A comprehensive assessment of the risk of bone morphogenetic protein use in spinal fusion surgery and postoperative cancer diagnosis

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The risk of postoperative cancer following the use of recombinant human bone morphogenetic protein (BMP)–2 in spinal fusion is one potential complication that has received significant interest. Until recently, there has been little clinical evidence to support the assertion of potential cancer induction after BMP use in spinal surgery. This report aims to summarize the findings from clinical data available to date from the Yale University Open Data Access (YODA) project as well as more recently published large database studies regarding the association of BMP use in spinal fusion and the risk of postoperative cancer. A detailed review was based on online databases, primary studies, FDA reports, and bibliographies of key articles for studies that assessed the efficacy and safety of BMP in spinal fusion. In an analysis of the YODA project, one meta-analysis detected a statistically significant increase in cancer occurrence at 24 months but not at 48 months, and the other meta-analysis did not detect a significant increase in postoperative cancer occurrence. Analysis of 3 large health care data sets (Medicare, MarketScan, and PearlDiver) revealed that none were able to detect a significant increase in risk of malignant cancers when BMP was used compared with controls. The potential risk of postoperative cancer formation following the use of BMP in spinal fusion must be interpreted on an individual basis for each patient by the surgeon. There is no conclusive evidence that application of the common formulations of BMP during spinal surgery results in the formation of cancer locally or at a distant site.

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KEY WORDS BMP; cancer; spinal fusion; oncology; technique

Bone morphogenetic proteins (BMPs) represent a family of differentiation factors that promote bone formation and remodeling.6,34,35 Clinical use of recombinant human BMP–2 (rhBMP-2) was approved by the FDA solely for anterior lumbar interbody fusion in 2002,7 but off-label usage in various spinal procedures has been reported and has dramatically increased in frequency.8,29 The widespread enthusiasm for BMP was based on the ability of this powerful compound to enhance the likelihood of postoperative bony fusion and thereby decrease the undesired outcome of pseudarthrosis or non-union.3,6 An additional potential clinical benefit relates to the decreased morbidity from autogenous bone graft harvest from sources such as the iliac crest.4,5 There are 2 BMP products commercially available for clinical use, rhBMP-2 (INFUSE, Medtronic) and BMP-7 (OP-1 Putty, Stryker). BMP-7 received a humanitarian device approval in 2003 for revision intertransverse lumbar fusion in compromised patients.

The creation of standards of practice and specific guidelines for BMP usage is difficult due to limited availability of randomized prospective clinical trials and the use of BMP in many diverse spinal applications. Mechanisms of delivery, carrier type, graft positioning, and concentrations of BMP are important variables that may differ from one surgery to the next. Consequently, there may also be a wide range in the potential for the development of side effects related to usage. Adverse events linked to BMP use...
Association between BMP, spinal fusion, and cancer

include ectopic bone formation, bone resorption or remodeling at the graft site, hematoma, swelling, and painful seroma. Carcinogenic effects related to BMP exposure have been previously thought to be theoretical concerns but are now receiving critical attention.

The risk of postoperative cancer formation following the use of BMP in spinal fusion procedures is a potential complication that has received significant interest due to the potential morbidity and mortality associated with the development of cancer. Until recently, there has been very little clinical evidence to support the assertion of potential cancer induction after BMP use in spinal surgery. The higher-dose AMPLIFY BMP product was denied FDA approval because of “notably increased cancer rates” in the BMP-treated arm (Executive Summary for P050036 Medtronic’s Amplify rhBMP-2 Matrix). Dr. Eugene Carragee from Stanford University presented data at the North American Spine Society meeting in Chicago and suggested a “2.5 times greater risk of developing cancer one year after the product was used and a five times greater risk after three years.” The results from the secondary analysis were later published and involve a further review of the primary and secondary data from the AMPLIFY randomized clinical trial of high-dose BMP formulation used in posterolateral fusions. In addition, more recent interest has been focused on the 2 landmark meta-analyses that are the result of the Yale University Open Data Access (YODA) project. These studies have analyzed all of the initial patient-level clinical trial data in an attempt to further clarify the risks of cancer associated with the more common formulations of BMP use after spine surgery. Finally, several recent large population-based retrospective series have been published that have used clinical claims-based databases to address the risk of cancer following BMP-2 usage during spine surgery. Given the potential morbidity and mortality associated with the development of certain cancer types as well as the widespread use of BMP in spinal fusion procedures, the goal of this analysis was to review and summarize the recently available data on the association of postoperative cancer development following the use of BMP in spinal fusion.

