Epidemiologial Studies of β-Carotene and Lung Cancer

Study	Parameter Measured	Outcome
Willett et al, 1984	Serum carotenes	0
Nomura et al, 1985	Serum β-carotene	+
Menkes et al, 1986	Serum β-carotene	+
Gey et al, 1987	Serum β-carotene	+
Wald et al, 1988	Serum β-carotene	+
Kune et al, 1989	Serum β-carotene	+
Connett et al, 1989	Serum β-carotene	+
Knekt et al, 1990	Plasma total carotene	+
Stäheline et al, 1991	Plasma total carotene	+
ATBC Trial, 1994	Serum β-carotene	+

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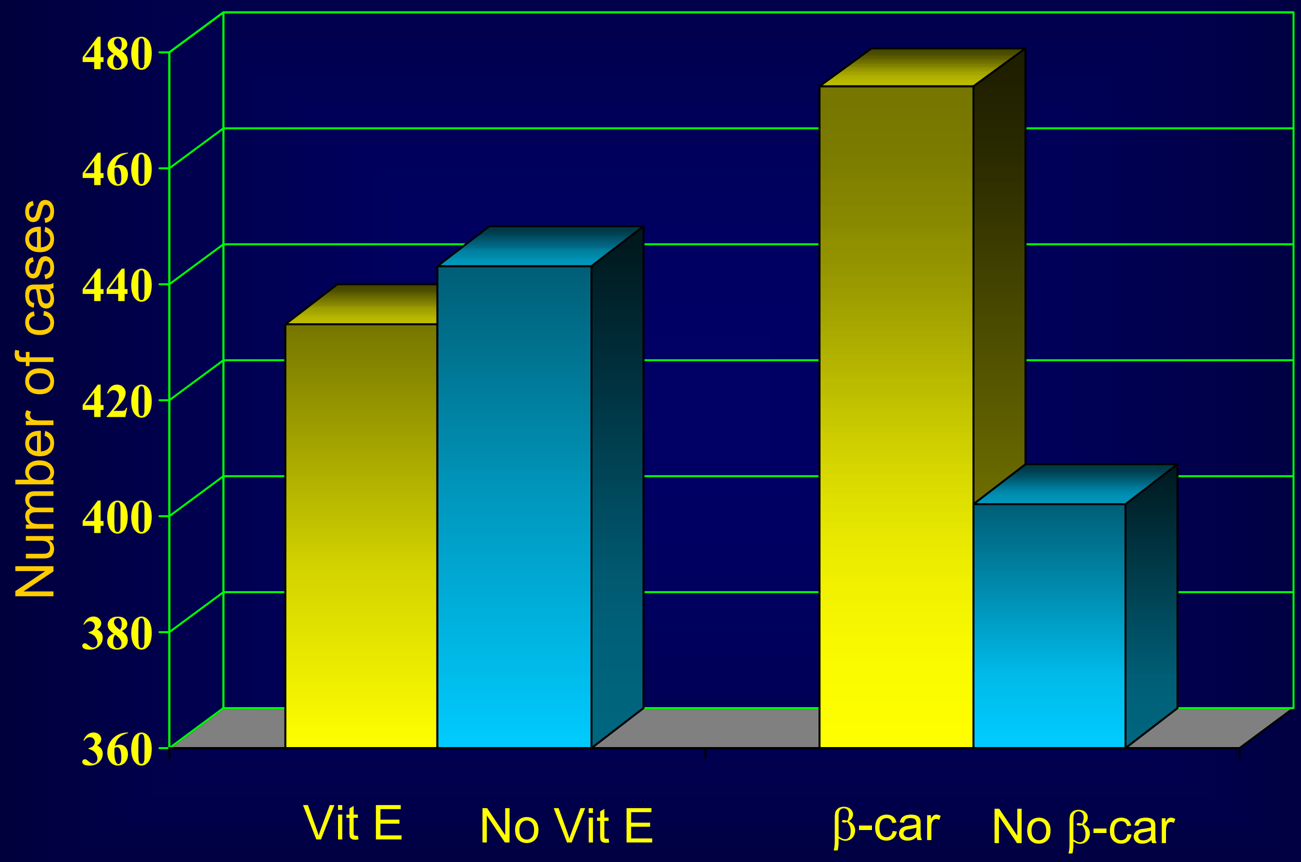
ATBC Trial



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Intervention Trials: β-Carotene and Lung Cancer[1]

Study	Study Population	Daily Dose	Results
ATBC (ATBC Cancer Prevention Group, 1994)	29.133 men 50-69 yr. Duration: 6 yr	20 mg β-carotene and/or 50 mg vitamin E	18% ↑ lung cancer in smokers
CARET (Omenn et al, 1996)	18,254 smokers and asbestos workers, 45-69 yr Duration: 4 yr	30 mg β-carotene and 25,000 IU retinol	25% ↑ lung cancer
PHS (Hennekens et al., 1996)	22,071 male physicians, 40-48 yr Duration: 12 yr	50 mg β-carotene (alternate days)	NS effects on cancer, including smokers

[1] primary Prevention Randomized, Double-Blind, Placebo-Controlled

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Average Serum Levels of β-Carotene in Intervention Trials

Study		μg/dl
ATBC		300
CARET		210
PHS		120
NHANES	5^{th} percentile	5
	95^{th} percentile	50

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Comparison of Lung β–Carotene and Retinol Levels in Man and Ferret [1,2]

	Control	Smoke + β-Carotene
	nmol/g tissue	
β-Carotene		
Human	0.24 ± 0.50	0.76 (n=2)
Ferret	0.10 ± 0.08	1.71 ± 0.22
Retinol		
Human	0.52 ± 0.21	0.56 (n=2)
Ferret	0.41 ± 0.07	0.38 ± 0.05

1)Redich et al., Cancer Epidemiol Biomarkers Prev 1998;7:211-4.
2)Wang et al., J Natl Cancer Inst 1999;91:60-6.

