Berry Polyphenols in the Prevention of Primary and Recurrent Breast Cancer

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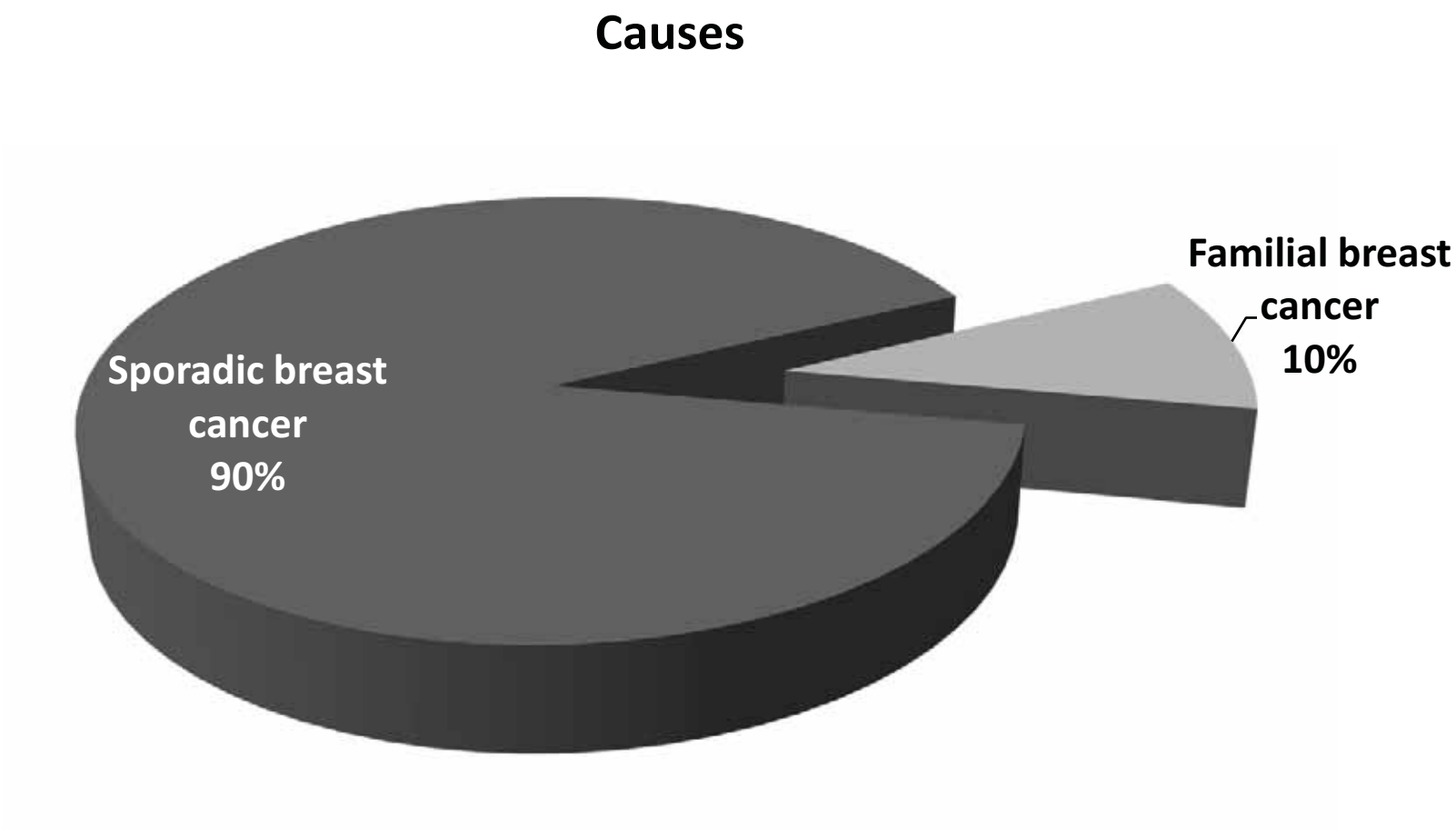
Overview