Methods

A review was based on a search of PubMed, ClinicalTrials.gov, the Cochrane Library, the Agency for Healthcare Research and Quality, systematic reviews, primary studies, and FDA reports, and bibliographies of key articles were searched. We used the PRISMA guidelines to improve the consistency and the scope of the review. Eligible studies that assessed the efficacy and safety of BMP in spinal fusion were considered if there was mention of postoperative cancer events. We reviewed the English-language literature for criteria of eligibility, entering the following key words: bone morphogenetic protein (BMP), spine fusion, and cancer. Only published articles of clinical studies with a minimum of 1 year of follow-up were included. In vitro and animal studies were not included. Sixteen articles were initially identified with this search, of which 6 were relevant articles. One study was a case series, 3 were systematic reviews of Medtronic investigational device exemption (IDE) data, and 3 were large population-based studies. Each applicable report was independently reviewed by the investigators. The principal summary measures were an analysis of whether the incidence of cancer, benign or malignant, was significantly increased in the various papers reviewed. The reviews of the Medtronic IDE study results were done by 2 independent academic organizations with no financial interests in the product to reduce the risk of bias. The Medtronic IDE data that were reviewed by these 2 study groups were not taken directly from the published papers; they were the primary data that were reviewed, thus minimizing the risk of bias. The other articles referenced are non-IDE study results, again not supported by industry.

Results

Reviews of Medtronic IDE Study Results

Yale University Open Data Access of Medtronic IDE data

The meta-analyses that resulted from the YODA project have been published in 2 reports produced by 2 independent research teams: Oregon Health & Science University (OHSU) and the University of York. The full reports from these efforts have been published on the YODA website, while the corresponding papers were published in the Annals of Internal Medicine. The data for these reports consisted of the de-identified patient-level data for all 17 Medtronic-funded studies of rhBMP-2 in spinal fusion. Additionally, broad literature searches using MEDLINE, Embase, the Cochrane Library, Scopus, ClinicalTrials.gov, and the FDA website were completed to identify other BMP studies and related publications for these studies.

Eleven of the 17 Medtronic-funded trials were primarily used for evaluation of effectiveness. The overall incidence of cancer in the 11 randomized controlled Medtronic trials was reported. In the 694 patients who received rhBMP-2, 20 new cases of cancer were reported. In the iliac crest bone graft control group (n = 608) there were 8 new cases of cancer. Cancer types identified included skin, breast, colon, larynx, leukemia, lung, non-Hodgkin lymphoma, ovarian, pancreatic, prostate, stomach, testicular, and thyroid (Table 1).

The OHSU team analyzed harms related to BMP use into 2 different postoperative periods, including 4 weeks and 24 months postoperatively. For cancer and death occurrences, results through 48 months were also included. Overall, the authors concluded that internal Medtronic documents indicated that cancer cases were underreported. There were only 5 Medtronic-sponsored trials that reported at least 1 cancer death and were included in the meta-analysis of postoperative cancer risk. Four of these included studies were anterior lumbar interbody fusion studies in which INFUSE was used in doses of 4.2 mg to 12.0 mg. One of the studies was the high-dose AMPLIFY trial in posterolateral fusion that used a 40.0-mg BMP dose. The included studies comprised 1450 patients.

In the OHSU analysis at 24 months, there were 17 cancer cases in 633 patients who received rhBMP-2 compared with 6 cancer cases in 817 control patients who did not receive BMP. At 48 months there were fewer total pa-
TABLE 1. Incidence of cancer in the Medtronic trials

<table>
<thead>
<tr>
<th>Cancer</th>
<th>rhBMP-2 (n = 694)</th>
<th>ICBG (n = 608)</th>
</tr>
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<tbody>
<tr>
<td>Skin</td>
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<tr>
<td>Melanoma</td>
<td>2</td>
<td>0</td>
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<tr>
<td>Basal cell carcinoma</td>
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<td>Squamous cell carcinoma</td>
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<td>Breast</td>
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<tr>
<td>Colon</td>
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<td>1</td>
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<tr>
<td>Larynx</td>
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<td>0</td>
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<td>Leukemia</td>
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<tr>
<td>Lung</td>
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<td>Non-Hodgkin lymphoma</td>
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<td>1</td>
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<tr>
<td>Ovarian</td>
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<tr>
<td>Pancreatic</td>
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<td>Prostate</td>
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<td>Stomach</td>
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<td>0</td>
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<tr>
<td>Thyroid</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Total</td>
<td>20</td>
<td>8</td>
</tr>
</tbody>
</table>

ICBG = iliac crest bone graft; rhBMP-2 = recombinant human bone morphogenetic protein-2.
* The data shown are the number of cases and include 3 cases (1 of thyroid cancer, 1 of testicular cancer, and 1 of melanoma) in rhBMP-2 recipients identified through extended follow-up of the LT-CAGE open trial from Annals of Internal Medicine, Simmonds MC, Brown JV, Heirs MK, Higgins JPT, Mannion RJ, Rodgers MA, et al. Safety and effectiveness of recombinant human bone morphogenetic protein-2 for spinal fusion: a meta-analysis of individual-participant data. Ann Intern Med 158(12):877–889. Copyright © 2013 American College of Physicians. All Rights Reserved. Reprinted with the permission of American College of Physicians, Inc.

...patients, as many of the studies did not extend to 48-month follow-up. At 48 months there were 16 cancer cases in the 483 patients who received BMP compared with 11 cancer cases in the 700 patients who did not receive rhBMP-2. At 24 months BMP was associated with a statistically significant increased risk for cancer (RR 3.45, absolute difference 1.9% points) but not at 48 months (RR 1.82) (Fig. 1). Of note, the pivotal AMPLIFY trial included in this analysis contained 10 of the 17 cancer cases at 24 months in the rhBMP group. The OHSU group also analyzed a recently published Canadian AMPLIFY study that included 98 patients and reported no cancer cases in the rhBMP-2 (doses of 40.0 mg to 63.0 mg) group (n = 48 patients) at 48 months.  

The OHSU study also included sensitivity analyses to determine the impact of the 7 Medtronic trials that did not report any cancer cases on the overall risk of cancer associated with BMP. Including these 429 patients in the analysis demonstrated an absolute increased risk of cancer in the BMP group of 1.3% (95% CI 0.2%–2.4% points) and a relative risk that remained statistically significant (RR 2.90). Likewise, a sensitivity analysis that included non-Surveillance, Epidemiology, and End Results (SEER) program cancer cases did not alter the statistically significant increased risk of cancer associated with BMP use. Additionally, analyses of postoperative mortality were performed. The overall risk of death through 24 months and 48 months did not differ between the BMP and control groups.

The University of York meta-analysis took a slightly different approach to the meta-analysis of postoperative cancer incidence. For this analysis all 11 Medtronic randomized controlled trials were included. The York group excluded cases of preexisting cancer. They did not include data from single-arm studies, and different time points were not considered. The overall relative risk of cancer in patients who received rhBMP-2 was increased but did not meet statistical significance (RR 1.98). The authors also performed a subgroup analysis comparing cancer risk between INFUSE and AMPLIFY and were unable to demonstrate that the risk of cancer in the AMPLIFY trial differed from that in the INFUSE trials. The York group performed a final analysis that included 3 cancer cases in patients who received rhBMP-2 in the INFUSE/LT-CAGE open pivotal trial and were identified through extended follow-up increased the relative risk to 2.33 and achieved statistical significance (95% CI 1.04–5.25).

