

ORIGINAL ARTICLE

Fracture risk in patients with different types of cancer

PETER VESTERGAARD, LARS REJNMARK & LEIF MOSEKILDE

Department of Endocrinology and Metabolism C, Aarhus Amtssygehus, Aarhus University Hospital, Aarhus, Denmark

Abstract

Background. Few studies on the risk of fractures in patients with cancer exist, and little is known on the mechanisms of fractures in patients with cancer. We studied the risk of fracture in patients with various types of cancer. **Subjects and methods.** Case control study. There were 124 655 fracture cases and 373 962 age and gender matched controls. **Results.** An increased risk of fractures, primarily within the first year after diagnosis was seen in patients with primary bone cancer (OR = 3.51, 95% CI: 1.54–8.01), multiple myeloma (OR = 5.21, 95% CI: 2.96–9.19), metastases to the bone (OR = 5.28, 95% CI: 3.58–7.79), metastases to other organs than bone (OR = 1.85, 95% CI: 1.50–2.29), lung cancer (OR = 1.90, 95% CI: 1.51–2.38), and cancer of the liver, gall bladder and pancreas (2.14, 95% CI: 1.39–3.31). For patients with prostate cancer an increase in the risk of fractures was seen with time. Other cancer types were not associated with an increased risk of fractures. **Conclusions.** A high risk group regarding fractures includes cancers primarily affecting the bone (primary bone cancer, multiple myeloma, metastases to the bone, metastases to other organs than bone, lung cancer, and cancer of the liver, gall bladder and pancreas, and prostate cancer). The main increase in risk of fractures in this group was seen within the first year following diagnosis. A low risk group for fractures included all other cancer types (e.g. cancer of the breast, colon, skin etc). This may have implication for which patients should be selected for prevention against fractures.

Certain cancer types have been associated with an increased risk of fractures. However, only few cancer types have been the object for detailed study of fracture risk.

Most research has focused on prostate cancer, where a decreased bone mineral density (BMD) and an increased risk of fractures, mainly linked to the use of anti-androgen therapy (androgen deprivation therapy) has been demonstrated [1]. Other types of cancer have not been studied in detail. In women with breast cancer an increased risk of vertebral fractures has been shown [2], whereas the overall risk of fractures was not increased [3]. Women with low BMD also have an increased risk of breast cancer [4], and may therefore also have an increased risk of fractures. Furthermore, recent randomised controlled trials have demonstrated that aromatase inhibitors were associated with a significantly higher risk of fractures than tamoxifen due to the lowering of estradiol levels by the aromatase inhibitors, whereas tamoxifen has partial estrogen agonistic properties [5]. Combining aromatase inhibitors with tamoxifen prevents much of the bone loss

associated with aromatase inhibitors [5]. However, the increase in BMD is much lower than with tamoxifen alone [5]. Surprisingly one study has shown an increased risk of hip fractures in women treated with tamoxifen [6]. Chemotherapy in women with breast cancer leads to a rapid decrease in BMD through lowering of estradiol levels [7]. The effect may thus be much larger in pre- than in postmenopausal women. High risk of fractures have also been reported in children with leukaemia, but the risk was not compared to that of the general population [8]. In children with acute lymphoblastic leukaemia an increased risk of fractures has been demonstrated compared to the general population [9]. However, it may seem that childhood survivors of leukaemia may regain normal BMD [10] although this may not be the case for all survivors. Fractures may also be frequent in Ewing sarcoma, but no comparison with the general population have been performed [11].

Most reviews have assumed that metastases to the skeleton were the main culprit as to any skeletal morbidity including fractures [12,13]. Regarding the causes of fractures little is known as most evidence

stems from the effects of treatment of the cancer on bone mineral density. Six main factors may be present: 1) hypogonadism either through the cancer directly destroying hormonally active tissue or through interference with the gonads through surgery, irradiation [14,15], chemotherapy [16,17] or other medical treatment (say aromatase inhibitors in breast cancer [18]) leading to osteoporosis in the same way as postmenopausal osteoporosis, 2) local invasion of cancer tissue leading to pathological fractures, 3) malnutrition following nausea and vomiting leading to deficiency in nutrients such as calcium and vitamin D, 4) immobilisation leading to muscle wasting and bone loss, 5) drugs (besides interference with gonadal steroids, drugs such as chemotherapeutics and corticosteroids may interfere with bone turnover, but pain medication such as morphine may also affect risk of fractures [19] through an increased risk of falls) and 6) hormonal or other activity of the tumour (e.g. production of cytokines, parathyroid hormone related peptide (PTHrP) [20] etc.) perhaps leading to an increased bone loss.

Differences between cancer types may give vital clues to the pathogenesis of osteoporosis in patients with malignant diseases, and with the improving survival for many cancer patients this may hold perspectives for preventive measures against long term consequences on the skeleton of the cancer patient and/or its treatment.

In recent years the advent of bisphosphonates has shown effect against skeletal metastases and fractures in patients with various forms of cancer [21–23].

Subjects and methods

In Denmark the extensive nature of registers covering contacts to the health sector offers good possibilities for studies on the occurrence of fractures [24]. Using the unique 10-digit civil registry number that is assigned to all Danish citizens shortly after birth, a complete hospital discharge and prescription history can be established for each individual, and valid linkage between population-based registries can be obtained. The unique civil registry number is used in all registers, i.e. if a person buys a drug on prescription, the drug is registered as bought by this individual, and the same calls for admissions to hospitals and contacts to general practitioners for reimbursement purposes.

This case-control study was performed within the Danish population that constituted approximately 5.3 million individuals during the study period.

The study was subject to control by the National Board of Health, and the Danish Data Protection Agency.

Study design

The study was designed as a classical case-control study. Cases were all subjects, men and women, children and adults, who sustained a fracture during the year 2000. Controls were matched subjects without a fracture in the year 2000. Exposure was use of drugs and diseases before the date of fracture or a matched dummy date in the controls. Information on fractures and diseases prior to the fracture was based on hospital records of in- and outpatients, and did not include diagnoses from general practitioners.

Identification of fracture cases

In Denmark, The National Hospital Discharge Register covers all contacts (on in- or out-patient basis) to the hospitals [25]. The register was founded in 1977, but outpatient records were first completely incorporated from 1995. The files of The National Hospital Discharge Register include information on the civil registry number of the patient, date of discharge, and discharge diagnoses, assigned exclusively by the physician at discharge according to the Danish version of the International Classification of Diseases, 8th revision (ICD-8) until the end of 1993, and to the Danish version of the International Classification of Diseases, 10th revision (ICD-10). The register has nationwide coverage of public hospitals with an almost 100% completeness of recordings and a high precision of diagnoses [25], especially of fracture diagnoses [26]. Using The National Hospital Discharge Register we identified all subjects (men and women, children and adults), who had sustained a fracture between January 1, 2000 and December 31, 2000 ($n=124\,655$).

