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Incidence and risk of osteoporotic refractures in cancer survivors compared to controls - a nationwide claims study in Korea

암 생존자에서 대조군 비교 시 골다공증성 재골절의 발생과 위험 - 건강보험공단 청구자료를 이용하여

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ABSTRACT

Incidence and risk of osteoporotic refractures in cancer survivors compared to controls – a nationwide claims study in Korea

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Background: Osteoporosis is the most common bone disorder and especially occurred on hip and vertebrae and frequently worsened to osteoporotic fracture. Osteoporotic fracture causes high mortality by disabling the physical activities. Incidence of cancer is a substantial risk factor on osteoporotic fracture and especially breast and prostate cancer contribute to incidence of refractures. Furthermore, relative risk of mortality of refracture patient is 1.4 to fracture patients who had no relapse. Recently, Fracture Liaison Service (FLS) and high adherence

rate of Bisphosphonate have reduced refracture rate on cancer patients. Although there are prior studies researching the association of refracture and cancer diagnosis, few studies with larger subjects and long-term time series study observed the refracture rate on cancer patients. The study purpose is to comprehend the overall incidence rate and survival rate of osteoporotic fracture and relapse on cancer patients and primary risk factors of osteoporotic fracture following the appropriate policy making which includes persistent monitoring on high-risk group.

Methods: Using patients' tailored claim data of National Health Insurance Services (NHIS) from 2006 to 2018, osteoporotic fracture patients who have history of breast or prostate cancer was set to exposure group and no history of cancer as controls to make the retrospective nested cohort study. To ascertain the fracture code as osteoporotic fracture, patients older than 50 years old were only included and subjects who had history of osteoporotic fracture in 2006 were excluded in the analysis. Hip, vertebra, radius and humerus fractures were defined by main or sub disorder with ICD-10 codes and operational codes. Refracture was defined as secondary fracture more or equal than 180 days after primary fracture index date. 1:1 Propensity score matching with age, sex, level of insurance payment, residence, Charlson's comorbidity index excluding breast and prostate cancer were conducted. Baseline demographic characteristics of exposure and control group will be analyzed by Pearson's chi-square test to categorical variable and student t-test to continuous variable. Primary endpoint is the incidence rate of osteoporotic refracture. Secondary endpoint will be two types of cancer and cumulative

incidence ratio of osteoporotic fractures in each fracture type and total fracture Survival rate will be calculated by cox-proportional hazards model with covariates including age, sex, location, CCI score.

Results: 1,179,400 patients were diagnosed as having primary osteoporotic fracture and 23,202 patients are cancer patients comorbid with osteoporotic fracture. Compared to both control group before and after propensity score matching, patients with cancer history were statistically lower survival rate. Odds ratio of refracture comorbid with cancer was higher in overall fractures while stratification of OR showed that cancer comorbidity had lower odds ratio than patients who had no cancer history. Vertebral fracture' s cumulative refracture rate was the highest in each group and refracture of radius, hip, humerus followed in sequence. Except for hip fracture, there is statistically different in trend of refracture incidence
and older age was the most powerful covariate of mortality (HR = 1.941, CI = 1.892, 1.991)

Conclusion: Cancer patients have higher incidence and mortality of most types of osteoporotic refracture than patients who have no history on cancer except for vertebral cancer. Longitudinal follow-up cares and adding medication and chemotherapy records are required to monitor cancer patients to prevent relapse of fracture.

Keywords: Breast cancer, Prostate cancer, Osteoporotic fracture, refracture, secondary fracture

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Chapter 1. Introduction

Osteoporosis is a systemic musculoskeletal disorder, which is characterized by low bone density and microstructural changes in bone tissues and increases the risk of fracture and weakness of bone structures (Kanis, 1997). Osteoporosis is the most common bone disorder in worldwide and frequently worsened to osteoporotic fracture especially occurred on hip and vertebrae where are strongly correlated to BMD (World Health Organization, 1994). The incidence of osteoporosis is the highest in Japan and Korea and 37% of women and 7.5% in men older than 50 years suffer from osteoporosis and incidence rate are consecutively growing (Kim, Lee, Kim, & Lee, 2016; Yang et al., 2020). In worldwide, around two hundred million patients suffer from osteoporosis, and 4.5% of patients turned out to have osteoporotic fracture (Pisani et al., 2016). Osteoporotic fracture significantly worsens the quality of life of patients by disabling the normal exercise, resulting the high mortality. In Korea, the 5-year mortality rate of osteoporosis was around 45% (Ha, 2016), and according to the claim data study in National Health Insurance Services (NHIS), total health insurance payment increased 9.2% in 2011, compared to 2017 and proportionated 17% in total medical service cost. Consequently, the socioeconomic burden will be consistently accrued (Kim et al., 2016).

Incidence of osteoporotic fracture is associated with the type of fracture and frequently occurred area. Perimenopausal women's osteoporotic fracture is related to serum estrogen deficiency and continuous reabsorption in trabecular bones, frequently occurred on vertebrae and wrist. Deficiency of cortical bone and trabecular bone

are followed to senile osteoporosis and it causes frequent hip, humerus, tibia and pelvic fracture.

Following the social phenomenon, persistent care and monitoring for high-risk group of osteoporotic fracture are required. Risk factors of osteoporotic fractures are elderly adults, persistent smoking, alcohol abuse, prior history of non-traumatic fractures, hypogonadism, increasing the threat of fallen, long-term exposure of glucocorticoid, disability to exercise, low weight, family history of osteoporotic fracture and menopause (Shapiro et al., 2019). Incidence of cancer is also one of the risk factor on osteoporotic fracture, cancer therapeutics including androgen deprivation therapies for prostate cancer and aromatase inhibitors for breast cancer can cause loss of bone mineral density. Additionally, as inflammations released by cancer evoke the reabsorption of bone and impede the regeneration of bone matrix, almost all types of cancer can cause adverse effect on bone health (Drake, 2013; Shapiro et al., 2019). Development of cancer therapies and researches prolonged the survival rate and importance of long-term care of anticancer therapies including bone health care have been introduced (Handforth, D'Oronzo, Coleman, & Brown, 2018). In the concept of bone health, breast and prostate cancer have importance as both cancer types are common in worldwide and survival rate are relatively higher than other major cancer types. Sex steroids including androgen, oestrogens, activins and inhibins maintain skeletal structures and enlarge prostate cancer. Androgen deprivation therapy (ADT) is the mainstream treatment of inhibiting the growth of prostate cancer by administrating luteinising hormone-releasing hormone (LHRH) agonists, antagonists and antiandrogens. After the start of ADT, sex steroid levels rapidly decrease, inducing bone turnover and net bone loss,

which symptoms are most frequent in the initial treatment year (Greenspan et al., 2005). Chemotherapies including Docetaxel commonly require gluco-corticosteroid treatment (Prednisolone) and the most common cause of secondary osteoporosis (Buehring, Viswanathan, Binkley, & Busse, 2013). With three month administration of prednisolone, risk of hip and vertebral fractures increases around 10 folds higher, while there is few studies scrutinizing the impact of the combination of chemotherapy and glucocorticoids with ADT on BMD and fracture risk in men with prostate cancer.

Breast cancer is the most continually researched with osteoporotic fracture. In Women's health initiative study, osteoporotic fracture risk was higher in BC survivors had a HR of 1.15 for any fracture compared with controls (Chen et al., 2005).

Breast cancer induces vertebral fracture while other types of fractures were not increased significantly (Vestergaard, Rejnmark, & Mosekilde, 2009). Breast cancer survivors have substantially higher fracture incidence rate than non-cancer patients independent of lower BMD, vitamin D or medications known as the for bone health such as systemic or topical steroids or anticonvulsants according to the Israel hospital's 8-years' retrospective EMR data analysis, though the role of BMD on fracture is still controversial (Fraenkel et al., 2015) because most of studies revealed that BMD is correlated with breast cancer AI therapy and increasing vertebral fracture risk (Sestak et al., 2014). Fracture risk assessment in Mayo Clinic, adjustment for age, they found that advanced disease (stage III/IV), any chemotherapy, alcoholism, and use of bisphosphonates were risk factors for osteoporotic fractures in BC survivors (Melton et al., 2012).

In Korea, prior studies in National Cancer Center in Korea illustrated

that breast, prostate, thyroid, uterine and gastric cancer patients had significantly higher rate of prevalence and incidence on osteoporotic fracture than normal subjects (Bruyère et al., 2017; Joung et al., 2017; Yubin Lee et al., 2015; Youjin Lee, Yoon, Lee, Chung, & Lee, 2019; Shin et al., 2019) According to the primary cancer incidence in Korea, formerly mentioned cancers are most common types in Korea with rapid growth (Jung, Won, Kong, & Lee, 2019). Refracture of bone is most highly occurred in vertebrae and hip and nearly 85% of incidence started within one year. As relapse of osteoporotic fracture can cause disability of patients and threaten the survival rate of patients, prevention and applicable screening are needed. Refracture rate are 5~10% in worldwide and relative risk ratio of mortality of refracture patient is 1.4 to fracture patients who had no relapse.

