37, P <.001; prostate: [aOR], 2.84, P <.001; testicular: [aOR], 4.45, P <.001). Bisphosphonates use associated with reduced risk of kidney ([aOR], 0.46, P <.001), bladder ([aOR], 0.61, P <.001), and prostate ([aOR], 0.66, P <.001) cancer bone metastasis.

Prostate cancer patients are also explored in large meta-analyses [41], large propensity score-matched retrospective studies [43], and other studies, Table 2. The most frequent detrimental effects identified are the presence of bone metastasis, the presence of prostate cancer, low BMI, advanced age, high dose glucocorticoids, inactivity, bilateral orchiectomy, and most notably ADT (androgen deprivation therapy) usage, which is the backbone of prostate cancer treatment in both metastatic and neo/adjuvant treatment [58]. One of the most cited protective factors is physical activity with many regimens being studied now [47] to determine the most effective regimen for this scenario. Other urological malignancies that imply a raised risk of OP development are renal cancers. For most non-metastatic cases of renal cancer, the routine treatment involves either radical nephrectomy or nephron-sparing surgery. Compared to the more radical surgical approaches nephron-sparing surgery has a protective effect on BMD [53].

Another cluster of studied cancers is gynecological malignancies. While most authors agree that cervical and ovarian cancers have a detrimental effect on BMD [39,45,55–56] even in the pretreatment setting, the same thing cannot be concluded for endometrial cancer [39; 45]. Treating all 3 types of malignancies has a deleterious effect on BMD. Changes in BMD are lowest after surgical treatment. The highest detrimental effect on BMD is observed when multimodal treatment involving chemoradiotherapy after surgery is used [45].

Other, more scarcely researched risk factors, like melatonin supplementation [54], statins administration [49], or post-operative thyroid-stimulating hormone suppression after surgery for papillary or follicular thyroid carcinoma surgery [46] have also been included in this review, summaries available in Table 2. Melatonin supplementation seems to have a protective effect on bone density, but notable changes in BMD have been observed only in prolonged administration regimens [54]. Statins appear to have a favorable impact on BMD, with multiple articles observing an inverse correlation between LDL cholesterol levels and BMD at multiple sites such as the spine and hip while HDL cholesterol levels have conflicting correlations with BMD, mostly measured at the femoral neck level in this scenario [49]. Postoperative thyroid–stimulating hormone suppression has also been explored, but no statistically significant difference has been observed [46].

**Table 2.** Studies that investigate risk factors for bone loss, defined as osteoporosis and osteopenia, for oncological patients .

Year	Country	No. of patients	Study type	Cancer subtype	Risk factor	Type of effect	Reported value or conclusion
Janice J.	2005 USA	30	Longitudinal	Breast	Weight Age	Protective NUL	Weight and BMD gm/cm2 score at the spine (r=.417,

Twiss [26]							Months since diagnosis	NUL	p=.022), and at the hip (r=.458, p=.011). The subjects were all postmenopausal women.
							Months since menopause	NUL	
							Daily calcium intake	NUL	
							Cigarettes per day		
							Daily caffeine intake		
Kristy M. Nicks [27]	2010	USA	-	Review	Breast	Gonadal inhibin of the transforming growth factor (TGF)-B superfamily levels	Protective	Bone loss in premenopausal women due to anti-cancer treatment – leads to low levels of inhibins	
L. Vehmanen [28]	2001	Finland	73	RCT	Breast	Adjuvant chemotherapy - CMF: cyclophosphamide, methotrexate, 5-fluorouracil	Deleterious	Chemotherapy-induced ovarian failure induced accelerated bone loss (p<0.001 in both spine and femoral neck; changes in BMD - 0,3% in the menstruating group and -5,8% in the amenorrhea group)	
Robert E. Coleman [29]	2013	UK	-	Review	Breast Prostate	ADT Ovarian failure High dose glucocorticoids Fatigue-related immobility	Deleterious Deleterious Deleterious Deleterious	Early chemotherapy-induced bone loss might not be caused by the direct action of the chemotherapy agent but due to induced menopause, corticoid use, and immobility	
T. Saarto [30]	1997	Finland	148	RCT	Breast	Adjuvant chemotherapy - CMF: cyclophosphamide, methotrexate, 5-fluorouracil  Ovarian failure	Deleterious  Deleterious	The mean difference at 2 years -4.6 CI (-6.9 to -2.3) in the amenorrhea group vs regular menses group at 2 years 0.0 CI (-3.9 to +3.9)	