For end points analyses of all fractures, hip, spine and forearm fractures were selected. These were selected as overall risk of fractures produces an impression of the gross effect of cancer on risk of fractures. Hip and forearm fractures are among the most frequent types of fractures, and a detailed analysis of these would provide insight into different patterns of fracture risk in patients with cancer. Metastases to the spine and pathological fractures of the hip are frequent skeletal manifestations of skeletal metastases, and were thus included. Hip, spine and forearm fractures are often considered osteoporotic fractures and may thus be indicative of

sex steroid deficiency as seen in several types of cancer induced either by surgery to the gonads, irradiation or by chemotherapy or other specific cancer treatment such as aromatase inhibitors in breast cancer. These were thus selected as they were considered the subtypes of fractures that potentially could provide the most information on changes in fracture risk and causes of any change in the risk of fractures.

Selection of population-based controls

Using the Civil Registration System, which has electronic records on all changes in vital status, including change of address and date of death for the entire Danish population since 1968, we randomly selected three controls for each case, matched gender and age by matching with year of birth ($n = 373\,962$). The controls were selected using the incidence-density sampling technique [27], i.e., the controls had to be alive and at risk for fracture diagnosis at the time the corresponding case was diagnosed.

Data on use of drugs

In Denmark, pharmacies are equipped with a computerised accounting system through which data are sent directly to a Register of Medicinal Product Statistics (i.e., a prescription database) at The Danish Medicines Agency with key information on prescriptions for refundable drugs. The prescription database

includes information on the patient's civil registry number, the type and amount of drug prescribed according to the Anatomical Therapeutic Chemical classification system (ATC) [28,29], and the date the prescription was filled. The database was started on January 1, 1996 and updated hereafter. We included all drugs bought during the observation period available in the database.

Each time a subject goes to the pharmacy with a prescription filled by a doctor, the pharmacy registers: 1) Who bought the drugs, 2) The date of filling the prescription, 3) The type of drugs, and 4) The number of tablets and the dose of the tablets (e.g. 100 pills of amitriptyline each of 25 mg).

Data on cancer diagnoses

The cancers were identified from the National Hospital Discharge register in the period January 1, 1977 to December 31, 2000. Only cancers occurring before the date of the fracture were included. The cancers were stratified into groups based on organ system affected (see Table I). Time since first occurrence of a diagnosis until the date of fracture or censoring was recorded.

Data on confounding factors

We analysed for presence of alcoholism [30], any fracture [31], use of pain medication (strong analgesics as morphine and other opioid agonists [19], and weak analgesics as acetaminophen, acetylsalicylic

Table I. Baseline characteristics of the patients with cancer. Figures for age and time since diagnosis is mean and SEM.

Cancer type	N	Age (1) (years)	Time from diagnosis (years)	Fractures in cases/controls (number)
Mouth, pharynx and salivary glands	653	70.0 $\pm$ 0.6	6.6 $\pm$ 0.2	221/432
Oesophagus, ventricle and small intestine	500	75.2 $\pm$ 0.7	7.8 $\pm$ 0.3	180/320
Liver, gall bladder, pancreas	304	73.1 $\pm$ 0.8	5.9 $\pm$ 0.4	109/105
Colon and rectum	3 869	78.4 $\pm$ 0.2	7.9 $\pm$ 0.1	1 032/2 837
Nose, larynx	394	70.4 $\pm$ 0.7	7.9 $\pm$ 0.3	128/266
Lung	1 193	70.5 $\pm$ 0.4	5.4 $\pm$ 0.2	486/707
Malignant melanoma	1 290	68.9 $\pm$ 0.4	9.0 $\pm$ 0.2	325/965
Non melanoma skin cancer	2 936	78.4 $\pm$ 0.3	5.7 $\pm$ 0.1	801/2 135
Kidney and urinary tract	1 564	74.9 $\pm$ 0.4	7.9 $\pm$ 0.2	477/1 087
Breast cancer (women only)	6 411	72.8 $\pm$ 0.2	8.7 $\pm$ 0.1	1 817/4 594
Female genitalia (women only)	3 789	73.1 $\pm$ 0.2	10.9 $\pm$ 0.1	1 006/2 783
Male genitalia (men only)	512	48.4 $\pm$ 0.8	8.9 $\pm$ 0.3	138/374
Prostate cancer (men only)	1 036	78.9 $\pm$ 0.3	4.7 $\pm$ 0.1	406/630
Primary bone cancer	188	60.8 $\pm$ 1.6	7.4 $\pm$ 0.5	83/105
Lymphomas and leukaemia	1 461	63.6 $\pm$ 0.6	7.3 $\pm$ 0.2	439/1 022
Multiple myeloma	238	73.8 $\pm$ 0.8	4.7 $\pm$ 0.3	123/115
Bone metastases	314	72.3 $\pm$ 0.7	3.4 $\pm$ 0.3	206/108
Other metastases excl. bone	1 416	70.9 $\pm$ 0.4	6.2 $\pm$ 0.2	536/880
Other and non-specified	1 178	63.3 $\pm$ 0.7	7.1 $\pm$ 0.2	372/806

(1) Age in years at time of fracture or comparative dummy date among the controls. N: Number of patients with cancer (fracture cases and control patients combined).

acid, and non-steroidal anti-inflammatory drugs (NSAIDs) [32]), and use of corticosteroids [33]. The presence of all confounders was recorded prior to the date of the fracture.

Information on alcoholism was collected as appearance of a diagnosis of alcoholism in the National Hospital Discharge Register [25] or in the Psychiatric Central Register [34], or a prescription of disulfiram in the Prescription database. Information on prior fractures was based on data from the National Hospital Discharge register [25].

Statistics

Data from the different registers were merged at the National Bureau of Statistics, and for each subject the 10 digit civil registry number was substituted by a unique case number i.e., as investigators we had no access to personally identifiable information. Mean and standard deviation were used as descriptive statistics. Crude odds ratios (OR's) were calculated and 95% confidence intervals approximated using the method of Miettinen [35]. A conditional logistic regression analysis was used to assess the association between the fracture in question and the exposure variables.

Analyses were performed using STATA 8.1 (STATA Corp., College Station, Tx) and SPSS 14.0 (SPSS Inc., Chicago Ill.) – both in the Unix version.

