SITC 2019

Gaylord National Hotel
& Convention Center

Nov. 6-10

NATIONAL HARBOR, MARYLAND

sitc

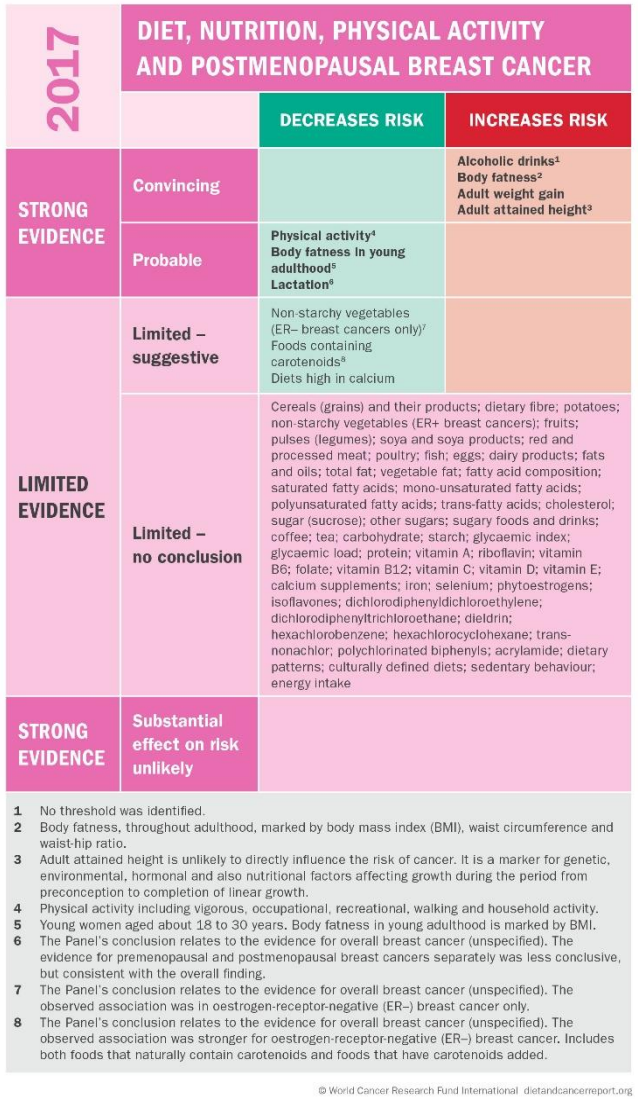
Society for Immunotherapy of Cancer

Diet and physical activity alter immunity and the tumor microenvironment

Connie J. Rogers, PhD, MPH
Department of Nutritional Sciences
Penn State University
Penn State Cancer Institute

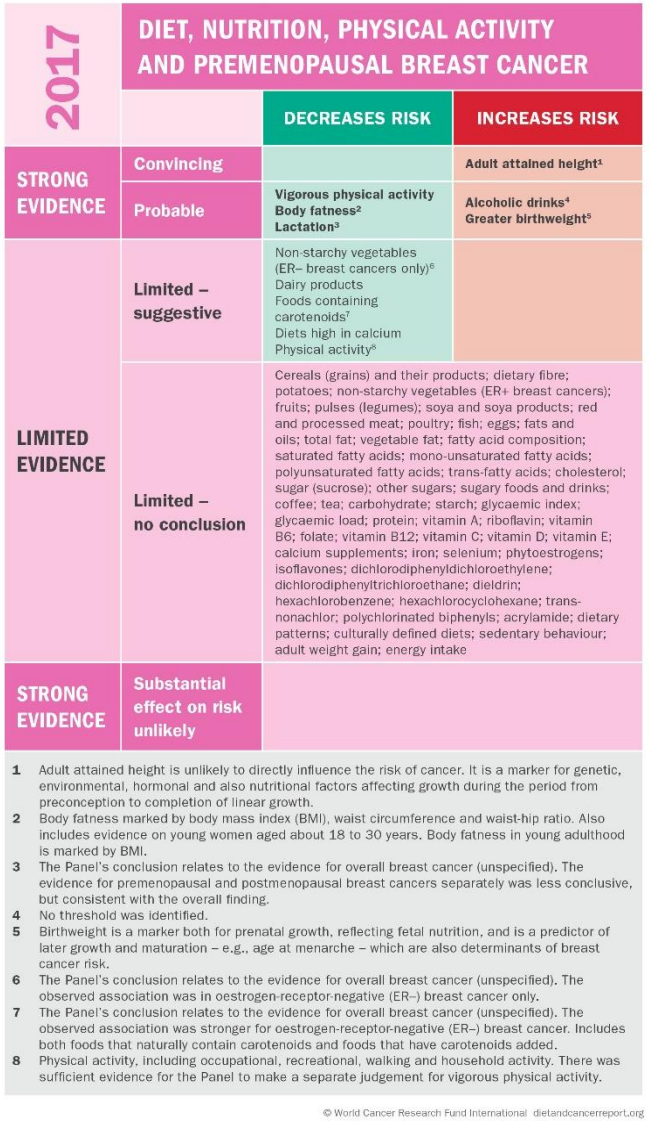
- There are no relevant disclosures for this presentation.

Role of Physical Inactivity and Weight Gain in Breast Cancer Risk



2017	DIET, NUTRITION, PHYSICAL ACTIVITY AND POSTMENOPAUSAL BREAST CANCER		
		DECREASES RISK	INCREASES RISK
STRONG EVIDENCE	Convincing		Alcoholic drinks[1] Body fatness[2] Adult weight gain Adult attained height[3]
	Probable	Physical activity[4] Body fatness in young adulthood[5] Lactation[6]	
LIMITED EVIDENCE	Limited – suggestive	Non-starchy vegetables (ER– breast cancers only)[7] Foods containing carotenoids[8] Diets high in calcium	
	Limited – no conclusion	Cereals (grains) and their products; dietary fibre; potatoes; non-starchy vegetables (ER+ breast cancers); fruits; pulses (legumes); soya and soya products; red and processed meat; poultry; fish; eggs; dairy products; fats and oils; total fat; vegetable fat; fatty acid composition; saturated fatty acids; mono-unsaturated fatty acids; polyunsaturated fatty acids; trans-fatty acids; cholesterol; sugar (sucrose); other sugars; sugary foods and drinks; coffee; tea; carbohydrate; starch; glycaemic index; glycaemic load; protein; vitamin A; riboflavin; vitamin B6; folate; vitamin B12; vitamin C; vitamin D; vitamin E; calcium supplements; iron; selenium; phytoestrogens; isoflavones; dichlorodiphenyldichloroethylene; dichlorodiphenyltrichloroethane; dieldrin; hexachlorobenzene; hexachlorocyclohexane; trans-nonachlor; polychlorinated biphenyls; acrylamide; dietary patterns; culturally defined diets; sedentary behaviour; energy intake	
STRONG EVIDENCE	Substantial effect on risk unlikely		

1 No threshold was identified.
2 Body fatness, throughout adulthood, marked by body mass index (BMI), waist circumference and waist-hip ratio.
3 Adult attained height is unlikely to directly influence the risk of cancer. It is a marker for genetic, environmental, hormonal and also nutritional factors affecting growth during the period from preconception to completion of linear growth.
4 Physical activity including vigorous, occupational, recreational, walking and household activity.
5 Young women aged about 18 to 30 years. Body fatness in young adulthood is marked by BMI.
6 The Panel's conclusion relates to the evidence for overall breast cancer (unspecified). The evidence for premenopausal and postmenopausal breast cancers separately was less conclusive, but consistent with the overall finding.
7 The Panel's conclusion relates to the evidence for overall breast cancer (unspecified). The observed association was in oestrogen-receptor-negative (ER–) breast cancer only.
8 The Panel's conclusion relates to the evidence for overall breast cancer (unspecified). The observed association was stronger for oestrogen-receptor-negative (ER–) breast cancer. Includes both foods that naturally contain carotenoids and foods that have carotenoids added.