										2-y mean difference 2.5% +/- 1.2% (95% CI, 0.2 to 4.9) – (P=.041) lumbar spine, 2.6%+/- 1.1% (95% CI, 0.3 to 4.8) – (P=.029) femoral neck
<b>P. D. Delmas [31]</b>	1997	France	53	RCT	Breast	Chemotherapy-induced ovarian failure		Deleterious		
<b>Michael Gnant [32]</b>	2011	Austria	404	RCT	Breast	OFS  Anastrozole + OFS Tamoxifen + OFS		Deleterious	GnRH analogs in pre-menopausal women – BMD after 3y reduced by 11.3% and 7.3% lumbar spine and trochanter – over the next 2y for the 75% of women who regained menses BMD at both sites recovered. Anastrozole + OFS – had higher bone loss than the tamoxifen + OFS – 13.6% vs -9% at 3y	
<b>I. Fogelman [33]</b>	2003	UK	1640 – sub-study involved 96 patients (53 in the goserelin group vs 43 in the CMF group)	RCT	Breast	OFS Adjuvant chemotherapy – CMF protocol		Deleterious	Premenopausal subjects – GnRH analog adjuvant vs adjuvant CMF chemotherapy – at 2y, lumbar spine -10.5% OFS group vs -6.5% CMF group (p=.0005). Femoral neck OFS group -6.4% and - 4.5% CMF group (p=.04).  At 3 y partial recovery was observed in the OFS group (ovarian function regain). By contrast the BMD loss in the CMF group was	

Detrimen- tal even after treatme-	Lumbar and total hip median BMD after 1 and 2 years of treatment cessation: -0.79%
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<b>Robert E. Coleman [38]</b>	2010	UK	4724 patients in the main study 206 patients in the bone sub-study	RCT	Breast	Tamoxifen vs Exemestane	The trend of persistence of the detrimental effect Detrimental effect fades	At 2 years from the end of treatment with Exemestane spine BMD increased by +1.53% (P=.001) and decreased by -1.93% (P=.0002) after cessation of Tamoxifen. Changes at 2y in the two groups were similar with both treatment strategies.
<b>HY Kim [39]</b>	2015	Korea	218 cervical cancer patients 85 endometrial cancer patients 259 healthy controls	RCT	Cervical cancer Endometrial cancer	Cervical cancer in postmenopausal status - pretreatment  Endometrial cancer in postmenopausal status – pretreatment	Detrimental No statistically relevant difference	Osteoporosis was more frequent in the cervical cancer group 18.81% vs 10.81% in the control group and osteopenia was 38.99% vs 36.29% in the control group  The endometrial cancer group also showed a higher incidence of osteoporosis (16.47%) while

