The multiple anti-cancer actions exerted by calcitriol, analogs or dietary vitamin D in rodent models of various cancers have been extensively reviewed \(^1\text{-}^5\). The following is a summary of the salient findings described in the animal studies.

### Inhibition of Cancer Initiation and Progression/Chemoprevention

#### Diet-induced hyperplasia

Western style diets high in fat and low in vitamin D and calcium caused hyper-proliferation of anterior and dorsal prostate epithelial cells. \([6]\)

Western style diets high in fat and low in vitamin D and calcium caused hyper-proliferation and hyperplasia in mouse mammary glands and prostate epithelial cells and this was suppressed by calcium and vitamin D supplementation. \([7,8]\)

Western style diets low in vitamin D and calcium and high in fat induced colonic tumors in mice while feeding diets supplemented with calcium and vitamin D reduced tumor incidence and multiplicity. \([9,10]\)

#### Chemical carcinogen-induced preneoplasia and cancer

Dietary vitamin D supplementation decreased AZO-induced preneoplastic lesions in mouse colon in a dose-dependent manner. Dietary vitamin D concentrations correlated inversely with dysplasia score and maximum impact was seen when mice consumed more than 2500 IU/kg diet. \([11]\)

Vitamin D administered prior to a carcinogenic insult (DMH) significantly reduced the incidence of colon adenocarcinomas in rats. \([12]\)

Vitamin D did not significantly alter incidence of colon carcinogenesis in rats when given after exposure to DMH. \([13]\)

The vitamin D analog (24, 25-dihydroxyvitamin D\(_3\)) diminished formation of aberrant crypt foci when administered before, after or along with DMH in rats. \([14,15]\)

1\(\alpha\)(OH)D\(_3\) decreased NMU-induced mammary tumor incidence and multiplicity in rats and AOM-induced aberrant crypt foci in mouse colon. However, in the DMBA-induced cancer model tumor progression was inhibited with no change in the incidence of mammary tumors. \([16]\)

VDR ablation increased the susceptibility to DBMA-induced carcinogenesis in a tissue specific manner. Increased incidence of mammary gland hyperplasia with a higher percentage of hormone-independent tumors were observed in Vdr null mice. \([17]\)

Gemini vitamin D analogs 0097 and 0072 inhibited NMU-induced mammary tumor burden in mice without causing hypercalcemia. \([18]\)

#### Genetically engineered cancer models

In Nkx3.1:Pten mice, a model that recapitulates the various stages of prostate cancer, calcitriol significantly reduced progression of prostatic intraepithelial neoplasia (PIN) to high grade-PIN when administered before the initial occurrence of these lesions. \([19]\)

A vitamin D-deficient diet increased the proliferation and severity of PIN lesions in the anterior prostate of TgAPT\(_{121}\) mice. \([20]\)

Rxr-\(\alpha\) null mice fed the new Western style diets high in fat and low in vitamin D and calcium developed high grade PIN. \([21]\)
In LH overexpressing mice EB1089 decreased the proliferation of mammary epithelial cells in preneoplastic glands and reduced growth rate of hormone-induced tumors.

MMTV-neu mice displaying haploinsufficiency of Vdr had shorter latency and increased incidence of mammary tumor formation.

LPB-Tag model of prostate tumors progressed faster in Vdr null when compared to their wild-type littermates.


Western diets low in calcium and vitamin D increased the number of polyps in the colons of APC\(^{1638N}\) mice.

Administration of a vitamin D\(_2\) analog decreased tumor burden in APC\(^{Min^{+}}\) mouse.

25(OH)D\(_3\) and two vitamin D analogs (NC and HP) failed to reduce tumor multiplicity or alter growth rates of colonic tumors in APC\(^{Pirc^{+}}\) rats or APC\(^{Min^{+}}\) mice.

**Tumor inhibitory effects in xenograft models of cancer**

**Single agents**

Gemini vitamin D analogs 0097 and BXL0124 inhibited growth of ER(-) MCF10DCIS cells implanted orthotopically into nude mice without causing hypercalcemia.

Vitamin D\(_2\) analog decreased the growth of HT-29 human colon cancer xenografts growth in mice but not SW-620 xenografts.

EB1089 decreased growth of LNCaP human prostate cancer xenografts in nude mice.

EB1089 dramatically reduced the growth of SUM-159PT human breast cancer xenografts and increased apoptosis.

Vitamin D deficiency accelerated and Gemini analogs of vitamin D and a vitamin D-sufficient diet effectively reduced the growth of MC26 mouse colon xenografts.

Diets low in vitamin D but with normal calcium levels increased the growth of DU145 prostate xenografts when compared to diets containing normal or high calcium with adequate vitamin D.

Calcitriol and dietary vitamin D exhibited equivalent anti-cancer activity to inhibit the growth of MCF-7 human breast xenografts and PC3 human prostate xenografts in nude mice.

**Combination Therapy**

Tumor volumes were significantly lower in animals irradiated after treatment with EB1089 than those that got radiation alone suggesting that vitamin D metabolites sensitized the tumor to radiation.

Vitamin D analogs PRI 2202 and 2205 demonstrated significant inhibition of 4T1 mouse breast cancer xenografts when combined with cytostatics but not when administered individually.

Calcitriol inhibited the growth of MCF-7 xenografts in a dose-dependent manner and combination with aromatase inhibitors further enhanced this effect, especially the regulation of the gene pathways contributing to the anti-cancer activity.

Combination of dietary soy with calcitriol enhanced both anti-cancer activity as well as hypercalcemic toxicity in mice with PC3 xenografts.
**Inhibition of Metastasis**

EB1089 decreased total number of bone metastasis, mean surface area of osteolytic lesions and tumor burden in nude mice after intra-cardiac injections of MDA-MB-231 human breast cancer cells.

Low vitamin D levels accelerated 4T1 mouse mammary tumor growth but did not affect metastasis to the Lungs.

EB1089 exerted a strong inhibitory effect on PTHrP-enhanced C4-2 prostate cancer xenograft growth and metastasis to the bone.

Vitamin D deficiency enhanced the growth of MDA-MB-231 breast cancer cells injected into the tibia of mice resulting in osteolytic lesions that appeared earlier and were larger than those seen in the vitamin D-sufficient mice.

Vitamin D deficiency increased bone turnover, osteolytic lesions, total tumor area and total mitotic activity in nude mice receiving intra-tibial injections of PC3 prostate cancer cells.

**Abbreviations:** AOM - azoxymethane; APC – adenomatous polyposis coli; AZO - azoxymethane; DCIS – ductal carcinoma in situ; DMBA – dimethylbenzanthracene; DMH – N,N'-dimethylhydrazine; LH – luteinising hormone; LPB-Tag - large probasin promoter directed SV40-large T-antigen; MMTV-ErB2 – mouse mammary tumor virus – HER2/neu; NMU - N-methyl-N-nitrosourea; PIN – prostate intraepithelial neoplasia; PTHrP – parathyroid hormone related protein; RXR – retinoid x receptor; VDR – vitamin D receptor;

**References**