Results

Table I shows baseline characteristics of the cancer patients. Most patients were above the age of 70 years at the time of the fracture, and in most cases the mean duration of cancer was above 5 years at the time of fracture. A total of 24 807 subjects had at least one diagnosis of a cancer (excluding metastases from the primary cancer), and among these 9.8% ($n = 2\,436$) had more than one diagnosis of cancer in different organs (say a case of skin cancer and breast cancer diagnosed at a later stage).

Table II shows the OR of any fracture with a diagnosis of cancer between 1977 and 2000. In most cases the crude analysis showed an increased overall risk of fractures. Upon adjustment the OR of any fracture was attenuated, especially after the introduction of adjustment for use of pain medication. Upon multiple adjustment the OR for fracture fell below that of the background population ($OR < 1$) for skin cancer (malignant melanoma and non-melanoma skin cancer), breast cancer, colon cancer, and cancer of female genitalia. After multiple adjustments for confounders, lung cancer, prostate cancer, multiple myeloma, bone metastases, and metastases in other locations were associated with an increased overall risk of fractures. The other cancer types were not associated with risk of any fracture.

Table III shows the effect of time since diagnosis on OR of any fracture. The crude ORs for any

Table II. Risk of any fracture in patients with various cancer forms compared to patients without any type of cancer.

Cancer type	Crude OR (95% CI)	Mutually Adjusted	Multiply Adjusted**
Mouth, pharynx and salivary glands	1.54 (1.31–1.81)*	1.38 (1.17–1.68)*	1.00 (0.84–1.18)
Oesophagus, ventricle and small intestine	1.69 (1.41–2.03)*	1.59 (1.32–1.91)*	1.13 (0.94–1.38)
Liver, gall bladder, pancreas	1.68 (1.33–2.12)*	1.52 (1.20–1.93)*	1.08 (0.84–1.38)
Colon and rectum	1.09 (1.02–1.17)*	1.04 (0.97–1.12)	0.79 (0.74–0.84)
Nose, larynx	1.44 (1.17–1.78)*	1.28 (1.04–1.59)*	1.00 (0.80–1.25)
Lung	2.07 (1.84–2.32)*	1.83 (1.63–2.08)*	1.30 (1.15–1.47)*
Malignant melanoma	1.01 (0.89–1.15)	0.95 (0.83–1.08)	0.87 (0.76–0.99)*
Non melanoma skin cancer	1.13 (1.04–1.22)*	1.08 (0.99–1.17)	0.85 (0.78–0.93)*
Kidney and urinary tract	1.32 (1.18–1.47)*	1.22 (1.09–1.36)*	0.96 (0.85–1.07)
Breast cancer (women only)	1.19 (1.13–1.26)*	1.11 (1.05–1.18)*	0.85 (0.81–0.91)*
Female genitalia (women only)	1.09 (1.01–1.17)*	1.05 (0.98–1.13)	0.84 (0.78–0.91)*
Male genitalia (men only)	1.11 (0.91–1.35)	1.06 (0.87–1.29)	1.03 (0.84–1.26)
Prostate cancer (men only)	1.94 (1.71–2.20)*	1.64 (1.44–1.87)*	1.35 (1.18–1.55)*
Primary bone cancer	2.37 (1.78–3.16)*	1.74 (1.29–2.34)*	1.35 (0.99–1.85)
Lymphomas and leukaemia	1.29 (1.15–1.44)*	1.17 (1.04–1.31)*	0.99 (0.88–1.12)
Multiple myeloma	3.21 (2.49–4.14)*	2.91 (2.25–3.76)*	1.96 (1.50–2.57)*
Bone metastases	5.73 (4.54–7.23)*	3.98 (3.13–5.06)*	3.01 (2.34–3.86)*
Other metastases excl. bone	1.83 (1.64–2.04)*	1.43 (1.28–1.61)*	1.30 (1.16–1.47)*
Other and non-specified	1.39 (1.23–1.57)*	1.18 (1.04–1.34)*	1.00 (0.87–1.14)

* $2p < 0.05$, Adjusted for other cancers (occurrence of mouth, pharynx, salivary gland cancer, oesophagus, ventricle and small intestine cancer, liver, gall bladder, and pancreas cancer etc.), **adjusted for other cancers, use of corticosteroids, alcoholism, use of pain medication (morphine and other opioid agonists, NSAIDs, Acetylsalicylic acid, and acetaminophen), and prior fracture.

Table III. Effect of time since diagnosis on risk of any fracture – multiply adjusted OR and 95% CI**.

Cancer type	≤1 year	1–5 years	>5 years
Mouth, pharynx and salivary glands	0.81 (0.49–1.34)	1.09 (0.83–1.43)	0.96 (0.75–1.24)
Oesophagus, ventricle and small intestine	0.84 (0.51–1.39)	1.44 (1.02–2.03)*	1.08 (0.83–1.41)
Liver, gall bladder, pancreas	2.14 (1.39–3.31)*	0.90 (0.56–1.46)	0.66 (0.43–1.01)
Colon and rectum	0.82 (0.66–1.03)	0.83 (0.73–0.94)*	0.77 (0.70–0.85)*
Nose, larynx	0.84 (0.44–1.59)	0.91 (0.61–1.35)	1.09 (0.81–1.47)
Lung	1.90 (1.51–2.38)*	1.33 (1.08–1.65)*	0.86 (0.69–1.07)
Malignant melanoma	1.12 (0.75–1.69)	0.95 (0.74–1.21)	0.81 (0.69–0.96)*
Non melanoma skin cancer	0.96 (0.75–1.22)	0.82 (0.72–0.93)*	0.86 (0.75–0.98)*
Kidney and urinary tract	1.25 (0.92–1.70)	0.98 (0.80–1.21)	0.86 (0.74–1.00)
Breast cancer (women only)	0.78 (0.64–0.96)	0.88 (0.79–0.98)*	0.87 (0.81–0.93)*
Female genitalia (women only)	0.76 (0.56–1.04)	0.87 (0.74–1.02)	0.84 (0.77–0.92)*
Male genitalia (men only)	0.70 (0.33–1.50)	1.19 (0.82–1.71)	1.03 (0.79–1.33)
Prostate cancer (men only)	1.19 (0.87–1.64)	1.36 (1.12–1.65)*	1.44 (1.14–1.81)*
Primary bone cancer	3.51 (1.54–8.01)*	1.34 (0.77–2.32)	1.01 (0.63–1.59)
Lymphomas and leukaemia	1.21 (0.98–1.64)	0.92 (0.75–1.14)	1.00 (0.85–1.17)
Multiple myeloma	5.21 (2.96–9.19)*	1.54 (1.01–2.33)*	1.31 (0.82–2.12)
Bone metastases	5.28 (3.58–7.79)*	2.39 (1.54–3.71)*	1.07 (0.62–1.86)
Other metastases excl. bone	1.85 (1.50–2.29)*	1.37 (1.10–1.71)*	0.88 (0.73–1.07)
Other and non-specified	1.39 (1.01–1.93)*	0.80 (0.63–1.01)	1.02 (0.85–1.23)