- 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

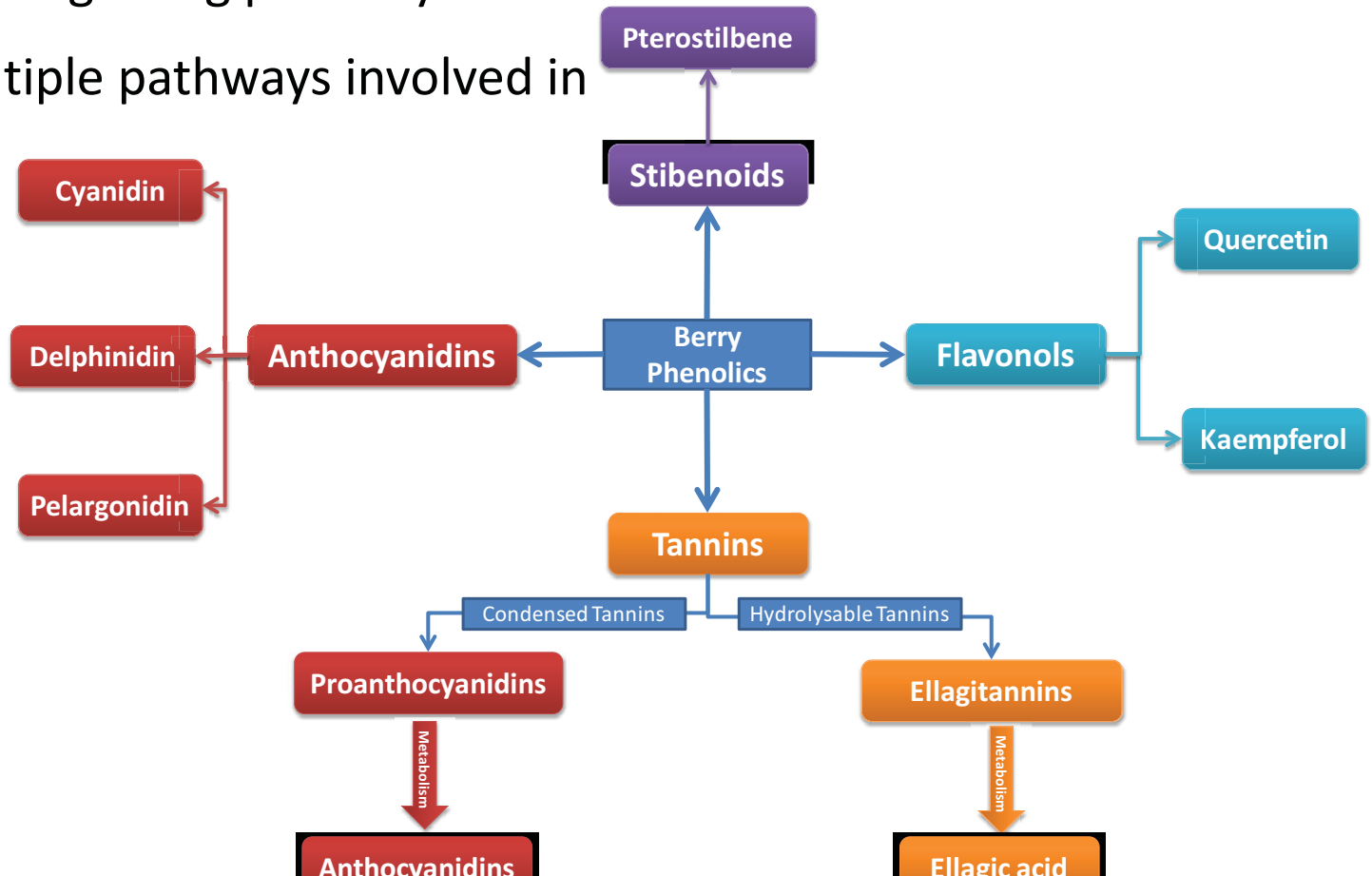


Breast cancer- risk factors

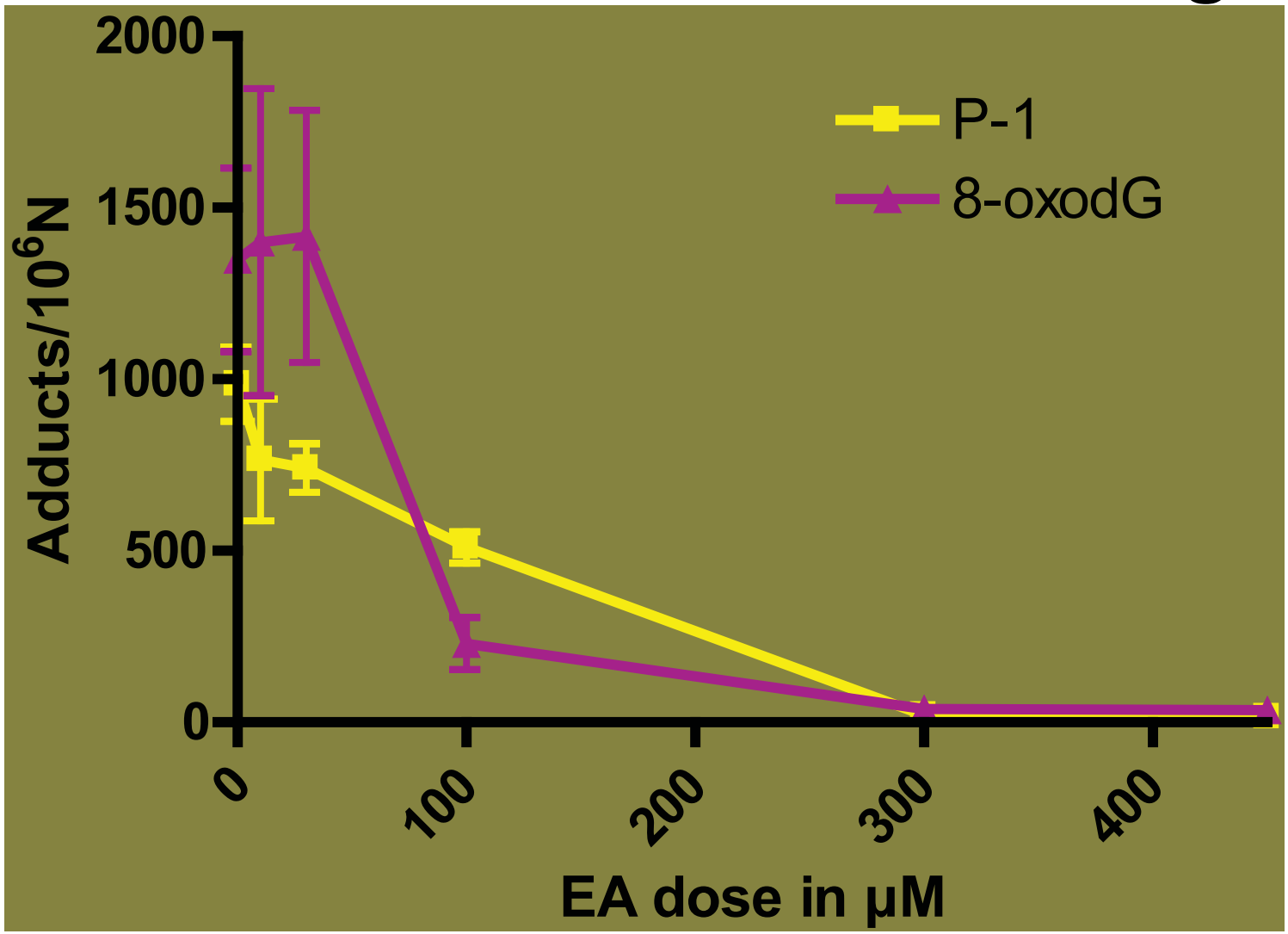
Non-Modifiable Risk Factors	Modifiable Risk Factors	Hormonal Risk Factors
Age ↑	Diet	**Cumulative exposure to estrogen ↑**
Gender	Alcohol ↑	Age at menarche and menopause
Genetics	Smoking ↑	Parity
Family history ↑	Body weight ↑	Lactation ↓
Previous breast disease ↑	Exercise ↓	Hormone replacement therapy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

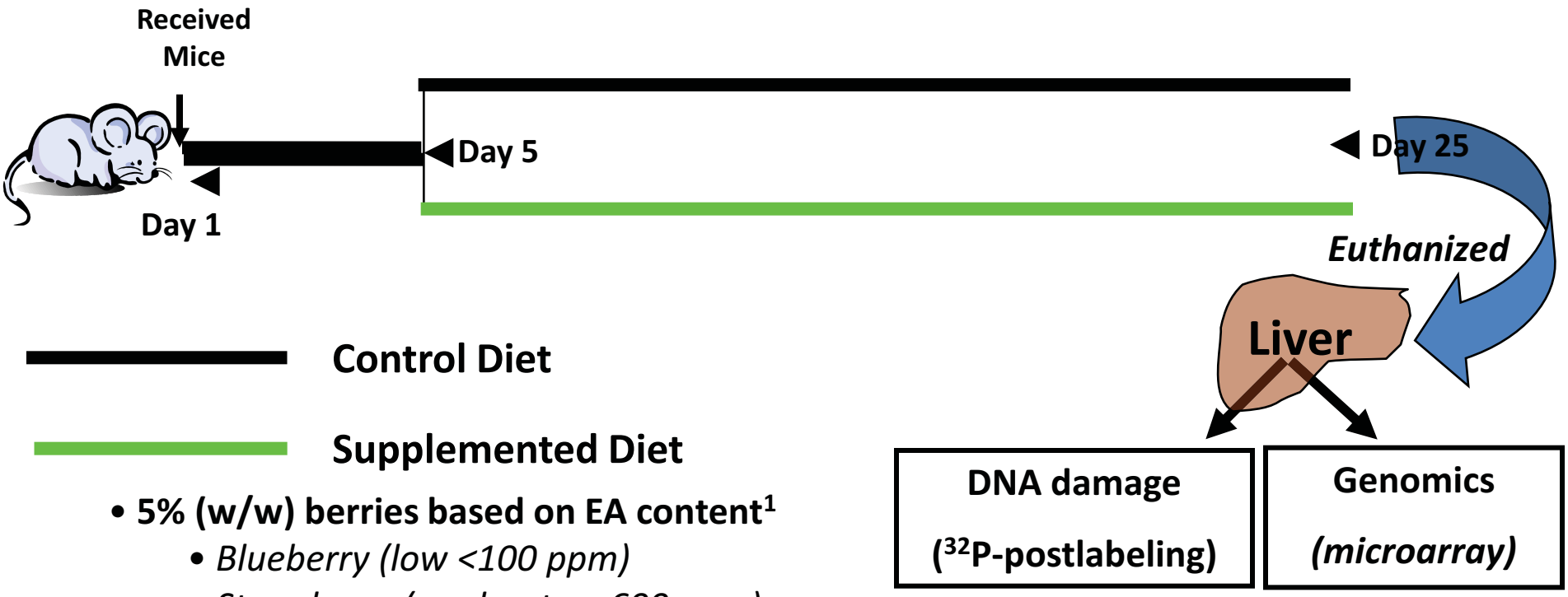


Effect of ellagic acid on 4-hydroxy etsradiol-induced oxidative DNA damage



Aiyer et al., Int J Mol Sci. 2008 Mar;9(3):327-41

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



Control Diet

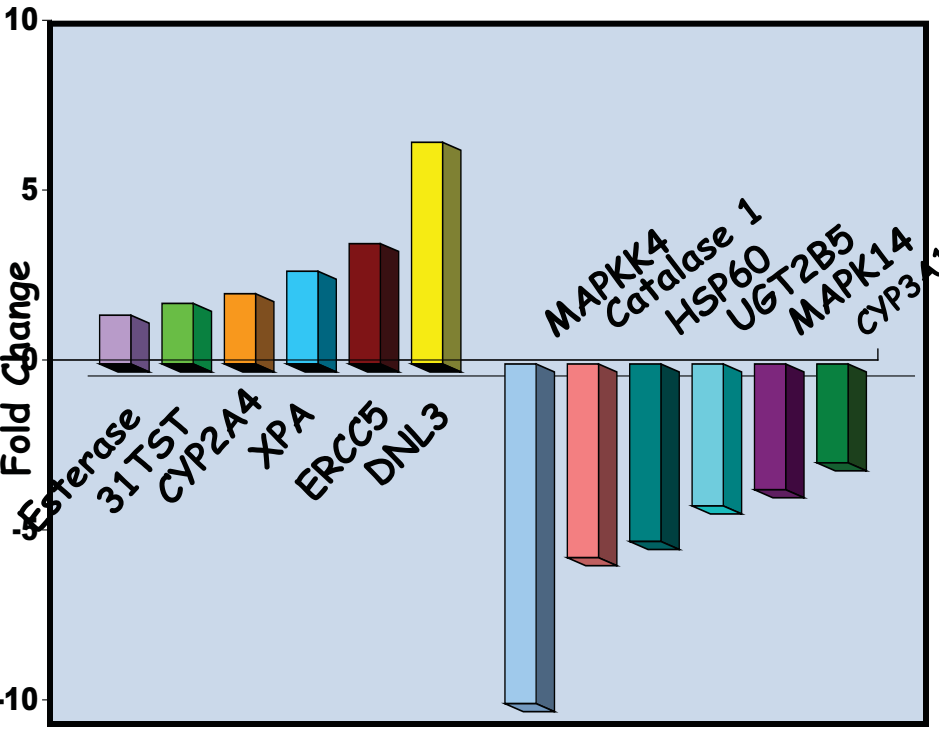
Supplemented Diet

- **5% (w/w) berries based on EA content[1]**
  - *Blueberry (low <100 ppm)*
  - *Strawberry (moderate ≈ 600 ppm)*
  - *Red raspberry (high ≈ 1500 ppm)*
- **Ellagic acid (400 ppm)**

