A commentary by Kern Singh, MD, et al., is linked to the online version of this article at jbjs.org.

Bone Morphogenetic Protein Use and Cancer Risk Among Patients Undergoing Lumbar Arthrodesis

A Case-Cohort Study Using the SEER-Medicare Database

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Background: Recombinant bone morphogenetic proteins (BMPs) are growth factors utilized in lumbar arthrodeses. Limited data from randomized trials suggest that BMP may increase cancer risk. We sought to evaluate cancer risk and mortality following the use of BMP in lumbar arthrodesis.

Methods: Within the linked Surveillance, Epidemiology, and End Results (SEER) Program-Medicare cohort, we conducted a case-cohort study of 7,278 individuals who were ≥ 65 years of age and had undergone a lumbar arthrodesis from 2004 to 2011. Of these patients, 3,627 were individuals in a 5% random subcohort of Medicare enrollees in SEER areas including 191 who developed cancer, and there were 3,651 individuals outside the subcohort who developed cancer. Weighted Cox proportional-hazards regression was used to estimate hazard ratios (HRs) and 95% confidence intervals (95% CIs) for cancer on the basis of exposure to BMP.

Results: In the SEER-Medicare subcohort, 30.7% of individuals who underwent a lumbar arthrodesis received BMP. BMP was not associated with overall cancer risk in univariate analyses (HR, 0.92 [95% CI, 0.82 to 1.02]) or after adjustment for demographic characteristics, comorbidities, hospital size, history of cancer, and calendar year (adjusted HR, 0.94 [95% CI, 0.84 to 1.05]). Individual cancer types were also not significantly elevated ($p > 0.05$ for all) in BMP users compared with nonusers. In addition, BMP use was not associated with a new cancer in people who had cancer prior to undergoing lumbar arthrodesis (adjusted HR, 1.04 [95% CI, 0.71 to 1.52]) or with mortality after a cancer diagnosis (adjusted HR, 1.05 [95% CI, 0.93 to 1.19]).

Conclusions: In a large population of elderly U.S. adults undergoing lumbar arthrodesis, BMP use was not associated with cancer risk or mortality.

Level of Evidence: Therapeutic Level III. See Instructions for Authors for a complete description of levels of evidence.

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Lumbar spinal arthrodesis is an increasingly common procedure intended to alleviate back pain attributed to degenerative spine conditions and is performed on more

than 150,000 U.S. patients per year¹. The procedure involves the arthrodesis of adjacent vertebral bodies, with autologous bone graft harvested from the patient's iliac crest or bone-graft

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Fig. 1
Study design for case-cohort study examining BMP use and cancer risk. The source population of 72,540 individuals who underwent a lumbar arthrodesis between 2004 and 2011 was estimated by multiplying the 5% subcohort population ($n = 3,627$) by 20.

substitutes. Bioengineered recombinant human bone morphogenetic proteins (BMP-2 and BMP-7) were approved by the U.S. Food and Drug Administration (FDA) in 2002 to facilitate bone fusion² and are currently used in ~25% of lumbar arthrodeses in the United States¹.

BMPs are growth factors and signaling molecules that promote bone formation and remodeling. BMPs regulate cell differentiation and growth in several tissues and are expressed on cancer cell lines^{3,4}, suggesting that BMP may promote cancer development. Of concern, analyses of randomized trial data have suggested that BMP use may increase the risk of cancer^{5,6}. These studies were limited by small samples (<30 cancer outcomes across the trials), grouped together by heterogeneous cancer types, and were based on short follow-up. Subsequently, larger observational studies that utilized administrative claims data did not confirm an elevation in cancer risk with BMP use⁷⁻⁹. However, reliance on claims for ascertainment of cancer outcomes is prone to misclassification^{10,11}.

Prior studies have not examined the association with BMP among people with a history of cancer prior to the surgical procedure, who may be at greater risk of subsequent cancer at another site¹²; indeed, “active malignancy” is listed by the FDA as a contraindication for BMP use^{2,13,14}. Because previous observational studies did not include information on prior cancers, they may have underestimated the risk of cancer with BMP use, especially if patients who were given BMP were less likely to have had a prior cancer¹². Finally, it is unknown whether patients who develop a cancer after exposure to BMP may have a shortened survival, indicating increased aggressiveness of their tumor. To more definitively assess the association of BMP with cancer risk and subsequent mortality, we utilized the Surveillance, Epide-

miology, and End Results (SEER) Program-Medicare linked database¹⁵. Our study evaluated elderly U.S. adults, who are an important population given the rise in the prevalence of both spine surgical procedures and cancer with increasing age.

