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Risk of Cancer Following Lumbar Fusion Surgery with Recombinant Human Bone Morphogenic Protein-2 (rh-BMP-2)

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Abstract

Study Design—Retrospective cohort study among Medicare beneficiaries with lumbar spinal fusion surgery.

Objective—Determine the risk of subsequent cancer among patients who received recombinant human bone morphogenic protein (rhBMP) at surgery compared to those who did not.

Summary of Background Data—rhBMP is commonly used to promote bone union after spinal surgery. BMP receptors are present on multiple cancer types but the risk of cancer after receiving rhBMP has not been well studied.

Methods—We identified 146,278 subjects aged 67 and older who underwent surgery in 2003–2008 and were followed through 2010 for a new diagnosis of one of 26 cancers. Proportional hazards models were used to determine cancer risk associated with rhBMP use.

Results—rhBMP was received in 15.1% of the cohort. After an overall average follow up of 4.7 years, 15.4% of rhBMP treated and 17.0% of untreated patients had a new cancer diagnosis, with most commonly recorded types as prostate, breast, lung and colorectal. In a multivariate proportional hazards model, there was no association of rhBMP with cancer risk (Hazard Ratio 0.99, 95% CI 0.95–1.02). There was also no association of rhBMP with risk of any individual cancer types. The results were consistent in analyses using two secondary definitions of incident cancer.

Conclusions—In this large population-based analysis of Medicare beneficiaries, we found no evidence that administration of rhBMP at the time of lumbar fusion surgery was associated with cancer risk.

Keywords

Recombinant human bone morphogenic protein-2; spinal fusion; neoplasms; Medicare; aged; SEER Program

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Introduction

The Bone Morphogenic Proteins (BMP's) are a member of a large family of growth factors known as the Transforming Growth Factor-β (TGF- β) superfamily (1). Because of their ability to induce new bone formation, BMP's are used clinically as a substitute for iliac crest bone grafting in patients undergoing lumbar fusion surgery. One of these proteins, recombinant human Bone Morphogenetic Protein-2 (rhBMP-2) is licensed in Europe and the US for anterior lumbar spinal fusion, and is delivered via an absorbable collagen sponge carrier (ACS). The combination of rhBMP-2 with ACS is marketed as INFUSE® Bone Graft (Medtronic Inc., Memphis TN). A second product, rhBMP-7, is mixed with bovine collagen and reconstituted with saline and administered as a paste.

In addition to their effect on bone formation, BMP's also have roles in cell lineage commitment, differentiation, proliferation and apoptosis and receptors are present in multiple cell types, including cancer cells. A large number of laboratory-based in vitro and in vivo studies have examined the role of BMP in promoting tumorigenesis and metastasis and have yielded conflicting results (2).

In the initial published clinical trials of the long-term safety of rhBMP, there appeared to be no association of rhBMP with subsequent cancer risk (3,4). However, because a postmarketing analysis indicated a nonsignificantly increased risk of pancreatic cancer in patients who received rhBMP, we previously performed a retrospective cohort study in the Medicare population (5). Although this analysis found no association of rhBMP with subsequent pancreatic cancer incidence, the study was restricted to one tumor type and had a relatively short duration of postsurgical follow up. In addition, two recently published analyses of clinical trial data reported a higher rate of cancers in the rhBMP treated patients compared to bone grafts (6,7), but only one found the differences to be statistically significant (7). Given the discordant findings, our goal was to compare the incidence of all cancers after lumbar spinal fusion among a population-based sample of patients treated with rhBMP with those who did not receive rhBMP.

Materials and Methods

Patients

The cohort was obtained from all Medicare beneficiaries who underwent lumbar fusion surgery between October 2003 (first month where Medicare provided reimbursement for rhBMP) and December 2008. The relevant files included the Medicare Provider Analysis and Review (MEDPAR) files, which included claims from inpatient hospitals, the Carrier file, which included claims from physicians and free standing ambulatory surgical centers, and the Outpatient file, which included claims from institutional outpatient providers. Patients were identified if they had a procedure code for a lumbar fusion operation by one of the following International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) or Current Procedural Terminology 4th Edition (CPT-4) codes: ICD-9-CM 81.06, 81.07, 81.08, 81.36, 81.37, 81.38, CPT-4 22558, 22630, 22612.

In order to obtain complete claims history, patients were excluded if they were not continuously enrolled in fee-for-service Medicare for at least 2 years prior to the index surgery date. Patients who did not continuously participate in Medicare Part B, which provides coverage for physician charges and outpatient services, were also excluded because their claims histories may have been incomplete. In addition, patients younger than 67 years were excluded – those younger than 65 who were enrolled in Medicare due to end stage renal disease or chronic disability not being representative of the general Medicare population, and those aged 65 or 66 with less than two years of enrollment data prior to the spinal surgery.