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Study Design

Ferret

β-Carotene | **Non- β-Carotene**

Smoking n=6 | **Non-Smoking n=6** | **Smoking n=6** | **Non-Smoking n=6**

6 months

Sacrificed

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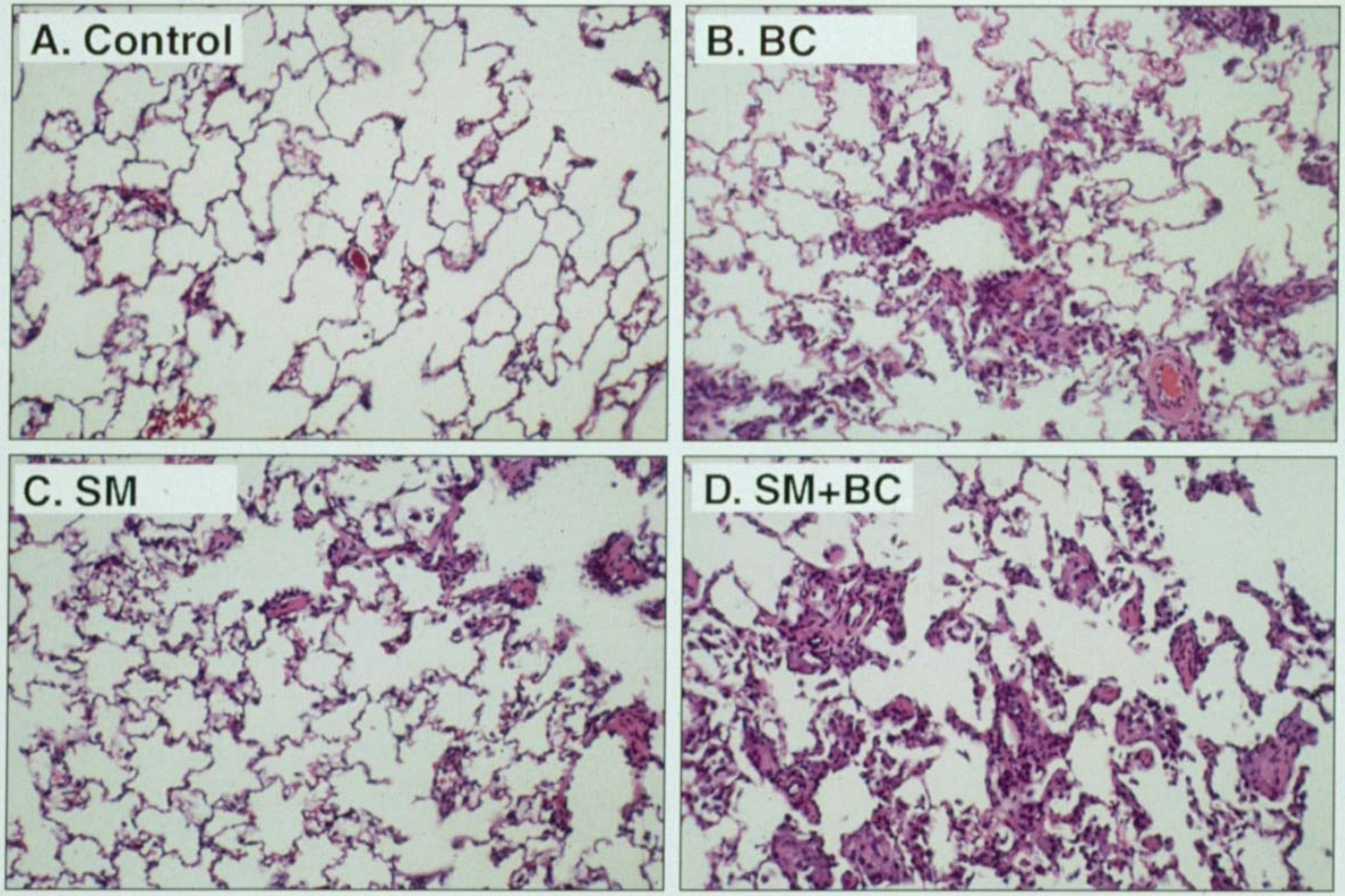

