Surgical Neurology International

SNI: Spine, a supplement to Surgical Neurology International

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Basic science and spine literature document bone morphogenetic protein increases cancer risk

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Received: 28 August 14 Accepted: 16 September 14 Published: 30 December 14

This article may be cited as:
Epstein NE. Basic science and spine literature document bone morphogenetic protein increases cancer risk. Surg Neurol Int 2014;5:S552-60.
Available FREE in open access from: http://www.surgicalneurologyint.com/text.asp?2014/5/16/552/148039

Abstract

Background: Increasingly, clinical articles document that bone morphogenetic protein (BMP/INFUSE: Medtronic, Memphis, TN, USA) and its derivatives utilized in spinal surgery increase the risk of developing cancer. However, there is also a large body of basic science articles that also document that various types of BMP and other members of the TGF-Beta (transforming growth factor beta) family promote the growth of different types of cancers.

Methods: This review looks at many clinical articles citing BMP/INFUSE's role, largely "off-label", in contributing to complications encountered during spinal surgery. Next, however, specific attention is given to the clinical and basic science literature regarding how BMP and its derivatives (e.g. members of the TGF-beta family) may also impact the development of breast and other cancers.

Results: Utilizing BMP/INFUSE in spine surgery increased the risk of cancers/new malignancy as documented in several studies. For example, Carragee *et al.* found that for single-level instrumented posterolateral fusions (PLF) using high-dose rhBMP-2 (239 patients) vs. autograft (control group; n = 224), the risks of new cancers at 2 and 5 years postoperatively were increased. In laboratory studies, BMP's along with other members of the TGF-Beta family also modulated/contributed to the proliferation/differentiation of breast cancer (e.g. bone formation/turnover, breast cancer-related solid tumors, and metastases), lung, adrenal, and colon cancer.

Conclusions: BMP/INFUSE when utilized clinically in spinal fusion surgery appears to promote cancer at higher rates than observed in the overall population. Furthermore, BMP and TGF-beta are correlated with increased cancer growth both in the clinic and the laboratory.

Key Words: Bone morphogenetic protein, Pulmonary hypertension, Spinal surgery

Access this article online

Website: www.surgicalneurologyint.com

DOI: 10.4103/2152-7806.148039

Quick Response Code:

INTRODUCTION

Bone morphogenetic protein (BMP/INFUSE: Medtronic, Memphis, TN, USA), other BMP's (e.g. BMP's 2 (rhBMP-2), 4, 7), and Transforming Growth Factor-Beta (TGF-β) play roles in increasing the cancer risk when utilized clinically (e.g. in spinal surgery or medicine) or in the laboratory [Table 1]. In this review, we first analyze how the majority of the clinical data coming from the spine surgery literature utilizing BMP/INFUSE, either

