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Clinical Study

Longer follow-up continues to reveal no increased risk of cancer with the use of recombinant human bone morphogenetic protein in spine fusion

Joseph R. Dettori, PhD[a,*], Jens R. Chapman, MD[b], John G. DeVine, MD[c], Robert A. McGuire, MD[d], Mark R. Junge, BS[a], Daniel C. Norvell, PhD[a]

[a] *Department of Evidence Based Medicine, Spectrum Research, Inc., PO Box 88998, Steilacoom, WA 98388, USA*
[b] *Swedish Medical Center, Swedish Neuroscience Institute, Jefferson Tower, 1600 E. Jefferson St, Seattle, WA 98122, USA*
[c] *Department of Orthopedics, Spine Surgery Service, Georgia Regents University, 1120 15th St, Augusta, GA 30912, USA*
[d] *Department of Orthopedic Surgery and Rehabilitation, University of Mississippi Medical Center, 2500 N State St, Jackson, MS 39216, USA*

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Abstract

BACKGROUND CONTEXT: Large observational studies on potential oncogenic effects of recombinant human bone morphogenetic protein (rhBMP) in spine fusion surgery are limited by relatively short follow-up times.

PURPOSE: To study the possible association between rhBMP and cancer risk in a long-term follow-up study.

STUDY DESIGN: A retrospective cohort study using a combination of the Washington State Comprehensive Hospital Abstract Reporting System, the Washington State Cancer Registry, State of Washington death certificates, and the Washington State Department of Licensing.

PATIENT SAMPLE: Participants were adults age ≥21 years who underwent spine fusion surgery enhanced by rhBMP for degenerative spine disease between January 1, 2002 and December 31, 2010. A comparison group matching each patient receiving rhBMP with three patients not receiving rhBMP was created using the indicators of age, sex, and year of treatment. We excluded patients receiving spine fusion for vertebral fractures or infection, and those with a diagnosis of cancer before or at the index procedure.

OUTCOME MEASURES: The primary outcome was the first diagnosis of any cancer as identified in the records of the state cancer registry or death certificate through the end of 2015.

METHODS: We compared cancer risk between those receiving spine fusion with and without rhBMP using survival analysis. We calculated incidence rates (hazards) by computing the ratio of the number of events and total time at risk. Unadjusted hazard ratios (HR) and adjusted HR (aHR) and their respective 95% confidence intervals (CI) were calculated assuming a Cox proportional hazard regression model. We adjusted the model to include the site of surgery (lumbar vs. cervical) as a covariate as this differed in frequency between the two treatment groups. To assess whether rhBMP adversely affects the progression of cancer, we compared mortality between rhBMP users and nonusers in those who developed cancer. Research support toward this study was received from Medtronic Sofamor Danek USA. The investigators alone, and not Medtronic, were solely responsible for the design, conduct, analysis, and reporting of this study.

RESULTS: We included 16,914 patients who had spine fusion, of whom 4,246 received rhBMP. During the study period, 1,342 patients were diagnosed with some form of cancer. The incidence

FDA device/drug status: Approved (rhBMP-2).

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* Corresponding author. Department of Evidence Based Medicine, Spectrum Research, Inc., PO Box 88998, Steilacoom, WA 98388, USA. Tel.: (253) 226-1521.

E-mail address: joe@specri.com (J.R. Dettori).

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rate was similar between the two groups: 11.2 per 1,000 person years in the rhBMP group and 10.4 per 1,000 person years in the non-rhBMP group, with an aHR of 0.96; 95% CI, 0.85 to 1.10. Similarly, rhBMP use was not associated with an increased risk of commonly occurring individual cancer types, nor with cancer specific mortality after a cancer diagnosis, aHR, 0.92; 95% CI, 0.69 to 1.22.
CONCLUSIONS: Long-term follow-up confirms previous findings that rhBMP application treated with elective spinal fusion did not result in an increased cancer risk in a large population of US adults.

