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Diet and physical activity alter immunity and the tumor microenvironment

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• 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				
50		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 aduithood 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 acids cholesterol; saturated fatty acids; trans-fatty acids; cholesterol; sugar (sucrose); other sugars; sugary foods and drinks; coffiec; 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; hexachiorobenzene; hexachlorocyclohexane; trans- nonachlor; polychlorinated biphenyls; acrylamide; dietary patterms; culturally defined diets; sedentary behaviour; energy intake			
STRONG EVIDENCE	Substantial effect on risk unlikely				
 Body fatness waist-hip ratio Adult attained environmenta 	o. d height is unlikely to di	marked by body mass index (Bl rectly influence the risk of cance tritional factors affecting growt	er. It is a marker for genetic,		

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.

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м М		DECREASES RISK	INCREASES RIS
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 ⁶	
	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 olls; total fat; vegetable fat; fatty acid composition; saturated fatty acids; mon-unsaturated fatty acids; polyunsaturated fatty acids; trans-fatty acids; cholest 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 B6; folate; vitamin B12; vitamin c; vitamin D; vitamin hexachlorodphenytichloroethylene; diethorodiphenytichloroethylene; dichlorodiphenytichloroethyle; citars- nonachlor; polychlorinated biphenyls; acrylamide; dietz patterns; culturally defined diets; sedentary behaviour adult weight gain; energy intake	
STRONG EVIDENCE	Substantial effect on risk unlikely		
environmenta preconceptio 2 Body fatness includes evid is marked by 3 The Panel's o evidence for	al, hormonal and also nu n to completion of linea marked by body mass i ence on young women a BMI. conclusion relates to the	ndex (BMI), waist circumference ged about 18 to 30 years. Bod e evidence for overall breast car stmenopausal breast cancers se	h during the period from e and waist-hip ratio. Als r fatness in young adulth cer (unspecified). The
 No threshold Birthweight is later growth a cancer risk. The Panel's c 	was identified. s a marker both for pren and maturation – e.g., a	atal growth, reflecting fetal nutr ge at menarche – which are also e evidence for overall breast car	determinants of breas

- Ine Panel's conclusion relates to the evidence for overail breast cancer (unspecified), ine 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.

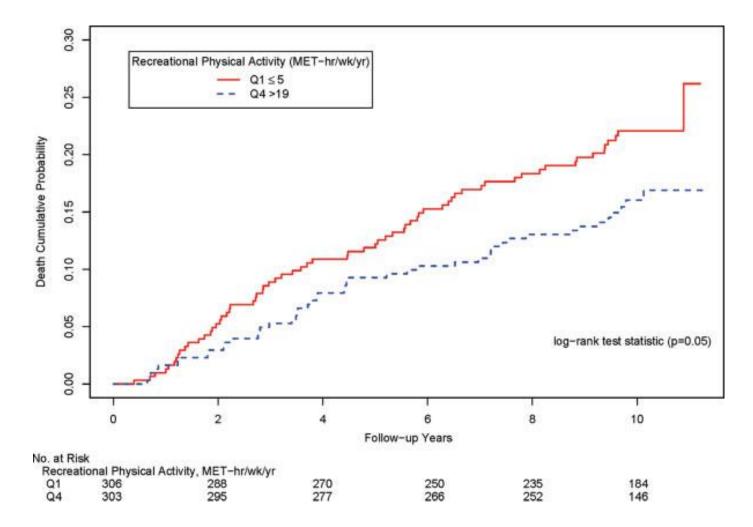
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AICR/WCRF. Continuous Update Project.