Table 1: Summary of data

Title of section	Summary
Spine surgery literature: BMP/infuse increases cancer risk BMP2 adverse events Reported to the manufacturer and user facility device experience database	In order to better define AE associated with the use of rhBMP-2 in spinal surgery, Woo reviewed the US Food and Drug Administration's postmarketing reports.[27] Of the 834 reports studied, only four (0.5%) noted that rhBMP-2 was used in an "on-label" fashion. Notably, 370 or 44.4% of studies observed that patients required revision surgery or other invasive procedures for AE. Significant AE are reported for the largely "off-label use of BMP-2 in spine surgery, and " surgeons may wish to consider when deciding when and how to use this product in their patients."
Complications due to BMP/INFUSE in spine surgery: The evidence continues to mount	Epstein evaluated AE due to the overwhelming "off-label" use of BMP/INFUSE in spine surgery.[9] The 2008 warning from the FDA included the following AE due to BMP/INFUSE: Marked dysphagia, hematoma, seroma, swelling, and/or the need for intubation/tracheostomy. Further studies noted additional AE; heterotopic ossification, osteolysis, infection, arachnoiditis, increased neurological deficits, retrograde ejaculation, and cancer.
Complications due to BMP/INFUSE in spine surgery include an increased cancer risk	When Carragee *et al.* reviewed 13 initial industry sponsored rhBMP-2 publications concerning BMP/INFUSE's safety and efficacy in 780 patients undergoing spinal procedures (prospective trials), they found no reported rhBMP-2 adverse events (0%).[2] Nevertheless, Carragee *et al.* found that utilizing BMP/INFUSE in spinal surgery correlated with a 10-50% increased risk of adverse events; for anterior cervical surgery the risk of AE was 40% in the early postoperative period. Furthermore, higher doses of rhBMP-2 were associated with a greater risk of new malignancy.
Cancer risk after using recombinant bone morphogenetic protein-2 for spinal fusion	Carragee *et al.* evaluated the impact recombinant human bone morphogenetic protein-2 (rhBMP-2: growth factor) had in vitro on the growth/invasiveness of cancer.[3] They evaluated data from patients undergoing single-level instrumented posterolateral fusion with high-dose rhBMP-2 (239 patients) vs. those in autograft (control group without rhBMP-2; $n=224$). At two years, 15 new cancers were found in 11 patients with rhBMP-2 vs. 2 in the control autograft group. Even though only 63% of patients could be evaluated at 5 postoperative years, there was a "significantly greater incidence of cancer events in the rhBMP-2 group". In particular, this correlated with a higher risk of cancer when the higher 40 mg dose of rhBMP-2/CRM was utilized.
Complications including theoretical increased carcinogenesis with BMP in spine surgery	Tannoury and An observed that BMP-2 usage in spinal surgery was associated with multiple major concerns; "retrograde ejaculation, antibody formation, postoperative radiculitis, postoperative nerve root injury, ectopic bone formation, vertebral osteolysis/edema, dysphagia/neck swelling, hematoma formation, interbody graft lucency, problems with wound healing", and its "theoretical carcinogenesis".[24]
BMP used in spinal fusions increased risk of benign tumors but not cancer	Lad *et al.* asked whether BMP increased the risk of cancer after spinal fusions performed in 4698 patients utilizing BMP.[14] They found that those receiving BMP exhibited a significantly higher rate (31% increase) of benign tumors of the nervous system, but not in malignancies.
Bone graft extenders and substitutes: Potential for complications	Kaiser *et al.* reviewed the role of BMP in achieving lumbar fusion while limiting the morbidity of harvesting autologous iliac crest bone.[12] As graft extenders/substitutes, calcium phosphate salts (Nanoss, Vitoss) plus locally harvested autograft and BMP-2 (BMP/INFUSE) have proven effective alternatives to AICB. However, concerns regarding BMP's heterotopic bone formation and other reported morbidities must be carefully considered.
Controversy regarding cancer risk of BMP/INFUSE	Devine *et al.* cited the increased cancer risk attributed to "both BMP and their receptors" as identified from tumor surgery.[8] Additionally the product AMPLIFY (rhBMP-2, 40 mg, Medtronic, Memphis, TN) was correlated with an even higher frequency of cancers in the investigational vs. control patients, particularly when used "off-label". For PLF, the risk of cancer was 3.8% with 40 mg of BMP-2 (AMPLIFY) vs. 0.9% with controls. For two randomized controlled trails using rhBMP-7 vs. controls (without BMP), the cancer risk was 12.5% vs. 5.6% and. 8.3% vs. 0% respectively. Notably, the sample size for these studies were small, and therefore, cancer risks with BMP-2 may be proportional to the dose utilized.
Literature againts BMP contributing to cancer in spine surgery	To large database studies must be reviewed with great skepticism, as one always has to question the quality/accuracy of the data being collected and by whom. "GIGO: Garbage in-garbage out" must always be considered when conclusions from these massive series appear so counter to those gleaned from the meticulous clinical surgical studies using BMP/INFUSE cited above, and the myriad of subsequent basic science/medical clinical studies to follow.
Risk of cancer not increased with lumbar fusion using rhBMP-2/INFUSE	Cooper and Kou found an equivocal correlation between the use of BMP/INFUSE for lumbar fusion surgery and cancer.[6] They retrospectively evaluated the risk of cancer following lumbar fusions in 146,278 Medicare patients (age 67 years or older) performed with or without rhBMP-2/INFUSE. The overall cancer frequency was 15.4% for rhBMP-2 vs. 17% for those without, with an average 4.7 year follow up). They concluded that they "found no evidence that (the) administration of rhBMP at the time of lumbar fusion surgery was associated with (an increased) cancer risk."

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Table 1: Contd...

