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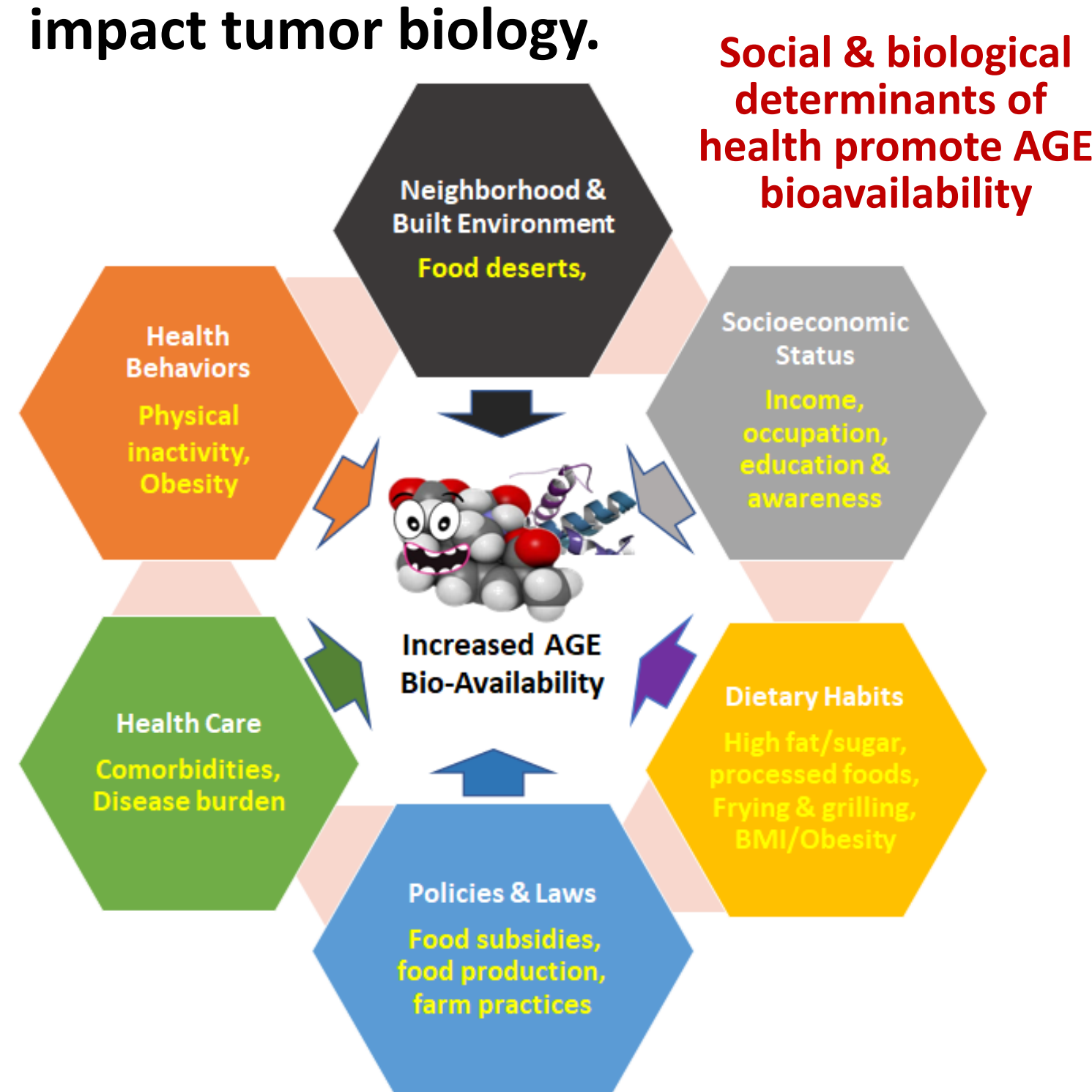
P13-043-23: Nutrition Derived Advanced Glycation End Products Are Bio-Social Determinants of Health That Inform on Cancer Disparities

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1. Background

Non-enzymatic glycooxidation is a chemical reaction between reducing sugars and amines on biological molecules that leads to the formation of reactive metabolites called advanced glycation end products (AGEs).

By lying at the intersection of social and biological determinants of health, nutrition associated AGEs represent a newly termed bio-social determinant of health and an unexploited opportunity to consider how integrated nutritional behaviors can impact tumor biology.