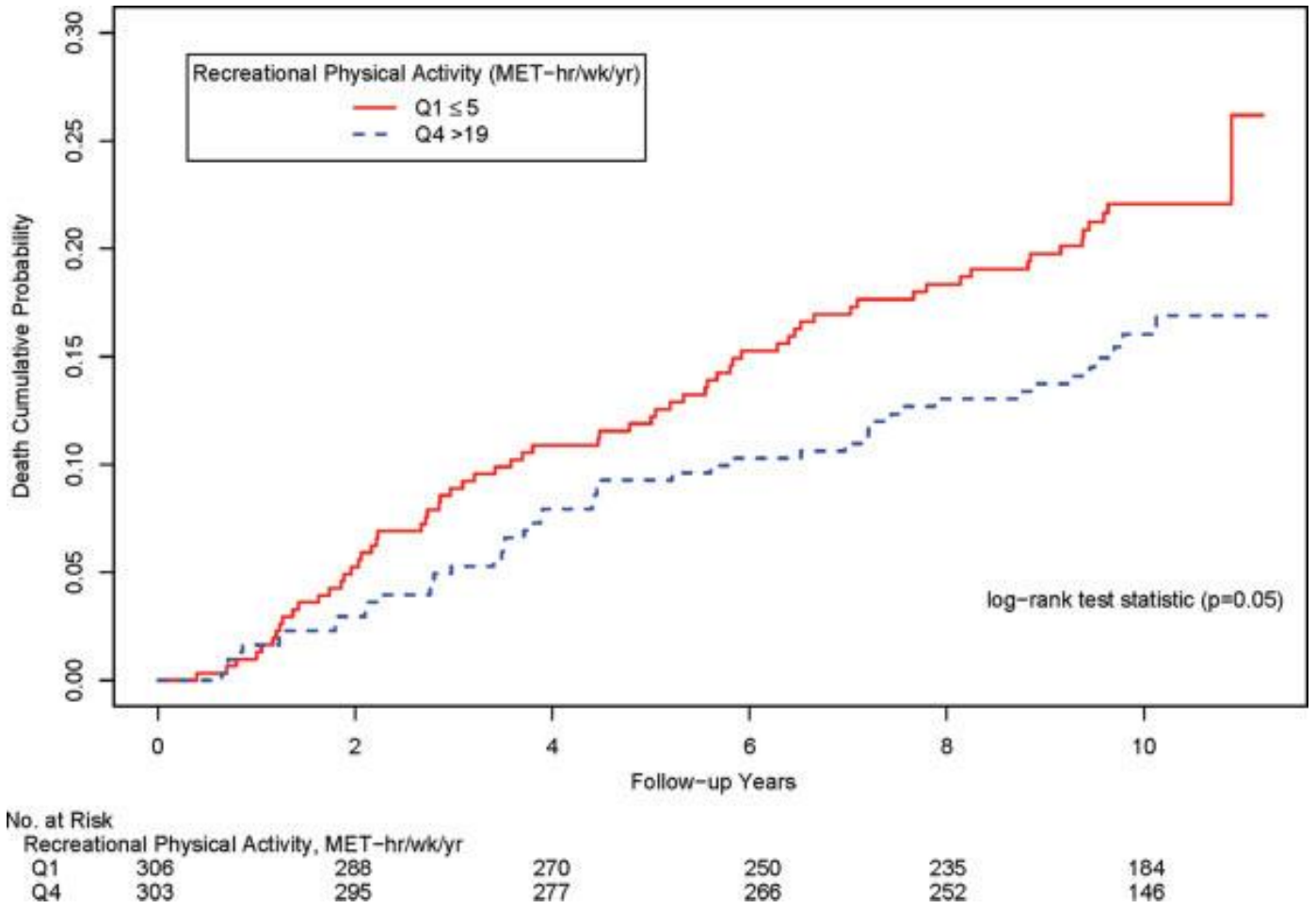


2017	DIET, NUTRITION, PHYSICAL ACTIVITY AND PREMENOPAUSAL BREAST CANCER		
		DECREASES RISK	INCREASES RISK
STRONG EVIDENCE	Convincing		Adult attained height[1]
	Probable	Vigorous physical activity Body fatness[2] Lactation[3]	Alcoholic drinks[4] Greater birthweight[5]
LIMITED EVIDENCE	Limited – suggestive	Non-starchy vegetables (ER– breast cancers only)[6] Dairy products Foods containing carotenoids[7] Diets high in calcium Physical activity[8]	
	Limited – no conclusion	Cereals (grains) and their products; dietary fibre; potatoes; non-starchy vegetables (ER+ breast cancers); fruits; pulses (legumes); soya and soya products; red and processed meat; poultry; fish; eggs; fats and oils; total fat; vegetable fat; fatty acid composition; saturated fatty acids; mono-unsaturated fatty acids; polyunsaturated fatty acids; trans-fatty acids; cholesterol; sugar (sucrose); other sugars; sugary foods and drinks; coffee; tea; carbohydrate; starch; glycaemic index; glycaemic load; protein; vitamin A; riboflavin; vitamin B6; folate; vitamin B12; vitamin C; vitamin D; vitamin E; calcium supplements; iron; selenium; phytoestrogens; isoflavones; dichlorodiphenyldichloroethylene; dichlorodiphenyltrichloroethane; dieldrin; hexachlorobenzene; hexachlorocyclohexane; trans-nonachlor; polychlorinated biphenyls; acrylamide; dietary patterns; culturally defined diets; sedentary behaviour; adult weight gain; energy intake	
STRONG EVIDENCE	Substantial effect on risk unlikely		

1 Adult attained height is unlikely to directly influence the risk of cancer. It is a marker for genetic, environmental, hormonal and also nutritional factors affecting growth during the period from preconception to completion of linear growth.
2 Body fatness marked by body mass index (BMI), waist circumference and waist-hip ratio. Also includes evidence on young women aged about 18 to 30 years. Body fatness in young adulthood is marked by BMI.
3 The Panel's conclusion relates to the evidence for overall breast cancer (unspecified). The evidence for premenopausal and postmenopausal breast cancers separately was less conclusive, but consistent with the overall finding.
4 No threshold was identified.
5 Birthweight is a marker both for prenatal growth, reflecting fetal nutrition, and is a predictor of later growth and maturation – e.g., age at menarche – which are also determinants of breast cancer risk.
6 The Panel's conclusion relates to the evidence for overall breast cancer (unspecified). The observed association was in oestrogen-receptor-negative (ER–) breast cancer only.
7 The Panel's conclusion relates to the evidence for overall breast cancer (unspecified). The observed association was stronger for oestrogen-receptor-negative (ER–) breast cancer. Includes both foods that naturally contain carotenoids and foods that have carotenoids added.
8 Physical activity, including occupational, recreational, walking and household activity. There was sufficient evidence for the Panel to make a separate judgement for vigorous physical activity.

AICR/WCRF.
Continuous Update Project.

Lifetime Recreational Physical Activity & Breast Cancer Mortality



Friedenreich, C. M., et al. *Int. J. Cancer. 2009.* 124, 1954–1962.