In addition, to exclude prevalent cases of cancer, as well as the inability to differentiate a newly treated cancer from treatment of cancer recurrence, any patient with a claim indicating a previous malignant tumor diagnosis during the two year period prior to surgery was excluded. A two year cut off was used to maximize the sensitivity of capturing and excluding patients who are long term cancer survivors. Previous malignant neoplasm diagnoses were identified from one or more ICD-9-CM diagnosis codes in any file. Patients were also excluded if they had one or more ICD-9 diagnosis codes indicating a “personal history of a malignant neoplasm” (V10.00–10.9), or had one or more codes for radiation or chemotherapy.

Measures

Consistent with our previous analysis (5), a claim for rhBMP (ICD-9-CM 84.52) on the same day as fusion surgery was used as a surrogate for exposure, which cannot be ascertained directly using Medicare data. This code also includes the administration of rhBMP-7, but the overwhelming majority of procedures use rhBMP-2. Because Medicare did not provide additional reimbursement for these products until October 2003, to reduce exposure misclassification, we limited our study to patients who underwent fusion surgery from this date onward.

A diagnosis of a malignant neoplasm after surgery was the major outcome of interest and was identified by one or more of the ICD-9-CM codes listed in any of the Medicare files in follow up (Appendix 1). We included codes consistent with any of the 26 cancer types that are included in the National Cancer Institute’s Surveillance, Epidemiology and End Results (SEER) classification (8), and followed patients through the end of calendar year 2010. This time interval was consistent with that of two recently published systematic reviews and meta-analyses (6,7) and would be more than adequate to detect a potential effect of rhBMP in promoting the growth of subclinical tumors.

Because a single code may not be valid and may reflect “rule out” or other diagnoses that were ultimately found to represent benign diseases, as in our pancreatic cancer analysis, we used two secondary definitions of cancer. These included: (1) an ICD-9-CM diagnosis code for the same type of cancer on more than one date of service and (2) two or more ICD-9 diagnosis codes for the same type of cancer on different dates of service and at least one procedure code consistent with cancer therapy. The latter codes included site specific procedure codes (Appendix 1) as well as procedure codes for radiation therapy and

chemotherapy. Per Centers for Medicare and Medicaid Services policy, because of patient confidentiality issues, any cell sizes with a frequency less than 11 were suppressed.

In addition to data about exposure and outcomes, we included potential confounders such as age (at time of index surgery), gender, race (white, black, other), and length of follow up. The presence of comorbid conditions was measured using a previously validated index, which includes diagnoses present in MEDPAR, Outpatient and Carrier files (9). In order to differentiate complications from comorbidities, only diagnoses that were present from two years through 30 days prior to date of surgery were included. Using this algorithm, a weighted score was assigned for each individual.

Analysis

Patients were followed from the date of index lumbar fusion surgery until the diagnosis of cancer, death, disenrollment, or end of the study period (December 31, 2010). Individuals who underwent an initial operation without rhBMP and a subsequent procedure with rhBMP were followed in the nonexposed group to the date of the second surgery and thereafter in the exposed group.

The association of demographic variables, comorbid conditions and rhBMP administration with each cancer site and with overall cancer risk was examined using the primary cancer definition (one or more diagnoses). Chi-square analysis was used to determine statistical significance. In addition, to account for variable length of follow up, a series of univariate Cox proportional hazards models were constructed to examine the association of rhBMP administration and risk of individual cancer types.

The independent association of rhBMP administration and cancer risk was then determined in multivariable analyses using Cox proportional hazards regression. In all models, covariates included demographic factors (age, race, gender if appropriate for that cancer), comorbidity score and rhBMP administration.

Finally, in order to determine if the observed incidence of cancer was different than expected from the general population, we used the standardized incidence ratio (SIR). The SIR determines the number of observed cases divided by the number of expected cases in both rhBMP-exposed and unexposed patient groups. The expected numbers were obtained by applying age- and gender-specific incidence rates for all cancers from the SEER Program (8) to the corresponding person–time.

Results

We initially identified 295,493 patients who underwent lumbar spinal fusion during the time period of interest. From that sample, patients were excluded for the following non-mutually exclusive reasons: not continuously enrolled in Medicare Parts A and B (n=69,398), enrolled in Medicare HMO's (n=53,107), age less than 67 (n=56,699), and previous cancer diagnosis (n=29,765). The remaining 146,278 patients were the subject of this analysis.