The association of cancer formation and the use of high-dose BMP, AMPLIFY, has also been analyzed by Carragee et al. using publicly available FDA documents from the IDE randomized trial of AMPLIFY in posterolateral fusion. In this clinical trial, 239 patients underwent single-level instrumented posterolateral fusion with high-dose BMP. These patients were compared with 224 control patients who underwent fusion with iliac crest graft. The 2-year follow-up rate for the study was 86%. In the earlier published report by Dimar et al., there were 8 cancers in the rhBMP-2 group compared with 2 cancers in the iliac crest control group. Additional cancer events were later revealed by the FDA review of the trial. The review by Carragee et al. included these later identified cancer events. These authors reported that the incidence rate per 100 person-years of new cancer events in the AMPLIFY group was 3.37 (95% CI 1.89–5.56) at 24 months and 2.15 (95% CI 1.31–3.32) at 48 months compared with 0.50 (95% CI 0.06–1.80) at 24 months and 0.60 (95% CI 0.19–1.39) at 48 months for patients who received iliac crest graft. The corresponding incidence rate ratio was 6.75 at 24 months (p = 0.0026). Analysis of the cumulative incidence of cancer events indicated that the incidence of cancer for the BMP group showed a steep increase during the first 2 postoperative years. After the first 2 postoperative years, the BMP and control groups had similar rates of accrual of new cancer cases. In comparison with the meta-analyses from the YODA project, the review by Carragee et al. did not include the other large recently published randomized trial of AMPLIFY from Canada, which included 197 patients. This in part accounts for the differences in the relative risks of BMP in the AMPLIFY publications between the Carragee review and the YODA review.

Independent Non-IDE Study Results

Case Reports

There have been no published clinical case reports of cancers such as osteosarcoma developing after local
application of BMP to the spine or with its use in dental surgery. On the other hand, heterotopic bone formation is a well-known complication from the use of BMP, particularly in high doses placed in and around the spine.11

Case Series

Mesfin et al. reviewed a large consecutive series of patients (n = 502) who received high-dose BMP for adult scoliosis at a single institution.26 The average dose of BMP used was 115 mg (range 40–315 mg), and the average patient age was 52.4 years. There were a total of 16 new cancers and 1 benign tumor identified during the average follow-up of 4 years, the most common of which was breast cancer (n = 8), followed by renal cell (n = 2). There was no correlation found between the development of cancer and the dosage of BMP used (p = 0.08). This lack of dosage effect is in contradistinction to a prior review article on BMP dosage and cancer.13 When comparing the overall incidence of cancer (3.4%) and the specific incidence of breast (1.6%) and renal (0.4%) cancer in their study to the SEER database, the incidence of all study-related tumors would be lower than predicted by the natural history of cancer in the 50- to 59-year-old age group.

Large Database Studies

In the meta-analysis data resulting from the YODA studies, the postoperative occurrence of cancer following spinal fusion is a rare event. As such, the event numbers in the analyses on the association of BMP with cancer risk were also very low. In the 11 Medtronic randomized trials, 28 new cancer cases were reported in a total of 1302 patients, corresponding to an approximate 2% overall incidence of cancer. Given the low incidence of postoperative cancer, more recent studies have used large databases for analysis of these rare clinical events. Three studies to date have used large data sets to examine the association between BMP use and postoperative cancer.

Medicare Beneficiary Data. Cooper and Kou recently reported their analysis of Medicare beneficiary claims data from 2003 to 2010.12 In this study the Medicare Provider Analysis and Review files were used to identify patients who underwent lumbar fusion with or without BMP using administrative claims data. The ICD-9-CM code 84.52 was used to identify exposure to BMP, and all lumbar fusion procedures were included. Patients with pre-existing cancer-related claims in the 2 years prior to the surgery were excluded. A total of 146,278 patients were included in the analysis, which included univariate and multivariate Cox proportional hazards models. The average length of follow-up was 4.8 years in the BMP group and 4.4 years in the control non-BMP group. The overall incidence of cancer was 17.0% in the non-BMP group and
15.4% in the BMP group with the most common cancers being prostate, breast, lung, colon, and rectal. In the univariate proportional hazards model as well as the adjusted model, there was no association of BMP with cancer incidence (HR 0.98 [95% CI 0.95–1.02] unadjusted and HR 0.99 [95% CI 0.96–1.03] adjusted). In secondary analyses using more stringent definitions for identification of cancer cases, there was a somewhat lower overall cancer risk with BMP use in unadjusted and adjusted proportional hazards models (HR 0.94 [95% CI 0.89–0.98] unadjusted and HR 0.95 [95% CI 0.90–0.99] adjusted).