Keywords: Bone morphogenetic protein; Cancer; Database; Oncology; Registry; Retrospective cohort; rhBMP; Spine fusion

Introduction

In 2013, publication of two meta-analyses of randomized controlled trials (RCTs) involving recombinant human bone morphogenetic protein (rhBMP) in spine fusion surgery raised concerns about possible oncogenic effects of this substance, with a reported two- to threefold increase in cancer risk affecting the study population [1,2]. However, definitive conclusions from these meta-analyses are limited caused by the short follow-up duration of the RCTs, the small number of subjects for a relatively rare outcome like cancer in the study population, and the likely incomplete ascertainment of cancer incidence. Several large observational studies attempted to address some of these limitations [3–8]. Nevertheless, the length of follow-up for most studies remained short for a large proportion of patients, especially in light of the potential time lag applicable to cancer emergence and diagnosis [3,4,6,7].

In 2016, we reported the results of a cohort study to assess the possible association between rhBMP and cancer risk using data obtained from combined analysis of the Washington State Comprehensive Hospital Abstract Reporting System (CHARS), the Washington State Cancer Registry (WSCR), and State of Washington death certificates [9]. Our study at the time was limited by the relatively short duration of available follow-up with 37% of the patients having <2 years and 68% <4 years of follow-up. We sought to revisit our study with the benefit of an additional 5 years of follow-up to address the concern of relatively short-term follow-up in the setting of delayed oncogenic effects of the study substance in question.

Material and methods

Data sources and linkage

Four distinct, purpose-dedicated state-wide databases with legally mandated reporting structures were used for our study, all from the State of Washington. They include the CHARS, the WSCR, the Washington State Department of Health's vital records, and the Washington State Department of Licensing (DOL).

CHARS is maintained by the Washington State Department of Health and forms the State's registry of hospital discharges. This registry contains data on all inpatient discharges from the State's public and private nonfederal hospitals to include patient demographic data, admission and discharge information, and International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) diagnosis and procedure (Current Procedural Terminology [CPT]) codes. The Department of Health verifies the data set elements set forth by State Administrative Code [10].

In 1990, Washington State law made cancer a reportable condition and mandated the Department of Health to establish a statewide cancer registry, the WSCR. This law requires all reporting entities that diagnose, or provide first course treatment to a patient with a cancer or a potential cancer report the cancer case to the registry. Furthermore, the health-care facility is responsible for reporting the case if the patient is referred to a facility with cancer registry staffing for diagnostic or first course treatment services [11]. Data collection began in 1992 and included all malignant neoplasms except for skin basal and squamous cell carcinoma, and cancer in situ of the uterine cervix. The WSCR has been certified since 1997 by the North American Association of Central Cancer Registries, which certifies cancer registries based on case completeness, timeliness of reporting, and quality of data.

Death certificate data (date and cause of death) are maintained by the Washington State Department of Health's vital records. The DOL provides information on residency through state driver license renewals.

CHARS was linked to the WSCR, the state death certificates, and DOL data using the following variables: last name, first name, zip code, sex, date of birth, partial social security number, and partial first and last names. This was done using a hierarchical deterministic and probabilistic program. Certain variables such as last and first name and zip code were weighted to give more credence to less-frequent values. Before 2007, only partial names are obtainable in CHARS. Full names and a partial Social Security Number (SSN) become available starting in 2007. For CHARS entries with only name initials, those initials, date of birth, and sex were required to be exact matches. The robustness of the conjoined datasets was tested with a variety of linkage strategies and for any possible discrepancy (eg, multiple deaths or cancer before admission). Though patient identifiers were used to link the data sets, a deidentified data set was used for the analysis. This study was

approved by the Washington State Institutional Review Board.

Study population

We identified adults age ≥21 years who received an elective spine fusion (procedure codes 81.00–81.08) or refusion (81.30–81.39) for degenerative spine disease between January 1, 2002 and December 31, 2010. The year 2002 was the first year rhBMP received FDA approval for a specific type of lumbar spine fusion. From these patients who received rhBMP (procedure code 84.52) we formed the "treatment group." The "comparison group" was selected by matching each patient in the treatment group (those receiving rhBMP) with three patients not receiving rhBMP based on three variables: age (within 2 years), sex, and year of treatment. We excluded patients with a diagnosis of cancer in the WSCR or CHARS before or at the index procedure, and those who received spine fusion as a result of vertebral fractures or infection as identified by CHARS procedure and ICD-9 codes.

Outcomes

The primary outcome was the first diagnosis of all reportable cancers except nonmelanotic skin cancers identified in either the WSCR or on the death certificate before December 31, 2015. In cases in which cancer was listed as a cause of death on the death certificate but not identified in the records of the WSCR, we used the date of death as the date of diagnosis. There were 47 instances where this was the case (34 in the non-rhBMP group and 13 in the rhBMP group).