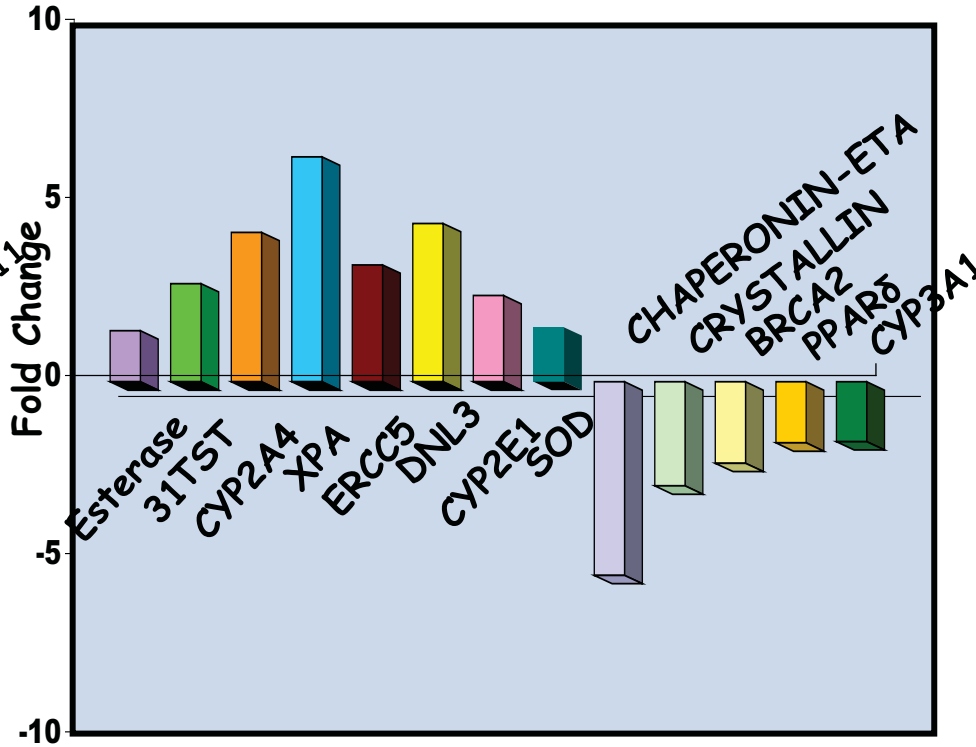
1- Daniel et al., 1993

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

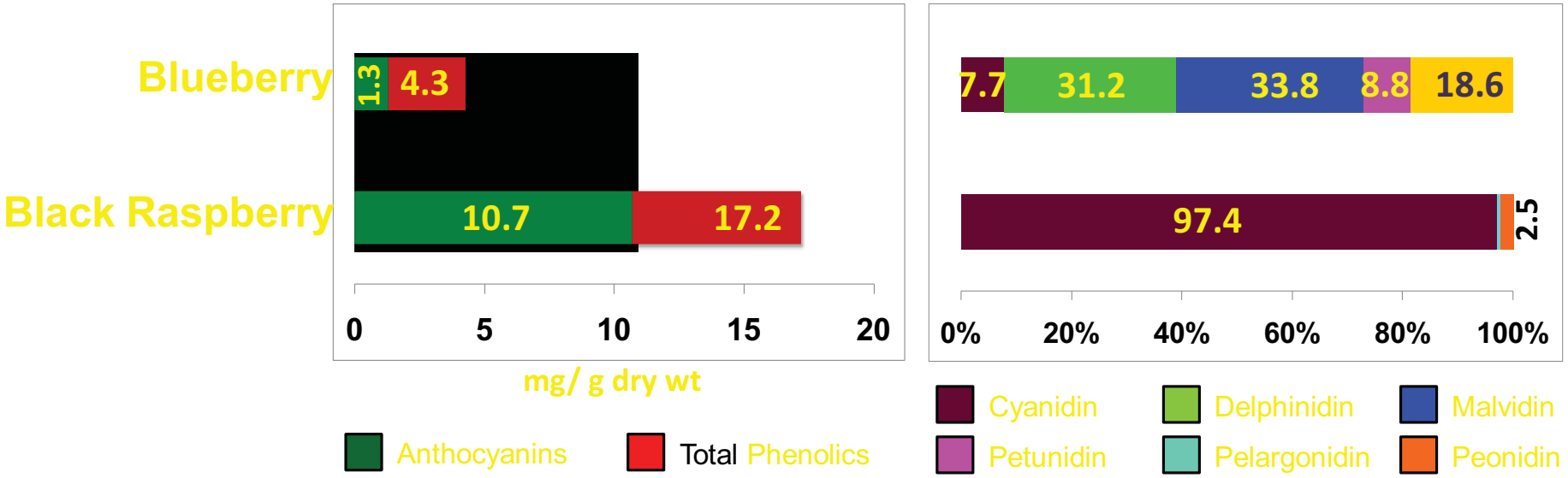
Aiyer et al., Int J Mol Sci. 2008 Mar;9(3):327-41