*2p < 0.05, **adjusted for use of corticosteroids, alcoholism, use of pain medication (morphine and other opioid agonists, NSAIDs, Acetylsalicylic acid, and acetaminophen), and prior fracture.

fracture were statistically significant for cancer of the mouth, pharynx and salivary glands at all time points with a declining trend. For cancer of the oesophagus, ventricle and small intestine significance was seen at all time points with no particular trend with time. For the liver, gall bladder and pancreas the pattern was similar for crude and adjusted ORs. For the colon and rectum the crude ORs were statistically significantly elevated for 1–5 years after diagnosis but not at other time points. For the nose and larynx, a statistically significant increase was seen for durations since diagnosis of more than 5 years. For the lungs the pattern for the crude ORs were similar to the adjusted ORs except that borderline statistical significance was obtained for durations >5 years. For malignant melanomas no statistical significance was obtained for the crude ORs while these were statistically significant for durations ≤1 year and >5 years for non-melanoma skin cancer. For the kidney and urinary tract the crude ORs were statistically significant for all durations with a declining trend with time. For breast cancer the crude ORs were statistically significantly increased for durations >1 year. For male and female genital cancers no statistical significant association was present with any duration for the crude ORs. Prostate cancer showed a statistically significant association with all durations with an increasing trend for the crude ORs. For primary bone cancer the pattern was similar for crude and adjusted ORs with the exception that statistical significance was present for ≤5 years in the crude analysis and ≤1 in the adjusted analysis. For the lymphomas and

leukaemias, multiple myeloma and bone metastases a statistically significant increase in risk of fractures was seen for all durations in the crude analysis with a declining trend with age. For metastases other than bone a significant increase in the crude analysis was present for duration ≤5 years. For other and non-specified cancers a statistically significant increase was present in the crude analysis for durations ≤1 year and >5 years. The factor with the greatest impact on risk of fractures was adjustment for use of analgesics.

In the adjusted analysis three distinctive patterns were present:

1. A high OR early after diagnosis followed by a decline in relative risk of fracture to the same levels as in the background population (seen for bone metastases, multiple myeloma, primary bone cancer, cancer of the liver/gall bladder or pancreas, metastatic disease in other locations than bone, lung cancer, and other and non-specified cancers)
2. No association with fracture risk (oral cavity, nose/larynx, kidney/bladder, male genitalia, and lymphomas/leukaemia)
3. Initially mainly no association, but a decline with time below that of the background population (colon cancer, malignant melanoma, non-melanoma skin cancer, breast cancer, and female genitalia).

Variations over this pattern were a) prostate cancer, which was associated with an increased risk even

with prolonged time of observation, and perhaps a small increase with time, and b) cancer of the oesophagus, ventricle, and small intestine, where a limited increase in fracture risk was seen within 1–5 years after diagnosis.

Among women with breast cancer, only 39 had used aromatase inhibitors, while 656 had used tamoxifen. Inclusion of tamoxifen or aromatase inhibitors did not significantly change the results. Further adjustment for use of hormone therapy (HT) did not completely increase the OR to that of the background population for breast cancer. Adjustment for use of HT also did not return the risk to that of the background population for cancer of the female genitalia or for colon cancer.

Table IV shows the OR of hip fractures. In general the pattern was the same as for any fracture, however, the OR was much more pronounced for hip fractures in patients with a duration since diagnosis of cancer of less than one year.

Table V shows the OR of forearm fractures. Overall the pattern tended to be similar to that for overall fracture risk in Table III.

Table VI shows the OR of vertebral fractures. In general the pattern was similar to that in Table IV, but tended to be more pronounced with a short duration of cancer.

Stratification for gender did not change the overall results (data not shown). Age stratification (≤ 65 years, 66–75 years, and > 75 years) did not change the overall results. There were too few subjects with cancer for detailed analysis of subjects younger than 50 years of age.

Discussion

In this large-scale population based case-control study, we have shown significant differences in the risk of fractures associated with various cancer types. This may point at different pathophysiological mechanisms, but may also help to identify patients at particular risk of fractures, which may be in need of preventive measures.

Regarding the different fracture patterns, the following may be pointed out:

1. Local cancer in bone (primary bone malignancy, multiple myeloma, and bone metastases) was highly associated with fractures most likely due to direct weakening of bone architecture. The same may be the case for metastases in other localisations than bone – although these do not directly affect bone, these patients may be more likely to develop further metastases to the skeleton and thus suffer fractures. Alternatively, the fractures may be caused by immobilisation, malnutrition, chemotherapy, calls etc.
2. Skin cancer (melanoma and non-melanoma skin cancer): These are associated with sun exposure and thus potentially a high average serum vitamin D level. High serum vitamin D levels may be protective from cancer [36,37], falls [38], and osteoporotic fractures [39]. Malignant melanoma carries a high risk of metastases in contrast to other types of skin cancer, however despite this both malignant melanoma and other types of skin cancer were

Table IV. Risk of hip fracture associated with various cancer types stratified by time since diagnosis – multiply adjusted OR and 95% CI**.

Cancer type	≤ 1 year	1–5 years	> 5 years
Mouth, pharynx and salivary glands	2.53 (0.56–11.4)	1.17 (0.64–2.15)	1.16 (0.70–1.91)
Oesophagus, ventricle and small intestine	1.28 (0.43–3.82)	1.68 (0.79–3.56)	0.99 (0.59–1.66)
Liver, gall bladder, pancreas	3.24 (1.49–7.05)*	4.53 (1.38–14.9)*	0.74 (0.33–1.68)
Colon and rectum	1.08 (0.69–1.70)	0.89 (0.67–1.18)	0.91 (0.75–1.10)
Nose, larynx	–	2.00 (0.82–4.90)	1.31 (0.68–2.50)
Lung	5.21 (2.97–9.16)*	3.04 (1.82–5.07)*	0.82 (0.51–1.33)
Malignant melanoma	2.05 (0.80–5.27)	0.96 (0.49–1.89)	0.83 (0.54–1.29)
Non melanoma skin cancer	1.06 (0.66–1.70)	0.96 (0.75–1.22)	1.12 (0.87–1.45)
Kidney and urinary tract	1.91 (1.00–3.62)*	1.50 (0.99–2.25)	1.11 (0.82–1.51)
Breast cancer (women only)	1.03 (0.63–1.69)	0.94 (0.74–1.20)	0.90 (0.76–1.07)
Female genitalia (women only)	1.25 (0.60–2.61)	0.81 (0.53–1.23)	0.86 (0.70–1.05)
Male genitalia (men only)	1.69 (0.31–9.37)	1.17 (0.32–4.27)	1.61 (0.59–4.39)
Prostate cancer (men only)	1.70 (0.95–3.03)	1.70 (1.20–2.40)*	1.30 (0.88–1.93)
Primary bone cancer	15.0 (1.45–155)*	2.56 (0.84–7.76)	1.74 (0.37–8.12)
Lymphomas and leukaemia	2.49 (1.27–4.89)*	0.89 (0.53–1.49)	1.13 (0.76–1.68)
Multiple myeloma	6.00 (1.68–21.4)*	1.76 (0.76–4.05)	0.60 (0.20–1.79)
Bone metastases	6.50 (2.78–15.2)*	2.91 (1.19–7.12)*	0.82 (0.25–2.65)
Other metastases excl. bone	2.34 (1.43–3.82)*	1.65 (1.00–2.71)*	1.14 (0.75–1.75)
Other and non-specified	1.12 (0.49–2.57)	1.05 (0.61–1.80)	1.15 (0.72–1.84)

