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Risk of Cancer Following Lumbar Fusion Surgery With Recombinant Human Bone Morphogenic Protein-2 (rhBMP-2): An Analysis Using a Commercially Insured Patient Population

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Background: Recombinant human bone morphogenetic protein-2 (rhBMP-2) is frequently used to promote new bone growth after lumbar fusion surgery. However, because BMP receptors are found on cancer cells, there is concern about potential cancer following treatment with rhBMP-2. Data from clinical trials have reported divergent results and have been limited by small sample sizes and relatively short follow-up. We therefore examined the long-term risk of cancer following treatment with rhBMP-2 after lumbar fusion surgery.

Methods: Using the MarketScan Commercial Claims and Encounters database, we identified all patients <65 years without prior cancer who underwent lumbar fusion surgery between October 2003 and December 2009 and were followed at least 3 years after surgery. Development of any Surveillance Epidemiology and End Results malignancy in follow-up was identified through diagnosis and procedure codes.

Results: Among 39 448 eligible patients, 2345 (5.9%) received rhBMP at surgery; the median follow-up in this population was 4.87 years. Cancer in follow-up was observed in 49 BMP-treated patients (0.43/100 person years) and 1072 nontreated patients (0.58/100 person years). Use of rhBMP was associated with a cancer risk similar to that of untreated patients in both univariate (hazard ratio, 0.80; 95%, CI 0.54–1.19) and multivariate proportional hazards analyses (hazard ratio, 0.81; 95% CI, 0.54–1.20). Similar findings were observed in a secondary analysis after adjustment for likelihood of rhBMP administration.

Conclusions: In this retrospective cohort with at least 3 years of follow-up, administration of rhBMP during lumbar fusion surgery was not associated with an increased risk of subsequent cancer.

Level of Evidence: 4

Lumbar Spine

Keywords: human BMP-2 protein, spinal fusion, carcinogenesis, claims analysis, MarketScan data

INTRODUCTION

Bone morphogenic proteins (BMPs) are growth factors that are known, among other properties, to induce bone formation and thus have been evaluated as an alternative to iliac crest bone grafting at the time of fusion of the lumbar spine.[1] Recombinant human BMP-2 (rhBMP-2) is indicated for anterior lumbar fusion and is administered via an absorbable collagen sponge carrier known as the Infuse Bone Graft (Medtronic Inc, Memphis, Tennessee). In addition, rhBMP-7 is available as a mixture with bovine collagen and after reconstitution with saline is administered as a paste. BMPs are thought to play a role in apoptosis as well as cell growth and differentiation, and receptors for BMP are found on multiple cell types, including cancer cells.[2] A review of the preclinical literature concluded that whereas BMP-2 likely does not cause de novo cancers, it may have potential to enhance tumor function, and thus more definitive research is needed.[3]

Although randomized clinical trial data did not suggest any association of rhBMP with development of cancers,[4,5] additional analyses of trial data found a greater frequency of malignancy in patients who received rhBMP compared with those who received bone grafts,[6–8] with two analyses achieving statistical significance.[7,8] In addition, observational studies using both Medicare[9–11] and commercial insurance claims[12,13] data did not show an increased cancer risk, but they were limited by relatively short duration of follow-up after surgery and/or questions of generalizability to younger patients. A recently

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published study that used a linked tumor-Medicare database found no risk of second primary cancers or cancer recurrence,[14] and a single-center study of over 500 patients also did not show an increased cancer incidence.[15] Finally, a review[16] of the clinical data found there was no conclusive evidence that rhBMP resulted in a higher risk of subsequent cancer but that the potential risk should be considered for each patient. However, because published studies typically had follow-up of 3 to 4 years and as little as under 2 years,[13] delayed carcinogenic effects may not have been apparent.