This analysis of Medicare claims data confirmed a prior study by the authors23 of essentially the data set that was focused solely on the association of pancreatic cancer with BMP exposure.23 In that analysis, 93,654 Medicare patients who underwent lumbar fusion surgery were included. Likewise, in that study there was no association demonstrated between BMP exposure and the development of pancreatic cancer in a proportional hazards model (HR 0.70 [95% CI 0.34–1.45]).

MarketScan Data Set. The Medicare claims data are primarily limited to elderly patients, and conclusions may not be useful in younger patients undergoing spinal fusion with BMP. The Thomson Reuter’s MarketScan data set is a commercially available health care claims data set that provides longitudinal utilization claims data for more than 100 million individuals. This data set has been recently used to perform a retrospective analysis of BMP exposure during spinal fusion and the subsequent development of cancer.25

For the MarketScan data set analysis by Lad et al.,25 patients who underwent lumbar, thoracic, and cervical fusion for spinal stenosis from 2003 to 2009 were identified based on billing claims data. In that data set there were 201,798 patients who underwent spinal fusion procedures; 103,969 were excluded due to limited follow-up data, and 57,220 were excluded due to preoperative diagnosis codes corresponding to cancer. The final cohort contained 35,854 patients, of whom 2349 patients underwent fusion with BMP. Propensity score matching was used to identify a control group of 2349 patients who closely resembled the BMP-exposed cohort. The overall risk of developing cancer in the BMP cohort was 9.4% compared with 7.9% in the control cohort, but it did not reach statistical significance (p = 0.078). Stratification by cancer type indicated that the only diagnostic group that was associated with BMP was benign tumors (6.3% in BMP group vs 4.9% in non-BMP group, p = 0.035). The increased incidence in benign tumors was only seen for benign tumors of the nervous system (particularly tumors of the meninges), uterus, and unspecified sites. Further analysis of the risk of developing multiple tumors demonstrated that BMP use was associated with a higher risk for developing 2 or more distinct benign tumors (1.15% in the BMP group vs 0.47% in the non-BMP group, p = 0.009).

PearlDiver Medicare Data. Finally, there has been a similar analysis using an additional commercially available claims-based data set, the PearlDiver Medicare database.22 This analysis included 110,808 patients who underwent fusion surgery with BMP from 2005 to 2010; follow-up ranged from 1 to 5 years with a mean of 2.9 years. The incidence of cancer in these patients was compared with that in 357,108 control patients in the same database who underwent fusion surgery without BMP. There was no difference in demographics or baseline characteristics between the groups. The overall incidence of new cancer formation was 5.9% in the BMP group compared with 6.5% in the control group. The lower risk of cancer in the BMP group was statistically significant and resulted in a relative risk ratio for cancer associated with BMP use of 0.91 compared with the control group.

Discussion

Given the potential for severe morbidity and mortality with the development of certain cancer types, it is evident that the risk of postoperative cancer formation following the use of BMP in spinal fusion procedures is critically important for clinicians to understand. Given that the company estimates that more than 1,000,000 units of BMP have been used worldwide and clinical application has now spanned over a decade, the importance of this risk assessment is further escalated. Fortunately, the rate of cancer occurrence following spinal fusion with or without BMP usage is relatively rare. Since the occurrence is rare, analysis of the event is difficult and determining statistically significant associations is even more difficult. Meta-analyses and large database analyses can be extremely useful for studying rare events, such as cancer following spinal fusion. The goal of this work was to serve as a single source for a review of the recently available clinical data on this topic.