Materials and Methods

Study Population and Design

SEER-Medicare covers a population of ~9.4 million U.S. Medicare beneficiaries living in SEER areas from 2004 to 2011¹⁶ (Fig. 1). Medicare is the U.S. government insurance program that provides hospital, medical, and surgical benefits for almost all people who are ≥65 years of age¹⁵. The SEER program comprises cancer registries that cover ~28% of the U.S. population and have reliable and detailed ascertainment of cancer diagnoses¹⁵⁻¹⁷.

Medicare beneficiaries (those ≥65 years of age) living in SEER areas who had undergone a lumbar arthrodesis between 2004 and 2011 were eligible for this analysis. The SEER-Medicare database includes Medicare claims data for 100% of SEER cancer cases in addition to a random 5% sample of Medicare beneficiaries in SEER areas. We used these data to conduct a case-cohort study of cancer among recipients of lumbar arthrodesis¹⁸. The case-cohort design is an efficient way to analyze large cohort data, incorporating the assessment of a random subset of the cohort along with all cases of the outcome of interest that arise in the cohort¹⁸; this approach allowed us to maximally utilize the available SEER-Medicare data. Specifically, we conducted a cohort study with a 5% subcohort of patients undergoing lumbar arthrodesis, supplemented with 100% of cancer outcomes in all recipients (Fig. 1).

Lumbar arthrodesis was defined using the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) procedure codes 8104 to 8108 and 8134 to 8138 reported in the discharge summary of hospital claims¹⁹. BMP use was defined using the ICD-9-CM procedure code 84.52, which includes both BMP-2 and BMP-7, recorded in hospital claims. Other covariates such as medical comorbidities, indications for lumbar arthrodesis, details of the surgical procedure, and hospital characteristics were ascertained utilizing ICD-9-CM codes and Current Procedural Terminology,

TABLE I Characteristics of the 3,627 Patients in the 5% Subcohort Who Had Undergone Lumbar Spinal Arthrodesis from 2004 to 2011

Characteristic	BMP Nonusers (N = 2,472)*	BMP Users (N = 1,155)*	P Value†
Age at the time of the lumbar arthrodesis (yr)	73.3 ± 5.8	72.9 ± 5.6	0.07
Sex			0.41
Male	923 (37.3%)	412 (35.7%)	
Female	1,549 (62.7%)	743 (64.3%)	
Race or ethnicity‡			0.92
White	2,239 (90.6%)	1,040 (90.0%)	
Black	128 (5.2%)	62 (5.4%)	
Asian	46 (1.9%)	26 (2.3%)	
Hispanic	21 (0.9%)	11 (1.0%)	
Other	37 (1.5%)	15 (1.3%)	
Year of the lumbar arthrodesis			0.01
2004 to 2005	516 (20.9%)	186 (16.1%)	
2006 to 2007	528 (21.4%)	263 (22.8%)	
2008 to 2009	656 (26.5%)	326 (28.2%)	
2010 to 2011	772 (31.2%)	380 (32.9%)	
Principal surgical procedure			<0.001
Anterior lumbar interbody arthrodesis	172 (7.0%)	150 (13.0%)	
Posterolateral spine arthrodesis	168 (6.8%)	46 (4.0%)	
Lumbar and lumbosacral arthrodesis, lateral transverse process technique	474 (19.2%)	196 (17.0%)	
Posterior lumbar interbody arthrodesis, transforaminal lumbar interbody arthrodesis, dorsal arthrodesis of the anterior column	1,658 (67.1%)	763 (66.1%)	
Indications for lumbar arthrodesis§			
Degenerative disease	2,196 (88.8%)	1,045 (90.5%)	0.007
Fracture or dislocation	142 (5.7%)	41 (3.5%)	0.003
Surgical aftercare or previous surgical procedure	250 (10.1%)	140 (12.1%)	0.10
Other	137 (5.5%)	40 (3.5%)	0.005
No. of vertebrae fused			0.29
2 to 3	2,204 (89.2%)	1,016 (88.0%)	
≥4	268 (10.8%)	139 (12.0%)	
Charlson-Deyo Comorbidity Index prior to lumbar arthrodesis (points)	1.9 ± 2.1	1.7 ± 1.8	0.003
Prevalent cancer prior to lumbar arthrodesis#			0.002
No	2,150 (87.0%)	1,045 (90.5%)	
Yes	322 (13.0%)	110 (9.5%)	
No. of doctor visits in year prior to lumbar arthrodesis			0.08
0 to 10	642 (26.0%)	320 (27.7%)	
11 to 16	673 (27.2%)	327 (28.3%)	
17 to 23	567 (22.9%)	284 (24.6%)	
≥24	590 (23.9%)	224 (19.4%)	
Type of hospital for lumbar arthrodesis**			0.16
Voluntary nonprofit	1,733 (70.1%)	845 (73.2%)	
Proprietary	384 (15.5%)	167 (14.5%)	
Government	352 (14.2%)	143 (12.4%)	
No. of beds in the hospital for lumbar arthrodesis			0.001
≤255	673 (27.2%)	268 (23.2%)	
256 to 384	667 (27.0%)	274 (23.7%)	