* $2p < 0.05$, **adjusted for use of corticosteroids, alcoholism, use of pain medication (morphine and other opioid agonists, NSAIDs, Acetylsalicylic acid, and acetaminophen), and prior fracture. –: Too few for analysis.

Table V. Risk of forearm fracture associated with various cancer types stratified by time since diagnosis – multiply adjusted OR and 95% CI**.

Cancer type	≤1 year	1–5 years	>5 years
Mouth, pharynx and salivary glands	0.78 (0.20–3.05)	1.63 (0.77–3.41)	0.59 (0.28–1.23)
Oesophagus, ventricle and small intestine	0.40 (0.04–3.95)	2.71 (1.25–5.87)*	1.03 (0.54–1.97)
Liver, gall bladder, pancreas	8.75 (1.73–44.3)*	0.39 (0.08–1.84)	0.26 (0.06–1.14)
Colon and rectum	0.93 (0.51–1.70)	0.89 (0.64–1.23)	1.11 (0.88–1.42)
Nose, larynx	0.67 (0.13–3.52)	0.86 (0.32–2.34)	1.77 (0.79–3.92)
Lung	0.91 (0.46–1.80)	1.22 (0.70–2.13)	0.83 (0.48–1.44)
Malignant melanoma	0.98 (0.26–3.73)	1.25 (0.65–2.40)	0.85 (0.56–1.29)
Non melanoma skin cancer	0.70 (0.32–1.54)	0.98 (0.72–1.32)	1.10 (0.78–1.55)
Kidney and urinary tract	1.25 (0.45–3.46)	0.77 (0.44–1.37)	0.72 (0.46–1.11)
Breast cancer (women only)	0.87 (0.55–1.36)	0.89 (0.69–1.14)	1.12 (0.95–1.32)
Female genitalia (women only)	0.39 (0.17–0.88)*	0.87 (0.61–1.24)	0.97 (0.80–1.19)
Male genitalia (men only)	6.06 (0.54–66.6)	1.15 (0.30–4.44)	1.33 (0.51–3.45)
Prostate cancer (men only)	1.53 (0.46–5.14)	1.44 (0.74–2.80)	2.94 (1.36–6.33)*
Primary bone cancer	1.81 (0.11–31.2)	0.24 (0.03–2.01)	0.92 (0.30–2.81)
Lymphomas and leukaemia	1.03 (0.49–2.15)	0.80 (0.44–1.45)	0.68 (0.43–1.08)
Multiple myeloma	–	0.90 (0.18–4.52)	1.81 (0.59–5.58)
Bone metastases	4.60 (1.29–16.5)*	1.02 (0.26–3.97)	0.81 (0.16–4.15)
Other metastases excl. bone	1.47 (0.85–2.57)	1.35 (0.77–2.37)	0.67 (0.42–1.06)
Other and non-specified	1.46 (0.56–3.83)	0.92 (0.49–1.73)	0.66 (0.38–1.16)

*2p < 0.05, **adjusted for use of corticosteroids, alcoholism, use of pain medication (morphine and other opioid agonists, NSAIDs, Acetylsalicylic acid, and acetaminophen), and prior fracture. –: Too few for analysis.

not associated with an increased risk of fractures, but rather a decrease.

3. Lung cancer is highly associated with risk of fractures. Lung cancer is associated with smoking, and smoking is associated with an increased risk of fracture [40], which may perhaps explain the increased risk of fractures. Other potential explanations include the association to chronic obstructive pulmonary dis-

ease (COPD) and thus use of corticosteroids, which predispose to fractures [33,41]. A further possibility is if tumour production of PTHrP [42].

4. Prostate cancer has a high likelihood of metastases to bone, and is treated with androgen deprivation therapy, which may lead to bone loss, and these two factors in combination may explain why a sustained increase in risk of

Table VI. Risk of vertebral fracture associated with various cancer types stratified by time since diagnosis – multiply adjusted OR and 95% CI**.

Cancer type	≤1 year	1–5 years	>5 years
Mouth, pharynx and salivary glands	0.89 (0.07–11.7)	0.86 (0.20–3.65)	2.10 (0.71–6.25)
Oesophagus, ventricle and small intestine	–	0.76 (0.20–2.84)	6.26 (2.10–18.7)*
Liver, gall bladder, pancreas	2.12 (0.18–25.2)	0.94 (0.06–14.4)	0.49 (0.07–3.30)
Colon and rectum	2.36 (0.96–5.81)	0.72 (0.38–1.39)	0.57 (0.34–0.94)
Nose, larynx	1.41 (0.11–17.6)	0.22 (0.01–4.96)	1.50 (0.41–5.40)
Lung	0.59 (0.21–1.68)	1.16 (0.47–2.84)	1.18 (0.40–3.44)
Malignant melanoma	–	–	0.13 (0.02–1.03)
Non melanoma skin cancer	2.32 (0.90–6.00)	0.54 (0.28–1.04)	1.10 (0.60–2.01)
Kidney and urinary tract	0.92 (0.26–3.23)	0.45 (0.14–1.50)	0.80 (0.37–1.71)
Breast cancer (women only)	1.30 (0.43–3.90)	0.65 (0.36–1.19)	0.62 (0.43–0.90)*
Female genitalia (women only)	0.46 (0.08–2.80)	0.41 (0.15–1.11)	0.87 (0.57–1.33)
Male genitalia (men only)	2.58 (0.40–16.5)	1.02 (0.15–6.85)	–
Prostate cancer (men only)	0.52 (0.10–2.65)	1.05 (0.33–3.32)	1.38 (0.44–4.39)
Primary bone cancer	–	2.54 (0.08–80.4)	0.38 (0.02–6.78)
Lymphomas and leukaemia	5.26 (1.18–23.5)*	1.20 (0.52–2.73)	1.19 (0.54–2.64)
Multiple myeloma	23.0 (2.40–220)	7.53 (0.67–85.1)	0.61 (0.06–6.13)
Bone metastases	6.96 (1.72–28.2)*	–	–
Other metastases excl. bone	1.94 (0.73–5.12)	0.69 (0.18–2.70)	1.11 (0.36–3.46)
Other and non-specified	1.44 (0.35–5.88)	0.27 (0.04–1.68)	2.51 (0.91–6.91)