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Lifetime Recreational Physical Activity & Breast Cancer Mortality



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

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Obesity and Breast Cancer Mortality

Study	RR (95% CI)	% Weight	BMI kg/m ²			
Underweight v normal weight Buck 2011 Conroy 2011 Lu 2011 Chen 2010 Heilmann 2010 Hielmann 2010 Abrahamson 2006 Kroenke 2005 Bernstein 2002 Subtotal (<i>I</i> -squared = 48.2%, <i>P</i> = 0.043)	1.98 (0.79, 4.96) 1.13 (0.89, 1.42) 0.89 (0.70, 1.14) 1.44 (0.88, 2.37) 1.70 (0.86, 3.33) 1.36 (0.87, 2.11) 1.75 (0.94, 3.25) 0.73 (0.52, 1.04) 0.89 (0.70, 1.13) 1.13 (0.43, 2.97) 1.10 (0.92, 1.31)	3.29 17.23 16.79 8.51 5.44 9.79 6.21 12.75 16.98 3.01 100.00	<18.5 v 18.5-24.9 <22.5 v 22.5-24.9 <20 v 20-24.9 <=18.4 v 18.5-24.9 <=19.9 v 20-25 <=19.9 v 20-25 <=18.4 v 18.5-24.9 <=18.4 v 18.5-24.9 <21 v 21-22 <=18.4 v 18.5-24.9			
Overweight v normal weight Kamineni 2013 Buck 2011 Conroy 2011 Conroy 2011 Lu 2011 Chen 2010 Emaus 2010 Heilmann 2010 Keegan 2010 Nichols 2009 Oal Maso 2008 Reeves 2007 Abrahamson 2006 Kroenke 2005 Reeves 2000 Zhang 1995 Hoimberg 1994 Subtotal (I-squared = 0.0%, P = 0.882)	$\begin{array}{c} 1.09 & (0.69, 1.72) \\ 1.03 & (0.69, 1.56) \\ 1.15 & (0.93, 1.42) \\ 0.99 & (0.84, 1.15) \\ 1.02 & (0.81, 1.27) \\ 1.02 & (0.81, 1.27) \\ 1.22 & (0.92, 1.61) \\ 1.16 & (0.92, 1.45) \\ 1.13 & (0.90, 1.42) \\ 0.98 & (0.78, 1.24) \\ 1.20 & (0.80, 1.70) \\ 1.02 & (0.83, 1.25) \\ 1.20 & (0.90, 1.60) \\ 1.02 & (0.83, 1.25) \\ 1.20 & (0.90, 1.60) \\ 1.02 & (0.84, 1.12) \\ 1.47 & (0.96, 2.24) \\ 1.11 & (0.91, 1.33) \\ 1.19 & (0.92, 1.53) \\ 1.00 & (0.50, 2.20) \\ 2.38 & (0.84, 6.77) \\ 1.07 & (1.02, 1.12) \\ \end{array}$	1.18 1.47 5.47 9.94 4.85 4.85 4.85 4.85 4.74 4.71 4.74 4.71 4.76 1.73 5.85 2.96 32.20 1.37 6.55 3.79 0.45 0.23 100.00	$\begin{array}{c} 25-29.9 \lor <25\\ 25-29.9 \lor 18.5-24.9\\ 25-29.9 \lor 20-24.9\\ 25-29.9 \lor 20-24.9\\ 25-29.9 \lor 18.5-24.9\\ 25-29.9 \lor 18.5-24.9\\ 25-29.9 \lor <85-24.9\\ 25-29.9 \lor <824.9\\ 25-29.9 \lor 81.5-24.9\\ 25-29.9 \lor 81.5-24.9\\ 25-29.9 \lor <824.9\\ 25-29.9 \lor 81.5-24.9\\ 25-29.9 \lor 18.5-24.9\\ 25-29.9 \lor 18.5-24.9\\ 25-29.9 \lor 18.5-24.9\\ 25-29.9 \lor 18.5-24.9\\ 25-29 \lor <824.9\\ 25-29.9 \lor 18.5-24.9\\ 25-29 \lor <84.9\\ 25-28 \lor \\84.9$ 25-28 \lor \\84.9			
Obese v normal weight Kamineni 2013 Buck 2011 Conroy 2011 Lu 2011 Chen 2010 Emaus 2010 Hellmann 2010 Keegan 2010 Nichols 2009 Wesst-Wright 2009 Cleveland 2007 Reding 2008 Cleveland 2007 Reves 2007 Abrahamson 2006 Kroenke 2005 Bernstein 2002 Reves 2007 Jang 1995 Holmberg 1994 Subtotal (I-squared = 37.6%, P = 0.043)	$\begin{array}{c} 1.31 \ (0.77, 2.22) \\ 1.15 \ (0.54, 2.46) \\ 1.54 \ (1.23, 1.91) \\ 1.23 \ (1.04, 1.47) \\ 1.58 \ (1.13, 2.22) \\ 1.47 \ (1.08, 1.99) \\ 1.61 \ (1.12, 2.33) \\ 1.21 \ (1.00, 1.48) \\ 1.52 \ (1.17, 1.98) \\ 1.42 \ (1.06, 1.48) \\ 1.60 \ (1.10, 2.30) \\ 1.29 \ (0.99, 1.68) \\ 1.60 \ (1.10, 2.30) \\ 1.29 \ (0.99, 1.68) \\ 1.60 \ (1.10, 2.50) \\ 1.63 \ (1.08, 2.45) \\ 1.66 \ (0.86, 1.30) \\ 2.93 \ (1.37, 6.29) \\ 1.20 \ (0.95, 1.52) \\ 1.18 \ (0.81, 1.72) \\ 1.49 \ (1.18, 1.86) \\ 1.50 \ (0.70, 2.90) \\ 5.93 \ (1.98, 17.80) \\ 5.93 \ (1.98, 17.80) \\ 1.41 \ (1.29, 1.53) \end{array}$	2.20 1.17 7.31 8.97 4.42 5.05 3.94 8.12 6.06 5.70 3.90 6.02 5.39 3.34 7.67 1.16 6.85 7.08 1.31 0.58 100.00	$\begin{array}{l} {} {} {} {} {} {} {} {} {} {} {} {} {}$			
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e 2. Categorical meta-analysis of pre-diagnosis BMI and total mortality.						