We determined time at risk for all patients to begin on the day of admission of the index spine fusion or refusion. The cancer incidence rate was established from the admission date until one of three events occurred: cancer was diagnosed; follow-up was censored caused by patient death; or the study period was concluded. To calculate the mortality rate with cancer as the underlying cause, time at risk was continued until the patient died or until the end of the study period. Mortality caused by cancer was analyzed separately for patients already diagnosed with cancer and all instances of cancer-related deaths. Time at risk was counted in days and converted to person years at risk.

Statistical methods

We performed a survival analysis to determine the frequency of our determined outcomes and the timing of their occurrences. Calendar dates of events and censoring times were converted to the number of days from initial surgery. Incidence rates (hazards) were computed by taking the ratio of the number of events and total time at risk. Unadjusted hazard ratios (HR) and adjusted HR (aHR) and their 95% confidence intervals (CI) were calculated assuming a Cox proportional hazard regression model for all cancers and for the more common cancers individually. The assumption of proportional hazards was tested by visualizing the slopes of the log-log plots of survival vs. analysis time. We adjusted the model to include the site of fusion (lumbar vs. cervical), the approach (anterior vs. posterior vs. combined anterior and posterior), and diagnosis. To assess whether rhBMP adversely could promote cancer progression, we compared mortality among patients who received rhBMP vs. non-rhBMP in those who developed cancer. Analyses were performed using Stata software, version 12.0 (College Station, TX, USA).

Results

Patient characteristics

We found 4,257 patients who received rhBMP during their elective spine fusion or revision fusion procedures performed in our State during the study period from 2002 through 2010. Our comparison group consisted of 12,748 patients with elective spine fusion surgeries that had not

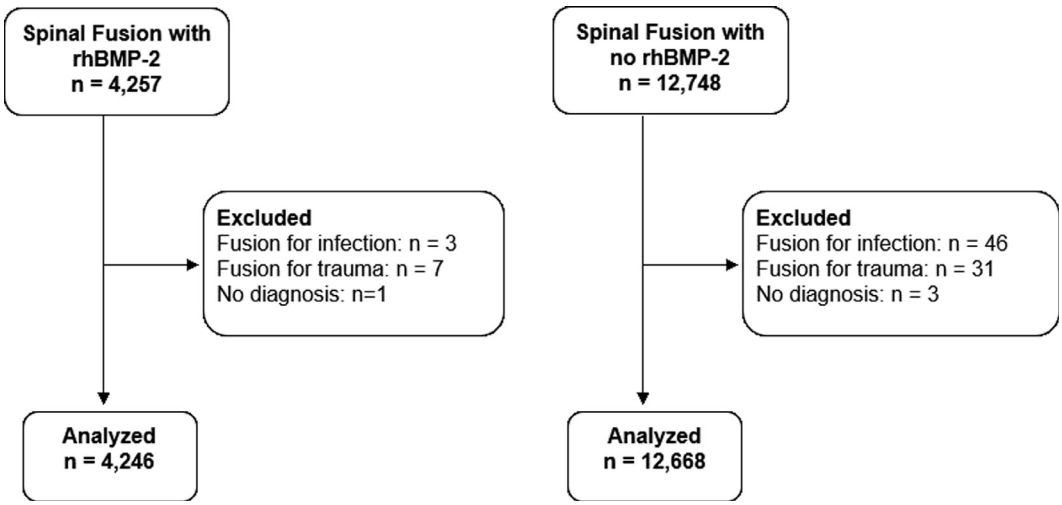

Fig. 1. Patient selection.

received rhBMP during the same time period. Following our selection criteria, we excluded 3 patients in the rhBMP group treated with fusion caused by spine infection and 7 patients for trauma indications. Accordingly, we excluded 46 patients treated with fusion surgery for spine infection and 31 as a result of trauma in our comparison group. We further excluded four patients without a listed diagnosis (one in the rhBMP group and three in the non-rhBMP group) leaving us with 4,246 patients in the rhBMP group and 12,668 in the non-rhBMP group for statistical comparison (Fig. 1). The study population had a mean age of 55.4 years, with 42% males. Average follow-up time was 8.0 years, with a range 5.0 to 14.0. The two groups were similar with respect to age, sex, primary diagnosis, surgical approach (anterior, posterior, and combined), timing of fusion (primary or revision), and year of fusion. We found a higher proportion of lumbosacral fusions in the rhBMP group (84%) compared with the non-rhBMP group (41%; Table 1).

