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Osteonecrosis of the Jaw Risk Factors in Bisphosphonate Treated Patients with Metastatic Cancer

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Running Head: ONJ Risk Factors

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ABSTRACT:

Background: A case control study was performed to define clinical and genetic risk factors associated with osteonecrosis of the jaw in patients with metastatic cancer treated with bisphosphonates.

Methods: Clinical data and tissues were collected from patients treated with bisphosphonates for metastatic bone disease who were diagnosed with osteonecrosis of the jaw (cases) and matched controls. Clinical data included patient, behavioral, disease, and treatment information. Genetic polymorphisms in *CYP2C8* (rs1934951) and other candidate genes were genotyped. Odds ratios from conditional logistic regression models were examined to identify clinical and genetic characteristics associated with case or control status.

Results: The study population consisted of 76 cases and 126 controls. In the final multivariable clinical model, patients with osteonecrosis of the jaw were less likely to have received pamidronate than zoledronic acid (odds ratio=0.18, 95% Confidence interval: 0.03-0.97, p=0.047) and more likely to have been exposed to bevacizumab (OR=5.15, 95% CI: 1.67-15.95, p=0.005). The exploratory genetic analyses suggested a protective effect for *VEGFC* rs2333496 and risk effects for *VEGFC* rs7664413 and *PPARG* rs1152003.

Conclusions: We observed patients with ONJ were more likely to have been exposed to bevacizumab and zoledronic and identified potential genetic predictors that require validation prior to clinical translation.

Introduction: Bone is a common site for cancer metastases. Approximately 400,000 US adults are living with evidence of bone metastases(Mundy 2002), which are associated with considerable morbidity and mortality. The common skeletal complications of malignancy designated “skeletal-related events” (SRE) include pathologic fractures, spinal cord

compression, hypercalcemia of malignancy and the need for radiotherapy, or surgery, to bone. Prior to the routine use of bisphosphonate therapy, patients with bone metastases would experience an SRE every 3-12 months.(Lipton 2010). The potent osteoclast inhibitors, bisphosphonates and denosumab decrease the rate of SREs by approximately 30%-50%(Coleman 2007; Ford et al. 2013). Therefore, these agents are routinely recommended in the management of patients with metastatic bone disease(Gralow et al. 2013; Van Poznak et al. 2017).

The bisphosphonates and denosumab are associated with an oral condition known as osteonecrosis of the jaw (ONJ) also known as antiresorptive agent-induced osteonecrosis of the jaw (ARONJ), bisphosphonate related osteonecrosis of the jaw (BRONJ) and medication related osteonecrosis of the jaw (MRONJ). The American Association of Oral and Maxillofacial Surgeons (AAOMS) 2014 position paper provides the case definition of (MR)ONJ in patients if all of three of the following conditions are met: 1) current or prior treatment with anti-resorptive or anti-angiogenesis agents, 2) exposed bone or bone that can be probed through an intraoral or extraoral fistula in the maxillofacial region that has persisted for more than eight weeks, and 3) no history of radiation to the jaws or obvious metastatic disease to the jaws(Ruggiero et al. 2014). An ONJ lesion typically is non-healing or slow to heal, and often is complicated by secondary infection with associated pain and swelling.

The prevalence of ONJ has not been well defined. In patients treated with zoledronic acid or denosumab for up to 36 months, the incidence appears to be 1%-2%(Saad et al. 2012); however, the rates of ONJ appear to increase over time. In patients with metastatic breast cancer or prostate cancer the rates of ONJ are between 5% and 8% with drug exposures of 5 to 5.6 years(Stopeck et al. 2016). The majority of the 400,000 patients with bone metastases in the US will be treated with an osteoclast inhibitor. If 1%-2% develop ONJ, then 4,000 to 8,000 of these patients will have ONJ at any given time. This estimate would be higher if one calculates the risk using rates reported with longer term exposure.

The etiology of ONJ is unknown. Potential mechanisms involved in the development of ONJ include infection, immune dysfunction, inflammation, vascular effect, over suppression of bone remodeling, drug interactions, and genetic predisposition(Van Poznak 2006). Identifying risk factors associated with the development of ONJ will aid in counseling patients on their individual risks, and may influence dental monitoring and early detection, as well as inform translational

research investigating the mechanism of ONJ. Therefore, we performed a case-control study to define clinical and genetic risk factors associated with ONJ.

