Alcol e Tumori:
Il Rischio in un Bicchiere

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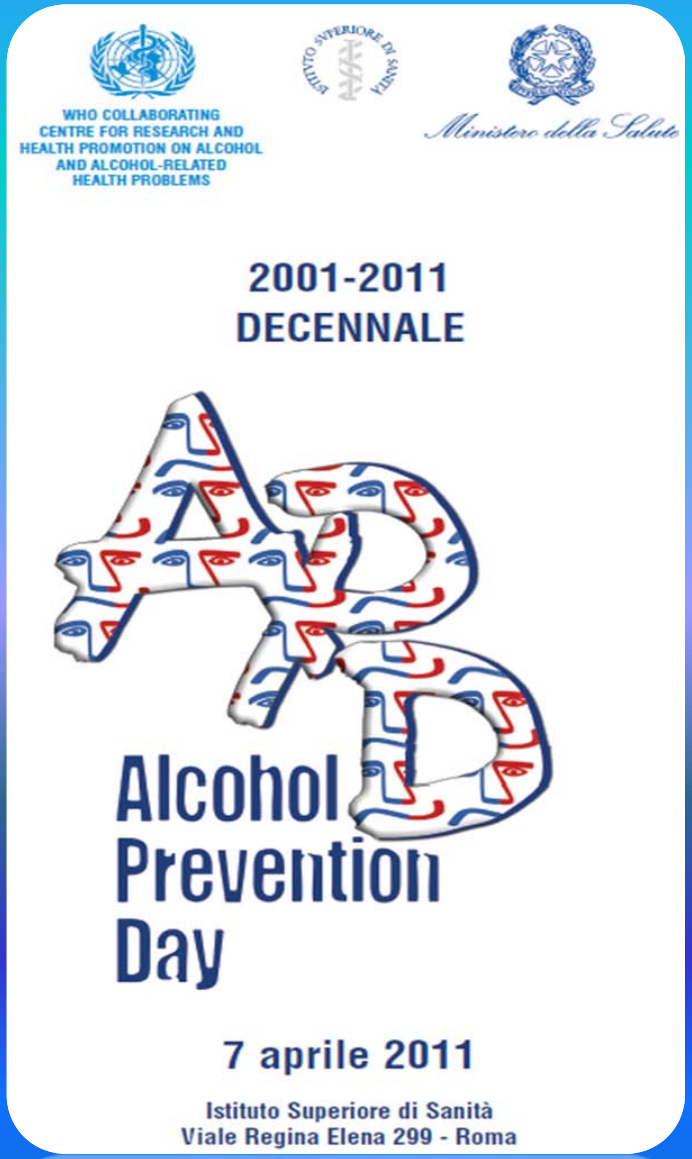
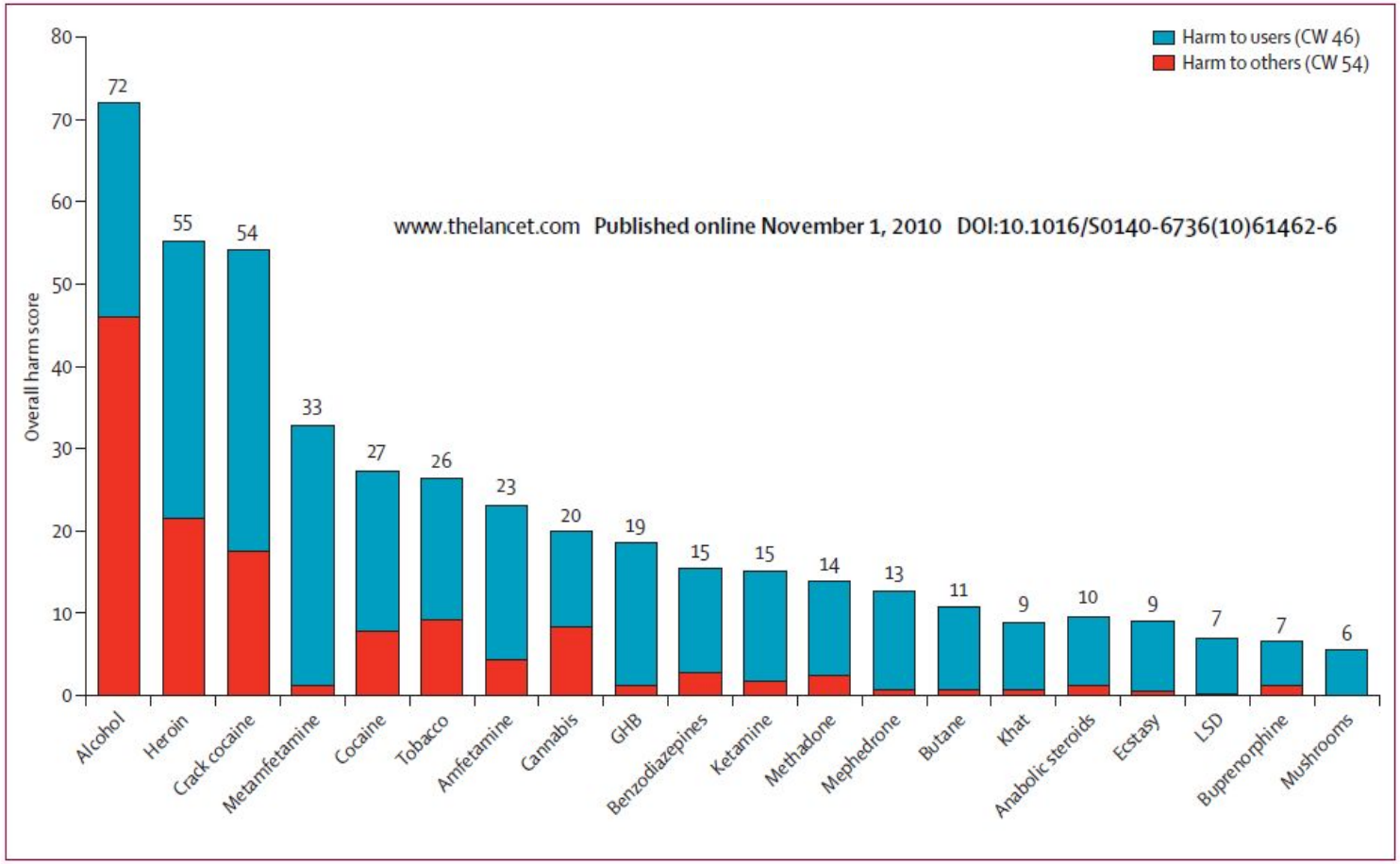


ALCOL socialmente più dannoso delle droghe



www.thelancet.com Published online November 1, 2010 DOI:10.1016/S0140-6736(10)61462-6

Figure 2: Drugs ordered by their overall harm scores, showing the separate contributions to the overall scores of harms to users and harm to others
The weights after normalisation (0–100) are shown in the key (cumulative in tl
all the criteria to others, 54). CW=cumulative weight. GHB=γ hydroxybutyric ac

Drug harms in the UK: a multicriteria decision analysis

David J Nutt, Leslie A King, Lawrence D Phillips, on behalf of the Independent Scientific Committee on Drugs

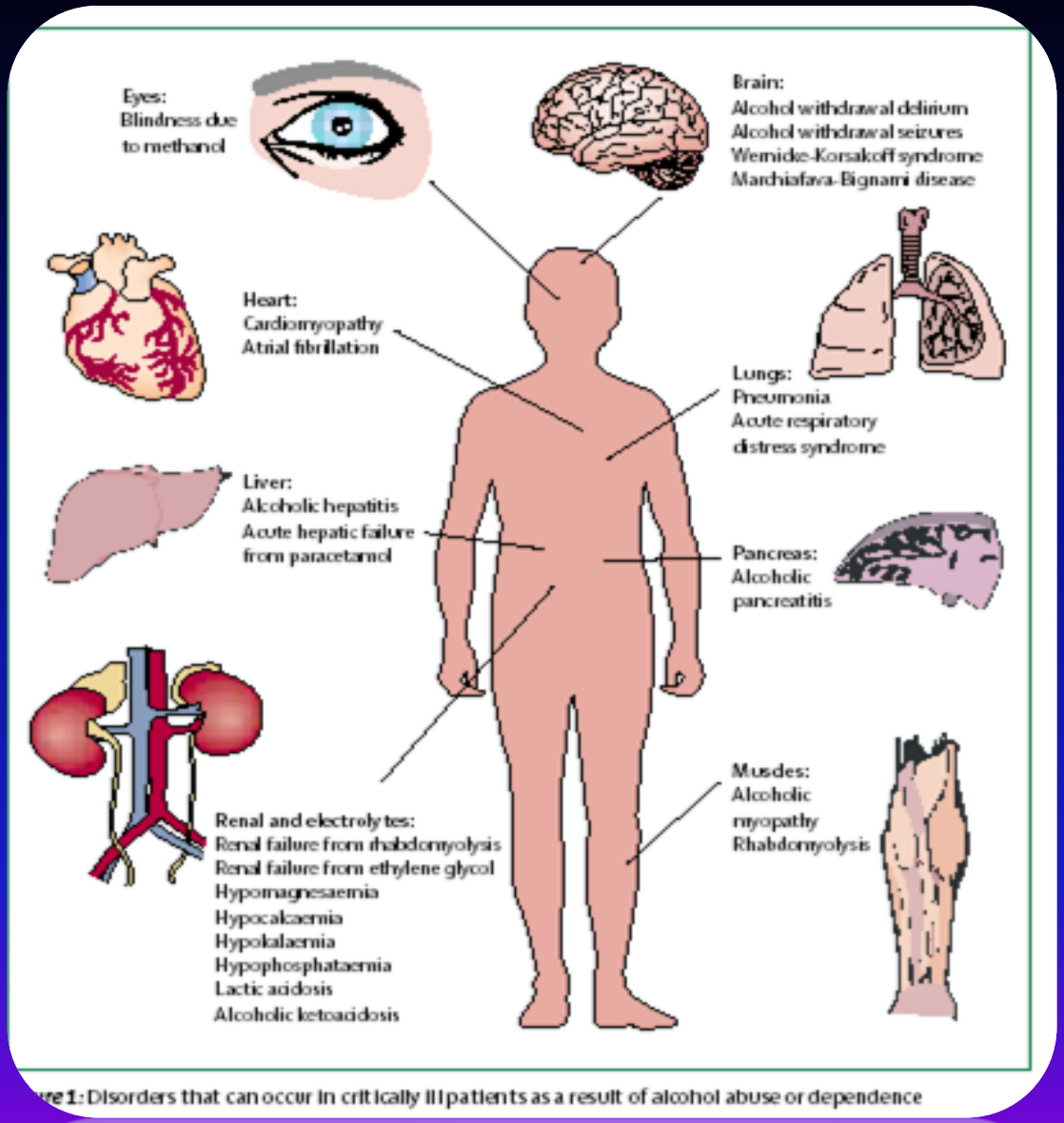
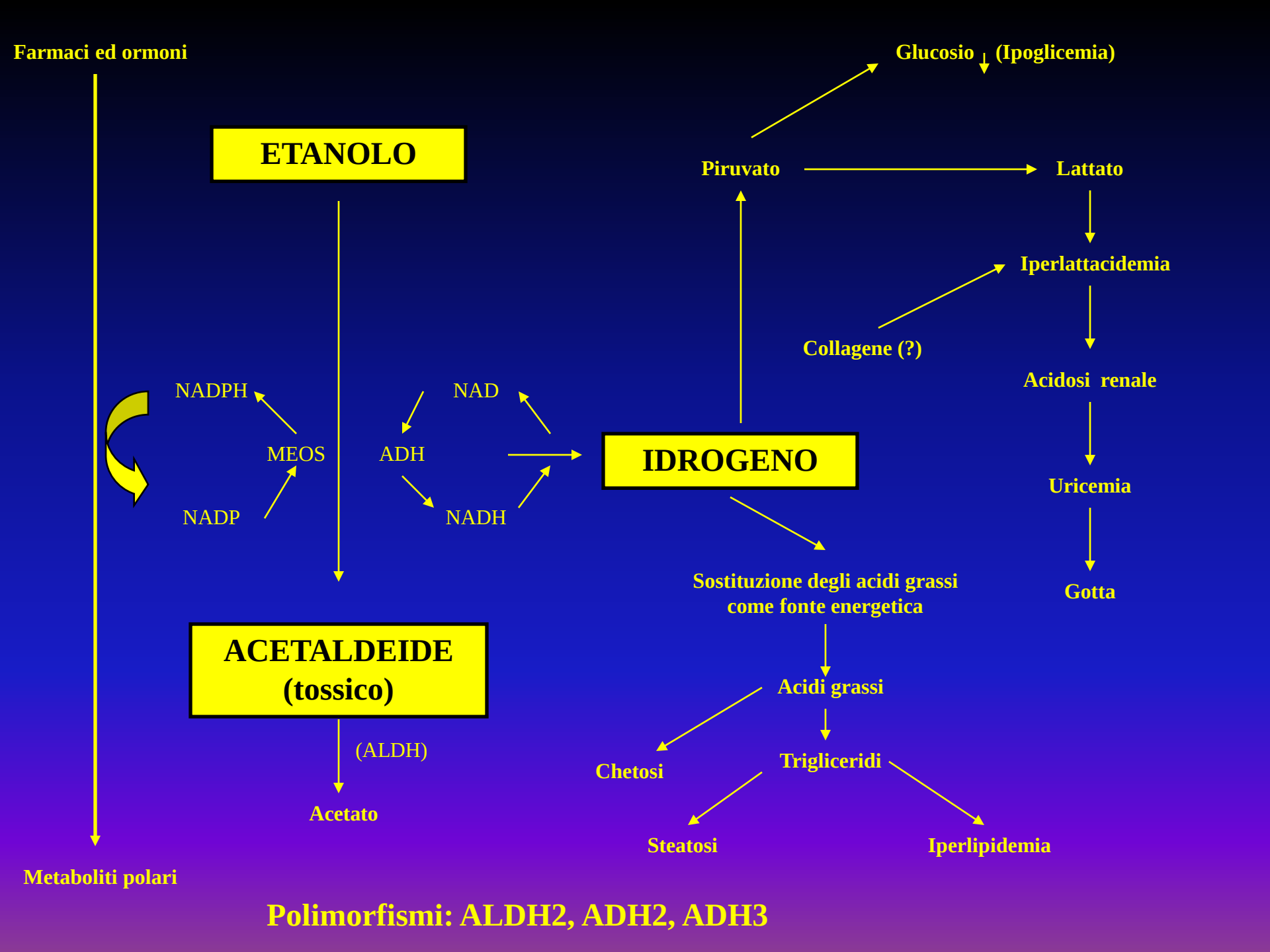


Figure 1: Disorders that can occur in critically ill patients as a result of alcohol abuse or dependence

Moss M. and Burnham E. L., The Lancet 2006


Farmaci ed ormoni
Glucosio (Ipoglicemia)
ETANOLO
Piruvato
Lattato
Iperlattacidemia
Collagene (?)
Acidosi renale
NADPH
NAD
MEOS
ADH
IDROGENO
NADP
NADH
Uricemia
Gotta
Sostituzione degli acidi grassi
come fonte energetica
ACETALDEIDE
(tossico)
Acidi grassi
(ALDH)
Chetosi
Trigliceridi
Acetato
Steatosi
Iperlipidemia
Metaboliti polari
Polimorfismi: ALDH2, ADH2, ADH3

ALCOHOL

Fatty Liver

Alcohol Hepatitis/Fibrosis

Cirrhosis

Hepatocellular Carcinoma

Chronic Pancreatitis

Parotid Hypertrophy

Glossitis

Stomatitis

Gastro-Esophageal Reflux

Mallory-Weiss Syndrome

Chronic Gastritis

Erosive Hemorrhagic Gastritis

Delayed Gastric Emptyimg

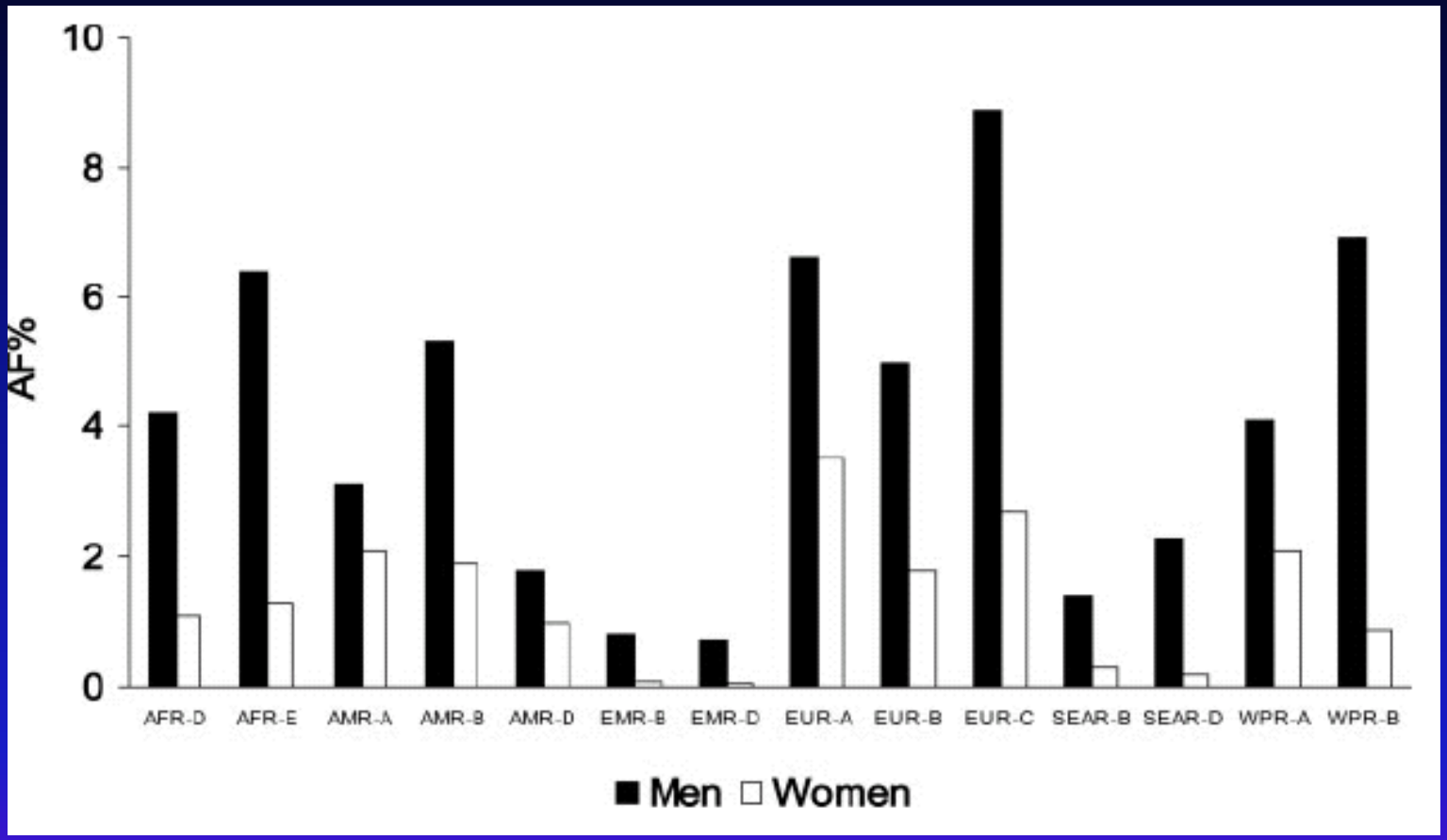
Malabsorption

Reduce Transit Time

Carcinogenesis*

***Upper Aero-Digestive Tract, Colon, Rectum, Breast, Liver, Pancreas**

Testino G.
Hepatogasroenterology 2008



Alcohol-Attributable fraction (AF) of all cancer by sex and WHO subregion

Boffetta et al, Int J Cancer 2006

IARC; Lancet Oncology, November 2009

	Tumour sites for which there is sufficient evidence	Tumour sites for which there is limited evidence	Tumour sites for which there is evidence suggesting lack of carcinogenicity
Tobacco smoking	Oral cavity, oropharynx, nasopharynx, and hypopharynx, oesophagus (adenocarcinoma and squamous-cell carcinoma), stomach, colorectum,* liver, pancreas, nasal cavity and paranasal sinuses, larynx, lung, uterine cervix, ovary (mucinous)*, urinary bladder, kidney (body and pelvis), ureter, bone marrow (myeloid leukaemia)	Female breast*	Endometrium (postmenopausal*), thyroid*
Parental smoking (cancer in the offspring)	Hepatoblastoma*	Childhood leukaemia (in particular acute lymphocytic leukaemia)*	
Second-hand smoke	Lung	Larynx,* pharynx*	
Smokeless tobacco	Oral cavity, oesophagus,* pancreas		
Areca nut			
Betel quid with added tobacco	Oral cavity, pharynx, oesophagus		
Betel quid without added tobacco	Oral cavity, oesophagus*	Liver*	
Alcohol consumption	Oral cavity, pharynx, larynx, oesophagus, liver, colorectum, female breast	Pancreas*	Kidney, non-Hodgkin lymphoma
Acetaldehyde associated with alcohol consumption	Oesophagus,* head and neck*		
Chinese-style salted fish	Nasopharynx	Stomach*	
Indoor emissions from household combustion of coal	Lung		

*New sites.