In Korean hospitals, treatment and awareness rate of osteoporotic fracture of patients after primary fracture are 25% and 12%, relatively lower than other countries where adopted Fracture Liaison Service (FLS) (Korean Society for Bone and Mineral Research, 2018). In Taiwan and England, FLS are actively introduced to care osteoporosis, and according to the 3-year follow up cohort in Taipei, hip refracture rate decreased 37% to the refracture rate prediction and when adherenace rate of Bisphosphonate was over 80%, the refracture rate was significantly lower than non-adherence group (Sun et al., 2017). According to the prospective chart reviews of patients who undertaken kyphoplasty and FLS in Taiwan, incidence of cancer is reported as significant risk factor. Although there are prior studies researching the association of refracture and cancer diagnosis, few studies with larger subjects and long-term time series study observed the refracture rate on cancer patients. The study purpose is to comprehend the overall

incidence rate of osteoporotic fracture and relapse and primary risk factors of ostoeoporotic fracture following the appropriate policy making which includes persistent monitoring on high-risk group. There are two hypotheses in the study to observe the difference of osteoporotic fracture patients comorbid with cancer.

1) H0: There is no difference of osteoporotic refracture rate between cancer comorbid patients and non-cancer osteoporotic fracture patients.

   H1: There is statistically significant difference of refracture incidence between cancer comorbid patients and non-cancer osteoporotic fracture patients.

2) H0: There is no difference of survival rate between cancer patients and non-cancer osteoporotic fracture patients.

   H1: There is statistically significant difference of survival rate between cancer comorbid patients and non-cancer osteoporotic fracture patients.

Chapter 2. Method

Study data and participants

The study is conducted using patients' claim data of National Health Insurance Services as the claim data contains health insurance reimbursement information and more than 97% of people are covered by national health insurance policy. Adapting the prior studies and clinical experiences of experts in osteoporotic fracture, operational definition of cancer and osteoporotic fracture criteria were previously described (Hwangbo et al., 2018; Shin et al., 2019). The study design is a nested-case control study, a type of retrospective cohort which exposure is history of cancer before osteoprotic fracture.

Inclusion and exclusion criteria

Exposure group

Cancer patients were defined as having history of cancer from 2007 to 2018 and there was no history of cancer before 2007. According to the operational definition of cancer, the start date of cancer history is first index date of main diagnosis of breast cancer (C50.x) and prostate cancer (C61) . Cancer history from 2006 January 1st to December 31th will be excluded as wash-out period as the period includes patients' histories whose initial date of disorder could be before 2006. Originally, cancer diagnosis was defined to use both main diagnosis and sub diagnosis of ICD codes, however, compared to the cancer incidence statistics in Korea from 2007 to 2016 by Korea Central Cancer Registry, excluding sub diagnosis of cancers is similar to the statistics on cancer registry (보건복지부, 2018). To ascertain the comorbidity of cancer and osteoporotic fracture, only index dates of fracture are after cancer

diagnosis in each patient are included in the comorbidity criteria.

Control group

Controls are defined to subjects who had no history of cancer between 2007 to 2018. From 2002 to 2005, there is no record of treatment claim data of recipients in medical aid program and to classify the osteoporotic fracture by operational definition, patients older than 50 years old are included (Park et al., 2011). Patients had history of osteoporotic fracture in 2006 were excluded in the analysis.

Study variables

Main or sub-diagnosis with ICD-10 codes are defined by operational definition by previous study (Ha, 2016). Hip fracture is diagnosed by main diagnosis or sub diagnosis codes (S720, S721) with operation code (N0601, N0991, N0981, N0641, N0652, N0654, N0715, N0711). Main or sub ICD-code of hip fracture should start between same day and 30 days earlier than index date defined by the surgery. Vertebral fracture (S220, S221, S320, S327, T080, M484, M485) and surgery code (N0471, N0472, N0473, N0474, N0630) and wrist fracture (S422, S423) and (N1601, N1611, N1603, N1613, N0996, N0998, N0983) and conservative treatment code (T6020, T6030, T6151, T6152), humerus fracture (S525, S526). Diagnosis of radius and humerus fracture should be defined by main diagnosis code if the treatment code contains conservative therapies using casts.

Refracture of bone is defined as secondary fracture more or equal than 180 days after primary fracture index date (start date of operation code of fracture). Hip, humerus, and radius refracture can be designed as only secondary fractures relapsing in opposite side of primary fracture, while vertebral fractures counted the first refracture after 180 days regardless of the direction.

Although BMD tests were widely used to diagnose osteoporotic fractures including dual-energy x-ray absorptiometry(DXA), (peripheral) quantitative computed tomography (QCT), those tests are partly covered by national health insurance and female over 60, males over 75 can receive the service and excluded the criteria (건강보험심사평가원, 2020),

Thoracic vertebra tomography codes (G430, G440, G450, G460) are commonly utilized to diagnose the thoracic vertebral fractures, however, those codes are not calculated in the system of providing specialized claim data in NHIS.

This study is a retrospective observational study and to compare the incidence of osteoporotic refracture between two groups and 1:1 Propensity score greedy matching will be utilized to adjust the baseline demographic characteristics of each group by propensity score matching age, sex, level of insurance payment (from 1 to 20) re-categorzied as one to five, residence(urban or rural area; cities so-called "Si" in Korea and metropolitans are categorized as urban area and others are regarded as rural area called as "Do") (E. Y. Lee et al., 2014), Charlson's comorbidity index excluding breast and prostate cancer by caliper matching(caliper size = 0.1) (Austin, 2014) will be used. To observe uncertainty of psm score within group, bootstraping method will be additionally utilized. Follow-up days after diagnosis of osteoporotic fracture for calculating death rate were calculated as the censoring date is December 31, 2019 and subtracted diagnose date.

Statistical analysis

To test the hypothesis, baseline demographic characteristics of exposure and control group will be analyzed by $\chi 2$ test to categorical variable and student t-test to continuous variable. To observe the age-adjusted

incidence rate of fracture and refracture, age-adjusted standardized incidence rate of fracture was conducted. Standard population was household of Census generalization in 2018, categorized by 5-year interval accessed by Korean Statistical Information Service (KOSIS) with weight of 10-year age interval. Primary endpoint is the incidence rate ratio and odds ratio of osteoporotic refracture in each group. Survival rate will be calculated by cox-proportional hazards model with covariates including age, sex, location, insurance level and CCI score. To compare the proportionality between two groups, log-rank test for assumption of risk proportionality between groups and fractures.
SAS 9.4 (SAS Institute Inc.) and R 3.6.2 version (R Foundation Inc.) will be used to analyze data. Basic statistical analysis will be conducted by SAS and data visualization will be conducted by using R software. All p-values will be measured using two-sided test and the threshold for statistical significance is less than 0.05.

Chapter 3. Result

From 2,317,000 participants from original claim data, after excluding patients under 50 years old and had history of cancer or osteoporotic fracture in 2006 as washout, 1,179,400 study subjects were included in the analysis. From the 349,660 cancer patients, patients had history of osteoporotic fracture after cancer diagnosis were 23,202. Patients who had no record of eligibility or unknown sex were also excluded (n=13,829) (Figure 1). Because of baseline characteristic difference, both non-psm adjusted data and psm-adjusted data were analysed (Table 1). After propensity score matching, number of cancer exposure group and control group are equal. Additionally, propensity score matching using bootstrap (n=10) was also executed (n=14,743 in each group).

Primary vertebral fracture were the highest incidence in both exposure and non-exposure group in 12 years. Regardless of remission, age from 80 to 89 had the highest incidence except radius fracture, highest incidence in age 60 to 69 group. All fracture and refracture incidence rate were annually increased in both exposure and unexposure group, especially in vertebral fracture incidence. (Table 2, Table 3, Table 4, Table 5)

Secondary humerus fracture with cancer were omitted as max number of annual humerus refracture in each age and exposure group is just one, hard to illustrate the tendency of refracture incidence in long-term. (Table 5.)

Although marginal odds ratio was higher in cancer group without stratification of refracture, conditional odds ratio on hip, vertebra and radius fracture were higher in non-cancer group, while humerus refracture was not statistically significant (Table 6).