continued

TABLE 1 (continued)

Characteristic	BMP Nonusers (N = 2,472)*	BMP Users (N = 1,155)*	P Value†
385 to 527	553 (22.4%)	293 (25.4%)	0.09
≥528	579 (23.4%)	320 (27.7%)	
Reason for ending follow-up			
End of study (administrative censoring)	1,839 (74.4%)	905 (78.4%)	
Incident cancer	135 (5.5%)	56 (4.9%)	
Discontinuation of Medicare Part A or B	205 (8.3%)	89 (7.7%)	
Migration to a non-SEER area	61 (2.5%)	22 (1.9%)	
Death	232 (9.4%)	83 (7.2%)	

*The values are given as the number of patients, with the percentage in parentheses, or as the mean and the standard deviation. †The p values were calculated using the chi-square or t test. ‡Two patients did not report a race or ethnicity. §These categories are not mutually exclusive. #This was cancer detected in the SEER database prior to lumbar arthrodesis (including cancers detected before and after the initiation of Medicare).

**Data were missing for 3 patients in the BMP nonuser group for this category.

Fourth Edition (CPT-4) codes from hospital, provider, and outpatient claims files¹⁶. Medical comorbidities were defined using the Charlson-Deyo Comorbidity Index score utilizing claims in the 1-year period prior to lumbar arthrodesis^{20,21}.

Statistical Analyses

BMP Use and Cancer Risk

We compared cancer risk in patients with and without exposure to BMP at the time of their first lumbar arthrodesis performed between 2004 and 2011. The follow-up time began at the date of each patient's arthrodesis, with exposure to BMP defined as use of the biological agent at the time of the index procedure. Patients were followed until they migrated out of a SEER area, discontinued Medicare Part A or Part B coverage (or entered a health maintenance organization, at which point medical claims are no longer submitted to Medicare), died, or survived through the end of the follow-up on December 31, 2011. Cancers diagnosed only at autopsy or by death certificate were not included as outcomes.

We considered risk for cancer overall, for cancers classified according to their stage at diagnosis, and for individual cancer types. In our primary analysis of overall cancer risk, we only counted a person's first cancer diagnosis following their lumbar arthrodesis. People who had a cancer diagnosed prior to the lumbar arthrodesis were included in this analysis, because they were still at risk for other cancer types. However, to examine specific cancer types, we excluded individuals with a prevalent diagnosis of the cancer of interest at baseline, and the remaining individuals were followed for that cancer without censoring for other types of cancer.

Weighted Cox proportional-hazards regression (SURVEYPHREG procedure in SAS 9.3; SAS Institute) was used to estimate hazard ratios (HRs) and 95% confidence intervals (95% CIs) assessing the association between BMP treatment and cancer risk. The weights incorporated the case-cohort sampling fractions (i.e., weight = 1 for cancer cases, because 100% were sampled, and weight = 20 for cancer-free individuals, because 5% were sampled)²². Regression models were adjusted for age at the time of the lumbar arthrodesis (continuous), sex, race, Charlson-Deyo Comorbidity Index score (0, 1 to 3, or ≥4 points), history of cancer, and 2 factors associated with BMP use (size of hospital, as captured by the number of beds, and year of the lumbar arthrodesis). In addition, cumulative incidence curves were utilized to depict the overall cancer incidence comparing BMP users and nonusers²³. We also report results for a simple cohort analysis, restricting consideration to individuals in the 5% subcohort and cancer outcomes that arose only in that subset.