Obesity and Breast Cancer Mortality

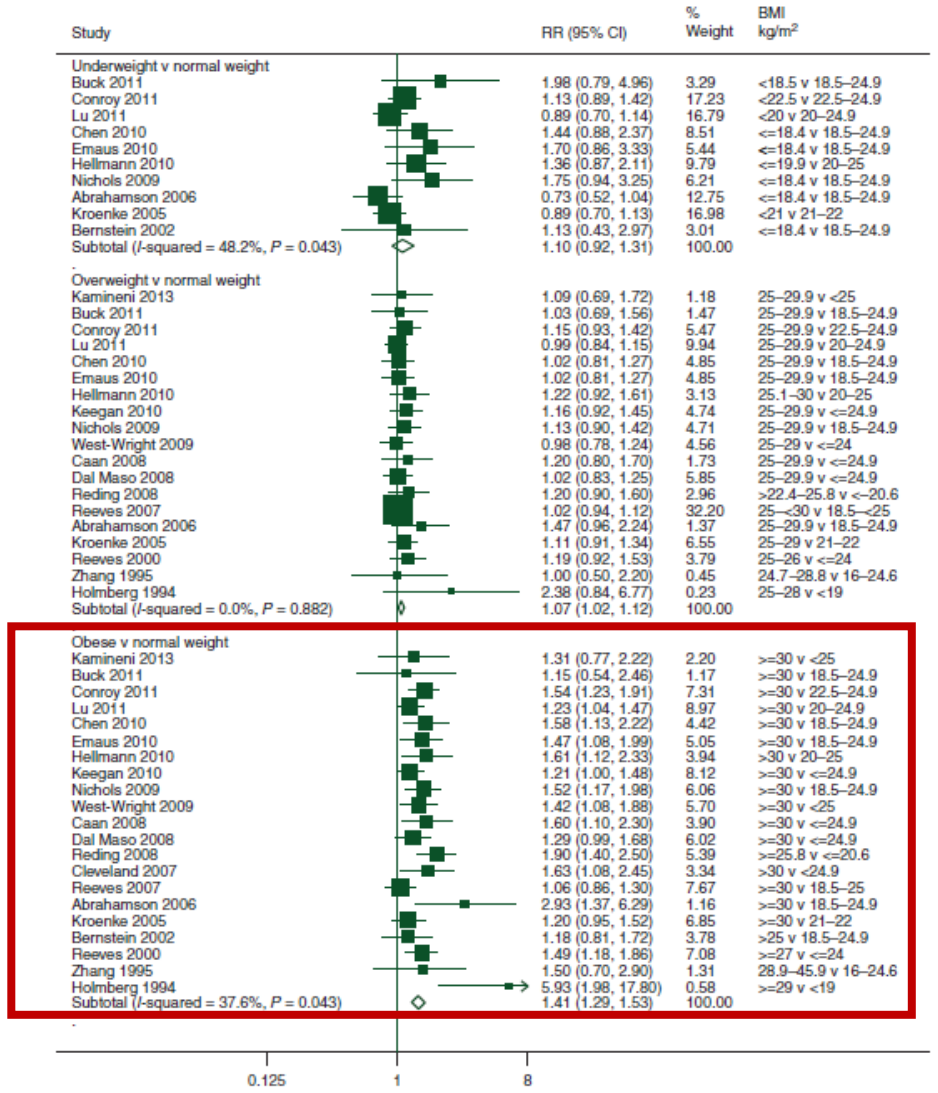
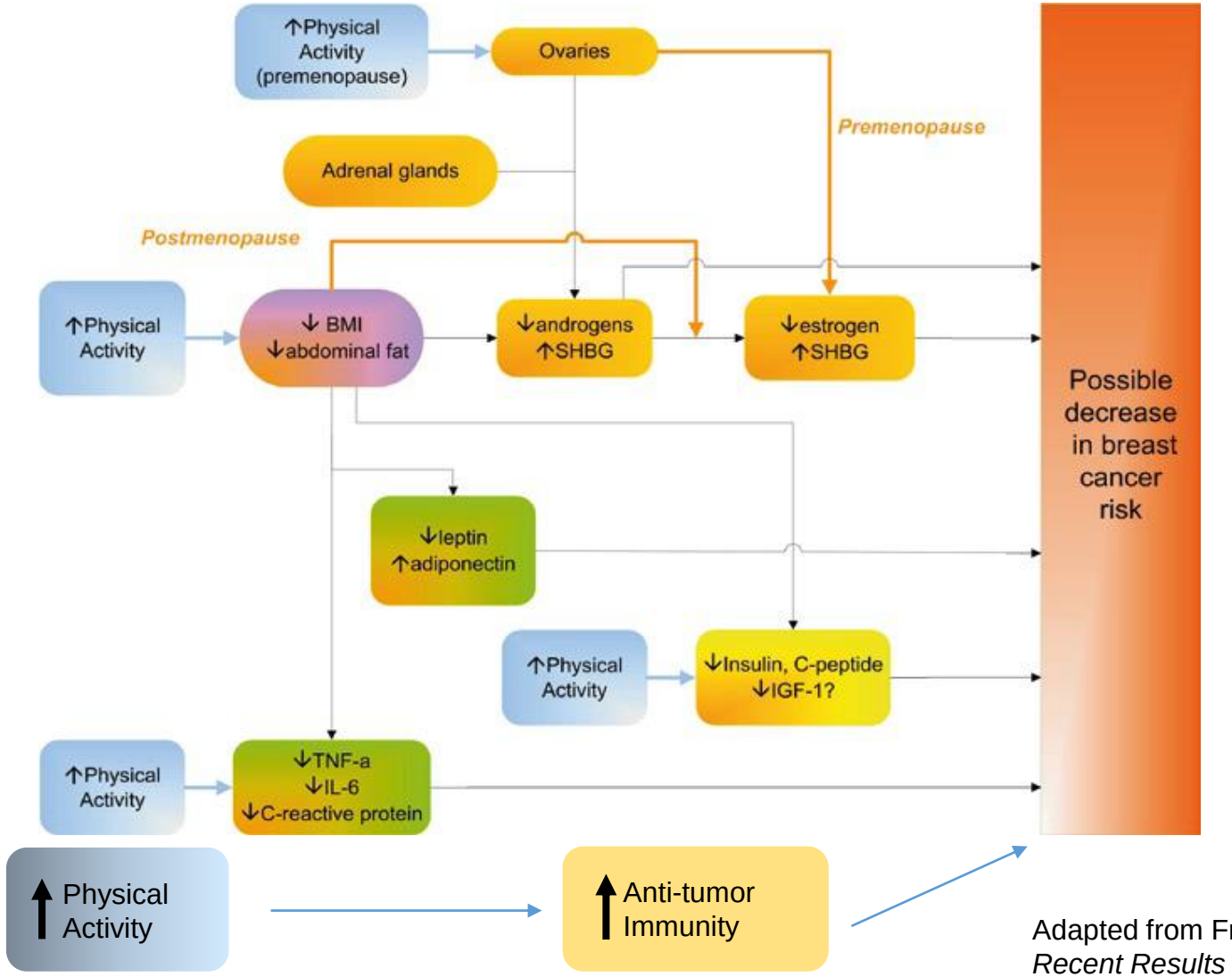


Figure 2. Categorical meta-analysis of pre-diagnosis BMI and total mortality.

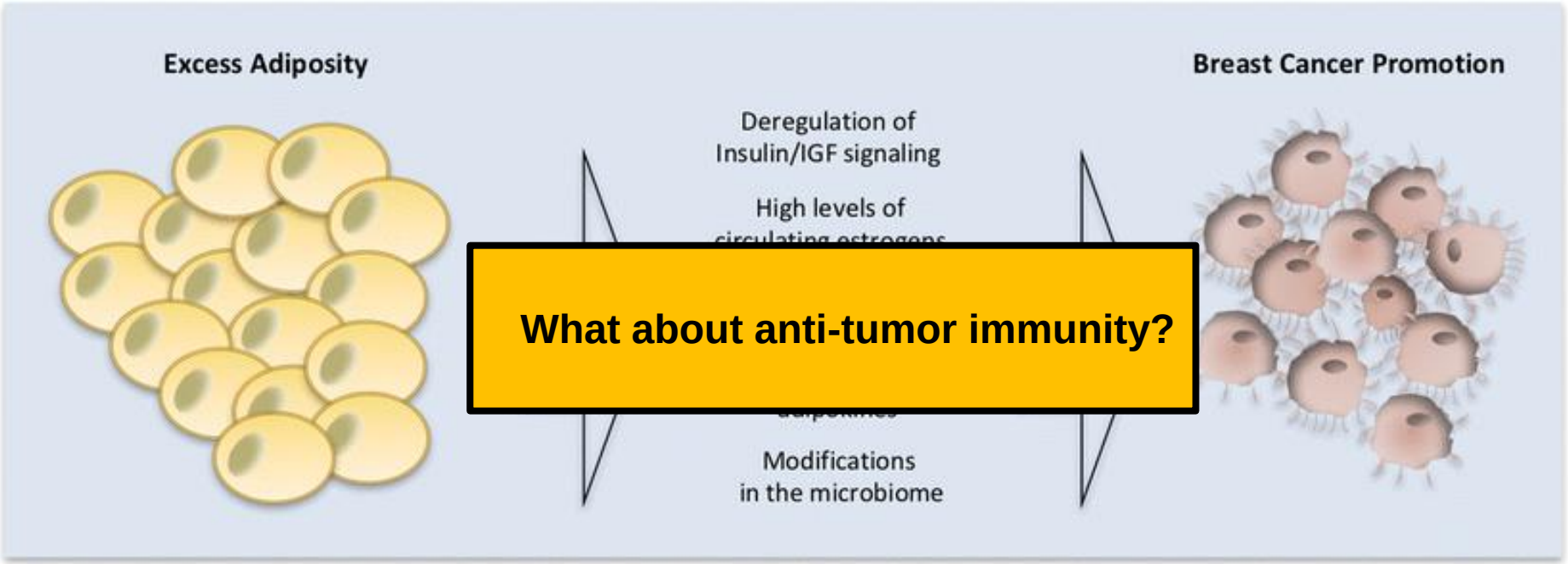
Chan, et al. *Ann Oncol*, 2014;25(10):1901-14.