Materials and Methods:

Trial Conduct:

A multi-institutional, translational study was performed. Indiana University, MD Anderson, Memorial Sloan-Kettering and University of Michigan (UM) collaborated to identify cases of ONJ and matched controls. The retrospective study protocol (ClinicalTrials.gov Identifier: NCT01325142) was reviewed and approved by the Institutional Review Board of each of the four collaborating sites and the work was conducted in full accordance with the Declaration of Helsinki.

All study patients had cancer involving the bone, had received bisphosphonate therapy and had not received radiation to the jaw. Cases were defined as having ONJ using the American Society of Bone and Mineral Research definition of ONJ(Khosla et al. 2007), which is consistent with present definition used by AAOMS(Ruggiero et al. 2014), as outlined above although antiangiogenic therapy was not included in the ONJ definition at the time of study data acquisition. Cases were identified using medical, dental and surgical databases as well as health care provider recall. Patients were selected as controls if they had bone metastases and received bisphosphonate treatment but did not have ONJ. Control subjects were matched to the case based on age (within 5 years), primary tumor type (breast, multiple myeloma, prostate, lung, other), and gender (male, female). The medical records were reviewed to confirm eligibility as a case or control. To assess clinical and epidemiologic characteristics associated with risk of ONJ, it is critical that the case and controls not be “over” matched to key suspected risks such as duration of bisphosphonate, steroid exposure, cancer therapies, and comorbidities which are evaluated as clinical risk factors. Of note, denosumab was not FDA approved for the treatment of bone metastases at the time this study was initiated.

Clinical and epidemiologic data were abstracted from the patient’s medical and dental health records as available at the patient’s home institution using study specific case report forms. Covariates from the clinical data contained patient demographics, including age at time of diagnosis of ONJ or for controls, age at last follow up at time of study, gender, tumor diagnosis, cancer therapies, history of bisphosphonate exposure, steroid exposure, tobacco and alcohol

use. Medical records from oral health providers were reviewed to categorize patients' dental hygiene as good, moderate, or poor and identify evidence of prior periodontal disease. Details of ONJ lesions included location and number of ONJ lesions and clinical presentation.

Genotyping

To assess for a genetic predisposition for developing ONJ, genotyping of candidate single nucleotide polymorphisms (SNPs) that had previously been reported as associating with ONJ or are associated with the angiogenesis or bisphosphonate mechanism of action were genotyped. The *a priori* defined primary SNP hypothesis was that *CYP2C8* rs1934951 would increase ONJ risk, as this SNP has been reported as a predictor of ONJ risk in several studies(Kastritis et al. 2017; Sarasquete et al. 2008; Zhong et al. 2013). *CYP2C8* rs1934951 was genotyped using Taqman Allelic Discrimination Assays, as previously described(Sikora et al. 2011). Additional SNPs of interest(Nicoletti et al. 2012; Yang et al. 2019) in *CYP2C8* (rs1341162, rs1934980), *PPARG* (rs1152003), *VEGFC* (rs7664413, rs2333496, rs6838834, rs3775203) *VEGFA* (rs833061, rs699947, rs2010963), *FDPS* (rs11264359, rs17367421), *IGFBP7* (rs11934877) and *ABCC4* (rs1678387) were genotyped on a single multiplex Sequenom panel as previously described(Hertz et al. 2015b) for inclusion in an exploratory pharmacogenetic analysis.

DNA was isolated from archived FFPE specimens, following our previously validated technique for confirming accurate germline genetic assessment using archived specimens(Hertz et al. 2015b). DNA was extracted from FFPE specimens using the DNeasy Blood and Tissue Kit (Qiagen, Valencia, CA) as previously described(Sikora et al. 2011). Amplification-Quality DNA (AQ-DNA) was quantified using a standard curve set with 100bp GAPDH fragment primers and SYBR Green real-time PCR. Samples with yields below the limit of AQ-DNA thresholds were excluded from genotyping analysis. Taqman genotyping methods are compatible with levels of FFPE DNA down to 50 pg whereas Sequenom requires a higher input of DNA(Hertz et al. 2015a). After AQ-DNA quantification 56 cases and 115 controls were acceptable for use with Taqman genotyping and 46 cases and 109 controls were acceptable for use with Sequenom genotyping.