*2p < 0.05, **adjusted for use of corticosteroids, alcoholism, use of pain medication (morphine and other opioid agonists, NSAIDs, Acetylsalicylic acid, and acetaminophen), and prior fracture, –: Too few for analysis.

fractures was seen. Furthermore, localised prostate cancer may be associated with a prolonged survival [43] and thus a sustained risk of even late metastases to the skeleton and detrimental effects of long-term androgen deprivation therapy [1,44].

Dickman et al. [45] reported an early and sustained increase in the risk of hip fractures in patients who underwent bilateral orchiectomy for prostate cancer. In our study the increase was seen later in the course of the prostate cancer and this may be due to the fact that not all patients underwent orchiectomy or received androgen deprivation therapy. Furthermore, patients treated with orchiectomy may have more advanced prostate cancer than those not undergoing orchiectomy, and this may also contribute to the differences between our results and those of Dickman et al. [45].

5. In general cancer of the genital organs (male or female) was not associated with an increase in the risk of fractures. The influence from deficiency in sex steroids was thus probably low as most women were postmenopausal. Why fracture risk was low in men remains to be determined, but testosterone production may to a large extent be conserved.
6. There was a striking difference in the risk of fractures within the gastrointestinal canal. Cancer of the liver, gall bladder and pancreas were associated with an early increase in the risk of fractures with a tapering to the levels of the normal population while cancer of the oesophagus, ventricle, and small intestine were not associated with an early increase in risk of fractures, but rather a temporary increase at a later stage. Cancer of the colon and rectum were not associated with an increase in the risk of fractures. This difference may be related to the differential effects on absorption of nutrients. Patients with cancer of the liver, gall bladder, and pancreas may have a decreased absorption of nutrients including calcium and vitamin D which may predispose to fractures. The same may be seen although perhaps at a later stage for cancer of the oesophagus, ventricle, and small intestine. Cancer of the colon and rectum do not affect absorption of nutrients except in the case of ileus.
7. Why breast cancer was not associated with a pronounced increased risk of fractures remains to be determined, but may be linked to the fact that most patients were postmenopausal, i.e. the loss of sex steroids was limited. The study was performed before aromatase inhibitors came into widespread use and thus may not

have confounded the risk of fractures. Adjustment for the use of tamoxifen did not significantly change the results.

Prior studies on fracture occurrence in women with breast cancer has included Chen et al. [46], Adami et al. [47], and Lamont et al. [48]. Chen et al. [46] in a cohort of 5 298 breast cancer survivors reported no increase in the risk of hip fractures (HR=0.93, 95% CI: 0.64–1.33), while an increased risk of forearm (HR=1.36, 95% CI: 1.16–1.59), spine (HR=1.31, 95% CI: 1.03–1.66) and overall risk of fractures (HR=1.31, 95% CI: 1.21–1.41). The increase in overall fracture risk and risk of forearm and spine fractures in the study by Chen et al. [46] are in contrast to our results. In contrast to our study Chen et al. [46] had information on weight, parameters related to hormone levels, and fall history and a number of life-style factors, which we did not have access to. However, in our study we had access to some confounders not addressed by Chen et al. [46] such as analgesics which may per se be associated with fractures. In combination these differences in confounders may explain some of the variations in results. Adami et al. [47] in a follow-up study of 9 673 women found a limited trend towards an increase in the risk of hip fractures (RR=1.1, 95% CI: 1.0–1.2) in contrast to the results by our study and the study by Chen et al. [46]. Lamont et al. [48] in a cohort of 5 980 breast cancer survivors diagnosed between the age of 55 and 64 reported a decreased adjusted risk of hospitalisation for hip fractures (RR=0.63, 95% CI: 0.43–0.94) in accordance with our results but in contrast to the results by Adami et al. [47] and Chen et al. [46]. In their study Lamont et al. [48] used breast cancer survivors (age >67 years, diagnosis made between age 55–64 years) who had been in lower stages of breast cancer (Stage 0, I or II), and this may have led to a selection bias. Adami et al. [47] in their study showed a somewhat declining risk of hip fractures with age, and the participants in the study by Lamont et al. [48] were older than in the other studies. Age at diagnosis may thus play a role perhaps related to estrogen status, which may explain the decreased risk of fractures in patients with breast cancer in our study compared to the studies by Adami et al. [47] and Chen et al. [46].

8. With prolonged survival, cure is likely, and the risk of fractures therefore returns to that of the general population. In some cases, the long term survivors after cancer may represent a

selected subgroup of individuals in better shape than the general population, which may perhaps explain why a modest decrease in the risk of fractures was seen in some groups.

The higher OR of vertebral fractures than for overall fracture risk may be due to the predilection of bony metastases for the spine. The absence of an effect of tamoxifen on overall risk of fractures is in accordance with observations from the similar drug raloxifene (also a selective estrogen receptor modulator) in patients with osteoporosis [49].

In general we did not observe an excess risk of fractures in patients with lymphomas and leukaemia. However, an increased risk of hip and vertebral fractures was seen within the first year following diagnosis. The absence of an increase in overall risk of fractures was in contrast to Hogler et al. [50]. However, this study only addressed children with ALL, and may have been significantly confounded by the fact that the risk of fractures among the patients was compared to the incidence of fractures in a control population from a different country.

The main strength of the study is the large sample size and the uniform nature of the registrations.

The main drawbacks are lack of information on chemotherapy and bisphosphonates administered while in hospital, as these are not registered in the database. However, this may represent a minor problem since these are incorporated into the effect of the cancer itself (different modes of chemotherapy, radiation therapy and surgical techniques are applied for different cancer types), but this adds up to the combined effect of the cancer type on risk of fractures.