Figure 1. Flowchart of the study

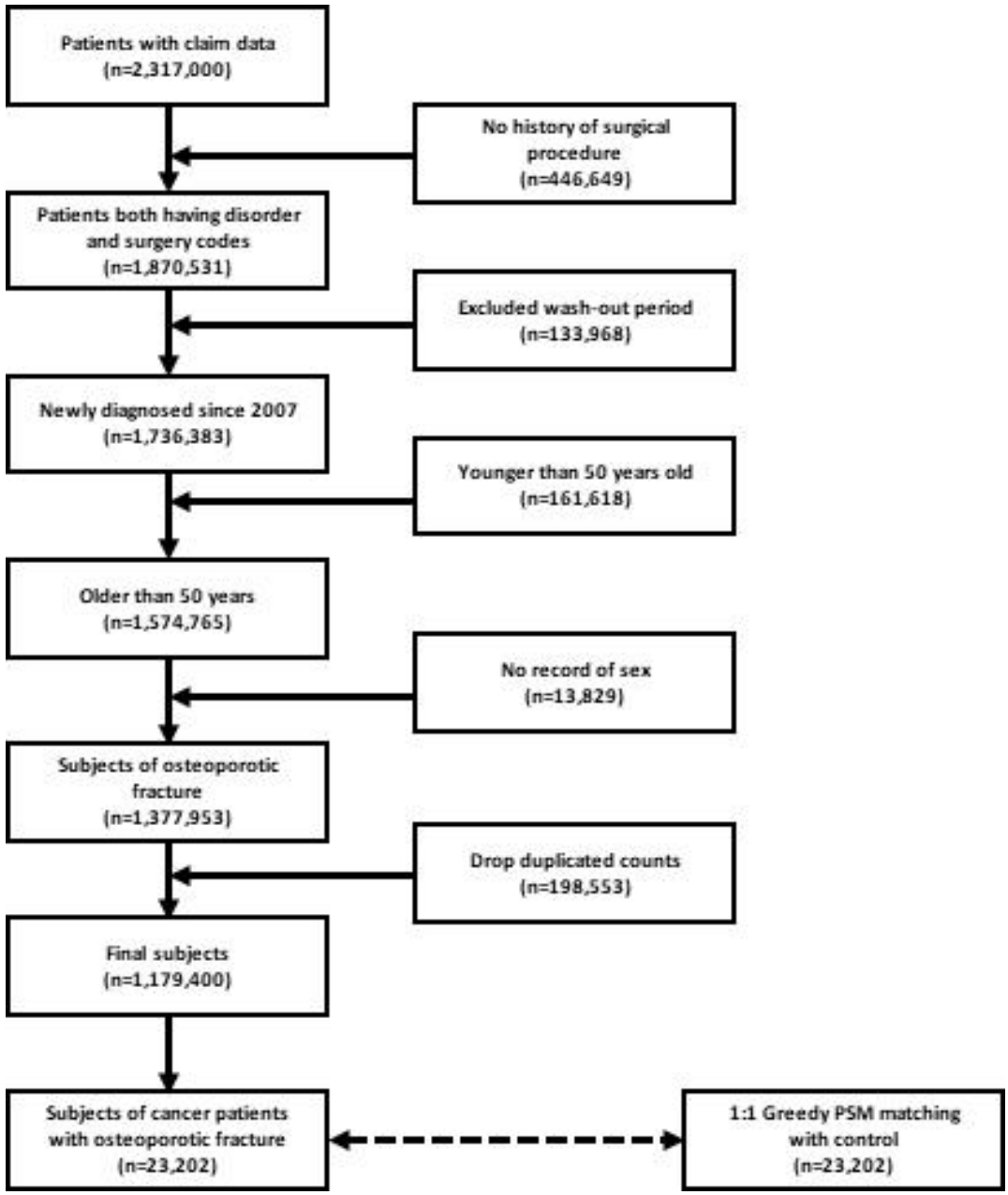


Table 1. Demographic characteristics of subjects before matching

Variable		Cancer patients	Control	p-value
Sex	M	12431	248460	<0.0001
	F	10771	907738	
region	Urban	19075	955215	<0.0001
	Rural	4127	224185	
Insurance level	1(1-4)	3417	192971	<0.0001
	2(5-8)	2993	166511	
	3(9-12)	3527	180609	
	4(13-16)	5051	244218	
	5(17-20)	7281	317913	
	Unrecorded	933	53976	
age	50_59	2349	141052	<0.0001
	60_69	4534	260823	
	70_79	7066	302942	
	80_89	7460	316558	
	over 90	1793	134823	
CCI group	0	7616	476769	<0.0001
	1	5711	300630	
	2	3994	180412	
	3	5881	198387	

Table 2. Age-adjusted standardized rate of osteoporotic primary fracture of non-cancer patients

Hip Fracture												
age	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018
50_59	0.65	0.7	0.75	0.96	0.98	1.05	1.2	1.28	1.37	1.57	1.79	1.72
60_69	1.03	1.19	1.34	1.66	1.54	1.89	2.19	2.26	2.33	2.49	2.98	3.17
70_79	2.23	2.64	2.9	3.32	3.66	4.71	5.28	5.7	6.3	7.02	8.69	9.29
80	15.9	16.95	17.74	18.98	18.91	22.5	22.87	23.25	23.05	23.91	24.86	24
Total	19.81	21.48	22.74	24.93	25.11	30.17	31.55	32.51	33.05	34.99	38.32	38.19
Vertebral Fracture												
50_59	0.74	1.00	1.22	1.53	1.74	2.2	2.72	3.08	3.47	4.28	5.47	6.09
60_69	3.69	5.15	6.53	8.68	10.24	12.95	15.91	16.79	19.1	22.44	26.64	29.31
70_79	15.2	21.14	25.82	33.17	36.05	46.32	53.2	55.06	60.05	67.29	75.58	80.67
80	52.97	67.84	77.96	91.76	92.12	108.64	114.92	113.73	115.05	117.68	118.35	113.8
Total	72.61	95.16	111.6	135.2	140.2	170.2	186.8	188.7	197.7	211.7	226.1	229.9
Radius Fracture												
50_59	10.99	12.21	12.46	16.24	16.91	20.7	23.54	23.45	23.52	26.01	31.26	32.68
60_69	21.55	25.8	27.15	39.75	38.14	44.65	47.78	41.49	36.41	37.54	42.38	41.87
70_79	24.75	27.52	27.56	38.43	34.47	39.48	40.09	33.51	28.46	28.67	33.16	31.41
80_89	26.52	28.06	27.5	33.9	29.62	31.85	30.9	25.8	22	21.36	21.81	20.33
Total	83.82	93.6	94.67	128.3	119.1	136.	142.3	124.3	110.4	113.6	128.6	126.3
Humerus Fracture												
50_59	0.68	0.73	0.84	1	0.97	1.23	1.33	1.54	1.5	1.73	1.96	2.08

60_69	0.86	0.89	1.06	1.35	1.42	1.69	1.9	1.87	1.94	2.11	2.41
70_79	0.97	1.18	1.29	1.42	1.4	1.82	2.07	2.17	2.25	2.35	2.69
80_89	1.95	2.16	2.33	2.53	2.56	3.01	2.75	2.68	2.63	2.69	2.58
Total	4.46	4.97	5.53	6.3	6.35	7.74	8.05	8.27	8.32	8.88	9.64

Table 3. Cause-specific and age-adjusted standardized incidence rate per 100,000 in cancer patients

Hip Fracture										
	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016
50_59	0	0	4.25	4.36	4.61	16.05	30.84	11.86	9.4	13.81
60_69	0	10.75	23.53	8.75	4.45	27.88	40.84	20.35	51.98	49.66
70_79	17.51	20.68	38.07	62.99	44.16	84.45	137.95	185.58	133.18	196.14
80_89	64.87	115.63	192.88	294.55	334.05	512.3	553.2	555.17	537.08	542.58
Total	48.9	95.88	170.86	247.98	270.9	443.92	528.04	536.96	515.22	571.28
Vertebral Fracture										
50_59	18.23	30.67	87.22	150.41	184.56	256.77	348.73	419.67	554.42	568.33
60_69	93.78	167.71	357.26	467.96	541.19	900.64	1088.48	1263.93	1451.05	1528.08
70_79	189.44	530.82	770.53	1105.98	1434.38	2020.96	2594.73	2861.47	3480.22	3836.55
80_89	444.07	1159.61	1918	2756.66	2971.5	3821.1	4452.89	4945.1	5035.34	5246.22
Total	458.44	1208.09	2056.9	3002.51	3563.44	4855.4	5891.87	6617.9	7424.87	7983.67
Radius Fracture										
50_59	18.23	20.45	121.25	239.79	216.86	387.44	967.91	509.77	486.29	566.03

60_69	24.46	152.66	331.59	566.36	510.01	714.08	675.96	879.26	840.31	862.22	1017.4
70_79	30.25	210.26	197.62	476.11	428.2	648.12	630.93	790.2	754.01	688.46	796.94
80_89	35.63	162.54	274.56	457.75	411.78	473.22	534.53	555.17	530.07	464.89	555.5
Total	67.24	351.56	611.16	1166.15	1090.57	1539.8	1952.38	1903.78	1842.1	1842.38	2279.3
Humerus Fracture											
50_59	0	0	4.25	21.8	20.76	38.97	30.84	47.42	28.19	41.42	40.66
60_69	0	10.75	10.7	37.17	33.41	38.6	44.93	28.49	51.98	36.11	48.45
70_79	0	10.34	19.94	50.02	44.16	43.21	30.43	53.88	54.84	70.61	78.88
80_89	11.88	20.85	24.11	54.56	48.71	50.32	112.05	117.21	78.31	53.45	82.53
Total	6.11	25.57	39.43	107.23	104.19	117.92	152.86	174.34	148.22	142.82	182.05

Table 4. Age-adjusted standardized rate of refracture on non-cancer patients

Hip fracture												
	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018
50_59	0	0.016	0	0.007	0.015	0.025	0.025	0.043	0.039	0.044	0.061	0.062
60_69	0	0.022	0.022	0.039	0.05	0.068	0.08	0.081	0.099	0.107	0.136	0.133
70_79	0.007	0.046	0.073	0.082	0.137	0.178	0.244	0.269	0.33	0.381	0.472	0.611
80_89	0.041	0.296	0.502	0.709	0.898	1.169	1.387	1.518	1.72	1.818	1.831	2.125
Total	0.037	0.368	0.625	0.834	1.103	1.441	1.735	1.912	2.187	2.349	2.5	2.933
Vertebral fracture												
50_59	0.039	0.187	0.302	0.453	0.46	0.723	0.964	1.268	1.567	1.968	2.542	2.946