Our primary analyses categorized patients by their BMP status at the time of the first lumbar arthrodesis. A subset of patients (9.4%) underwent at least 1 additional lumbar arthrodesis between 2004 and 2011. Therefore, in a sensitivity analysis, we treated BMP as a time-dependent exposure. In this analysis, an

individual was classified as BMP-exposed after the first surgical procedure utilizing BMP. In other words, we updated BMP status if an unexposed person received BMP at a later surgical procedure date, but once an individual received BMP, he or she was considered to be BMP-exposed regardless of whether BMP was utilized in subsequent lumbar arthrodeses. In addition, we separately assessed the cancer risk among patients who received BMP at ≥2 surgical procedures, utilizing a similar time-updated exposure assessment.

BMP Use and Cancer Risk Among Subgroups of Interest

We also examined associations with BMP in several subgroups of interest. Although Medicare claims data do not include BMP dosage, patients who undergo complex operations (i.e., more vertebrae fused) may be more likely to receive a higher dose. We therefore conducted stratified analyses according to the number of vertebrae fused during the surgical procedure. In addition, we separately stratified results by the type of lumbar arthrodesis performed, given that the FDA has only approved BMP for a subset of arthrodeses (i.e., anterior lumbar interbody arthrodeses). We also stratified by history of cancer prior to the lumbar arthrodesis, to examine the risk of a second cancer. Prevalent cancers detected prior to lumbar arthrodesis were defined using the SEER database and included all cases detected while living in SEER areas after the registries were initiated (i.e., including before 65 years of age, as Medicare benefits begin at 65 years of age). The first 9 SEER-area registries were initiated in 1973 to 1975, and 8 subsequent areas were added from 1992 to 2000¹⁵⁻¹⁷, indicating that, for some individuals, this measure of cancer history is restricted to ascertainment of recent cancers.

BMP Use and Risk of Mortality

To examine if BMP adversely affects the progression of cancer, we compared overall and cancer-specific mortality between BMP users and nonusers in those who developed cancer. Individuals were followed from cancer diagnosis until death or December 31, 2011. Cause-of-death information was missing on 251 individuals, who were excluded from the cancer-specific mortality analyses. We report differences in overall and cancer-specific mortality, for all patients with cancer and for those with the 4 most common cancers.

Results

Study Population Characteristics

Approximately 72,540 Medicare beneficiaries who were ≥65 years of age in SEER areas had undergone lumbar arthrodesis from 2004 to 2011 (i.e., the source population) (Fig. 1). In this case-cohort study, we evaluated a 5% random subcohort

TABLE II BMP Use and Subsequent Cancer Risk at Different Anatomical Sites in This Case-Cohort Study