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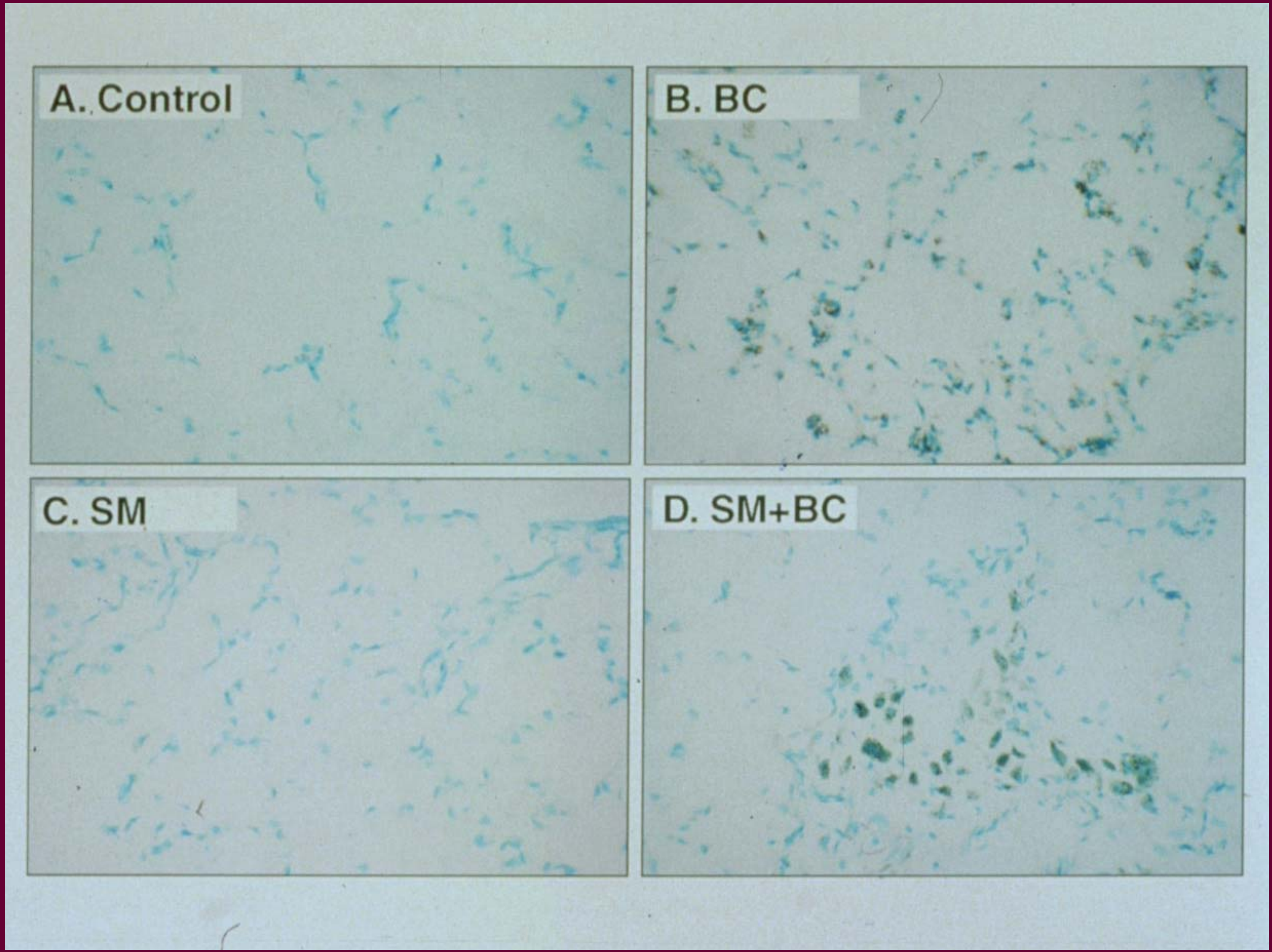

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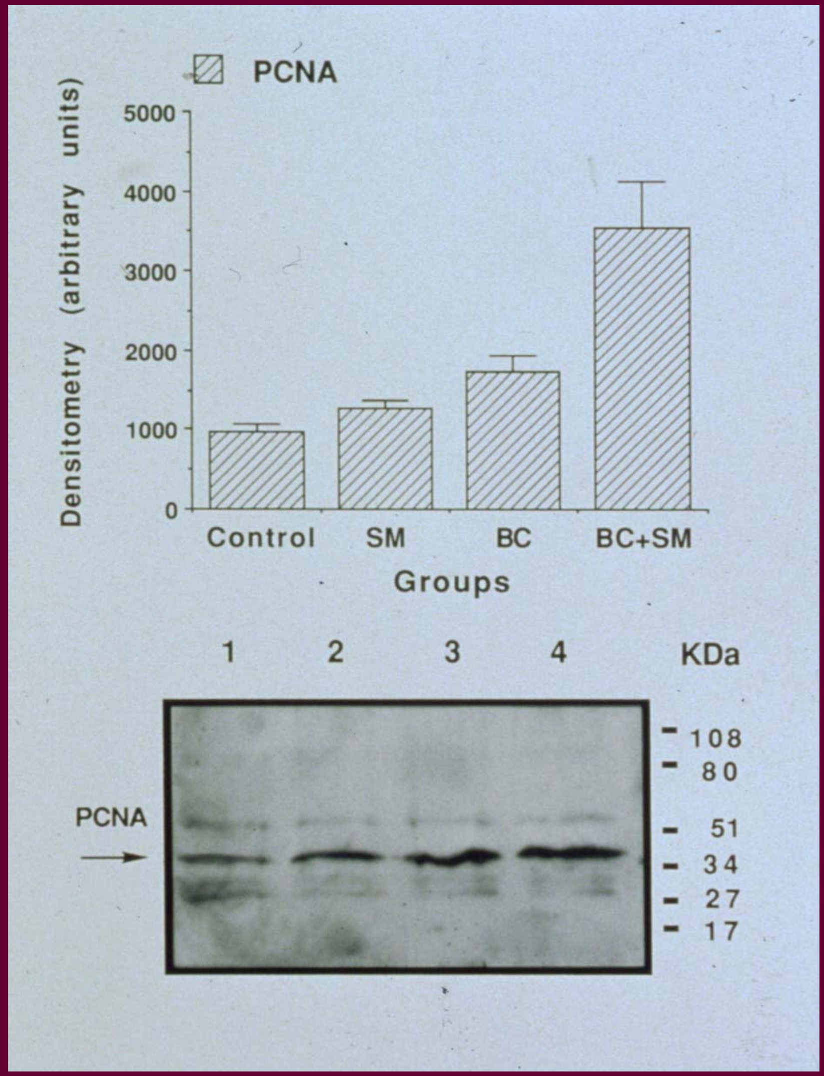