Title of section	Summary
Use of BMP in thoracolumbar fusions; No increased cancer risk	From 2006-2010, Veeravaqu *et al.* looked at the use of BMP in thoracolumbar fusions by utilizing the Marketscan Longitudinal database (e.g. that included 52,259 matched cohorts of patients undergoing TL fusions with or without BMP matched 2:1).[25] Although they noted that those receiving BMP had "fewer refusions, decompressions, posterior revisions, anterior revisions, or any revision", they did observe an increased frequency of dysrhythmia, delirium, and chronic pain within 30 days of surgery. Furthermore, despite concluding that BMP was "not associated with the post-operative development of cancer", they acknowledged the lack of long-term follow-up.
BMP used in spinal fusions does not increase risk of pancreatic cancer	Mines *et al.* looked at the impact of BMP-2 on pancreatic CA in a retrospective cohort Medicare study.[18] From 2003-4, patients over the age of 66 who had undergone lumbar fusions utilizing BMP-2 were evaluated regarding the subsequent frequency of pancreatic CA. Of 93,654 patients studied, the average age was 75, and 16.5% had received BMP. Over the average follow up duration of 1.4 years, 91 had pancreatic CA: 8 with BMP-2 and 83 without BMP-2. They concluded that BMP-2 did not increase the risk of pancreatic CA.
Basic science studies document BMP (BMP-2) and TGF-beta contribute to breast cancer	A review of the basic science literature, moreso than the spine literature, documents a positive correlation between bone morphogenetic protein, its derivatives (e.g. BMP, and multiple other variants of BMP), and TGF-Beta in the promotion and growth of breast cancers.
Breast cancer: BMP2 promotes migration and invasion of breast cancer cells	Jin *et al.* stipulated that BMP2 modulates and or contributes to the proliferation/differentiation of breast cancer cells, and promotes the migration/invasion of MCF-7 cells.[10] The authors concluded that it was critical to assess the oncogenicity of BMP2 if utilized for tissue engineering.
BMP-2 induces *in vitro* invasion/*in vivo* hormone independent growth of breast cancer	Clement *et al.* noted that breast cancer cell lines migrated toward BMP-2 sources, and the rate was dose dependent dependent on the concentration of BMP-2.[5]
BMP-Related stem cell activity may impact development of malignant mammary epithelial cells	Balboni *et al.* looked at how BMP-related stem cell activity may impact the development of malignant mammary epithelial cells.[1] They concluded "hyperactivation of BMP signaling is common in human breast cancers, most notably in the basal molecular subtype, as well as in several mouse models of breast cancer."[1]
Bone morphogenetic proteins contribute to the development/ progression of breast cancer	Ye *et al.* reviewed how BMP's play a critical role in bone formation/turnover, and likely contribute to how breast CA develops/progresses. They additionally showed "BMPs can regulate a range of biological functions of breast cancer cells."[28]
BMP stimulate mammary fibroblasts to promote breast cancer	Owens *et al.* noted that BMPs are " highly expressed in human breast cancers", and that BMP4 can "enhance mammary carcinoma cell invasion", and stimulate tumor progression.[20]
Humoral bone morphogenetic protein 2 induces breast cancer microcalcification	Liu *et al.* noted that micro calcifications are utilized as critical markers for diagnosing breast cancer on mammograms, but the etiology/physiology of these calcifications are not well understood.[16] This study served as the "first reproducible rodent model of breast cancer micro calcification", and "proved that BMP-2 expression was sufficient for initiating the process."
Induction of estrogen receptor α-36 expression by BMP2 in breast cancer cells	Wang *et al.* noted, "expression of estrogen receptor-α is one of the most important diagnostic and prognostic factors of breast cancer."[26] BMP2, in a dose dependent manner, induced ERα-36 expression in breast cancer cells, and significantly up-regulated ERα-36.
Osteomimicry of mammary adenocarcinoma cells in vitro	Cox *et al.* observed that bone metastases are extremely common with breast cancer, and therefore, "mammary cells possess osteomimetic capabilities that may allow them to adapt to, and flourish within, the bone microenvironment."[7] When exposed to BMP-2/phosphate supplemented media, they exhibited; increased mineralization within 3D collagen glycosaminoglycan scaffolds (e.g. a model mimicking bone metastases), and increased mineralization of 4T1 adenocarcinoma cells, confirming their preferential metastasis to bone.
Differential gene expression of TGF-beta/osteopontin in breast cancer	Reinholz *et al.* observed the different types of cytokines, members of the TGF-beta family, and tumor necrosis factor are involved in the modulation of bone metabolism and breast cancer metastasis."[22] They concluded that BMP-2 amongst other bone-related proteins contribute to the invasiveness/ metastatic potential of breast cancer.
Animal model of breast cancer microcalcification	Liu *et al.* determined a better animal model for detecting breast cancer micro calcification.[17] The authors concluded that rBMP-2 injections in rats bearing a syngeneic breast cancer resulted in " dose-dependent and time-dependent micro calcifications."
Clinical study documents BMP (BMP-2) and TGF-beta contribute to breast cancer	Slattery *et al.* studied the impact of BMP on the risk of developing breast cancer in Hispanic (2111 vs. controls 2597) vs. non-Hispanic (1481 vs. 1586) white females.[23] They concluded that genetic variations in BMPs were associated with different rates/risks of breast cancer in admixed populations, and were correlated with their menopausal status.
Genetic variation in BMPs correlate with increased breast cancer risk in admixed populations	

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Table 1: Contd...