Cancer Type	Total Cases	BMP Users*	Unadjusted HR†	Adjusted HR†‡
Non-cases in the subcohort	3,436	1,099 (32.0%)	Reference	Reference
All cancers	3,842	1,126 (29.3%)	0.92 (0.82 to 1.02)	0.94 (0.84 to 1.05)§
By cancer stage				
Local	1,306	395 (30.3%)	0.95 (0.82 to 1.10)	0.96 (0.83 to 1.12)
Regional	624	189 (30.3%)	0.96 (0.79 to 1.16)	0.95 (0.78 to 1.15)
Distant	784	218 (27.8%)	0.84 (0.71 to 1.01)	0.88 (0.74 to 1.06)
Local or regional prostate cancer#	487	137 (28.1%)	0.85 (0.69 to 1.06)	0.89 (0.69 to 1.16)
Unknown	641	187 (29.2%)	0.91 (0.75 to 1.10)	0.96 (0.79 to 1.18)
By cancer type**				
Lung	632	207 (32.8%)	1.09 (0.90 to 1.30)	1.14 (0.94 to 1.38)
Prostate	549	149 (27.1%)	0.82 (0.66 to 1.00)	0.84 (0.66 to 1.08)
Breast	548	155 (28.3%)	0.89 (0.73 to 1.10)	0.86 (0.69 to 1.07)
Colorectum	289	85 (29.4%)	0.94 (0.72 to 1.23)	0.97 (0.74 to 1.28)
Bladder	219	61 (27.9%)	0.86 (0.63 to 1.18)	0.90 (0.65 to 1.25)
Non-Hodgkin lymphoma	214	59 (27.6%)	0.84 (0.62 to 1.15)	0.89 (0.64 to 1.22)
Melanoma	176	48 (27.3%)	0.82 (0.59 to 1.16)	0.87 (0.62 to 1.24)
Pancreas	148	42 (28.4%)	0.89 (0.61 to 1.28)	0.88 (0.60 to 1.28)
Kidney or renal pelvis	138	38 (27.5%)	0.84 (0.57 to 1.23)	0.85 (0.57 to 1.26)
Leukemia	118	26 (22.0%)	0.64 (0.41 to 0.99)	0.65 (0.41 to 1.02)
Uterus	82	32 (39.0%)	1.41 (0.90 to 2.22)	1.37 (0.87 to 2.17)
Myeloma	78	21 (26.9%)	0.79 (0.48 to 1.32)	0.78 (0.46 to 1.30)
Oral cavity or pharynx	68	21 (30.9%)	1.01 (0.60 to 1.69)	1.02 (0.60 to 1.74)
Stomach	64	18 (28.1%)	0.87 (0.50 to 1.52)	0.89 (0.50 to 1.56)
Ovary	58	16 (27.6%)	0.84 (0.47 to 1.50)	0.82 (0.46 to 1.48)
Thyroid	44	—††	0.50 (0.23 to 1.10)	0.50 (0.22 to 1.10)
Brain	43	17 (39.5%)	1.46 (0.79 to 2.69)	1.45 (0.76 to 2.76)
Liver	42	17 (40.5%)	1.51 (0.81 to 2.80)	1.61 (0.84 to 3.10)
Esophagus	37	16 (43.2%)	1.72 (0.90 to 3.29)	1.88 (0.93 to 3.79)
Larynx	21	—††	2.07 (0.87 to 4.92)	2.13 (0.79 to 5.72)
Bone or joint	—††	—††	1.41 (0.24 to 8.42)	2.62 (0.31 to 21.6)
Miscellaneous or unknown	208	57 (27.4%)	0.85 (0.62 to 1.17)	0.89 (0.65 to 1.24)

*The values are given as the number of patients, with the row percentage in parentheses. †The values are given as the HR, with the 95% CI in parentheses. ‡HRs are adjusted for age, race, sex, comorbidity index, history of cancer, size of hospital, and calendar year of lumbar arthrodesis. §The results were similar when also adjusting for the type of principal surgical procedure prior to arthrodesis, with an adjusted HR of 0.94 (95% CI, 0.84 to 1.05). #SEER groups local and regional stages together for prostate cancer. **Cancer types with >20 cases were included. Bone and joint cancers were also assessed, despite their rarity, given that BMP is a bone growth factor. ††Sample sizes are not shown for <11 cases, in accordance with the SEER-Medicare data use policy.

of these individuals ($n = 3,627$). In addition, we included all incident cancers arising in the entire source population after lumbar arthrodesis ($n = 3,842$), of which 191 (5.0%, as expected) were in the subcohort (Fig. 1).

Among the 3,627 individuals in the 5% subcohort, 1,115 (30.7%) received BMP during the first lumbar arthrodesis. The median follow-up time after lumbar arthrodesis was 2.4 years (range, 0 to 8 years) and was the same in BMP users and nonusers (median, 2.4 compared with 2.4 years; $p = 0.89$). BMP users were similar ($p > 0.05$ for all comparisons) to BMP nonusers with regard to age, sex, and race (Table I). BMP users were significantly more likely ($p \leq 0.01$ for all) to undergo a lumbar arthrodesis in

more recent years, to undergo an anterior lumbar interbody arthrodesis (13.0% compared with 7.0%), to have degenerative spine disease, and to undergo a surgical procedure at a larger hospital (Table I). Additionally, BMP users were less likely to have had a cancer diagnosis prior to the lumbar arthrodesis (9.5% compared with 13.0%, $p = 0.002$) and had fewer comorbidities prior to the surgical procedure (mean Charlson-Deyo Comorbidity Index of 1.7 points compared with 1.9 points, $p = 0.003$) (Table I).