In the case control design applied in the present study, cases were selected on the basis of fracture occurrence. This may have led to undersampling of cancer cases with a less favourable prognosis. Cancers with a rapidly progressive course may however also be the ones most likely to present with metastases and these were shown to be associated with an increased risk of fractures. Cancers with a prolonged survival may perhaps for some types approach the risk of fractures of the general population, whereas others such as prostate cancer may have an increased risk of fractures due to e.g. androgen deprivation. It is thus less likely that the design per se may have led to severe sampling bias. Examples of cancers with less favourable prognosis are liver, gall bladder, pancreas, oesophagus and gastric cancer. For these no increase in risk of fractures was observed with prolonged survival (>5 years of observation), while a trend towards more fractures were seen within the first year after diagnosis for liver, gall bladder and pancreas cancer and within 1–5 years after diagnosis

for oesophagus and ventricle, and small intestine cancers. With prolonged survival the risk of fractures may approach the general population because those cured may have had less advanced cancers and may survive with low systemic damage to the gastrointestinal canal, while those with a short observation time had more advanced cancers with loss of absorption capability and thus deficiency in say calcium and vitamin D.

In some strata the number of subjects was limited, and this has decreased the power of detecting differences especially for some of the rarer cancer forms. However, in most cases in Tables II–VI, the confidence intervals were rather narrow, indicating high power and precise estimates.

Upon introduction of confounders particularly use of analgesics, the ORs associated with fractures were attenuated. Having a diagnosis of several cancers may thus be associated with an increased risk of fractures. However, in the present analysis confounders in particular use of analgesics seemed responsible for some of the increase.

In conclusion differences exist between cancer types in the risk of fractures. High risk of fractures was seen for cancers primarily affecting the bone (primary bone cancer, metastases to the bone, metastases to other organs than bone, lung cancer, and cancer of the liver, gall bladder and pancreas, and prostate cancer). The main increase in risk of fractures in this group was seen within the first year following diagnosis. A low risk group for fractures included all other cancer types (e.g. cancer of the breast, colon, skin etc).

Acknowledgements

Danmarks Statistik (Statistics Denmark) is acknowledged for the help without which this project would not have been possible. Research Librarian Ms. Edith Clausen is acknowledged for invaluable help with the references.

The Danish Medical Research Council granted financial support (Grant number 22-04-0495).

References

- [1] Lopez AM, Pena MA, Hernandez R, Val F, Martin B, Riancho JA. Fracture risk in patients with prostate cancer on androgen deprivation therapy. *Osteoporos Int* 2005;16: 707–11.
- [2] Kanis JA, McCloskey EV, Powles T, Paterson AH, Ashley S, Spector T. A high incidence of vertebral fracture in women with breast cancer. *Br J Cancer* 1999;79:1179–81.
- [3] Utz JP, Melton III LJ, Kan SH, Riggs BL. Risk of osteoporotic fractures in women with breast cancer: A population-based cohort study. *J Chron Dis* 1987;40: 105–13.