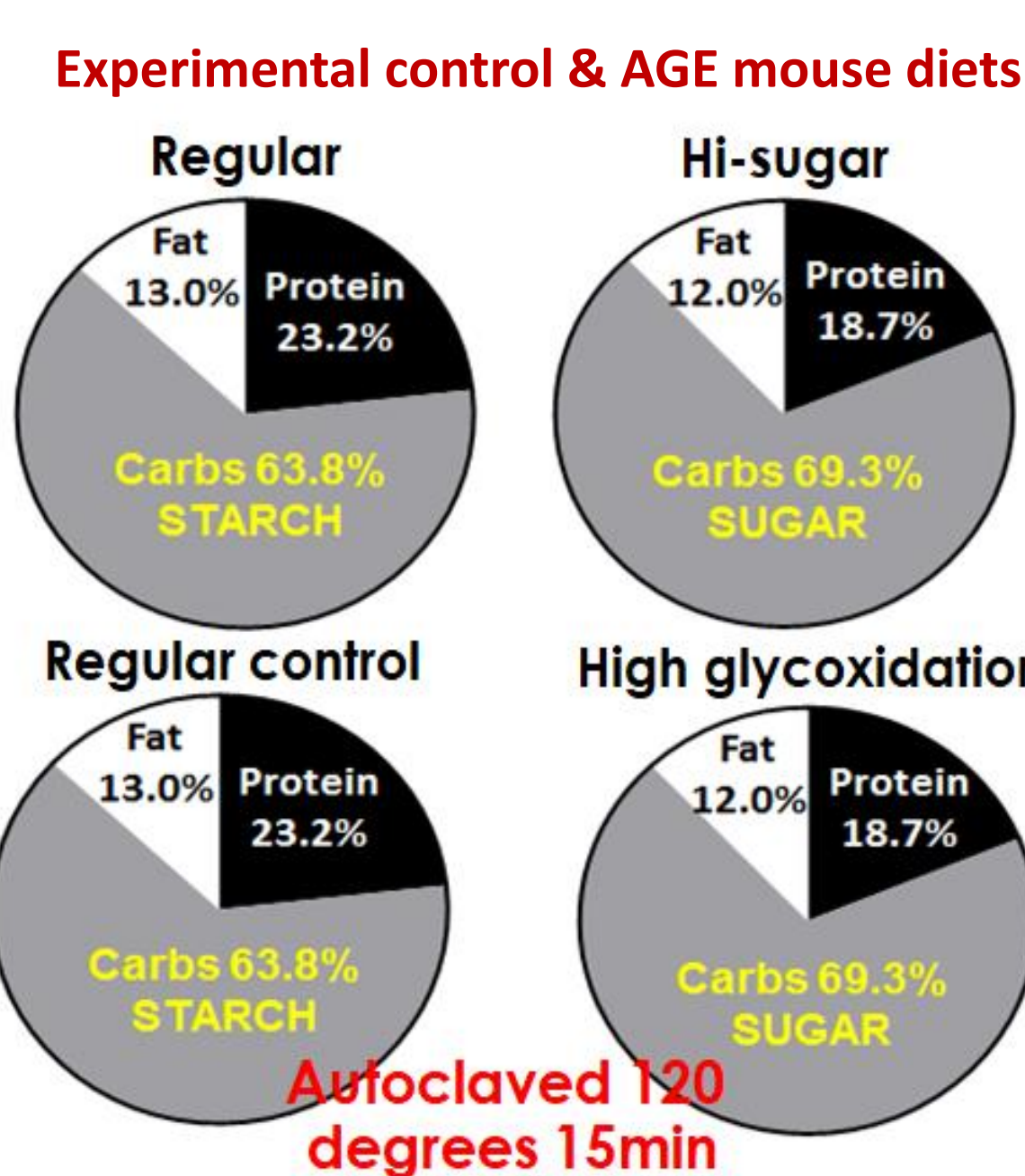


Communities with poorer cancer outcomes tend to have higher poverty rates, require food subsidies, and/or reside in designated food deserts. This often results in the consumption of cheaper unhealthy foods that are highly processed and/or high in sugar and fat. This can provide a superfluous source of the carboxyl and amine groups that fuel non-enzymatic glycooxidation. Cooking and food manufacturing increases AGE content if foods are and is now an significant exogenous source of AGE intake.

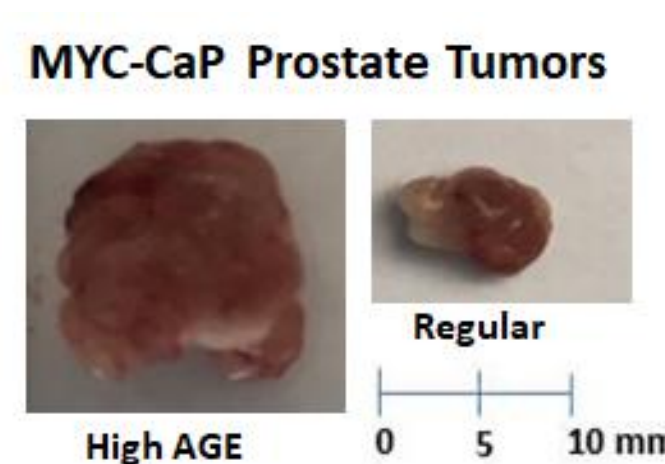
2. Methods

Nutritional AGE research has been hampered by a failure to define *in vivo* oncogenic cause-and-effect relationships to support epidemiological studies. To address this, the investigators used heat to induce non-enzymatic glycooxidation in mouse TestDiets® to increase AGE content.