BMP Use and Cancer Risk

Within the 5% subcohort, the overall cancer incidence was 18.8 cases per 1,000 person-years among the patients who did not

TABLE III BMP Use and Cancer Risk Among Subgroups of Patients in This Case-Cohort Study

Subgroup	Patients without Incident Cancer in the Subcohort*	Cancer Cases*	Unadjusted HR†	Adjusted HR††
No. of vertebrae fused in lumbar arthrodesis				
2 to 3	3,055	3,411	0.93 (0.83 to 1.05)	0.95 (0.84 to 1.07)
≥4	381	431	0.81 (0.59 to 1.11)	0.74 (0.51 to 1.07)
Type of lumbar arthrodesis				
Anterior lumbar interbody arthrodesis§ (FDA-approved)	310	249	0.91 (0.63 to 1.32)	0.94 (0.63 to 1.40)
Non-anterior lumbar interbody arthrodesis (off label)	3,126	3,593	0.92 (0.82 to 1.04)	0.94 (0.84 to 1.06)
No. of surgical procedures that utilized BMP#				
1	1,130	1,156	0.90 (0.81 to 1.00)	0.92 (0.82 to 1.03)
≥2	49	63	0.88 (0.56 to 1.40)	0.94 (0.58 to 1.52)
Cancer prior to first lumbar arthrodesis**				
Yes	695	863	0.98 (0.69 to 1.38)	1.04 (0.71 to 1.52)††
No	2,741	2,979	0.91 (0.81 to 1.02)	0.92 (0.82 to 1.04)††

*The values are given as the number. †The values are given as the HR, with the 95% CI in parentheses. ‡HRs are adjusted for age, race, sex, comorbidity index, size of hospital, history of cancer, and calendar year. §BMP is FDA-approved for anterior lumbar interbody arthrodeses, but not for other spinal arthrodeses. #BMP use is treated as a time-updated variable, with a trend of $p = 0.26$. **This was cancer detected in the SEER database prior to lumbar arthrodesis (including cancers detected before and after the initiation of Medicare). ††HRs did not adjust for history of cancer.

receive BMP compared with 17.1 cases per 1,000 person-years in the patients who received BMP. In the case-cohort analysis, which assessed all incident cancer events (including those outside the subcohort), the overall cancer risk was not associated with BMP use, both in an unadjusted analysis (HR, 0.92 [95% CI, 0.82 to 1.02]) and after multivariate adjustment (adjusted HR, 0.94 [95% CI, 0.84 to 1.05]) (Table II). This lack of an association held throughout the 8 years of follow-up after the surgical procedure (Fig. 2). The result was similar when we conducted an analysis limited to only the 5% subcohort, excluding cases outside the subcohort (adjusted HR, 0.94 [95% CI, 0.68 to 1.31]).

BMP use was not associated with localized-stage cancer (adjusted HR, 0.96 [95% CI, 0.83 to 1.12]), regional-stage cancer (adjusted HR, 0.95 [95% CI, 0.78 to 1.15]), or distant-stage cancer (adjusted HR, 0.88 [95% CI, 0.74 to 1.06]). Similarly, BMP use was not associated with risk of any of 21 individual cancer types or with miscellaneous or unknown cancers ($p > 0.05$ for all) (Table II). The results were similar when BMP use was considered as a time-varying covariate for patients undergoing >1 lumbar arthrodesis (adjusted HR, 0.92 [95% CI, 0.83 to 1.03] for overall cancer risk).

BMP Use and Cancer Risk Among Subgroups of Interest

Table III describes additional subgroup and sensitivity analyses. We assessed risk in 2 groups of patients who likely received a higher BMP dose: those with multiple vertebrae fused and

those who received BMP with multiple arthrodeses. BMP use was not associated with cancer risk among patients with ≥ 4 vertebrae fused (adjusted HR, 0.74 [95% CI, 0.51 to 1.07]) or among those with who received BMP in ≥ 2 surgical procedures

Number at risk*
No BMP use: 49430 37673 28016 20105 14956 10162 6075 2663 0
BMP use: 23052 18084 13179 9428 6604 3746 2265 543 0

Fig. 2

Cumulative incidence of cancer according to BMP use in patients who underwent lumbar spinal arthrodesis (fusion) in this case-cohort study. The asterisk indicates that the number of patients at risk of cancer at the start of each year of follow-up was estimated as 20 times the size of the 5% subcohort, given that 100% of the cancer cases were included in this study.