Statistical Design: Conditional logistic regression was used to adjust for the matched nature of the data(BRESLOW et al. 1978). Odds ratios from conditional logistic regression models were examined to assess the univariate association between clinical characteristics and ONJ status. The study then created multivariable conditional logistic regression models to evaluate the

adjusted associations between the clinical characteristics with ONJ status. A stepwise selection procedure was implemented to aid in the variable selection for the final multivariable model, where the significant univariate clinical characteristics were considered for the multivariable model selection. Once the multivariable model was selected, odds ratios were examined to determine which factors have a significant adjusted association with ONJ status. The analysis here was limited to use of pamidronate and zoledronic acid.

A similar conditional logistic regression analysis was used to determine the association between each SNP and ONJ status. Each SNP analysis evaluated the unadjusted linear effect from conditional logistic regression models assuming an additive genetic effect, expecting that the risk of ONJ will be greatest in the variant (A) group in the primary analysis of *CYP2C8* rs1934951, as previously reported(Kastritis et al. 2017; Sarasquete et al. 2008; Zhong et al. 2013). Exploratory statistically uncorrected pharmacogenetic analyses of all other SNPs were conducted similarly, using conditional logistic regression assuming additive genetic models. All nominally significant univariate associations ($p<0.05$) were introduced into multivariable logistic regression models adjusting for bisphosphonate (pamidronate vs. zoledronic acid) and bevacizumab (yes vs. no).

During the course of the study, it became apparent that the target 100 cases and 200 controls would not be obtained. The availability of study materials was less than expected, and the duration of time to collect data abutted the end date of funding support. Plans were made to adjust the analysis to optimize conditions including adjustments for the matching with the analysis of the collected data with odds ratios. All analyses were performed at the University of Michigan using SAS, version 9.4 (SAS Institute Inc.). **Results**:

Patients:

The study population consisted of 202 patients with cancer involving bone who received bisphosphonate therapy without radiation therapy to the jaw. There were 76 cases of ONJ and 126 controls. All cases had at least one matched control, and none had more than 2 matched controls, **Figure 1**. The demographics of the patients included in the analysis stratified by case or control designation are outlined in **Table 1**. Eight patients had exposure to oral bisphosphonates used for osteoporosis, four each in the case and control group (data not shown). Although not matched on duration of bisphosphonate use, the cases and controls had similar duration of exposure.

Analysis of Clinical Factors

Univariate analysis was performed to identify clinical and epidemiologic characteristics associated with an increased risk for ONJ (**Table 2**). Exposure to the anti-angiogenic therapy, bevacizumab was associated with increased ONJ (Odds Ratio (OR) = 5.82, 95% Confidence Interval (95% CI): 1.92-17.65, p=0.002). ONJ cases were less likely to have received pamidronate than zoledronic acid (OR=0.244, 95% CI: 0.07-0.80, p=0.04). Irritants of the aerodigestive tract (tobacco or alcohol), the status of dental hygiene or periodontal disease, and the number of months a patient had taken zoledronic acid or pamidronate were not associated with the presence of ONJ.

Only bevacizumab exposure and which bisphosphonate was used were significant in the univariate analysis and considered in multivariable model building. Stepwise selection procedures selected both covariates for the final multivariable model (**Table 2**). In the fully adjusted model, ONJ cases were more likely to have received bevacizumab (OR=5.15, 95% CI: 1.67-15.95, p=0.005) and less likely to have received pamidronate than zoledronic acid alone (OR=0.18, 95% CI: 0.03-0.97, p=0.047).