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

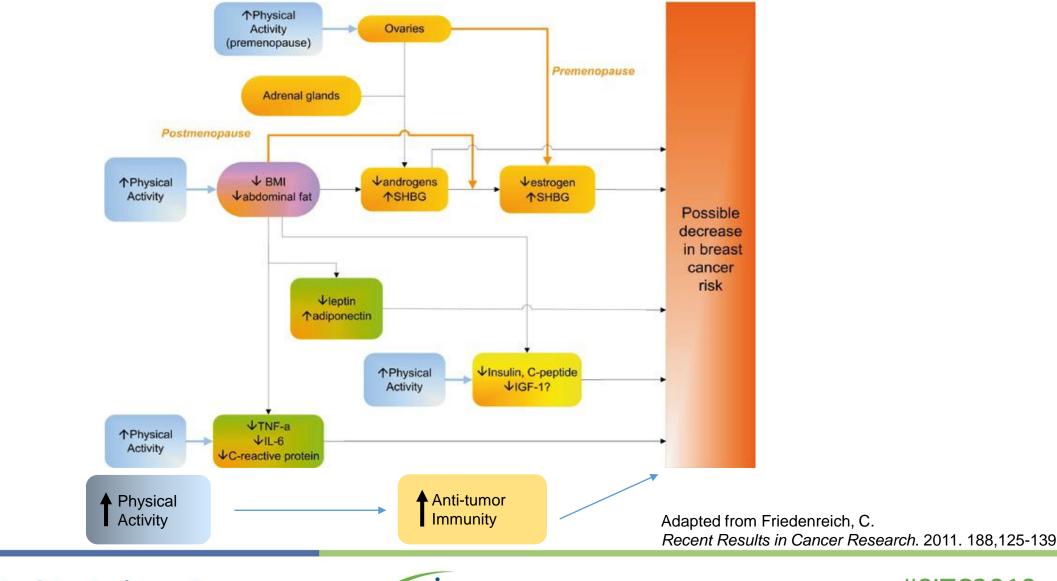
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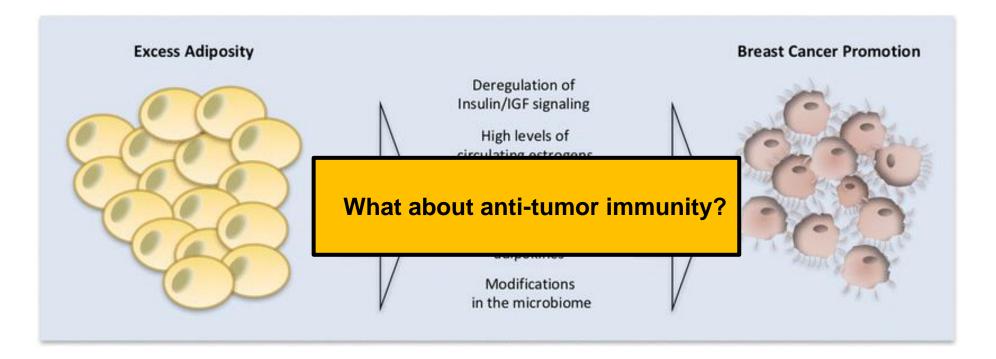
Proposed biological mechanisms linking physical activity and breast cancer prevention



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Mechanisms Linking Obesity and Breast Cancer: Mouse Models



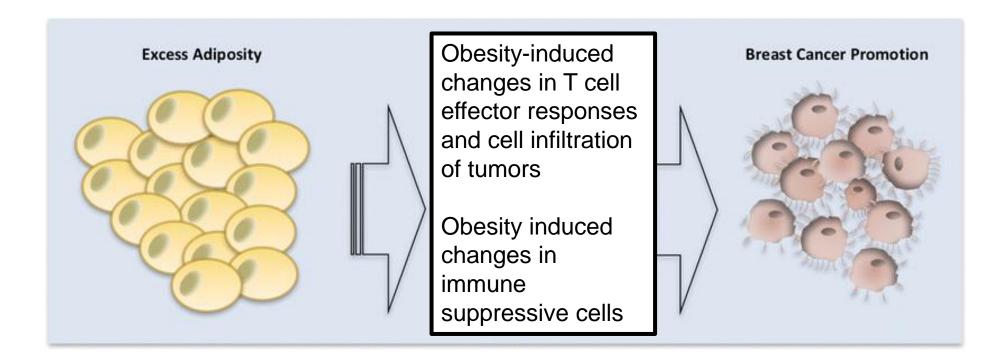
Adapted from Argolo, et al. Current Oncology Reports. 2018. 20: 47

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Mechanisms Linking Obesity and Breast Cancer: Mouse Models



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Can we ask this question differently ?



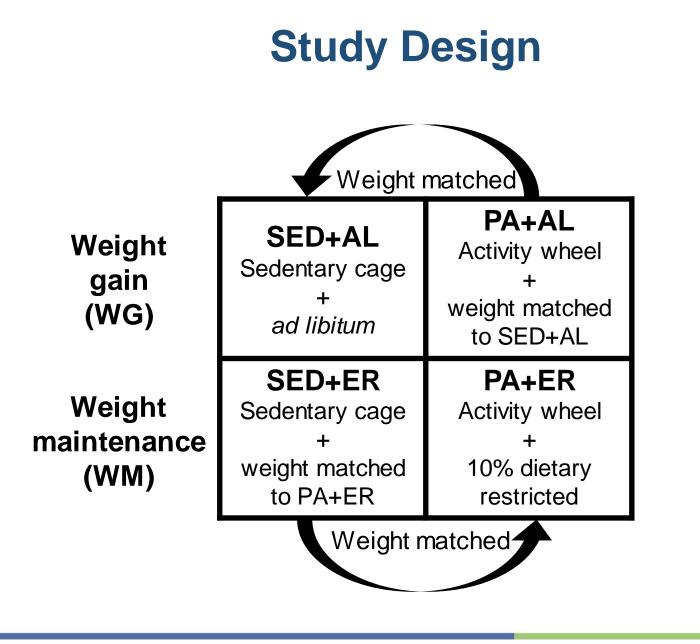
What can we learn about the prevention of weight gain over the course of life?

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

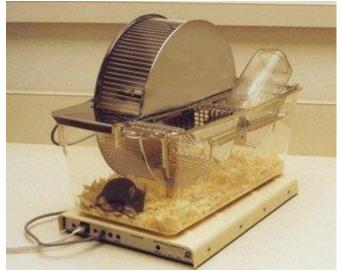
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Voluntary Running Wheel



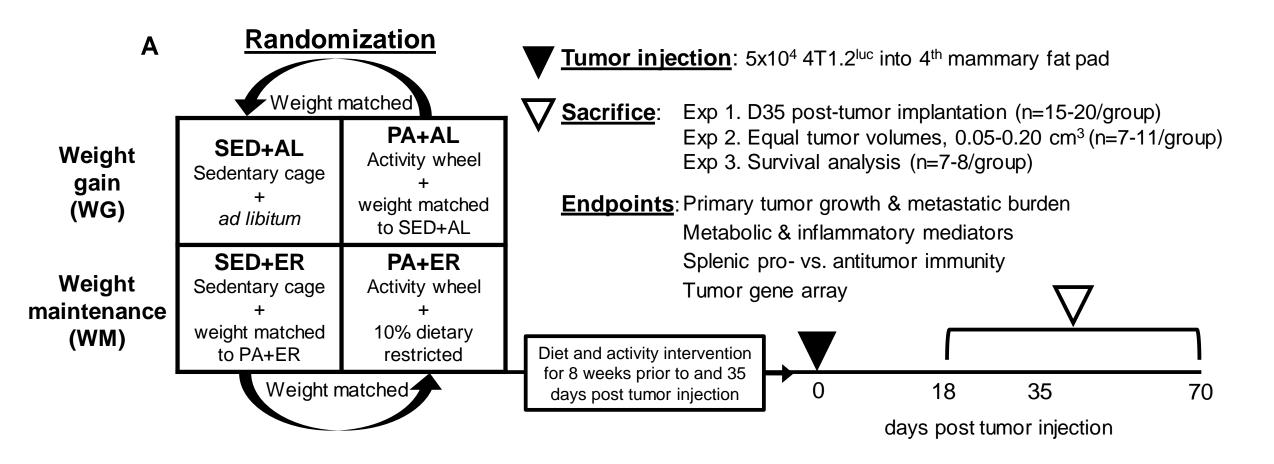
10% Reduction in Calories





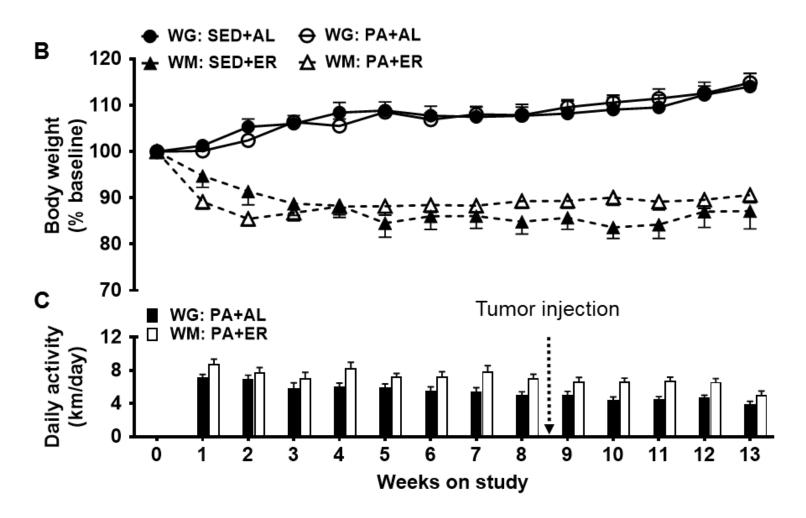


Experimental Design





Body Weight & Running Wheel Activity

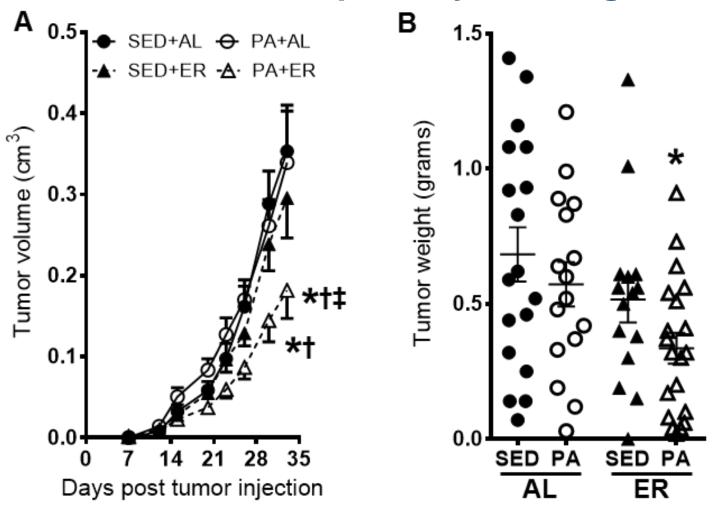


Turbitt, et al. Cancer Prevention Research. 2019;12(8):493-506.