TABLE IV BMP Use and Mortality Among the 3,842 People Diagnosed with Cancer in This Case-Cohort Study

Cancer Type and BMP Use	No. of Cancer Cases	Deaths*	Adjusted HR†	Cancer-Specific Deaths*‡	Adjusted HR†
All cancers					
No BMP use	2,716	1,024 (37.7%)	Reference	774 (28.5%)	Reference
BMP use	1,126	405 (36.0%)	1.05 (0.93 to 1.19)	311 (27.6%)	1.07 (0.94 to 1.23)
Lung cancer§					
No BMP use	425	285 (67.1%)	Reference	237 (55.8%)	Reference
BMP use	207	126 (60.9%)	0.99 (0.79 to 1.24)	94 (45.4%)	0.89 (0.68 to 1.16)
Breast cancer§					
No BMP use	393	41 (10.4%)	Reference	15 (3.8%)	Reference
BMP use	155	14 (9.0%)	1.21 (0.63 to 2.34)	—#	1.84 (0.71 to 4.78)
Prostate cancer§					
No BMP use	400	53 (13.3%)	Reference	14 (3.5%)	Reference
BMP use	149	14 (9.4%)	0.74 (0.39 to 1.40)	—#	1.45 (0.44 to 4.72)
Colorectal cancer§					
No BMP use	204	72 (35.3%)	Reference	34 (16.7%)	Reference
BMP use	85	27 (31.8%)	1.00 (0.62 to 1.61)	11 (12.9%)	0.88 (0.43 to 1.80)

*The values are given as the number of patients, with the row percentage in parentheses. †The values are given as the HR, with the 95% CI in parentheses. HRs are adjusted for cancer stage, age, race, sex, comorbidity index, size of hospital, and calendar year. ‡The death date was based on information from Medicare, but the specific cause of death was based on SEER information. SEER cause-of-death information was missing on 251 individuals who had cancer. These individuals were excluded from the cancer-specific mortality analyses. §Analyses by cancer type were restricted to people who were diagnosed with that cancer type during follow-up. #Sample sizes are not shown for <11 cases, in accordance with the SEER-Medicare data use policy.

during follow-up (adjusted HR, 0.94 [95% CI, 0.58 to 1.52]). Additionally, there was no association between BMP and cancer among patients who underwent a surgical procedure that was FDA-approved for BMP use, specifically, anterior lumbar interbody arthrodesis (adjusted HR, 0.94 [95% CI, 0.63 to 1.40]), or in those who received BMP that was used off-label (adjusted HR, 0.94 [95% CI, 0.84 to 1.06]). We also observed no evidence of an association when restricting the analysis to individuals with a cancer diagnosis prior to the lumbar arthrodesis (adjusted HR, 1.04 [95% CI, 0.71 to 1.52]).

BMP Use and Risk of Mortality

Among the individuals who developed cancer after undergoing lumbar arthrodesis, overall mortality was similar in those who had and had not received BMP (adjusted HR, 1.05 [95% CI, 0.93 to 1.19]) (Table IV). Cancer-specific mortality was similar in BMP users and nonusers, following any diagnosis of cancer (adjusted HR, 1.07 [95% CI, 0.94 to 1.23]) or following lung, breast, prostate, or colorectal cancers (Table IV).

Discussion

This case-cohort study found that BMP usage during lumbar arthrodesis was not associated with subsequent cancer risk or progression after a cancer diagnosis in a large U.S. population of elderly Medicare beneficiaries. The lack of an association with cancer risk was consistent across a broad range of cancers and was observed among individuals who may have received a higher

BMP dose. These data provide evidence that BMP use with lumbar arthrodesis may not promote the development of cancer.

