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ORIGINAL REPORT

Recombinant human bone morphogenetic protein-2 and pancreatic cancer: a retrospective cohort study†

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ABSTRACT

Purpose To assess whether use of recombinant human bone morphogenetic protein-2 (rhBMP-2) during lumbar spinal fusion surgery affects subsequent risk of pancreatic cancer.

Methods Using US Medicare claims data, we performed a retrospective cohort study of patients who underwent lumbar spinal fusion surgery between October 2003 and December 2005. The study population, all >66 years, was identified from procedure codes for lumbar fusion. Claims for a bone morphogenetic protein (BMP) served as a proxy for rhBMP-2 exposure (another BMP product shared the same code). Pancreatic cancer was identified from claims indicating this diagnosis and cancer-specific therapy. We used Cox proportional hazard regression to estimate hazard ratios (HRs) and 95%CIs.

Results Of the 93 654 patients in the study, the mean age was 75 years, and 16.5% had claims for BMP. During a mean 1.4 years of follow-up, 91 patients were diagnosed with pancreatic cancer (eight in the BMP- and 83 in the non-BMP cohort). Consistent with previous research, pancreatic cancer was associated with older age, male gender, black race, and diabetes mellitus. Compared to those who did not receive BMP, patients exposed to BMP were not at increased risk of pancreatic cancer (adjusted HR = 0.70, 95%CI: 0.34–1.45). A chart review substudy validated the exposure measure; 52/55 patients with claims for BMP received rhBMP-2.

Conclusions In this large study of elderly patients who underwent lumbar fusion surgery, exposure to BMP was not associated with an increased risk of pancreatic cancer.

KEY WORDS — bone morphogenetic proteins; pancreatic cancer; cohort studies; Medicare

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INTRODUCTION

Bone Morphogenetic Proteins (BMPs) are endogenous signaling factors that play an important role in human bone formation and remodeling.[1] Bioengineered versions of these proteins have been developed for therapeutic use in spinal fusion,[2–4] orthopedic trauma,[5,6] and oral-maxillofacial surgery.[7] Recombinant human Bone Morphogenetic Protein-2 (rhBMP-2) was first approved in the US in 2002 for anterior lumbar interbody fusion to treat degenerative disc disease. In 2004, recombinant BMP-7 (OP-1 Putty) was approved for revision of posterloateral lumbar spine fusion. The BMPs obviate need for bone graft harvest from the patient's iliac crest, the traditional practice in spine fusion surgery. An estimated 150 000–250 000 patients undergo lumbar fusion each year in the US, predominantly for degenerative conditions such as spondylolisthesis, disk disorders, and spinal stenosis.[8,9]

While the BMPs are named for their ability to induce bone formation, they are now recognized to regulate cell differentiation and growth in other tissues as well.[10] In addition, several malignancies express BMP or BMP receptors, including cancers of the bone, breast, lung, prostate, and pancreas.[11] The US Food and Drug Administration (FDA) required post-approval *in vitro* studies to evaluate the effect of both

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BMPs on the growth of malignant tumors.[12,13] Use of both products was also contraindicated in the vicinity of a resected tumor.

In late 2004, Wyeth, the manufacturer of rhBMP-2, identified a potential signal of pancreatic cancer from its routine safety review of clinical trials in lumbar fusion. Across 14 randomized trials, in the 18 months following surgery, three cases of pancreatic cancer were observed among 1008 patients who received rhBMP-2, while none was observed in the 1007 patients who received usual care (2-sided Fisher's exact $p = 0.25$). Using US population-based cancer incidence rates as a reference,[14] the observed frequency of pancreatic cancer in the rhBMP-2 arm was substantially greater than expected (standardized incidence ratio (SIR) of 16, [95%CI 3.3–46.8]). No pancreatic cancers, however, were observed in smaller trials of rhBMP-2 in tibial fracture and maxillofacial surgery, and the overall incidence of cancer between treatment groups was similar.

To assess the risk of incident pancreatic cancer among patients exposed to rhBMP-2 during lumbar spinal fusion surgery, we conducted a retrospective cohort study using Medicare claims data. Medicare is a US government-sponsored health insurance plan that provides hospital, medical, and surgical benefits for people age 65 and older and people with certain disabilities.