Proposed biological mechanisms linking physical activity and breast cancer prevention



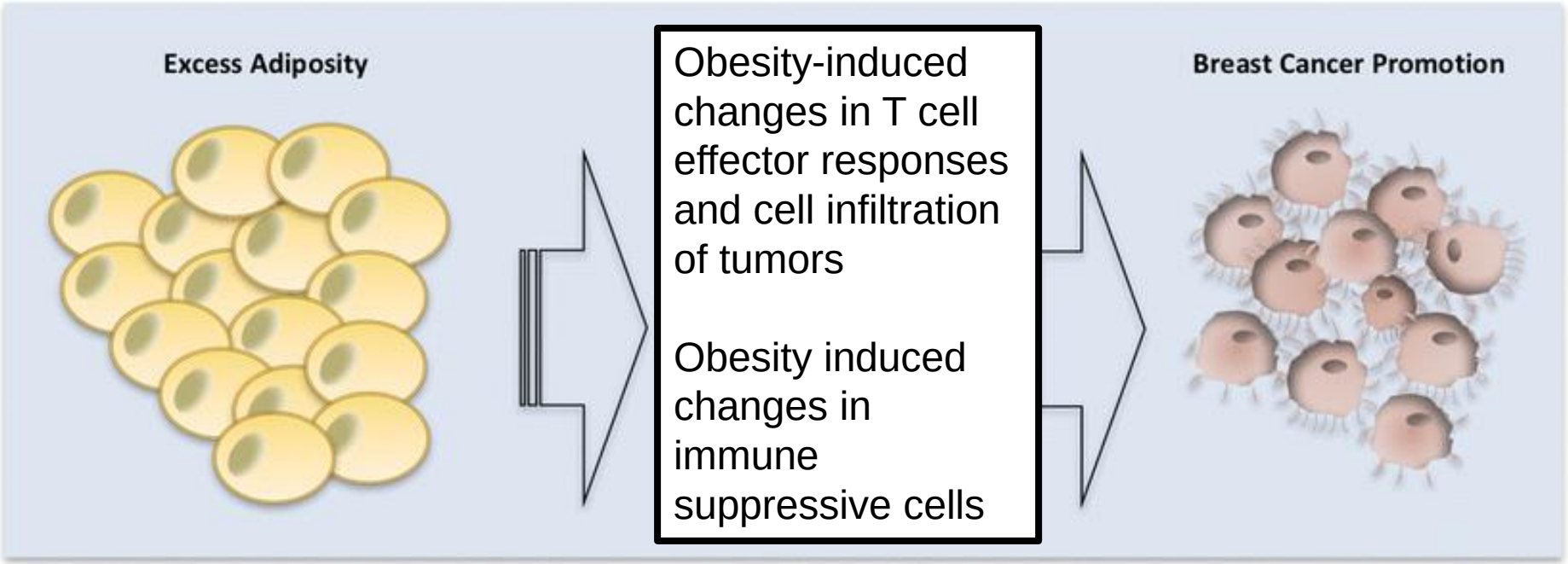
Adapted from Friedenreich, C.
Recent Results in Cancer Research. 2011. 188,125-139

Mechanisms Linking Obesity and Breast Cancer: Mouse Models

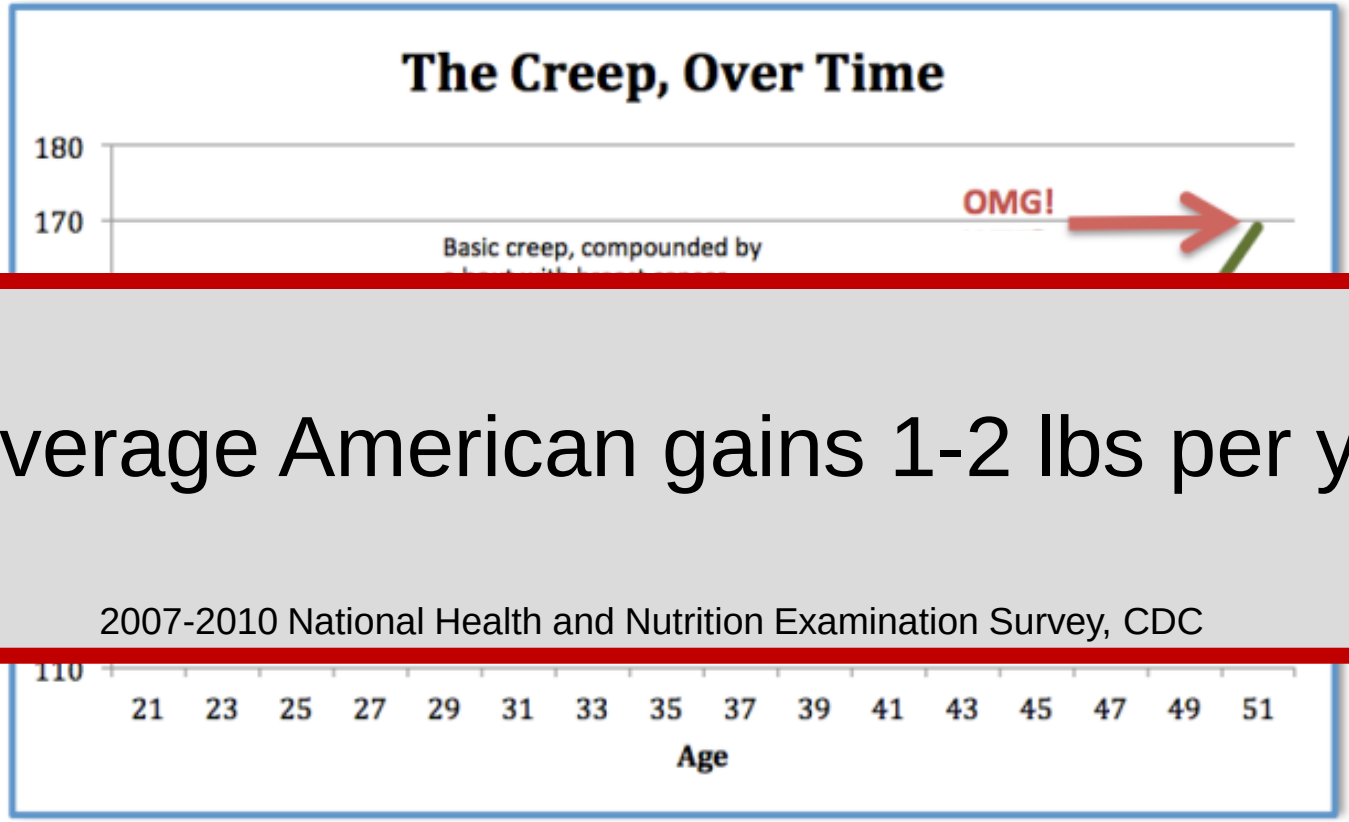


Adapted from Argolo, *et al*. *Current Oncology Reports.* 2018. 20: 47

Mechanisms Linking Obesity and Breast Cancer: Mouse Models



Can we ask this question differently ?