									osteopenia was lower (28.24%) but no statistical difference (P=.228)
Barbara Altieri [40]	2020	Germany	-	Review	GEP-NET	GEP-NET	Supplementation with vitamin D	Detrimental	Up to 76% of cases of GEP-NET patients present osteoporosis or osteopenia. Potential benefits of Vit. D supplementation in cases of insufficient or deficient Vit. D levels
Annie-Clau de M. Lasse millante [41]	2015	Australia	5812 studies initial search 15 articles for final review	Meta-analysis	Prostate cancer	Prostate cancer		Detrimental	Up to 37.8% of PC hormone naïve patients show osteoporosis, thus PC through bone resorption promotion might be a risk factor
Cinzia Balde ssari [42]	2023	Italy	-	Review	Prostate cancer	LHRH analogs Older age Lower body mass index Bilateral orchiectomy		Detrimental Detrimental Detrimental Detrimental	The usual rate of bone loss in men varies between 0,5% and 1%. In patients with metastatic PC in the first year of ADT, bone loss varies between 2-8% at the lumbar spine level, and between 1,5-6.5% at the hip.  At the end of ADT, BMD may increase in the lumbar spine while remaining low at other sites.
Taekmin Kwon [43]	2014	Korea	3122: 502 PC group matched with 502 matched	Retrospective propensity score	Prostate cancer	Prostate cancer Bone metastasis BMI		Detrimental Detrimental	Higher osteoporosis incidence in the PC group (P=.0001)

					control group				Low - detrimental	Independent predictor of osteoporosis (OR 3.45, P=.002) Continuous, OR 0.75, P<.001)
Sue A. Brown [44]	2009	USA	-	Review	Breast cancer	Tamoxifen	Detrimental/Protective	Tamoxifen's effect varies based on estrogen levels in premenopausal women More tissue level estrogen deprivation thus BMD losses		
							Detrimental			
							Detrimental			
							Detrimental			
							Detrimental			
Jeong Eun Lee [45]	2020	Korea	243 gynecological cancer patients: 105 cervical; 63 endometrial 75 ovarian 240 controls	Retrospective	Cervical cancer Endometrial cancer Ovarian cancer	Cervical cancer Endometrial cancer Ovarian cancer		Lower BMD for cervical cancer group -1st,2nd lumbar and femoral neck – average score and SD, -0.9 +/- 1.4, P=.013; -0.8+/-1.5, P=.029; -0.9+/-1.0, P=.029 No statistical difference for the endometrial group Lower BMD from the 1st to the 4th lumbar at each level: -1.2+/- 1.4, P=.00; -1.1+/- 1.5, P=.001; -0.9+/- 1.5, P=.007; -0.7+/-1.5, P=.004;		
							Cervical cancer		Detrimental	
							Endometrial cancer		No statistically relevant difference	
							Ovarian cancer		Detrimental	
						Cervical cancer post-treatment 1y Endometrial cancer post-treatment 1y	Detrimental	Differences in BMD of L3, L4 and femoral neck (P=.043; P=.022; P=.026) BMD of the endometrial group decreased		
							Detrimental			

						Ovarian cancer post-treatment 1y	Detrimental	significantly after the treatment
								Changes in BMD are lowest in patients who only underwent surgical treatment
								Highest bone loss in patients who underwent chemoradiotherapy after surgery
			225					
			postmenopausal women with DTC			Differentiated thyroid carcinoma – papillary and follicular carcinoma		
Pei Zhan g [46]	2018	China	thyroid residual ablation or metastasis treatment	RCT		Postoperative thyroid-stimulating hormone suppression	No statistically relevant difference	Reduction of 1.9% in BMD in lumbar spine at 2y, but not statistically different
Benjamin Singh [47]	2021	Australia	26 trials, interventions ranging from 12 weeks to 2 years	Meta-analysis	Cancer survivors – mostly breast cancer	Mixed-mode exercises: aerobic, resistance, mixed-mode and others	Protective	Whole body BMD, trochanter BMD, femoral neck BMD, and hip BMD were positively impacted, SMD range: .19-0.39, all p<.05) vs controls
L. Joseph Melton [48]	2003	USA	429	Retrospective	Prostate cancer	Bilateral orchiectomy Age Inactivity	Detrimental Detrimental Detrimental	Cumulative incidence of fractures after 15 years of 40% vs 19% expected (P=<.001)
Chandi C. Mandal [49]	2015	India	-	Review	Breast cancer, multiple myeloma	Statins	Protective	Levels of cellular cholesterol of cells occupying the bone microenvironment e.g. osteoblasts, osteoclasts, and metastasized cancer cells,