Table 1
Patient and procedure characteristics by use of rhBMP in spine fusion

Characteristics	rhBMP (n=4,246)	Non-rhBMP (n=12,668)	p value*
Age at surgery (y), mean±SD	55.4±13.4	55.4±13.3	.999
Sex, n (%)			.869
Men	1,800 (42.4)	5,352 (42.3)	
Women	2,446 (57.6)	7,316 (57.8)	
Site of surgery, n (%)			
Cervical	578 (13.6)	7,119 (56.2)	.000
Dorsolumbar	105 (2.5)	300 (2.4)	.700
Lumbosacral	3,556 (83.8)	5,228 (41.3)	.000
Unspecified	7 (0.2)	21 (0.2)	.990
Primary diagnosis, n (%)			
Degenerative disc/ spondylosis	1,733 (40.8)	5,658 (44.7)	.000
Stenosis	590 (13.9)	1,941 (15.3)	.024
Herniated disc	426 (10.1)	2,657 (21.0)	.000
Spondylolisthesis	1,264 (29.8)	1,852 (14.6)	.000
Scoliosis/kyphosis	105 (2.5)	261 (2.1)	.110
Failed prior surgery	101 (2.4)	224 (1.8)	.012
Other	27 (0.6)	75 (0.6)	.750
Approach, n (%)			
Anterior	3,701 (87.2)	11,508 (90.8)	.000
Posterior	406 (9.6)	874 (6.9)	.000
Anterior and posterior	114 (2.7)	213 (1.7)	.000
Unspecified	25 (0.6)	73 (0.6)	.926
Fusion, n (%)			.847
Primary	4,025 (94.8)	11,998 (94.7)	
Revision	221 (5.2)	669 (5.3)	
Year of surgery, n (%)			.999
2002	14 (0.3)	42 (0.3)	
2003	108 (2.5)	321 (2.5)	
2004	264 (6.2)	793 (6.3)	
2005	411 (9.7)	1,233 (9.7)	
2006	557 (13.1)	1,664 (13.1)	
2007	587 (13.8)	1,740 (13.7)	
2008	708 (16.7)	2,118 (16.7)	
2009	754 (17.8)	2,233 (17.6)	
2010	843 (19.9)	2,524 (19.9)	

rhBMP, recombinant human bone morphogenetic protein.
* p values were calculated using the chi-square or *t* test.

Recombinant human bone morphogenetic protein use and cancer incidence

During our study period, 1,342 patients were diagnosed with cancer: 354 (8.34%) in the rhBMP group and 988 (7.80%) in the non-rhBMP group. The incidence rate was similar between the two groups: 11.2 per 1,000 person years in the rhBMP group and 10.4 per 1,000 person years in the non-rhBMP group (HR, 1.07; 95% CI, 0.95–1.21; Table 2). The aHR was 0.96 (95% CI, 0.84–1.09) controlling for the site of fusion, the surgical approach, and the diagnosis. This lack of association remained throughout the 14 years of follow-up (Fig. 2). Similarly, we were unable to find an association of rhBMP application and any of the 12 most common individual cancer types (Table 2). The rate of cancer was also not different between the two groups based on fusion site (cervical or lumbar) or type of surgical approach (anterior, posterior, or combined anterior/posterior; Table 3).

Recombinant human bone morphogenetic protein use and cancer-related mortality

Among the individuals with a diagnosis of cancer after undergoing spinal fusion, mortality caused by cancer was similar between groups, aHR, 0.92 (95% CI, 0.69–1.22). The results were similar following a diagnosis of lung/bronchus, breast, lymphohematopoietic, prostate, and melanoma cancers (Table 3).

Discussion

The potential or real risk of cancer associated with environmental man-made substances that come in contact with humans is of enormous public interest, resulting in ongoing debate regarding causation [12,13]. The introduction of genetically recombinant implanted therapeutic agents for elective nononcologic surgical interventions could conceivably create a hitherto unknown oncogenic risk for receiving patients [14,15]. The potential to miss out on a potential cancer risk of de novo devices or therapeutic agents is real, even in well-designed conventional clinical studies, as their focus usually targets nonrelated outcomes and usual enrollment criteria for elective procedures often exclude patients with history of neoplastic disorders. Moreover, the proscribed observation window for most pharmaceutical and device-related studies rarely exceeds a few years, simply for practical purposes. This background helps put into perspective the considerable echo of the initial publication of the potential oncogenic effect of rhBMP used in the initial FDA studies for applications in the lumbar spine.