METHODS

Study population

We identified Medicare patients who underwent lumbar fusion surgery between October 2003 (when Medicare began reimbursement for BMP) and December 2005. Patients were selected if their records contained a procedure code for lumbar fusion surgery, identified 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 or CPT-4 22558, 22630, 22612.

The study population was limited to patients continuously enrolled in fee-for-service Medicare for at least two years prior to the index surgery. Any patient with a claim for pancreatic cancer (ICD-9-CM 157.xx) during the two years prior to surgery was excluded. We also excluded participants in Medicare-funded health maintenance organizations (HMOs), as well as patients without continuous participation in Medicare Part B (which covers physician charges and outpatient services), since their claims histories may have been incomplete. Patients covered by Medicare due to end-stage renal disease or chronic disability were excluded because they are not representative of the overall Medicare population. Additionally, patients younger than 67 years were excluded—those younger than 65 did not reflect the general Medicare population, and those aged 65 or 66 had less than two years of pre-surgery enrollment data.

Data for this study were obtained from three Medicare sources: the Medicare Provider Analysis and Review (MEDPAR) file, which includes services provided in Medicare-certified inpatient hospitals; the Carrier file, which includes claims from physicians and free-standing ambulatory surgical centers; and the Outpatient file, which includes claims from outpatient providers, including outpatient hospital visits. The data sources were combined and records unduplicated by the encrypted beneficiary identification code, procedure, and date of service.

Exposure

A claim for BMP (ICD-9-CM 84.52) on the same day as fusion surgery was used as a surrogate for rhBMP-2 exposure, which cannot be specifically ascertained from Medicare claims. Although this code covers use of both BMPs marketed during the study period, rhBMP-2 and rhBMP-7, we suspected that utilization of rhBMP-2 was substantially greater.

Outcome

Incident pancreatic cancer was the outcome of interest for this study. Our primary case definition required two or more ICD-9-CM diagnosis codes for pancreatic cancer (code 157.xx) in any file type on different service dates *and* at least one procedure code consistent with cancer therapy, including gastrointestinal bypass surgery, pancreatectomy, radiation therapy, and chemotherapy (see Appendix for specific codes). We also evaluated two alternative case definitions that were less restrictive. The first required a single diagnosis code for pancreatic cancer, and the second required a diagnosis code for pancreatic cancer on more than one service date. We selected the most stringent (and presumably the most specific) case definition as the primary outcome based on concerns that one or even two diagnosis codes could represent either a false-positive (a provisional ''rule-out'' diagnosis that ultimately was recognized as benign disease) or a prevalent case.

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Covariates

We considered potential confounders including age, sex, race (white, black, other), length of follow-up, and previously described risk factors for pancreatic cancer, including diabetes mellitus, alcohol abuse, chronic pancreatitis, gastrectomy, and cholecystectomy (see Appendix for specific codes).[15]

Supplementary Medical Chart Study

To facilitate interpretation of the Medicare claims study, we conducted a chart review substudy among a separate sample of Medicare-eligible patients who underwent lumbar fusion surgery. The principal motivation was to evaluate the potential confounding effects of smoking, which is not captured in Medicare. Smoking is a strong risk factor for both pancreatic cancer[16–18] and poor bone healing,[19,20] we suspected that concerns about poor bone healing might lead to preferential use of BMP in smokers. The chart review substudy also sought to assess the positive predictive value of BMP claims and the proportion of BMP-2 use in patients who had claims for BMP. To identify medical records for review, we used the HealthCore Integrated Research Database, which includes claims data from several commercial carriers that offer Medicare Advantage Plan products or Medicare supplemental insurance. Records for a sample of patients were subsequently requested from hospitals and physician offices and abstracted by HealthCore's contract research staff.

Statistical analysis

Patients were followed from the date of index lumbar fusion surgery until diagnosis of pancreatic cancer, death, disenrollment, or end of the study period (December 2005), which ever came first. Individuals who underwent an initial operation without BMP and a subsequent procedure with BMP (about 1% of the cohort) were followed in the non-exposed group until the second surgery and thereafter in the exposed group.