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

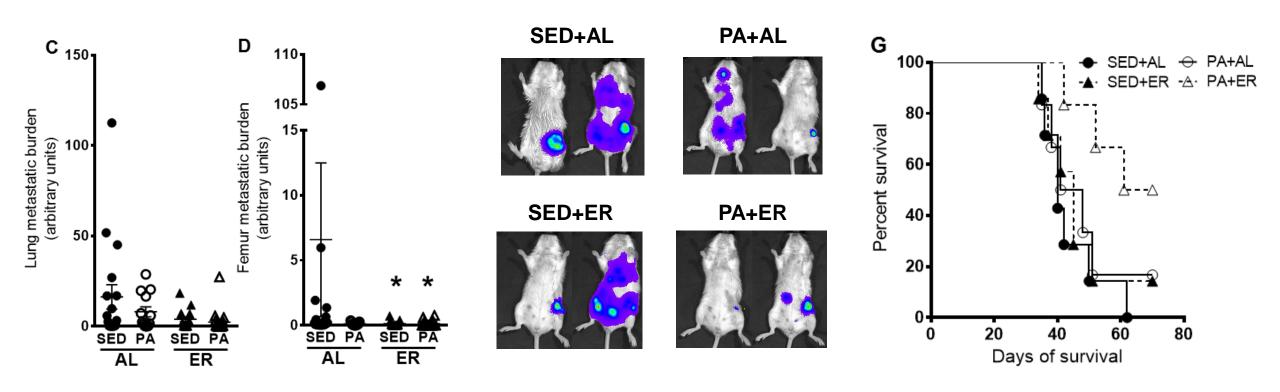


Turbitt, et al. Cancer Prevention Research. 2019;12(8):493-506.





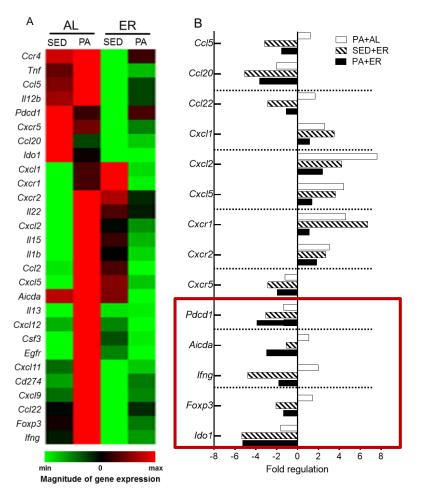
The combination of physical activity and energy restriction reduces metastatic burden and improves survival



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

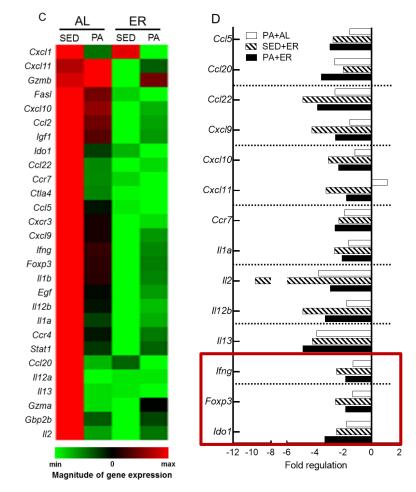


Physical activity and energy restriction alters gene expression in the tumor microenvironment