60_69	0.226	1.204	2.15	3.128	3.849	5.562	7.358	8.708	10.219	12.625
70_79	0.991	5.946	9.96	14.163	16.603	23.784	29.773	33.082	37.568	43.486
80_89	3.368	18.907	30.717	41.619	45.13	59.319	67.68	71.082	75.292	79.241
Total	4.624	26.254	43.142	59.378	66.058	89.408	105.8	114.166	124.66	137.34
Radius	Fracture									
50_59	0.013	0.107	0.159	0.25	0.421	0.71	1.004	1.19	1.495	1.937
60_69	0.021	0.258	0.491	0.954	1.47	2.213	2.721	3.342	3.338	3.826
70_79	0.043	0.306	0.517	1.077	1.431	2.077	2.551	2.684	2.568	2.931
80_89	0.047	0.249	0.522	0.869	1.118	1.409	1.611	1.808	1.599	1.748
Total	0.125	0.919	1.691	3.15	4.441	6.411	7.885	9.025	9.003	10.444
Humerus	fracture									
50_59	0.002	0.015	0.038	0.038	0.041	0.039	0.046	0.077	0.059	0.077
60_69	0	0.01	0.026	0.039	0.041	0.07	0.066	0.062	0.072	0.105
70_79	0	0.012	0.033	0.033	0.025	0.052	0.078	0.068	0.066	0.066
80_89	0.004	0.023	0.039	0.047	0.041	0.06	0.082	0.049	0.074	0.082
Total	0.007	0.059	0.136	0.154	0.147	0.221	0.272	0.257	0.272	0.331

Table 5. Age-adjusted standardized rate of refracture on cancer comrobid with fracture

Hip Fracture											
	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017
50_59	0	0	0	0	0	0	0	3.56	0	0	0
60_69	0	0	0	0	0	0	0	0	0	0	11.4
70_79	0	0	0	0	0	0	7.48	0	10.19	6.8	5.7
80_89	0	0	0	0	4.07	7.76	26.17	35.6	40.78	20.39	19.95
Total	0	0	0	0	1.103	1.996	8.34	9.24	11.48	6.123	7
Vertebral fracture											
50_59	5.92	0	9.638	13.6	28.53	85.34	85.99	135.28	180.08	196.74	287.77
60_69	0	10.5	72.29	122.42	154.89	267.66	388.84	477.05	570.83	652.82	797.79
70_79	11.8	94.46	202.4	321.91	444.28	640.06	990.8	1174.8	1539.2	1699.11	2154.03
80_89	11.8	220.4	433.7	865.98	1067.9	1404.24	1757.3	2175.2	2296.9	2560.59	2986.01
Total	11.6	113.2	229.4	397.96	458.22	616.55	798.92	935.27	1033.3	1009.76	1176.05
Radius Fracture											
50_59	0	0	0	0	0	15.52	26.17	17.8	16.99	50.68	25.64
60_69	0	0	0	0	12.23	46.55	37.39	35.6	33.98	62.6	74.08
70_79	0	0	0	17.75	12.23	11.64	26.17	24.92	23.78	38.75	62.68
80_89	0	0	0	5.92	16.3	19.4	7.48	39.16	37.38	20.87	22.79
Total	0	0	0	9.29	11.01	23.94	24.1	27.73	25.26	34.17	34.99

Table 6. Age-adjusted incidence rate ratio and odds ratio of refracture by exposure for 12 years

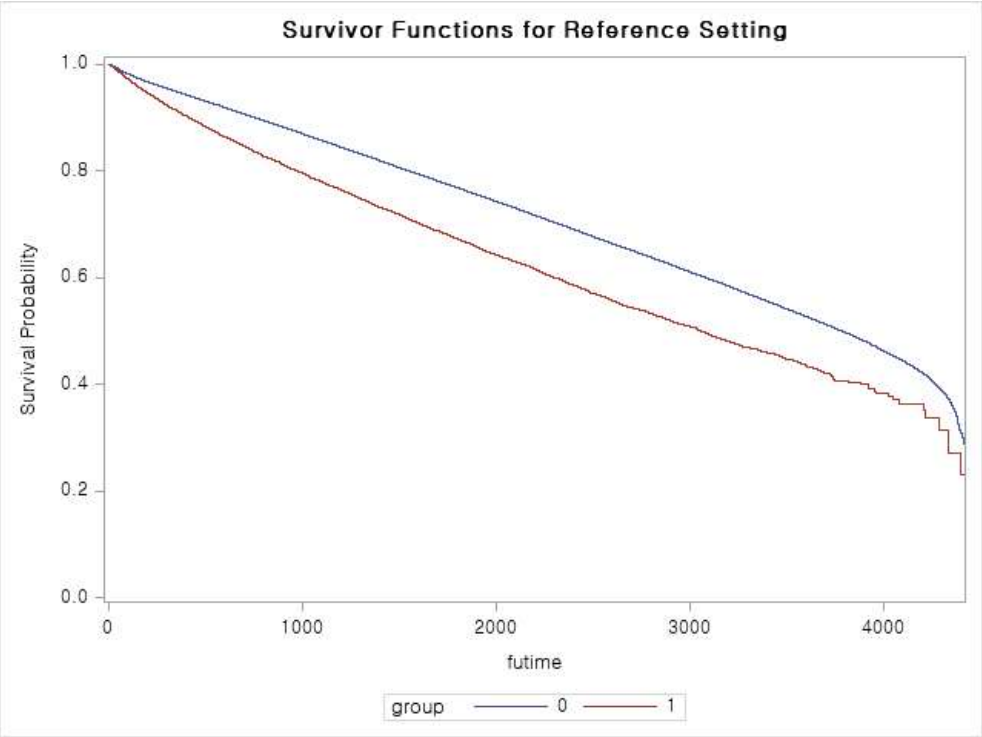
Mantel-Haenszel age-adjusted rate (100,000 person years)		
All fracture		p-value
IRR	1.03 (1.01, 1.05)	
OR	1.05 (1.02, 1.07)	<0.001
Hip Fracture		
IRR	0.66 (0.52, 0.83)	
OR	0.65 (0.51, 0.82)	<0.001
Vertebra Fracture		
IRR	0.76 (0.74, 0.77)	
OR	0.61 (0.59, 0.63)	<0.001
Radius Fracture		
IRR	0.88 (0.80, 0.98)	0.01
OR	0.87(0.78, 0.97)	
Humerus Fracture		
IRR	0.73 (0.42, 1.28)	0.27
OR	0.72 (0.41, 1.29	

Before adjusting psm, all covariates were found statistically significant to mortality and the rate of survivors are higher in control group. Survival rate is 0.05 point higher in control groups in 5 year follow up and 10 year follow up period (5-year : Cancer group : 0.70, Control group : 0.77, 10-year : Cancer group : 0.4, Control group : 0.5). After executing log-rank test to evaluate the assumption of proportionality between cancer and control group, survival rate between two groups were not proportional and executed stratified Cox proportional hazard ratio to compare survival rate. Except vertebral fracture, patients without cancer condition had longer survival rate than cancer patients.

Table 7. Censoring rate after the follow-up period (before PSM)

Groups	Total	Event	Censored	Percent of Censored
Control	1156198	244536	911662	78.85
Cancer	23202	6226	16976	72.39
	1179400	250762	928638	78.72

Figure 2 Survival plot before PSM



*Group 0 : Control group, Group 1 : Cancer group, futime : Follow-up days

Table 8. Hazard ratio before PSM (Reference : Male, 50-59 years old, highest insurance level, largest cci score, living in urban area)

Parameter		Parameter Estimate	Standard Error	Pr > ChiSq	Hazard Ratio	95% Hazard Ratio and CI	
ages		0.95388	0.00222	184183.33	2.596	2.584	2.607
sex	Female	-0.87951	0.00436	40753.225	0.415	0.411	0.419
insurance	0	0.40848	0.00731	3123.7746	1.505	1.483	1.526
insurance	1	0.12592	0.00602	438.1839	1.134	1.121	1.148
insurance	2	0.1088	0.00657	274.6481	1.115	1.101	1.129
insurance	3	0.09385	0.0064	214.7143	1.098	1.085	1.112
insurance	4	0.03667	0.00569	41.4973	1.037	1.026	1.049
CCI_group	0	-0.53656	0.00519	10673.703	0.585	0.579	0.591
CCI_group	1	-0.43618	0.00529	6786.8655	0.646	0.64	0.653
CCI_group	2	-0.30965	0.0057	2953.6942	0.734	0.726	0.742
region	0	-0.02225	0.00459	23.5419	0.978	0.969	0.987

Table 9. Censoring rate after PSM

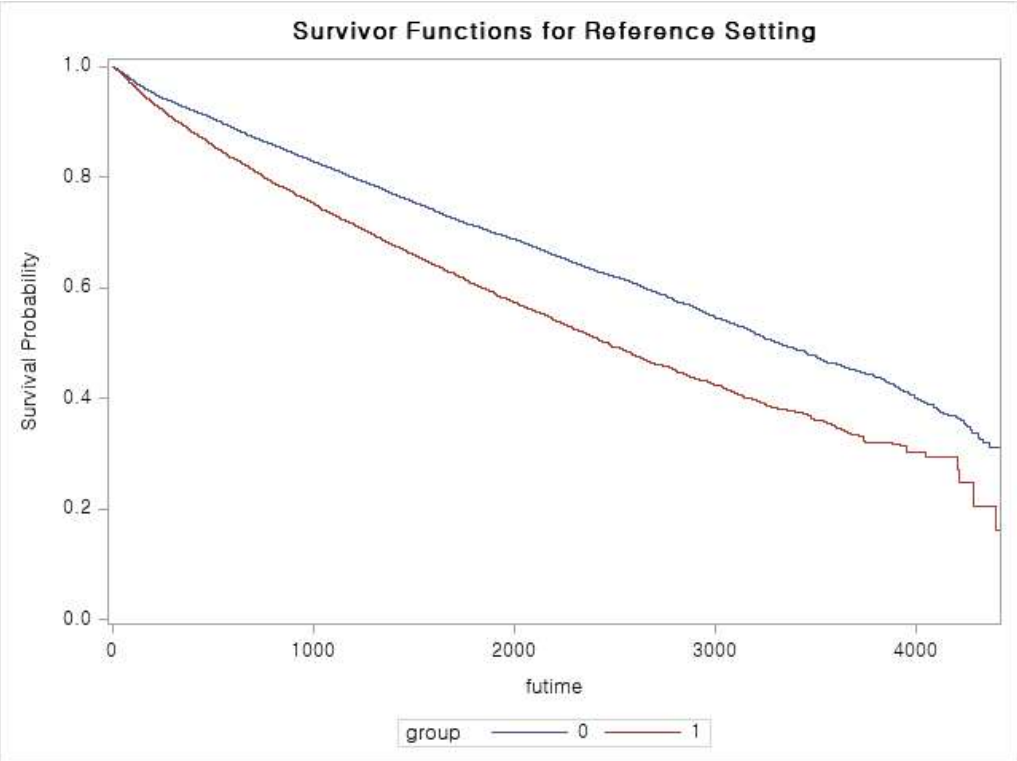
groups	Total	Event	Censored	Percent of Censored
Control	23,202	16615	6587	71.61
Cancer	23,202	16679	6523	71.89
Total	46,404	33294	13110	71.75