Analysis of Genetic Factors

All SNP analyses are described as the effect of carrying the variant, relative to the wild-type allele. In the pre-specified primary SNP analysis, *CYP2C8* rs1934951 was not associated with ONJ status (OR=0.96, 95% CI: 0.55-1.68, p=0.89, **Table 3**). Several SNPs were nominally associated with ONJ status in the statistically uncorrected secondary genetic analyses. *VEGFC* rs7664413 was associated with increased ONJ risk (β=3.22, 95% CI: 1.32-7.84, p=0.01) and maintained significance after adjustment for bevacizumab and bisphosphonate use (OR=4.08, 95% CI: 1.29-12.87, p=0.02). *VEGFC* rs2333496 had a protective effect (OR=0.52, 95% CI: 0.27-0.97, p-0.04) and *PPARG* rs1152003 had a risk effect (OR=1.90, 95% CI: 1.09-3.30, p=0.02) on ONJ in univariate analyses, however, neither maintained significance after covariate adjustment (both p>0.05).

Discussion

In this retrospective case control study, individuals with ONJ were more likely to have been exposed to zoledronic acid and bevacizumab. Lesions occurred more commonly in the mandible and were not affected by duration of bisphosphonate therapy or dental hygiene. The genetic analysis did not confirm an increased ONJ risk for patients carrying *CYP2C8*

rs1934951, though hypothesis-generating associations were detected for SNPs in *VEGFC* (rs7664413, rs2333496) and *PPARG* (rs1152003).

Our results are consistent with the literature demonstrating that ONJ occurs more commonly in the setting of exposure to zoledronic acid than with pamidronate and zoledronic acid or pamidronate alone(Estilo et al. 2008; Hoff et al. 2008). Interestingly, oral hygiene and periodontal disease, conditions that typically correlate with dental extraction(McFall 1982; Services 2000) were not associated with an increased risk for developing ONJ in this study. Epidemiologic studies have suggested poor oral health status and dental extraction increase the likelihood of ONJ(Barasch et al. 2013)Yarom et al 2019). The lack of association in this study between oral health and ONJ is likely due to the limitations of the retrospective abstraction of oral health data from clinical notes. Prospective analysis of SWOG S0702, an ONJ registry study, will likely provide insight into associations between oral health and risk of ONJ.

The findings of this study support the previously reported association between increased risk for ONJ and bevacizumab, a monoclonal antibody targeting VEGF that is known to affect vascularization(Arjaans et al. 2016; McArthur et al. 2008). Indeed, a history of antiangiogenic therapy was incorporated into the definition of ONJ in an updated American Association of Oral and Maxillofacial Surgeons(Ruggiero et al. 2014). The 2019 guideline addressing medication related ONJ produced by the American Society of Clinical Oncology, the Multinational Association of Supportive Care in Cancer and the International Society of Oral Oncology also includes exposure to anti-angiogenic therapies in the definition of medication related ONJ(Yarom et al. 2019). The strong (OR>5) association of ONJ with antiangiogenic therapies in our study may reflect alterations in vascular/wound healing that may increase risk for developing ONJ. Although bevacizumab is a monoclonal antibody targeting VEGF and zoledronic acid is a nitrogen containing bisphosphonate with different chemical structures and mechanisms of action, zoledronic acid has also been shown to impact the angiogenesis pathway in preclinical models(Wood et al. 2002)(Fournier et al. 2002; Ohba et al. 2014) and clinically(Ferretti et al. 2005; Santini et al. 2003; Vincenzi et al. 2005). In addition, a phase II study using zoledronic acid and bevacizumab together with docetaxel, thalidomide and prednisone reported an usually high incidence of ONJ of 18%(Aragon-Ching et al. 2009) suggesting a possible additive risk when multiple therapies are co-administered. It is of note that a meta-analysis of clinically relevant studies demonstrated that bisphosphonates use did not delay fracture healing time(Li et al. 2015) as might be expected if there were a clinically

meaningful impact on the healing process and angiogenesis The etiology of ONJ remains undefined, and may be multifactorial(Allen and Burr 2009; Van Poznak 2006).