								might be a good predictor for bone health, thus agents that modulate the levels of intracellular cholesterol might improve bone health.
								The bone density in the fracture group was significantly lower than in the non-fracture group.
T. Hatanono [50]	2002	Japan	218	RCT	Prostate cancer	ADT	Deleterious	There is a need to evaluate and treat secondary osteoporosis in patients receiving long-term ADT.
								Low levels of 17 beta-estradiol due to menopause will lead to accelerated bone loss, and microarchitectural deterioration which in turn can lead to increased risk of fractures and uncoupling in the remodeling unit.
F. Salamanna [51]	2018	Italy	-	Review	Breast cancer Prostate cancer Lung cancer Others	17 beta-estradiol levels	Low – deleterious	Higher incidence of osteopenia and osteoporosis in the femoral neck vs controls (39.3% vs 9%, P=.0005). Lumbar spine BMD did not differ between groups. OR 6.90, 95% CI 5.57-9.77 OR 0.24, 95% CI 0.06-0.98
P. Ferreira Poloni [52]	2017	Brazil	112 breast cancer survivors 224 controls	Prospective case-control study	Breast cancer survivors	Breast cancer Chemotherapy history Regular physical activity High BMI (≥30)	Deleterious Protective Protective	



										OR 0.09, 95% CI 0.02-0.37
Eric Ballo n-Landa [53]	2019	USA	-	Review	Prostate cancer	Long term ADT	Deleterious	Protective		Average BMD decreased between 1.4 to 2.6% per year between 3 to 8 years of ADT treatment
					Renal cell carcinoma	Nephron sparing surgery				Significantly less osteoporosis between NSS 3.7 vs RN 7.0, P<.0001
Ioana J. McD onald [54]	2021	Taiwan	-	Review	Breast, prostate, lung, bladder, and others (e.g. osteosarcoma)	Melatonin supplementation	Protective			After 1y of treatment, femoral neck BMD increased by 0.5% with 1mg/day supplementation and 2.3% with 3mg/day.
										6 months of supplementation showed only a trend of bone resorption decrease
Yao-Ching Hung [55]	2002	Taiwan	50 cervical cancer patients	Prospective	Non-metastatic cervical cancer	Cervical cancer	Deleterious			Over 1y of treatment improved lumbar spine BMD by 4.3%.
			50 controls							Significantly lower BMD in the cervical cancer group P<.05
Sooh Cho [56]	1991	Korea	85 cervical cancer patients	Prospective	Cervical cancer patients	Cervical cancer	Deleterious			Age-adjusted and mean menopause duration-adjusted, cervical cancer group presented 12.8% lower spinal BMD, P=.0003
			148 controls							

Nunes FA [57]	2021	Brazil	34 postmenopausal women with breast cancer	Cross-sectional study	Breast cancer	AI exposure vs post-chemotherapy patients	Deleterious	AI group had lower areal bone mineral density and T-scores at the hip. There is a higher incidence of osteoporosis on DXA scan, 47% in the AI group vs 17.6% in the non-AI group.
			17 AI group					

3.4. Quality Assessment

As mentioned before, Quality assessment for the studies that analyzed the study's main objective, as seen in Table 1, was performed using the NIH Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies [21]. Scoring between 0-5 points was interpreted as being Poor, 6-10 as being Fair, and 11-14 as being Good. The first two authors evaluated the studies, and the third author mediated any conflicts. All three studies were graded as being Fair.

**Table 3.** Quality assessment of studies investigating the main objective using the NIH Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies.

