Cancer-associated weakness is a therapeutic challenge. We found skeletal muscle weakness in six mouse models of human osteolytic bone metastases [breast (3), lung (2), prostate (1)], and in multiple myeloma, but not in mice without cancer in bone, implicating the tumor-bone microenvironment in muscle weakness. Tumor-induced bone destruction released TGF-β. TGF-β upregulated NADPH oxidase 4 (Nox4) which oxidized skeletal muscle proteins, including the ryanodine receptor/calcium release channel (RyR1). Humans with breast or lung cancer bone metastases also had oxidized skeletal muscle RyR1. Oxidized RyR1 leaked calcium causing muscle weakness. Inhibiting RyR1 leak, TGF-β signaling, TGF-β release from bone (with bisphosphonate zoledronic acid) or Nox4 all improved muscle function. Increasing muscle mass alone, with activating receptor antibody, did not improve muscle function. Skeletal muscle weakness, increased Nox4 and oxidation of RyR1 were present in a mouse model of Camurati-Engelmann disease, a non-malignant metabolic bone disorder associated with increased TGF-β and high bone turnover. Thus, bone-derived TGF-β contributes to muscle weakness by decreasing calcium induced muscle force production and this may occur even before the loss of muscle mass. These findings indicate that important cross-talk exists between bone (via bone destruction) and muscle that could be targeted to prevent both bone loss and muscle weakness.