This study did not validate an association between *CYP2C8* rs1934951 and increased ONJ risk, which has been reported in several independent cohorts(Kastritis et al. 2017; Sarasquete et al. 2008; Zhong et al. 2013). Our results (OR=0.96, p=0.89) suggest that our lack of finding was not merely due to lack of power, but formal meta-analysis approaches are needed to further explore this possibility. The secondary pharmacogenetic analysis detected an increased ONJ risk in patients carrying *PPARG* rs1152003, which has been previously reported to be both a risk(Kastritis et al. 2017) and protective(Di Martino et al. 2011) factor. *PPARG* is a biologically plausible candidate gene due to its involvement in bone homeostasis and remodeling(Wan 2010), however, the inconsistent direction of effect across studies and lack of significance after adjustment in our study necessitate additional studies to confirm this association. Similarly, the hypothesis generating finding that *VEGFC* rs7664413 increases ONJ risk warrants further research in independent cohorts to determine whether this SNP could be useful for predicting ONJ risk. *VEGFC* rs7664413 has not been previously investigated as a genetic predictor of ONJ to our knowledge; however, it has been associated with increased risk of other phenotypes related to VEGF function including preeclampsia(Srinivas et al. 2010). SNPs in *VEGFC* and *VEGFA* have been a major focus of candidate-gene ONJ pharmacogenetic studies based on the anti-angiogenic effects of bisphosphonates and role of VEGF in angiogenesis(Arduino et al. 2011; Yang et al. 2019)(Choi et al. 2015). (Srinivas et al. 2010)There are additional potential SNPs of interest that were reported to be associated with ONJ after our genetic analyses were conducted that were not included in this analysis.(Yang et al. 2019). In this study, different genotype techniques were used for different SNPs, but cases and controls were always genotyped using the same technique, thereby eliminating concern for bias

The small sample size and the retrospective study design limit confidence in our findings, particularly the lack of association for some clinical factors such as race, oral hygiene, time on bisphosphonates, and periodontal disease that have been reported to be associated with ONJ(McFall 1982; Services 2000; Yang et al. 2019). Additionally, genetic risk factors for ONJ from bisphosphonates and bevacizumab may be distinct, though a pharmacogenetic analysis in the subset of cases and controls not receiving bevacizumab did not have meaningfully different findings (data not shown). Yet, with these limitations, the data generated on risk of ONJ were consistent with the findings of most clinical and epidemiologic data demonstrating both

zoledronic acid and bevacizumab as drugs associated with increased ONJ risk. Our case control study was performed prior to the introduction of denosumab into the routine clinical care of patients with bone metastases. Hence, we cannot comment on ONJ and denosumab, a drug that is in common use at this time.

With potentially hundreds of thousands of patients with metastatic bone disease at risk of ONJ, the condition remains a clinically relevant concern. This study demonstrated exposure to bevacizumab and use of zoledronic acid are associated with ONJ, as well as a suggestion that a genetic vulnerability to ONJ could exist. These data, along with other case control studies, provide a solid foundation for targeted analysis of ONJ risk factors in the prospective, observational clinical study run through SWOG "S0702: Observational study of osteonecrosis of the jaw (ONJ) in patients with metastatic bone disease starting zoledronic acid", NCT00874211. Developing an index to use for ONJ risk assessment remains a worthy target. Patients, dentists and medical oncologists will benefit from an instrument that will provide a personalized ONJ risk assessment to guide both oral care interventions and use of systemic anticancer therapies. By identifying a population at high risk for ONJ, future studies may provide evidence-based guidelines for dental monitoring and management of early detected ONJ, as well as inform research investigating the mechanism of ONJ.

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Author contributions Catherine Van Poznak: Contributed to conception, design, data acquisition and interpretation, drafted and critically revised the manuscript. Evan L. Reynolds: Contributed to data interpretation, performed all statistical analyses, drafted and critically revised the manuscript. Cherry L. Estilo: Contributed to data acquisition and critically revised the manuscript. Mimi Hu: Contributed to data acquisition and critically revised the manuscript. Bryan

Paul Schneider: Contributed to data acquisition and critically revised the manuscript. Daniel L. Hertz: Contributed to data interpretation and critically revised the manuscript. Christina Gersch: Contributed to data acquisition and critically revised the manuscript. Jacklyn Thibert: Contributed to data acquisition and critically revised the manuscript. Daffyd Thomas: Contributed to data acquisition and critically revised the manuscript. Mousumi Banerjee: Contributed to data acquisition and critically revised the manuscript. James M. Rae: Contributed to design, data interpretation, and critically revised the manuscript. Daniel F. Hayes: Contributed to conception, design, data acquisition and interpretation, drafted and critically revised the manuscript. All authors gave their final approval and agree to be accountable for all aspects of the work

Data Availability:

Data available upon reasonable request to corresponding author.