We examined the univariate association of baseline characteristics (age, sex, race, diabetes, chronic pancreatitis, alcoholism, cholecystectomy, and BMP use) and pancreatic cancer using the χ^2 test. We then developed a multivariate Cox proportional hazard model to determine whether risk of pancreatic cancer was different for BMP recipients compared to non-recipients, adjusting for all factors associated with pancreatic cancer in univariate analyses as well as clinically important factors.

We repeated these analyses using alternative definitions of pancreatic cancer. We also used group-level smoking prevalence in BMP-exposed and non-exposed patients estimated from the HealthCore study to further adjust results for smoking.[21]

Finally, SIR (number of observed cases/number of expected cases) were calculated to assess whether the frequency of pancreatic cancer in BMP-exposed and -unexposed patient groups was consistent with that in the general US population. The expected numbers were obtained by applying age- and gender-specific incidence rates from the Surveillance Epidemiology and End Results (SEER) Program to the corresponding person–time.

Ethical approvals. The Medicare study was reviewed by the institutional review board at the University Hospitals Case Medical Center and deemed to be exempt from human subjects consideration. The Quorum Review Institutional Review Board (Seattle, Washington, US) granted a Waiver of Authorization for patient consent for the HealthCore substudy, which required use of protected health information.

Role of sponsor. This study was sponsored by Wyeth Pharmaceuticals, which manufactures rhBMP-2. Two authors (DM, YG) were full-time employees of Wyeth at the time of the study. Wyeth contracted with University Hospitals Case Medical Center for research services associated with the Medicare study and with HealthCore for the chart review substudy. It also paid for fees that Medicare charges to access its data, which were obtained by Dr Cooper. The company did not have access to protected health information for study participants. The sponsor had the opportunity to comment on the protocol and manuscript. Wyeth's policy is to publish results of all hypothesis-testing clinical studies regardless of the outcome.

RESULTS

We identified 154 689 Medicare beneficiaries with at least one procedure code for lumbar fusion surgery. Of these, we excluded 28 151 patients with end stage renal disease or chronic disability, 25 048 patients who were members of Medicare-sponsored HMOs, 39 927 patients who were less than 67 years old at the time of surgery, and 74 patients with a prior diagnosis code for pancreatic cancer (patients may have been excluded for more than one indication).

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The remaining 93 654 patients constituted the study population.

Descriptive statistics for the study population appear in Table 1. The mean age of the cohort was 74.7 ± 5.1 years; 66% were female and 94% white. The most common comorbidity was diabetes, while chronic pancreatitis, alcoholism, and previous cholecystectomy were much less common. Because codes for gastrectomy were present in only 0.08% of the cohort, this variable was not included in further analyses.

Codes for BMP administration were present for 16.5% of patients. In the BMP group, average follow-up duration was 1.04 ± 0.73 years (range: 1–1094 days); for the non-BMP group, it was 1.46 ± 0.86 years (range: 1–1095 days). BMP administration was more common among younger patients, women, blacks, and those with diabetes or prior cholecystectomy (Table 1). BMP administration was not associated with chronic pancreatitis or alcoholism. Nearly all study participants survived to the end of the follow-up period (BMP cohort, 96.9%; non-BMP cohort, 94.9%).

Using our primary (most restrictive) case definition, 91 patients were diagnosed with pancreatic cancer during follow-up. Using the most inclusive alternate case definition, there were 182 cases, and 129 cases using the second alternate case definition.

Among the 91 cases of pancreatic cancer, the median time to diagnosis was 0.86 years. Compared to the youngest age group (67–69), pancreatic cancer was more frequent among patients aged 70–79 but not among those older than 80 years (Table 2). Pancreatic cancer was more common among men, blacks, and people with diabetes.

In a multivariate Cox proportional hazards model (Table 3), factors independently associated with increased cancer risk (time to cancer diagnosis) included older age (except among those ≥80), male sex, black race, and diabetes. No significant associations were found with ''other'' race, chronic pancreatitis, alcoholism, or cholecystectomy. Consistent with the univariate analyses, BMP administration was not associated with pancreatic cancer (HR = 0.70, 95%CI: 0.34–1.45). Findings were similar in sensitivity analyses that used alternate case definitions (Supplemental Table 1).