In our detailed analyses, BMP was not associated with risk for any of a large array of cancer types. BMP was also not associated with an increased risk of advanced-stage cancers (which might reflect an adverse effect on tumor behavior) or with cancer-specific mortality. As expected because of the FDA warning, we observed that patients who received BMP were less likely to have had a history of cancer, but, contrary to previous speculation¹², this difference did not materially affect the association with subsequent cancer risk, and BMP use was not associated with risk of developing a new cancer among people who previously had cancer.

BMPs are growth factors that regulate cell differentiation and growth in several tissues³. Concern has been raised that the therapeutic use of BMP and other growth factors and hormones, such as erythropoietin²⁴, salmon calcitonin²⁵, and parathyroid hormone²⁶, may increase cancer risk or may adversely affect progression and mortality after a cancer diagnosis. Notably, BMPs are members of the transforming growth factor beta-1 superfamily, which has a mechanistic role in tumor suppression and promotion²⁷, and several cancer cell lines express BMP or its receptors⁴. Nonetheless, BMP is applied locally, and systemic levels could perhaps be too low to affect the development of cancer at distant sites.

The results from previous studies have been mixed. Randomized trials have suggested a potential association between

BMP and subsequent cancer^{5,6}, and a recent meta-analysis of 5 trials yielded a result pointing to increased cancer risk after 2 years of follow-up (relative risk, 3.45 [95% CI, 1.98 to 6.00])⁶. However, that meta-analysis evaluated <30 cancer cases that developed over a limited period of follow-up time. Also, the outcomes in the trials comprised a heterogeneous grouping of diagnoses including non-melanoma skin cancers, which have a considerably lower risk of mortality compared with other cancers. In contrast to the randomized trials, 3 retrospective observational studies have suggested no association between BMP and cancer after 5 to 7 years of follow-up⁷⁻⁹. Those studies ascertained cancer cases using administrative claims, which are prone to misclassification^{10,11}, and excluded individuals with a prior cancer.

Our case-cohort study had several strengths. First, we incorporated reliable ascertainment of outcomes from SEER cancer registries, which have high completeness and accuracy standards¹⁶. Second, we based our analyses on a large and representative sample of Medicare beneficiaries in SEER areas, so there were a large number of evaluable cancer cases, and the results are largely generalizable to the U.S. elderly population^{15,16}. However, the results of this study may not generalize to younger populations (those who are <65 years of age). Third, we carefully assessed the comparability of patients who did and did not receive BMP. The groups were largely similar, although there were modest differences related to the calendar year of the lumbar arthrodesis, surgical procedures and indications for a surgical procedure, medical comorbidities including history of cancer, and hospital characteristics. Most of these characteristics are unrelated to cancer risk, and our adjusted analyses confirmed an absence of association between BMP and cancer.

The limitations of our study should also be acknowledged. Although Medicare claims for use of BMP likely had a high sensitivity and positive predictive value (given BMP's high expense)¹⁹, we could not assess dosage or carrier materials from these claims. A systematic review of randomized trials suggested a dose-response relationship²⁸, with the non-approved higher-dose BMP-2 formulation (40 mg of AMPLIFY [Medtronic]) manifesting the strongest association with cancer¹². Nonetheless, we did not observe evidence of increased cancer risk among 2 groups who may have received a higher BMP dose: patients undergoing a multilevel arthrodesis and patients receiving BMP in multiple surgical procedures. The present study also did not include information on non-melanoma skin cancers or cancer risk factors such as smoking status, although available information suggested that BMP users were largely

similar to nonusers in terms of demographic characteristics and comorbidities. However, given the current study's observational nature, we could not exclude confounding by indication or other unmeasured factors. We also could not exclude a delayed effect of BMP beyond the follow-up of 8 years. Finally, although we did not observe a significant association between BMP and bone or joint cancers, our study included few cases. Because BMP is a bone growth factor, further research may be warranted to better clarify whether there exists an association with these rare malignancies or in less common subgroups.

The results of this large, longitudinal, case-cohort study suggest that BMP use is not associated with risk of developing cancer or with mortality after a cancer diagnosis in older adults. Additional research should be especially aimed at addressing the remaining gaps in our understanding (e.g., associations of BMP with rare cancers and long-term effects). In the meantime, our results should be reassuring to clinicians and patients, and they support an approach in which the use of BMP in lumbar arthrodesis is guided by the consideration of potential benefits, harms, and costs. ■

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