From the 2 separate meta-analyses of the Medtronic clinical trial, the YODA project, it is evident that there were 20 new cases of cancer reported in 694 patients who received BMP.18,22 In the iliac crest bone graft control group there were 8 new cases of cancer in 608 patients. The 2 study teams then analyzed the data further and reached slightly different conclusions. The University of York meta-analysis determined that the overall relative risk of cancer in patients who received rhBMP-2 was increased but did not meet statistical significance. The OHSU meta-analysis of the identical data indicated that at 24 months BMP was associated with a statistically significant increased risk for cancer, but not at 48 months. Interpretation of the YODA project results must take into consideration the inherent limitations of the meta-analyses. First, the initial clinical trials were not designed to evaluate the association of cancer with BMP usage. The studies were not powered to detect differences in the rare occurrence of postoperative cancer formation. Likewise, there was an overall underreporting of cancer cases. In fact, only 5 of the clinical trials reported at least 1 cancer occurrence. Furthermore, the types of cancer cases reported were very heterogeneous, and there was not a trend toward certain cancer types. Finally, a detailed analysis of the impact of dosage on the risk of cancer occurrence could not be performed. The University of York team concluded that the relative risk for cancer in the high-dose AMPLIFY trials was no greater than that for trials that used INFUSE. However, due to small event rates and sample sizes, no formal analysis of difference formulation of INFUSE and the risk of cancer could be performed.
Unfortunately, the review by Carragee et al.\textsuperscript{9} on the risk of cancer in the AMPLIFY trial did not include the Canadian AMPLIFY study,\textsuperscript{20} making it difficult to compare results with the more extensive meta-analyses from the YODA project. It should be noted that the Canadian trial included the development of a new cancer as a secondary and not a primary outcome measure as in the AMPLIFY trial.

The population-based analyses offer a different technique for analysis of the rare event of postoperative cancer formation. By using extremely large data sets such as the MarketScan or Medicare claims data, an additional perspective on postoperative cancer formation following spinal fusion is available. Using the Medicare data set, the authors determined that there was no association of BMP with cancer incidence, and, surprisingly, in secondary analyses using more stringent definitions for identification of cancer cases, there was a somewhat lower overall cancer risk with BMP-2 usage.\textsuperscript{12} In the MarketScan analysis the overall risk of developing cancer in the BMP cohort was not statistically different from that in the non-BMP cohort. The authors were only able to detect an increased association of BMP with benign tumors in a secondary stratified analysis.\textsuperscript{25}

The strength of these population-based studies is clearly the larger sample size that is attainable using these large data sets. Unfortunately, there are significant limitations to the conclusions drawn from claims-based data sets. First, these are retrospective studies using data that have relatively limited clinical information. It is extremely difficult to ensure clinical comparability between patients who received BMP and those who did not. In most spinal fusion cases, the surgeon decides if BMP is needed based on the clinical details of the case. In the MarketScan study, there was greater BMP usage in women and patients with significant comorbidities, indicating that this patient population is different from that of patients who did not receive BMP. Likewise, a critical clinical detail not available in these data sets is the smoking status of the patient. Smoking is a known risk factor for failed fusion and pseudarthrosis and would certainly be a motivating factor for surgeons to add BMP to the fusion construct. Smokers have a higher risk for cancer, and findings of an increased incidence of lip, oral cavity, and pharyngeal cancers may be a reflection of this. Inclusion of more smokers in the BMP group may independently increase the risk of the cancer in the BMP group. An argument could be made that surgeons might exclude patients who had a prior history of cancer from receiving BMP, and thus the control group in these large database studies could represent a higher risk group for the development of subsequent cancers; however, patients with a history of cancer in the 2 years prior to the index procedure were excluded in the analysis.\textsuperscript{12,22,25} Finally, the accuracy of the coding that is used for billing purposes and construction of these data sets is questionable and may not directly reflect the clinical details.