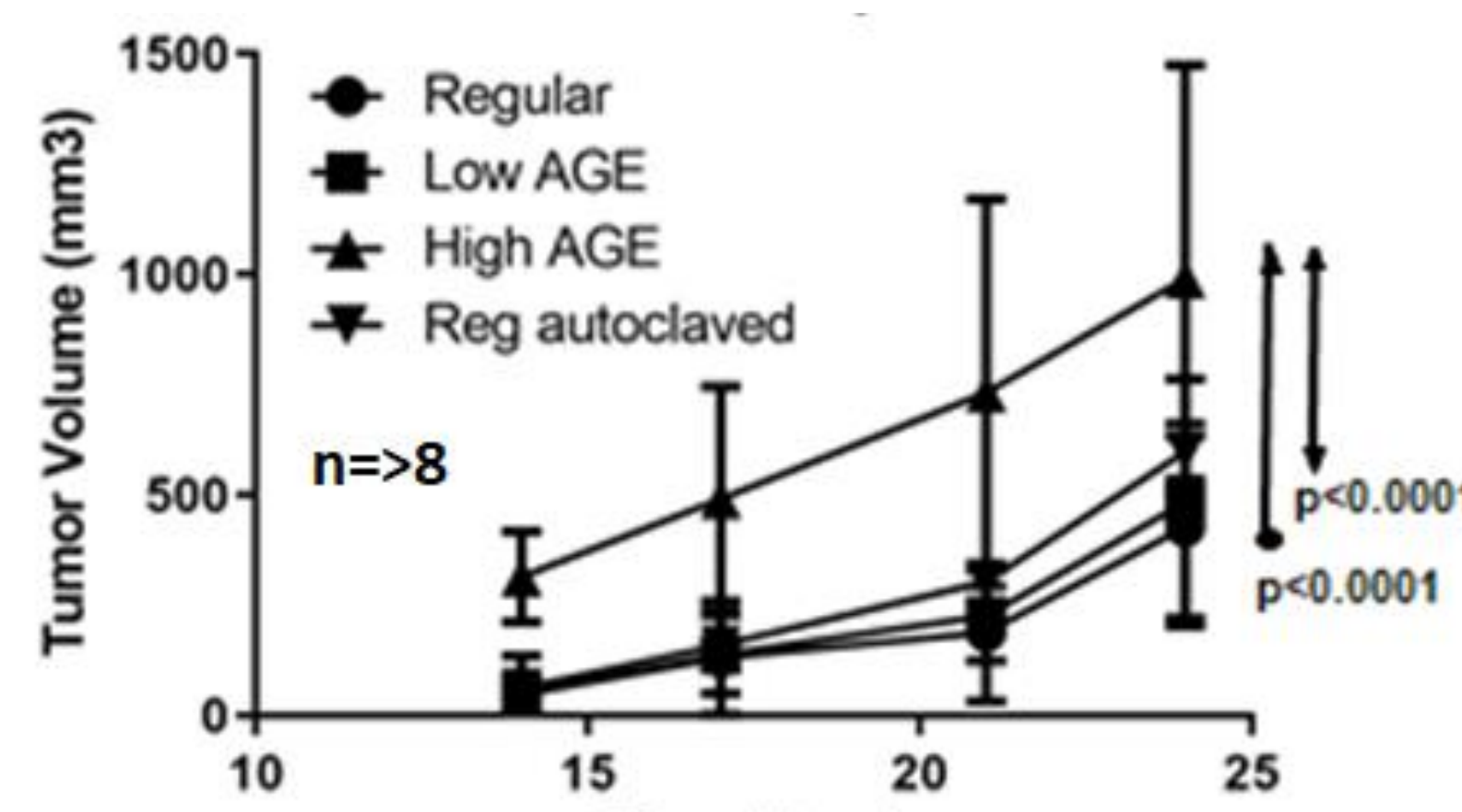
The oncogenic potential of diet associated AGEs on prostate carcinogenesis mice were fed one of four diets: 1) regular control, 2) heat-treated regular control, 3) unheated high sugar control, and 4) high AGE experimental diet produced by heat-treating the high sugar control. The effects on prostate tumor growth and progression was assessed in allograft and spontaneous tumor models.