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Concentrations of carotene and retinoids in four groups of ferrets after six months of treatment

Lung Tissue	Control	Smoke Exposed	β-Carotene supplemented	Smoke-exposed & β-C supplemented
		(pmol/100 mg)		
β-Carotene	9	Trace	2618	171
Retinol	41	37	44	38
Retinoic acid	1.7	ND*	0.4	ND*

(ND* = not detectable)

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Cigarette Smoke

$\downarrow$

High dose β-Carotene $\longrightarrow$ **oxidative metabolites**

$\downarrow$

$\downarrow$ retinoic acid

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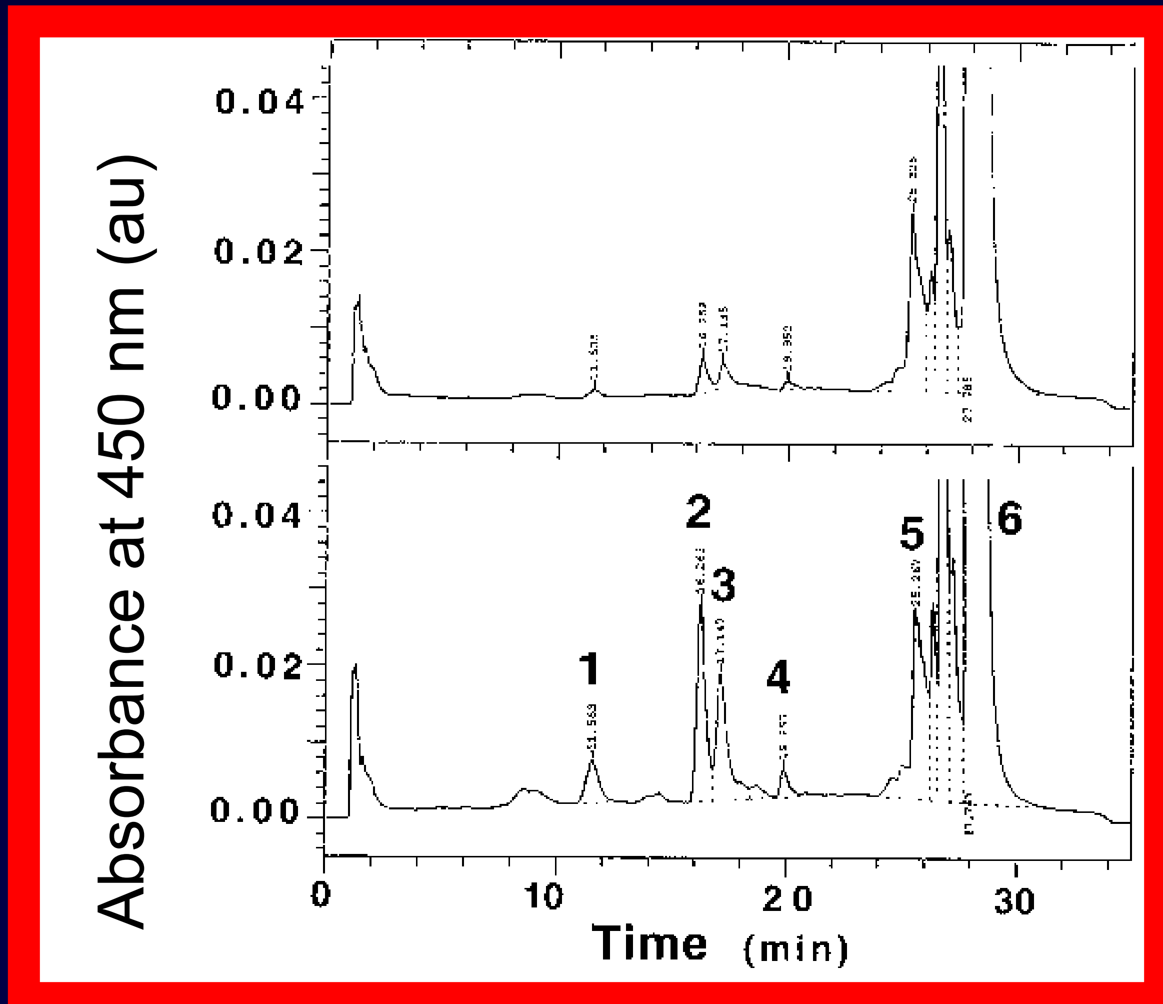

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RA Destruction by CYP 450 Enzymes