Table: Evidence for carcinogenicity in humans of Group 1 agents assessed

Table 1 | **Alcohol and experimental carcinogenesis**

Animal species	Sex	No.	Exposure time	Ethanol administration	Effects	Comments	Ref
B6C3F1 mice	F and M	281	104 weeks	2.5% and 5.0% in dw	More male animals with HCA and HCC	Significant dose-related trend ($P<0.05$)	31
ICR mice	F	40	25 months	10% and 15% in dw	45% more animals with papillary and meduallary adenocarcinomas of the breast ($P=0.0012$)	No tumours in control group	32
C57/B6^{APCmin} mice	M	24	10 weeks	15% and 20% in dw	More intestinal tumours ($P=0.027$); more tumours in the distal small intestine ($P=0.01$)	C57/B6 ^{APCmin} mice respresent a genetic model that resembles that of FAP in humans.	33
SD Rats	F and M	440	Life long	10% in dw	More tumours of oral cavity, lips, tongue and forestomach ($P=0.001$)	More animals developed malignant tumours, and more tumours per animal were observed after alcohol feeding	34

dw, drinking water; F, female; FAP, familial adenomatous polyposis; HCA, hepatocellular adenoma; HCC, hepatocellular carcinoma; M, male.

Seitz and Stickel, Nature Rev. 2007

Selection process and main characteristics of the studies selected for the meta-analysis

Condition	History of studies selection			Study design		No. of cases	RR (and 95% CI) for selected doses of alcohol intake[a]		
	Retrieved[b]	Included[c]	Selected[d]	Case-control	Cohort		25 g/day	50 g/day	100 g/day
Neoplastic conditions (cancer site)									
Oral cavity and pharynx	58	24	15	14	1	4507	1.86 (1.76–1.96)	3.11 (2.85–3.39)	6.45 (5.76–7.24)
Esophagus	51	28	14	13	1	3233	1.39 (1.36–1.42)	1.93 (1.85–2.00)	3.59 (3.34–3.87)
Larynx	38	20	20	20	0	3789	1.43 (1.38–1.48)	2.02 (1.89–2.16)	3.86 (3.42–4.35)
Colon		16	16	12	4	5360	1.05 (1.01–1.09)	1.10 (1.03–1.18)	1.21 (1.05–1.39)
Rectum	}49	14	6	4	2	1420	1.09 (1.08–1.12)	1.19 (1.14–1.24)	1.42 (1.30–1.55)
Liver	43	19	10	8	2	1321	1.19 (1.12–1.27)	1.40 (1.25–1.56)	1.81 (1.50–2.19)
Breast	72	48	29	24	5	32,175	1.25 (1.20–1.29)	1.55 (1.44–1.67)	2.41 (2.07–2.80)
Non neoplastic conditions									
Essential hypertension	11	3	2	0	2	5801	1.43 (1.33–1.53)	2.04 (1.77–2.35)	4.15 (3.13–5.52)
Coronary heart disease	196	51	28	0	28	49,640	0.81 (0.79–0.83)	0.87 (0.84–0.90)	1.13 (1.06–1.21)
Ischemic stroke		7	6	3	3	893	0.90 (0.75–1.07)	1.17 (0.97–1.44)	4.37 (2.28–8.37)
Hemorrhagic stroke	}56	9	9	6	3	1192	1.19 (0.97–1.49)	1.82 (1.46–2.28)	4.70 (3.35–6.59)
Gastroduodenal ulcer	9	3	2	1	1	425	0.98 (0.77–1.25)	0.97 (0.59–1.57)	0.93 (0.35–2.45)
Liver cirrhosis	27	15	9	6	3	2202	2.90 (2.71–3.09)	7.13 (6.35–8.00)	26.52 (22.26–31.59)
Chronic pancreatitis	4	2	2	2	0	247	1.34 (1.16–1.54)	1.78 (1.34–2.36)	3.19 (1.82–5.59)
Injures and violence	34	18	12	1	11	4501	1.12 (1.06–1.18)	1.26 (1.13–1.40)	1.58 (1.27–1.95)
Total	561	240	156	99	57	116,706	–	–	–

Corrao et al, Preventive Medicine 2004

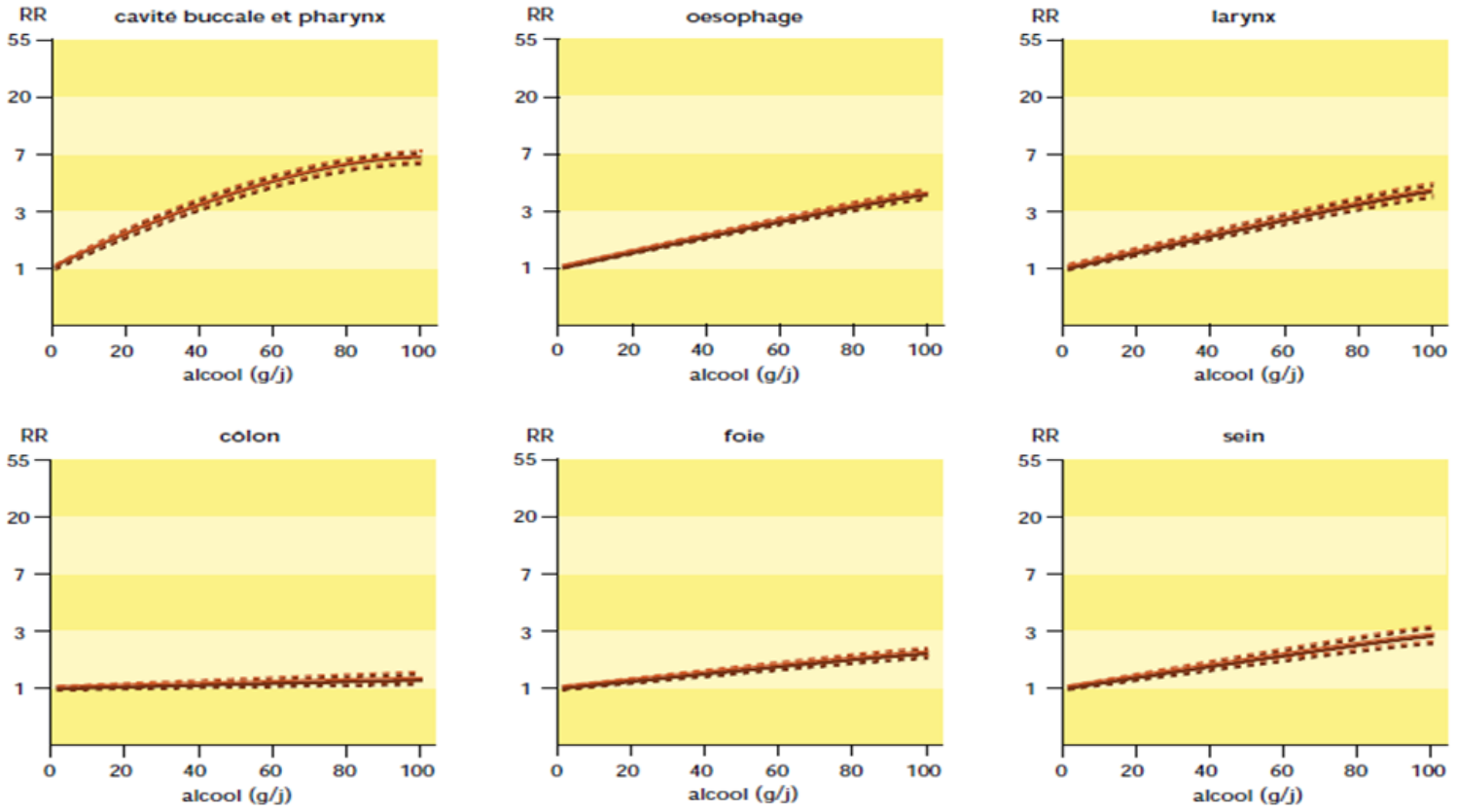
	Cases	Controls	Relative risk (95% CI)	p for trend	Ref
Oral, pharynx					
Men					
None	13	78	1·00 (Reference)	<0·001	13
<1 OWE	20	90	1·33 (0·57–3·13)		
1·0–2·9 OWE	19	48	2·37 (1·00–5·64)		
3·0–6·9 OWE	13	27	2·89 (1·10–7·60)		
≥7 OWE*	8	11	4·36 (1·39–13·68)		
Women					
None	55	192	1·00 (Reference)	1·0	13
<1 OWE*	34	127	0·93 (0·53–1·64)		
1·0–2·9 OWE*	7	28	0·87 (0·29–2·59)		
3·0–6·9 OWE*	1	8	0·44 (0·03–7·09)		
≥7 OWE*	3	4	2·62 (0·51–13·34)		
Non-drinkers	4	202	1·00 (Reference)	0·03	14
<35 years of drinking	16	382	2·9 (0·9–9·2)		
≥35 years of drinking	22	278	3·6 (1·2–11·2)		
Missing data	0	2			
Oesophagus					
Never drinkers	91	423	1·00 (Reference)	0·002	15
1–24 mL ethanol/day	14	65	1·43 (0·72–2·84)		
25–49 mL ethanol/day	12	43	1·61 (0·75–3·48)		
50–149 mL ethanol/day	14	69	1·77 (0·85–3·67)		
≥150 mL ethanol/day	9	18	5·70 (2·11–15·44)		
Missing data	4	12			
Larynx					
<8 drinks/day	31	142	1·00 (Reference)	NA	16
≥8 drinks/day	9	18	2·46 (0·98–6·20)		

OWE=ounces of whiskey equivalent: combined intake of beer, wine, and liquor.

Table 1: Relative risk of cancer of upper aerodigestive tract with alcohol consumption, never-smokers

Lancet, February 2006

FIGURE 10 : ILLUSTRATION SYNTHÉTIQUE DES RISQUES RELATIFS DE CANCER DE LA CAVITÉ BUCCALE ET DU PHARYNX, DE L'ŒSOPHAGE, DU LARYNX, DU CÔLON, DU FOIE ET DU SEIN SELON LES QUANTITÉS D'ALCOOL CONSOMMÉES



Institute National du Cancer, www.e-cancer.fr, 2007

Site of cancer (ICD 7)	Men				Women			
	Obs	Exp	SIR	(95% CI)	Obs	Exp	SIR	95% (CI)
All cancers except non-melanoma skin cancer (140–205 minus 191)	2145	1140.8	1.9	(1.8–2.0)**	601	239.1	2.5	(2.3–2.7)**
Buccal cavity and pharynx (140–148)	227	48.2	4.7	(4.1–5.4)**	42	3.2	13.1	(9.5–17.7)**
Lip (140)	3	14.5	0.2	(0.0–0.6)*	0	0.3	0.0	(0.0–12.7)
Tongue (141)	47	5.7	8.3	(6.1–11.0)**	10	0.5	20.4	(9.8–37.5)**
Salivary glands (142)	6	3.2	1.9	(0.7–4.1)	1	0.4	2.3	(0.0–12.9)
Mouth (143–144)	76	11.0	6.9	(5.5–8.7)**	11	1.0	10.7	(5.3–19.1)**
Pharynx (145–148)	95	13.8	6.9	(5.6–8.4)**	20	1.0	21.1	(12.9–32.5)**
Digestive organs and peritoneum (150–159)	473	297.8	1.6	(1.5–1.7)**	55	38.4	1.4	(1.1–1.9)*
Oesophagus (150)	80	19.6	4.1	(3.2–5.1)**	8	1.1	7.1	(3.1–14.0)**
Stomach (151)	68	49.6	1.4	(1.1–1.7)*	7	3.7	1.9	(0.8–3.9)
Colon (153)	89	87.5	1.0	(0.8–1.3)	14	15.7	0.9	(0.5–1.5)
Rectum (154)	81	66.6	1.2	(1.0–1.5)	4	7.4	0.5	(0.2–1.4)
Liver (155)	64	13.6	4.7	(3.6–6.0)**	8	1.3	6.0	(2.6–11.9)**
Gall bladder (155.1)	9	7.6	1.2	(0.5–2.3)	4	1.7	2.3	(0.6–6.0)
Pancreas (157)	61	36.5	1.7	(1.3–2.2)**	6	4.8	1.2	(0.5–2.7)
Respiratory system (160–164)	661	276.7	2.4	(2.2–2.6)**	96	24.2	4.0	(3.2–4.9)**
Larynx (161)	121	26.1	4.6	(3.9–5.5)**	4	1.0	3.9	(1.0–9.9)*
Lung (162)	523	238.2	2.2	(2.0–2.4)**	90	22.4	4.0	(3.2–5.0)**
Pleura (162.2)	11	6.5	1.7	(0.8–3.0)	1	0.3	3.6	(0.1–19.9)
Urinary system (180–181)	174	156.3	1.1	(1.0–1.3)	16	10.7	1.5	(0.9–2.4)
Kidney (180)	64	44.4	1.4	(1.1–1.8)*	10	4.8	2.1	(1.0–3.8)*
Urinary bladder (181)	110	112.0	1.0	(0.8–1.2)	6	5.9	1.0	(0.4–2.2)
Breast (170)	3	2.2	1.4	(0.3–4.1)	93	75.9	1.2	(1.0–1.5)
Female genital organs (171–176)	–	–	–	–	58	45.8	1.3	(1.0–1.6)
Cervix uteri (171)	–	–	–	–	29	16.3	1.8	(1.2–2.6)*
Corpus uteri (172)	–	–	–	–	8	13.2	0.6	(0.3–1.2)
Ovary (175)	–	–	–	–	16	13.8	1.2	(0.7–1.9)
Male genital organs (177–179)	170	133.6	1.3	(1.1–1.5)*	–	–	–	–
Prostate gland (177)	135	100.7	1.3	(1.1–1.6)**	–	–	–	–
Testis (178)	27	28.1	1.0	(0.6–1.4)	–	–	–	–

*$P < 0.05$.
**$P < 0.001$.

Thygesen et al, Alcohol and Alcoholism 2009

IARC; Lancet Oncology, November 2009

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Parental smoking (cancer in the offspring)	Hepatoblastoma*	Childhood leukaemia (in particular acute lymphocytic leukaemia)*	
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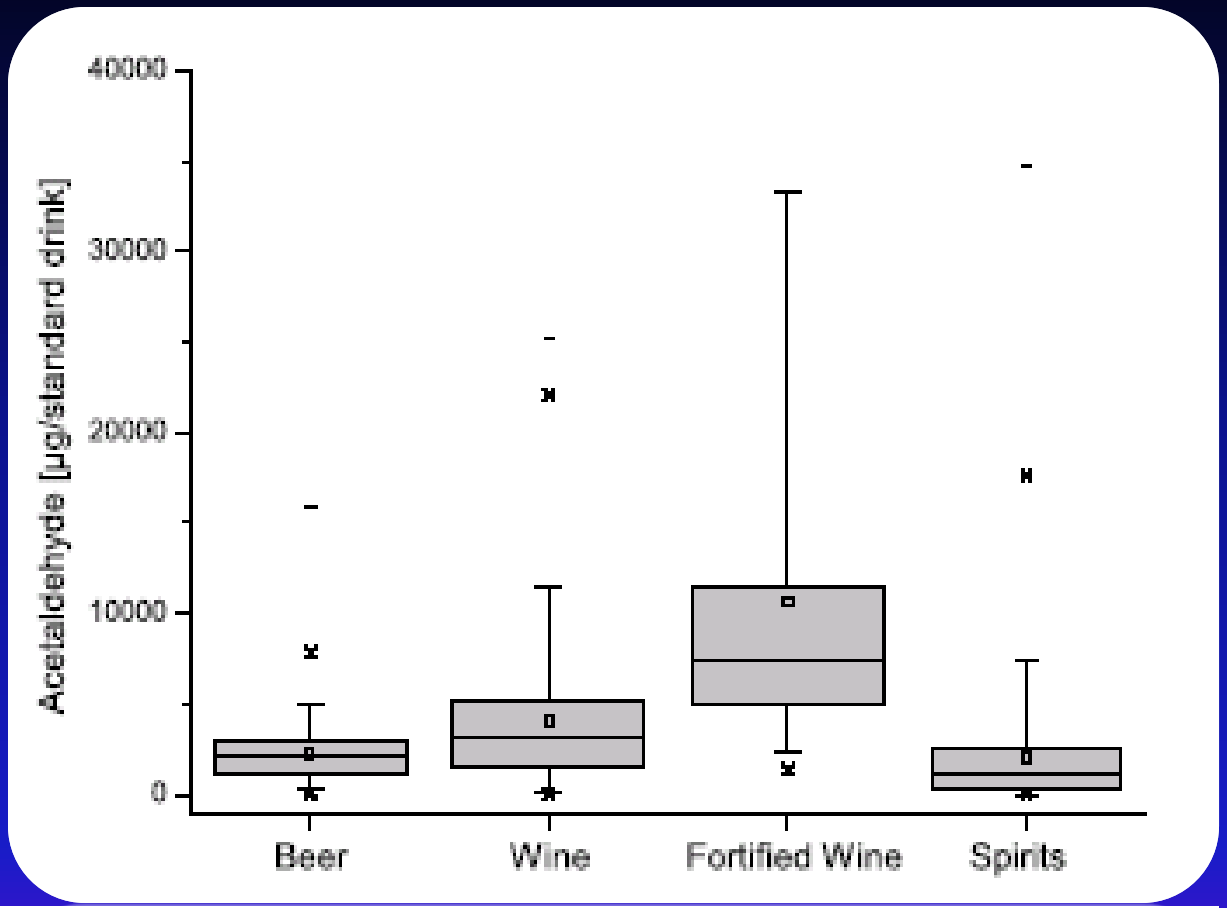
Chinese-style salted fish	Nasopharynx	Stomach*	
Indoor emissions from household combustion of coal	Lung		

*New sites.