From their basic structure, BMPs belong to a class of molecules capable of transforming growth factor-β toward de novo bone formation [16]. This effect, however, has in vitro been shown to result in both, bone formation and tumor disease development [16,17]. Through their ability to interact with transforming growth factor-β, BMPs have

Table 2
Cancer rate by rhBMP use at different anatomic sites

Outcome	No. of cancers	Incidence rate*		Unadjusted HR	Adjusted HR†
		rhBMP	Non-rhBMP	(95% CI)	(95% CI)
All cancers‡	1,342	11.2	10.4	1.07 (0.95, 1.21)	0.96 (0.84, 1.09)
Cancer type by site§					
Breast	242	2.0	1.9	1.08 (0.81, 1.43)	0.90 (0.66, 1.22)
Lung/bronchus	179	1.5	1.4	1.08 (0.78, 1.51)	0.99 (0.69, 1.41)
Prostate	148	1.3	1.1	1.15 (0.80, 1.64)	0.99 (0.67, 1.45)
Skin melanoma	112	1.1	0.8	1.31 (0.87, 1.96)	1.18 (0.76, 1.82)
Lymphohematopoietic	110	1.0	0.8	1.18 (0.78, 1.78)	1.06 (0.68, 1.65)
Colorectum	83	0.5	0.7	0.72 (0.41, 1.23)	0.73 (0.41, 1.30)
Central nervous system	68	0.7	0.5	1.44 (0.87, 2.39)	1.19 (0.69, 2.05)
Kidney	50	0.4	0.4	1.06 (0.56, 1.99)	1.22 (0.61, 2.43)
Bladder	45	0.3	0.4	0.65 (0.30, 1.39)	0.52 (0.23, 1.15)
Thyroid	30	0.3	0.2	1.09 (0.49, 2.45)	0.96 (0.40, 2.28)
Pancreas	26	0.2	0.2	0.90 (0.36, 2.24)	0.87 (0.33, 2.30)
Liver	24	0.3	0.2	1.80 (0.79, 4.11)	1.45 (0.59, 3.52)

* Per 1,000 person years.
† Adjusted for site of fusion, surgical approach, and diagnosis.
‡ Excludes nonmelanoma skin cancers.
§ Cancer types with >20 cases were included.

been shown to potentially play a role in tumor development and dissemination [17,18]. More detailed biological function studies have supported of a dual and balancing role of BMPs in regards to cancer development as well as cancer suppression [17]. Caused by the potential concern for BMP promoting tumor growth, it has remained contraindicated to be applied in the vicinity of a resected or extant tumor, as well as for patients with any known active malignancy, or those receiving treatment for a malignancy [19].

Results from previous efforts studying the potential association of rhBMP use in elective spine surgery and de novo cancer diagnoses have been mixed. In 2011, Carragee et al. [20] reported the results of industry-sponsored trials of rhBMP-2 as published in the peer-reviewed literature compared with data available from US FDA data summaries. He found a higher number of new cancer diagnoses in the investigational rhBMP group in contrast to the non-rhBMP group. There were a number of confusing or