1) Gradelet et al. 1996

2) Paolini et al. 1999

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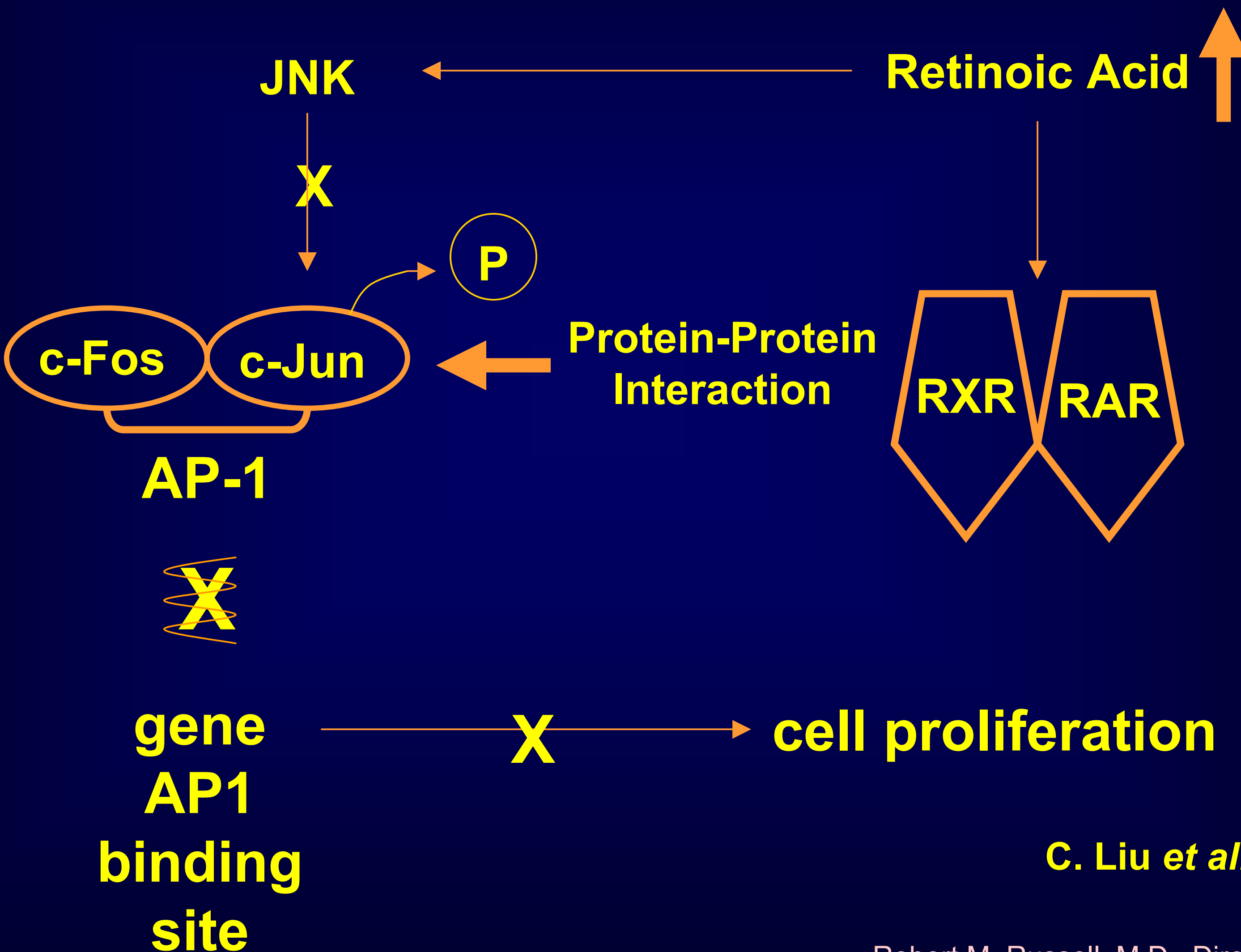
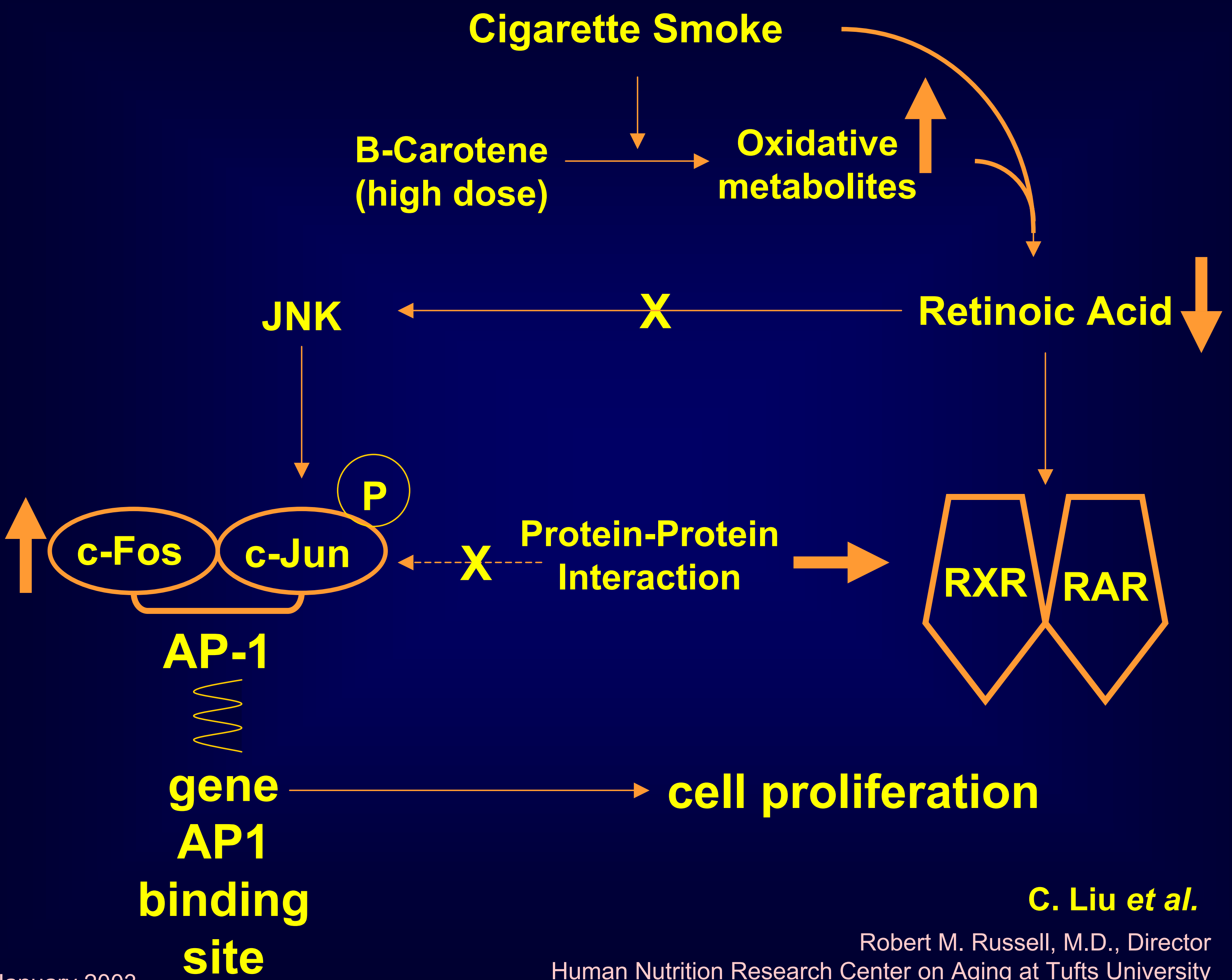