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

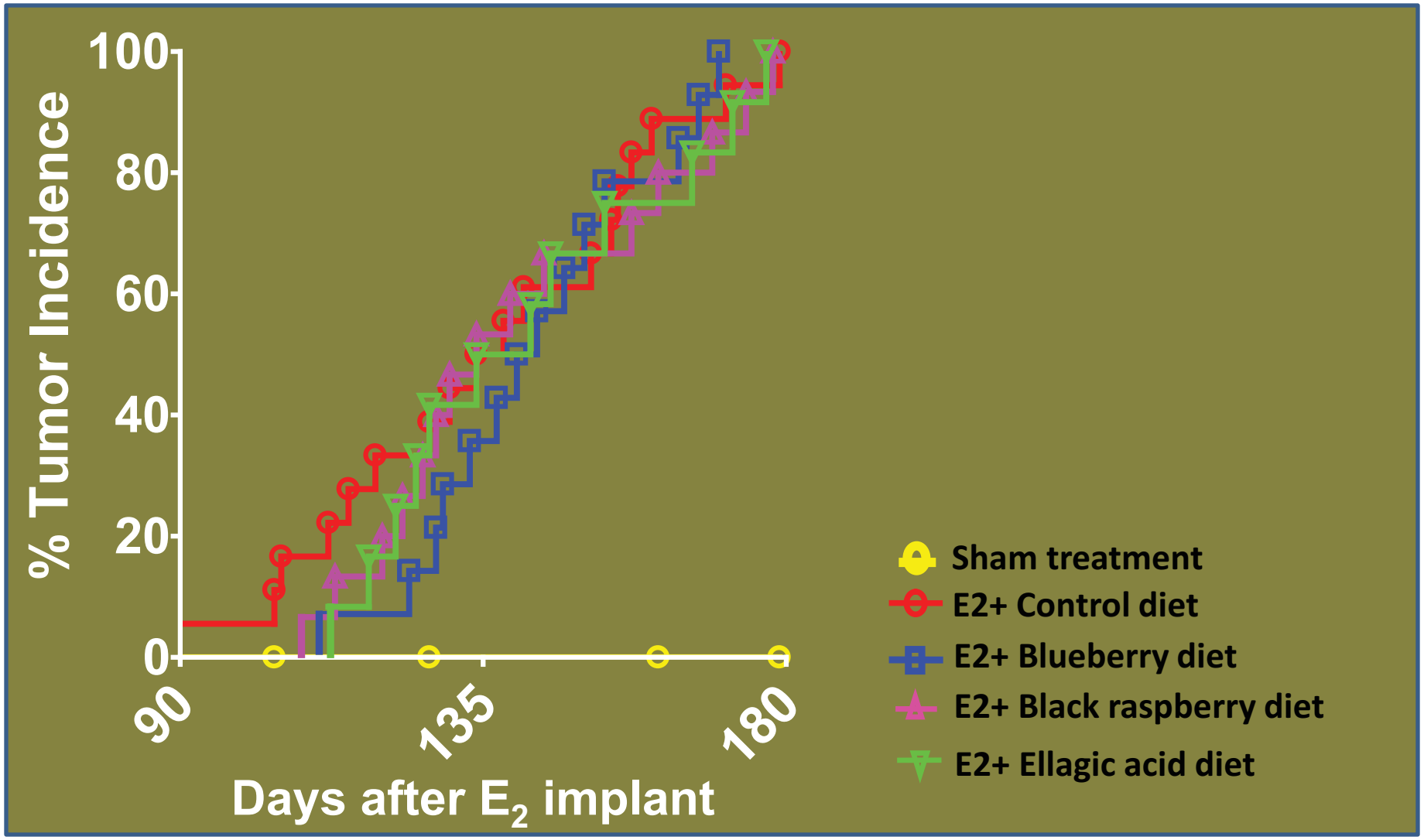
Rationale for berry types used

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



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

Berry diets increase mammary tumor latency



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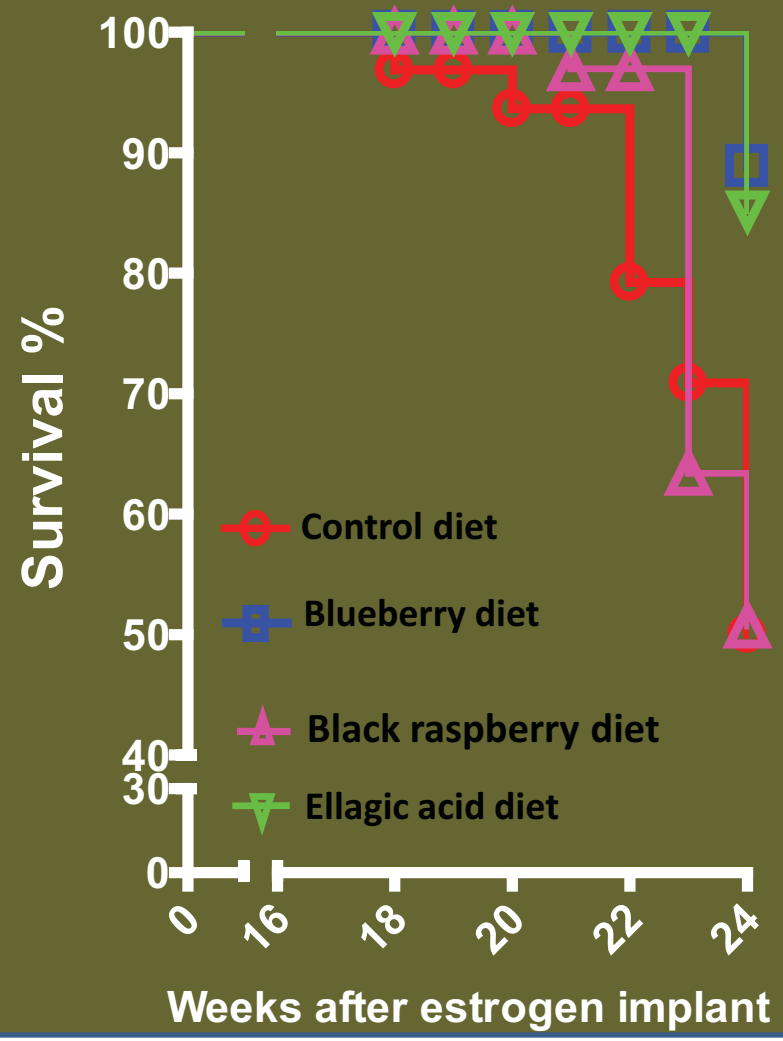
Estrogen treatment associated morbidity in ACI rats