After psm adjustment, region was not significant factor to risk of death. Regardless of cancer diagnosis, hip fracture was the most fatal factor to earlier death and vertebral fracture was secondly fatal factor to earlier death in all groups (will attach the stratified cox model in future). Survival rate is 0.1 point higher in control groups in 5 year follow up and 10 year follow up period (5-year : Cancer group : 0.60, Control group : 0.70, 10-year : Control group : 0.50, Cancer group: 0.35). After adjusting the baseline characteristic discrepancy, region is not statistically significant while other parameters are significant hazard ratio with reduced the parameters' effect sizes.

Table 10. Hazard ratio after PSM

Parameter		Parameter Estimate	Standard Error	Pr > ChiSq	Hazard Ratio	95% Hazard Ratio and CI	
ages		0.66315	0.01306	<.0001	1.941	1.892	1.991
sex	**Female**	-0.70696	0.0267	<.0001	0.493	0.468	0.52
insurance	**0**	0.37327	0.04607	<.0001	1.452	1.327	1.59
insurance	**1**	0.11337	0.03457	0.001	1.12	1.047	1.199
insurance	**2**	0.1865	0.03579	<.0001	1.205	1.123	1.293
insurance	**3**	0.15255	0.0334	<.0001	1.165	1.091	1.244
insurance	**4**	0.08561	0.02972	0.004	1.089	1.028	1.155
CCI_group	**0**	-0.55707	0.02936	<.0001	0.573	0.541	0.607
CCI_group	**1**	-0.41913	0.02812	<.0001	0.658	0.622	0.695
CCI_group	**2**	-0.29977	0.0296	<.0001	0.741	0.699	0.785
region	**0**	-0.00596	0.0255	0.8152	0.994	0.946	1.045

Figure 3. Survival plot after PSM

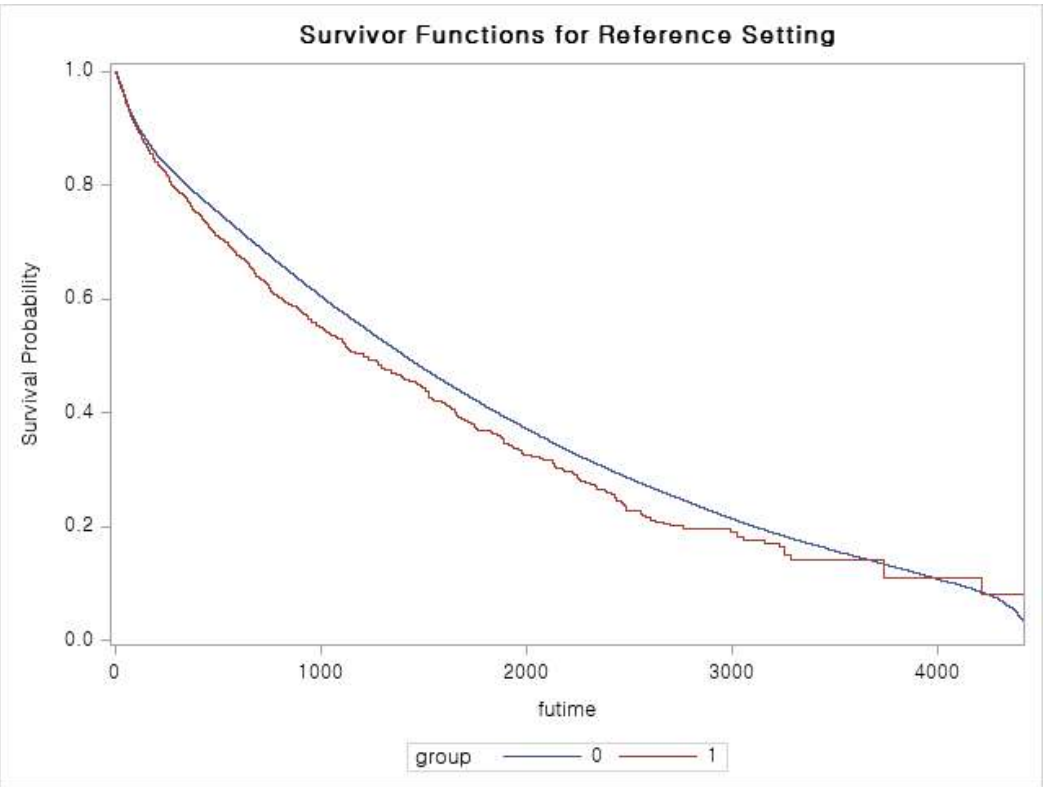


*Group 0 : Control group, Group 1 : Cancer group, futime : Follow-up days

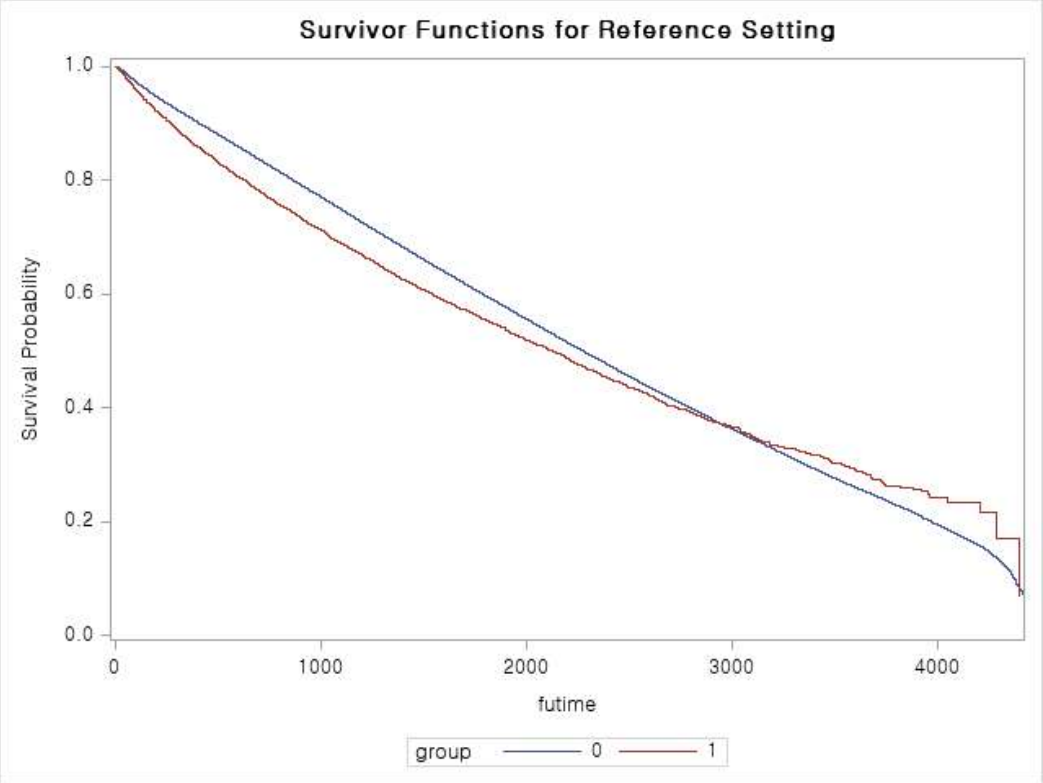
To observe individual survival rate by fracture type, stratified cox to group and fracture types were executed. Through all types, cancer comorbid with fracture patients had lower survival rate than non-cancer patients. Risk factors equally affected to the survival rate, while higher incidence level had not full effect on enhancing survival rate on after PSM.