JNK
Retinoic Acid
X
P
c-Fos
c-Jun
Protein-Protein
Interaction
RXR
RAR
AP-1
X
gene
AP1
binding
site
X
cell proliferation

C. Liu *et al.*



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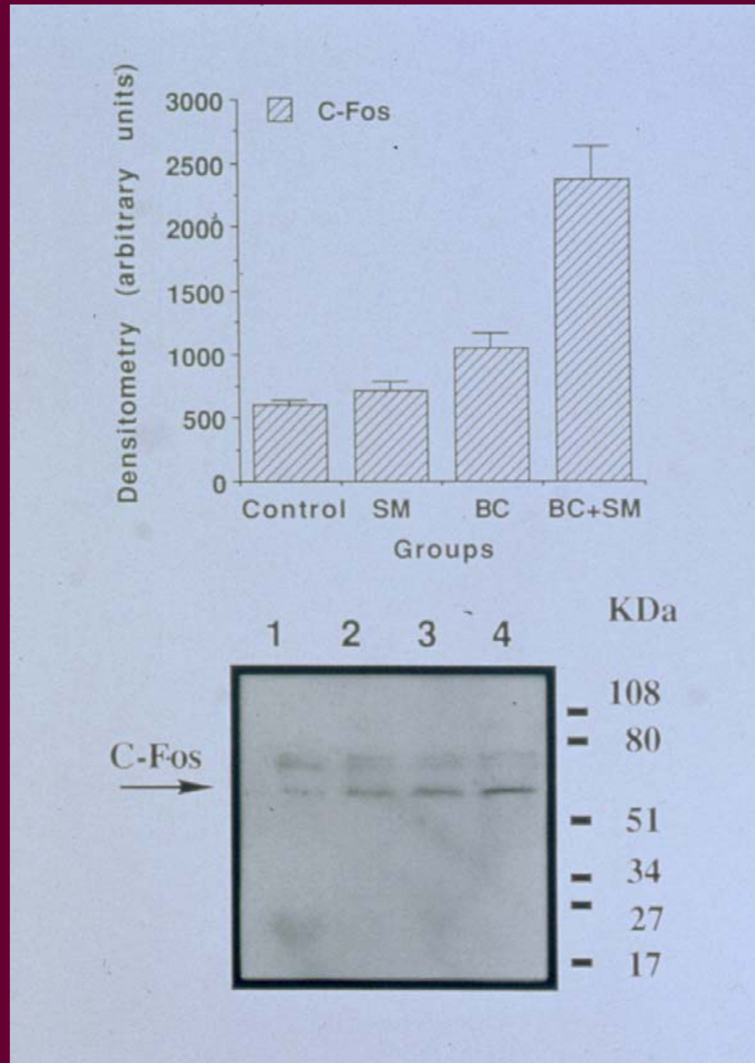