Table 1 Demographics of the study population

	Demographic	Case N=76	Control N=126
Age	Years	63.4(±10.6)	65.6 (±10.5)
Gender	Female	32 (42.1%)	50 (39.7%)
Race	White	68 (89.5%)	101 (80.2%)
	Asian	1 (1.3%)	3 (2.4%)
	Black	6 (7.9%)	19 (15.1%)
	Other	1 (1.3%)	2 (1.6%)
	Not reported	0 (0%)	1 (0.79%)
Tumor diagnosis	Breast	37 (48.7%)	63 (50%)
	Multiple myeloma	19 (25%)	39 (31%)
	Prostate	14 (18.42%)	17 (13.5%)
	Other	6 (7.9%)	7 (5.6%)
Bisphosphonate use	Pamidronate	6 (7.9%)	24 (19.0%)
	Zoledronic acid	56 (73.7%)	75 (59.5%)
	Pamidronate and zoledronic acid	14 (18.4%)	27 (21.4%)
Months of Bisphosphonate	Pamidronate	29.0 (±12.4)	38.6 (±40.6)
	Zoledronic Acid	25.7 (±121.7)	28.8 (±24.1)

Treatment	Zoledronic Acid plus Pamidronate	55.1 (±43.6)	51.0 (±36.2)
Radiation to head or neck area	Yes (%)	9 (11.8%)	0 (0%)
Tobacco use*	Prior or present	40 (52.6%)	24* (48.0%)
Alcohol use	Prior or present	34 (44.7%)	52 (41.3%)
Exposure to Bevacizumab	Yes (%)	20 (26.3%)	11 (8.7%)
Exposure to multiple classes of chemotherapy	Yes (%)	34 (44.7%)	65 (51.6%)
ONJ Characteristics at presentation	Mandible	29 (38.2%)	X
	Maxilla	11 (14.5%)	X
	Multiple lesions	34 (44.7%)	X
	Unspecified location(s)	2 (2.6%)	X
	Pain	29 (38%)	X
	Inflammation/Infection	24 (31.6%)	X

*Tobacco data not available for 76 controls. All data reported as mean (± standard deviation) or n (%)

Table 2 Clinical Associations with ONJ

Clinical Variables	Comparison vs Reference	Odds Ratio	95% Confidence Interval	P-Value	Adjusted Odds Ratio	95% Confidence Interval	P-Value
Race/Ethnicity	Asian vs White	0.593	0.047-7.432	0.94			
	Black vs White	0.405	0.138-1.188	0.42			
	Other vs White	0.720	0.060-8.674	0.91			
Osteoporosis	Yes vs No	1.636	0.639-4.192	0.37			
Tobacco History	Yes vs No	1.195	0.482-2.965	0.70			
Alcohol History	Yes vs No	1.186	0.652-2.158	0.58			
Dental Hygiene	Moderate vs Good	0.718	0.288-1.792	0.46			
	Poor vs Good	1.070	0.357-3.209	0.68			
Periodontal Disease History	Yes vs No	0.575	0.253-1.307	0.19			
Steroid Exposure	Yes vs No	1.238	0.633-2.422	0.53			
Bevacizumab Exposure	Yes vs No	**5.816**	**1.916-17.652**	**0.002**	**5.152**	**1.665-15.945**	**0.005**
Bisphosphate agent	Pamidronate vs Zoledronic Acid	**0.244**	**0.074-0.799**	**0.04**	**0.181**	**0.033-0.974**	**0.047**
	Zoledronic & Pamidronate vs Zoledronic Acid	0.653	0.283-1.507	0.54	0.580	0.217-1.552	0.28
Time on Bisphosphonate	Months (reported as β-coefficient)	0.995	0.982-1.007	0.49			

Bold indicates statistically significant associations ($p<0.05$)

Table 3 Genetic Associations with ONJ

Gene	rsID	Odds Ratio	95% Confidence Interval	P-Value	Adjusted* Odds Ratio	95% Confidence Interval	P-Value