Figure 4. Survival plot of stratified group and fracture type (before PSM)

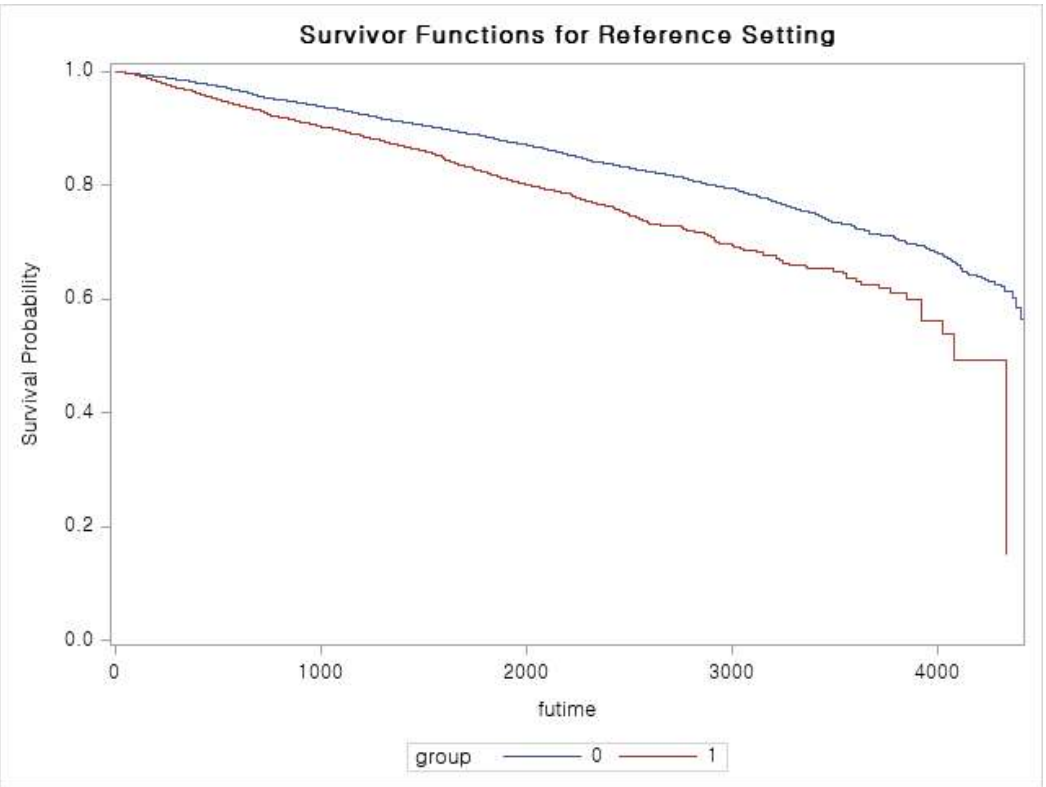
Hip Fracture



Vertebral fracture



Radius fracture



Humerus Fracture

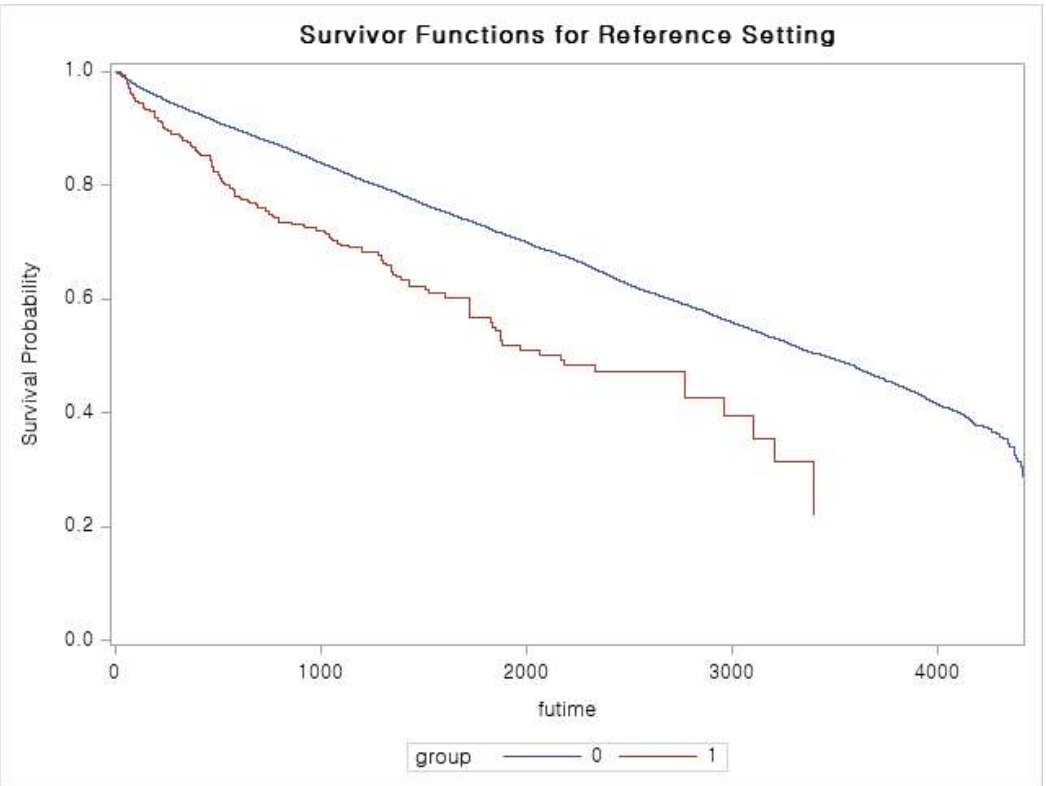
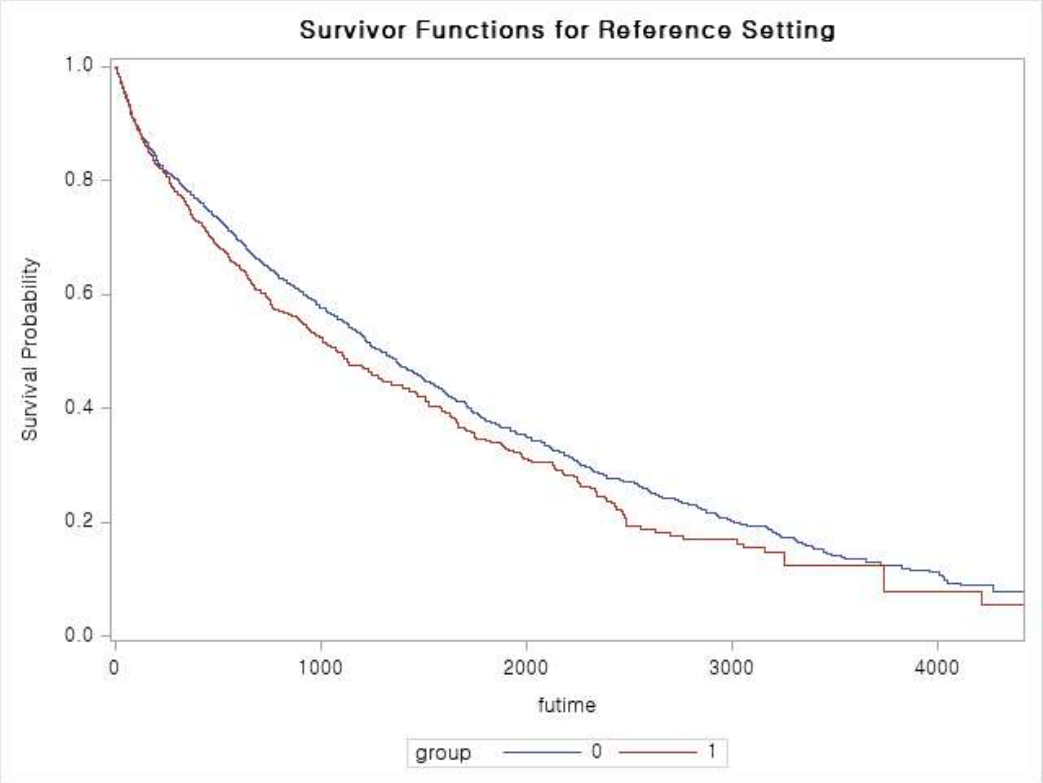
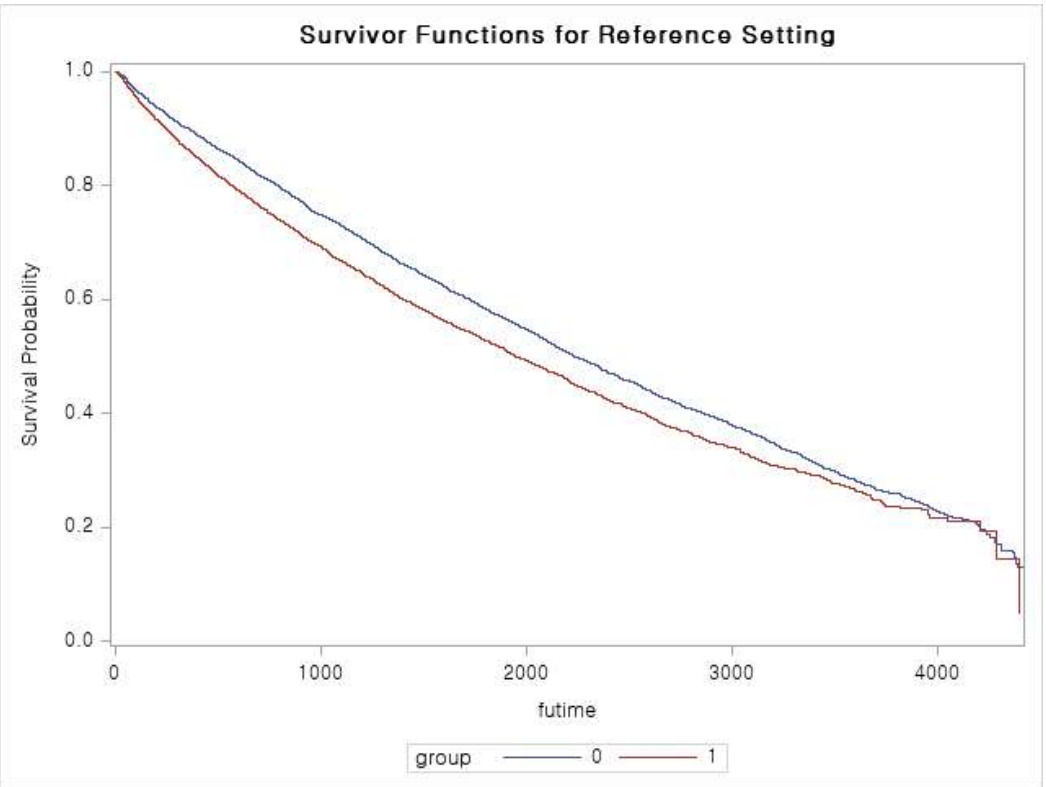