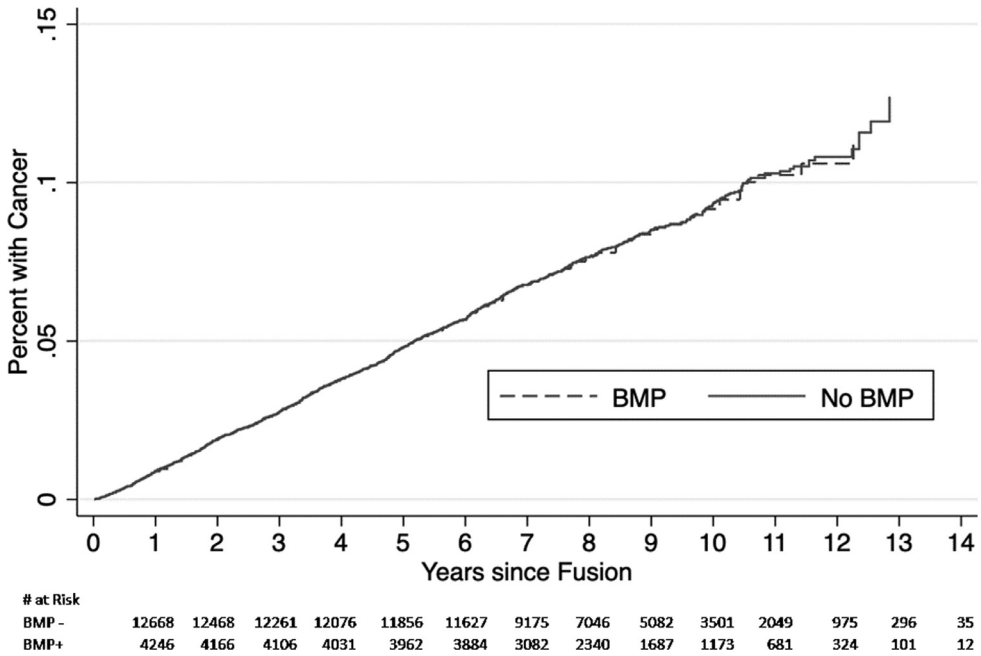

Fig. 2. Cumulative incidence of cancer according to rhBMP use in spinal fusion patients.

Table 3
Recombinant human bone morphogenetic protein use and mortality among those diagnosed with cancer

	rhBMP		Non-rhBMP		Adjusted HR[†]
Cancer type	Cancers	Deaths[*]	Cancers	Deaths[*]	(95% CI)
All cancer[‡]	354	68	988	233	0.92 (0.69, 1.22)
Lung/bronchus	47	28	130	73	0.95 (0.60, 1.51)
Breast	64	4	178	19	0.55 (0.18, 1.66)
Lymphohematopoietic	31	6	79	14	1.55 (0.50, 4.79)
Prostate	41	3	107	4	1.16 (0.26, 5.27)
Skin melanoma	34	2	78	3	1.65 (0.24, 11.41)

* Death attributed to cancer from death certificate.
† Adjusted for fusion site.
‡ Excludes nonmelanoma skin cancers.

limiting factors brought up in early discussion about these results. For one, the listed cancer types were heterogeneous and they were not of systemic or disseminated disease variants that clinicians would be most concerned about relative to a growth-enhancing substance such as rhBMP. Instead, the investigators reported isolated and localized cancers such as basal cell, squamous cell, prostate, and ocular cancers, but no patients presenting with bone or joint cancers, for instance. As a follow-up to this initial effort, a commissioned study known as the Yale University Open Data Access project published two meta-analyses based on available randomized trials in 2013. Their findings suggested a two- to threefold increase in cancer risk (with all sites combined) among rhBMP recipients compared with patients who were treated in conventional fashion [1,2]. Serious limitations of these meta-analyses revolved around the problem of the low incidence of de novo cancer diagnoses (<32 cancer cases), and relative brief follow-up relative to the potential for cancer development follow-up (≤4 years), as well as heterogeneous neoplasia diagnoses, making definitive conclusions regarding an actual cancer risk in rhBMP recipients inconclusive in the eyes of the authors.

To address these shortcomings, substantially larger observation groups with longer follow-up beyond the framework of formal controlled trials would be necessary. Detection of rare case events unfolding in large real life populations is a desirable feature of well-constructed and maintained patient registries. Although there are several limitations inherent to registry-derived analyses, they do afford an efficient observational-based study opportunity of large patient cohorts treated in real life scenarios with longer follow-up than available with formal FDA studies. They also provide a possibility to study off-label rhBMP use, both in terms of application (anterior and posterior cervical, posterior lumbar) as well as dosing, which could provide an enhanced insight into relatively rare but significant case events like cancer.