CYP2C8	rs1934951**	0.960	0.548-1.682	0.89			
	rs1341162	0.913	0.505-1.651	0.76			
	rs1934980	0.911	0.473-1.754	0.78			
PPARG	rs1152003	**1.898**	**1.093-3.297**	**0.02**	1.918	0.996-3.692	0.05
VEGFC	rs7664413	**3.222**	**1.324-7.844**	**0.01**	**4.078**	**1.292-12.873**	**0.02**
	rs2333496	**0.516**	**0.273-0.973**	**0.04**	0.542	0.257-1.141	0.11
	rs6838834	2.000	0.518-7.718	0.31			
	rs3775203	1.245	0.646-2.397	0.51			
VEGFA	rs833061	1.995	0.974-4.087	0.06			
	rs699947	1.407	0.767-2.583	0.27			
	rs2010963	1.347	0.677-2.683	0.40			
FDPS	rs11264359	0.788	0.417-1.489	0.46			
	rs17367421	2.253	0.336-15.112	0.40			
IGFBP7	rs11934877	1.310	0.642-2.672	0.46			
ABCC4	rs1678387	0.757	0.212-2.701	0.67			

*Significant associations in the univariate analysis were adjusted for Bevacizumab and Bisphosphonate

**Pre-specified primary SNP analysis

Bold indicates statistical significance ($p<0.05$)

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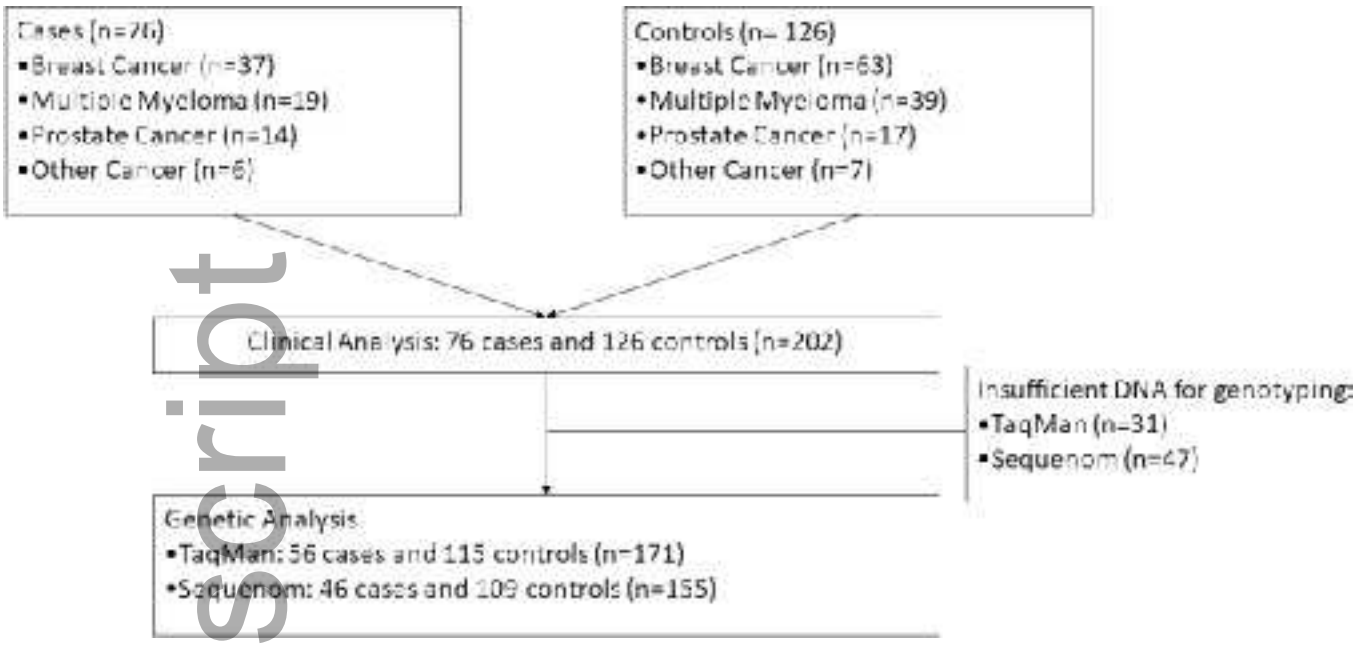
Figure Legends

Figure 1: Diagram illustrating patient matriculation from the clinical through the genetic analyses.



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