3. A high AGE diet promotes prostate tumor growth

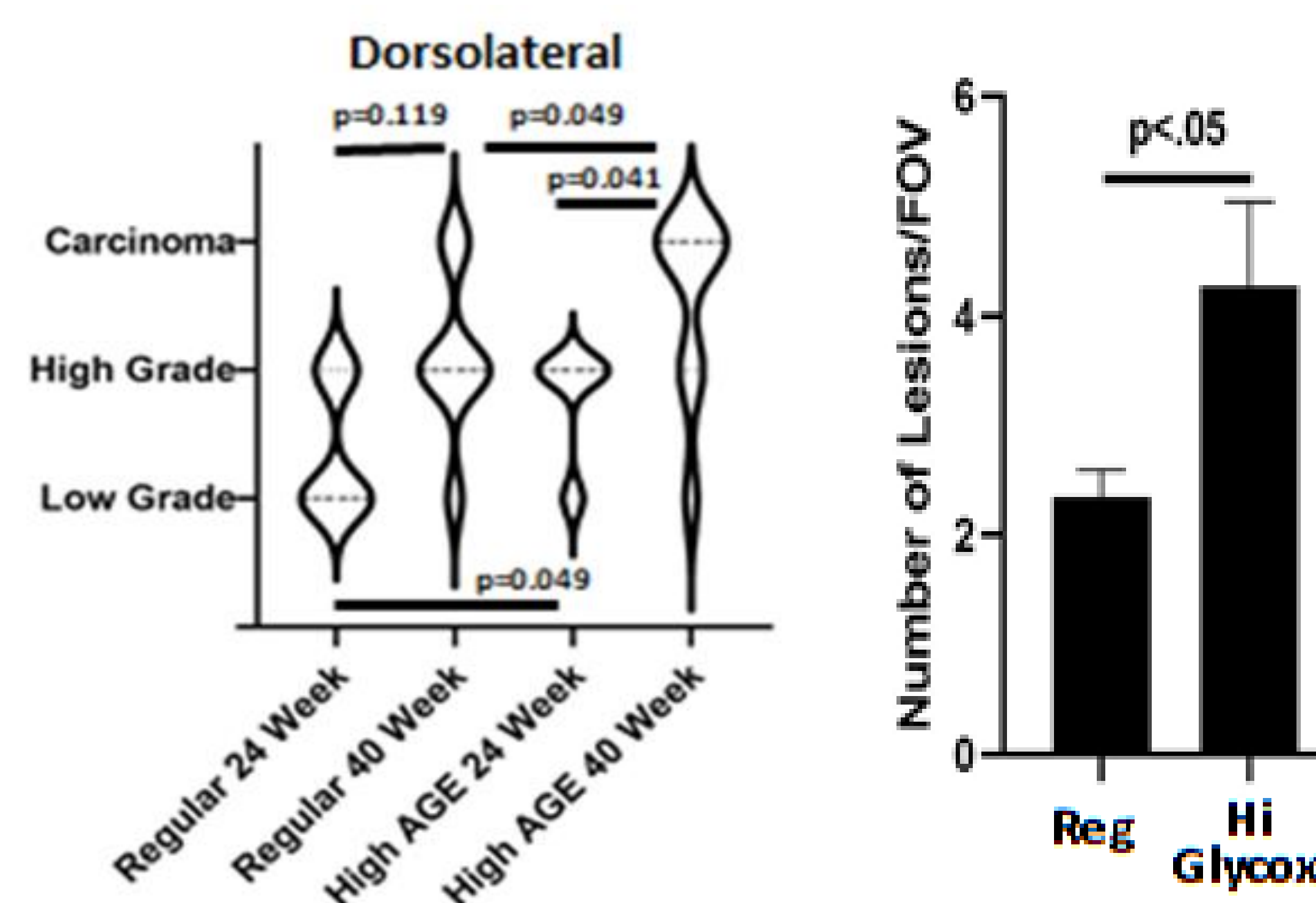


After 5 weeks of diet consumption, mouse MYC-CaP prostate cancer cells were injected into the left flank of mice and syngeneic tumor growth assessed. Consumption of the high AGE diet significantly accelerated prostate tumor growth compared to the three diet controls.



4. High AGE consumption drives PIN progression and metastatic potential

To assess the effect of AGE consumption in a heterogenous prostate tissue environment, Regular Control and High AGE diets were fed to male FVB-Tg(C3-1-Tag)CJeg/JegJ (C3-TAg) offspring, and the effects on T-antigen driven prostate tumor progression recorded. Assessed in the dorsolateral lobe, AGE consumption accelerated tumor progression towards high grade prostate intraepithelial neoplasia (PIN) at 24-weeks, and adeno-carcinoma and lung metastasis at 40 weeks. This was compared to the regular control.