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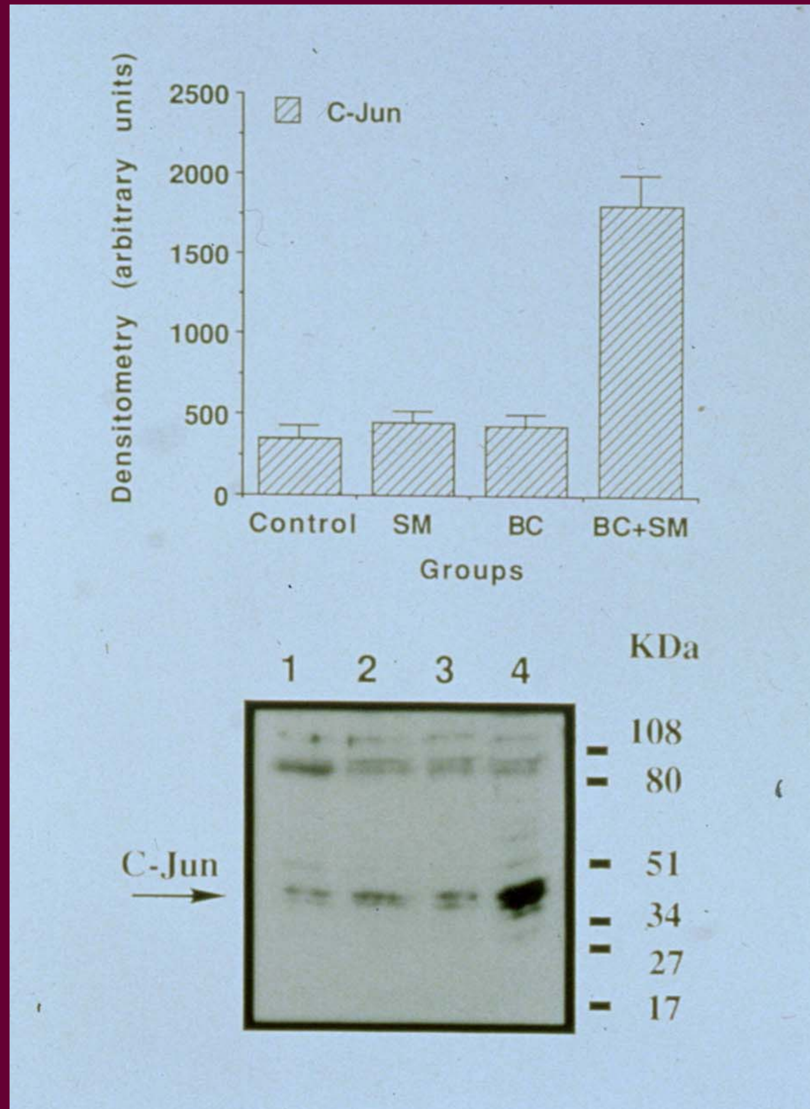

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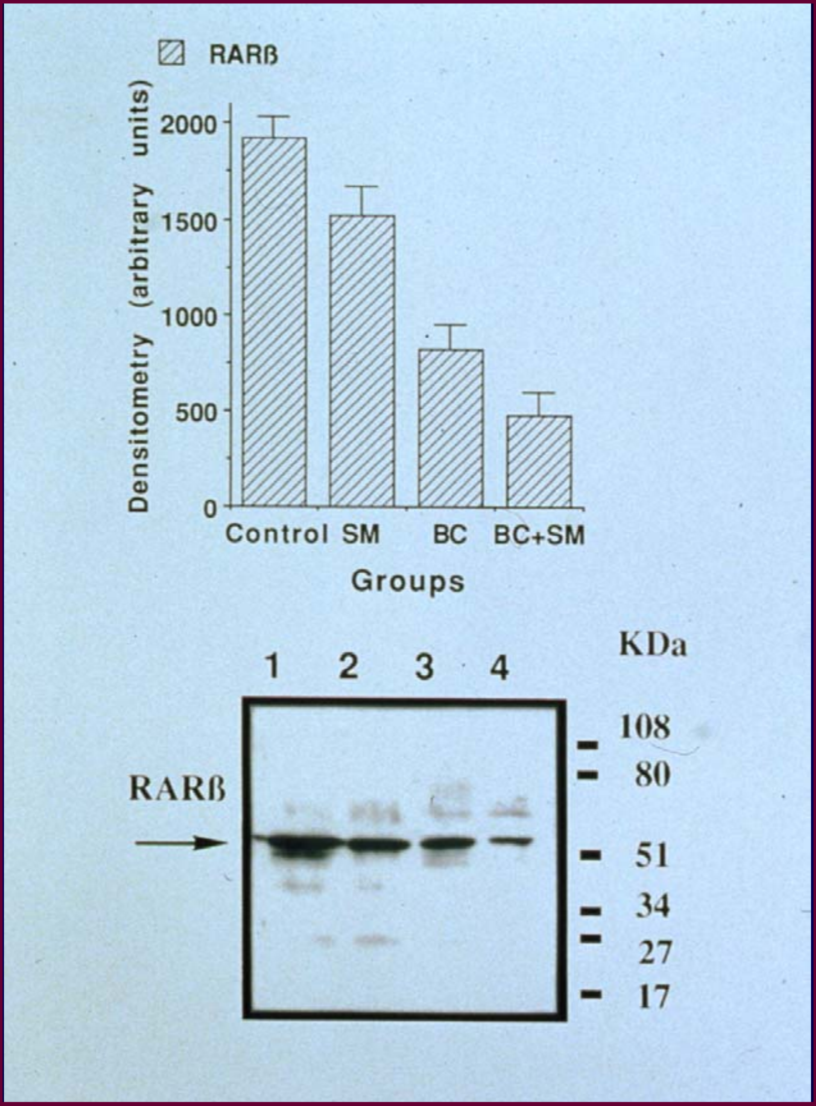