The average American gains 1-2 lbs per year!

2007-2010 National Health and Nutrition Examination Survey, CDC

What can we learn about the prevention of weight gain over the course of life?

What is the role of physical activity vs. a reduction in calories in this process?

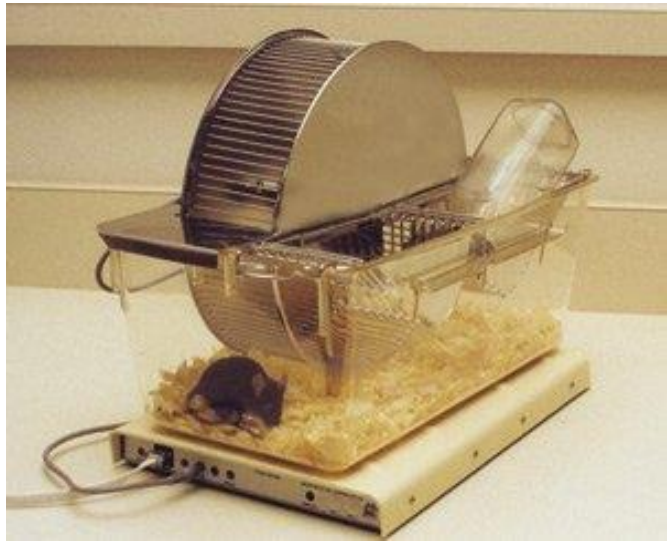
Study Design

Weight gain (WG)	**SED+AL** Sedentary cage + *ad libitum*	**PA+AL** Activity wheel + weight matched to SED+AL
Weight maintenance (WM)	**SED+ER** Sedentary cage + weight matched to PA+ER	**PA+ER** Activity wheel + 10% dietary restricted