Table: Evidence for carcinogenicity in humans of Group 1 agents assessed



Box chart of the acetaldehyde content of alcoholic beverages (in µg/portion).

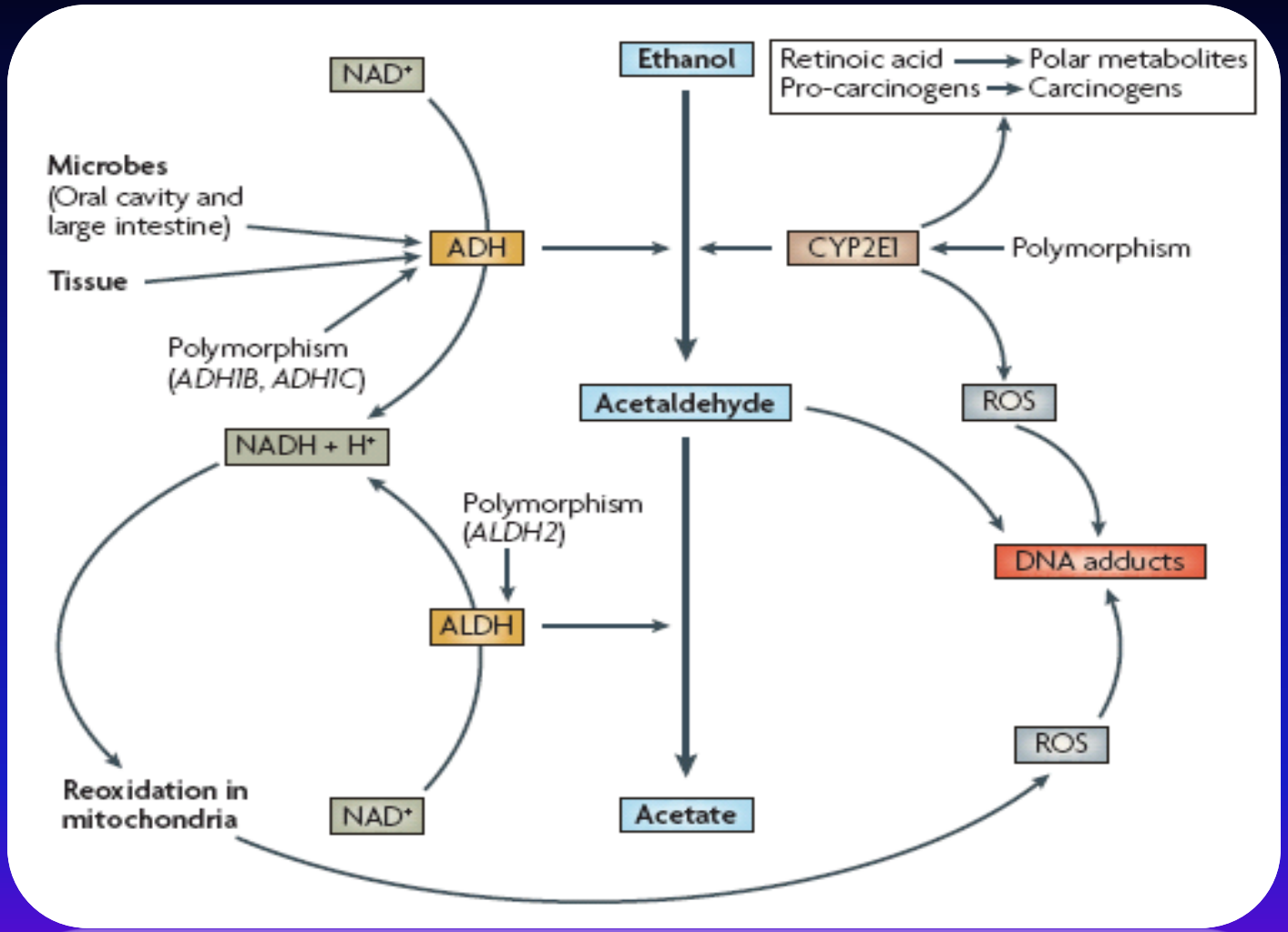
D.W. Lachenmeier, Food and Chemical Toxicology 2008

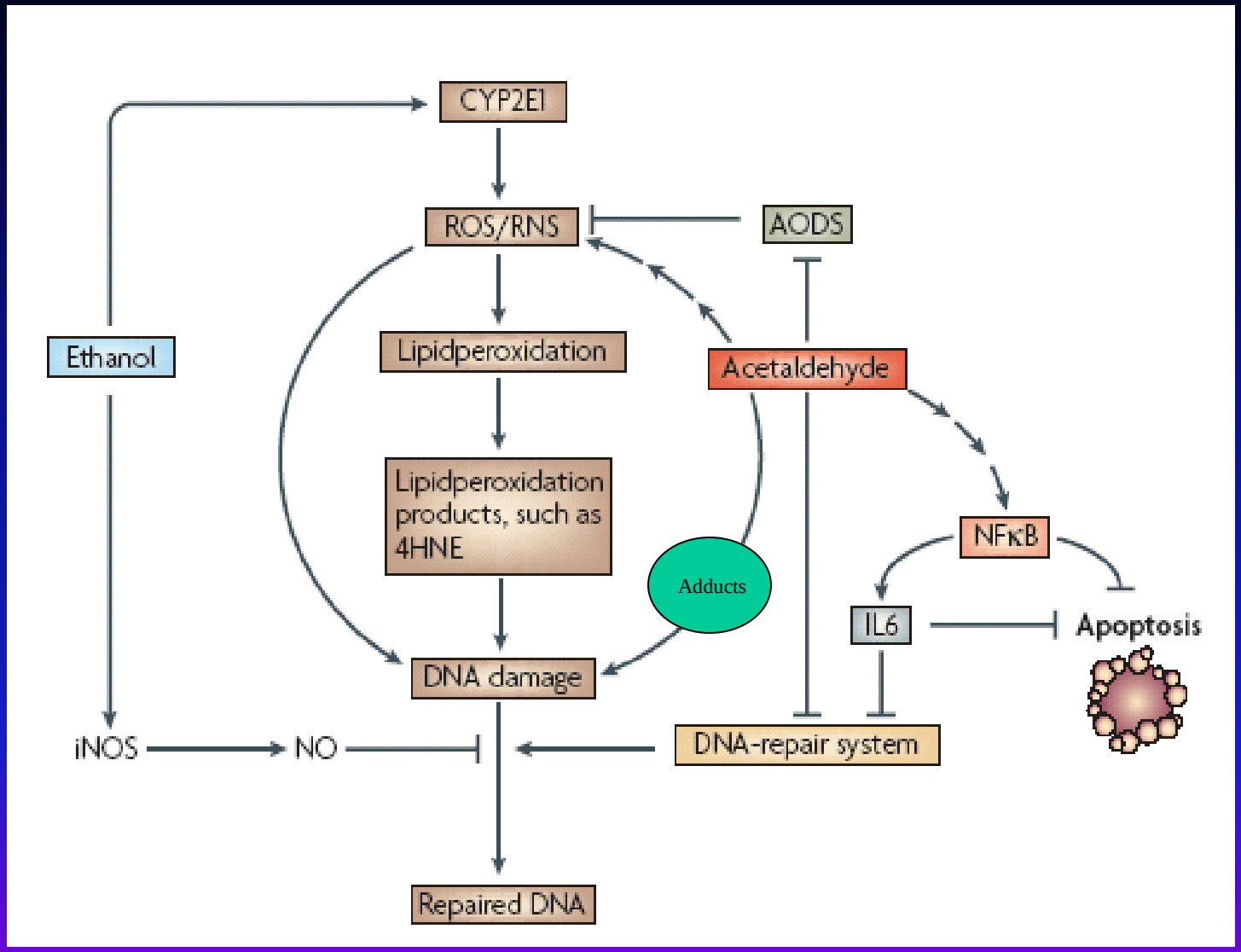
D.W Lachenmeier et al, Addiction 2009

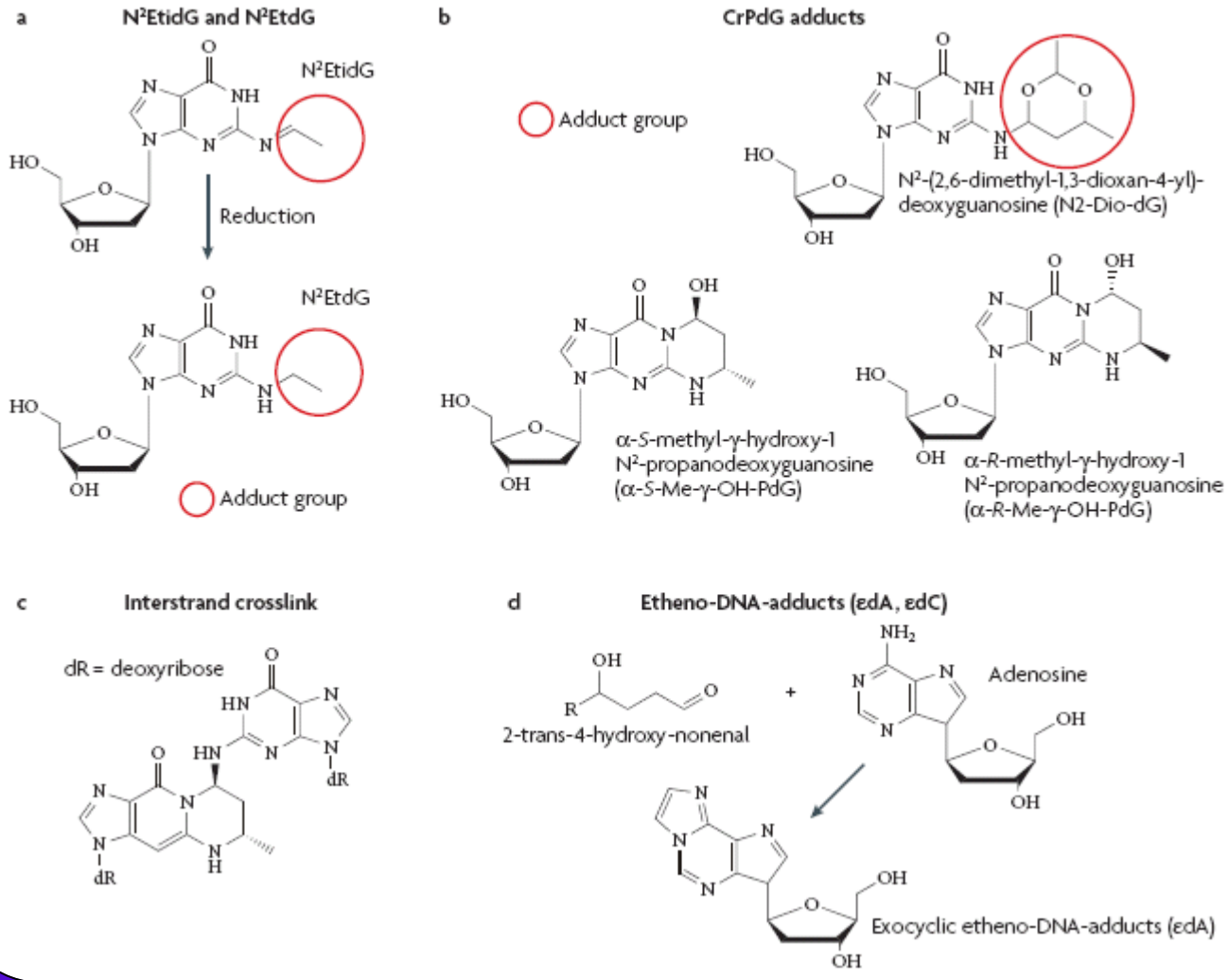
ALCOHOL AND CARCINOGENESIS

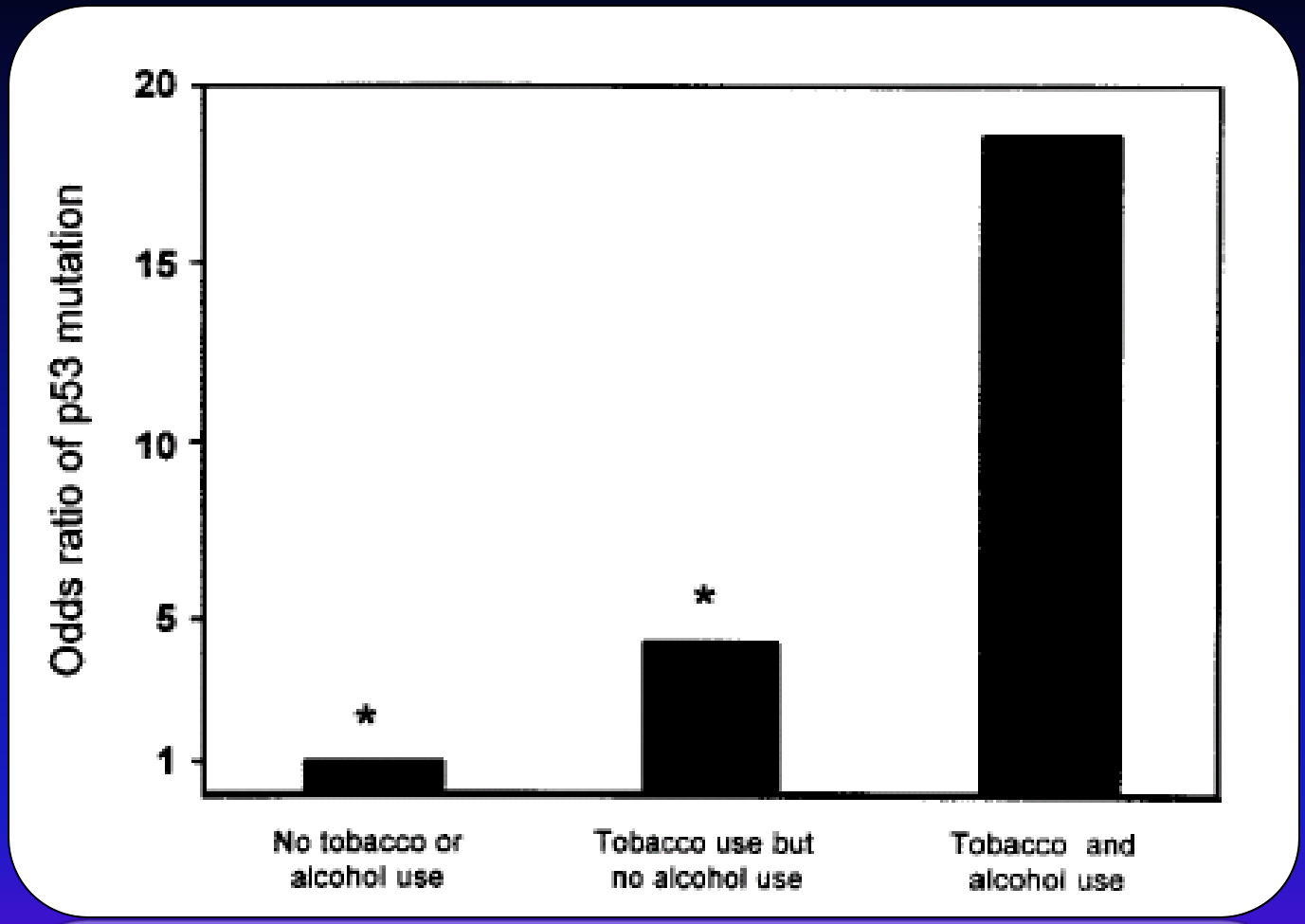
- ✓ Local Effect
- ✓ Acetaldehyde (ALDH isoenzymes polymorphism)
- ✓ Polymorphisms of ADH1B, ADH1C
- ✓ Induction of CYP2E1 (conversion of various xenobiotics)
- ✓ Nutritional Deficiencies
- ✓ Interaction with Retinoids
- ✓ Changes in the degree of Methylation
- ✓ Immune Surveillance

Testino G, Hepatogastroenterol 2008


NAD+
Ethanol
Retinoic acid → Polar metabolites
Pro-carcinogens → Carcinogens
Microbes
(Oral cavity and
large intestine)
Tissue
ADH
CYP2E1
Polymorphism
Polymorphism
(ADH1B, ADH1C)
Acetaldehyde
ROS
NADH + H+
Polymorphism
(ALDH2)
DNA adducts
ALDH
ROS
Reoxidation in
mitochondria
NAD+
Acetate


CYP2E1
ROS/RNS
AODS
Ethanol
Lipidperoxidation
Acetaldehyde
Lipidperoxidation products, such as 4HNE
NFκB
Adducts
IL6
Apoptosis
DNA damage
iNOS
NO
DNA-repair system
Repaired DNA


a
N²EtidG and N²EtdG
N²EtidG
Reduction
N²EtdG
Adduct group
b
CrPdG adducts
Adduct group
N²-(2,6-dimethyl-1,3-dioxan-4-yl)-deoxyguanosine (N2-Dio-dG)
α-S-methyl-γ-hydroxy-1 N²-propanodeoxyguanosine (α-S-Me-γ-OH-PdG)
α-R-methyl-γ-hydroxy-1 N²-propanodeoxyguanosine (α-R-Me-γ-OH-PdG)
c
Interstrand crosslink
dR = deoxyribose
d
Etheno-DNA-adducts (εdA, εdC)
2-trans-4-hydroxy-nonenal
Adenosine
Exocyclic etheno-DNA-adducts (εdA)



Ahrendt et al, Cancer Research 2000

PREDISPOSITION TO ALCOHOLIC LIVER DISEASE

Mutations and Polymorphism of genes

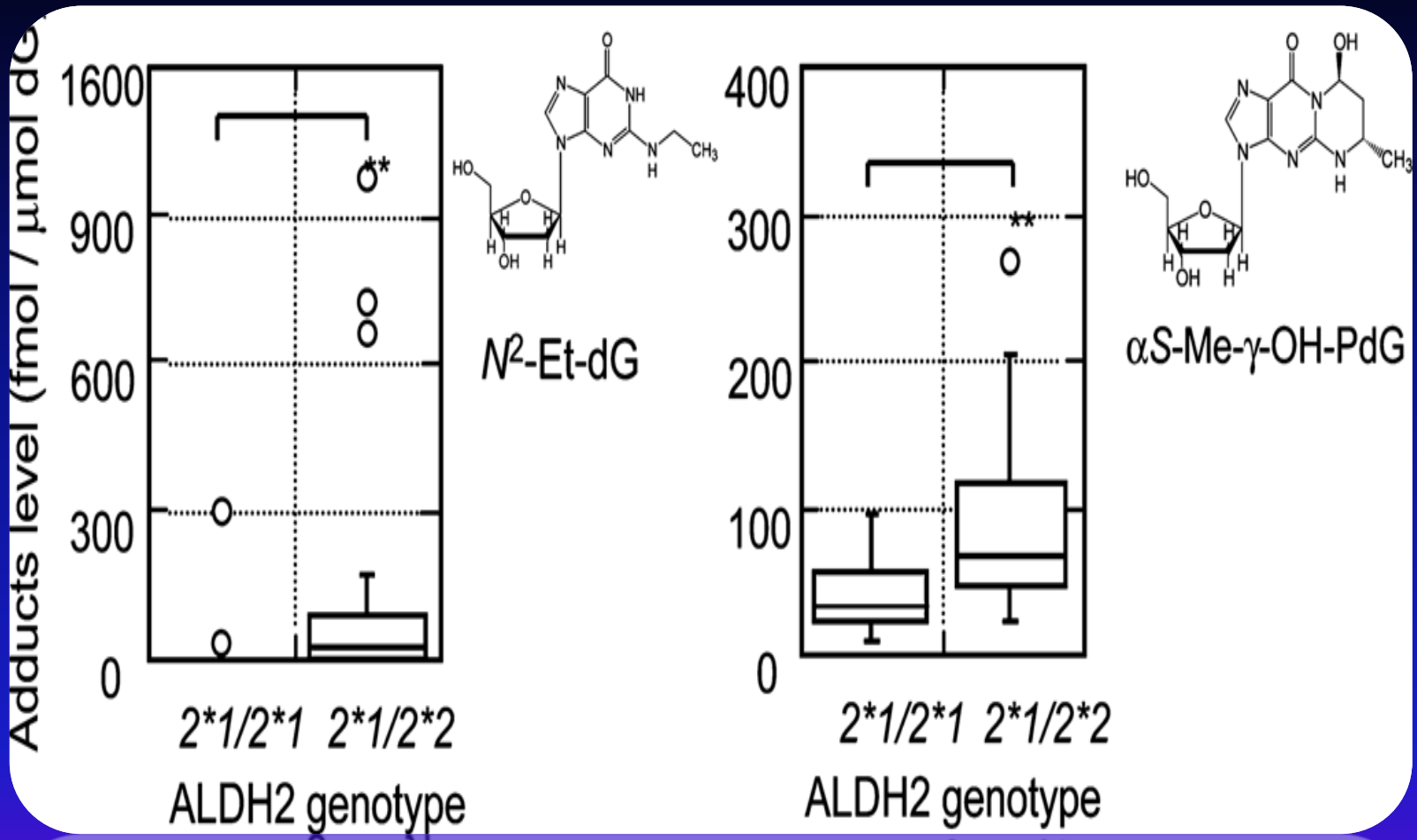
- Ethanol metabolism (ADHs, ALDHs, CYP2E1, Mitochondrial Superoxide Dismutase, Myeloperoxidase)
- Cytokines of the inflammatory response (TNF alpha, TNF alpha promoter polymorphisms, IL1, IL10,TNF-alpha-type-1 receptor,….)
- Polymorphisms in DNA repair genes (DNA ligase III, DNA polymerase b, poly-ADB-ribose-polymerase….)
- Genes involved in estrogen synthesis and metabolism (CYP17, CYP19, CYP1B1, catechol-0-methyltransferase)
- Polymorphisms in methylenetetrahydrofolate reductase
- GABA-ergic, dopaminergic, serotoninergic systems
- Components of immune systems (innate, adaptive)

IARC, 2010

TABLEAU 1 : POLYMORPHISMES GÉNÉTIQUES ASSOCIÉS AUX ENZYMES QUI MÉTABOLISENT L'ALCOOL

Enzyme	Allèles humains	Ancienne nomenclature	Activité enzymatique	Fréquence par population	Référence
ADH1B	*ADH1B*1*	*ADH2*1*	Active		Bosron, 1986 ; Quertemont, 2004 ; Brennan, 2004b ; Coutelle, 1998
	ADH1B*2	***ADH2*2***	**Hyperactive** (x 43 / *ADH1B*1*)	Européenne 0-10 % Africaine 0-15 % Asiatique 10-90 %	
	*ADH1B*3*	*ADH2*3*	Hyperactive		
ADH1C	***ADH1C*1***	***ADH3*1***	**Hyperactive** (x 2,5 / *ADH1C*2*)	Européenne 45-70 % Africaine 75-90 % Asiatique 85-100 %	Bosron, 1986 ; Quertemont, 2004 ; Brennan, 2004b ; Coutelle, 1998
	*ADH1C*2*	*ADH3*2*	Active		
ALDH2	*ALDH2*1*		Active		Crabb, 1989 ; Brennan, 2004b
	ALDH2*2		**Inactive** (/ *ADLH2*1*)	Européenne 0-5 % Asiatique 0-35 %	
CYP2E1	*c1*		Active		Bouchardy, 2000 ; Hildesheim, 1997
	c2		**Hyperactive** (/ *CYP2E1 c1*)	Européenne 0-10 % Asiatique 20-25 %	

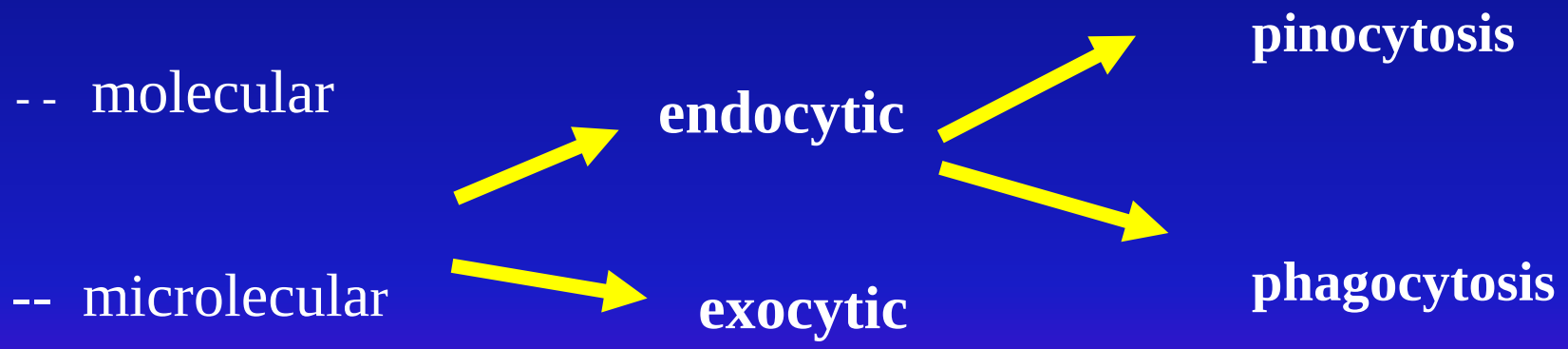
Institute National du Cancer, www.e-cancer.fr 2007



Matsuda et al, Chem Res Toxicol 2006

ALCOHOL AND ORAL CANCER

Cytological alterations (reduction cytoplasmic area,abnormal DNA profile...)
- mucosal transport : intercellular passage
- mucosal transport : intracellular mechanisms



Cowpe et al, 1988; Axford et al, 1999; Howie et al, 2001; Graham, 2005; Tramacere et al, Oral Oncology 2010

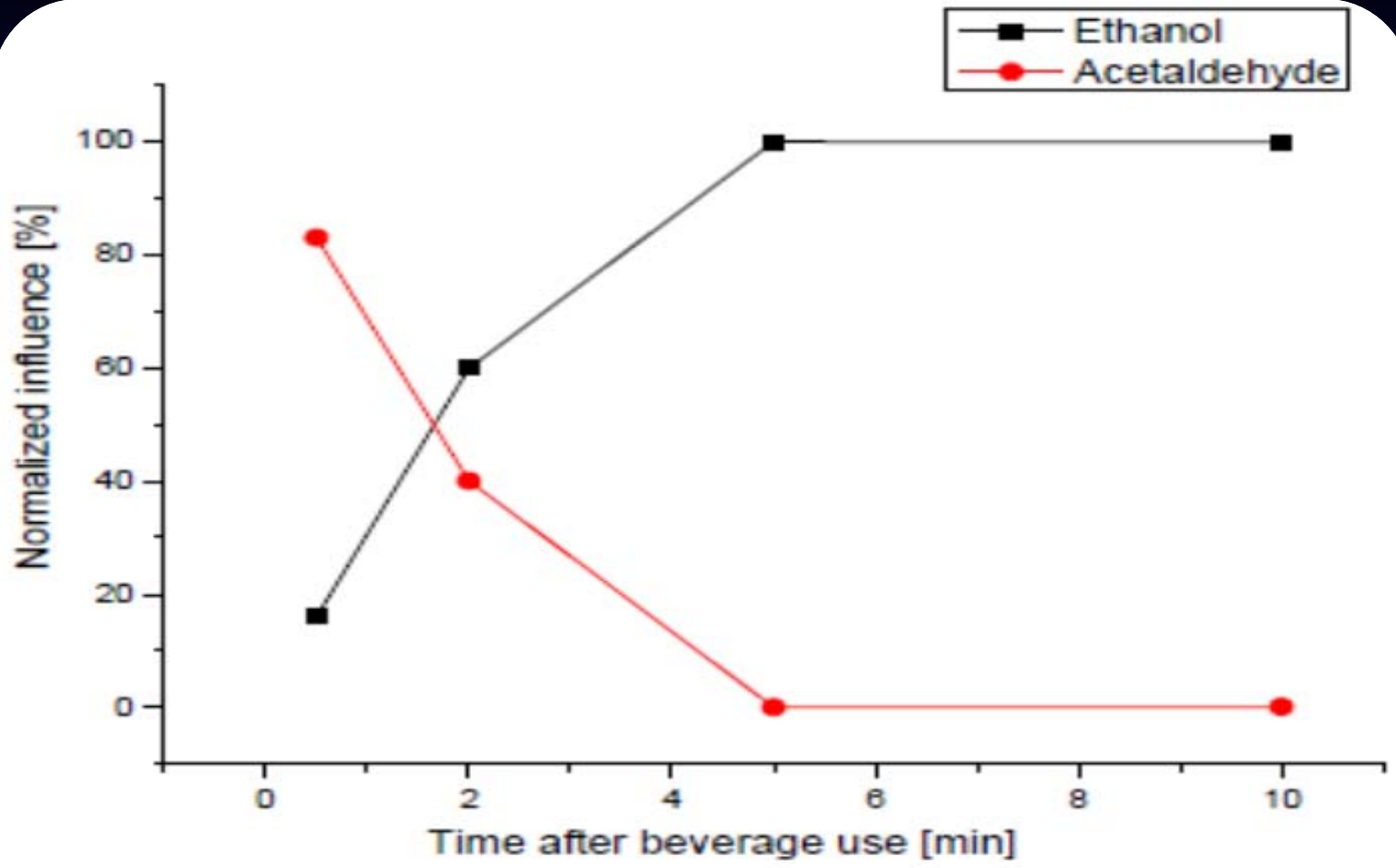


Figure 2 Influence of ethanol and acetaldehyde content of the beverages on the salivary acetaldehyde concentration.

Lachenmeier and Monakhova, J Exp Cin Cancer Res 2011

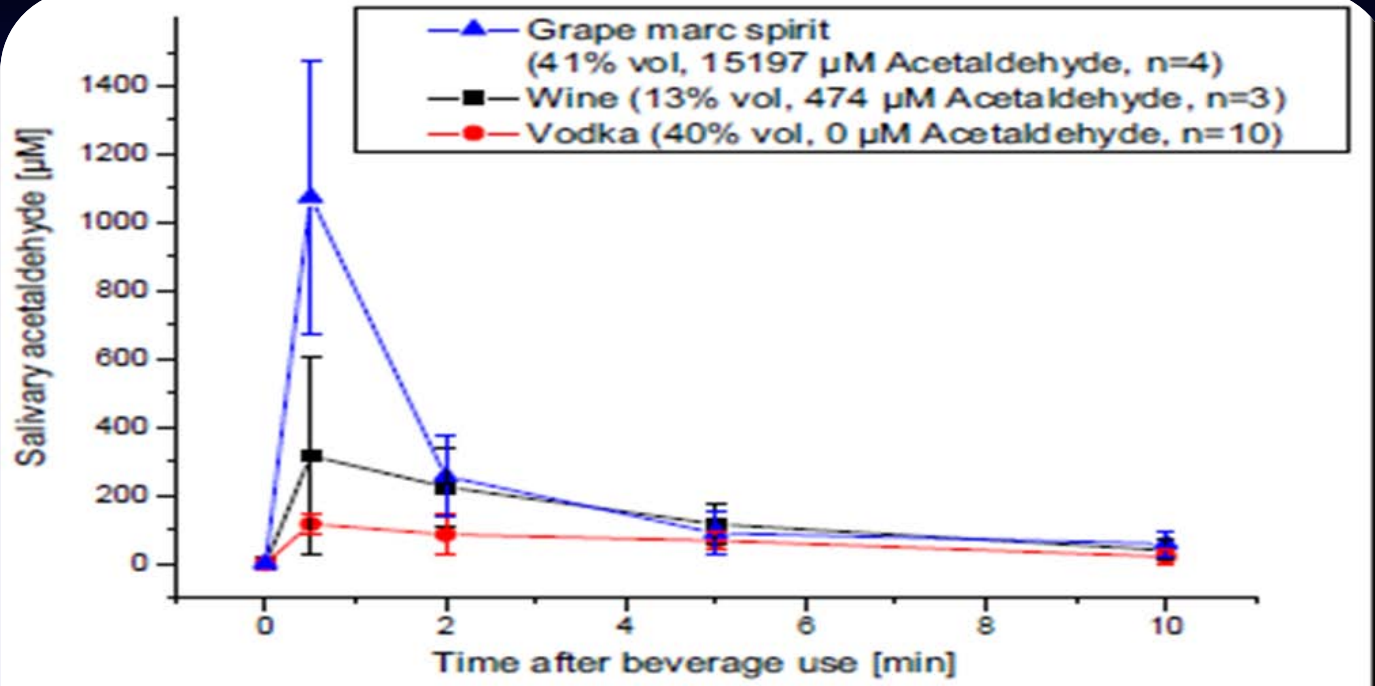
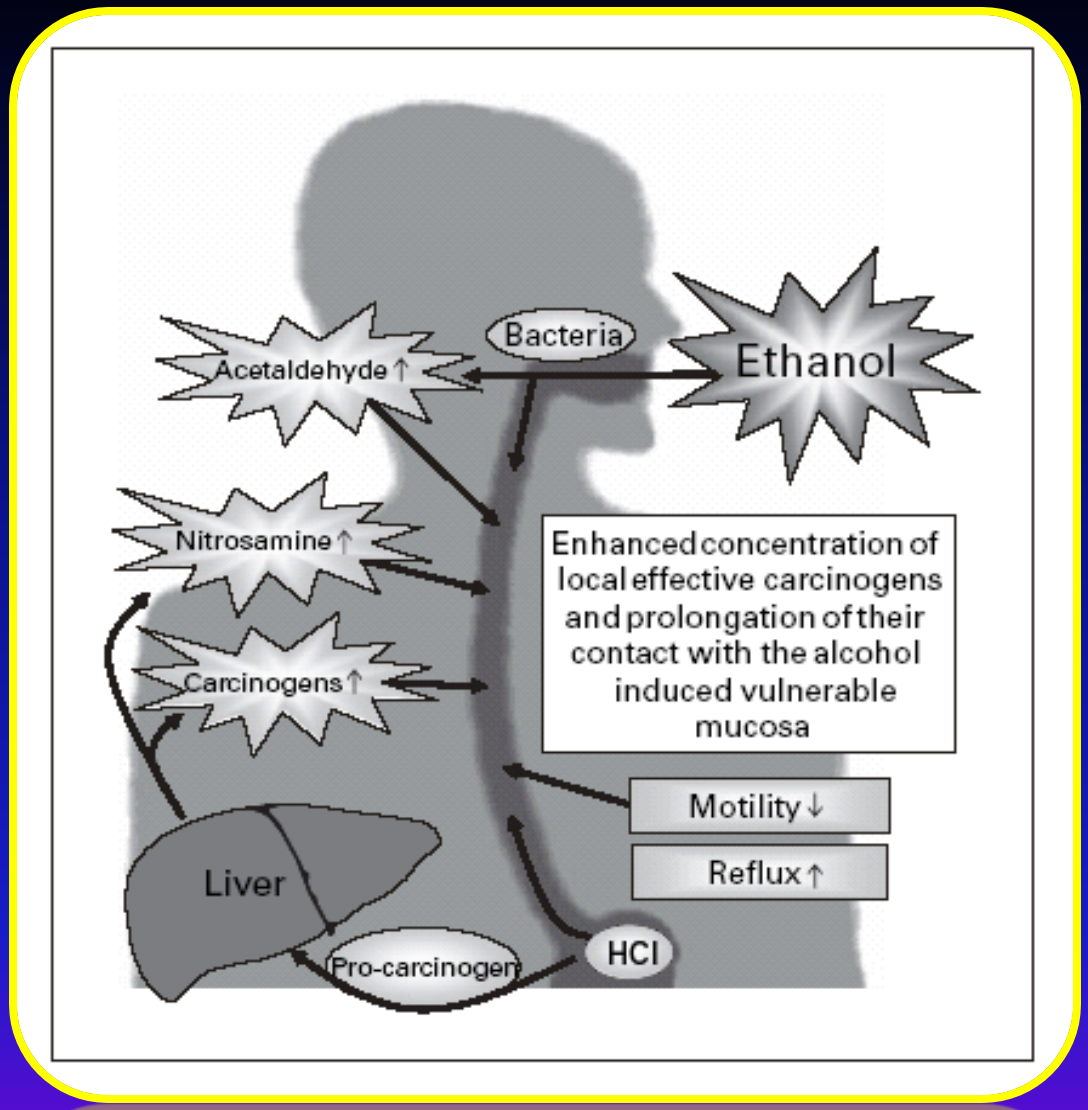


Figure 1 Salivary acetaldehyde concentrations after alcoholic beverage use in three different samples. The values are average and standard deviation of all assessors. The figure legend states the alcoholic strength (in % vol) and the acetaldehyde content (in µM) in the beverages, as well as the number of assessors used for each beverage.

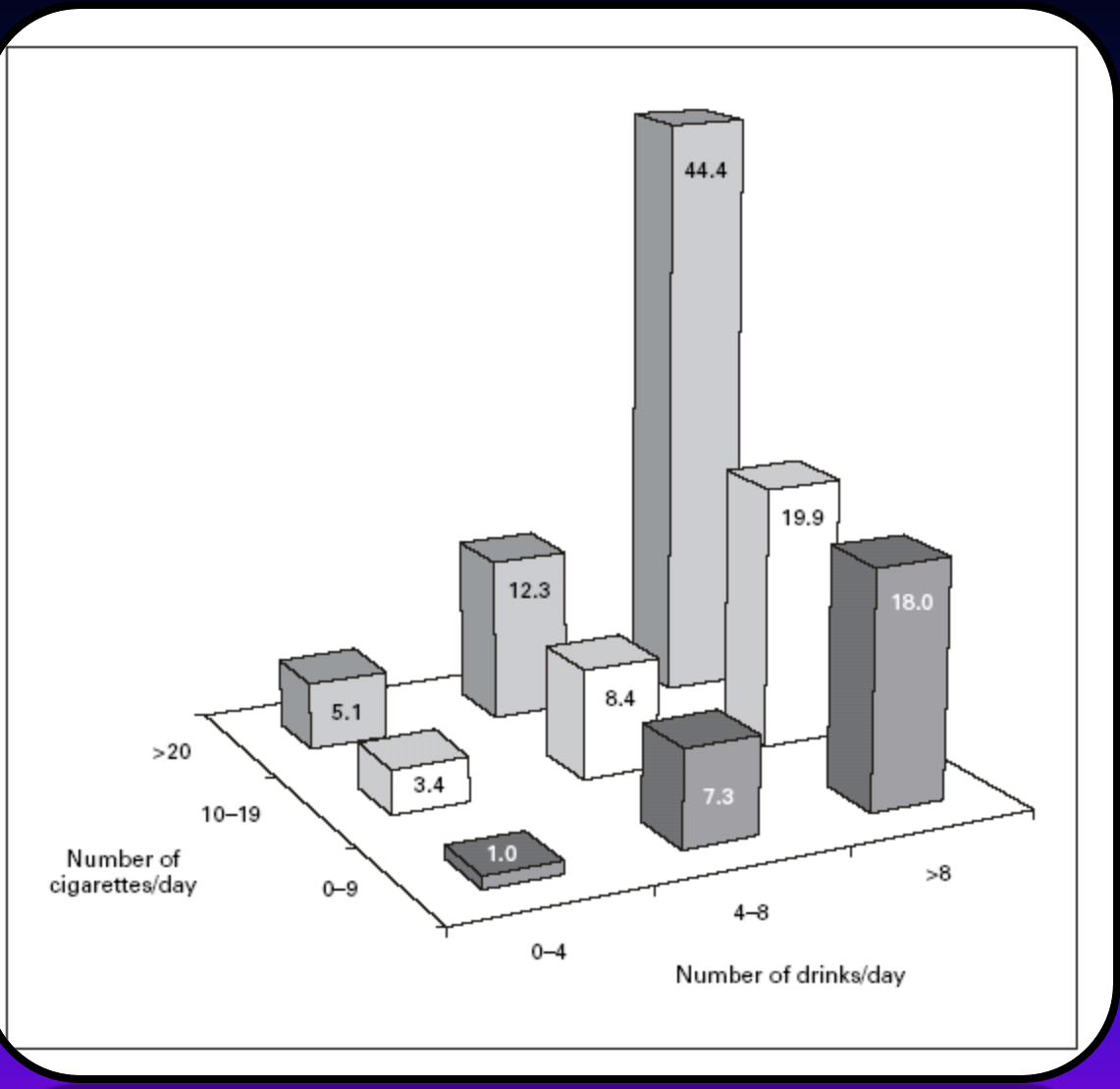
Lachenmeier and Monakhova, J Exp Clin Cancer Res 2011

Effects of acute and chronic consumption on esophageal motility

Parameter	Acute effects (healthy humans)	Chronic effects (alcoholics)
Tonus of the lower esophageal sphincter	Decreased	Increased,normalization during abstinence
Tubullary contractions	Decreased amplitudes and propagation	Increase in higher amplitudes and simultaneous contraction
	Increase in double- peaked and simultaneous contractions	Prolongation of each contraction,no normalization during abstinence
Esophageal clerance	Decreased	Decreased , normalization during abtinence
Number of refluxes	Icreased	No data



Franke et al, Dig Dis 2005



Franke et al, Dig Dis 2005

CARCINOGENESIS
NUTRITIONAL FACTORS

Ethanol and Retinoid Metabolism

vitamin A and Retinoic Acid in the liver
(> catabolism by rthanol – induced CYP2E1)

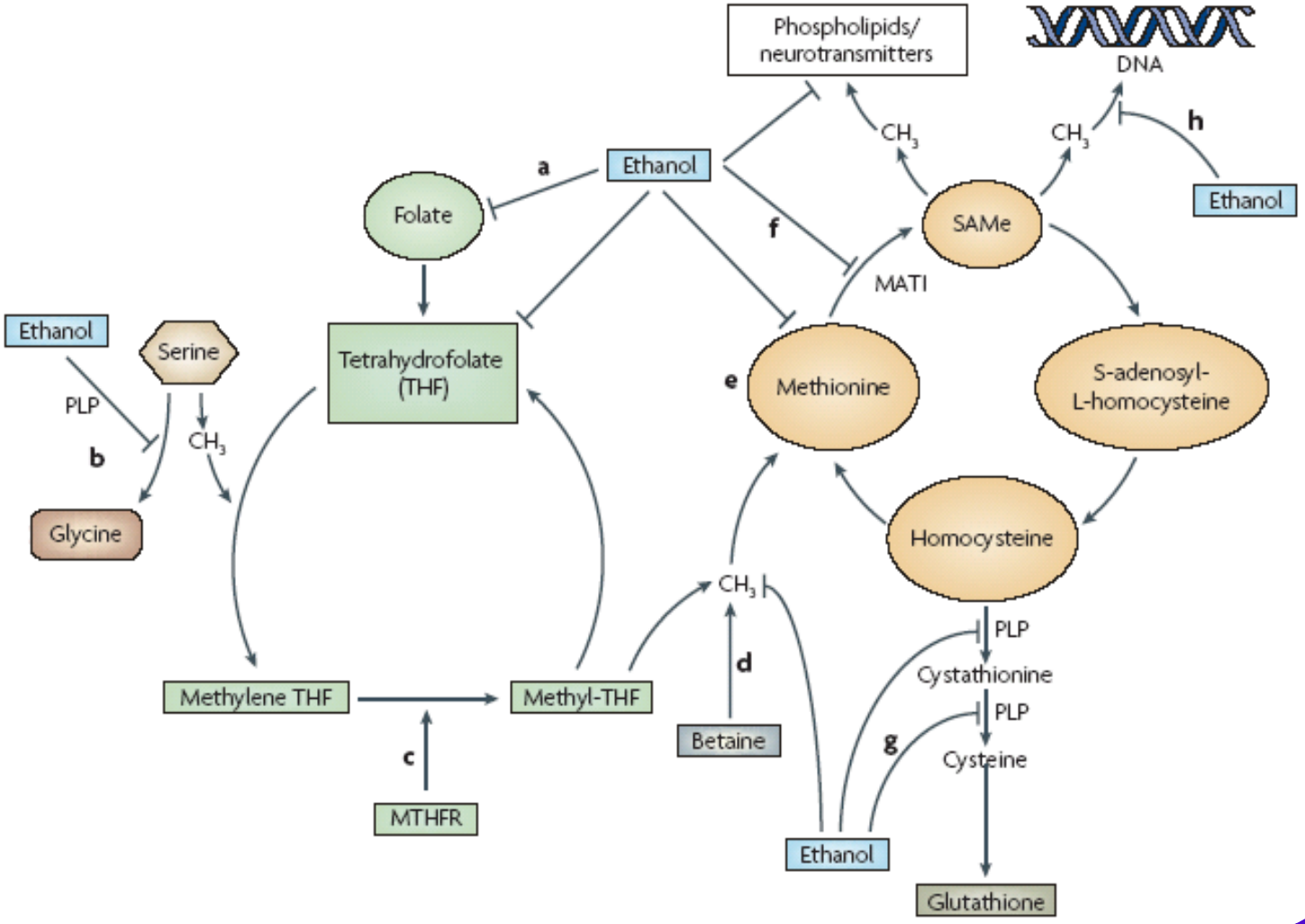
< in mitogen -activaded protein kinase (MAPK)
> in levels of phosphorylated JNK

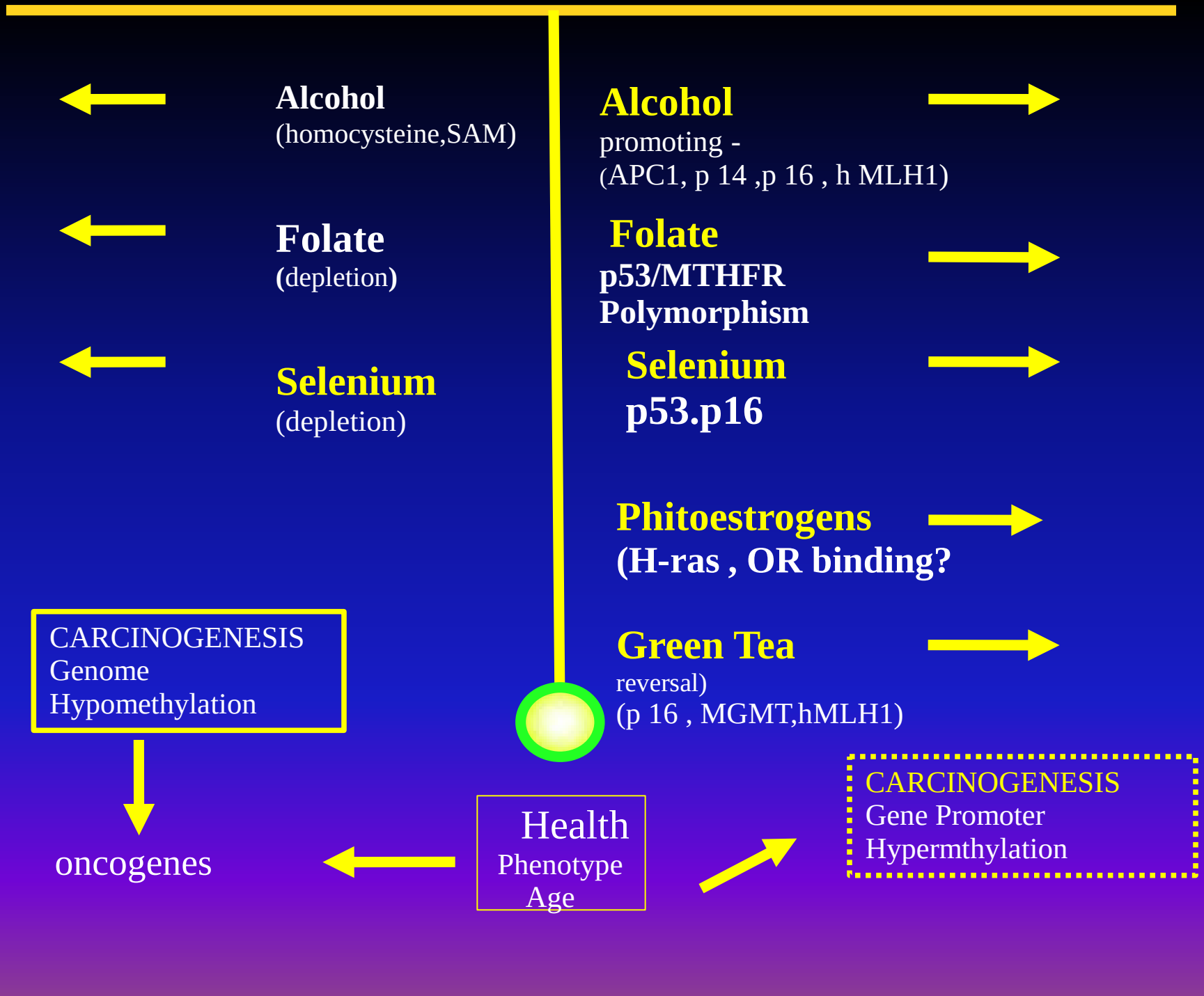
expression AP1 (JUN and FOS) transcripttional complex

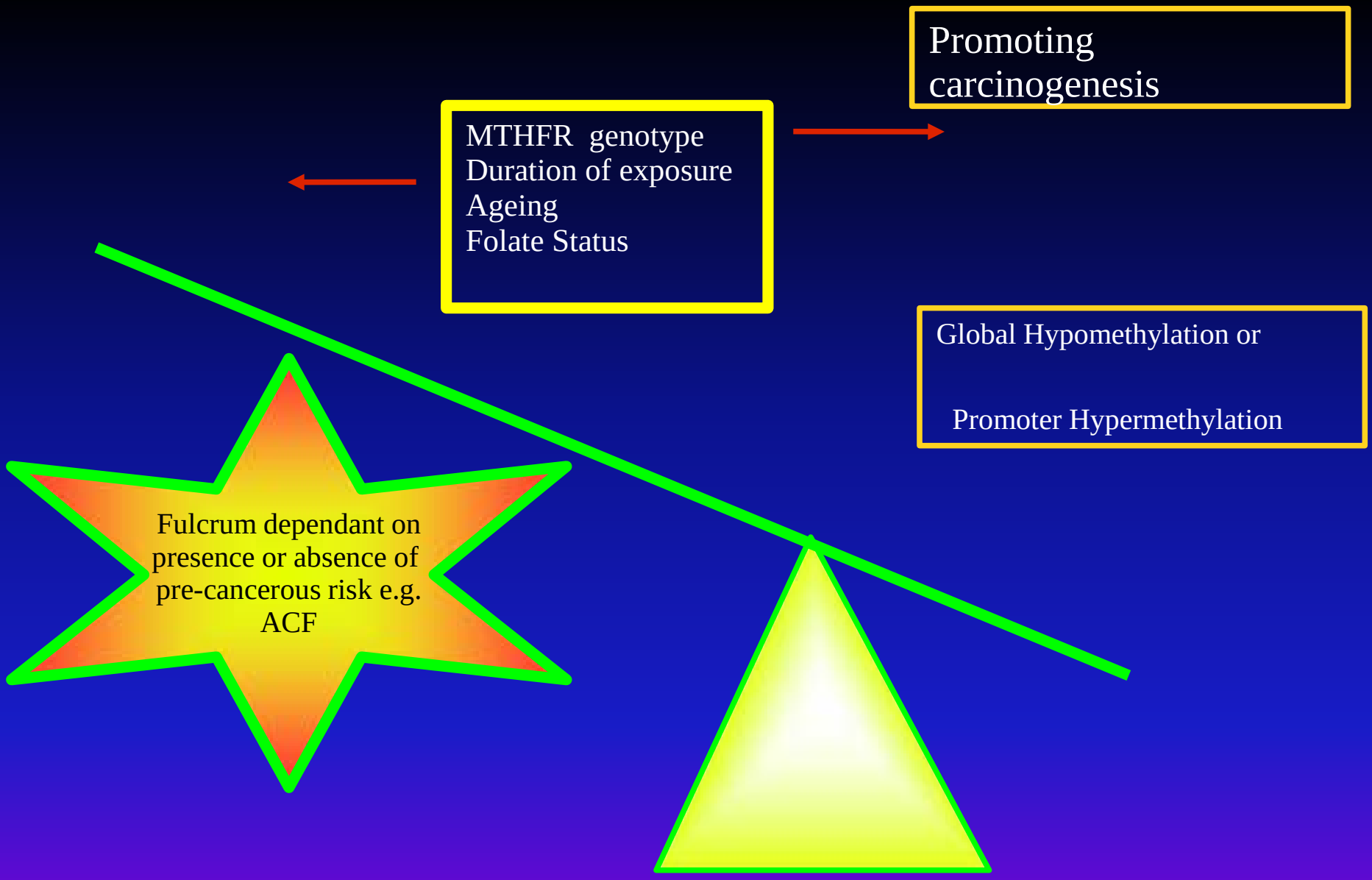
> cell hyperproliferation/ < apoptosis

Liu et al, Gastroenterology 2001; Chung et al Carcinogenesis 2001;
Liu et al , Alcoholism Clin Exp Res 2002

- **Ethanol and Altered Methyl Group Transfer**


Phospholipids/
neurotransmitters
DNA
CH3
CH3
h
Ethanol
a
Ethanol
Folate
f
SAMe
MATI
Ethanol
Serine
Tetrahydrofolate
(THF)
e
Methionine
S-adenosyl-
L-homocysteine
PLP
b
CH3
Glycine
Homocysteine
CH3
PLP
Cystathionine
d
PLP
g
Cysteine
Methylene THF
Methyl-THF
Betaine
c
MTHFR
Ethanol
Glutathione


Alcohol
(homocysteine,SAM)
Folate
(depletion)
Selenium
(depletion)
Alcohol
promoting -
(APC1, p 14 ,p 16 , h MLH1)
Folate
p53/MTHFR
Polymorphism
Selenium
p53.p16
Phitoestrogens
(H-ras , OR binding?
Green Tea
reversal)
(p 16 , MGMT,hMLH1)
CARCINOGENESIS
Genome
Hypomethylation
oncogenes
Health
Phenotype
Age
CARCINOGENESIS
Gene Promoter
Hypermthylation

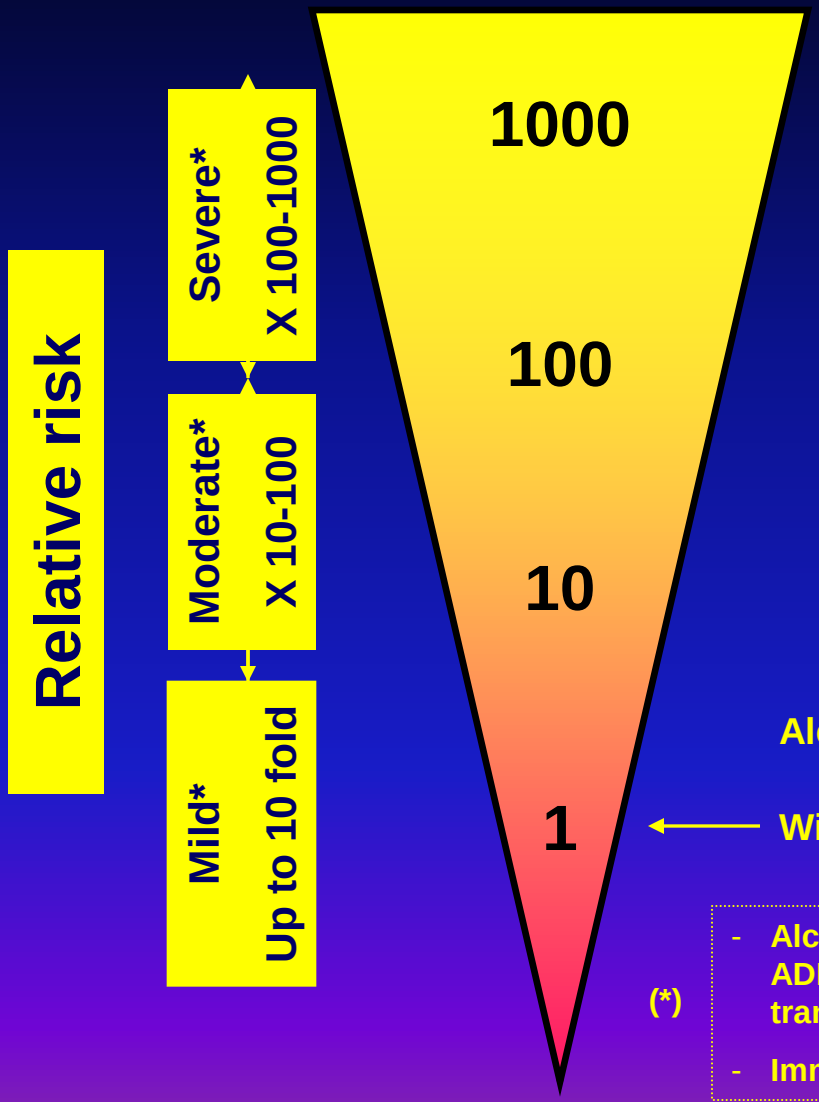


Arasdaradnam et al, Epigenetics 2008

Most alcohol- induced disease increases in a linear fashion as intake increases; oral oesophagus, breast and colon cancer fall into this pattern, with no "safe level"of consumption

Sheron et al, Gut 2008

Strenght of genetic and environmental risk factors of chronic pancreatitis



N291/R122H + smoking

N291/R122H

SPINK1/N34S (homozygous)/alcohol

PRSS1/Smoking/Alcohol

N34S + alcohol

N34S/CFTR

Alcohol 80 g/d

Without detectable risk

(*)

- Alcohol-Metabolizing/Detoxifying Genes (ADH2, ADH3, CYP2E1 polimorphisms, Glutathione S-transferase, ALDH2)
- Immune Response Genes (HLA patterns)

Dufour, Pancreas 2003; Teich, Med Sci Monit 2004; Keim, Scand J Surg 2005; Conwell 2008

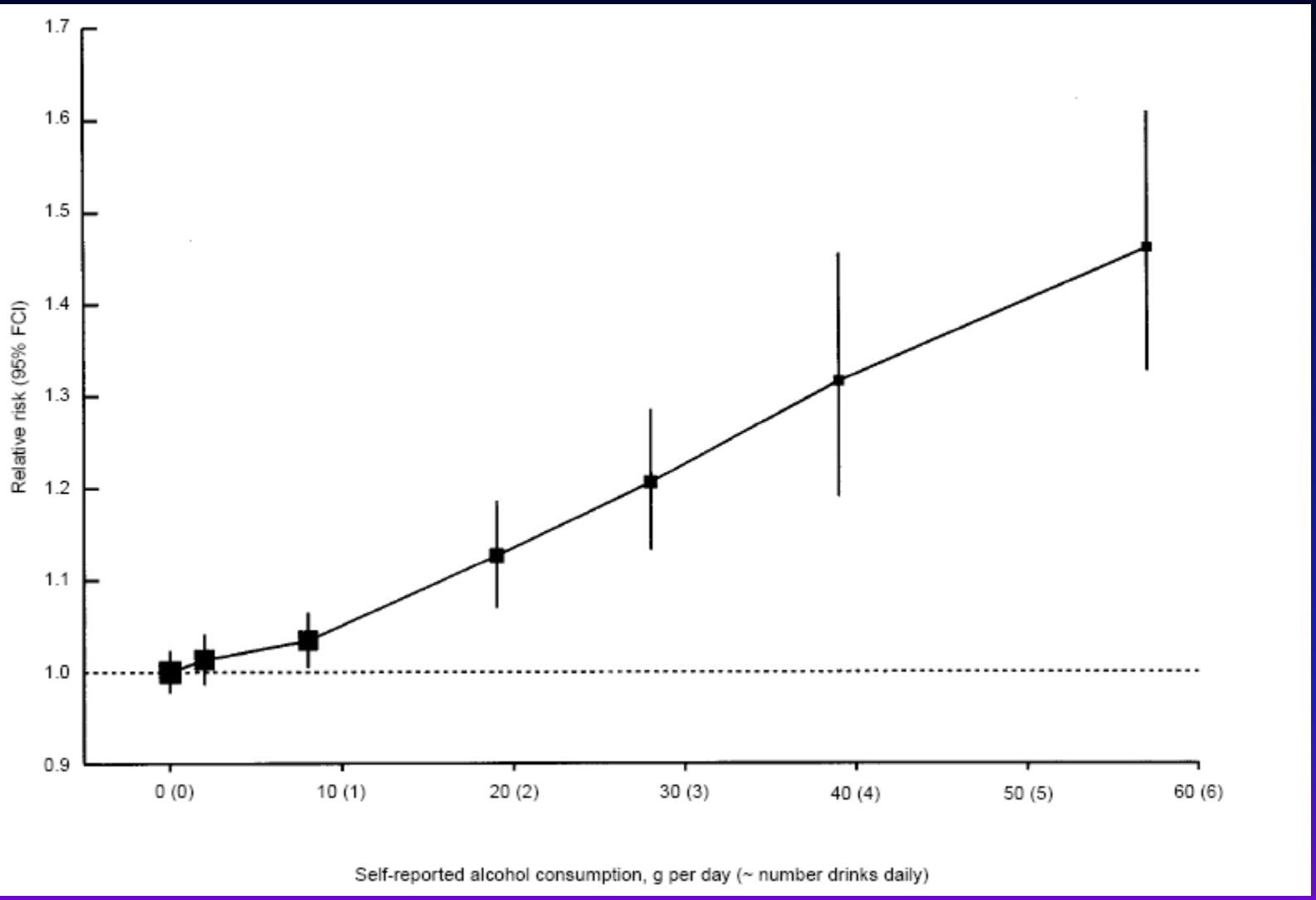
Distribution of pancreatic cancer cases and controls , Ors and corresponding 95% Ci[a] by smoking and drinking habits , Italy 1991 - 2008

	Drinking habits (drinks / week)[b]						Total
	< 7		7- 20		> 21		
	Ca:Co	OR (95%CL)	Ca:Co	OR (95%CL)	Ca:Co	OR (95%CL)	OR(95%CL)
Smoking habits							
Never	47:133	1[c]	54:119	1.68(1.00-2.82)	25:53	2.42(1.20-4.86)	1[c]
Former	19:40	1.09(0.53-2.21)	19:51	1.52(0.74-3.12)	41:76	2.67(1.38-5.17)	1.09(0.73-1.63
Current (cigarettes/days)							
<20	12:24	1.65(0.71-3.85)	17:27	1.76(0.81-3.82)	22;24	4.15(1.87-8.18)	1.53(0.97-2.41
>20	11:8	3.33(1.08-10.23)	9:8	3.78(1.15-12.36)	21:27	4.29(1.93-9.56)	2.38(1.37-4.1
Total	1[c]			1.46(0.98-2.17)		2.53(1.58-4.07)	

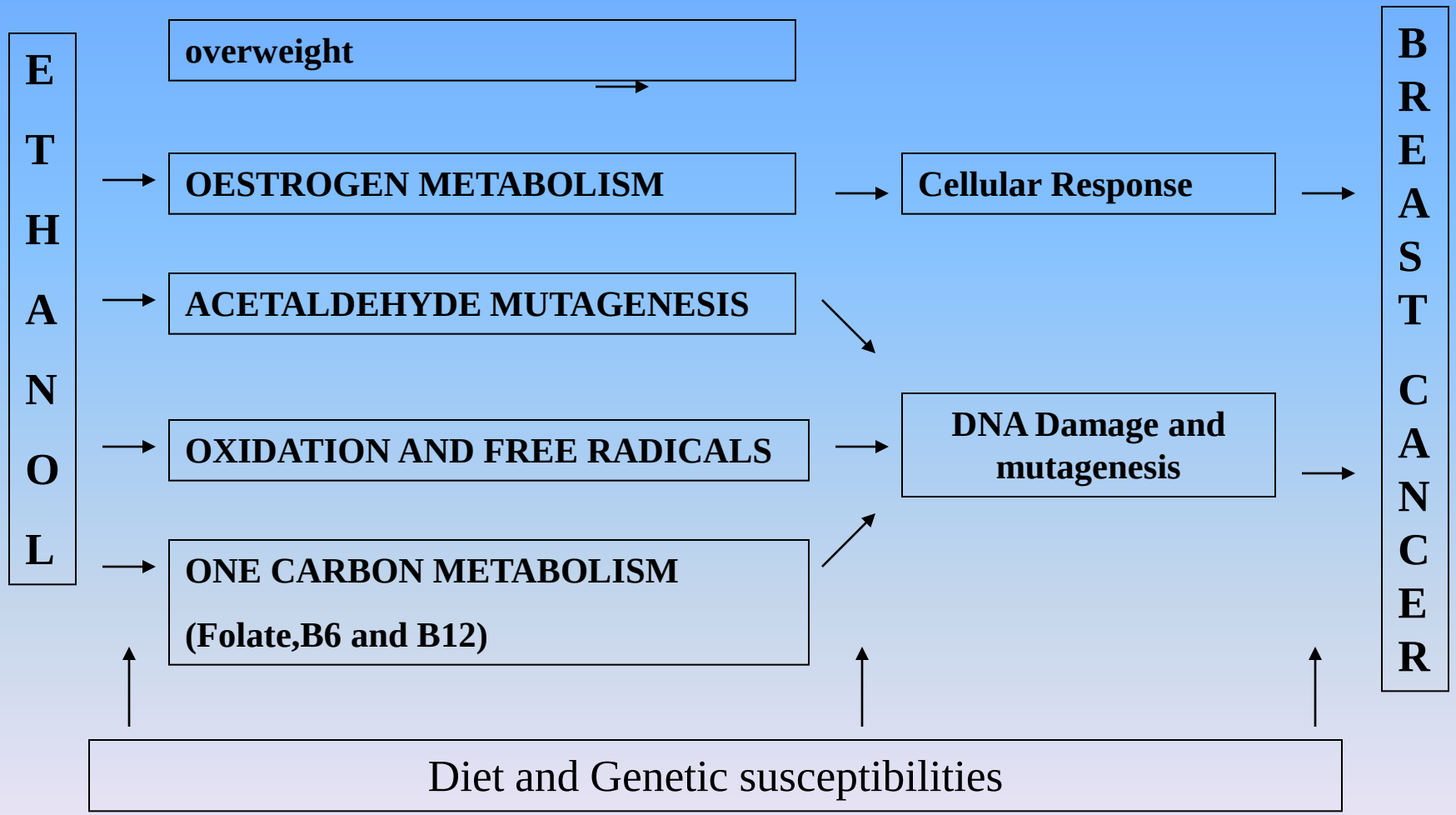
[a] Estimates from conditional logistic regression conditioned on cente , sex and age , and adjusted for year of interview ,education,historyof diabetes mellitus and body max index