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Mechanism

- ↑ P450 enzymes
- ↓ Retinoic Acid
- ↑ c-Fos, c-Jun
- ↓ RARβ
- ↑ Cell proliferation

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Oxidized Products Facilitate Carcinogenesis

Salgo et al. 1999

Perocco et al. 1999

Prakash et al

> **β- Apo 10’ and 14’ (not β-Carotene) can facilitate DNA binding of benzo[a]pyrene metabolites**

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Oxidized Products

1) Induce P450 enzymes

2) ↑ Binding of smoke derived carcinogens to DNA

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Strategy

Limit amount of β-Carotene metabolites formed

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Ferret Study Design

Ferret

High dose β-Carotene = 30 mg/day | Low dose β-Carotene = 6 mg/day | Control = 1.8 mg/day

Smoking | Non-Smoking | Smoking | Non-Smoking | Smoking | Non-Smoking

6 months

Sacrificed

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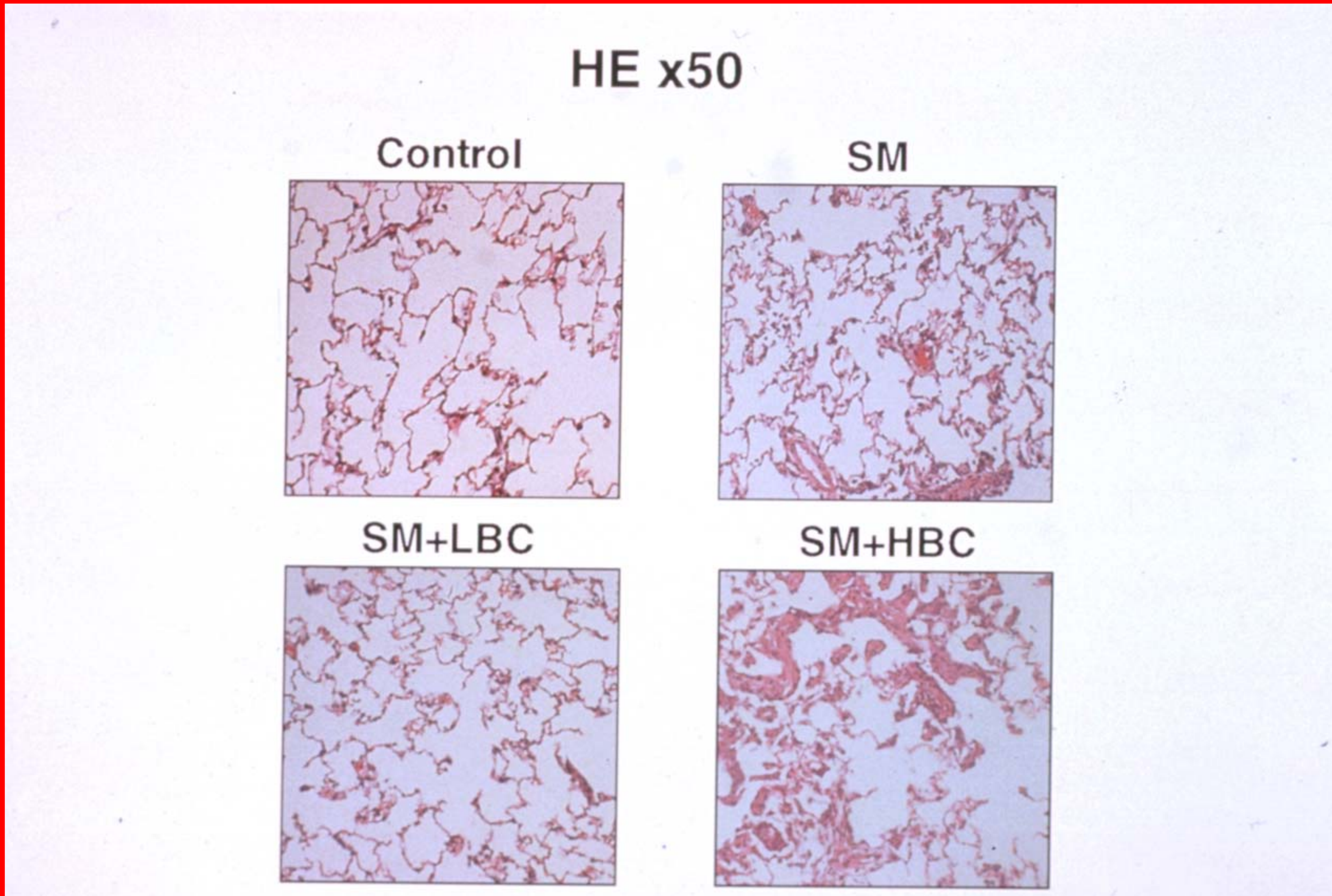

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	Control	SM	SM+Lβ-C	SM+Hβ-C
RA	—	↓↓	↓	↓↓↓
RAR β	—	↓	↓	↓↓↓
AP-1	—	↑	↑	↑↑↑
PCNA	—	↑	↑	↑↑↑

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1. Dose counts

2. Mechanisms

3. Importance of animal studies

4. Genomics

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Future Research Needs

1) Animal Models (dose response)
2) Metabolism, breakdown; and biologic activity
3) Genomics

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