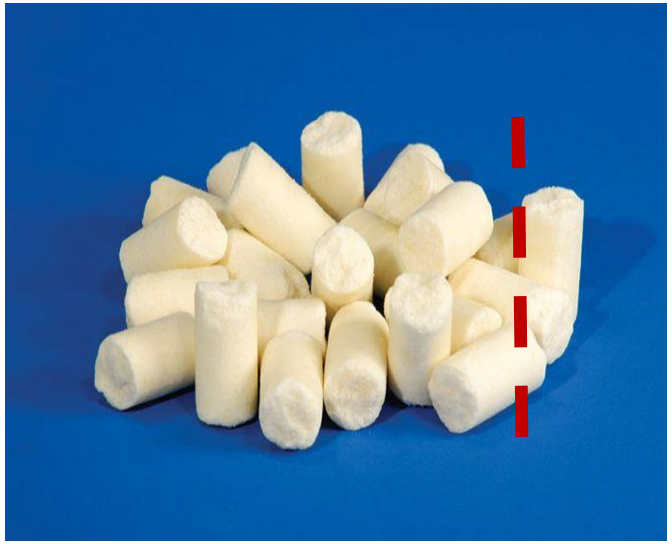
Weight matched

Weight matched

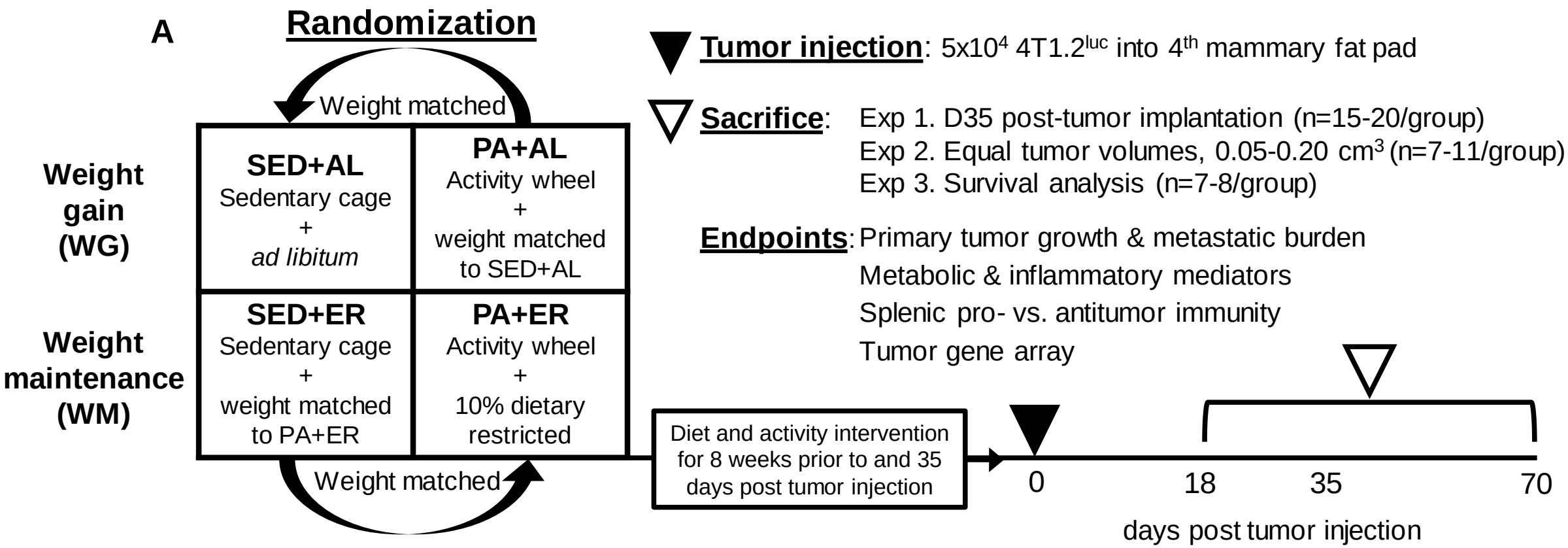
Voluntary Running Wheel



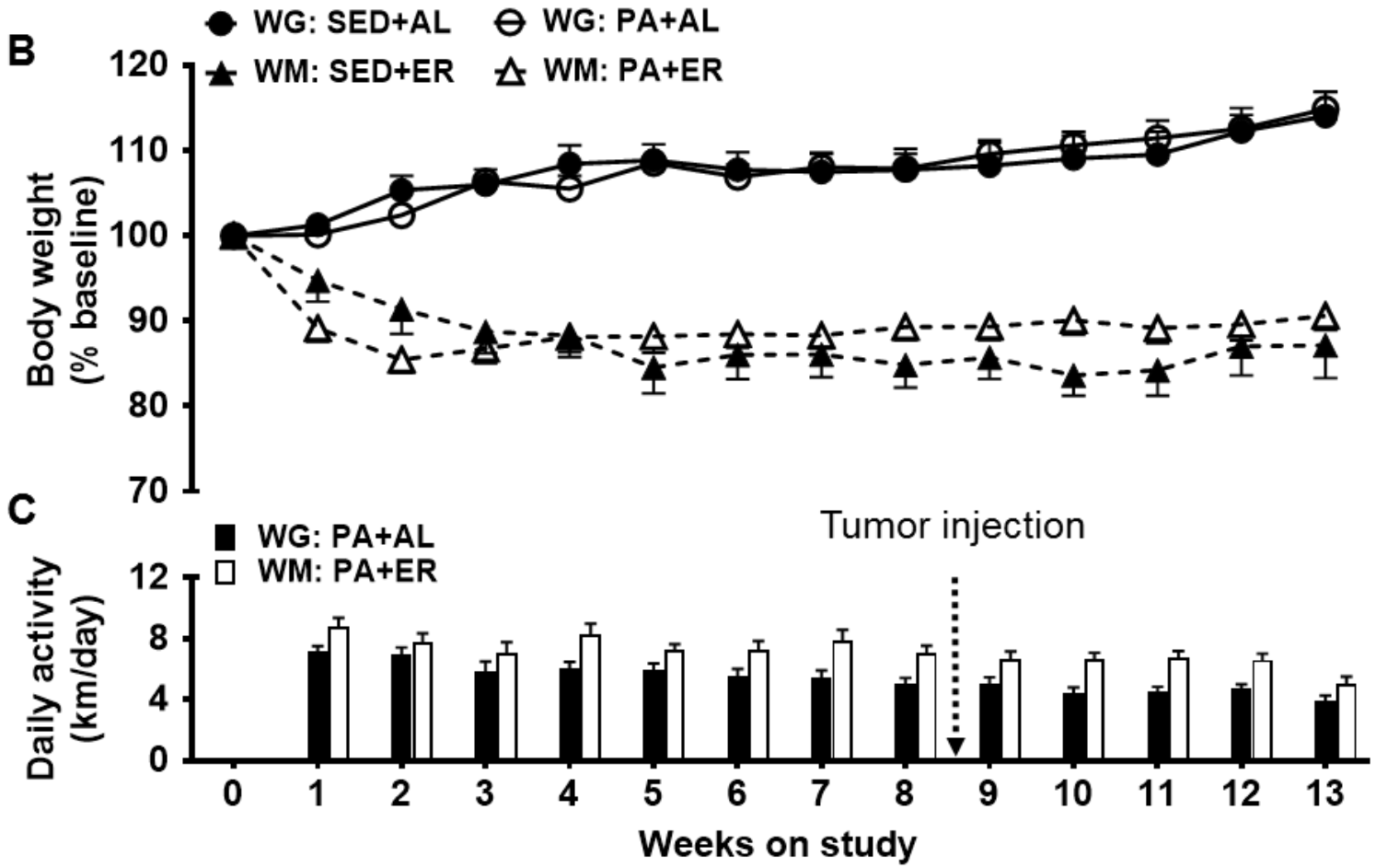
10% Reduction in Calories



Experimental Design

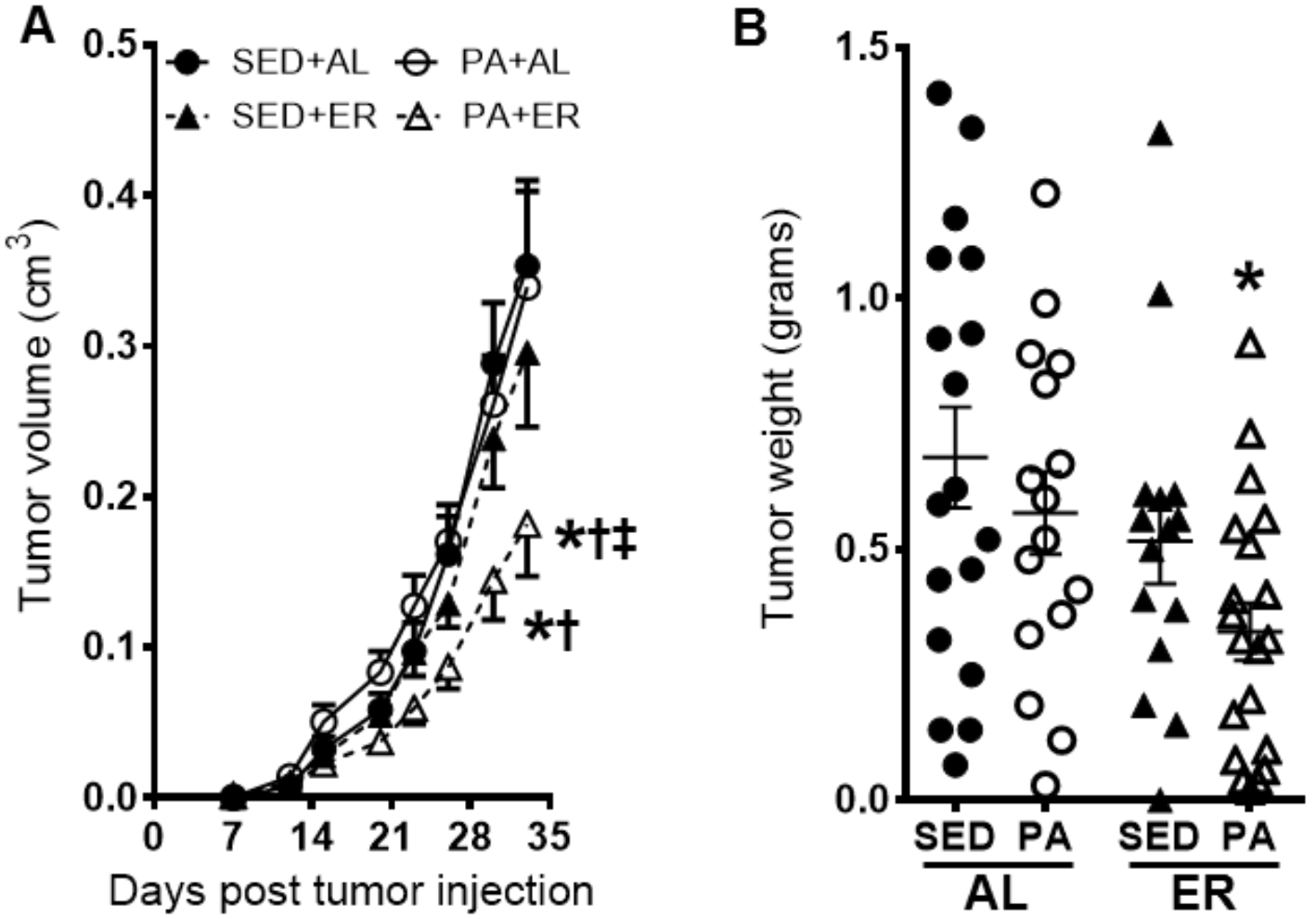


Body Weight & Running Wheel Activity



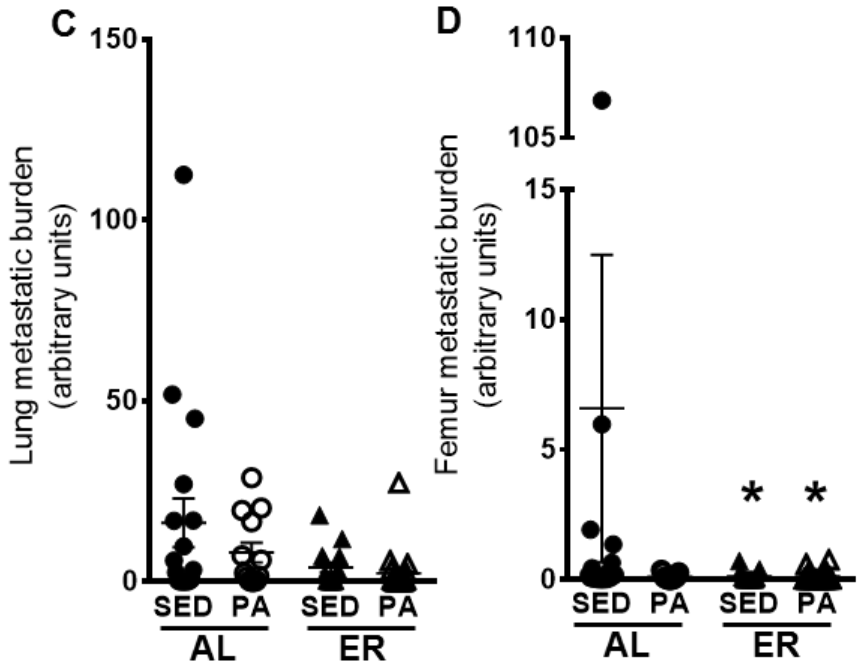
Turbitt, *et al*. *Cancer Prevention Research*. 2019;12(8):493-506.