Title of section	Summary
BMP-2 associated with other multiple malignancies and angiogenesis	Chu *et al.* noted that BMP-2, part of the TGF-β transforming growth factor super family, closely correlated with an increase in multiple malignancies, especially lung cancer.[4] They found that the high BMP-2 mRNA presence in 61 non-small cell lung cancer samples closely correlated with the presence of lymph node metastases and tumor stage ($P<0.05$).
Angiogenesis: BMP is associated with many malignancies; silencing BMP-2 expression inhibits A549 and H460 cell proliferation/migration	
Angiogenesis: BMP-2 induces tumor angiogenesis	Raida *et al.* looked at how BMP's and TGF-β compounds contributed to tumor angiogenesis.[21] They evaluated the impact of "BMP-2 on human dermal microvascular endothelial cells" and analyzed " BMP-2's over expression on tumor vascularization of human xenografts with transfected MCF-7 breast cancer cells (MCF-7/BMP2) in mice."
Angiogenesis: BMP protein receptors and signal transduction	Miyazon *et al.* observed that BMPs, part of the TGF-β family, have a wide-ranging impact on bone, cartilage, blood vessels, heart, kidney, neurons, liver and lung tissues.[19] They further determined that alterations of BMP "signaling pathways" may be correlated with "vascular diseases, skeletal diseases, and cancer."
Basic science behind multiple other malignancies due to BMP	This section deals with the basic scientific literature pertaining to animal models of cancers, other than breast, and focuses on how exposure to BMP's (and other members of the TGF-Beta family) resulted in the up-regulation of different tumor lines.
BMP increases risk of growth of lung cancer in mouse model	Having observed that bone morphogenetic proteins and transforming growth factor-beta promote skeletal metastases via autocrine cells, Lee *et al.* asked whether BMP spp24 would increase the rate of growth of lung cancer cells in a mouse model.).[15] They also asked whether these cancer cells would be inhibited by phospoprotein 24kDA (spp24) (e.g. the latter binds to and inhibits the osteogenic potential of these factors).[15] They found in an in-vivo mouse model that the latter successfully inhibited lung tumor growth in both "soft tissue and intraosseous environments".
Role of BMP in adrenal tumorigenesis	Johnsen and Beuschlein observed that BMPs regulate many biological processes that include cell specification, differentiation, organogenesis, and tumorigenesis.[11] For example, BMP-dependent mechanisms modulate" catecholamine synthesis, steroidogenesis, and dysregulation of BMP signaling in adrenal tumorigenesis."
Colorectal cancer risk-associated variant Ly×25Ser in proximity to BMP-2	Khan *et al.* noted that colorectal cancer is the "third most prevalent cancer and fourth leading cause of cancer-related deaths globally."[13] Importantly, several CRC risk associated genetic sites are located in close proximity to bone morphogenetic protein 2.
Conclusion	The role of the BMP's and other members of the TGF-Beta family in promoting different cancers either clinically or in the laboratory need to be brought to light. The reason for emphasizing the potential increased risk of cancer utilizing these growth factors is that spinal surgeons are implanting BMP/INFUSE to perform spinal fusions on a daily basis in extremely high doses either "on" or "off-label". Nevertheless, due to the lack of "cross-talk" between basic scientists and spine surgeons, we, as spine surgeons, are not sufficiently aware of how we are exposing our patients to an increased cancer risk. Therefore, we must educate ourselves and our colleagues so that we may avoid subjecting our patients to an increased cancer risk.

ACDF: Anterior cervical discectomy and fusion, AE: Adverse events, AICB: Autologous iliac crest bone, ALIF: Anterior lumbar interbody fusion, BMP: Bone morphogenetic proteins, BMP-2: Bone morphogenetic proteins, BMP-4: Bone morphogenetic proteins, BMP-7: Bone morphogenetic proteins, CA: Cancer, CRC: Colorectal cancer, CT: Computed tomography, DBM: Demineralized Bone Matrix, ERα: Estrogen receptor-α, FDA: Food and drug administration, HDMEC: Human dermal microvascular endothelial cells, HO: Heterotopic ossification, ICM : Inductive Conductive Matrix, NSCLC: Non-small cell lung cancer, OPG: Osteoprotegerin, OPN: Ostteopontin, PLF: Posterolateral lumbar fusion, PLIF: Posterior lumbar interbody fusion, PTEN: Phosphatase and tensin homologue deleted on chromosome ten, rhBMP-2: Bone morphogenetic protein, SPECT: Single photon emission computed tomography, TGF-β: Transforming growth factor-beta, TL: Thoraco-lumbar, TLIF: Transforaminal lumbar interbody fusion, TNF: Tumor necrosis factor

"on-" or "off-label", documents an increased cancer risk. Subsequent sections review basic science and clinical studies in which the various BMP's and TBG-Beta's contribute to angiogenesis and multiple malignancies, including most predominantly breast cancer, but also lung, adrenal, and colorectal tumors.

SPINE SURGERY LITERATURE: BMP/INFUSE INCREASES CANCER RISK

Bmp2 adverse events reported to the manufacturer and user facility device experience database

In order to better define adverse events (AE) associated with the use of rhBMP-2 in spinal surgery, Woo reviewed the US Food and Drug Administration's (FDA) post marketing reports[27] [Table 1]. The Manufacturer and User Facility Device Experience database was searched for AE utilizing "infuse bone graft," from 2002-2011. Of the 834 reports, only four (0.5%) noted that rhBMP-2 was used in an "on-label" fashion. Notably, 370 or 44.4% of studies observed that patients required revision surgery or other invasive procedures for AE. AE included; swelling, fluid collections, osteolysis, pain/radiculopathy, heterotopic bone, pseudarthrosis, surgical site infections, other wound complications, thromboembolic events, respiratory distress, and cancer" amongst others.

The main conclusion was that significant AE are reported for the largely "off-label use of BMP-2 in spine surgery, and "surgeons may wish to consider when deciding when and how to use this product in their patients."

Complications due to BMP/INFUSE in spine surgery: The evidence continues to mount

In 2013, Epstein evaluated AE due to the overwhelming "off-label" use of BMP/INFUSE in spine surgery.[9] The 2008 warning from the Food and Drug Administration (FDA) included the following AE due to BMP/INFUSE: Marked dysphagia, hematoma, seroma, swelling, and/or the need for intubation/tracheostomy. Further studies noted additional AE; heterotopic ossification (HO), osteolysis, infection, arachnoiditis, increased neurological deficits, retrograde ejaculation, and cancer. In 2011, Carragee *et al*. observed that 13 original industry-sponsored BMP/INFUSE spinal surgery studies largely underrepresented the multiple AE attributed to BMP/INFUSE. Also noted was the higher frequency of retrograde ejaculation reported for BMP/INFUSE used "on-label" to perform Anterior Lumbar Interbody Fusion with the Lumbar Tapered Fusion-Cage Device (ALIF/LT-Cage); again a finding that was largely "under-reported."