Tumors 0.05-2.0 cm³

Day 35 post tumor implantation



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

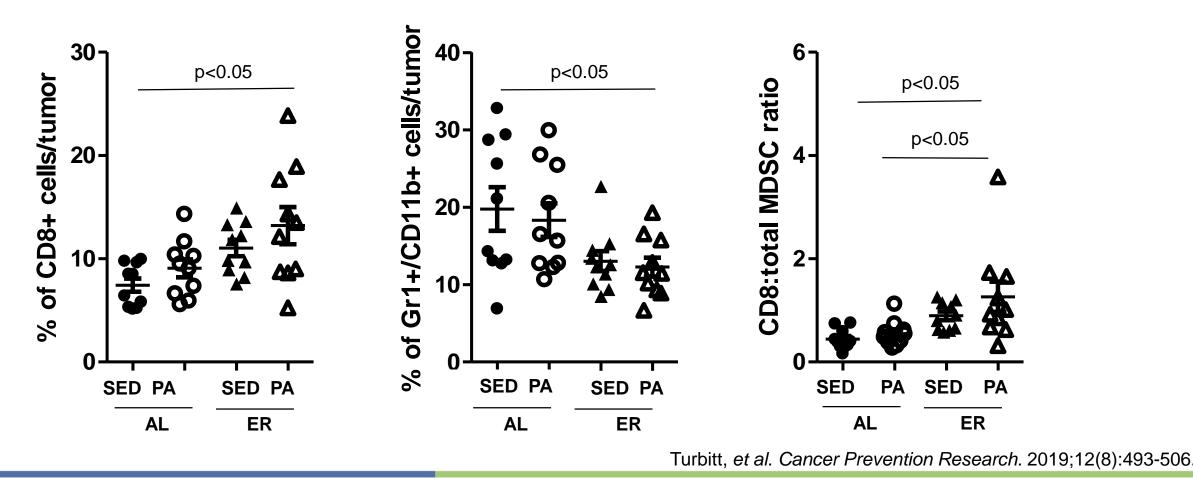
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¹⁷ Physical activity and energy restriction increases CD8⁺ T cell infiltration and reduces the infiltration of MDSCs in the tumor microenvironment

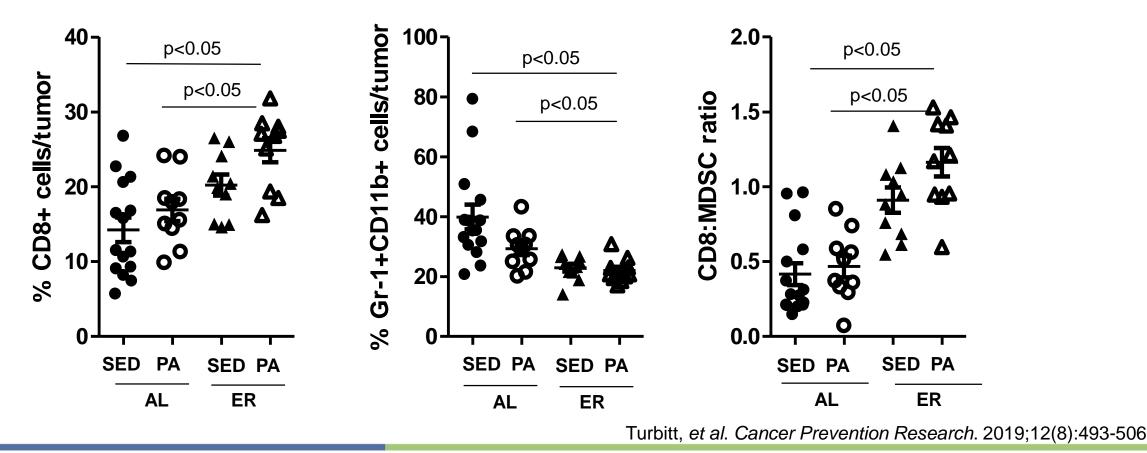
Tumors 0.05-2.0 cm³



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¹⁸ 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

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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.







 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.

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