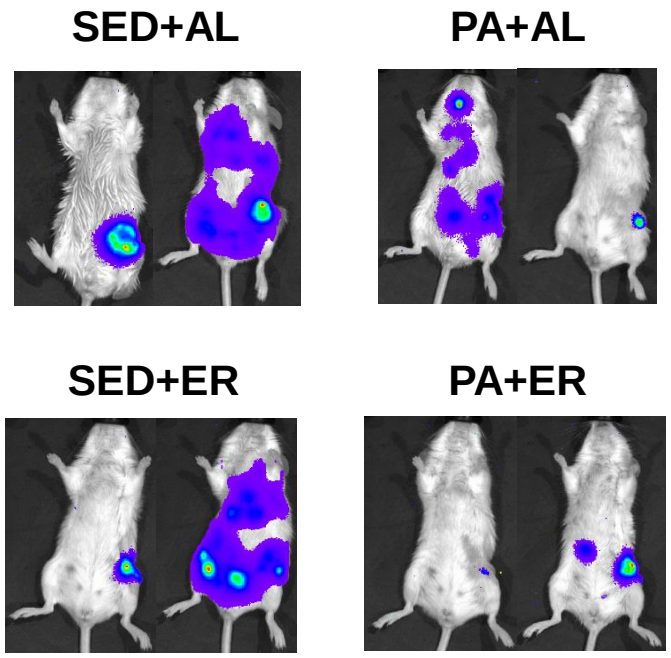
The combination of physical activity and energy restriction reduces primary tumor growth

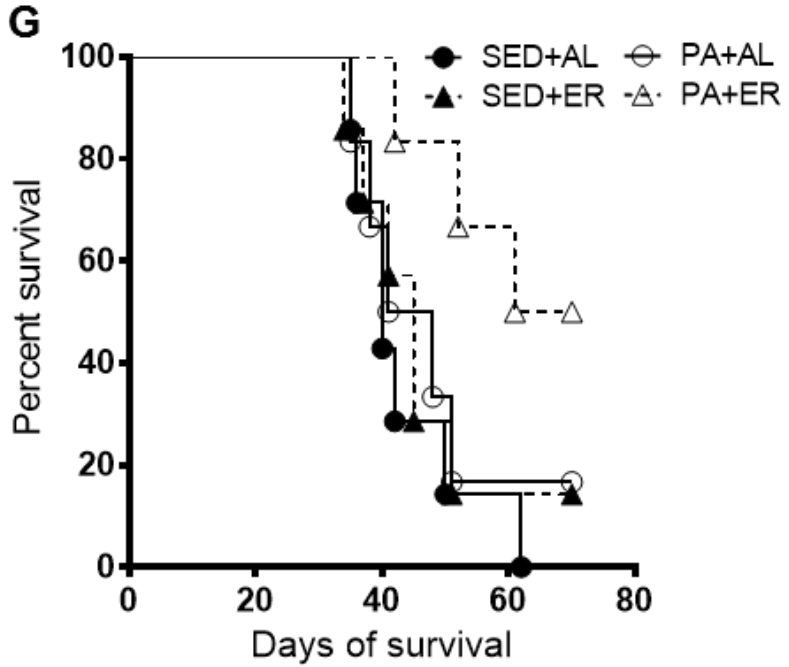


Turbitt, *et al*. *Cancer Prevention Research*. 2019;12(8):493-506.

The combination of physical activity and energy restriction reduces metastatic burden and improves survival



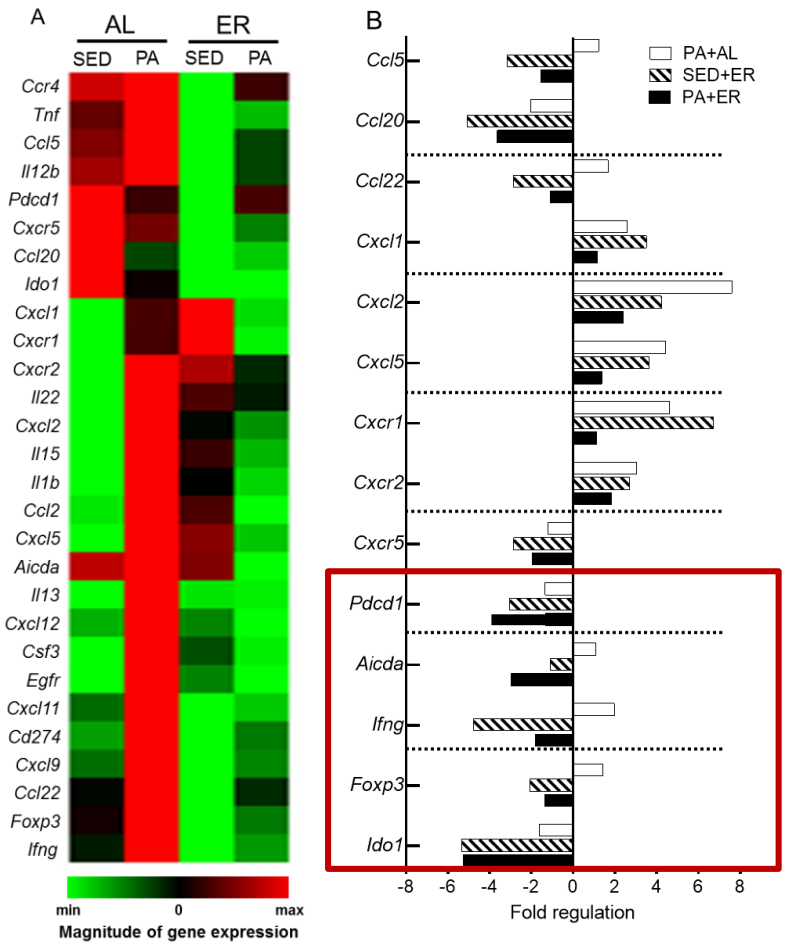




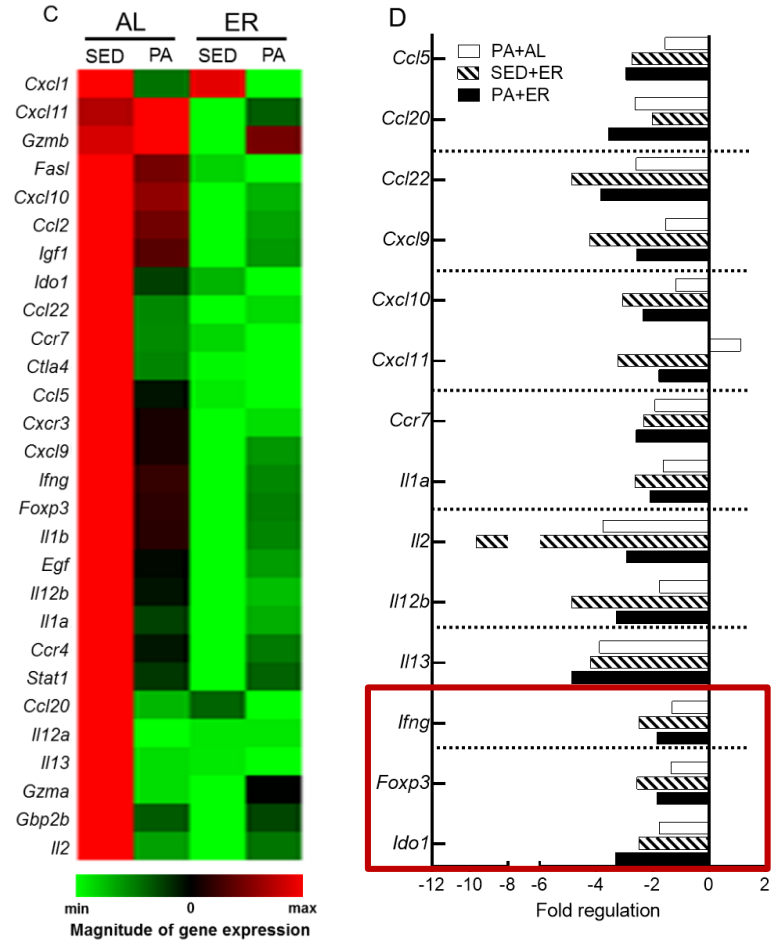
Turbitt, *et al*. *Cancer Prevention Research*. 2019;12(8):493-506.