	Hsiu-Man Chen [1]	Seungju Lee [2]	Gartrell C. Bowling [3]
Was the research question or objective in this paper clearly stated?	1	1	1
Was the study population clearly specified and defined?	1	1	1
Was the participation rate of eligible persons at least 50%?	0	NA	1
Were all the subjects selected or recruited from the same or similar populations (including the same time period)?			
Were inclusion and exclusion criteria for being in the study prespecified and applied uniformly to all participants?	0	1	1
Was a sample size justification, power description, or variance and effect estimates provided?	0	0	0
For the analyses in this paper, were the exposure(s) of interest measured prior to the outcome(s) being measured?	1	1	1
Was the timeframe sufficient so that one could reasonably expect to see an association between exposure and outcome if it existed?	1	1	1
For exposures that can vary in amount or level, did the study examine different levels of the exposure as related to the outcome (e.g., categories of exposure, or exposure measured as a continuous variable)?	0	0	0
Were the exposure measures (independent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?	1	1	1
Was the exposure(s) assessed more than once over time?	1	1	1

Were the outcome measures (dependent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?	1	0	1
Were the outcome assessors blinded to the exposure status of participants?	0	0	0
Was loss to follow-up after baseline 20% or less?	0	NA	NA
Were key potential confounding variables measured and adjusted statistically for their impact on the relationship between exposure(s) and outcome(s)?	1	0	1
Score	8	7	10

4. Discussion

While investigating OP as a risk factor for BM, from the studies included in Table 1, it becomes clear that there is a high grade of heterogeneity in the behavior of each type of cancer in its dynamic concerning bone metastasis, and thus, OP might have different behaviors as a risk factor depending on the situation. When investigating breast cancer, regardless of intrinsic subtype, untreated OP seems to increase the incidence of BM when compared to the normal BMD group or the treated subgroup after it has been diagnosed [22]. The same things cannot be said about the risk of BM in the OP group vs. the normal BMD group at diagnosis [22]. Also, breast cancer needs to be investigated in this regard considering the intrinsic subtype investigated, because, for example, lower BMD does not seem to impact Luminal A breast cancer patients in the same way [23]. Recent ESMO breast cancer guidelines have included adjuvant bisphosphonates as part of the standard therapy in early breast cancer, with the mention that bisphosphonate therapy is approved for treating bone metastases and osteoporosis and not for the prevention of relapse, with a level of evidence of [I, A] [59].

By contrast, urological cancers seem to exhibit a more homogenous behavior. The strongest association between OP and BM is observed 1 week after diagnosis, with adjusted odds ratios for bladder: 2.37; kidney: 2.37; and prostate: 2.84 being similar and statistically significant (all  $P<.001$ ) [24]. The only outlier is testicular cancer in which the adjusted odds ratio was reported to be 4.45 with a  $P<.001$  [24]. Still, this result only supports the trend presented by the other urological malignancies. Data regarding low bone mineral density and its effect on the risk of bone metastasis in other cancers is lacking. More studies are needed to understand and adjust treatment intensity with antiresorptive agents. Data thus far points towards a necessity in screening oncological patients for osteoporosis and osteopenia and treating it accordingly as it may also impact the oncological outcomes.

The need for implementing a coherent screening of bone mineral density in all oncological patients is also backed by the plethora of risk factors that oncological patients who receive treatment are subjected to. Multiple solid cancers present an increased risk of osteoporosis development, such as prostate cancer [41], cervical cancer [45,55,56], ovarian cancer [45], and BM presence [43]. Also, most treatments used that induce ovarian failure, testicular failure, complex multimodal treatments, and high doses of corticosteroid usage also seem to create a context favorable for BMD degradation, Table 2.

5. Conclusions

In conclusion, it has been found that oncological patients with low bone mineral density have an increased tendency to develop bone metastases. The importance of osteoporosis as a risk factor for developing bone metastases varies depending on the type of cancer that it interacts with. A good example in this regard is a heterogeneity of behavior in this regard can be observed when investigating different types of breast cancer. Also, there are a myriad of cancer-related risk factors and cancer treatment-related risk factors that predispose oncological patients to bone loss. There is a need for data regarding cancer subtypes that have not been explored concerning their interaction with the skeletal system in a low bone mineral density scenario. These results can lead to the development of a coherent strategy and an intensive osteoporosis treatment can lead to improved quality of life due to a decrease in bone metastasis incidence.

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