Complications due to BMP/INFUSE in spine surgery include an increased cancer risk

In 2011 Carragee *et al*. reviewed industry-sponsored reports (reported, underreported, or not reported) regarding the frequency and severity of complications attributed to using BMP/INFUSE in spinal surgery.[2] They observed a significant failure to report complications as observed in many of these studies (e.g. industry affiliated studies, Food and Drug Administration (FDA) data summaries, non-industry sponsored publications, and other databases) that they variously attributed to "inadequate peer review and editorial oversight." When they reviewed 13 initial industry sponsored rhBMP-2 publications concerning BMP/INFUSE's safety and efficacy in 780 patients undergoing spinal procedures (prospective trials), they found no rhBMP-2 reported adverse events (0%). They found, however, "unpublished adverse events and internal inconsistencies" that were not made readily available, that reflected insufficient reporting and bias in industry-sponsored rhBMP-2 trials. This was particularly true for one of the studies looking at posterolateral fusions (PLF) and posterior lumbar interbody fusion (PLIF) vs. control populations. Furthermore, they noted gross exaggerations in the morbidity associated with harvesting iliac crest autograft (e.g. donor site pain) for anterior cervical procedures. They concluded that the frequency of AE attributed to BMP-2 for performing fusions varied from 10% to 50%. With anterior cervical fusions, a 40% risk of AE was noted in the early postoperative period, wherein it contributed to even life-threatening events. ALIF (anterior interbody lumbar fusion) adverse events due to BMP included: An increased frequency of "implant displacement, subsidence, infection, urogenital events, and retrograde ejaculation" versus controls. PLIF (posterior lumbar interbody fusion) were also associated with increased "radiculitis, ectopic bone formation, osteolysis, and poorer global outcomes". Furthermore, higher doses of rhBMP-2 were also associated with a greater apparent risk of new malignancy.

Cancer risk after using recombinant bone morphogenetic protein-2 for spinal fusion

Carragee *et al*. evaluated the impact recombinant human bone morphogenetic protein-2 (rhBMP-2: Growth factor) had in-vitro on the growth/invasiveness of cancer.[3] They utilized "publicly available data from a pivotal, multicenter, randomized controlled trial of patients" with degenerative lumbar spine conditions having single-level instrumented posterolateral fusions utilizing high-dose rhBMP-2 (n = 239 patients) vs. autograft (control group; n = 224). The risk for developing new cancers was assessed 2 and 5 years postoperatively. At two years, 15 new cancers were found in 11 patients with rhBMP-2 vs. 2 in the control autgraft group. Even though only 63% of patients could be evaluated at 5 postoperative years, there was a "significantly greater incidence of cancer events in the rhBMP-2 group". They also observed a higher risk of cancer with "a high dose of 40 mg of rhBMP-2/CRM in lumbar spinal fusion.

Complications including theoretical increased carcinogenesis with BMP in spine surgery

Tannoury and An observed that recombinant human bone morphogenetic protein 2 (rhBMP-2) is an extremely strong growth factor that promotes bone formation and is utilized to perform spinal fusions, avoiding the need for autograft harvesting (e.g. from the iliac crest, avoiding harvest morbidity).[24] This study reviewed the following multiple adverse events (AE)/complications attributed to BMP-2 in the lumbar and the cervical spine; "retrograde ejaculation, antibody formation, postoperative radiculitis, postoperative nerve root injury, ectopic bone formation, vertebral osteolysis/edema, dysphagia and neck swelling, hematoma formation, interbody graft lucency, and wound healing complications." Furthermore, they considered BMP-2's costs, dosages, carriers, and "theoretical carcinogenesis".

BMP used in spinal fusions increased risk of benign tumors but not cancer

Lad *et al*. looked asked whether BMP increased the risk of cancer after spinal fusion.[14] Using the Market-Scan database, the authors looked at the frequency of benign and malignant tumors at a minimum of two years following lumbar fusions with BMP. There were 4,698 patients who received BMP; they exhibited a significantly higher rate (31% increase) of benign tumors of the nervous system, but not in malignancies.

Bone graft extenders and substitutes: Potential for complications

Kaiser *et al*. reviewed the role of BMP in achieving lumbar fusion while limiting the morbidity of harvesting autologous iliac crest bone (AICB).[12] Alternatives to AICB include; local autograft, calcium-phosphate derivatives ((Nanoss Bioactive (Pioneer Surgical, Marguette, MI, USA); Vitoss, (Stryker Corporation, Indianapolis, In, USA)), demineralized bone matrix ((DBM, e.g. ICM Inductive Conductive Matrix (Medtronic, Memphis, TN, USA)), and the family of bone morphogenetic proteins (BMPs (predominantly BMP/INFUSE, Medtronic, Memphis, TN, USA).[12] As graft extenders/substitutes, calcium phosphate salts plus locally harvested autograft and BMP-2 have proven effective alternatives to AICB. However, there are concerns regarding heterotopic bone formation and other morbidities attributed to BMP.