Given the conflicting data about cancer risk, we performed a retrospective cohort study in a commercially insured population of patients less than 65 years of age, which would complement previous studies on the Medicare population[9–11] and evaluate a population that was at lower baseline cancer risk. In addition, we restricted our analysis to patients with at least 3 years of follow-up. We hypothesized that the incidence of cancer in follow-up after surgery would be similar in the rhBMP-treated and untreated patients.

METHODS

Database

The Truven Health MarketScan Commercial Claims and Encounters database was established in 1988 and contains inpatient and outpatient records, with all patients purchasing insurance via large employers that are mostly self-insured. Since establishment, the database has included approximately 138 million unique, deidentified patients. Data are available for purchase directly from the vendor.

Patients

The cohort consisted of all patients between 18 and 65 years who underwent lumbar spine fusion between October 2003, which was when reimbursement was first provided for rhBMP administration, and December 2009. Data sources included claims from hospitals, physicians, ambulatory surgery centers, and institutional outpatient providers. Eligibility criteria included fusion of the lumbar spine as evidenced by the following *International Classification of Diseases, Ninth Revision, Clinical Modification* (*ICD-9-CM*) or *Current Procedural Terminology, 4th Edition* (*CPT-4*) codes: ICD-9-CM 81.06, 81.07, 81.08, 81.09, 81.36, 81.37, 81.38, CPT-4 22558, 22630, 22612. Given potential for incomplete claims, patients were excluded if they were not listed in the MarketScan database for a minimum of 2 years before the surgery date. In order to exclude patients with prevalent cancers, as well as to differentiate newly diagnosed tumors from recurrence, we excluded all patients with a diagnosis code for cancer during the 24-month period prior to fusion, as well as patients with one or more *ICD-9-CM* codes for "personal history of a malignant neoplasm" (V10.00–10.9) or at least one *ICD-9-CM* code for chemotherapy or radiation therapy.

As in previous studies,[9,10] we identified exposure to rhBMP through the procedure code (ICD-9-CM 84.52) that was recorded on the lumbar fusion surgery date. Higher doses of rhBMP (ie, >40 mg) have been proposed to be associated with an increased risk of cancer compared with lower doses.[8] Because rhBMP dose was not available in the database, we used indicator variables for two procedures more likely to be associated with higher doses, multiple level procedures, and refusion procedures.

Measures

The primary outcome was a diagnosis of any of the 26 malignant neoplasms included in the Surveillance Epidemiology and End Results (SEER) registries,[17] and this was ascertained through the presence of at least one of the *ICD-9-CM* codes present in any files beginning at 3 years after the after the surgery date[10] (Appendix). Thus, cancers that occurred within 3 years of surgery were not included. We used as a case definition $\geq$2 codes for the same malignancy on different service dates and $\geq$1 procedure code consistent with site-specific treatment (where applicable), chemotherapy, and/or radiation therapy. This definition most closely approximated the standardized incidence ratio for any cancer in both the non-BMP and BMP-treated groups in a previous study.[10]

Other relevant variables included age in years (at the surgery date), gender, and length of follow-up. Data on race were not included in MarketScan files. To measure comorbidity, we used a previously validated, weighted index that included diagnoses contained in any of the files.[18] In addition, as previously recommended to differentiate postoperative complications from preexisting comorbidities,[18] we only included diagnoses that were

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contained in the files between 24 months and 30 days prior to the surgical date.

We followed all patients from 3 years after the surgical date through the earliest of cancer diagnosis (excluding cancers diagnosed within 3 years), death, disenrollment from the insurer, or end of the observation period (December 31, 2012).

Analysis

All analyses were performed using Statistical Analysis System, version 9 (SAS Inc, Cary, North Carolina). The primary analysis examined the association of demographics, comorbidities, and use of rhBMP with risk of any one of the SEER malignancies using the prespecified definition of 2 or more diagnoses on separate dates of service and evidence of treatment. Chi-square analysis was used to measure statistical significance. In order to account for different lengths of observation, Cox regression was used to evaluate the impact of rhBMP on development of individual SEER malignancies as well as overall cancer risk. Given the multiple comparisons and potential model overfitting, we used a Bonferroni correction when assessing statistical significance, which assigned a *P* value of .0019 (eg, .05/26 sites) as significant. We compared the observed with expected cancer incidence in both groups using the expected gender- and age-specific incidence rates from SEER. We also constructed Kaplan-Meier curves to compare the risk of malignant neoplasms over time.

We then determined the association of rhBMP with risk of malignancy using multivariable Cox regression. As in univariate analysis, the primary analysis determined the association of rhBMP with overall cancer risk using the prespecified definition. In all models, we adjusted for demographics (age in years, gender if appropriate for that site) and comorbidity.

Due to the potential selection bias in treatment allocation, to further examine differences in long-term cancer risk we used propensity score adjustment.[19,20] In this analysis, all variables potentially associated with use of rhBMP treatment decisions were included in a multivariable logistic model predicting likelihood of rhBMP therapy. By including all measurable factors that could affect rhBMP use, it is assumed that at least some of the nonmeasurable factors also track with these. Variables included age, gender, comorbidity score, year of surgery, geographic region, type of insurance, surgical approach, and use of a multilevel or redo procedure. The propensity score was then added as a covariate to the model, and risk of cancer was compared with the non-BMP group using Cox regression.

We also performed a secondary Cox regression analysis that was limited to patients who underwent multiple level procedures or redo procedures, both of which are associated with higher rhBMP dose.

The study protocol was approved by the local institutional review board.

RESULTS

From the MarketScan database, we identified 356 306 patients who underwent lumbar spinal fusion. We then excluded 112 164 patients with surgery before October 2003 or after December 2011; 124 154 patients without continuous enrollment for at least 2 years prior to surgery; 47 450 with less than 3 years of follow-up; 12 890 with a history of cancer; and 20 200 who were under 18 or over age 64. The remaining 39 448 patients were the subject of this analysis.

The characteristics of 39 448 patients are shown in Table 1. The mean age was 51.7 ± 7.8 years, 53.6% were women, 46.4% were men, and most patients had low comorbidity scores. There was evidence of rhBMP administration in 2345 patients (5.9%). Compared with others, those who received rhBMP tended to be younger (51.2 ± 8.1 years versus 51.7 ± 7.7 years, $P < .0001$), to be women, to have higher comorbidity indices, and were also more likely to undergo anterior procedures as well as multiple level or redo procedures. The use of rhBMP increased over the duration of the study. The mean and median length of follow-up were 4.90 and 4.87 years, respectively, in the rhBMP-treated patients (total of 11 246 person years) and 5.00 and 5.04 years, respectively, in others (total of 187 033 person years). All persons in both groups had a minimum of 3 years follow-up and a maximum of 9.2 years follow-up.

A cancer diagnosis in follow-up was observed in 1121 patients, corresponding to an incidence of 0.57/100 person years. A total of 49 cancers were observed in the BMP-treated patients (incidence, 0.43/100 person years) and 1072 in the nontreated patients (0.58/100 person years). This corresponded to an incidence rate ratio of 0.75 (95% CI, 0.56–0.99), which indicates a slightly lower risk of cancer in the rhBMP-treated patients. Of note, in the age-

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Table 1. Cohort characteristics of BMP-treated and untreated patients.

Characteristic	Total, n	%	BMP, n	%	No BMP, n	%	*P* Value
Age at surgery, y							<.0001
<40	3708	9.4	262	11.2	3446	9.3	
40–49	11 200	28.4	659	28.1	10 541	28.4	
50–59	18 481	46.9	1077	45.9	17 404	46.9	
60–64	6059	15.4	347	14.8	5712	15.4	
Gender							<.0001
Male	18 320	46.4	988	42.1	17 332	46.4	
Female	21 128	53.6	1357	57.9	19 771	53.3	
Comorbidity score							<.0001
0	29 314	74.3	1502	64.1	27 812	75.0	
1	9491	24.1	787	33.6	8704	23.5	
≥ 2	643	1.6	56	2.4	587	1.6	
Surgery date							<.0001
2003	456	1.2	12	0.5	444	1.2	
2004	4323	11.0	199	8.5	4124	11.1	
2005	5150	13.1	316	13.5	4834	13.0	
2006	6868	17.4	372	15.9	6496	17.5	
2007	6469	16.4	391	16.7	6078	16.4	
2008	7969	20.2	524	22.4	7445	20.1	
2009	8213	20.8	531	22.6	7682	20.7	
Approach							
Anterior	3135	8.0	450	19.2	2685	7.2	<.0001
Posterior or lateral transverse	36 313	92.1	1895	80.8	34 418	92.8	
Multiple levels	10 846	27.5	1038	44.3	9808	26.4	<.0001
Refusion	829	2.1	83	3.5	746	2.0	<.0001

Abbreviation: BMP, bone morphogenic protein.

and gender-matched general population, the incidence rate is 0.45/100 person years. The incidence of individual cancers by site is shown in Table 2. The most frequently observed sites were breast, non-Hodgkins lymphoma, melanoma, lung, prostate, myeloma, renal, and colorectal cancers. Although the incidence of lung cancer was somewhat higher in the rhBMP-treated patients (0.04/100 versus 0.02/

Table 2. Incidence of malignant neoplasia in BMP-treated and untreated patients.

			BMP Treated		BMP Untreated	
Tumor Type	n	Incidence (/100 py)	N	Incidence (/100 py)	N	Incidence (/100 py)
Any	1121	0.57	49	0.43	1072	0.58
Bone	0	0.00	0	0.00	0	0.00
Brain and CNS	34	0.02	0	0.00	34	0.02
Breast	217	0.20	7	0.11	210	0.21
Cervix uteri	8	0.01	0	0.00	8	0.10
Colon and rectum	74	0.04	2	0.02	72	0.04
Corpus uteri	31	0.03	0	0.00	31	0.03
Esophagus	8	0.00	0	0.00	8	0.00
Hodgkins lymphoma	31	0.03	2	0.02	29	0.02
Non-Hodgkins lymphoma	188	0.09	7	0.06	181	0.10
Kaposi sarcoma	3	0.00	0	0.00	3	0.00
Kidney and renal pelvis	62	0.03	3	0.03	59	0.03
Larynx	2	0.00	0	0.00	2	0.00
Leukemia	71	0.04	3	0.03	68	0.04
Liver and intrahepatic bile duct	11	0.01	0	0.00	11	0.01
Lung and bronchus	39	0.02	4	0.04	35	0.02
Melanoma	114	0.06	7	0.06	107	0.06
Mesothelioma	0	0.00	0	0	0	0.00
Myeloma	80	0.04	4	0.04	76	0.04
Oral cavity and pharynx	21	0.01	0	0.00	21	0.01
Ovary	23	0.02	1	0.02	22	0.02
Pancreas	18	0.01	0	0	18	0.01
Prostate	93	0.10	5	0.10	88	0.10
Stomach	12	0.01	0	0.00	12	0.01
Testis	4	0.00	0	0.00	4	0.00
Thyroid	62	0.03	3	0.03	59	0.03
Urinary bladder	40	0.02	2	0.02	38	0.02

Abbreviations: BMP, bone morphogenic protein; CNS, central nervous system; py, person year.