Chart Review Substudy

Using HealthCore claims data, we identified 2011 patients who underwent lumbar fusion surgery between October 2003 and August 2006 and met other entry criteria for the Medicare study. Chart review was completed for 158 patients, and smoking status was recorded for 135 (85.4%). We found no substantial difference in smoking by BMP use. The

Table 1. Demographic and clinical characteristics of the study cohort

Variable	Non-BMP group (%)	BMP group (%)	*p* value
Patients	78 194 (83.5)	15 460 (16.5)	
Patient-years	114 498	16 018	
Median follow-up time, years (IQR)	1.47 (0.73–2.21)	0.91 (0.41–1.54)	
Patients with at least 12 months of follow-up	51 419 (65.76)	7043 (45.56)	
Mean age ± SD	74.6 ± 5.2	74.2 ± 5.1	<0.001
Age group			
67–69	16 554 (21.2)	3660 (23.7)	
70–74	26 956 (34.5)	5455 (35.3)	
75–79	21 742 (27.8)	4058 (26.3)	
80–84	10 254 (13.1)	1828 (11.8)	
≥85	2688 (3.4)	459 (3.0)	<0.001
Gender			
Male	27 071 (34.6)	5102 (33.0)	
Female	51 123 (65.4)	10 358 (67.0)	<0.001
Race			
White	73 537 (94.0)	14 567 (94.2)	
Black	2899 (3.7)	596 (3.9)	
Other	1758 (2.3)	297 (1.9)	0.029
Comorbid conditions			
Diabetes mellitus	27 777 (35.5)	5625 (36.4)	0.041
Chronic pancreatitis	744 (1.0)	140 (0.9)	0.590
Alcoholism	1068 (1.4)	225 (1.5)	0.383
Cholecystectomy	2321 (3.0)	539 (3.5)	<0.001

IQR, inter-quartile range; SD, standard deviation.

Table 2. Demographic and clinical factors associated with pancreatic cancer in univariate analysis

Variable	Pancreatic cancer		OR (95%CI)
	Yes *n* (%)	No *n* (%)	
Mean age (SD)	74.9 (4.1)		
67–69	11 (12.1)	20 203 (21.6)	1.00
70–74	37 (40.7)	32 374 (34.6)	2.10 (1.07, 4.11)
75–79	34 (37.4)	25 766 (27.5)	2.42 (1.23, 4.78)
80–84	7 (7.7)	12 075 (12.9)	1.06 (0.41, 2.75)
≥85	2 (2.2)	3145 (3.4)	1.17 (0.26, 5.27)
Gender			
Male	41 (45.1)	32 132 (34.3)	1.00
Female	50 (54.9)	61 431 (65.7)	0.64 (0.42, 0.96)
Race			
White	81 (89.0)	88 023 (94.1)	1.00
Black	7 (7.7)	3488 (3.7)	2.18 (1.00, 4.72)
Other	3 (3.3)	2052 (2.2)	1.59 (0.50, 5.03)
Comorbid conditions			
Diabetes	42 (46.2)	33 360 (35.7)	1.56 (1.03, 2.35)
Chronic pancreatitis	2 (2.2)	882 (0.94)	2.37 (0.58, 9.66)
Alcoholism	1 (1.1)	1292 (1.4)	0.80 (0.11, 5.73)
Cholecystectomy	4 (4.4)	2856 (3.1)	1.46 (0.54, 4.00)
BMP use	8 (8.8)	15 452 (16.5)	0.49 (0.24, 1.02)

OR, odds ratio; CI, confidence interval.

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Table 3. Factors associated with pancreatic cancer in unadjusted and multivariate Cox regression analyses

Variable	HR (95%CI)	
	Unadjusted	Multivariable-adjusted*
Age		
67–69	1.00	1.00
70–74	2.08 (1.06–4.08)	2.08 (1.06, 4.08)
75–79	2.41 (1.22–4.76)	2.42 (1.23, 4.78)
80–84	1.09 (0.42–2.82)	1.12 (0.44, 2.91)
≥ 85	1.27 (0.28–5.71)	1.33 (0.29, 6.01)
Sex		
Male	1.00	1.00
Female	0.61 (0.41–0.93)	0.61 (0.41, 0.93)
Race		
White	1.00	1.00
African American	2.28 (1.05–4.94)	2.24 (1.03, 4.89)
Other	1.63 (0.52–5.17)	1.48 (0.47, 4.68)
Comorbid conditions		
Diabetes	1.70 (1.12–2.56)	1.58 (1.04, 2.40)
Chronic pancreatitis	2.77 (0.68–11.26)	2.53 (0.62, 10.38)
Alcoholism	0.90 (0.13–6.47)	0.79 (0.11, 5.71)
Cholecystectomy	1.73 (0.63–4.70)	1.66 (0.60, 4.55)
BMP use	0.68 (0.33–1.42)	0.70 (0.34, 1.45)

HR, hazards ratio; CI, confidence interval.
*Results adjusted for each of the variables listed in the table.

prevalence of ever smoking at the time of surgery was 27 and 32% for patients with and without BMP, respectively. Using this group-level information[21] on smoking by BMP use, we further adjusted results from the multivariate Cox model in the main study, assuming a relative risk of 2.0 for pancreatic cancer among ever-smokers compared to never-smokers.[16–18] There continued to be no association between BMP administration and pancreatic cancer after this adjustment (HR = 0.73).

BMI data were recorded in 133/158 (84.2%) of charts reviewed. On average both cohorts were overweight. Mean BMI (± SD) was 29.5 ± 6.3 for patients who received BMP and 29.2 ± 5.0 for patients who did not.

All of the 57 patients with claim for BMP received BMP according to the medical record, indicating a positive predictive value of 100% for the BMP code. Chart review identified 96 patients who received BMP, and of the 55 (57.3%) patients for whom the type of BMP was specified, 52 (94.5%) received rhBMP-2. Because HealthCore data included only three of the six data fields for hospital procedures on the Medicare claim form (UB92), we judged that these data were insufficient to evaluate sensitivity of the 84.52 code. Not surprisingly, the prevalence of BMP exposure was substantially lower (5.2%) in this setting compared to that in the primary Medicare study (16.5%).

Comparison of pancreatic cancer incidence to SEER data

Among BMP recipients, there were eight identified cases of pancreatic cancer. Based on age- and gender-specific SEER data, 9.4 cases were expected, corresponding to an SIR of 0.85 (95%CI: 0.26–1.44). In the non-BMP group, 83 cases were identified and 48.5 cases were expected, corresponding to an SIR of 1.71 (95%CI: 1.34–2.08).

Sensitivity analysis

We explored the potential effect of an unmeasured confounder using an array-based sensitivity analysis[22] in scenarios that varied the prevalence of the confounder in each exposure group and strength of association between the confounder and study outcome (Table 4). Assuming a confounder-outcome association of a magnitude typically described for binary measures of obesity (highest vs. lowest quartile of BMI), tobacco use, or alcohol abuse (RR = 2)[16–18,23,24] one would expect the relative risk point estimate to move from 0.7 to 1.02 if the unmeasured confounder were present in 30% of exposed and 90% of unexposed patients. Some scenarios involving stronger confounders yielded higher adjusted relative risks, but they required similarly extreme assumptions about confounder prevalence.

DISCUSSION

In this large retrospective cohort study of Medicare patients who underwent lumbar spinal fusion surgery, we found no association between the intra-surgical administration of BMP and increased pancreatic cancer risk over an average of 1.4 years of follow-up. Further, we found that the observed frequency of incident pancreatic cancer among BMP-exposed patients was no higher than what would be expected in the general population. Consistent with the previously described epidemiology of pancreatic cancer,[15] we found that risk was higher among older patients, men, blacks, and diabetics.

In our study population, the prevalence of diabetes (about 36%) was higher than the 19.7% prevalence reported in 2001 among unselected Medicare beneficiaries at least 67 years old.[25] We suspect that this difference is explained by obesity, which is strongly associated with both diabetes and degenerative disease of the lumbar spine. It is also possible that differences in operational definition of diabetes may account for this difference; in our study patients qualified for diabetes with a single claim, while the other study required claims on two separate days for outpatient diagnoses.

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Table 4. Sensitivity analysis adjusting apparent relative risk point estimate of 0.7 for the association of BMP with pancreatic cancer by an unmeasured confounder over a range of conditions

Prevalence of confounder in patients exposed to BMP	Prevalence of confounder in patients not exposed to BMP	Ratio of confounder prevalence exposed to unexposed	"True" (fully adjusted) RR if the association between confounder and outcome has a RR of:				
			2	3	4	5	10
0.05	0.075	1.5	0.72	0.73	0.75	0.76	0.81
0.05	0.1	2	0.73	0.76	0.79	0.82	0.92
0.05	0.15	3	0.77	0.83	0.88	0.93	1.13
0.1	0.15	1.5	0.73	0.76	0.78	0.80	0.87
0.1	0.2	2	0.76	0.82	0.86	0.90	1.03
0.1	0.3	3	0.83	0.93	1.02	1.10	1.36
0.2	0.3	1.5	0.76	0.80	0.83	0.86	0.93
0.2	0.4	2	0.82	0.90	0.96	1.01	1.15
0.2	0.6	3	0.93	1.10	1.23	1.32	1.60
0.3	0.45	1.5	0.78	0.83	0.87	0.89	0.96
0.3	0.6	2	0.86	0.96	1.03	1.08	1.21
0.3	0.9	3	1.02	1.23	1.36	1.46	1.72
0.4	0.6	1.5	0.80	0.86	0.89	0.92	0.97
0.4	0.8	2	0.90	1.01	1.08	1.13	1.25

RR, relative risk, estimated from the adjusted hazard ratio.
Approach based on Schneeweiss[22].

Several possible limitations to this study deserve mention. We used the ICD-9-CM code 84.52 as a proxy for rhBMP-2 exposure. Since this code is used for the administration of both rhBMP-2 and BMP-7, misclassification could be a concern. However, in our separate study of HealthCore medical charts we found that among those for whom the type of BMP could be characterized, 94.5% received rhBMP-2. The positive predictive value for the ICD-9-CM code 84.52 was 100%, based on validating claims of BMP use against the medical record. We did not formally evaluate the sensitivity of the exposure measure in this study. However, we judge that the probability of underascertainment of BMP-2 use was low given its cost (approximately $3400 per dose[26]) and the availability of a supplemental payment for BMP above the flat Medicare Diagnosis Related Group (DRG) reimbursement for lumbar fusion during the study period.

Given the administrative nature of Medicare data, we did not confirm pancreatic cancer diagnoses using clinical records. Nonetheless, we believe that our primary case definition (at least two claims for pancreatic cancer associated with cancer-specific therapy) has strong clinical face validity. In addition, analyses that used alternate case definitions yielded similar results.

The proportion of spinal fusion procedures using BMP in the US gradually increased over the study period.[27] We suspect that this trend likely explains the discrepancy in average follow-up time between the BMP group (1.04 ± 0.73 years) compared to the non-BMP group (1.46 ± 0.86 years).

It could be argued that the follow-up was too short to detect any BMP effect on cancer risk. This would almost certainly be true if the question was whether BMP was carcinogenic. We are aware of no literature that suggests this, and Ames mutagenicity testing of BMP-2 was negative.[28] Rather than carcinogenicity, the biological effect in question is whether BMP hastens the growth of cells that have already undergone malignant transformation. Moreover, the three pancreatic cancers observed in the lumbar spine clinical trials were all diagnosed within 13 months of surgery (1 month, 11 months, and 13 months). Nonetheless, our results cannot exclude a long-term effect of BMP on pancreatic cancer risk.

Some potential confounders may have been underascertained since our medical history information was limited to the 2 years prior to surgery. Factors most likely to be missed for this reason include past cholecystectomy, gastrectomy, and chronic pancreatitis. However, we expect that the true prevalence of these factors was low and that they are unlikely to be associated with BMP use.

Another potential limitation is the possibility of unmeasured confounding by smoking, which is not reflected in Medicare claims. Our supplementary chart review study found that smoking prevalence was slightly higher in the non-BMP group, and adjustment for this small difference did not change our results. Smoking histories were missing for about 15% patients, however, and our analysis did not account for different intensities of tobacco use.

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KEY POINTS

- Recombinant bone morphogenetic proteins (BMPs) are used in orthopedic surgery to induce bone growth.
- Clinical trials of BMP-2 in lumbar fusion found an unexpected number of pancreatic cancers associated with its use.
- To evaluate this signal, the authors used Medicare claims data to study more than 90 000 elderly patients who underwent lumbar fusion surgery. Exposure to BMP was not associated with an increased risk of pancreatic cancer.

Several inherited conditions that increase risk for pancreatic cancer[29] were not measured in this study, but given their rarity[30–32] we judge that they were unlikely to have confounded our results, even if they were strongly associated with non-use of BMP (Supplemental Table 2).

We were surprised to find that the incidence of pancreatic cancer in the non-BMP group was higher than expected for the general US population. We suspect that patient factors, such as obesity[24], smoking,[16–18] or alcohol abuse,[23] may account for this finding. It is possible that unmeasured confounding could have masked a true association in our study, but sensitivity analyses suggest that this is unlikely. Relative risk estimates greater than 1.2 occurred only under assumptions that the unmeasured confounder was common and strongly associated both with non-use of BMP and pancreatic cancer. In contrast, the prevalence of measured confounders in this study was similar across exposure groups, and none differed by more than 2%.

Confidence in our findings is strengthened by several factors. This was a very large study of Medicare enrollees, was population-based, and reflected routine clinical practice. We used a specific definition of incident pancreatic cancer to exclude misdiagnoses. Most new diagnoses of pancreatic cancers occur among individuals in the age range served by Medicare. Between 1998 and 2002, almost 70% of new pancreatic cancer cases occurred among those 65 years or older[14]

CONCLUSION

In this study of more than 90 000 elderly patients who underwent lumbar spinal fusion surgery, there was no increased risk of pancreatic cancer among patients exposed to BMP compared to those who were not exposed.

CONFLICT OF INTEREST

When this research was conducted, Drs. Mines and Gu were full-time employees of Wyeth Pharmaceuticals, which manufactures rhBMP-2. Wyeth provided salary support to Drs. Kou and Cooper for research services associated with this study. Drs. Mines and Cooper have been paid as consultants to Medtronic, which markets an orthopedic device that uses rhBMP-2. Dr. Cooper has also received support from Medtronic for additional research involving rhBMP-2.

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APPENDIX
CODES FOR COVARIATES

The diagnosis and procedure codes captured were as follows: diabetes mellitus (ICD-9-CM 250.xx, 790.2), alcohol abuse (ICD-9-CM 291.xx, 303.0, 303.9, 425.5, 571.0, 571.1, 571.2, 571.3, V11.3), chronic pancreatitis (ICD-9-CM 577.1, 577.2, 577.8), gastrectomy (ICD-9-CM 43.5, 43.6, 43.7, 43.8, 43.9; CPT-4 43620, 43622, 43631, 43632, 43633, 43634, 43638, 43639, 43640), and cholecystectomy (ICD-9-CM 51.2x; CPT-4 47562, 47563, 47564, 47600, 47605, 47610, 47612, 47620).

CODES FOR CANCER-SPECIFIC PROCEDURES

These included gastrointestinal bypass surgery (ICD-9-CM: 44.39, 51.36, 51.39, 51.42. CPT-4: 43820, 43825, 47720 - 47790), pancreatectomy (ICD-9-CM: 52.50–52.79. CPT-4: 48140–48144, 48146, 48147, 48149 - 48155), radiation therapy (CPT-4: 77401–77799) and chemotherapy (CPT-4: 77305–77334, 77401–77417, 77750–77799, 96400, 96408–96414, 96440, 96445, 96545, 96549. HCPCS: J9000–J9999).

SUPPORTING INFORMATION

Additional supporting information may be found in the online version of this article:

Supplemental Table 1. Factors associated with pancreatic cancer in multivariate Cox regression analyses using alternate case definitions

Supplemental Table 2. Sensitivity analysis adjusting apparent relative risk point estimate of 0.7 for the association of BMP with pancreatic cancer by an unmeasured cancer hereditary syndrome, assuming its prevalence in the non-BMP group was 5-fold that of the general population

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