Controversy regarding cancer risk of BMP/INFUSE

Devine *et al*. cited the increased cancer risk attributed to "both BMP and their receptors" identified from tumor surgery.[8] Additionally the product AMPLIFY (rhBMP-2, 40 mg: Medtronic, Memphis, TN, USA) was correlated with an even higher frequency of cancers in the investigational group vs. control patients. The authors then systematically evaluated the cancer risk of BMP/INFUSE in spinal fusions utilizing the peer reviewed literature and FDA available data (through January 2012). They found, using specific exclusion criteria, that only 5 peer reviewed articles and 2 FDA studies regarding cancer should be considered valid when assessing AE for spinal fusions utilizing rhBMP-2 or 7. Cancer was reported for on-label rhBMP-2/INFUSE use by the FDA; it appeared to be the same in the rhBMP-2 vs. control groups; the frequency was 0.7% at 24 months. However, the off-label use of BMP for posterolateral fusions did correlate with a somewhat higher risk of cancer vs. controls in three randomized/controlled studies and one poorer quality study (retrospective analysis). For PLF the risk of cancer was 3.8% with 40 mg of BMP-2 (AMPLIFY) vs. 0.9% with controls. For two randomized controlled trails using rhBMP-7 vs. controls (without BMP), the cancer risk was 12.5% vs. 5.6% and 8.3% vs. 0% respectively. The authors concluded: The sample size for these studies were small, and therefore, the cancer risk with BMP-2 may be proportional to the dose utilized. Therefore, longer follow up studies are needed, and "more refined guidelines are required for the use of BMP."

LITERATURE AGAINST BMP CONTRIBUTING TO CANCER IN SPINE SURGERY

The two large database studies which follow must be reviewed with great skepticism, as one always has to question the quality/accuracy of the data being collected and by whom [Table 1]. "GIGO: Garbage in-garbage out" must always be considered when conclusions from these massive series appear so counter to those gleaned from the meticulous clinical surgical studies using BMP/INFUSE cited above, and the myriad of subsequent basic science/medical clinical studies to follow.

Risk of cancer not increased with lumbar fusion using rhBMP-2/INFUSE

Cooper and Kou found an equivocal correlation between the risk of cancer and the use of BMP/INFUSE for performing lumbar fusion surgery.[6] Specifically, they retrospectively evaluated the risk of cancer following lumbar fusions performed with or without rhBMP-2/INFUSE. They analyzed data from 146,278 Medicare patients age 67 or older who had spinal procedures between 2003-8; patients were followed through 2010. One to 26 types of cancers were analyzed in this population; prostate, breast, lung, and colon. The overall cancer frequency was 15.1% for patients with an average 4.7-year follow; 15.4% for those receiving rhBMP-2 vs. 17% for those managed without BMP. Using a multivariate proportional hazards model, they found no evidence that administration of rhBMP at the time of lumbar fusion surgery was associated with cancer risk."

Use of BMP in thoracolumbar fusions; no increased cancer risk

In Veeravaqu *et al*. they looked at the use of BMP in thoraco-lumbar (TL) fusions utilizing the Market Scan Longitudinal database.[25] The study included 52,259 matched cohorts of patients having TL fusions with or without BMP (matched 2:1) from 2006-2010. Those receiving BMP had "fewer refusions, decompressions, posterior revisions, anterior revisions, or any revision". They did note, however, that at 30 days, BMP was associated with an increased frequency of: Dysrhythmia, delirium, and chronic pain (single/multilevel procedures). Although they concluded that BMP was "not associated with the post-operative development of cancer", they acknowledged the "lack of long-term follow-up precluded the detection of inter-group differences in malignancies and other rare events that may not appear until later".

BMP used in spinal fusions does not increase risk of pancreatic cancer

Mines *et al*. looked at whether BMP used in spinal fusions contributed to the risk of pancreatic cancer in a Medicare population.[18] This was a retrospective cohort study performed from 2003-5, which involved patients over the age of 66 undergoing lumbar fusions utilizing BMP-2. Of the 93,654 patients identified, averaging 75 years of age, 16.5% had claims for BMP usage. With an average 1.4 year follow up, 91 patients had pancreatic CA; 8 in the BMP group and 83 in the non BMP group.

The authors therefore concluded that for "elderly patients who underwent lumbar fusion surgery, exposure to BMP was not associated with an increased risk of pancreatic cancer."

BASIC SCIENCE STUDIES DOCUMENT BMP (BMP-2) AND TGF-BETA CONTRIBUTE TO BREAST CANCER

A review of the basic science literature, moreso than the spine literature, documented a positive correlation between bone morphogenetic protein (BMP), its derivatives (e.g. BMP/INFUSE, and multiple other variants of BMP), and TGF-Beta (transforming growth factor beta) in the promotion and growth of breast cancers [Table 1].

Breast cancer: BMP2 promotes migration and invasion of breast cancer cells

Jin *et al*. stipulated that BMP2 modulates/contributes to the proliferation/differentiation of breast cancer cells, and promotes the migration/invasion of Michigan Cancer Foundation-7 (MCF-7) cells.[10] The authors concluded that it was critical to assess the oncogenicity of BMP2 if utilized for tissue engineering.