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

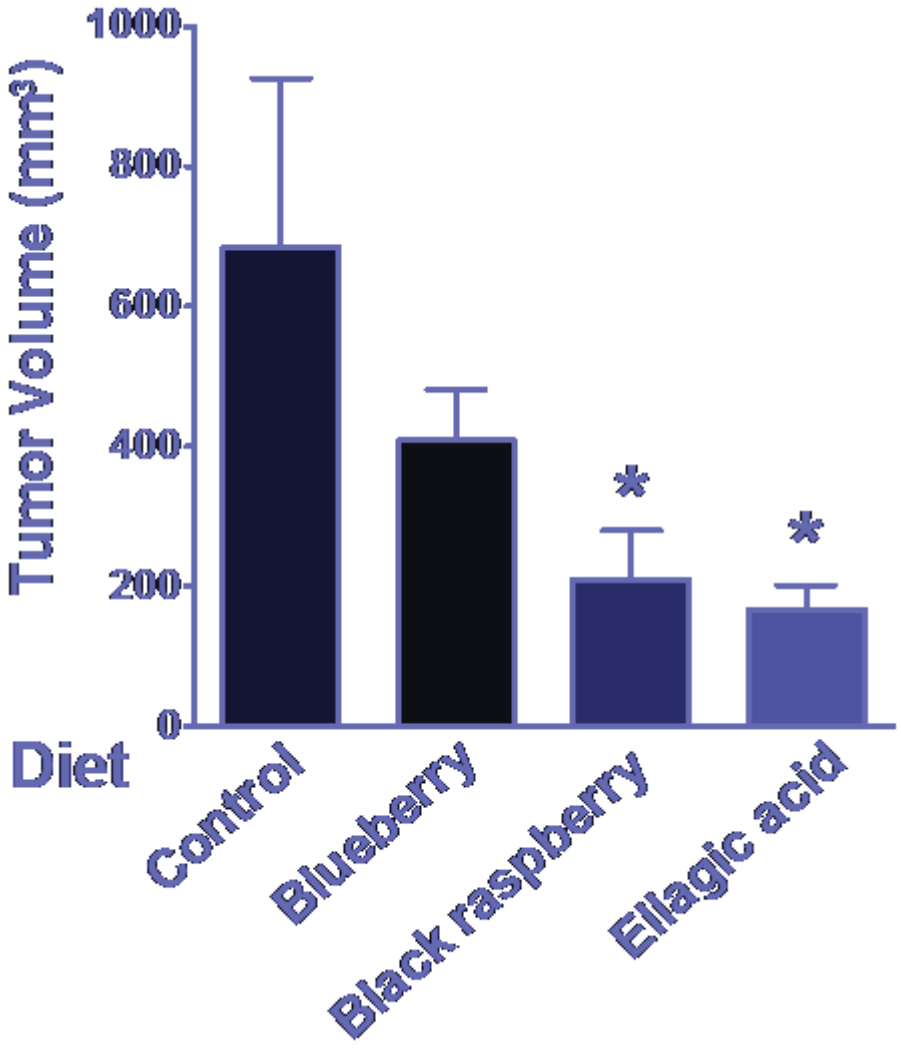
Eye deposits ≥3

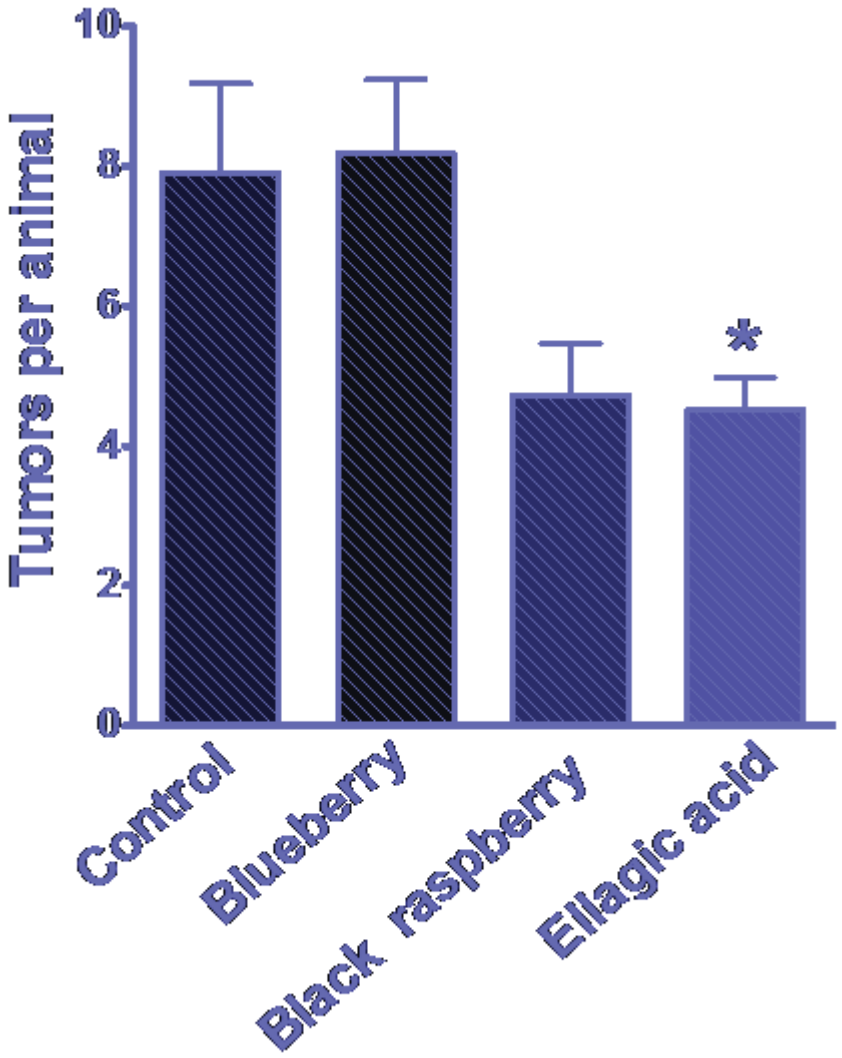
Loss of balance ≥3

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

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

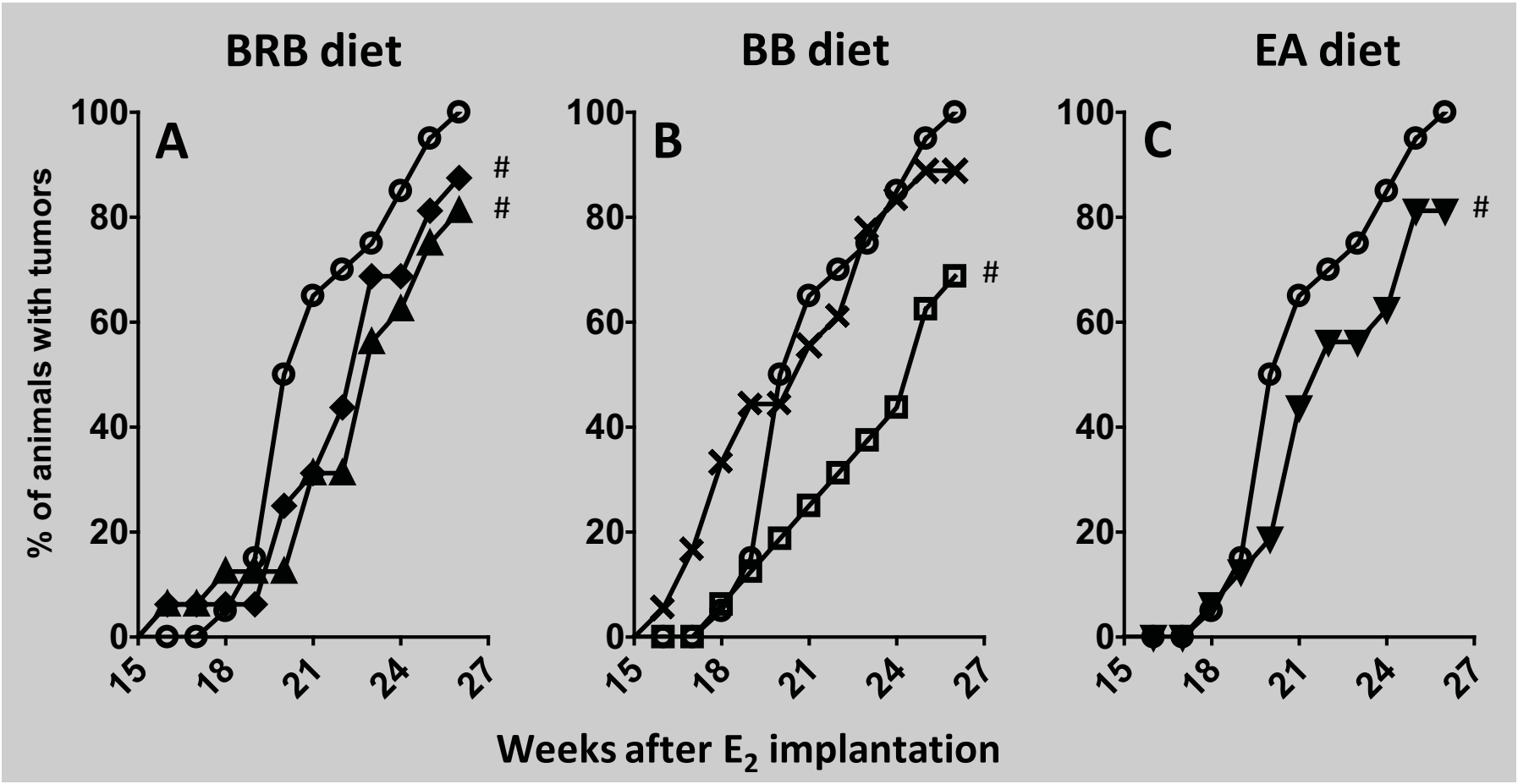
Berry diets decrease tumor volume and multiplicity





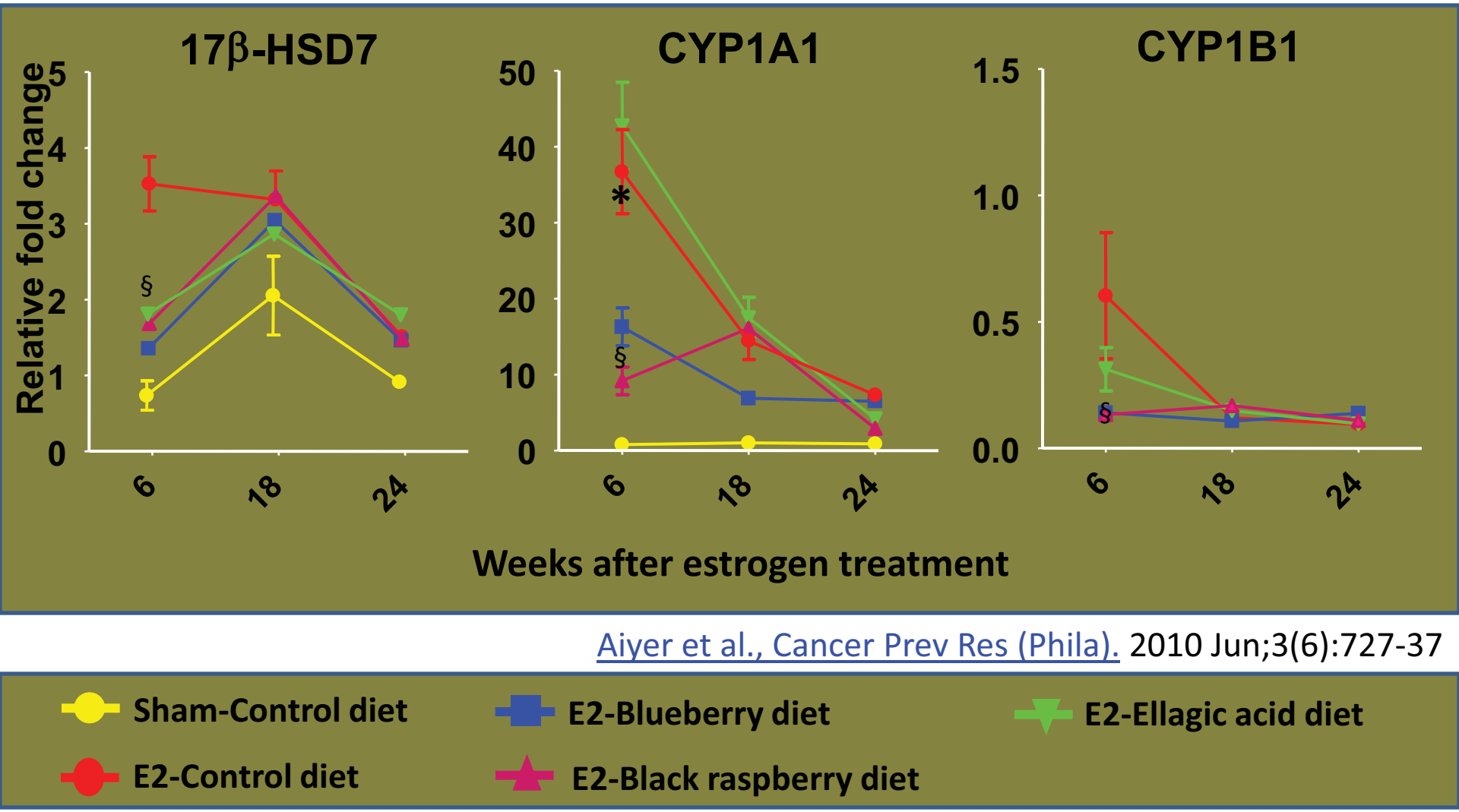
Aiyer et al., Nutr Cancer. 2008;60(2):227-34.