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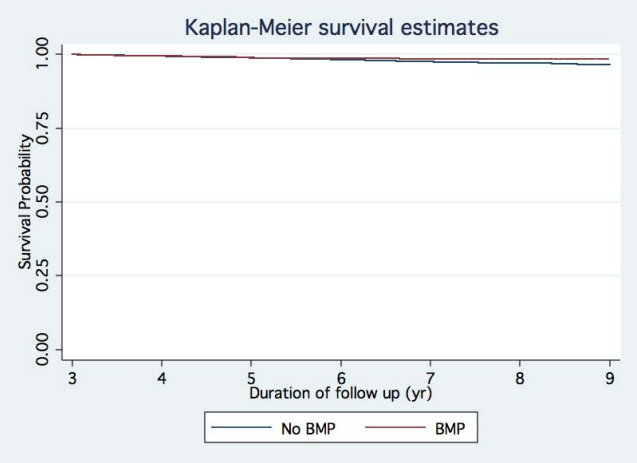

Figure. Kaplan-Meier plot of malignant neoplasia risk in recombinant human bone morphogenic protein (rhBMP)-treated and untreated patients. Through a follow-up period of up to 8 years, patients receiving rhBMP were at similar risk to receive a cancer diagnosis as untreated patients ($P = .2687$ by log-rank test).

100 person years), the difference was not statistically significant ($P = .13$), and the incidence of other cancer types in rhBMP-treated patients never exceeded that of others. In a Kaplan-Meier analysis (Figure), patients who received rhBMP were at a risk for cancer development that was similar to those who did not ($P = .2687$ by log-rank test).

We also compared the observed with expected incidence of malignant neoplasms in an age- and gender-matched population according to SEER data. The standardized incidence ratio for the entire sample was 0.80 (95% CI, 0.74–0.87). For patients treated with rhBMP, the standardized incidence ratio was 0.42 (95% CI, 0.30–0.58), compared with a standardized incidence ratio of 0.83 (95% CI, 0.77–0.90) in others. These findings indicate a somewhat lower cancer risk in both groups compared with the general population, but especially in the BMP treated patients.

We then used proportional hazards models to examine the association of rhBMP with cancer risk. For all cancers combined, use of rhBMP was associated with a similar risk of cancer in both univariate (hazard ratio [HR], 0.80; 95% CI, 0.54–1.19, $P = .276$) and mulitivariate analyses (HR, 0.81; 95% CI, 0.54–1.20, $P = .283$). Other factors associated with cancer risk in multivariate analysis included older age (ages 40–49 years: HR, 1.50; 95% CI, 1.01–2.23, $P = .05$; ages 50–59 years: HR, 2.78; 95% CI, 1.91–4.06, $P < .0001$; ages 60–64 years: HR, 12.02; 95% CI, 7.53–19.20; $P < .0001$ compared with ages 18–39 years) and increased comorbidity score (1 comorbidity HR, 1.46; 95% CI, 1.23–1.73, $P < .0001$, ≥ 2 comorbidities HR, 1.12; 95% CI, 0.60–2.09, $P = .730$). Data for individual sites are shown in Table 3. In both

Table 3. Proportional hazards models to risk of malignant neoplasms associated with BMP treatment.