BMP-2 induces in vitro invasion/*in vivo* hormone independent growth of breast cancer

Clement *et al*. noted that breast cancer cell lines migrated toward BMP-2 sources, and the rate was dose dependent on the concentration of BMP-2.[5] They found "elevated levels of BMP-2 enhance the tumorigenic properties of breast carcinoma cells and drive the cells towards a more aggressive phenotype with estrogen independent growth."

BMP-related stem cell activity may impact development of malignant mammary epithelial cells

Balboni *et al*. assessed whether/how BMP (specifically BMP-7)-related stem cell activity contributes to the production of malignant mammary epithelial cells.[1] They report Np63 increased bidirectional "target gene regulation" affected by binding to more than 5000 sites in the genome. Their immunohistochemical analysis showed "hyperactivation of BMP signaling is common in human breast cancers, most notably in the basal molecular subtype, as well as in several mouse models of breast cancer."

Bone morphogenetic proteins contribute to development/progression of breast cancer

Ye *et al*. reviewed how BMP's play a critical role in bone formation/turnover, and contribute to breast cancer-related solid tumors and bone metastases.[28] They noted aberrations of both BMP expression/signaling and their impact on how breast CA develops/progresses. Furthermore, in-vitro studies showed that "BMP's can regulate a range of biological functions of breast cancer cells."

BMP stimulate mammary fibroblasts to promote breast cancer

Owens *et al*. observed that BMPs are "highly expressed in human breast cancers".[20] They found that fibro blasts exposed/stimulated by BMP4 "enhance mammary carcinoma cell invasion", and "may stimulate tumor progression within the tumor microenvironment."

Humoral bone morphogenetic protein 2 induces breast cancer micro calcification

Liu *et al*. noted that micro calcifications are utilized as critical markers for diagnosing breast cancer on mammograms, but the etiology/physiology of these calcifications are not well understood.[16] Utilizing a R3230 rat model of breast tumors (adapted to cell culture), they asked whether BMP-2 promoted "bone formation and pathologic vasculature calcification", and whether it could be "transduced with adenoviral BMP-2, and inoculated (it) into a syngeneic host." They studied tumor growth, calcium salt deposition (e.g. micro-computed tomography and near-infrared fluorescence), and quantitated plasma BMP-2 levels (e.g. with immunosorbent assays). At 3 weeks, 100% of the breast tumors developed micro calcifications (vs. none in normal tissues). This study served as the "first reproducible rodent model of breast cancer micro calcification", and "proved that BMP-2 expression was sufficient for initiating the process".

Induction of estrogen receptor α-36 expression by BMP2 in breast cancer cells

Wang *et al*. noted, "expression of estrogen receptor-α (ERα) is one of the most important diagnostic and prognostic factors of breast cancer."[26] BMP's control and cancer development and ER, both need further investigation of the interaction between the two. BMP2s, in a dose dependent manner, induced ERα-36 expression in breast cancer cells, and significantly up-regulated ERα-36 (e.g. seen with western blot assays). It also changed tumor resistance to endocrine treatment by changing the expression profile of ERs.

Osteomimicry of mammary adenocarcinoma cells in vitro

Cox *et al*. observed that bone metastases are extremely common with breast cancer, and therefore, "mammary cells possess osteomimetic capabilities that may allow them to adapt to, and flourish within the bone microenvironment."[7] Since these cells typically calcify within breast tissue, the authors developed an in-vitro model of mammary mineralization with murine mammary adenocarcinoma 4T1 cells. When exposed to BMP-2/phosphate supplemented media, they exhibited increased mineralization within 3D collagen glycosaminoglycan scaffolds (e.g. a model mimicking bone metastases), and

increased mineralization of 4T1 adenocarcinoma cells, confirming preferential metastasis to bone.

Differential gene expression of TGF-beta/osteopontin in breast cancer

Reinholz *et al*. observed that different types of cytokines (e.g. members of the TGF-beta family), and tumor necrosis factors (TNF) are involved in the modulation of bone metabolism and spread of breast cancer (e.g. metastasis).[22] They noted that primary breast tumor tissues differentially modulated bone cell function which contributed to their ability to metastasize to bone. Here, the authors examined how multiple members of the TGF-beta and TNF family, osteoprotegerin (OPG), and osteopontin (OPN), interacted with bone morphogenetic protein-2 (BMP-2), in "normal, non-invasive, invasive, and metastatic human breast cancer specimens." They concluded that BMP-2's amongst other bone-related proteins contribute to the invasiveness/metastatic potential of breast cancer.

Animal model of breast cancer micro calcification

Liu *et al*. determined the need for a better animal model for detecting breast cancer micro calcification.[17] They developed a model based upon "a single systemic injection of recombinant bone morphogenetic protein-2 (rBMP-2) utilizing Fischer 344 rats bearing syngeneic R3230 breast tumors. After the rats received a single intraperitoneal injection of rBMP-2, tumor micro calcifications were followed utilizing micro-single photon emission computed tomography (SPECT) and micro computed tomography (CT). They found that just one injection of > or = 50 microg rBMP-2, administered when tumors were not yet palpable, resulted in dose-dependent micro calcification in 8 of 8 R3230 tumors." Tumor calcifications increased from 2 to 4 following the administration of rBMP-2 and constituted "dose-dependent and time-dependent micro calcifications".