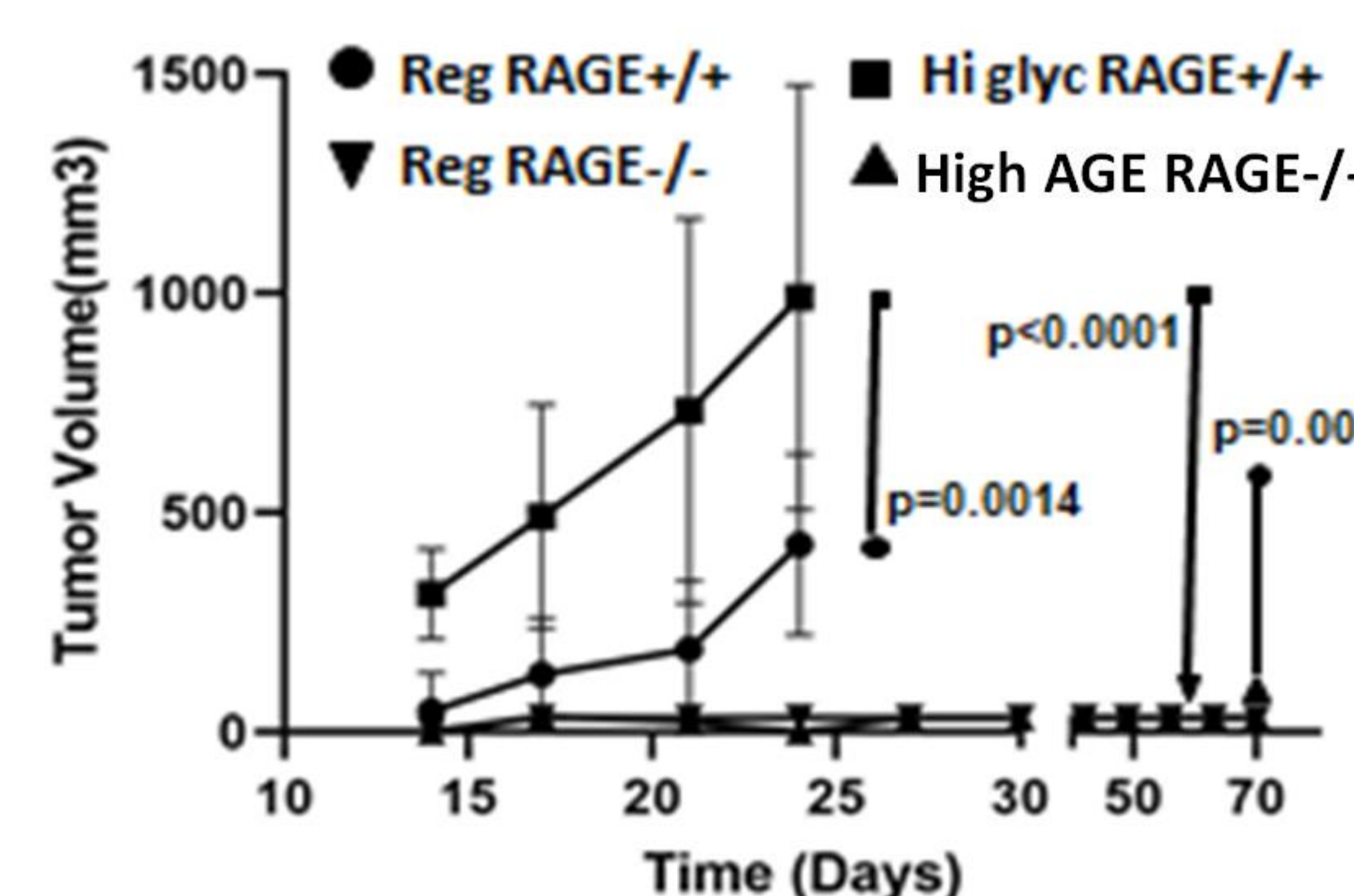


5. Diet mediated tumor growth was dependent upon stromal RAGE

AGE activation of the receptor for AGE (RAGE) causes matrix remodeling, vascular permeability, and metabolic dysregulation.

RAGE expressing MYC-CaP tumor cells were injected into the flanks of RAGE null mice with no host tissue RAGE expression. Even though RAGE was present in the injected tumor cells, no prostate tumor growth was observed in the RAGE null mice fed either the high AGE or regular control diets even after 70 days.