BERRY DIETS REDUCE TUMOR INCIDENCE



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

BERry diets modulate phase I enzymes



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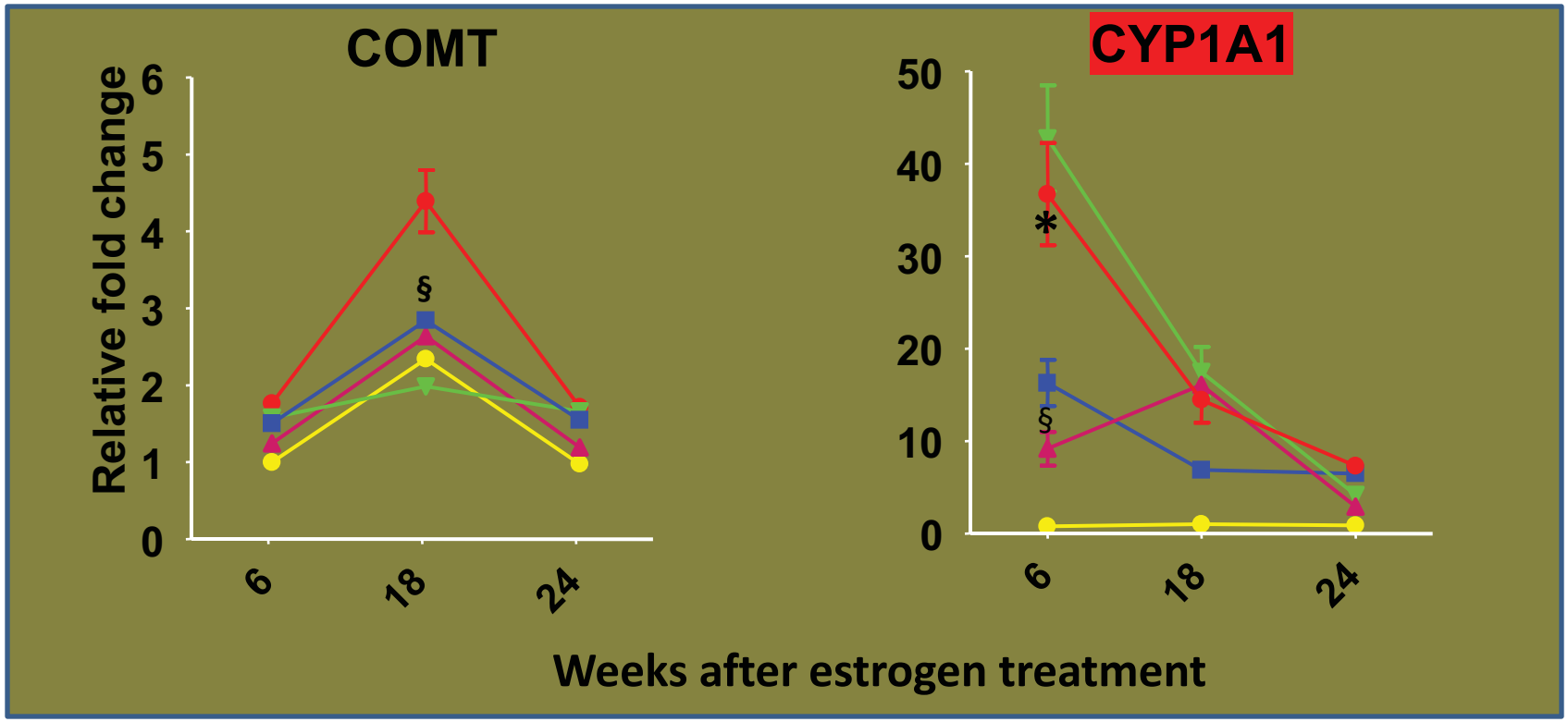
BERRY diets also modulate phase II enzyme