CLINICAL STUDY DOCUMENTS BMP (BMP-2) AND TGF-BETA CONTRIBUTE TO BREAST CANCER

Genetic variation in BMPs correlate with increased breast cancer risk in an admixed populations

With the hypothesis that BMPs are important in the promotion/progression of breast cancer, Slattery *et al*. studied the impact of BMP on the risk of developing breast cancer in Hispanic (2111 vs. controls 2597) vs. non-Hispanic (1481 vs. 1586) white females[23] [Table 1]. They concluded that genetic variations in BMP's were associated with different rates/risks of breast cancer in admixed populations, and were correlated with their menopausal status.

BMP-2 ASSOCIATED WITH OTHER MULTIPLE MALIGNANCIES AND ANGIOGENESIS

Angiogenesis: BMP is associated with many malignancies; silencing BMP-2 expression inhibits A549 and H460 cell proliferation/migration

Chu *et al*. noted that BMP-2, part of the TGF-β transforming growth factor super family, closely correlated with an increase in multiple malignancies, especially lung cancer.[4] In their study, BMP-2 mRNA expression was observed in 61 non-small cell lung cancer (NSCLC) samples. They found "high BMP-2 expression levels were significantly associated with the occurrence of lymph node metastases and tumor stage ($P < 0.05$)". They concluded that BMP-2 mRNA is a risk factor for survival in patients with NSCLC.

Angiogenesis: BMP-2 Induces tumor angiogenesis

Raida *et al*. evaluated BMP's and TGF-β compounds' contribution to tumor angiogenesis.[21] They evaluated the impact of "BMP-2 on human dermal microvascular endothelial cells (HDMECs)" and analyzed "BMP-2's over-expression on tumor vascularization of human xenografts with transfected MCF-7 breast cancer cells (MCF-7/BMP2) in mice."

Angiogenesis: BMP protein receptors and signal transduction

Miyazon *et al*. observed that BMP's, part of the TGF-β family, have a wide-ranging impact on bone, cartilage, blood vessels, heart, kidney, neurons, liver, and lung tissues.[19] They further determined that alterations of BMP "signaling pathways" may be correlated with "vascular diseases, skeletal diseases, and cancer. "

BASIC SCIENCE BEHIND MULTIPLE OTHER MALIGNANCIES DUE TO BMP

This section deals with the basic scientific literature pertaining to animal models of cancers, other than breast cancer, and focuses on how exposure to BMP's (and other members of the TGF-Beta family) result in the up-regulation of different tumor lines [Table 1].

BMP increases risk of growth of lung cancer in mouse model

Having observed that bone morphogenetic proteins (BMPs) and transforming growth factor-beta (TGF-β) promote skeletal metastases via autocrine cells, Lee *et al*. asked whether BMP spp24 would increase the rate of growth of lung cancer cells in a mouse model.[15] They also asked whether the growth of lung cancer cells would be inhibited by phospoprotein 24kDA (spp24) (eg. the latter binds to and inhibits the osteogenic potential of these

factors). They found that in a mouse model (*in vivo*), the latter successfully inhibited lung tumor growth in both "soft tissue and intraosseous environments".

Role of BMP in adrenal tumorigenesis

Johnsen and Beuschlein observed that BMPs regulate many biological processes that include cell specification, differentiation, organogenesis, and tumorigenesis.[11] They found that BMPs also regulate adrenal physiology and that BMP-dependent mechanisms modulate "catecholamine synthesis, steroidogenesis, and dysregulation of BMP signaling in adrenal tumorigenesis."

Colorectal cancer risk-associated variant Lyx 25Ser in proximity to BMP-2

Khan et. al. noted that colorectal cancer (CRC) is the "third most prevalent cancer and fourth leading cause of cancer-related deaths globally."[13] Importantly, several CRC risk associated genetic sites are located in close proximity to bone morphogenetic protein 2 (BMP2).

CONCLUSION

The role of the BMP's and other members of the TGF-Beta family in promoting different cancers either clinically or in the laboratory need to be brought to light. The reason for emphasizing the potential increased risk of cancer utilizing these growth factors is that very day, spinal surgeons are implanting BMP/INFUSE in extremely high doses "on" or "off-label" to patients undergoing spinal fusions. The question is whether that patient is at higher risk for developing cancer early on or in the future? According to laboratory work, the BMP's and members of the TGF-Beta family promote breast cancer. There is also increasing data regarding their potential roles in other malignancies. Nevertheless, due to the lack of "cross-talk" between basic scientists and spine surgeons, we, as spine surgeons, are not sufficiently aware of how we are exposing our patients to an increased risk of cancer. Certainly, industry has not largely come forward to acknowledge this risk. Therefore, we must take on the responsibility of educating ourselves and our colleagues so that we may avoid subjecting our patients to cancers that may appear rapidly, or even several decades later.

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