Site of Cancer	Univariate HR for rhBMP	Lower 95% CI	Upper 95% CI	*P* Value	Multivariate HR for rhBMP	Lower 95% CI	Upper 95% CI	*P* Value
Bone	0	0	0		0	0	0	
Brain and other central nervous system	0.22	0.03	1.61	.138	0.26	0.04	1.92	.188
Breast	0.79	0.48	1.31	.359	0.86	0.52	1.43	.560
Cervix uteri	0.00	0.00	–	.992	0.00	0.00	–	.991
Colon and rectum	0.72	0.32	1.64	.438	0.90	0.39	2.05	.794
Corpus uteri	0.29	0.04	2.12	.223	0.29	0.04	2.14	.226
Esophagus	0.00	0.00	–	.990	0.00	0.00	–	.994
Hodgkins lymphoma	1.23	0.38	3.99	.733	1.24	0.38	4.08	.725
Non-Hodgkins lymphoma	0.72	0.43	1.22	.222	0.72	0.43	1.22	.218
Kaposi sarcoma	0.00	0.00	–	.993	0.00	0.00	–	.996
Kidney and renal pelvis	0.78	0.34	1.76	.543	0.71	0.31	1.62	.414
Larynx	0.00	0.00	–	.997	0.00	0.00	–	.999
Leukemia	0.77	0.34	1.75	.530	0.65	0.28	1.48	.301
Liver and intrahepatic bile duct	0.00	0.00	–	.990	0.00	0.00	–	.994
Lung and bronchus	1.18	0.47	2.95	.719	1.05	0.42	2.65	.913
Melanoma	0.72	0.37	1.41	.336	0.70	0.36	1.38	.302
Mesothelioma	0.00	0.00	–	.997	0.00	0.00	–	.999
Myeloma	0.70	0.33	1.50	.358	0.64	0.30	1.38	.254
Oral cavity and pharynx	0.59	0.08	4.33	.601	0.67	0.09	5.03	.699
Ovary	0.71	0.17	2.96	.643	0.72	0.17	3.05	.660
Pancreas	0.00	0.00	–	.984	0.00	0.00	–	.990
Prostate	0.74	0.35	1.58	.433	0.72	0.33	1.54	.394
Stomach	0	0.00		.988	0.00	0.00		.992
Testis	1.94	0.24	15.80	.536	2.03	0.24	17.48	.519
Thyroid	0.53	0.17	1.68	.282	0.50	0.16	1.60	.245
Urinary bladder	0.51	0.13	2.10	.353	0.58	0.14	2.40	.453

Abbreviations: HR, hazard ratio; rhBMP, recombinant human bone morphogenic protein. Dashes in cells indicate that that the confidence interval could not be estimated because of sample size.

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univariate and multivariate analyses, there was no association of rhBMP use with risk of any of the malignant neoplasms, though for many sites, the infrequent number of events precluded the calculation of reliable estimates.

In order to adjust for potential selection bias in rhBMP treatment allocation, we developed a propensity score to predict the probability of receipt of rhBMP. The propensity score had good discrimination in predicting the likelihood of receiving rhBMP, as evidenced by a receiver operating characteristic curve area of 0.810, which indicates a much better likelihood of prediction than by chance alone (0.50). After adjustment for the propensity score, the use of rhBMP was associated with a similar risk of malignant neoplasia as that of untreated patients (HR, 0.76; 95% CI, 0.51–1.14). Finally, we performed a secondary proportional hazards model that was limited to patients who underwent multiple level or redo procedures, which are often associated with higher rhBMP doses. In this cohort, the multivariate HR for rhBMP exposure was 0.71 (95% CI, 0.46–1.11; $P = .134$) and thus not associated with cancer risk.

DISCUSSION

The effect of rhBMP on cancer risk is controversial. Although a meta-analysis failed to demonstrate increased risk of malignant tumors with rhBMP,[21] a tumor-promotion effect of rhBMP cannot be excluded on a molecular level.[3] In the current study, which included a relatively long duration of follow-up, we did not demonstrate any cancer risk associated with rhBMP administration. The findings were robust when we attempted to adjust for confounding factors, including the likelihood of receiving rhBMP, as well as when restricted to indications that may be associated with higher rhBMP doses. The observed cancer incidence (0.43 case/100 person years versus 0.58 case/100 person years in non-BMP patients) was lower than in studies that included a Medicare-aged population (1.7–2.1 cases/100 person years)[11,14] and in the same range as in non-BMP-treated patients from clinical trial data (0.50 case/100 person years).[8] The latter study[8] also found a much higher incidence in BMP-treated patients (3.37 cases/100 person years).