Characteristics of the cohort are shown in Table 1. The mean age was 74.5 ± 5.1 years, 66.5% were female and 93.7% were white. Most patients had comorbidity scores of 0 or 1.

A code for rhBMP administration was documented in 15.1% of surgeries. Compared to others, patients who received rhBMP were younger, somewhat more likely to be female or white, and had higher comorbidity scores. The proportion of patients who received rhBMP generally increased over the study period. The average length of follow up was 4.8 ± 1.5 years (range 1.23–7.25 years) in the rhBMP treated patients and 4.4 ± 1.3 years (range 1.16–7.25 years) in others. Death rates during the follow up period were 3.27% in the rhBMP group and 3.45% in others.

One or more diagnosis codes for cancer were documented in follow up in 24,481 patients including 21,079 in the non-rhBMP group (17.0%) and 3,402 in the rhBMP treated patients (15.4%). Consistent with the known incidence of cancers in the older US population (8), the most commonly recorded cancer diagnoses were prostate, breast, lung and colon and rectum.

Using a proportional hazards model, we determined the risk of cancer as a whole and within individual tumor types (Table 2). Overall, there was no association of rhBMP administration with cancer incidence (Hazard Ratio 0.98, 95% CI 0.95–1.02). Similarly, when individual cancer sites were considered, there were no significant differences between the two groups. In an adjusted analysis, the risk of cancer was similar between rhBMP treated patients and others (Hazard Ratio 0.99, 95% CI 0.96–1.03). As with the unadjusted analysis, there were no significant differences among specific cancer sites.

In a secondary analysis, we considered two other definitions of incident cancer. Using a criterion of a diagnosis on two or more different dates, we identified 18,942 cancer cases, with similar frequencies in rhBMP treated (12.0%) and other patients (13.1%) (Appendix 2). The overall cancer risk was similar in unadjusted (Hazard Ratio 0.97, 95% CI 0.93–1.01) and adjusted (Hazard Ratio 0.98, 95% CI 0.94–1.02) proportional hazards models. The risk was also similar among individual tumor types. Using the most stringent definition of two or more diagnoses and cancer treatment codes, we identified 14,362 cases with an incidence of 8.7% and 10.0% in rhBMP treated and untreated patients, respectively (Appendix 3). With this definition, there was a somewhat lower overall cancer risk with rhBMP use in both unadjusted (Hazard Ratio 0.94, 0.89–0.98) and adjusted (Hazard Ratio 0.95, 0.90–0.99) proportional hazards analysis. When individual sites were examined, there was a lower risk of brain tumors in rhBMP treated patients in unadjusted (Hazard Ratio 0.65, 95% CI 0.46–0.90) and adjusted (Hazard Ratio 0.64, 95% CI 0.46–0.90) models. No other significant differences were observed.

In the SIR calculations, using the primary case definition of 1 diagnosis code, the incidence of all cancers combined was higher than expected in both the rhBMP treated and untreated groups. For rhBMP treated patients, the SIR was 177.79 (95% CI, 172.00–185.00) and for untreated patients, the SIR was 177.00 (95% CI 175.00–179.00). Consistent with more stringent diagnostic criteria, the SIR's were lower for both rhBMP treated and untreated patients using the other two case definitions. For a diagnosis code on two or more service dates, the SIR in the treated patients was 135.26 (95% CI 130.00–141.00) and for untreated patients was 136.30 (95% CI 134.00–138.00). For the criteria of two or more diagnosis codes as well as treatment, the SIR's closely approximated that of SEER. The SIR in rhBMP

treated patients was 96.99 (95% CI 92.00–101.00) and in untreated patients was 101.66 (95% CI 100.00–103.00).

Discussion

rhBMP is commonly used as an adjunct to orthopedic surgical procedures to promote bone growth and is used as an alternative option to bone grafting. Although most safety reports have focused on local events such as bony overgrowth, wound healing and neurological events (3, 10–12), there is at least a theoretical concern about the increased risk of malignant tumors among patients treated with rhBMP. Cancer case ascertainment through analysis of clinical trial data is limited by issues of power and sample size as well as relatively short duration of follow up. In the current study, which included a population-based sample of a large number of surgical patients with a median follow up of over four years, we did not demonstrate an increased risk of malignancy across multiple tumor sites.