Figure 5. Survival plot of stratified group and fracture type (after PSM)

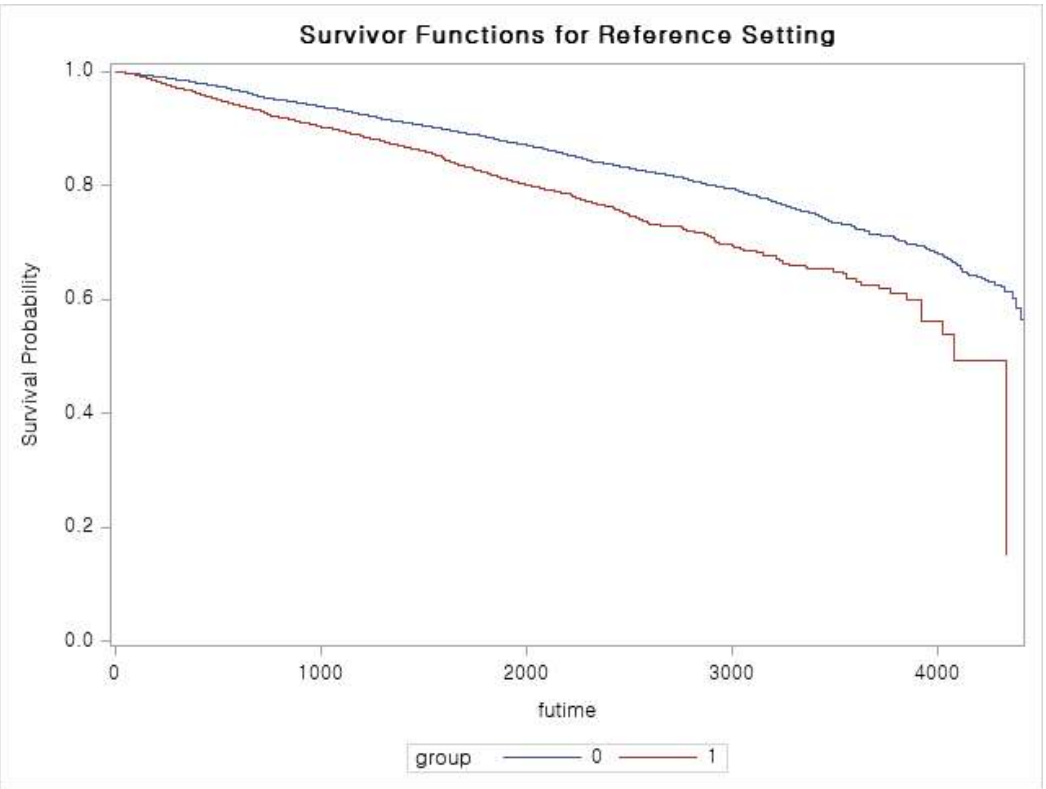
Hip fracture



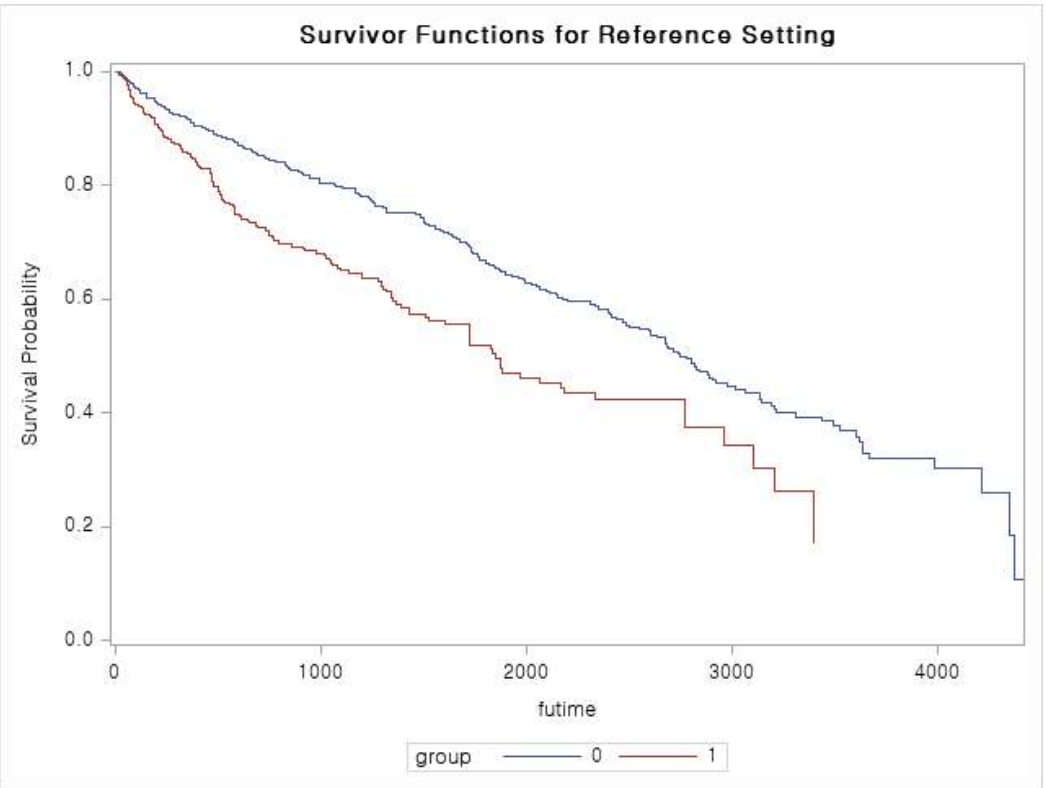
Vertebral fracture



Radius fracture



Humerus fracture



Chapter 4. Discussion

Osteoporotic fracture is a non-traumatic fragility fracture and more than a half of women and quarter of male patients suffer from osteoporotic fracture more than one time in life (Adachi et al., 2003). To reflect the fracture type as osteoporotic in insurance claim data, not classically considered osteoporotic fractures such as patella, clavicle, and lower legs were not included the research. The main osteoporotic fracture sites are hip, spine, wrist, and forearm (Johnell & Kanis, 2005) though the survival rates are different by types.

Osteoporotic fractures, especially hip fractures are associated with higher mortality rate despite the advances in the management of osteoporotic fracture cases (Nazrun, Tzar, Mokhtar, & Mohamed, 2014), Hip fracture has the highest mortality and death mostly occurs within a year, excess mortality rates are between 10% to 36% (Bass, French, Bradham, & Rubenstein, 2007). Comorbidity of cancer, infections, and cardiovascular diseases can increase the risk of death (Cameron et al., 2010). Vertebral fractures have an increased mortality risk that is lower than that for hip fractures and the mortality rate also peaks in one year after index date (Teng, Curtis, & Saag, 2008). The most common types of hip fractures are femoral neck fracture and intertrochanteric hip fractures where can cause avascular necrosis due to cessation of blood supply (Koval & Zuckerman, 1994)

Early diagnosis of vertebral fracture is difficult due to incidence without traumatic events (Lorentzon & Cummings, 2015) and history of vertebral fracture is stronger parameter to future incidence of fractures. Though BMD is a main diagnostic score to decide osteoporosis, secondary osteoporosis in FRAX does not affect fracture probability when BMD is included in the calculation (Leslie et al., 2019). Regardless of BMD, osteoporotic fracture patients are targeted to treat and prevent fracture as past histories of osteoporotic fracture significantly accrue the probability of refracture incidence. Females who have history of vertebral fractures have 3.8 higher odds ratio of hip fractures and mortality risk also increase. Preventing additional osteoporotic fracture is important to reduce the disease burden (Korean Society for Bone and Mineral Research, 2018). Checking out osteoporotic fracture patient' s prognosis is utmost useful method to make prognosis of sequent fracture.

However, cancer patients tend to focus on the treatment of cancer itself rather than

osteoporotic fractures. The diagnosis and treatment rates of osteoporosis have lagged behind those of breast cancer screening (72.7%)(National Committee for Quality Assurance, 2017). In China, lack of screening infrastructures for cancer patients in cancer-specialized hospitals also delayed the timely inverventions (Hsieh et al., 2018).

To compare the incidence rate of refracture and whether cancer history can increase the risk of mortality on fracture patients, we used the national claim data in Korea covering the greater part of healthcare cost consumption. In the study, osteoporotic fracture comorbid with cancer can significantly increase risk of death compared to patients who had no history of cancer. Higher age, male, lower level of insurance payment, higher score of comorbidity affects to the mortality of osteoporotic fracture on both cancer and non-cancer patients with osteoporotic fracture across all types of fracture. Hip fracture was the most malignant fracture type to all osteoporotic fracture patients. Male breast cancer survivors (n=125) are not included in the analysis as more than 80% incidence of male breast cancer were caused by BRCA1/2 variants, pathogenically far from female breast cancer.

The strength of the study is that the research data can cover greater part of tentative osteoporotic fracture patients and cancer patients comorbid with osteoporotic fracture. Second, this is the first study to observe the refracture rate of cancer patients and patients have history of primary fracture to grasp the excessive effect of cancers on osteoporotic fracture.