[b] Former drinkers excluded

[c] **R**eference category

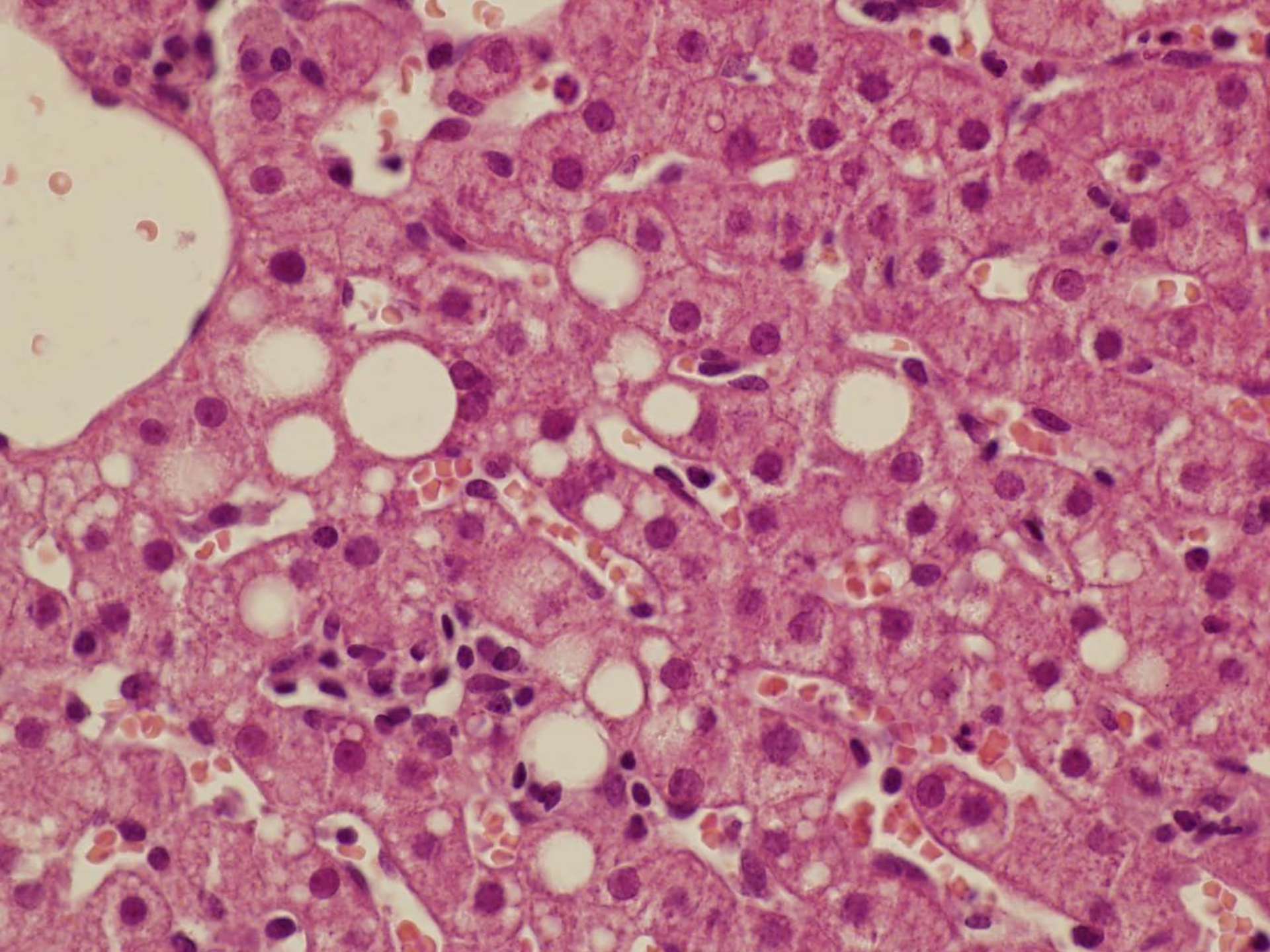


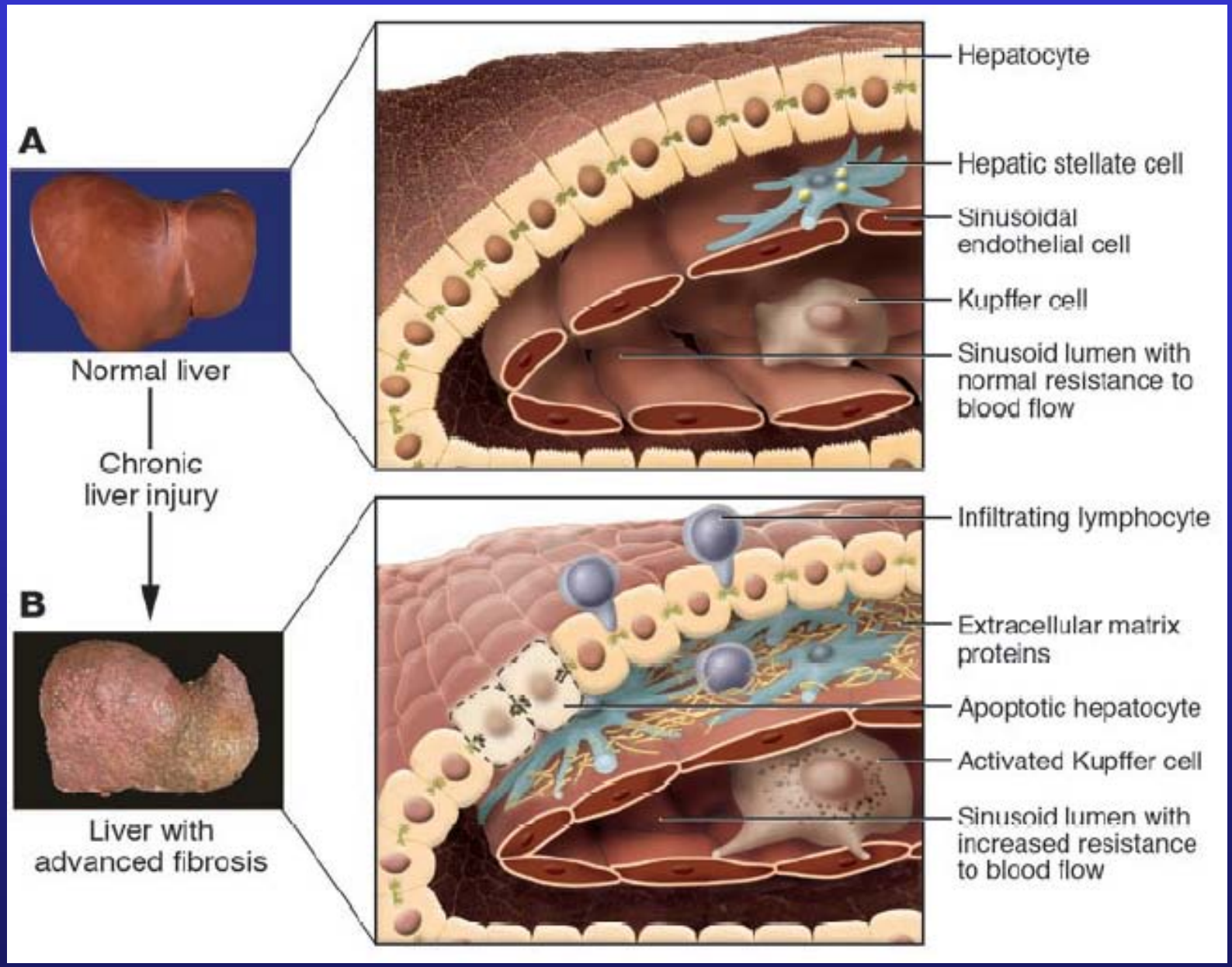
Br J of Cancer, 2002

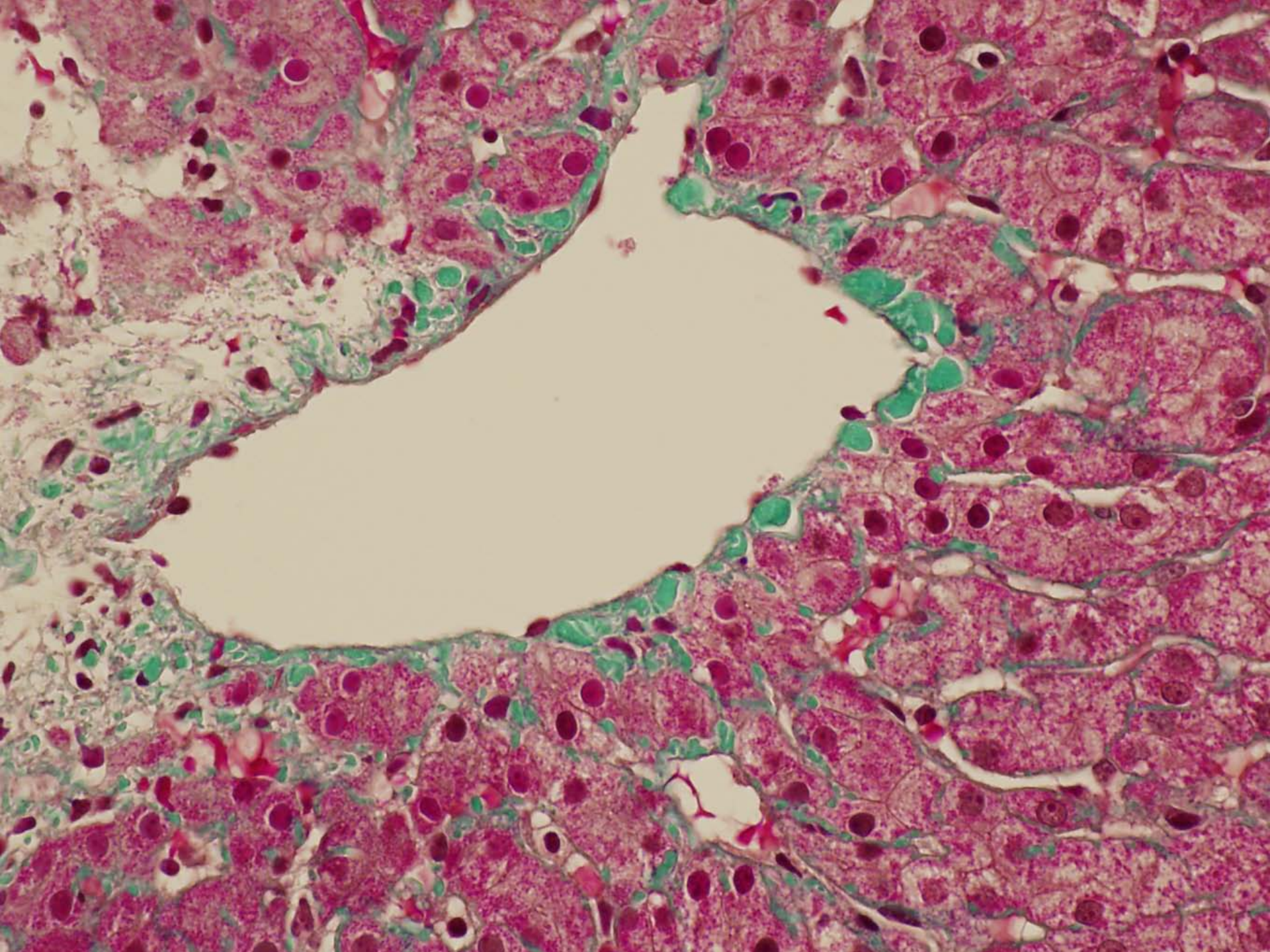

ETHANOL
overweight
OESTROGEN METABOLISM
ACETALDEHYDE MUTAGENESIS
OXIDATION AND FREE RADICALS
ONE CARBON METABOLISM
(Folate,B6 and B12)
Cellular Response
DNA Damage and mutagenesis
BREAST CANCER
Diet and Genetic susceptibilities

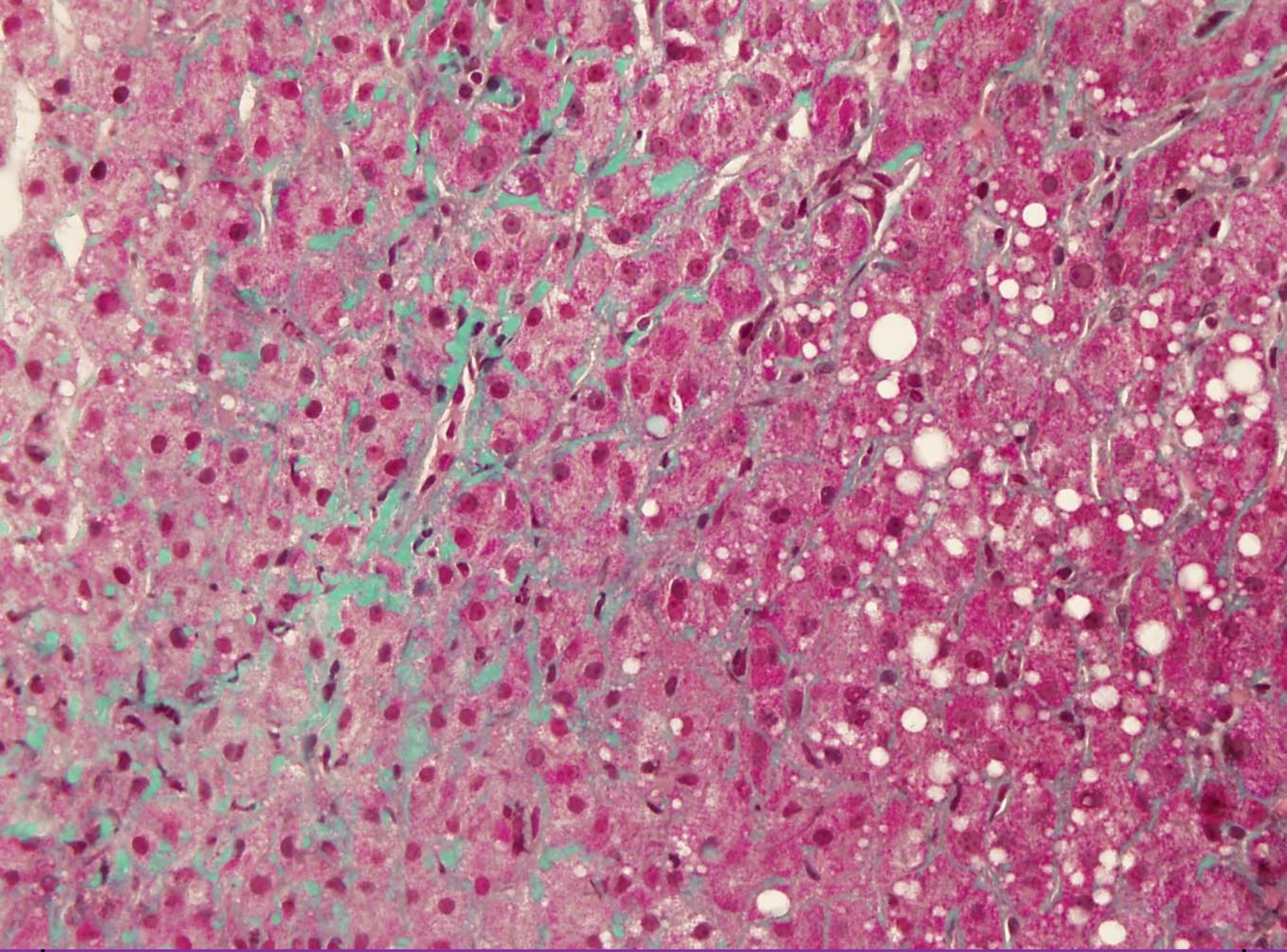
… women who do not drink should not start,
and those who do drink should do so in moderation ,
which is generally recognized to be about a drink per day.
Alcohol intake is one of the few modifiable breast cancer risk factors yet identified

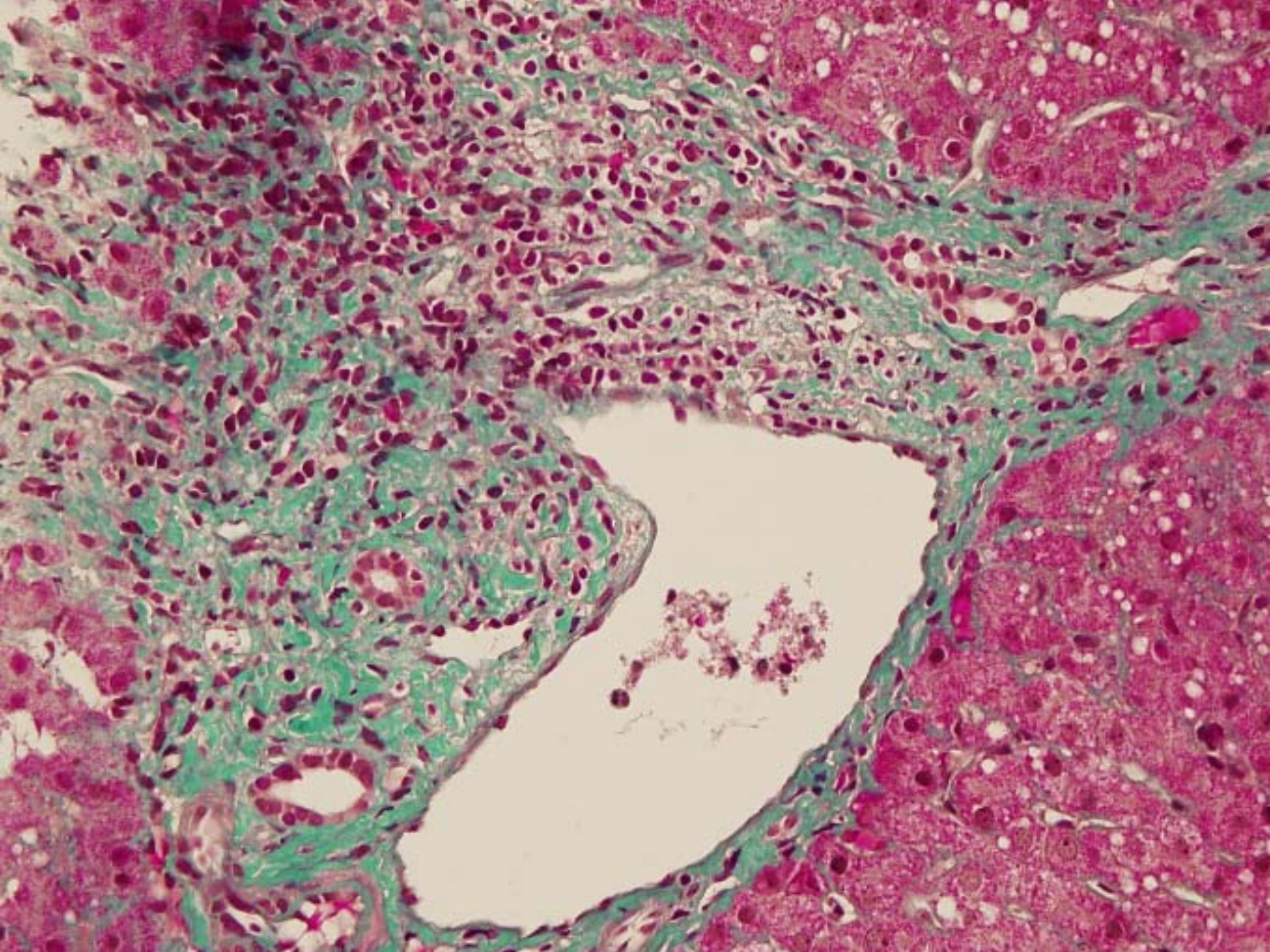
Singletary and Gapstur, JAMA 2001



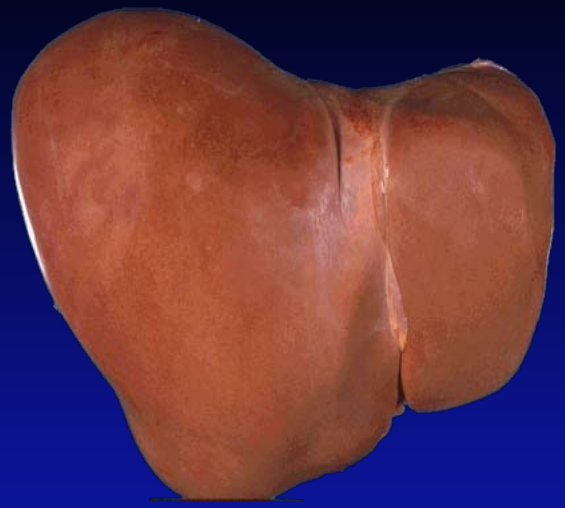

A
Normal liver
Chronic liver injury
B
Liver with advanced fibrosis
Hepatocyte
Hepatic stellate cell
Sinusoidal endothelial cell
Kupffer cell
Sinusoid lumen with normal resistance to blood flow
Infiltrating lymphocyte
Extracellular matrix proteins
Apoptotic hepatocyte
Activated Kupffer cell
Sinusoid lumen with increased resistance to blood flow