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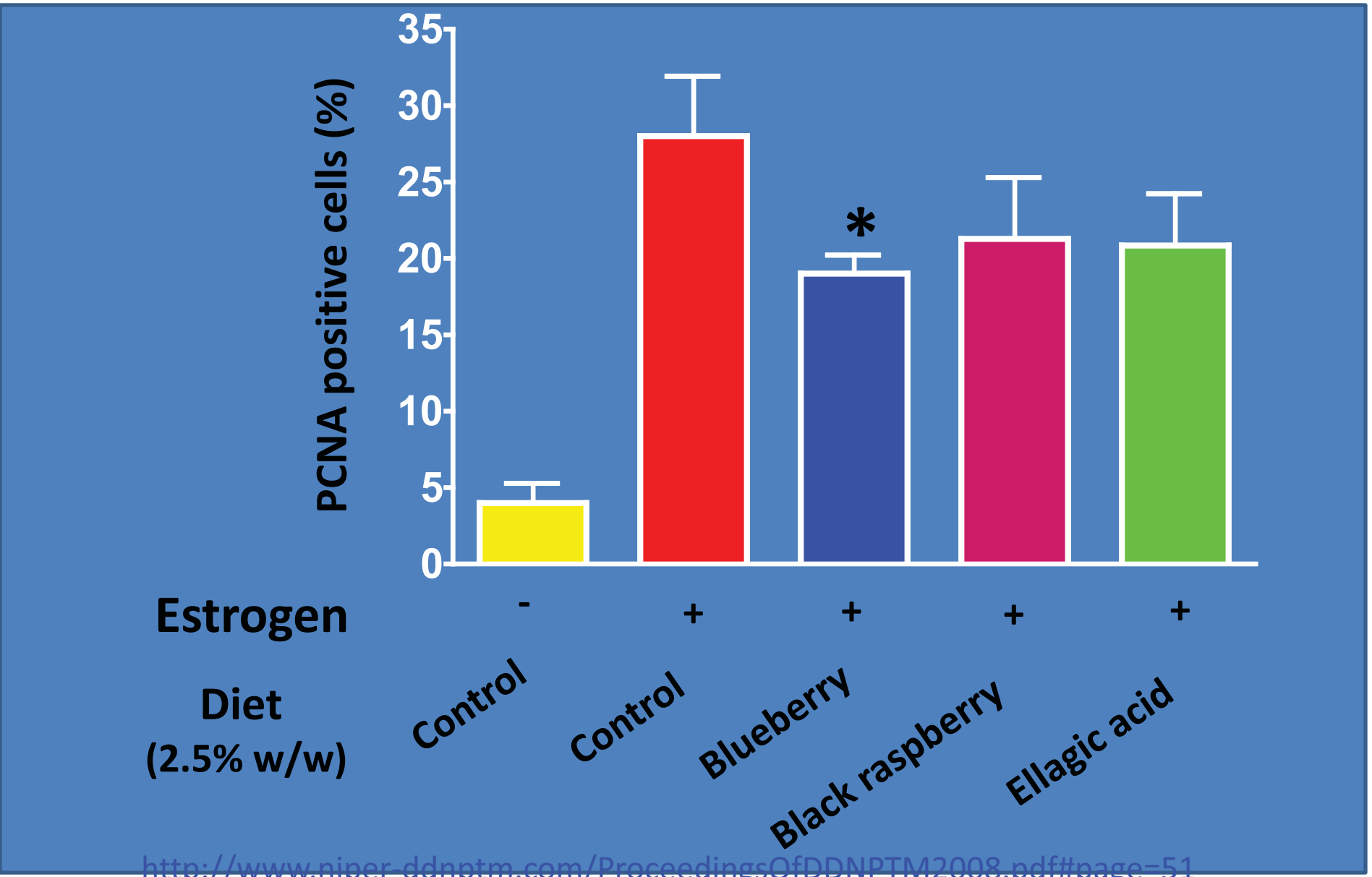
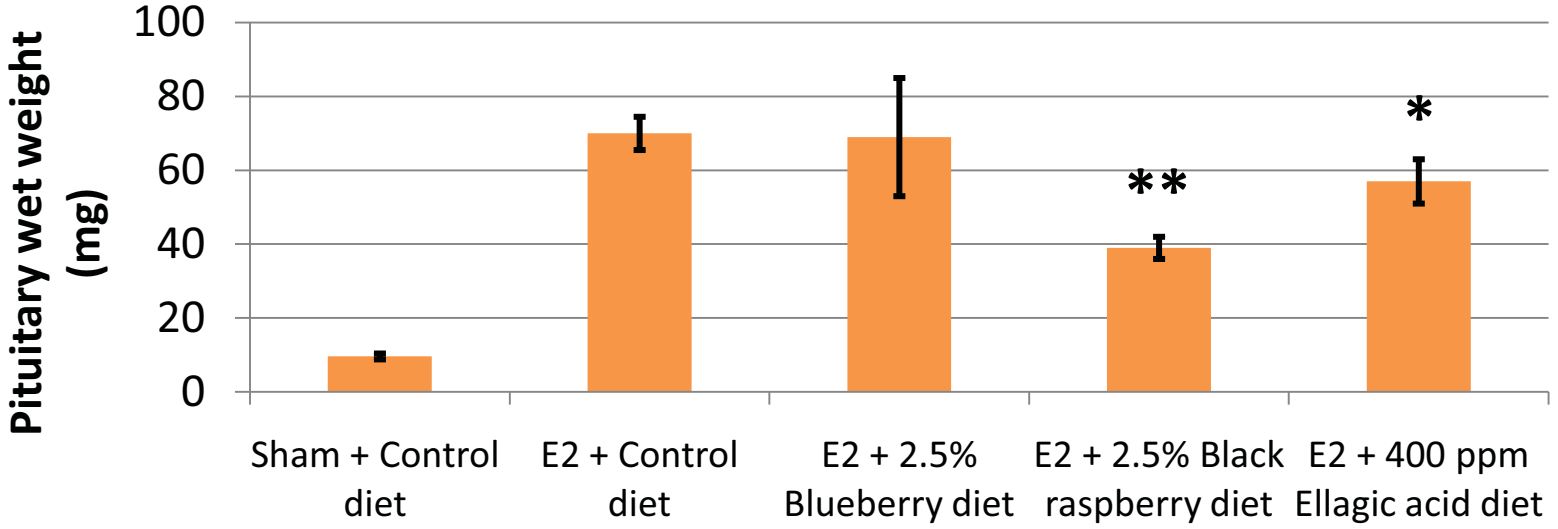
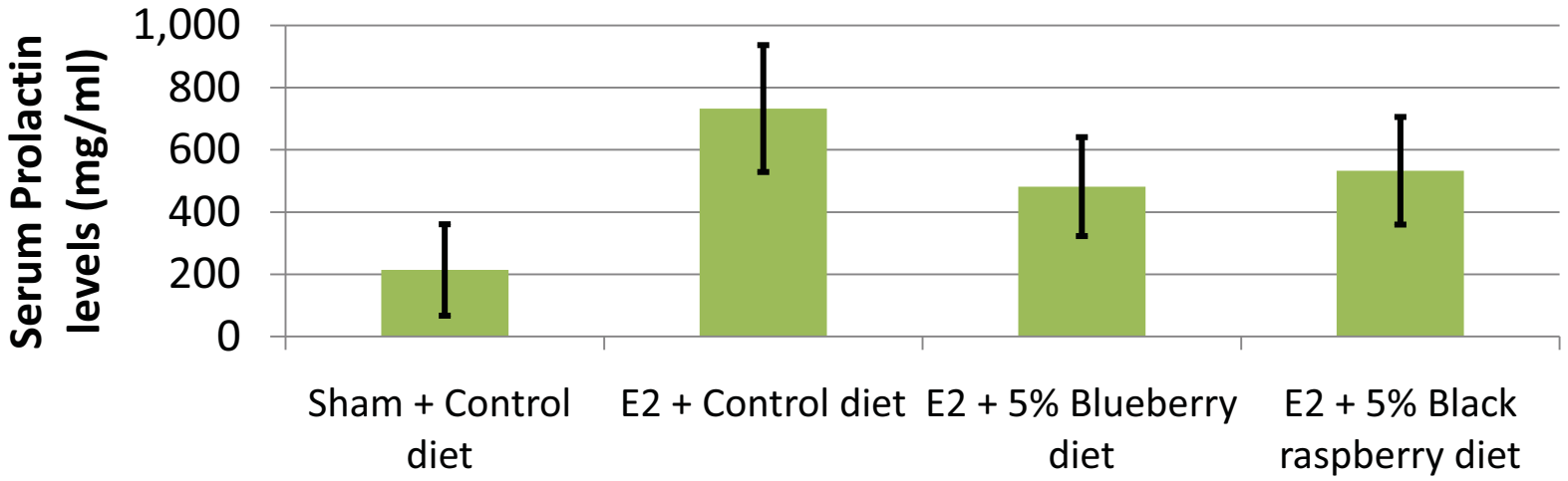
Berry diets inhibit E2-induced cell proliferation



http://www.niper-ddnptm.com/ProceedingsOfDDNPTM2008.pdf#page=51

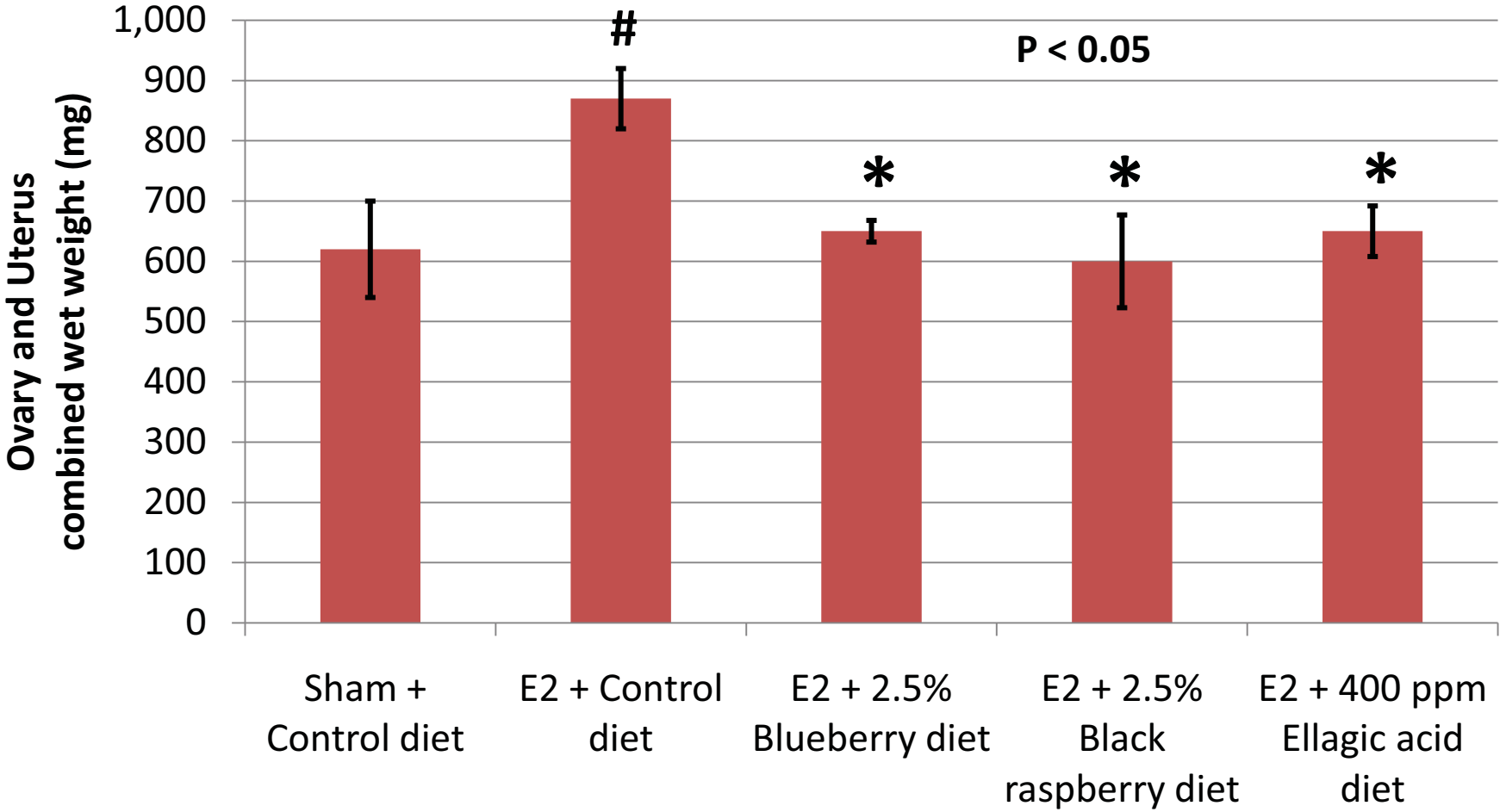
Berry phytochemicals act as antiestrogens