Local application of BMP to the spine to promote bone formation can lead to exuberant bone growth, particularly if high doses are used and if containment of the protein is not controlled.\textsuperscript{11,14} BMP receptors are present on a number of cancer cells (see the review by Thawani et al. for a detailed analysis of in vitro effects of BMP on cancer cell lines\textsuperscript{33}). However, few cell lines actually respond to BMP by increasing cellular proliferation, even in supra-physiological doses. Some cancers, particularly breast cancers, are inhibited by local application of BMP, and its use as a tumor inhibitory strategy is being investigated.\textsuperscript{28} In animal studies,\textsuperscript{171}I-rhBMP-2 is slowly released from the implant site with a mean residence time of approximately 8 days. The peak amount of radiolabeled rhBMP-2 detected in the blood is small (0.1% of the implanted dose) and consistent with the rapid systemic clearance of the drug by the liver and kidneys.\textsuperscript{17} Even with the documented low blood levels of BMP after a single, local application and the known BMP receptor profile of many systemic cancers, the cancers reported in the IDE studies are incredibly heterogeneous in type. They range from skin cancer to solid organ cancers, such as pancreas, prostate and thyroid, as well as blood-borne neoplasias like leukemia and lymphoma. One of the best documented examples of environmentally induced cancers is the link between asbestos exposure and risk of mesothelioma.\textsuperscript{21} This cancer association represents repeated exposure to a carcinogen and a relatively rare malignancy type. The link between a single application of BMP, with its rapid clearance from the blood stream and the potential association with a variety of more common and diverse cancer types, presents a very different level of evidence.

Conclusions

It is well known that BMP is contraindicated at fusion sites that have had tumor removed or currently have tumor in the area due to the theoretical concern that exposure of the tumor cells to BMP could promote growth of the preexisting oncological cells. An additional concern has been the ability of BMP-2 to promote cancer formation in patients without preexisting cancer. It is somewhat more difficult to understand how a local, single application of BMP would produce a malignancy in a remote area of the body. There has been a suggestion that development of cancers within a 2- to 4-year time window supports a prorocogenic mechanism; however, differences in cancer rates when significant were detected early (2 years).\textsuperscript{16} Regardless, there has been significant interest in determining the risk of postoperative cancer formation associated with BMP use in spinal fusion. Ultimately, the reader will have to distill the current data and fit it to his or her specific practice requirements. The current report demonstrates, by combining case reports, case series, and a meta-analysis of the IDE data as well as several recent large postsurveillance databases, that the overall risk of cancer development is low and that there is no clear association between postoperative cancer formation and BMP use in spinal fusion surgery.

Summary Statements of Data

- Of the 2 meta-analyses of the IDE studies that resulted from the YODA project, one was able to detect a statistically significant increase in cancer occurrence at 24 months postoperatively but not at 48 months. The other meta-analysis did not detect a significant increase in cancer occurrence.
• An independent review of one AMPLIFY trial indicated that BMP was associated with a 6.75 cancer incidence rate ratio compared with iliac crest graft (a second AMPLIFY study was not included in the analysis).
• There are no case reports that have identified the formation of local malignant tumors, such as osteosarcomas, after use of BMP in the spine or after dental applications.
• One large case series using high doses of the standard formulation of BMP did not identify an increase risk of cancer when comparing with the SEER database.
• Using the Medicare data set, there was no association of BMP with cancer incidence and in secondary analyses there was a somewhat lower overall cancer risk with BMP usage.
• Using the MarketScan data set, the overall risk of developing cancer in the BMP cohort was not statistically different from that in the non-BMP cohort, but there was an increased association of BMP with benign tumors in a secondary stratified analysis.
• Using the PearlDiver data set, the overall risk of cancer development was slightly lower in the BMP group with a statistically significant difference.

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Association between BMP, spinal fusion, and cancer


**Author Contributions**

Conception and design: all authors. Acquisition of data: all authors. Analysis and interpretation of data: all authors. Drafting the article: all authors. Critically revising the article: all authors. Reviewed submitted version of manuscript: Levi. Approved the final version of the manuscript on behalf of all authors: Levi. Study supervision: Levi.

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