A large cohort study [4] assessed the effect of rhBMP on the risk of cancer in 146,278 Medicare beneficiaries treated with lumbar fusion surgery from 2003 to 2008. This study used two or more ICD-9-CM diagnosis codes and a single procedure code consistent with cancer therapy as identifiers for a positive diagnosis of malignant neoplasia. Based on this methodology, 17% of the non-rhBMP patients and 15.4% of the rhBMP group were reported to have a new cancer diagnosis within their average follow-up of 4.7 years. After accounting for potential confounders, the investigators concluded that there was absence of any association with cancer risk and rhBMP application (all types combined; aHR, 0.99; 95% CI, 0.95−1.02). Furthermore, they could not demonstrate any association of rhBMP use with any specific type of cancer. Similarly, a more recent case-cohort study of 7,278 Medicare beneficiaries with a median 2.4 years of follow-up found no correlation of rhBMP association and cancer (HR, 0.94; 95% CI, 0.84−1.05) [3]. Additionally, three separate studies using a commercially available database (MarketScan, Truven Health Analytics, Ann Arbor, MI, USA) [5,7,21] also failed to identify an increased risk of cancer with rhBMP use with an average follow-up ranging from 1.5 to 5.0 years. Likewise, our previous study, which used a unique combination of high quality state mandated and curated databases, could not demonstrate an association between rhBMP and cancer risk after elective adult spine fusions performed in the State of Washington. Similar to the previous studies quoted above, our study was limited by relatively short follow-up relative to the question of de novo cancer disease [9].

In contrast to these previous studies, our current study sought to address the more time-limited follow-up range of previous comparison studies by including only individuals with a minimum of 5 years of follow-up, thus extending the follow-up period to an average of 8.0 years (range 5.0−14.0 years). The results confirmed our earlier reported results that rhBMP use in adult elective spinal fusion surgery in our state was not associated with an increased cancer risk or death related to cancer after a diagnosis of cancer even when viewed from the perspective of a much longer follow-up [9]. This lack of a demonstrable association of cancer-related illness or death and rhBMP application was consistent across a range of cancer types, and was seen independent of the site of fusion (lumbar or cervical) or type of fusion (anterior or posterior) throughout our extended follow-up surveillance period.

It is important to realize several potential inherent limitations to our study. Accuracy of all administrative databases can be adversely affected by improper coding and subsequent misclassifications. In principle, misclassifications associated with treatment or diagnosis derived from the CHARS database likely should be nondifferential with respect to the two comparison groups. From our data sources, we were unable to assess the effect of disease severity, invasiveness of spinal surgery, and actually administered rhBMP-2 doses to aid in study of potential exposure-related factors surrounding cancer risk. One previous systematic review suggested cancer risk might be dose dependent when comparing two studies of rhBMP-2, noting a stronger association using the non-FDA approved higher dose rhBMP-2 formulation of 40 mg [22]. However, when using surgical approach types as a potential surrogate of rhBMP dose exposure, we did not observe an increased risk in patients who received a posterior fusion with a potential for an increased dose of rhBMP-2 compared with anterior fusions with likely more limited fusion levels. It is also possible that those patients who received rhBMP were in general more involved spine cases. It is, however, unclear how this would affect a potential rhBMP-cancer association. Our sample showed a smaller proportion of patients receiving off-label rhBMP-2 applications for cervical spine fusion surgery compared with the control group. This discrepancy likely reflects the more limited off-label clinical use of BMP in anterior cervical spine surgery given potential safety concerns with respect to airway obstruction. As we were able to identify the anatomic surgical site from the data bases (ie, cervical vs. lumbar fusion), we could statistically adjust for this disparity in our analysis. Furthermore, rates of cancer could also be influenced by a potential imbalance in the comparison groups of patients who have out-migrated from Washington State after undergoing their index procedure. To account for this in our original analysis, we had linked our data to the State's DOL data to identify "known" residents as our targeted study population. For purposes of the study, we had defined "known" residents as individuals holding a valid state license renewal within 5 years of the index procedure. As we found that any potential oncogenic effect of rhBMP was similar between known residents and all patients in our study cohort, we concluded that any effect of out-migration would therefore be nondifferential [9].

The results of our long-term follow-up study again support absence of a causal relationship of rhBMP administration and an increased cancer risk or mortality after a cancer diagnosis in adults in the setting of elective spine fusion surgery. We therefore believe that the consistently reported findings of nonassociation of cancer diagnosis and rhBMP administration derived from several large database surveillance cohort studies, including our own longer term follow-up study, provide a more reassuring clinical picture in terms of the oncogenic device safety compared with the early positive results reported in the original RCTs with their critical limitations of their likely incomplete ascertainment of cancer cases, their reliance on short mandated FDA follow-up periods, and the relatively smallish cohort sizes not suitable for rare case event evaluation.

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