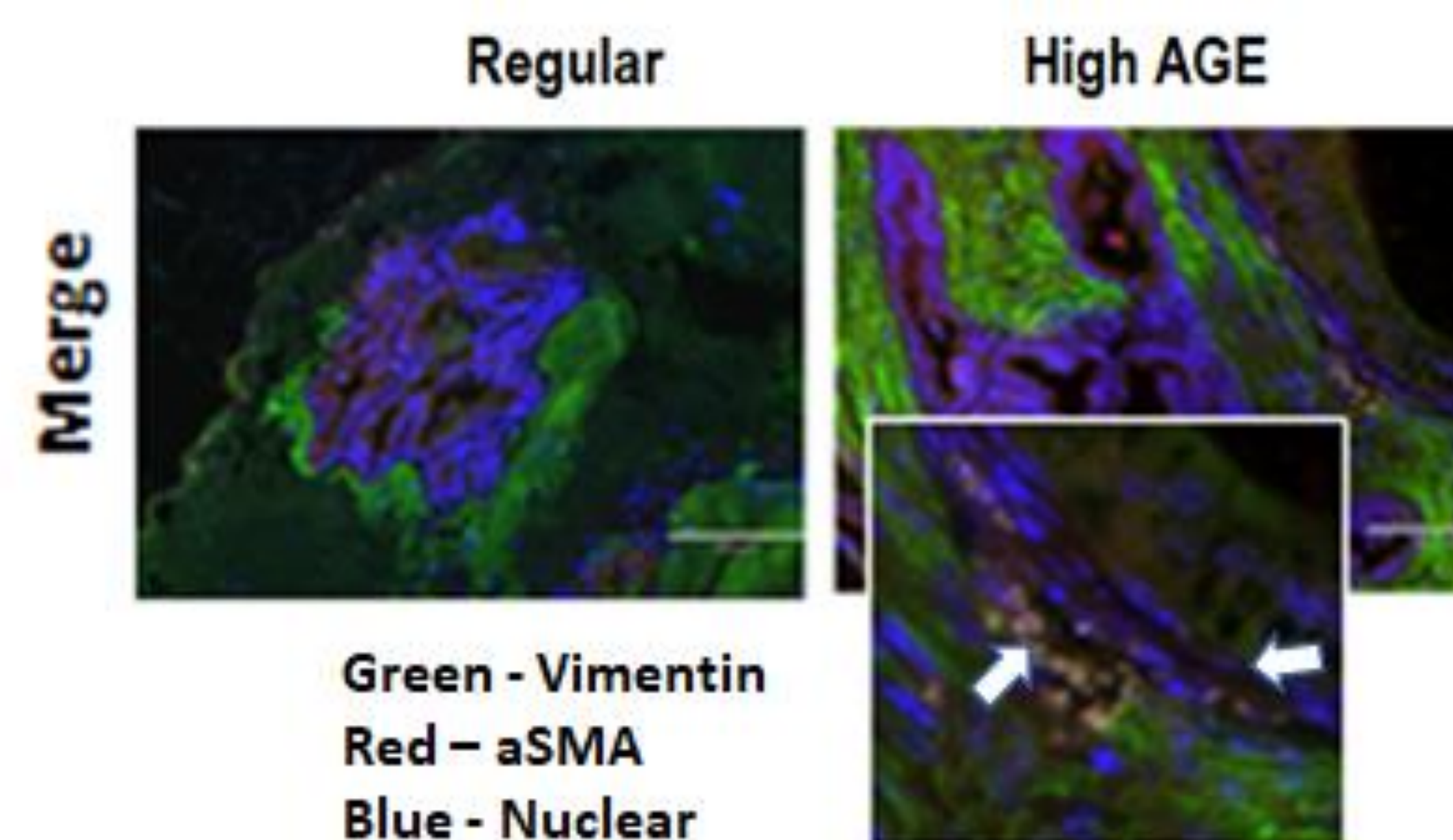
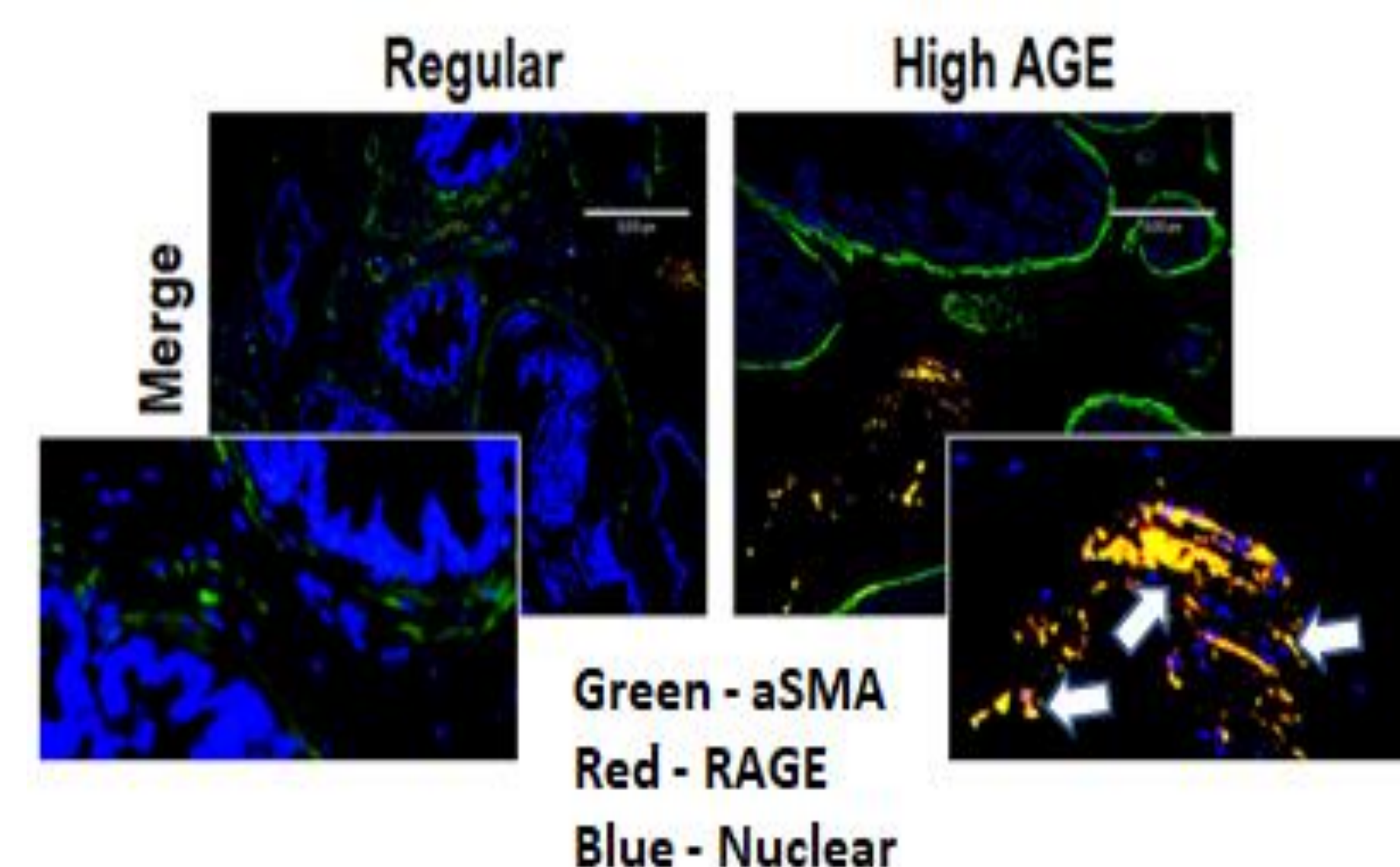
This indicates that stromal RAGE is required for dietary-AGE induced tumor growth



6. AGE-RAGE signaling promotes CAF recruitment

Malignant transformation is orchestrated by extracellular crosstalk between cancer associated fibroblasts (CAFs) and tumor epithelia.