- [4] Cauley JA, Lucas FL, Kuller LH, Vogt MT, Browner WS, Cummings SR. Bone mineral density and risk of breast cancer in older women: the study of osteoporotic fractures. Study of Osteoporotic Fractures Research Group. *JAMA* 1996;276:1404–8.
- [5] Eastell R, Hannon RA, Cuzick J, Dowsett M, Clack G, Adams JE. Effect of an aromatase inhibitor on bmd and bone turnover markers: 2-year results of the Anastrozole, Tamoxifen, Alone or in Combination (ATAC) trial (18233230). *J Bone Miner Res* 2006;21:1215–23.
- [6] Kristensen B, Ejlersen B, Mouridsen HT, Andersen KW, Lauritzen JB. Femoral fractures in postmenopausal breast cancer patients treated with adjuvant tamoxifen. *Breast Cancer Res Treat* 1996;39:321–6.
- [7] Bruning PF, Pit MJ, de Jong-Bakker M, van den Ende A, Hart A, van Enk A. Bone mineral density after adjuvant chemotherapy for premenopausal breast cancer. *British J Cancer* 1990;61:308–10.
- [8] Halton JM, Atkinson SA, Fraher L, Webber C, Gill GJ, Dawson S, et al. Altered mineral metabolism and bone mass in children during treatment for acute lymphoblastic leukemia. *J Bone Miner Res* 1996;11:1774–83.
- [9] Hogler W, Wehl G, van Staa T, Meister B, Klein-Franke A, Kropshofer G. Incidence of skeletal complications during treatment of childhood acute lymphoblastic leukemia: Comparison of fracture risk with the General Practice Research Database. *Pediatr Blood Cancer* 2007;48:21–7.
- [10] Mandel K, Atkinson S, Barr RD, Pencharz P. Skeletal morbidity in childhood acute lymphoblastic leukemia. *J Clin Oncol* 2004;22:1215–21.
- [11] Wagner LM, Neel MD, Pappo AS, Merchant TE, Poquette CA, Rao BN, et al. Fractures in pediatric Ewing sarcoma. *J Pediatr Hematol Oncol* 2001;23:568–71.
- [12] Brown SA, Guise TA. Cancer-associated bone disease. *Curr Osteoporos Rep* 2007;5:120–7.
- [13] Coleman RE. Clinical features of metastatic bone disease and risk of skeletal morbidity. *Clin Cancer Res* 2006;12:6243s–9s.
- [14] Maduro JH, Pras E, Willemse PH, de Vries EG. Acute and long-term toxicity following radiotherapy alone or in combination with chemotherapy for locally advanced cervical cancer. *Cancer Treat Rev* 2003;29:471–88.
- [15] Wall JE, Kaste SC, Greenwald CA, Jenkins JJ, Douglass EC, Pratt CB. Fractures in children treated with radiotherapy for soft tissue sarcoma. *Orthopedics* 1996;19:657–64.
- [16] Theriault RL. Pathophysiology and implications of cancer treatment-induced bone loss. *Oncology (Williston Park)* 2004;18:11–5.
- [17] van Leeuwen BL, Kamps WA, Jansen HW, Hoekstra HJ. The effect of chemotherapy on the growing skeleton. *Cancer Treat Rev* 2000;26:363–76.
- [18] Baum M, Budzar AU, Cuzick J, Forbes J, Houghton JH, Klijn JG, et al. Anastrozole alone or in combination with tamoxifen versus tamoxifen alone for adjuvant treatment of postmenopausal women with early breast cancer: first results of the ATAC randomised trial. *Lancet* 2002;359:2131–9.
- [19] Vestergaard P, Rejnmark L, Mosekilde L. Fracture risk associated with use of morphine and opiates. *J Intern Med* 2006;260:76–87.
- [20] Yoshida A, Nakamura Y, Shimizu A, Harada M, Kameda Y, Nagano A, et al. Significance of the parathyroid hormone-related protein expression in breast carcinoma. *Breast Cancer* 2000;7:215–20.
- [21] Atkins CD. Re: A randomized, placebo-controlled trial of zoledronic acid in patients with hormone-refractory metastatic prostate carcinoma. *J Natl Cancer Inst* 2003;95:332–4.
- [22] Berenson JR, Lichtenstein A, Porter L, Dimopoulos MA, Bordoni R, George S, et al. Efficacy of pamidronate in reducing skeletal events in patients with advanced multiple myeloma. Myeloma Aredia Study Group. *N Engl J Med* 1996;334:488–93.
- [23] Body JJ, Diel IJ, Lichinitzer M, Lazarev A, Pecherstorfer M, Bell R, et al. Oral ibandronate reduces the risk of skeletal complications in breast cancer patients with metastatic bone disease: results from two randomised, placebo-controlled phase III studies. *Br J Cancer* 2004;90:1133–7.
- [24] Frank L. Epidemiology. When an entire country is a cohort. *Science* 2000;287:2398–9.
- [25] Andersen TF, Madsen M, Jørgensen J, Møller-Jensen L, Olsen JH. The Danish National Hospital Register. *Danish Medical Bulletin* 1999;46:263–8.
- [26] Vestergaard P, Mosekilde L. Fracture risk in patients with celiac disease, Crohn's disease, and ulcerative colitis: A nation-wide follow-up study in 16,416 patients in Denmark. *Am J Epidemiol* 2002;156:1–10.
- [27] Wacholder S, McLaughlin JK, Silverman DT, Mandel JS. Selection of controls in case-control studies. I. Principles. *Am J Epidemiol* 1992;135:1019–28.
- [28] Capella D. Descriptive tools and analysis. In: Dukes MNG, ed. *Drug Utilization Studies: Methods and Uses*. Copenhagen: WHO Regional Publications, European Series No. 45; 1993. p 55–78.
- [29] Nielsen GL, Sørensen HT, Zhou W, Steffensen FH, Olsen J. The pharmaco-epidemiologic prescription database of North Jutland. *Int J Risk Saf Med* 1997;10:203–5.
- [30] Vestergaard P, Rejnmark L, Mosekilde L. Socioeconomic aspects of fractures within universal public healthcare: A nationwide case-control study from Denmark. *Scand J Public Health* 2006;34:371–7.
- [31] Klotzbuecher CM, Ross PD, Landsman PB, Abbott III TA, Berger M. Patients with prior fractures have an increased risk of future fractures: a summary of the literature and statistical synthesis. *J Bone Miner Res* 2000;15:721–39.
- [32] Vestergaard P, Rejnmark L, Mosekilde L. Fracture risk associated with use of nonsteroidal anti-inflammatory drugs, acetylsalicylic acid, and acetaminophen and the effects of rheumatoid arthritis and osteoarthritis. *Calcif Tissue Int* 2006;79:84–94.
- [33] van Staa TP, Leufkens HGM, Abenhaim L, Zhang B, Cooper C. Use of oral corticosteroids and risk of fractures. *J Bone Mineral Res* 2000;15:993–1000.
- [34] Munk-Jørgensen P, Mortensen PB. The Danish Psychiatric Central Register. *Danish Medical Bulletin* 1997;44:82–4.
- [35] Miettinen OS. Theoretical epidemiology: Principles of occurrence research in medicine. New York: Wiley & Sons; 1985. p 1–359.
- [36] Grant WB. An estimate of premature cancer mortality in the U.S. due to inadequate doses of solar ultraviolet-B radiation. *Cancer* 2002;94:1867–75.
- [37] Grant WB. Ecologic studies of solar UV-B radiation and cancer mortality rates. *Recent Results Cancer Res* 2003;164:371–7.
- [38] Bischoff HA, Stähelin HB, Dick W, Akos R, Knecht M, Salis C, et al. Effects of vitamin D and calcium supplementation on falls: A randomized controlled trial. *J Bone Miner Res* 2003;18:343–51.
- [39] Tang BM, Eslick GD, Nowson C, Smith C, Bensoussan A. Use of calcium or calcium in combination with vitamin D supplementation to prevent fractures and bone loss in people aged 50 years and older: a meta-analysis. *The Lancet* 2007;370:657–66.

- [40] Vestergaard P, Mosekilde L. Fracture risk associated with smoking – a meta-analysis. *J Intern Med* 2003;254:572–83.
- [41] Vestergaard P, Rejnmark L, Mosekilde L. Fracture risk associated with systemic and topical corticosteroids. *J Intern Med* 2005;257:374–84.
- [42] Nishigaki Y, Ohsaki Y, Toyoshima E, Kikuchi K. Increased serum and urinary levels of a parathyroid hormone-related protein COOH terminus in non-small cell lung cancer patients. *Clin Cancer Res* 1999;5:1473–81.
- [43] Coleman RE. Clinical features of metastatic bone disease and risk of skeletal morbidity. *Clin Cancer Res* 2006;12: 6243s–9s.
- [44] Diamond TH, Bucci J, Kersley JH, Aslan P, Lynch WB, Bryant C. Osteoporosis and spinal fractures in men with prostate cancer: risk factors and effects of androgen deprivation therapy. *J Urol* 2004;172:529–32.
- [45] Dickman PW, Adolfsson J, Astrom K, Steineck G. Hip fractures in men with prostate cancer treated with orchiectomy. *J Urol* 2004;172:2208–12.
- [46] Chen Z, Maricic M, Bassford TL, Pettinger M, Ritenbaugh C, Lopez AM, et al. Fracture risk among breast cancer survivors: results from the Women's Health Initiative Observational Study. *Arch Intern Med* 2005;165:552–8.
- [47] Adami HO, Zack M, Kressner U, Persson I, Berglund A, Naessen T, et al. Hip fractures in women with breast cancer. *Am J Epidemiol* 1990;132:877–83.
- [48] Lamont EB, Lauderdale DS. Low risk of hip fracture among elderly breast cancer survivors. *Ann Epidemiol* 2003;13: 698–703.
- [49] Ettinger B, Black DM, Mitlak BH, Knickerbocker RK, Nickelsen T, Genant HK, et al. Reduction of vertebral fracture risk in postmenopausal women with osteoporosis treated with raloxifene: results from a 3-year randomized clinical trial. *JAMA* 1999;282:637–45.
- [50] Hogler W, Wehl G, van Staa T, Meister B, Klein-Franke A, Kropshofer G. Incidence of skeletal complications during treatment of childhood acute lymphoblastic leukemia: comparison of fracture risk with the General Practice Research Database. *Pediatr Blood Cancer* 2007;48:21–7.