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

Berry phytochemicals act as antiestrogens



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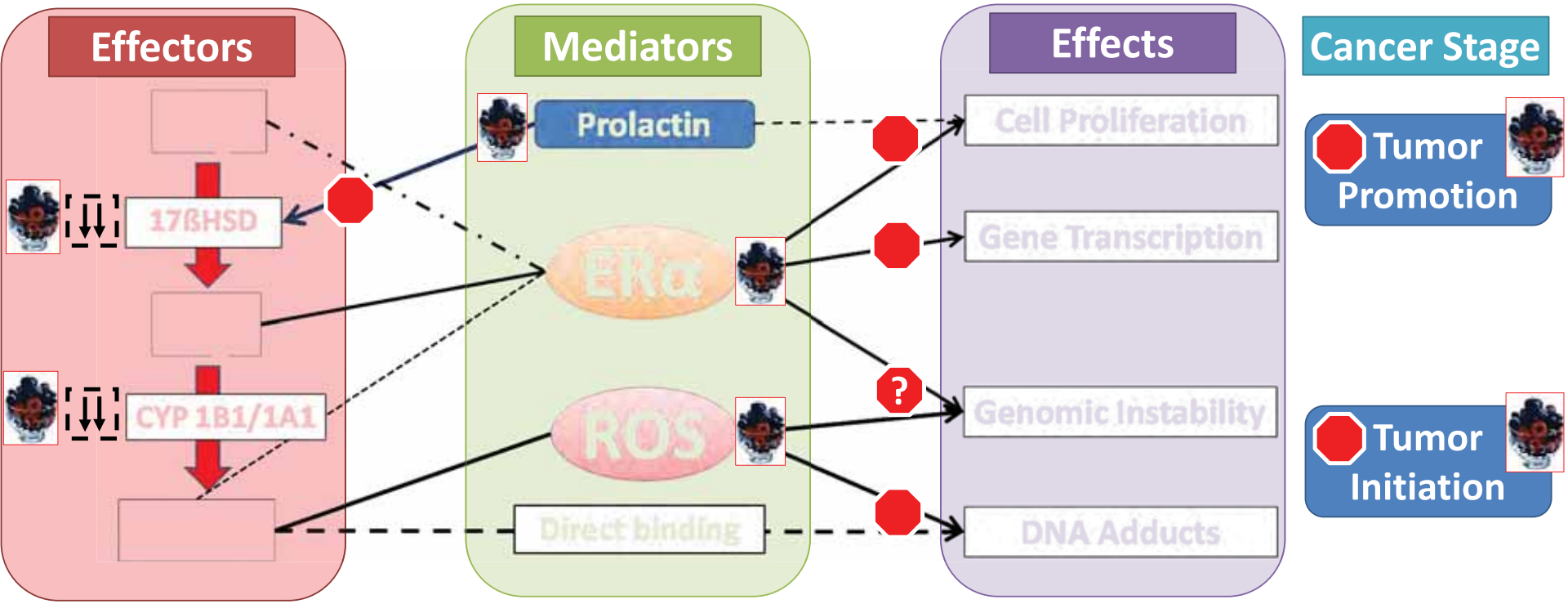
Overall mechanism of primary cancer prevention by berries



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So how much berries do you need to eat?

1 cup a day

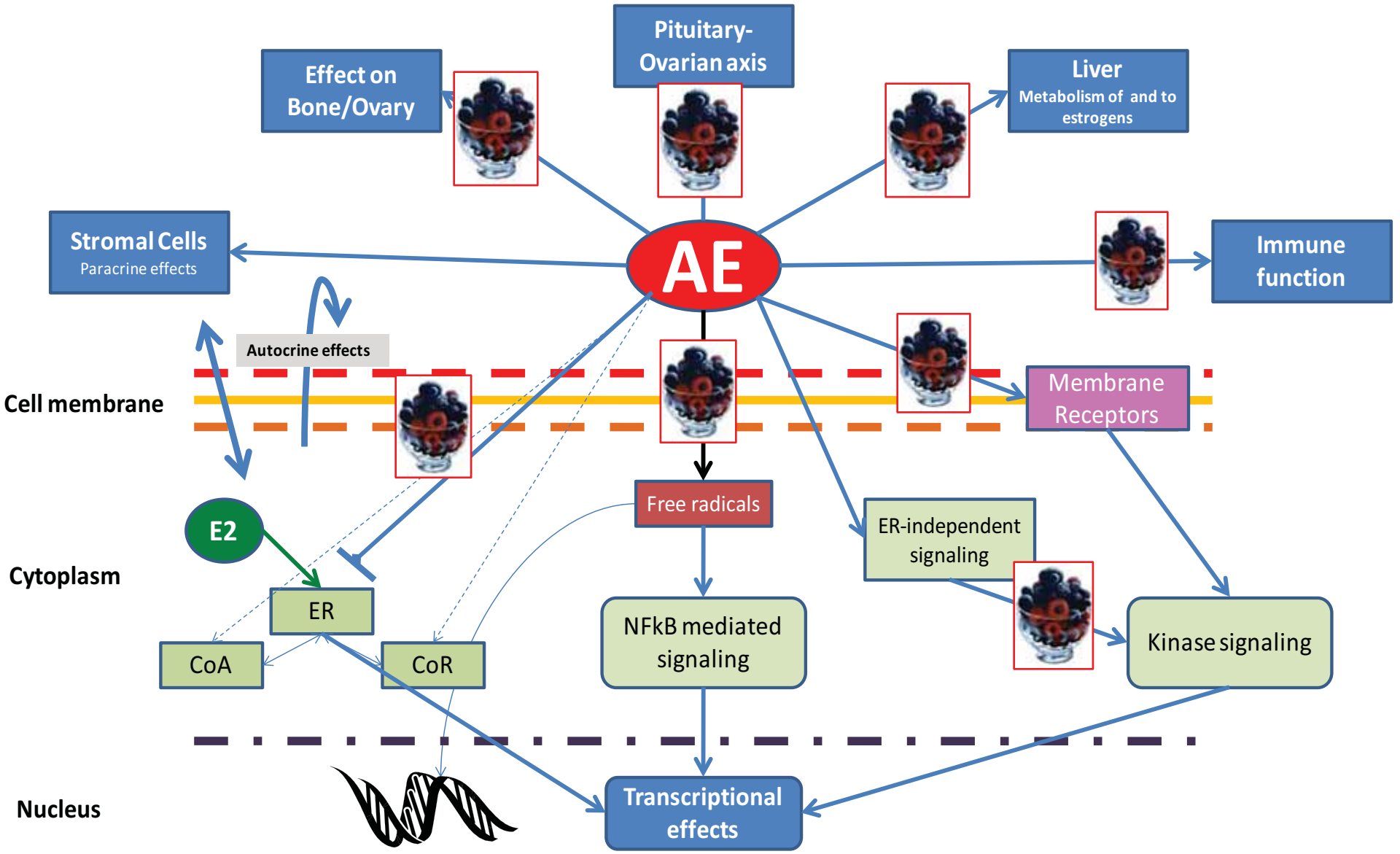
		Control Diet	Blueberry diet			Black raspberry diet		
	Units		***1%***	***2.5%***	***5%***	***1%***	***2.5%***	***5%***
Berries consumed by rats based on caloric intake (1g feed = 4 kcal)	mg/kcal /day	-	2.5	6.25	12.5	2.5	6.25	12.5
Allometric scaling to human consumption (2,000 kcal/day)	g dried berry 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



Adapted from Clarke et al., 2001

Acknowledgements

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