When assessed in excised C3-TAg tumors by immunofluorescence, dual staining with vimentin and smooth muscle actin (αSMA) showed increased CAF activation (grey staining) around PIN lesions in mice fed the high AGE mice fed the high glycooxidation chow at 24-weeks. Scale bar = 90 μm

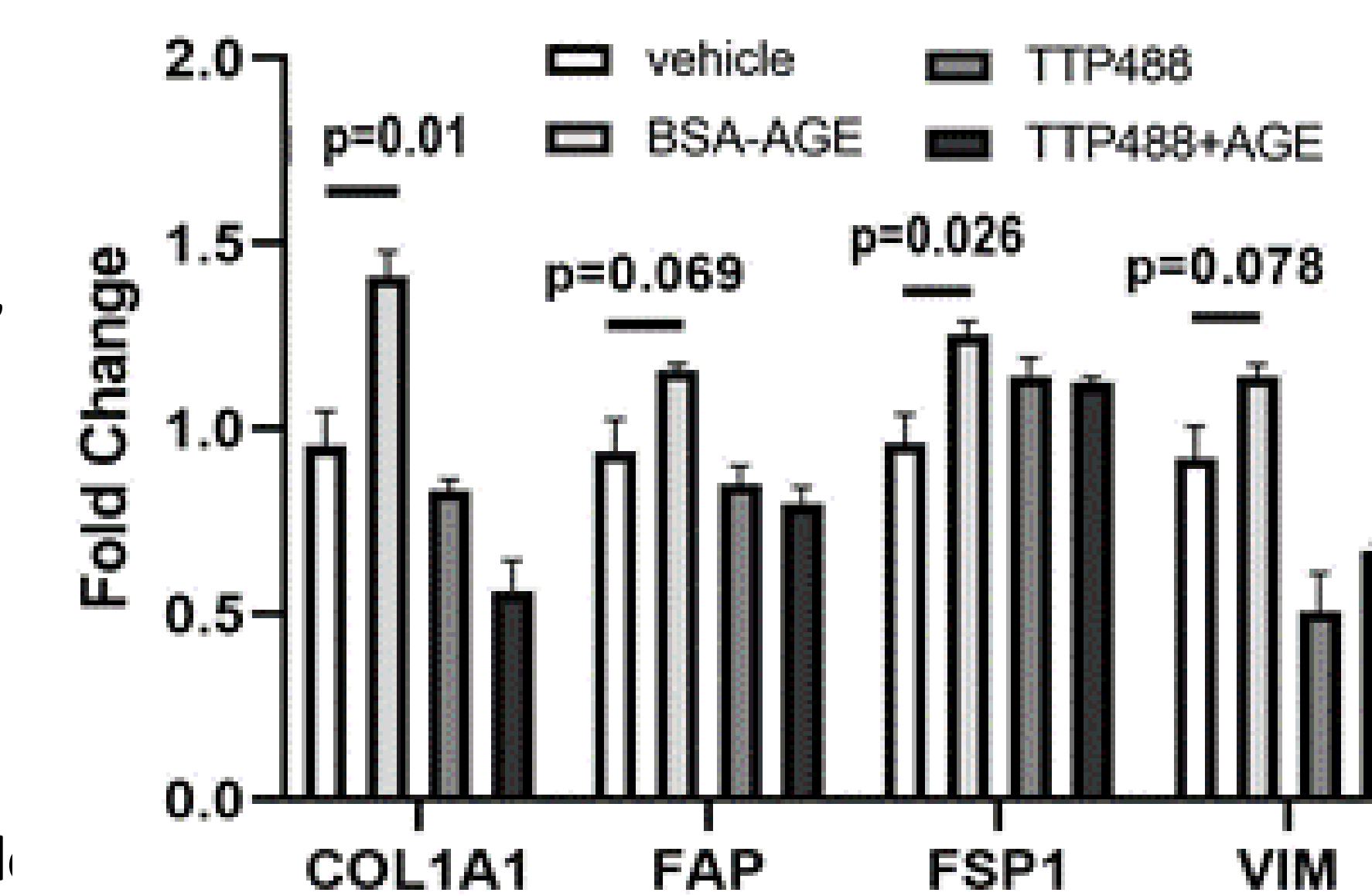


In the same 24-week C3-TAg tumors, co-immunofluorescent staining was also used to assess RAGE co-localization with the fibroblast marker αSMA. RAGE expression was increased and clearly co-stained (yellow staining) with αSMA around PIN lesions in the tissue of mice fed the high AGE diet while no detectable co-staining was observed in prostates excised from the regular fed mice. Scale bar = 90 μm

These data indicate that diet-associated AGEs can increase RAGE expression in fibroblast leading to their functional activation