In theory, given the presence of BMP receptors of a variety of tumors, including lung, pancreatic, renal, brain, osteosarcoma, ovarian, breast and prostate cancers (2), there is a potential risk of BMP in promoting tumorigenesis as well as metastases. In different models, BMP promotes angiogenesis (13,14), cancer cell growth (15), bone metastases (16), and cancer cell motility and invasiveness (16). However, BMP can also act as a growth and proliferation inhibitor and thus have antineoplastic effects (16,17). The only individual tumor type for which we found a significant difference in incidence was brain tumors, where there was a somewhat higher incidence in patients who were not treated with rhBMP-2. This finding is consistent with previous studies which showed an anti-tumor effect of rhBMP-2 (18,19). Although clinical trials to date have failed to show a conclusively increased risk of malignancy, given the theoretical risk of cancer progression, rhBMP is not indicated in the vicinity of a resected or extant tumor in patients with active malignancy or undergoing treatment for malignancy (20). Our study results included the entire spectrum of SEER cancers and a relatively long follow up period. However, if a potential risk of BMP is in mutagenesis, a longer observation period may be required to provide additional clinical evidence against the malignant potential of rhBMP.

As with other analyses, our methodology has a number of strengths and limitations. The strengths of the study include the large sample size, the representation of diverse practice sites and the ability to follow patients for an average of 4.7 years after spinal surgery. Limitations include that the sample was restricted to patients aged 67 and older, and generalizability of the findings to younger patients is uncertain. However, most cancers increase in incidence with age, and the older population accounts for a significant proportion of patients undergoing spinal fusion surgery. The study was also limited to fee-for-service beneficiaries who were enrolled in Medicare Part B. The diagnoses of previous and subsequent cancer were ascertained through ICD-9-CM codes, which are used for billing purposes and not research. However, the results were consistent across three different definitions of incident cancer, increasing the face validity of the findings. The study lacked data on other risk factors such smoking, alcoholism, obesity and family history of cancer, which are either significantly underreported or absent in Medicare data. As the study was observational and not randomized, there may have been systematic differences between

groups that could have biased the results. However, in our previous analysis of pancreatic cancer risk (5), we found on medical record review that there was no association of rhBMP use with established cancer risk factors such as smoking and obesity. Despite the large sample size, the study lacked precision to measure the incidence of rare cancers in the elderly such as testicular cancer and Kaposi's sarcoma. Finally, since we used a procedure code as a proxy for exposure to rhBMP-2, misclassification could be a concern. However, a previously conducted chart review study demonstrated a specificity of the code for rhBMP-2 (as opposed to other forms of rhBMP) of 95%, and a positive predictive value of 100% (5).

In summary, in this large cohort of older patients, the study provides evidence that treatment with rhBMP at the time of lumbar spinal fusion surgery does not increase the risk of subsequent malignancy. The results should be reassuring to providers and patients.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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The study protocol was approved by the Institutional Review Board at University Hospitals Case Medical Center.

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Key Points

1. Bone morphogenic protein (rhBMP) use has been postulated to increase the risk of subsequent cancer.
2. In an population-based sample of Medicare beneficiaries undergoing lumbar spinal fusion, we found no association of rhBMP administration with subsequent cancer risk.
3. The lack of cancer risk was consistent across all tumor types and different definitions of cancer incidence.

Table 1

Characteristics of Patients According to Use of BMP

			BMP Use				
	Full Cohort		NO		YES		
	n	%	n	%	n	%	p value
Gender							
Male	49003	33.5	41840	33.7	7163	32.5	0.0006
Female	97275	66.5	82398	66.3	14877	67.5	
Age at procedure							
67–69	28187	19.3	23604	19.0	4583	20.8	<.0001
70–74	52274	35.7	44219	35.6	8055	36.6	
75–79	40335	27.6	34497	27.8	5838	26.5	
80+	25482	17.4	21918	17.6	3564	16.2	
Race							
White	137023	93.7	116275	93.6	20748	94.1	0.0001
Black	5733	3.9	4884	3.9	849	3.9	
Other	3522	2.4	3079	2.5	443	2.0	
Comorbidity Index							
0	59213	40.5	51063	41.1	8150	37.0	<.0001
1	79182	54.1	66595	53.6	12587	57.1	
2+	7883	5.4	6580	5.3	1303	5.9	
Year of Surgery							
2003	1898	1.3	1740	1.4	158	0.7	
2004	29202	20.0	26628	21.4	2574	11.7	
2005	29308	20.0	25263	20.3	4045	18.4	
2006	29067	19.9	24022	19.3	5045	22.9	
2007	28350	19.4	23023	18.5	5327	24.2	
2008	28453	19.5	23562	19.0	4891	22.2	
Diagnosis in Follow Up							