This study has several limitations. First, there is no current information of cancer registration based on ICD codes and histological cancer stages. Only operational definition of cancer and osteoporotic fracture can be accessed from claim database as the claim data only contain the main diagnosis and sub-diagnoses of cancer with operational codes and drug ingredient codes related to the disorder. Second, unobserved covariates such as alcohol consumption, record of using chemotherapy including AI, GnRH agonists and ADT, glucocorticoids, compliance rate of drugs which target on osteoporotic fractures such as Bisphosphonate are not utilized in this research. These unobserved covariates can have causal inference to incidence of refracture rate and survival rate of patients. Finally, the exact lesion of osteoporotic fracture cannot be known as claim data only contain ICD codes and treatment codes for deciding the disorder.

More sensitive selection of patient can be achieved via integrated data such as cancer

registration statistics. Ministry of Health and Welfare in Korea (MOHW) founded a healthcare big-data platform in 2018, aim to the integrated health information of individual with encrypted codes, connecting the cancer registration data, Korean genetic epidemiology data and health insurance claim data. Analyzing the integrated data will strengthen the evidence of study by exact health status. More detailed postoperative surveillance and pharmacological intervention should be considered to prevent fracture. Future studies with analyzing the change of insurance policy which enlarged coverage in osteoporotic fracture treatment including bisphosphonate pharmaceuticals in two times in 2011 and 2015, need to focusing on the osteoporotic fracture more than now or not can be researched. Health examination records containing the menstrual health questionnaire, alcohol and smoking consumption, physical activity can empower the causality of study.

4.2 Conclusion

Cancer patients have higher incidence and mortality of overall types of osteoporotic refracture than patients who have no history on cancer, while fracture type stratified conditional odds ratio was lower than non-cancer patients, converse to the marginal association. Longitudinal follow-up cares and finding unobserved confounders are required to cancer patients to prevent relapse of fracture.

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Appendix

Table S1. STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No.	Recommendation	Page No.	Relevant text from manuscript
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	0 (Abstract)	osteoporotic fracture patients who have history of breast or prostate cancer was set to exposure group and no history of cancer as controls to make the retrospective nested cohort study.
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	0 (abstract)	osteoporotic fracture patients who have history of breast or prostate cancer was set to exposure group and no history of cancer as controls to make the

				retrospective nested cohort study.
Introduction				
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	2	Incidence of cancer is also one of the..
Objectives	3	State specific objectives, including any prespecified hypotheses	4-5	There are two hypotheses
Methods				
Study design	4	Present key elements of study design early in the paper	6	Study data and participants The study is..
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6	We obtained the claim data between 2006 and 2018
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	6	Inclusion and exclusion criteria
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed	8	1;1 Propensity score matching will be utilized

		Case-control study—For matched studies, give matching criteria and the number of controls per case		
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7-8	Study variables Main or sub-diagnosis
measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*6*	Claim data of national health insurance
Bias	9	Describe any efforts to address potential sources of bias	8	PSM to adjust the baseline demographic
Study size	10	Explain how the study size was arrived at		Flowchart of study
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	8	Age, sex, level of insurance payment(1 to 5)
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	8	Chisq test and student t-test..
		(*b*) Describe any methods used to examine subgroups and interactions	N	
		(*c*) Explain how missing data were addressed	11	No record of eligibility..
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods	11	Flowchart of the study

		taking account of sampling strategy		
		(*e*) Describe any sensitivity analyses	NA	
Results				
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	11	From 2317000..
		(b) Give reasons for non-participation at each stage	11	Figure 1. used flowchart
		(c) Consider use of a flow diagram	11	Figure 1. used flowchart
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	12	Table 1. Demographic
		(b) Indicate number of participants with missing data for each variable of interest	11	No record of sex
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	10	primary fracture incidence
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	*13-17*	*Table 2-5*
		Case-control study—Report numbers in each exposure category, or summary measures of exposure		
		Cross-sectional study—Report numbers of outcome events or summary measures		
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	20-21	Hazard ratio and coefficient
		(*b*) Report category boundaries when continuous variables were	NA	

		categorized		
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	22	Fracture type survival rate
Discussion				
Key results	18	Summarise key results with reference to study objectives	27	In the study, osteoporotic fracture comorbid with cancer..
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	27	The study has several limitations
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	28	Analyzing the integrated data will strengthen..
Generalisability	21	Discuss the generalisability (external validity) of the study results	NA	
Other information				
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	NA	

국문 초록

암 생존자에서 대조군 비교 시 골다공증성 재골절의 발생과 위험 – 건강보험공단 청구자료를 이용하여

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연구배경 및 목적: 골다공증은 가장 흔한 골질환 중 하나로 고관절 및 척추에서 가장 많이 발생하며, 골다공증성 골절로 자주 악화된다. 골다공증성 골절은 신체 거동을 어렵게 하여 욕창, 요로감염 등 내과적 합병증 및 사망률을 높이며 암의 발생도 골다공증성 골절 발생의 유의한 요인이 된다. 거의 모든 종류의 암은 항암요법 및 면역 반응 등으로 골다공증성 골절을 유발시키는 위험요인이 되며, 상대적으로 암의 병력이 없는 사람들보다 골다공증성 골절을 호발시킬 수 있다. 골다공증성 골절은 재골절의 예방이 중요한데, 골다공증성 골절이 한 번만 일어난 환자에 비하여 재골절이 발생한 환자는 사망의 상대 위험도가 1.4배 높아지는 것으로 알려져 있다. 골절 예방 프로그램 및 높은 복약 순응도가 암 환자의 골절 예방에 도움이 된다고 외국에서 연구된 바가 있으나 암 환자 및 골절 환자의 재골절 발생에 대하여 비교적 대규모의 연구나 장기 추적 관찰 연구는 부족한 실정이다. 본 연구를 통하여 전체적인 주요 암 환자에서의 골다공증성 골절 및 재골절의 발생율을 파악하고 골다공증성 골절 발생의 위험 요인을 분석하여 골다공증성 골절의 고위군을 파악하고, 골절 예방을 적극적으로 도입할 필요성을 검토하고자 한다.

연구방법: 본 연구는 건강보험공단의 맞춤형 청구자료를 신청하여 2006년부터 2018년 안에 유방암 및 전립선암, 골다공증성 기록이 있는 환자군을 추출하였다. 골다공증성 골절의 병력이 있는 환자 중 골절보다 먼저 유방암, 전립선암 병력이 있는 경우를 노출군으로 설정하였고, 암 병력이 없는 골절 환자를 대조군으로 설정하였다. 골절의 진단 코드를 골다공증성 골절로 설정하기 위하여 50세 이상의 환자만 연구에 포함하였고 2006년에 골절 관련 기록이 있는 환자는 연구 대상에서 재외하였다. 골절의 범위는 고관절, 척추, 원위요골 및 근위상완골이며 재골절의 정의는 첫 번째

골절이 일어난 이후 최소 180일 이후로 설정하였으며, 척추 골절을 제외한 나머지 골절은 첫 번째 재골절만 재골절로 인정하였다. 1:1 성향 점수 매칭을 통하여 연령, 성별, 보험지불 등급, 거주지역, 노출에 해당하는 암을 제외한 찰슨동반질환지수를 공변량으로 설정하였다. 일차 평가 변수는 골다공증성 재골절의 군별 발생률이며 층화 콕스 비례위험모형을 이용하여 생존율을 이차 평가 변수로 설정하였다.

연구결과: 1,179,400 명의 환자들이 골다공증성 골절의 병력이 있는 것으로 나타났고 23,202명의 전립선 및 유방암 환자들이 골다공증성 골절을 경험하였다. 골다공증성 골절과 재골절은 연도별로 단조증가하였으며, 암 환자와 암의 병력이 없는 환자 모두 척추 골절의 발생률이 가장 높은 것으로 나타났고, 80세에서 89세의 발생률이 가장 높았으며, 원위요골 골절의 경우는 60 – 69세의 발생률이 모든 연도에서 가장 높은 것으로 나타났다. 성향점수 매칭 전후로 비교하였을 때에 척추 골절의 경우만 제외하고 모든 골절에서 암의 병력이 있는 골절 환자들의 생존율이 더 낮았으며, 전체적인 암 환자의 골다공증성 재골절의 승산비는 암이 없는 환자들보다 더 높게 나타났지만 골절 종류별로 층화하였을 때 근위상완골의 경우는 오즈비 차이가 유의하지 않았고 고관절, 척추, 원위요골의 경우는 승산비가 암이 있는 경우에 더 낮은 것으로 나타났으며 골절별 사망률은 고관절이 가장 높았고 척추 골절, 근위 상완골, 원위 요골 순이었다. 거주 지역을 제외하고 사망 위험비에 높은 연령, 남성, 낮은 보험 지불 등급 및 높은 CCI score가 통계적으로 유의한 영향을 미쳤으며, 높은 연령의 기여 위험도가 가장 높은 것으로 나타났다 (HR = 1.941, CI = 1.892, 1.991).

결론: 암 환자들은 암 병력이 없는 환자들보다 높은 재골절의 발생과 전체적으로 낮은 생존율을 보였으나 골절별로 층화하였을 때 승산비는 암의 병력이 없는 골절 종류별 환자들보다 일부 낮은 것으로 나타났다. 암 환자에게 사용된 화학 요법의 종류 및 골다공증성 골절 특이적 약물 소지율에 따른 추가적인 종단 연구가 암의 병력과 골다공증성 재골절 발생의 인과성 분석을 위하여 필요할 것으로 생각된다.

주요단어: 골다공증성 재골절, 유방암, 전립선암, 이차성 골절, 사망위험

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