7. RAGE inhibition decreases the expression of CAF activation markers

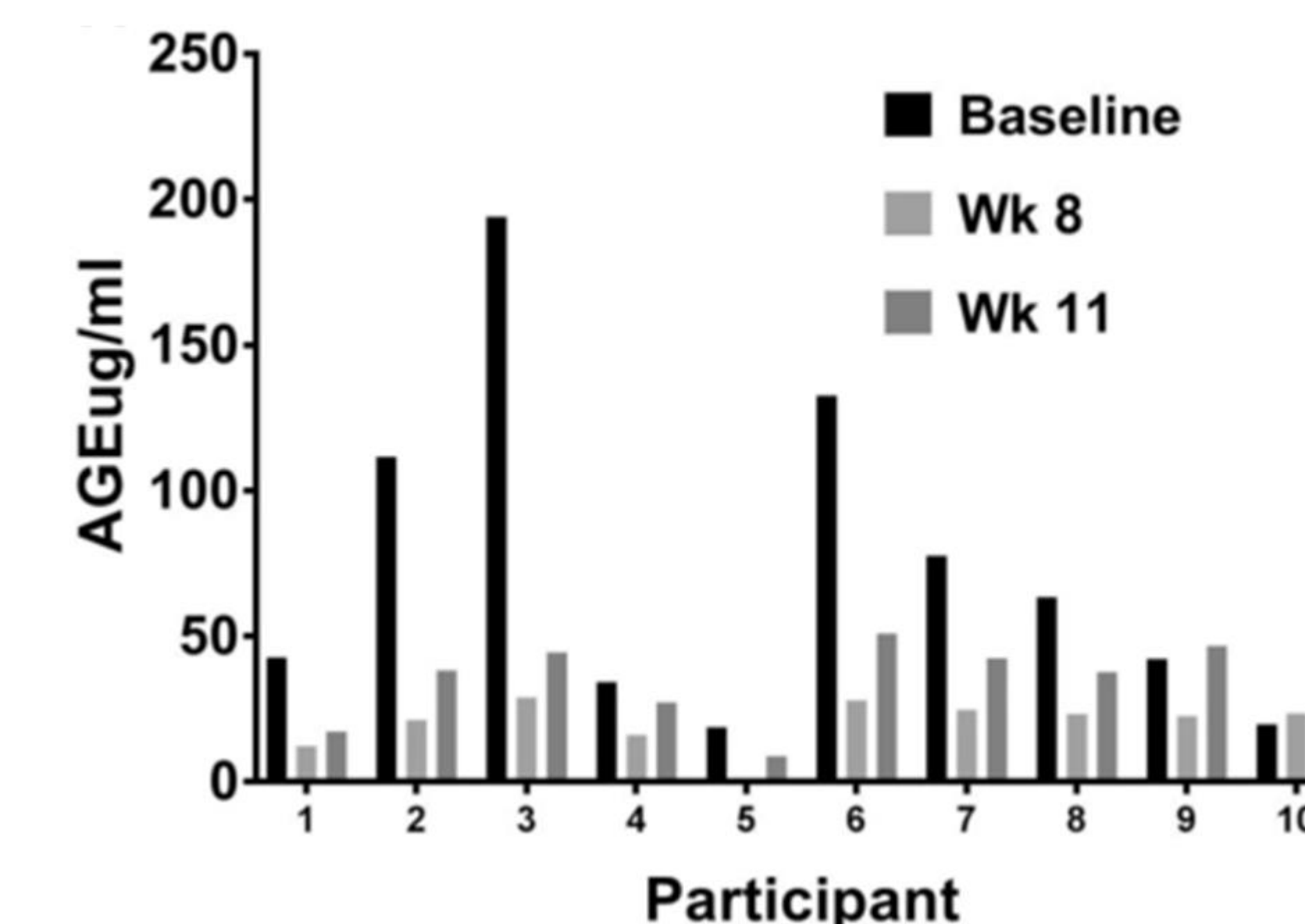
Exogenous AGE treatment (25ug/ml BSA-AGE for 24 hours) of human primary fibroblasts cultured from radical prostatectomy tissue, increased COL1A1, FAP, FSP1 CAF marker transcript expression. AGE-mediated increases were inhibited by pre-treatment (10nM for 1 hour) with the RAGE small molecule inhibitor TTP-488



8. Intervention reduces circulating AGEs in cancer survivors

In a proof of concept pilot study, the ability of lifestyle intervention to lower AGE levels was assessed in ten obese post-menopausal women with non-metastatic ER+ breast cancer. Significant reductions in circulating AGE levels were observed when fasting serum samples were analyzed by ELISA

Median AGE levels at baseline were 53ug/ml compared to 23ug/ml at week 8 and 38 μg/ml at week 11



9. Significance

These data represent a significant advance in the field. AGEs are a molecular consequence of nutritional behavior as a whole rather than any single nutrient of macronutrient. We provide compelling evidence that increased nutritional AGE exposure leads to the RAGE mediated activation of fibroblasts to sustain a tissue microenvironment conducive for aggressive tumor growth. The data identify increased AGE bioavailability as an unexploited molecular concept with which to assess the combined effects of nutritional behavior on tumor biology. Due to intrinsic links between AGEs, nutritional behavior and increased cancer risk, these studies lay a strong foundation for the design and translation of innovative cancer prevention and survivorship strategies. Such design would require multidisciplinary collaborations aimed at reducing nutritional AGE exposure and/or AGE accumulation especially in at-risk populations through educational, lifestyle, and preventative interventions.