Receptors for BMP are found on a variety of cancer cells,[2] and thus there is potential concern for BMP in the promotion of tumor growth both locally and at metastatic sites. Although at the cellular level, BMP has been shown to promote angiogenesis,[22,23] cell growth,[24] bone metastases,[25] and malignant cell motility and invasiveness,[26] BMP is also capable of inhibiting proliferation and growth and thus could have potential antineoplastic effects.[25,26] However, given at least the potential concern for BMP promoting progression, rhBMP is not indicated in the vicinity of a resected or extant cancer or in those receiving treatment for malignancy.[27]

The methodology and data sources that we used have several strengths and limitations. Our study had a very large sample and consisted of a wide range of practices and captured multiple cancer diagnoses. The data were limited by the absence of clinical detail, including factors such as smoking, alcohol use, obesity, family history of cancer, and differences in intraoperative technique that may have been associated with rhBMP use and/or cancer risk. However, consistent results were observed in an analysis that included a propensity score for likelihood of rhBMP administration. Also, in a previous study[9] of pancreatic carcinoma after rhBMP exposure, medical record review found no association of rhBMP with other cancer risk factors such as obesity and smoking. We also could not rule out differences in treatment allocation, although patients at increased cancer risk at baseline were preferentially not given rhBMP. In addition, although the patients receiving rhBMP were somewhat younger and therefore at lower baseline cancer risk, the differences were maintained after adjustment for age as well as gender and comorbidity. We also could not measure the actual rhBMP dose, but in analyses limited to procedures typically associated with higher doses, there was no association with malignancy. Although the follow-up was at least 3 years after surgery, with some patients followed as long as 8 years, if the potential risk of rhBMP is mutagenesis rather than tumor promotion, an even longer follow-up period may be required to definitively exclude its malignant potential. We also ascertained previous and subsequent cancers through the use of *ICD-9-CM* codes, which were developed for reimbursement and not for research. However, the algorithm that was used included fairly stringent criteria to define the presence of malignant tumors. Our study was limited to lumbar fusion procedures in adult patients. We recognize that the product is not uncommonly used off label and therefore included posterior or transverse

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procedures, neither of which were approved indications. However, we did exclude patients with contraindications to BMP including age <18 years or previous cancer diagnoses, and no women in the sample were known to be pregnant. Despite the large sample, we did not have sufficient power to detect any differences in the incidence of rare tumors and did not capture neoplasms not contained in SEER such as nonmelanoma skin cancers. Finally, because we used a procedure code as a measure of rhBMP administration, there is the potential for misclassification. However, in previous work,[9] the specificity of the procedure code for receipt of rhBMP-2 (compared with rhBMP-7) was 95% and the positive predictive value of the code was 100%.

CONCLUSIONS

In this large sample of commercially insured patients, we found that treatment with rhBMP during fusion of the lumbar spine did not increase the subsequent risk of cancer. Although some previous studies did show an increased cancer risk, the findings of this and other database studies should provide reassurance to both patients and providers.

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Appendix. Cancer diagnosis and procedure codes.