Physical activity and energy restriction alters gene expression in the tumor microenvironment

Tumors 0.05-2.0 cm^3



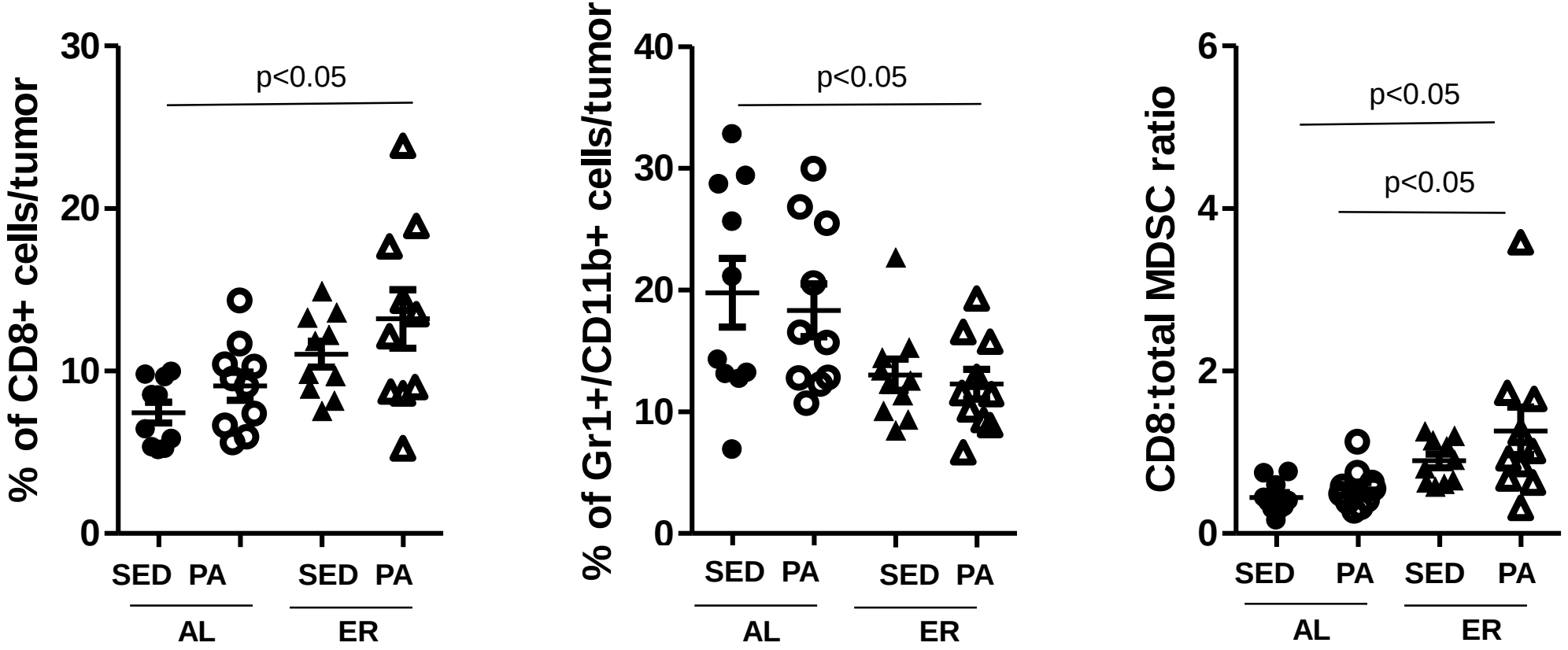
Day 35 post tumor implantation



Turbitt, *et al*. *Cancer Prevention Research*. 2019;12(8):493-506.

Physical activity and energy restriction increases CD8+ T cell infiltration and reduces the infiltration of MDSCs in the tumor microenvironment

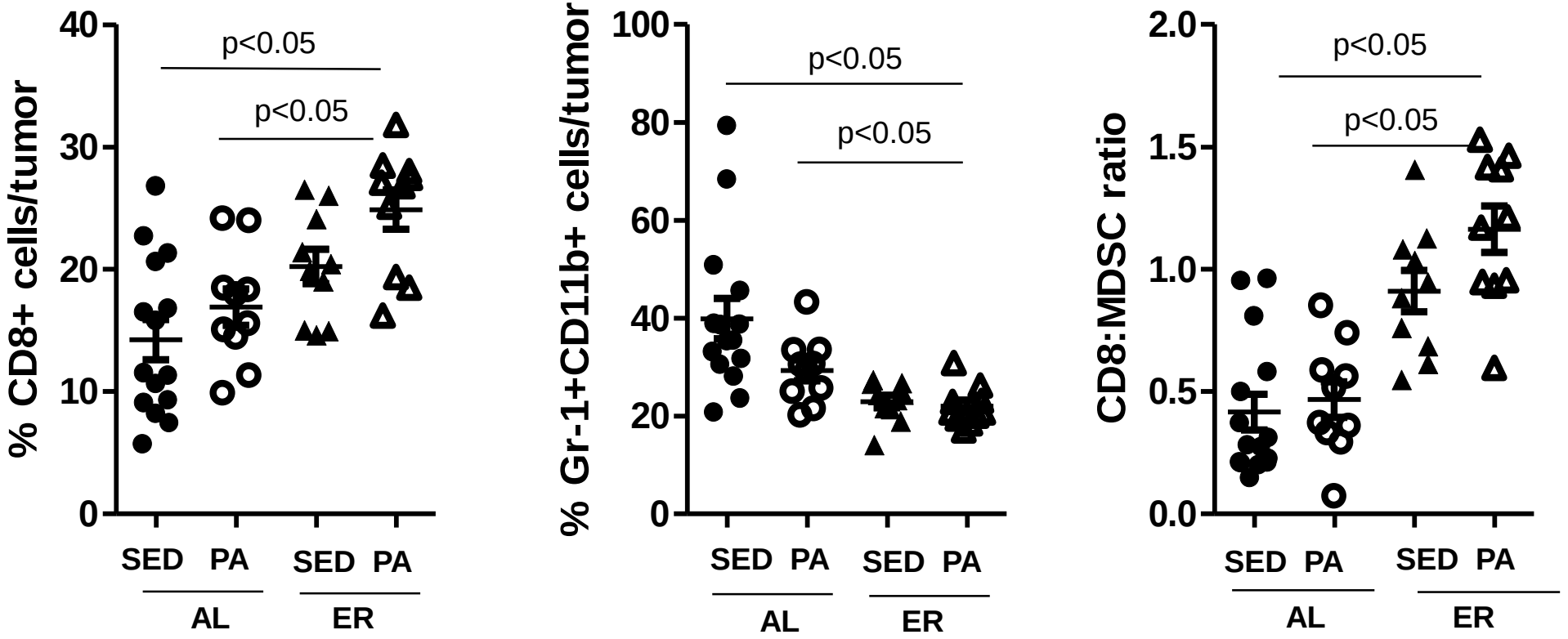
Tumors 0.05-2.0 cm^3



Turbitt, *et al*. *Cancer Prevention Research*. 2019;12(8):493-506.

Physical activity and energy restriction increases CD8+ T cell infiltration and reduces the infiltration of MDSCs in the tumor microenvironment

Day 35 post tumor implantation



Turbitt, *et al*. *Cancer Prevention Research*. 2019;12(8):493-506.

Summary

- The prevention of weight gain by energy restriction and physical activity reduces mammary tumor growth, metastatic burden and survival. These beneficial effects do not occur with either single intervention, and are independent of body weight.
- These changes occur concurrently with an increase in $CD8^+$ T cells and a reduction in MDSCs in the tumor microenvironment; and a change in the expression of PD1, and PDL1 and IDO on T cells and MDSCs, respectively.

Summary

- The response to PD-1 blockade is influenced by weight status. However, this is likely mediated by beneficial changes in the tumor microenvironment as a result of physical activity and energy restriction.

Acknowledgements

Rogers Lab

- Bill Turbitt, Ph.D.
- Sherry Xu
- Ester Oh
- Shizhao Duan, M.S.
- Shawntawnee Collins, Ph.D.
- Huicui Meng, Ph.D.
- Donna Sosnoski, M.S.

Collaborators

- Dr. Andrea Mastro, Ph.D.

Support: