

Berry Polyphenols in the Prevention of Primary and Recurrent Breast Cancer

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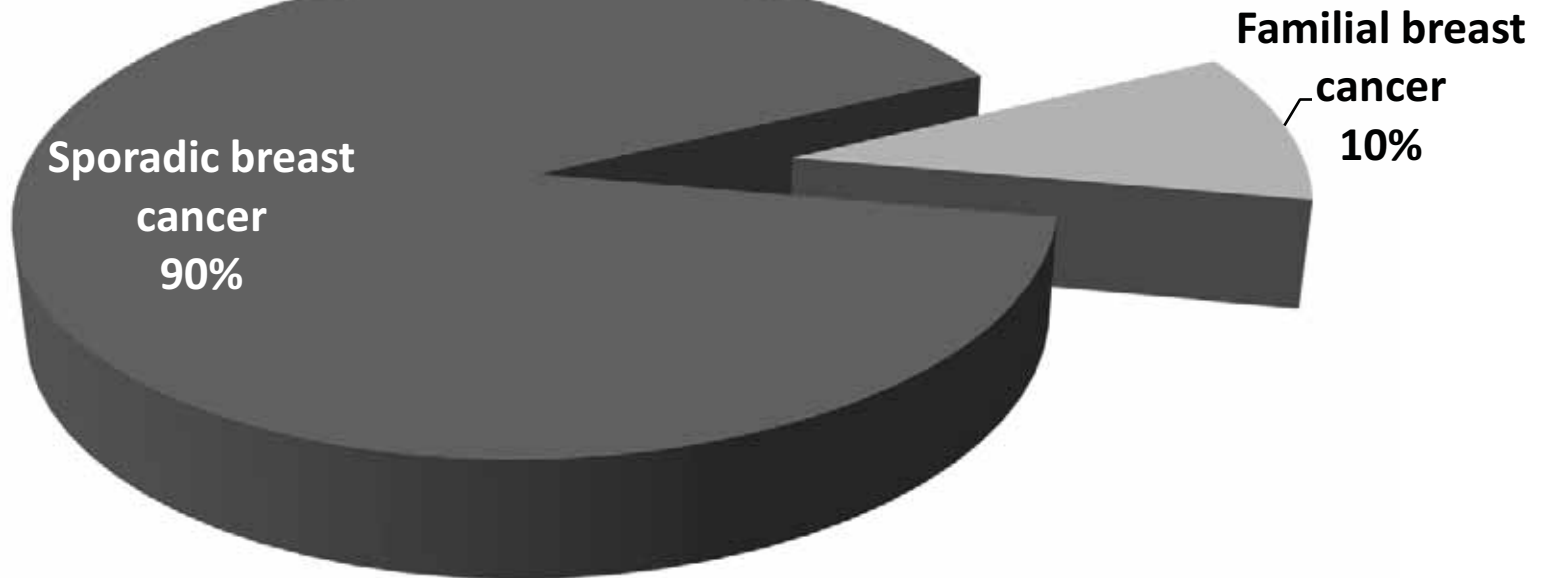
Berry Health Symposium
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Overview

- Breast cancer – incidence and risk factors
- Selection of berries for breast cancer prevention
- Berries in mammary tumor prevention
- Mechanisms by which berries prevent breast cancer
- Future directions

Breast Cancer- Causes

Causes

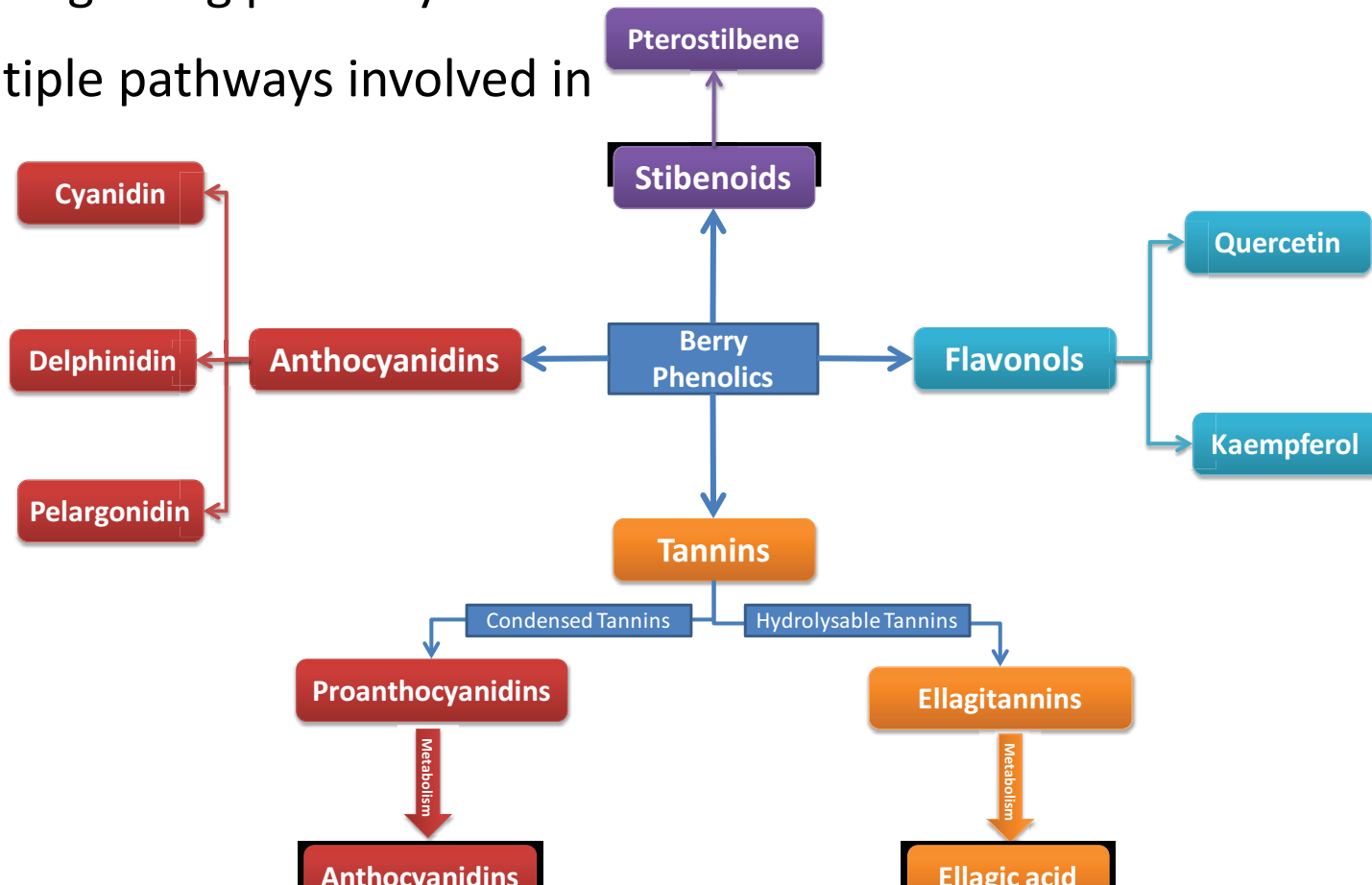


Breast cancer- risk factors

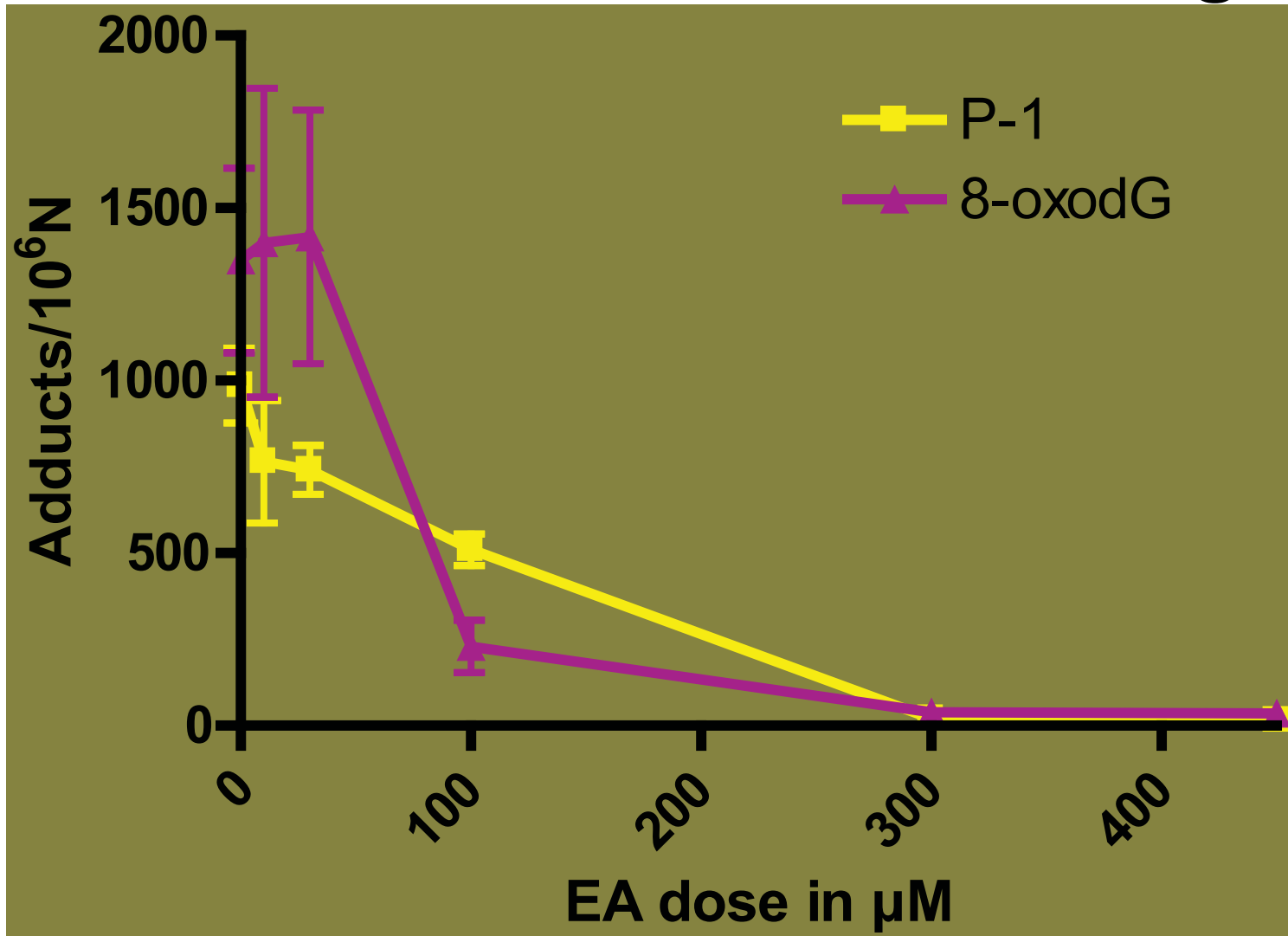
Non-Modifiable Risk Factors	Modifiable Risk Factors	Hormonal Risk Factors
Age ↑	Diet	Cumulative exposure to estrogen ↑
Gender	Alcohol ↑	Age at menarche and menopause
Genetics	Smoking ↑	Parity
Family history ↑	Body weight ↑	Lactation ↓
Previous breast disease ↑	Exercise ↓	Hormone replacement therapy ↑
	Radiation	

Berry polyphenols

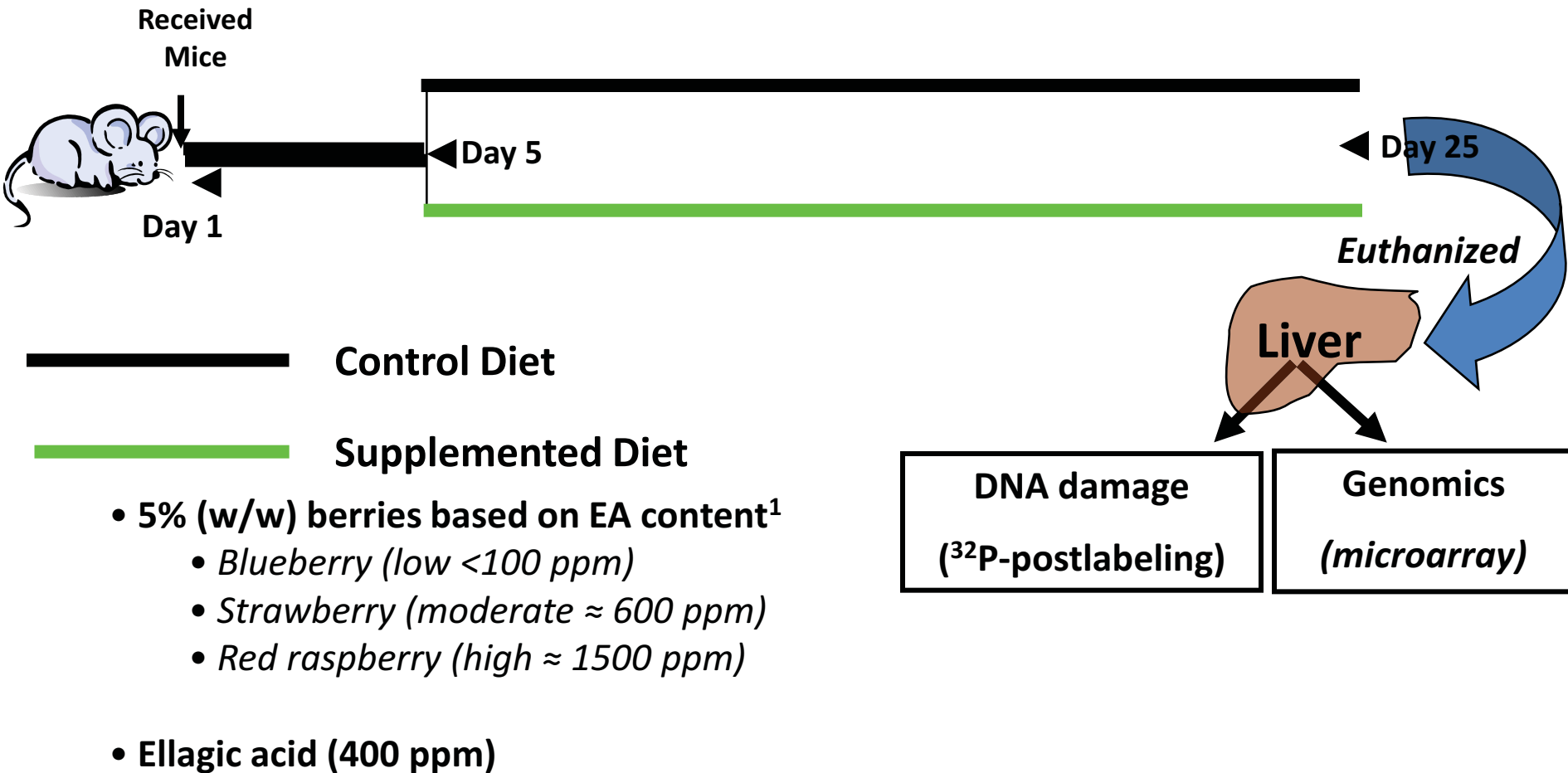
- ❖ Excellent antioxidant properties
- ❖ Interaction with Estrogen receptor
- ❖ Cause cell-cycle arrest
- ❖ Interfere with cell-signaling pathways
- ❖ Interact with multiple pathways involved in carcinogenesis



Effect of ellagic acid on 4-hydroxy estradiol-induced oxidative DNA damage

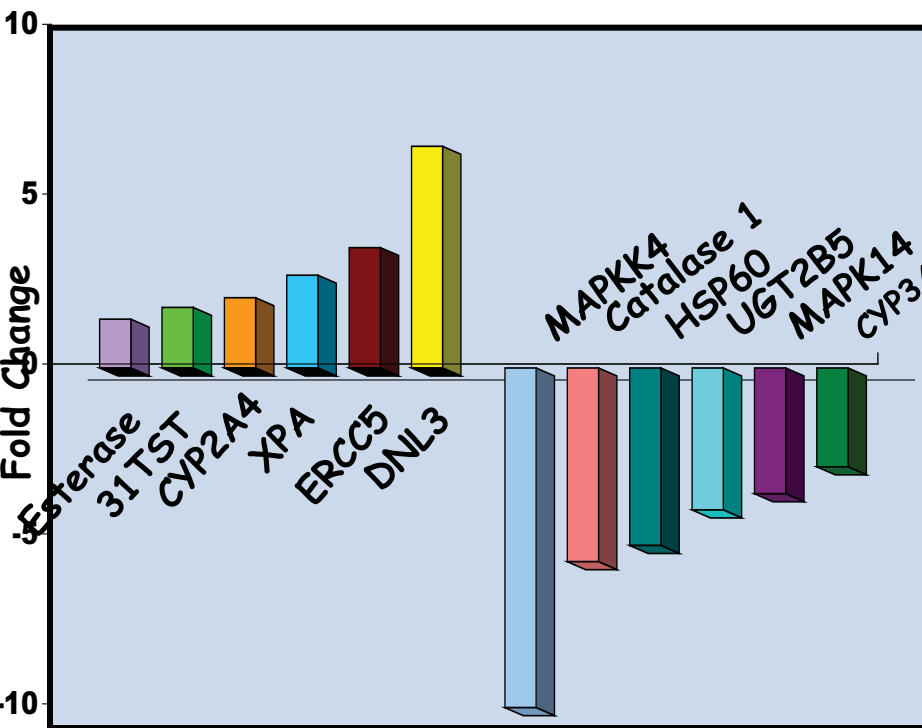


Next step-*in vivo* study (Short-Term)

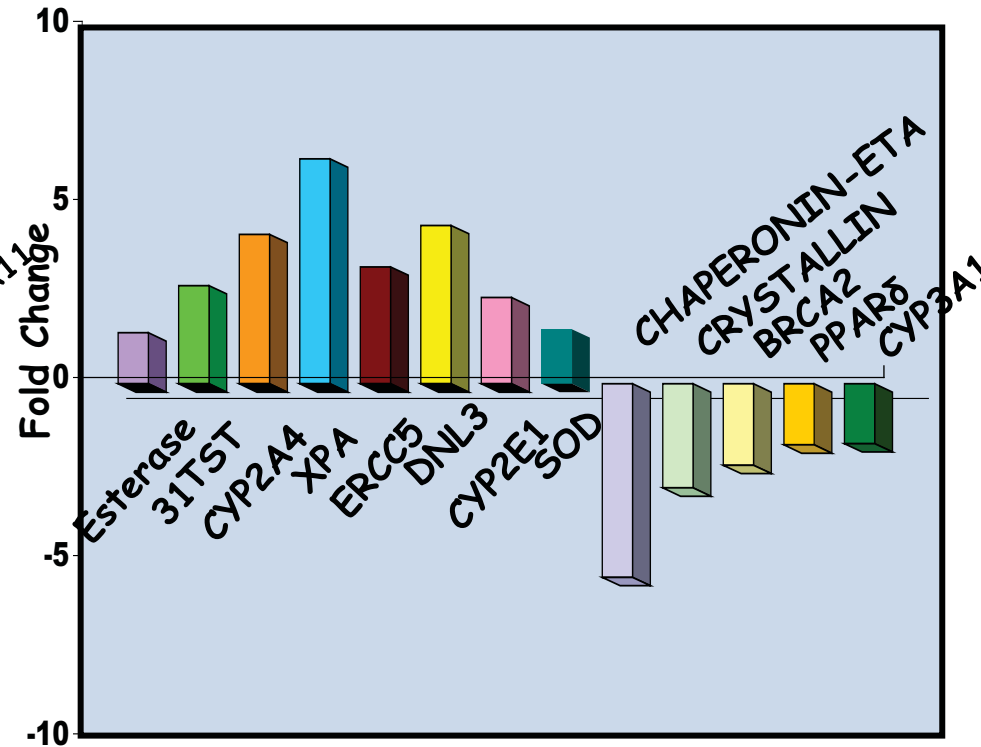


Short-term *in vivo* study

Raspberry supplemented diet

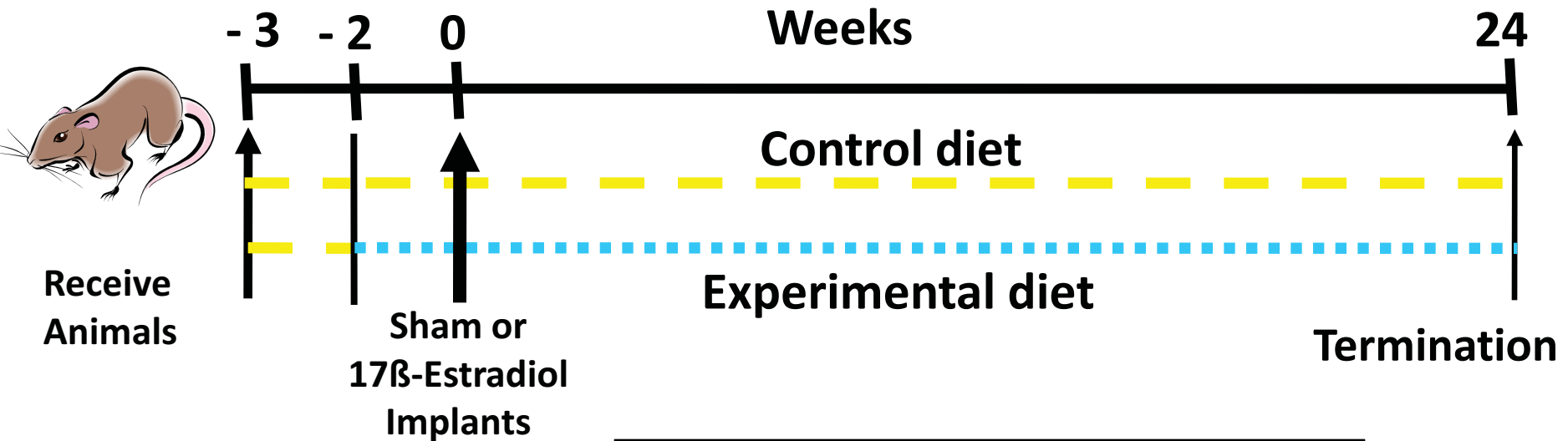


Ellagic acid supplemented diet



These diets also significantly reduced baseline hepatic-DNA damage in a similar fashion

Next step- tumorigenesis study

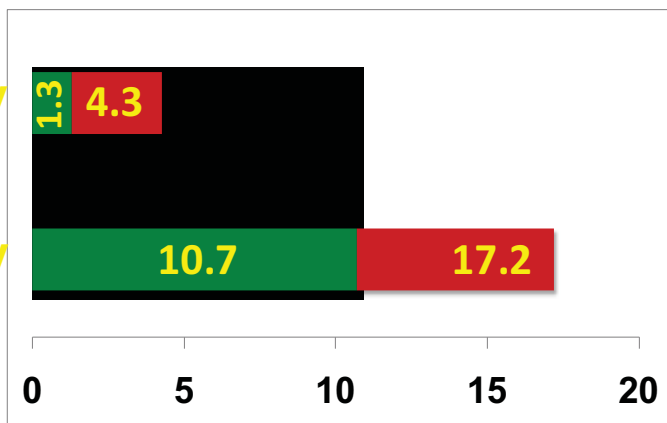


DIET	DOSE
Control (AIN 93M)	NA
Blueberry	2.5% (w/w)
Black raspberry	2.5% (w/w)
Ellagic acid	400 ppm

Rationale for berry types used

DIET	DOSE	Ellagic acid content	Anthocyanin content
Blueberry	2.5% (w/w)	Low (<100 ppm)	Moderate (\approx 4000 ppm)
Black raspberry	2.5% (w/w)	High (\geq 1500 ppm)	High (\approx 7000 ppm)
Ellagic acid	400 ppm	Pure compound	

Blueberry

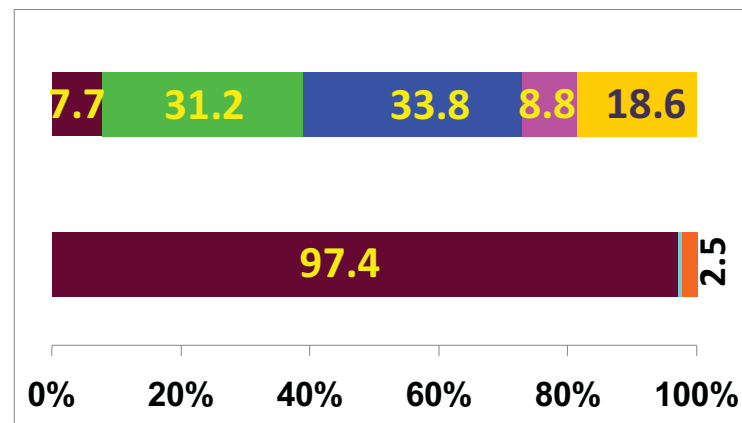


Black Raspberry



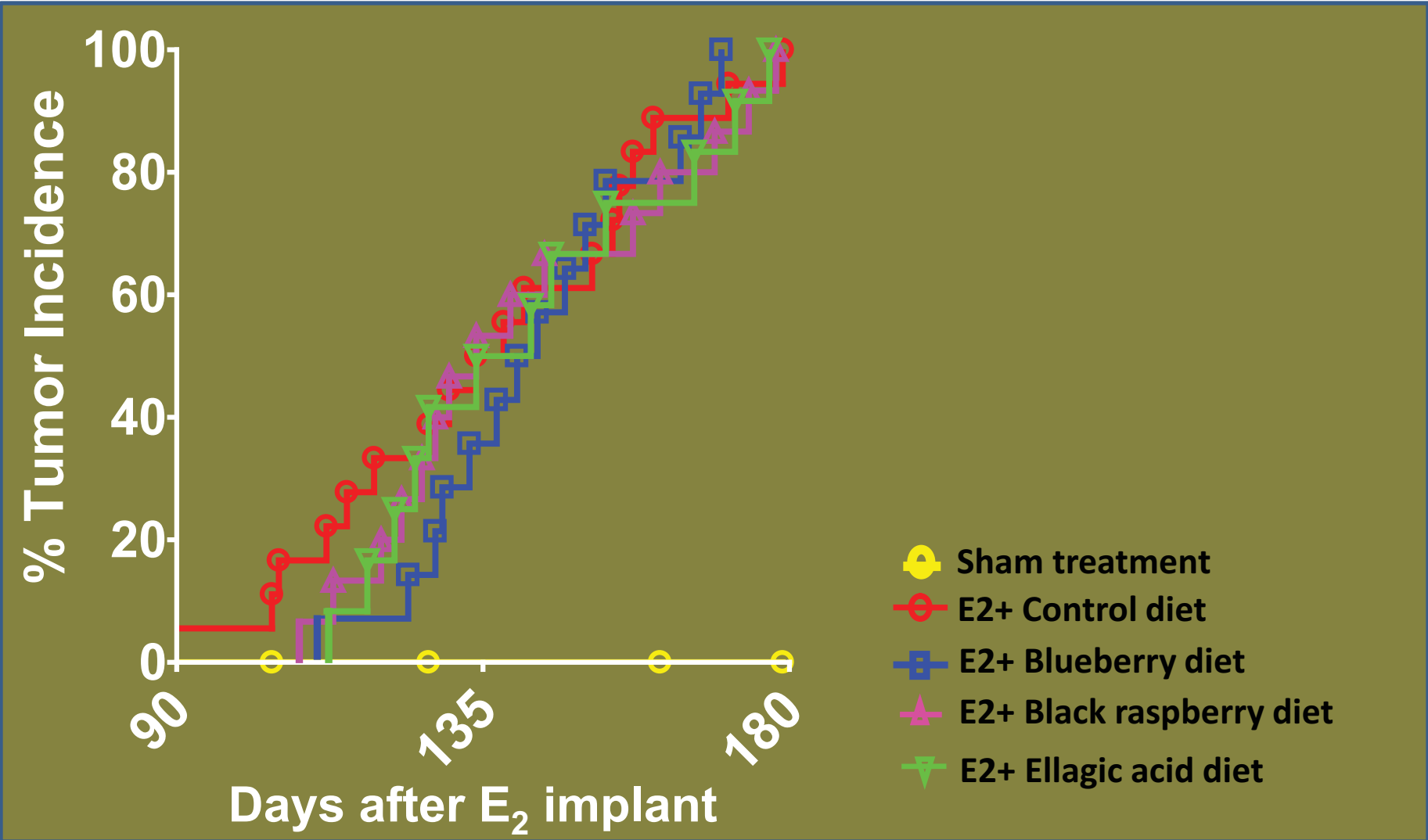
mg/ g dry wt

Anthocyanins Total Phenolics



Cyanidin Delphinidin Malvidin
Petunidin Pelargonidin Peonidin

Berry diets increase mammary tumor latency



<http://archive.uky.edu/bitstream/10225/627/AiyerDissertation.pdf>

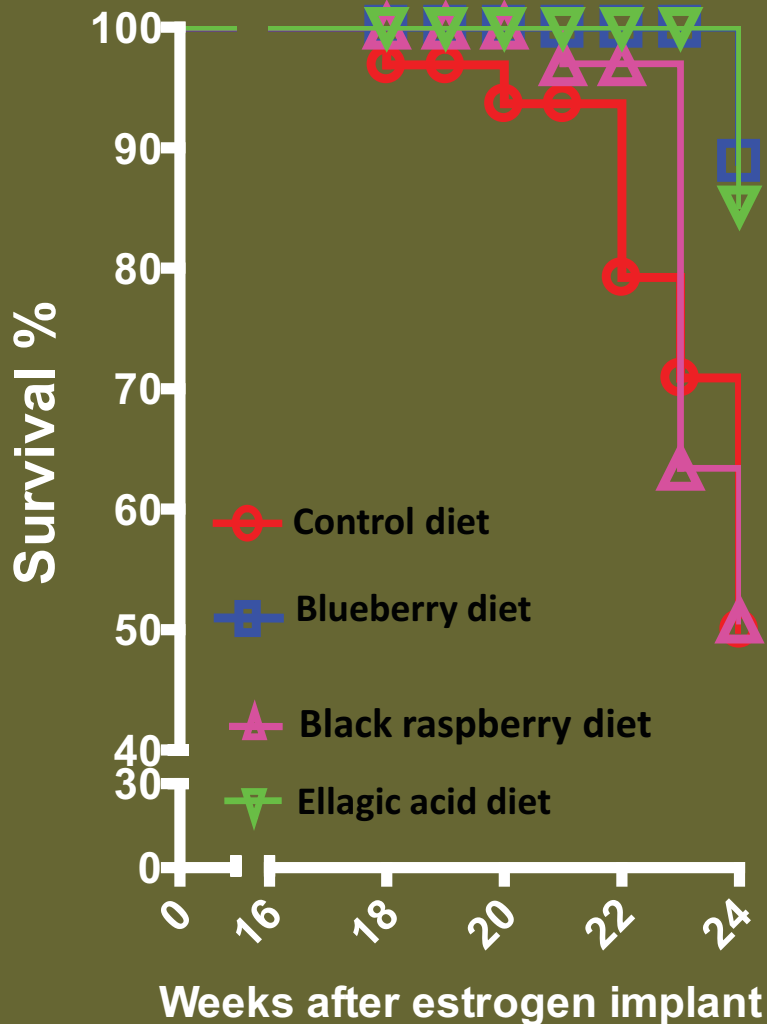
Estrogen treatment associated morbidity in ACI rats



Berry diets reduce treatment-associated morbidity in ACI rats



Berry diets diminish treatment-associated mortality



Morbidity score – 1 to 5
(1- best; 5-worst.)

Weight loss > 1 g per day

Hair loss ≥ 3

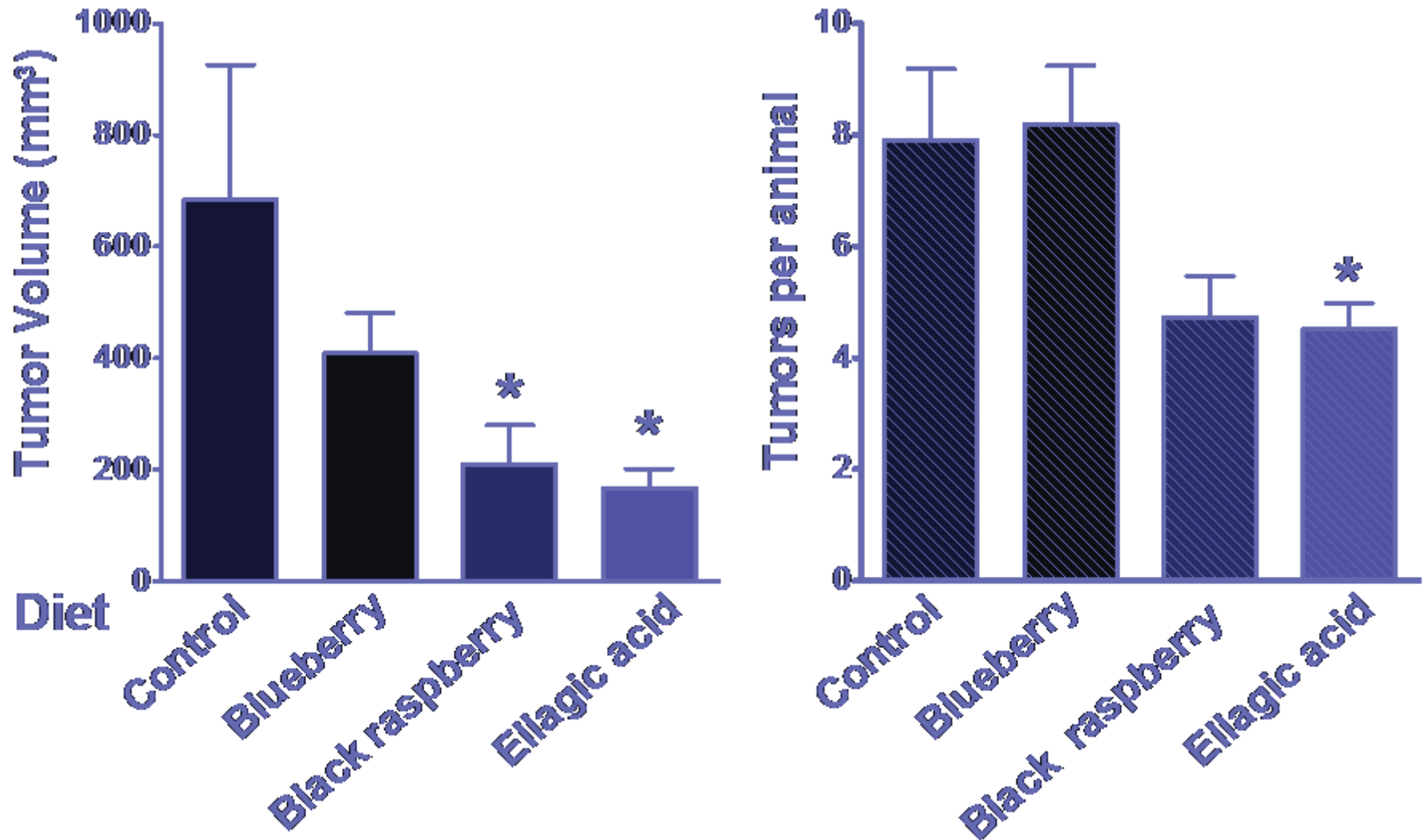
Crouch ≥ 3

Eye deposits ≥ 3

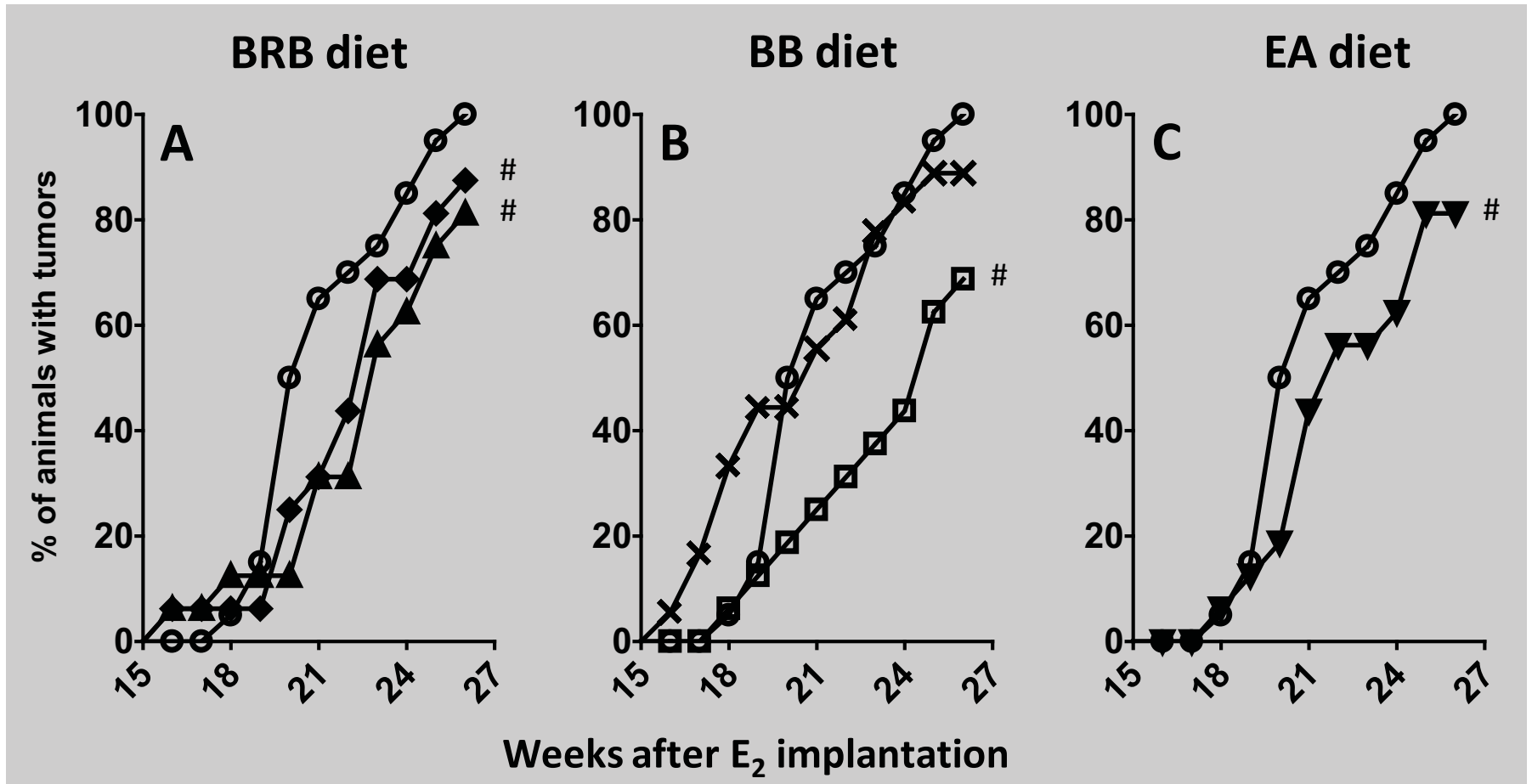
Loss of balance ≥ 3

Tumor size ≥ 1.3 cm (not included
in mortality index)

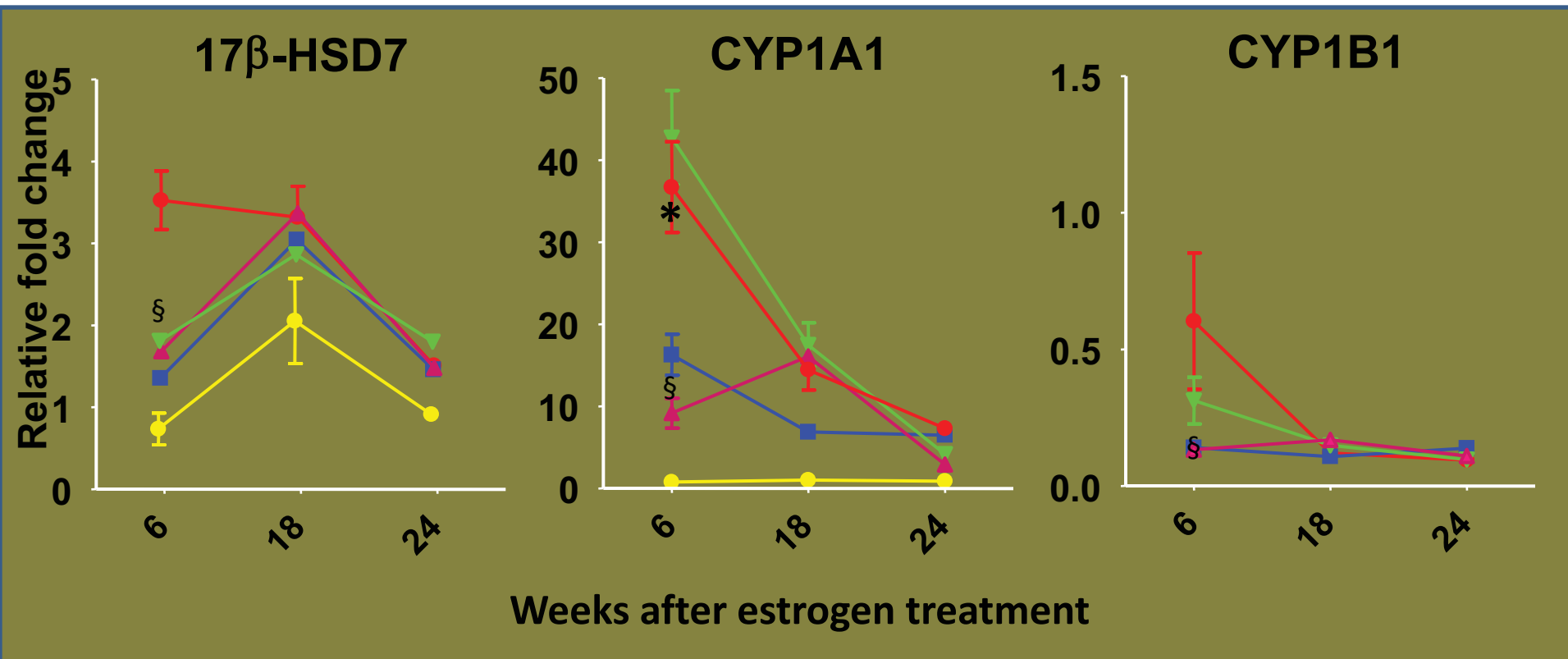
Berry diets decrease tumor volume and multiplicity



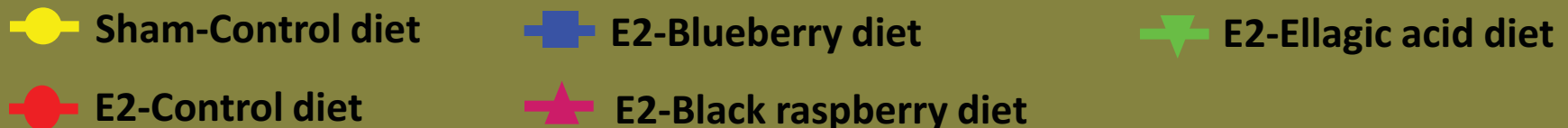
BERRY DIETS REDUCE TUMOR INCIDENCE



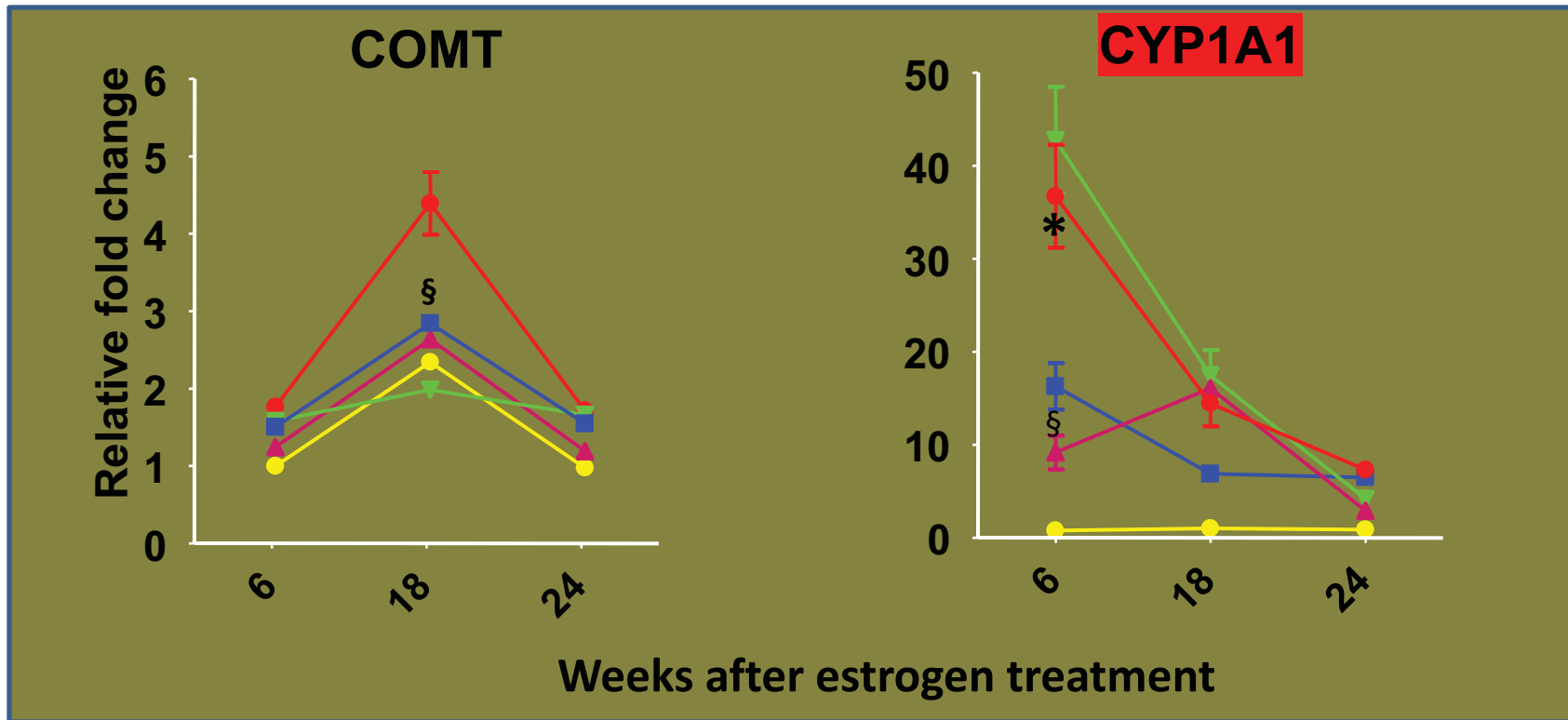
BERry diets modulate phase I enzymes



[Aiyer et al., Cancer Prev Res \(Phila\). 2010 Jun;3\(6\):727-37](#)



BERRY diets also modulate phase II enzyme



[Aiyer et al., Cancer Prev Res \(Phila\). 2010 Jun;3\(6\):727-37](#)

● Sham-Control diet

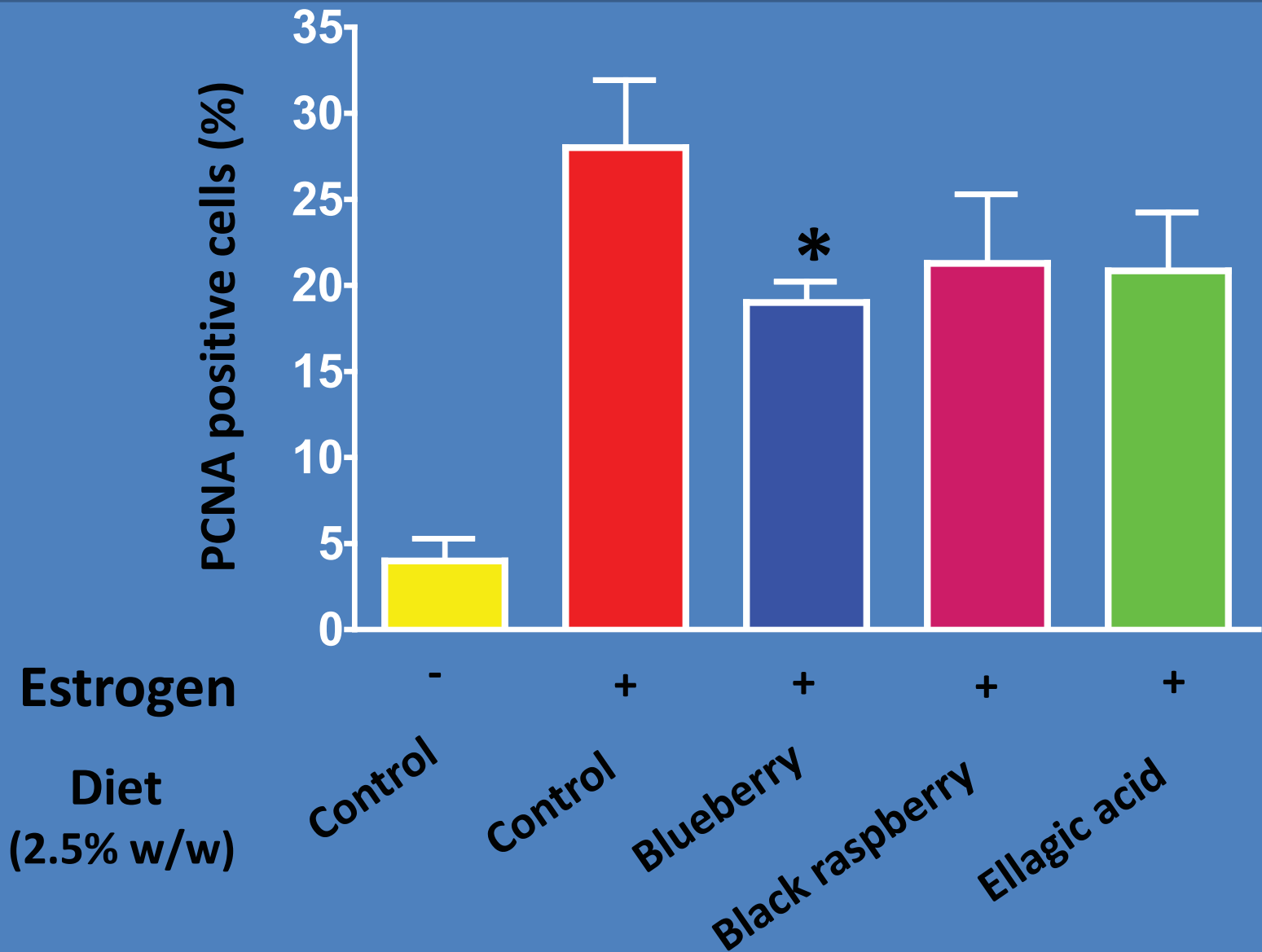
■ E2-Blueberry diet

▼ E2-Ellagic acid diet

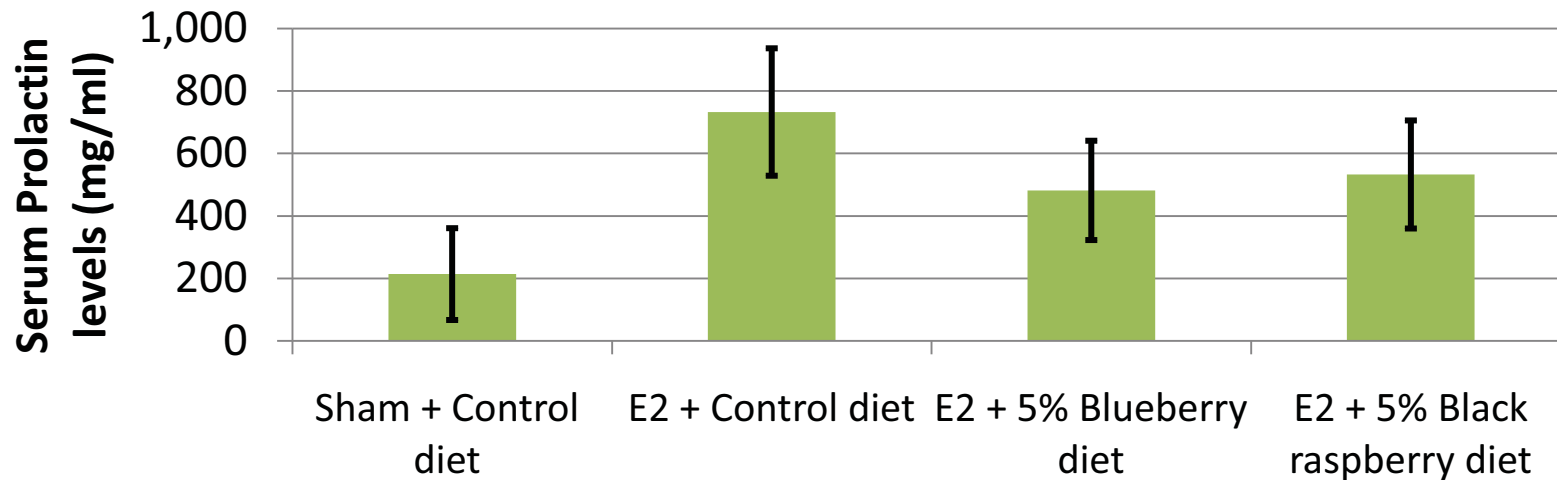
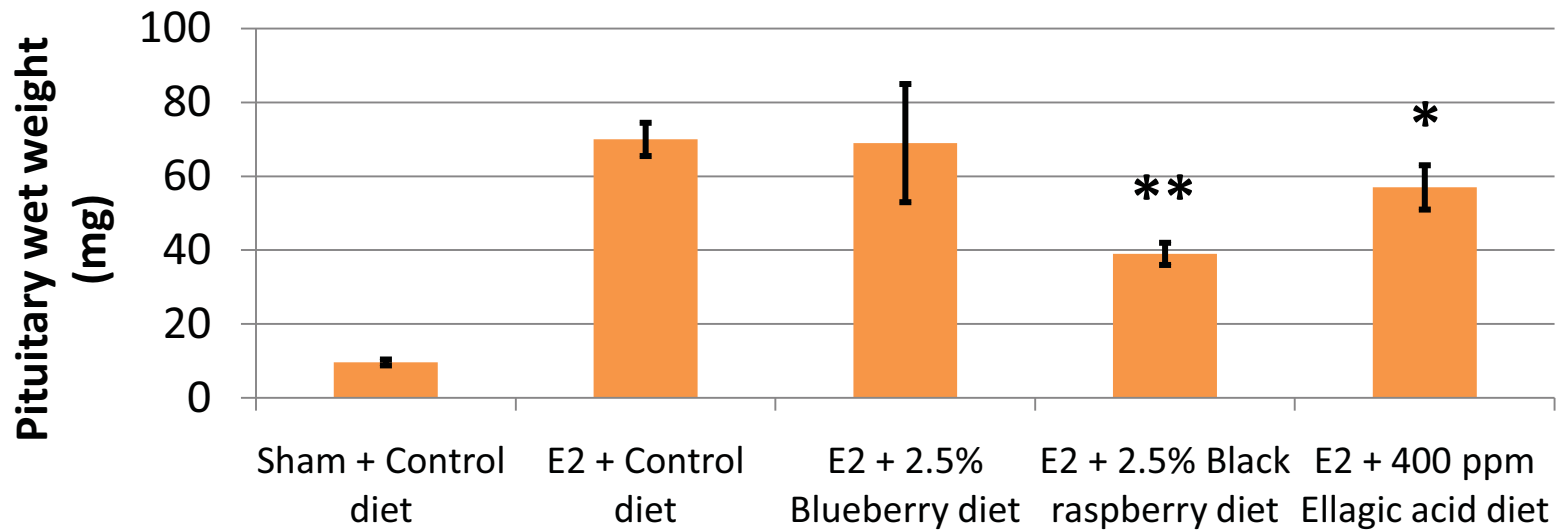
● E2-Control diet

★ E2-Black raspberry diet

Berry diets inhibit E2-induced cell proliferation

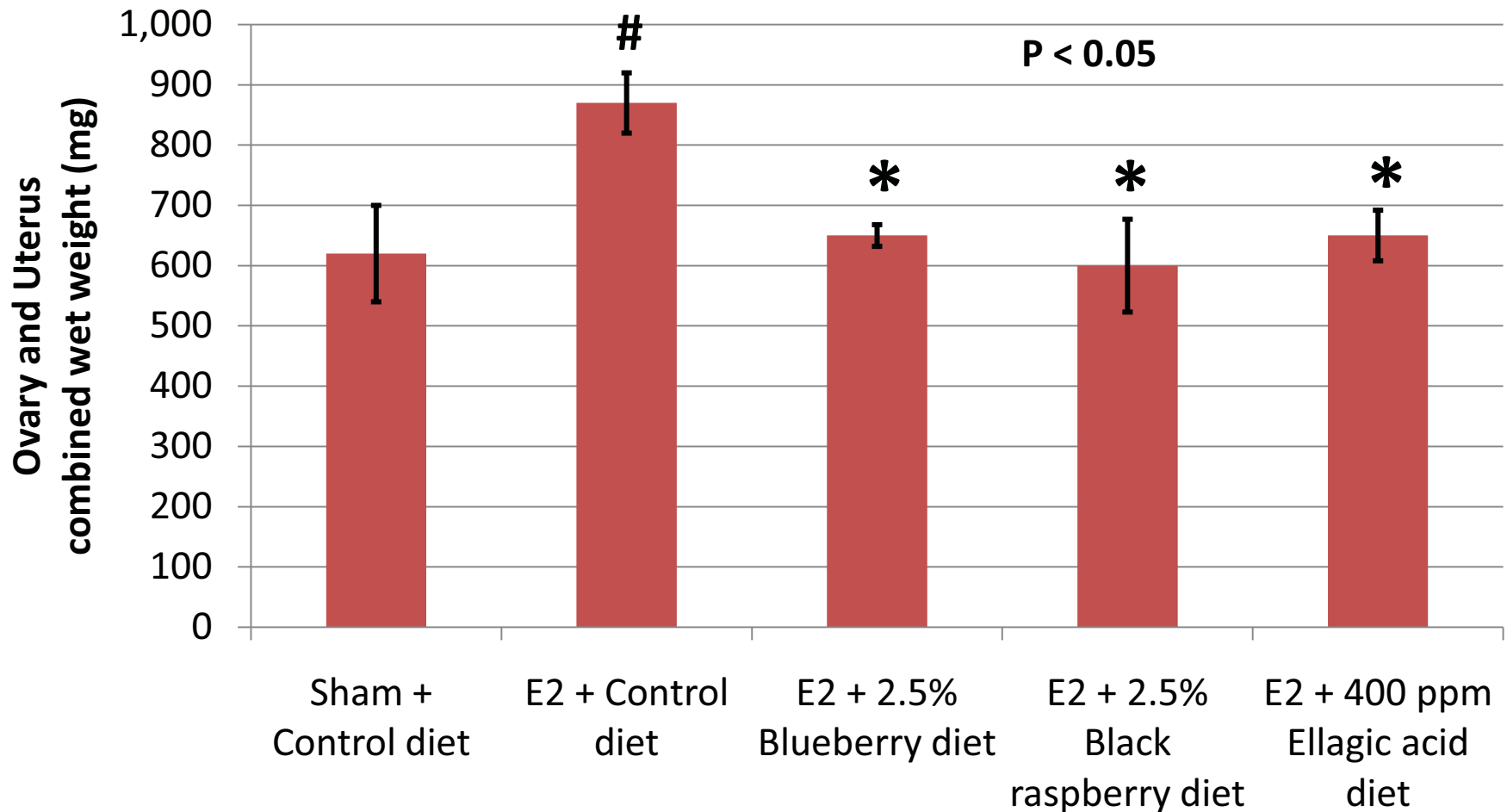


Berry phytochemicals act as antiestrogens

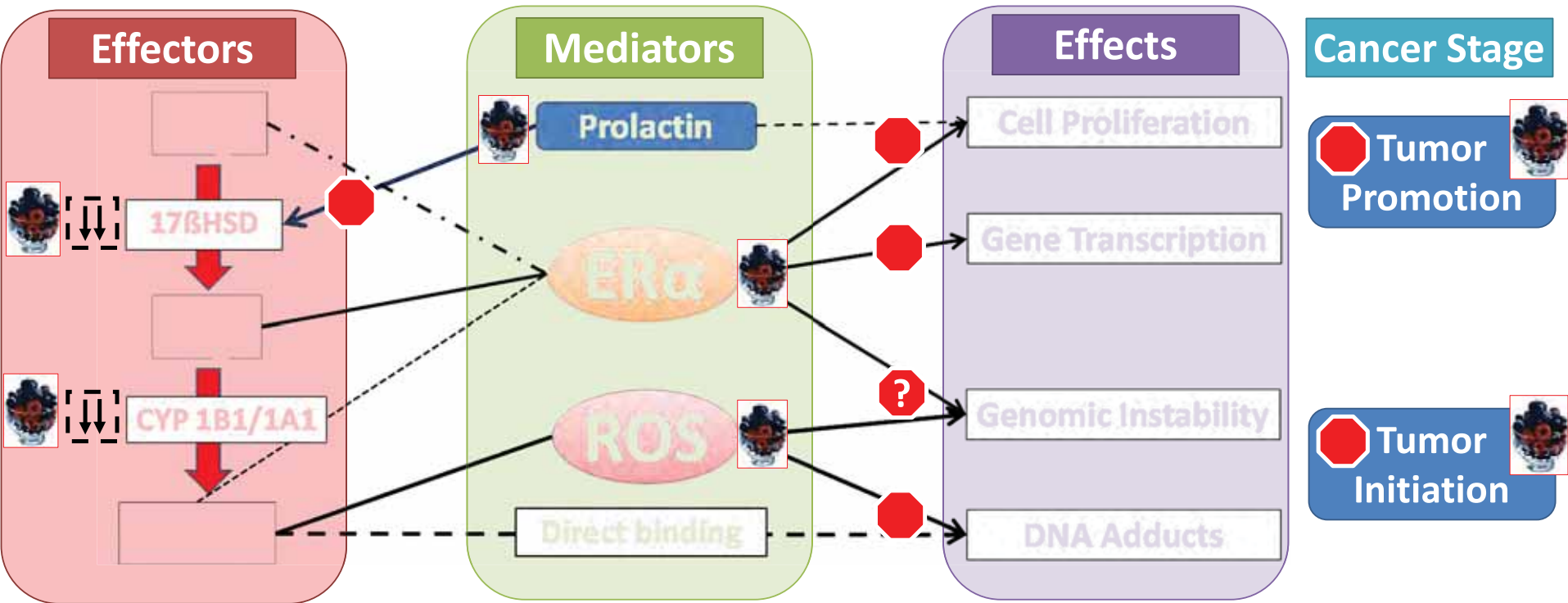


Adapted from Aiyer et al., *Berries and Cancer Prevention*, Eds Stoner GD and Seeram NP, Springer, 2011

Berry phytochemicals act as antiestrogens



Overall mechanism of primary cancer prevention by berries



So how much berries do you need to eat?

1 cup a day

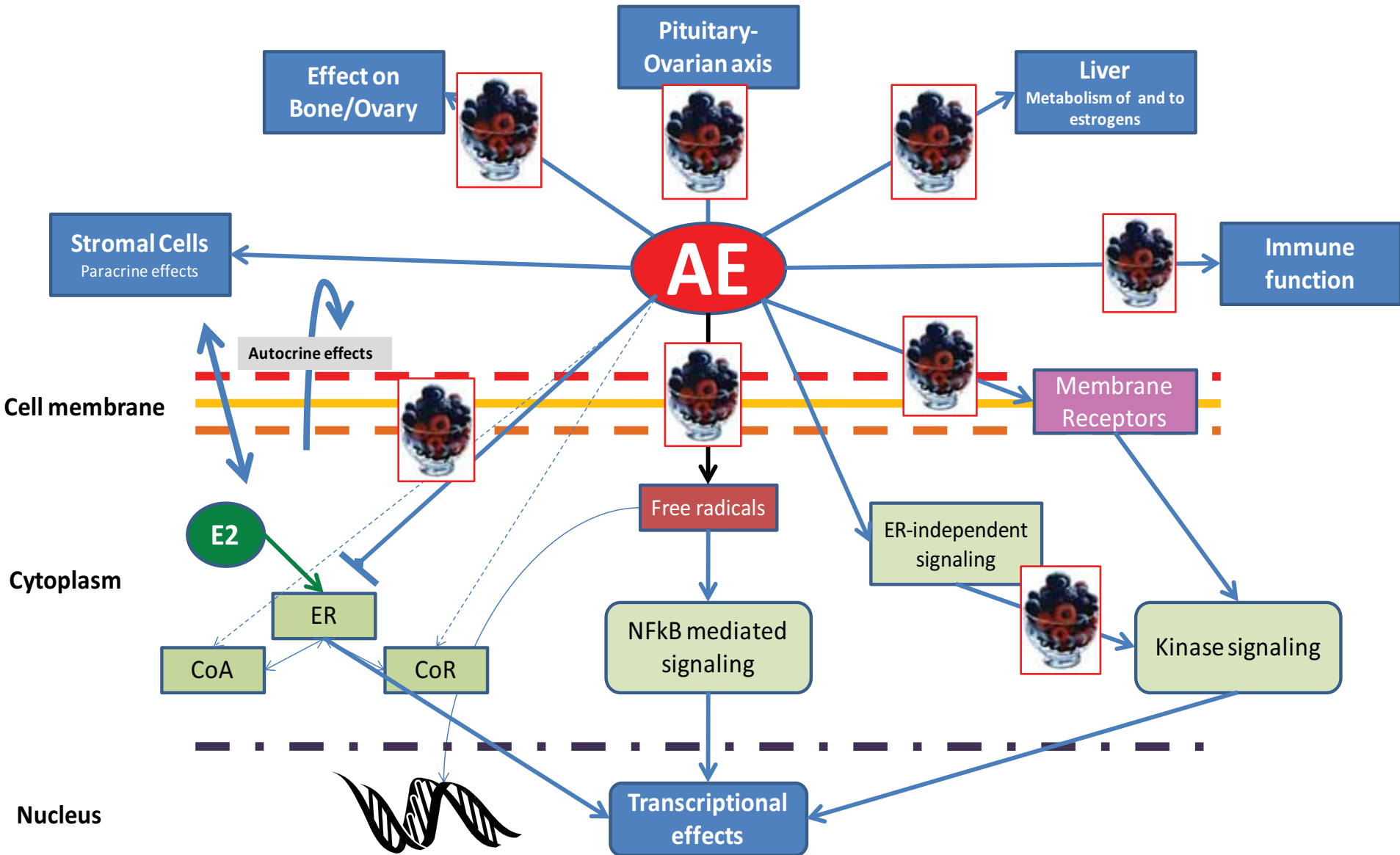
		Control	Blueberry diet			Black raspberry diet		
		Diet						
			1%	2.5%	5%	1%	2.5%	5%
		<i>Units</i>						
Berries consumed by rats based on caloric intake (1g feed = 4 kcal)	mg/kcal /day	-	2.5	6.25	12.5	2.5	6.25	12.5
Allometric scaling to human consumption (2,000 kcal/day)	g dried berry powder	-	5	12.5	25	5	12.5	25
Common conversion for dried berries	Tbsp/d	-	0.5	1.25	2.5	0.5	1.25	2.5
Common conversion for fresh berries	Cups/d	-	0.4	1	2	0.4	1	2

Source: Aiyer et al., *Berries and Cancer Prevention*, Eds Stoner GD and Seeram NP, Springer, 2011

Future- questions & directions

- Mechanistic
 - What is the effect of berry diets on E2 metabolism and clearance in the liver?
 - What is the effect of berry diets on pituitary-ovarian axis?
 - Do berry diets affect other cell-signaling pathways (ErbB2, MAPK etc) involved in E2-induced tumorigenesis?
- Translational
 - What is the effect of berry-intervention on women who have been diagnosed with breast cancer?
 - What are the possible interactions between berry constituents and current chemotherapy regimens in breast cancer?

Proposed mechanisms of AntiEstrogen action



Acknowledgements

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