Type of Malignant Tumor	*ICD-9-CM* Diagnosis Codes	*ICD-9-CM* Procedure Codes	*CPT-4* Procedure Codes
Bone	170.0-170.9	84.0-84.19	23900-23921, 24900-24940, 25900-25931, 26910-26952, 27290, 27295, 27590-27598, 27880-27889, 28800-28825
Brain and other central nervous system	191.0-192.3	01.1-01.59	61510, 61516, 61518, 61520, 61521, 61524, 61526, 61530, 61534, 61536, 61544, 61545
Breast	174.0-175.9	84.4-85.48, 85.20-85.23	19120, 19125, 19126, 19160, 19162, 19180-19240
Cervix uteri	180.0-180.9	68.3-68.9	57530, 57531, 58150, 58180, 58200, 58210, 58240, 58260, 58262, 58275, 58285, 58940
Colon and rectum	153.0-154.8	45.71-45.79, 45.8, 48.5, 48.62, 48.63	44140, 44141, 44143, 44144, 44145-44147, 44150-44153, 44155, 44156, 44160, 45110-45114, 45116, 45119
Corpus uteri	179, 182.0-182.8	68.3-68.9	58150, 58180, 58200, 58210, 58240, 58260, 58262, 58275, 58285, 58940
Esophagus	150.0-150.9	42.4-42.69	43107-43124
Hodgkins lymphoma	201.0-201.9	Chemotherapy and/or radiation therapy[a]	Chemotherapy and/or radiation therapy[a]
Non-Hodgkins lymphoma	200.0-200.8, 202.0-202.9	Chemotherapy and/or radiation therapy[a]	Chemotherapy and/or radiation therapy[a]
Kaposi sarcoma	176.0-176.9	Chemotherapy and/or radiation therapy[a]	Chemotherapy and/or radiation therapy[a]
Kidney and renal pelvis	189.0-189.9	55.4-55.54, 56.4-56.51	50220-50240, 50650, 50660
Larynx	161.0-161.9	25.2-25.4, 29.33, 30.1-30.4	31360-31420, 41120-41155, 42120, 42410-42426
Leukemia	205.0-208.9	Chemotherapy and/or radiation therapy[a]	Chemotherapy and/or radiation therapy[a]
Liver and intrahepatic bile duct	155.0-155.2, 156.0-156.9	50.22, 50.3, 50.4, 51.36	47120-47130, 47711, 47712, 47760, 47765, 47780, 47785, 47800
Lung and bronchus	162.0-163.9	32.29, 32.3, 32.4, 32.5, 32.6, 32.9	47120-47130, 47711, 47712, 47760, 47765, 47780, 47785, 47800
Melanoma	172.0-172.9	86.24, 86.4	11600-11646, 17260-17286, 17304-17310
Mesothelioma	163.0-163.9	32.29, 32.3, 32.4, 32.5, 32.6, 32.9	32440, 32442, 32445, 32480, 32482, 32484, 32486, 32488, 32500, 32520, 32522, 32525, 32657, 32663
Myeloma	203.0, 238.6	Chemotherapy and/or radiation therapy[a]	Chemotherapy and/or radiation therapy[a]
Oral cavity and pharynx	140.0-149.9	25.2-25.4, 29.33, 30.1-30.4	31360-31420, 41120-41155, 42120, 42410-42426
Ovary	183.0-183.9	65.0, 65.4, 65.5, 65.6, 68.3-68.9	58150, 58180, 58200, 58210, 58240, 58260, 58262, 58275, 58285, 58940, 58943, 58950-58952, 58960
Pancreas	157.0-157.3, 157.8, 157.9	44.39, 51.36, 51.39, 51.42, 52.50-52.79;6	43820, 43825, 47720 - 47790, 48140-48144, 48146, 48147, 48149 - 48155
Prostate	185	60.5, 62.4-62.42	54520, 54530, 55810-55815, 55840-55845
Stomach	151.0-151.9	42.5-43.99	43620-43634, 43638
Testis	186.0-186.9	62.3, 62.4	54520, 54535, 54690
Thyroid	193	06.11-06.12, 06.2-06.52	60210-60271
Urinary bladder	188.0-188.9	57.33, 57.4, 57.49, 57.71, 57.79	51570, 51575, 51580-51597, 51720, J8520, J8521

Abbreviations: *International Classification of Diseases, Ninth Revision, Clinical Modification* (*ICD-9-CM*) or *Current Procedural Terminology, 4th Edition* (*CPT-4*).
[a]Chemotherapy defined by *ICD-9-CM* codes 99.25, V58.1, V66.2, or V67.2, *CPT-4* codes 96400-96549, J9000-J9999, and Q0083-Q0085 and revenue center codes of 0331, 0332, and 0335. Radiation therapy was defined by *ICD-9-CM* diagnosis codes V58.0, V 66.1 and V 67.1, *ICD-9-CM* procedure codes 92.2-92.39, *CPT-4* codes of 77261-77431, 77499, 77750-77799 and revenue center codes of 0330 and 0333.

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