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			BMP Use				
	Full Cohort		NO		YES		
	n	%	n	%	n	%	p value
Any Cancer	24481	16.7	21079	17.0	3402	15.4	
Bone	555	0.4	494	0.4	61	0.3	
Brain	759	0.5	669	0.5	90	0.4	
Breast	3689	3.8	3152	3.8	537	3.6	
Cervix Uteri	227	0.2	197	0.2	30	0.2	
Colon and Rectum	2493	1.7	2148	1.7	345	1.6	
Corpus Uteri	491	0.5	430	0.5	61	0.4	
Esophagus	299	0.2	258	0.2	41	0.2	
Hodgkins Lymphoma	203	0.1	173	0.1	30	0.1	
Non Hodgkins Lymphoma	1722	1.2	1463	1.2	259	1.2	
Kaposi Sarcoma	41	0.0	*	*	*	*	
Kidney and Renal Pelvis	1120	0.8	963	0.8	157	0.7	
Larynx	197	0.1	172	0.1	25	0.1	
Leukemia	884	0.6	755	0.6	129	0.6	
Liver and Intrahepatic Bile Duct	719	0.5	608	0.5	111	0.5	
Lung and Bronchus	3300	2.3	2855	2.3	445	2.0	
Melanoma	2096	1.4	1789	1.4	307	1.4	
Mesothelioma	144	0.1	125	0.1	19	0.1	
Myeloma	1118	0.8	974	0.8	144	0.7	
Oral Cavity and Pharynx	170	0.1	148	0.1	22	0.1	
Ovary	647	0.7	548	0.7	99	0.7	
Pancreas	831	0.6	707	0.6	124	0.6	
Prostate	4028	8.2	3497	8.4	531	7.4	
Stomach	385	0.3	329	0.3	56	0.3	
Testis	69	0.1	*	*	*	*	
Thyroid	363	0.3	306	0.3	57	0.3	
Urinary Bladder	1462	1.0	1265	1.0	197	0.9	

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* Cells suppressed because of n < 11

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Table 2

Risk of Cancer Associated with BMP Administration in Unadjusted and Adjusted Models

	Crude Hazard Ratio			Adjusted Hazard Ratio		
	HR	95%CI		HR	95%CI	
Diagnosis in Follow Up						
Any Cancer	0.98	0.95	1.02	0.99	0.96	1.03
Bone	0.76	0.59	1.00	0.77	0.59	1.01
Brain	0.83	0.66	1.03	0.82	0.66	1.03
Breast	1.05	0.96	1.15	1.05	0.95	1.15
Cervix Uteri	0.91	0.61	1.34	0.91	0.61	1.34
Colon and Rectum	0.99	0.88	1.11	1.00	0.89	1.12
Corpus Uteri	0.84	0.64	1.10	0.85	0.64	1.11
Esophagus	0.98	0.71	1.37	1.00	0.72	1.39
Hodgkins Lymphoma	1.09	0.96	1.25	1.10	0.97	1.26
Non Hodgkins Lymphoma	1.01	0.93	1.10	1.02	0.94	1.11
Kaposi Sarcoma	0.67	0.24	1.87	0.67	0.24	1.87
Kidney and Renal Pelvis	1.01	0.85	1.20	1.02	0.86	1.21
Larynx	0.89	0.58	1.35	0.90	0.59	1.37
Leukemia	1.06	0.88	1.28	1.08	0.90	1.30
Liver and Intrahepatic Bile Ducts	1.15	0.94	1.41	1.17	0.95	1.43
Lung and Bronchus	0.96	0.87	1.06	0.96	0.87	1.07
Melanoma	1.06	0.94	1.20	1.09	0.96	1.22
Mesothelioma	0.95	0.58	1.54	0.96	0.59	1.56
Myeloma	0.90	0.76	1.07	0.91	0.76	1.08
Oral cavity and Pharynx	0.92	0.59	1.45	0.94	0.60	1.48
Ovary	1.10	0.89	1.37	1.10	0.89	1.37
Pancreas	1.10	0.74	1.62	1.11	0.75	1.64
Prostate	0.95	0.87	1.05	0.96	0.87	1.05
Stomach	1.06	0.80	1.41	1.08	0.81	1.43
Testis	1.18	0.60	2.32	1.17	0.60	2.30
Thyroid	1.14	0.86	1.52	1.12	0.84	1.48

	Crude Hazard Ratio			Adjusted Hazard Ratio		
	HR	95%CI		HR	95%CI	
Urinary bladder	0.96	0.83	1.12	0.99	0.85	1.15