gr/die ⟶



12-20 women, 25-80 men

O'Shea, 2010

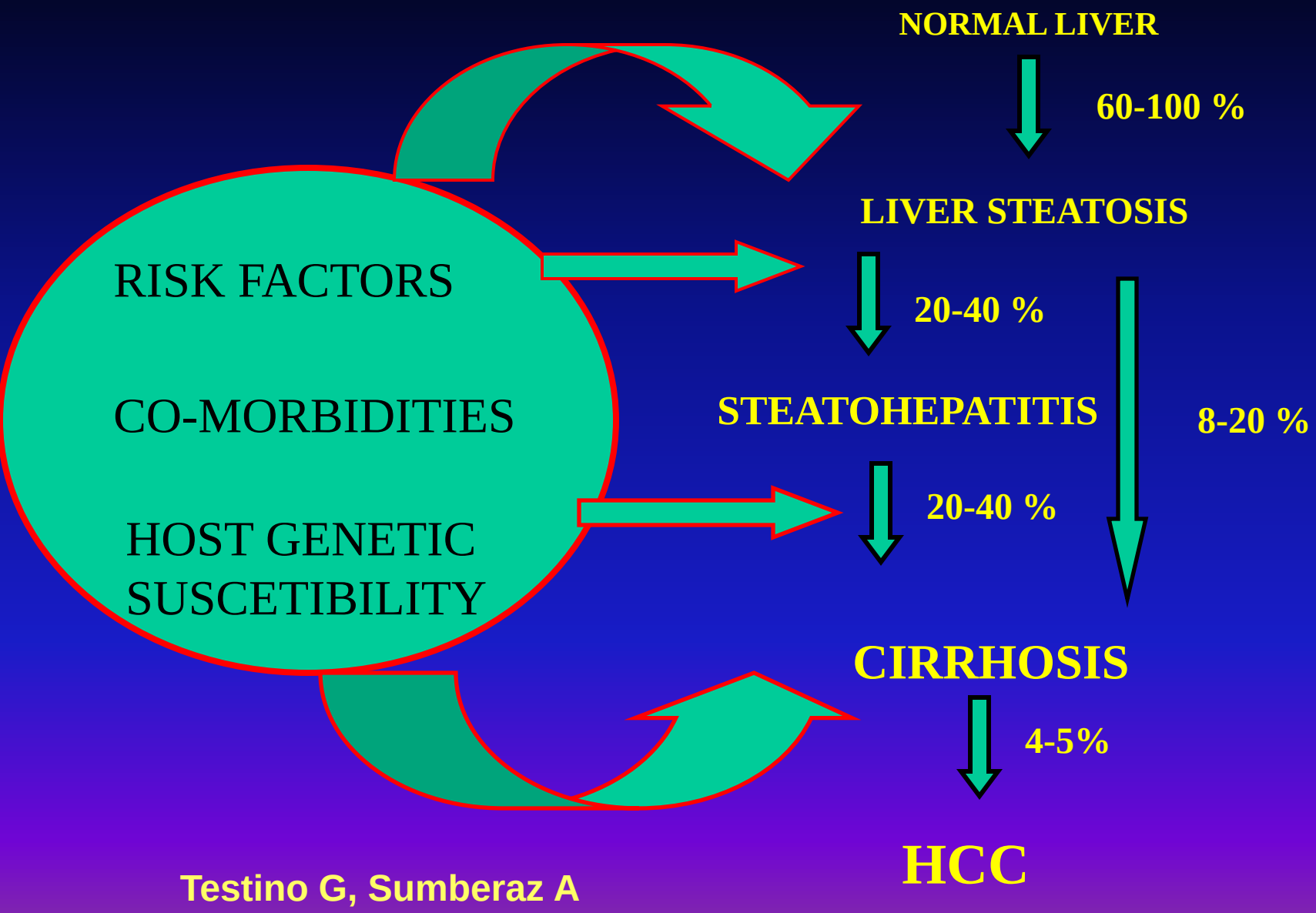
Daily Alcohol Intake > 30 g/day

Odds of developing cirrhosis or lesser degrees of liver disease

cirrhosis: 13.7; lesser degrees: 23.6

Bellentani et al, 1997

CHRONIC ALCOHOL DRINKER

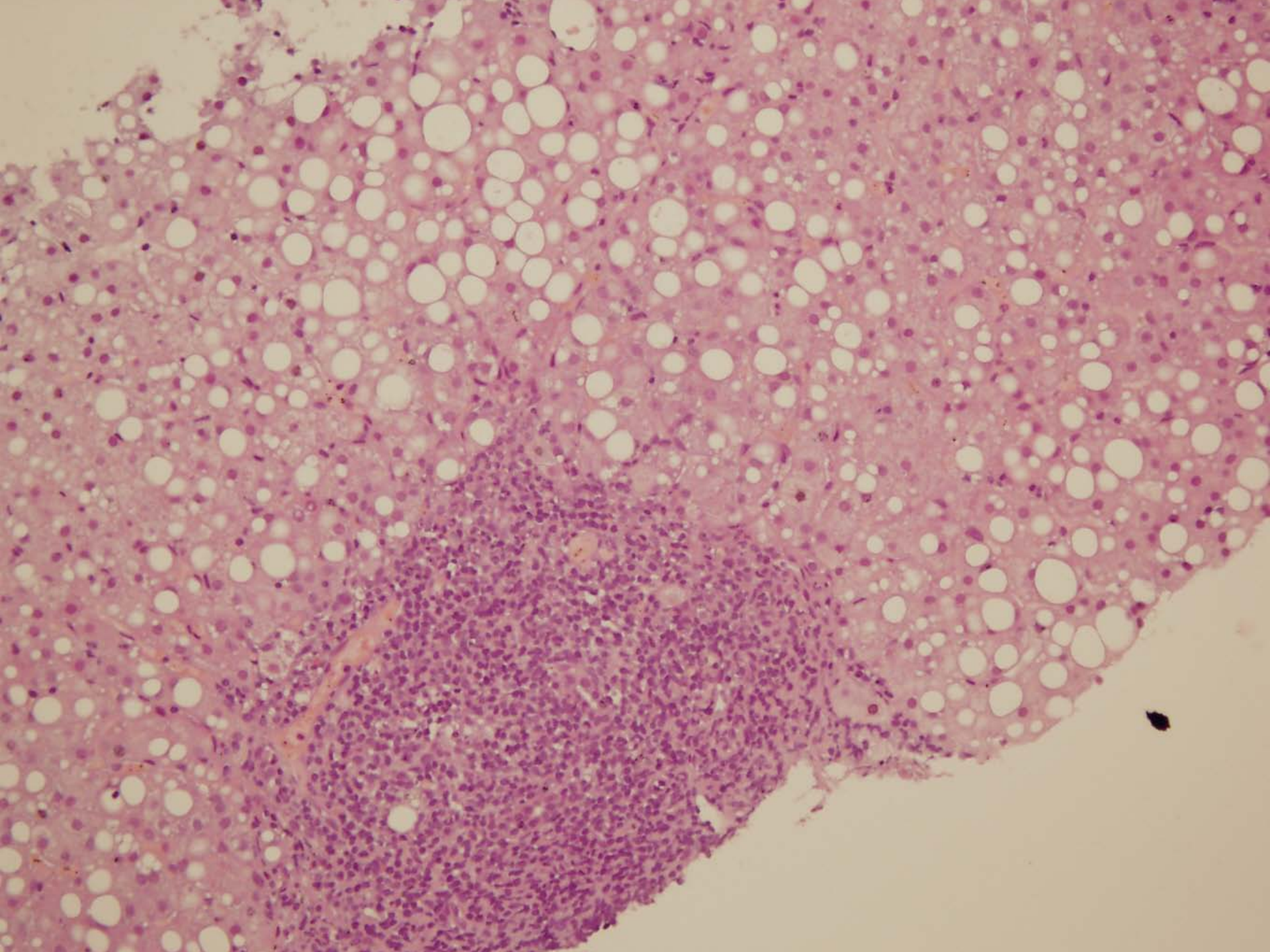


Testino G, Sumberaz A
Hepatogastroenterol, 2008

Mechanisms by which alcohol worsens virus induced liver disease

Mechanism	HCV	HBV
Enhanced viral replication	Debated [9,15–28]	Demonstrated [42]
Increased oxidative stress	Demonstrated [29–31]	Not demonstrated
Impaired immune response	Demonstrated [32,33]	Not demonstrated
Induction of steatosis	Demonstrated [34]	Not demonstrated
Hepatocyte apoptosis	Demonstrated [37]	Not demonstrated
Iron overload	Demonstrated [35,36]	Not demonstrated
Decreased antiviral therapy response	Demonstrated [38–40]	Not demonstrated

Numbers of corresponding references are reported in square brackets.



Alcol – HCV : Epidemiologia

8-55.5 % dei pazienti affetti da epatite cronica alcolica sono positivi per anticorpi anti-HCV

(Sata J Viral Hepat 1996; Kwon 2000 J Gastroenterol Hepatol; Ashwani J Clin Gastroenterol 2007)

HCV-RNA positivo 4-82 % (Befrits Scand J Gastroenterol 1995)

HCV –RNA POSITIVO / EPATOPATIA ALCOLICA : 40%

(Testino G et al, 2009)

HCV REPLICATION AND ALCOHOL

Increase in release of HCV RNA from alcohol – damaged hepatocytes

Direct stimulatory effect of alcohol on HCV replication

Endotoxin activates NF – KB nuclear transcription

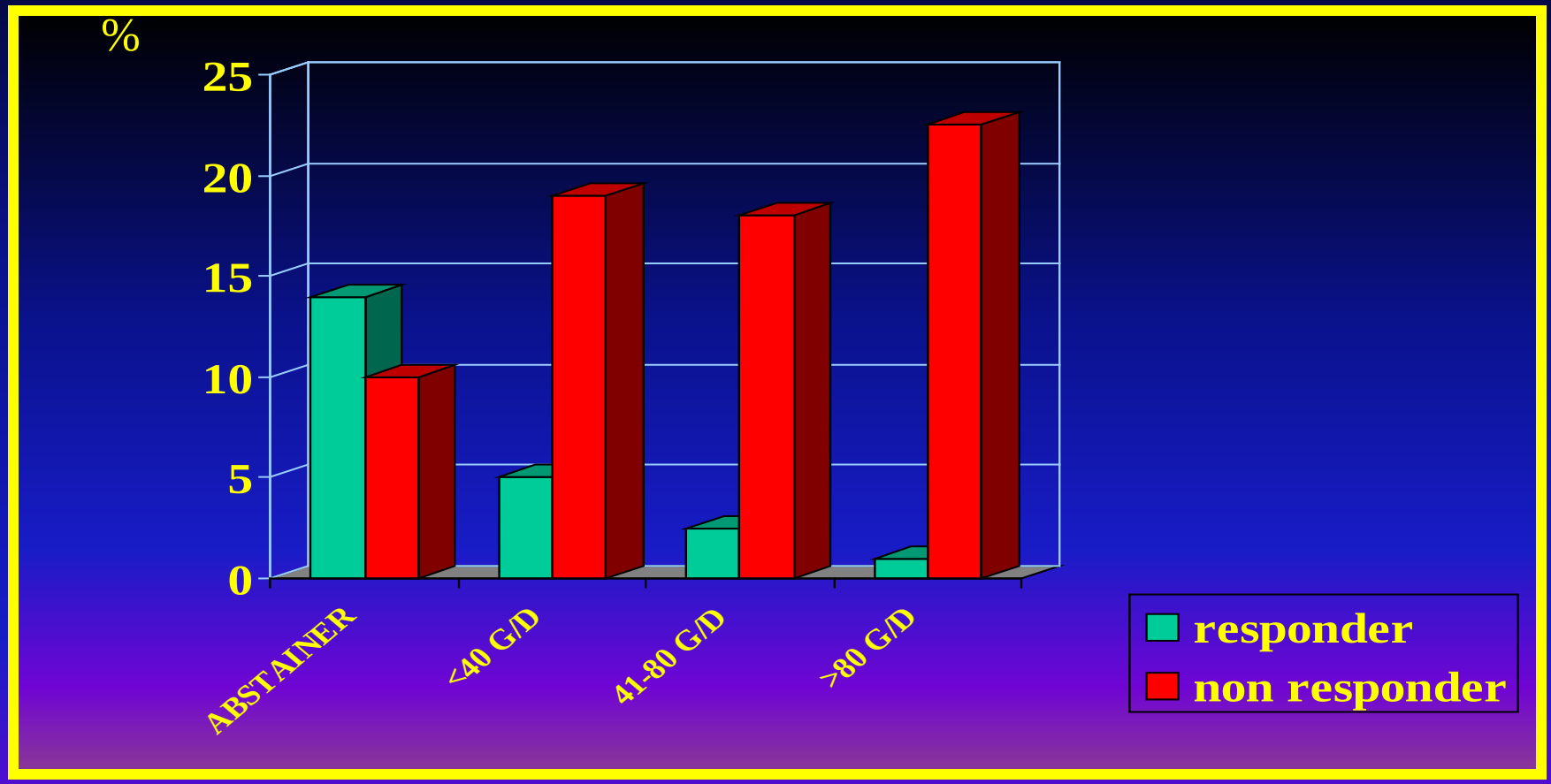
Upregulate cyclooxygenase-2 expression

Modulation of innate and acquired immune responses to HCV

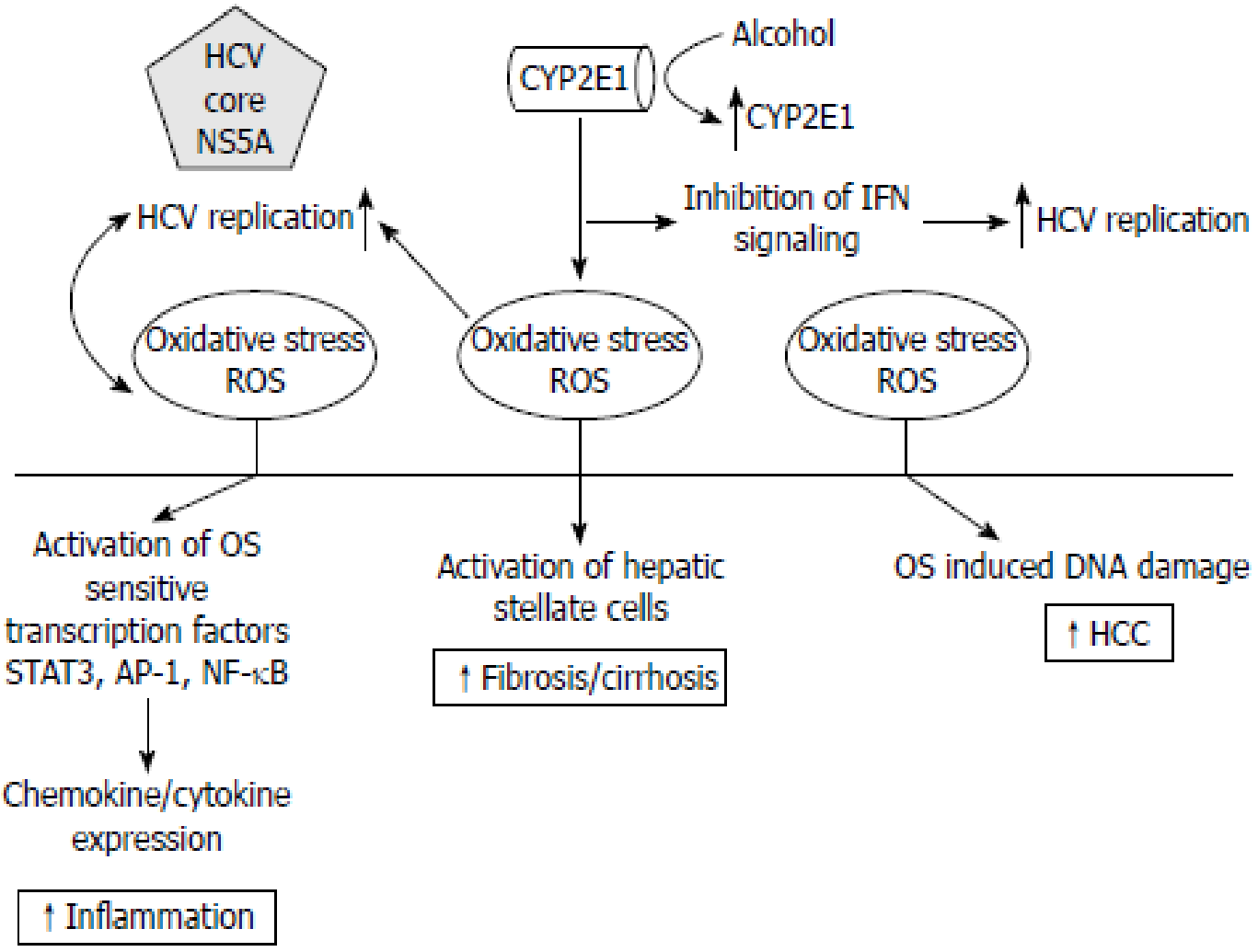
Synergistic induction of oxidative stress

Plumlee et al, Virology Journal 2005
Dey and Cederbaum, Hepatology 2006
Ashwani et al, J Clin Gastroenterol 2007
Reuben A, Current Op Gastroent 2008
McCartney and Beard, WJG 2010

Percentage of chronic hepatitis patients responding to interferon as a function of ethanol use

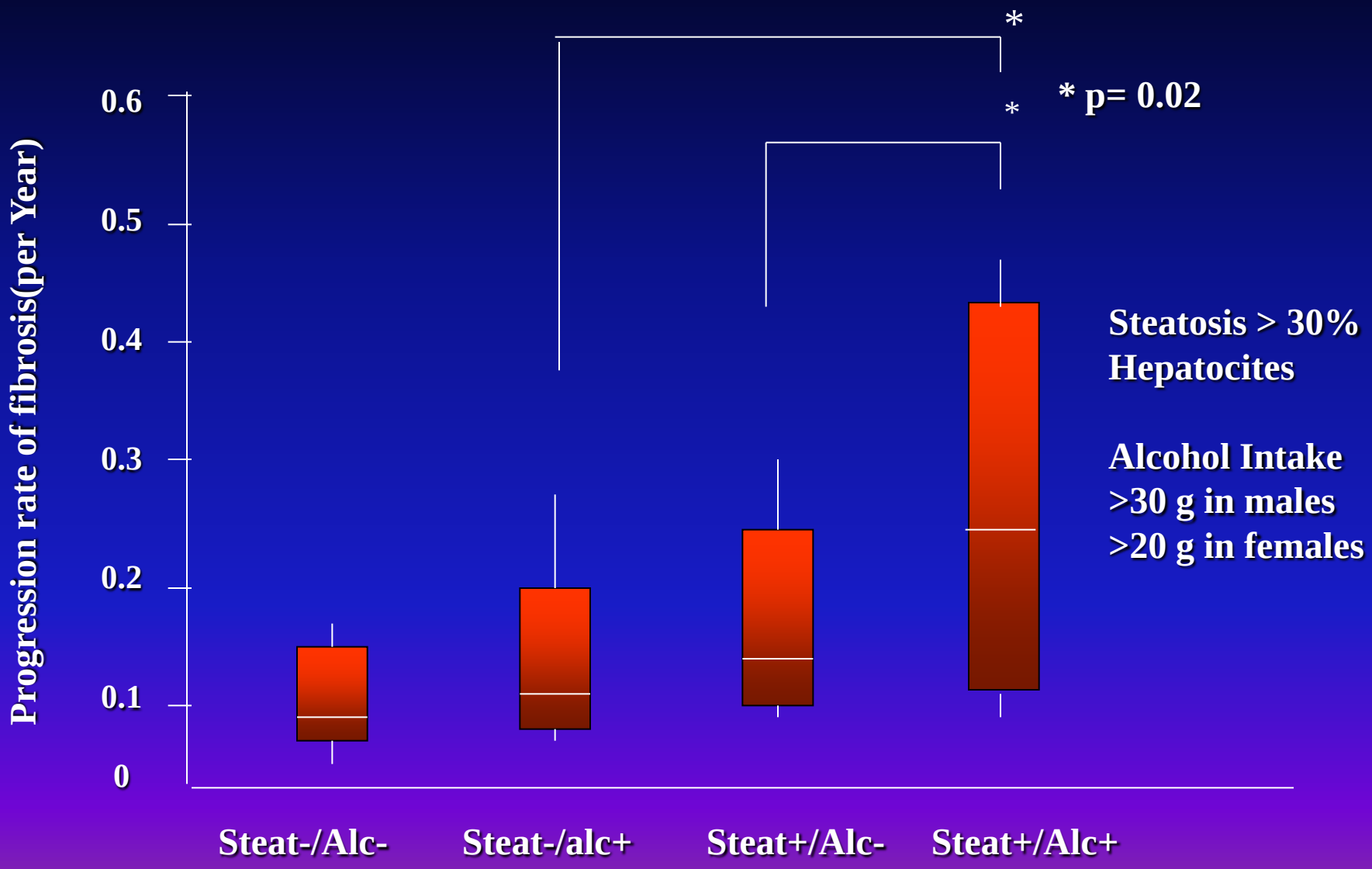


G. Testino, 2006



McCartney and Beard, WJG 2010

Effect of the Interaction Between Steatosis and Alcohol Intake on Liver Fibrosis Progression in Chronic Hepatitis C.



Serfaty L.: Am J Gastroenterology 2002

Histological grading of necroinflammation, staging of fibrosis, and risk of liver cirrhosis in patients with hepatitis C virus (HCV) infection and alcohol consumption

Parameter	Group A (N = 14)	Group B (N = 40)	Group C (N = 42)	Group D (N = 24)
Necroinflammation	1,8 ± 0,7	3,4 ± 1,6[a]	2,9 ± 1,3[a]	3,1 ± 1,1[a]
Fibrosis	2,9 ± 1,0	2,9 ± 0,9	3,4 ± 1,0[a]	3,6 ± 0,7[a]
Cirrhosis, n (%)	5 (8,4)	10 (16,9)[b]	28 (47,5)[b]	16 (27,2)[b]

Group A, alcoholic liver disease; Group B, HCV only; Group C, HCV + <80 g/day of alcohol; Group D, HCV+ > 80 g/Day of alcohol

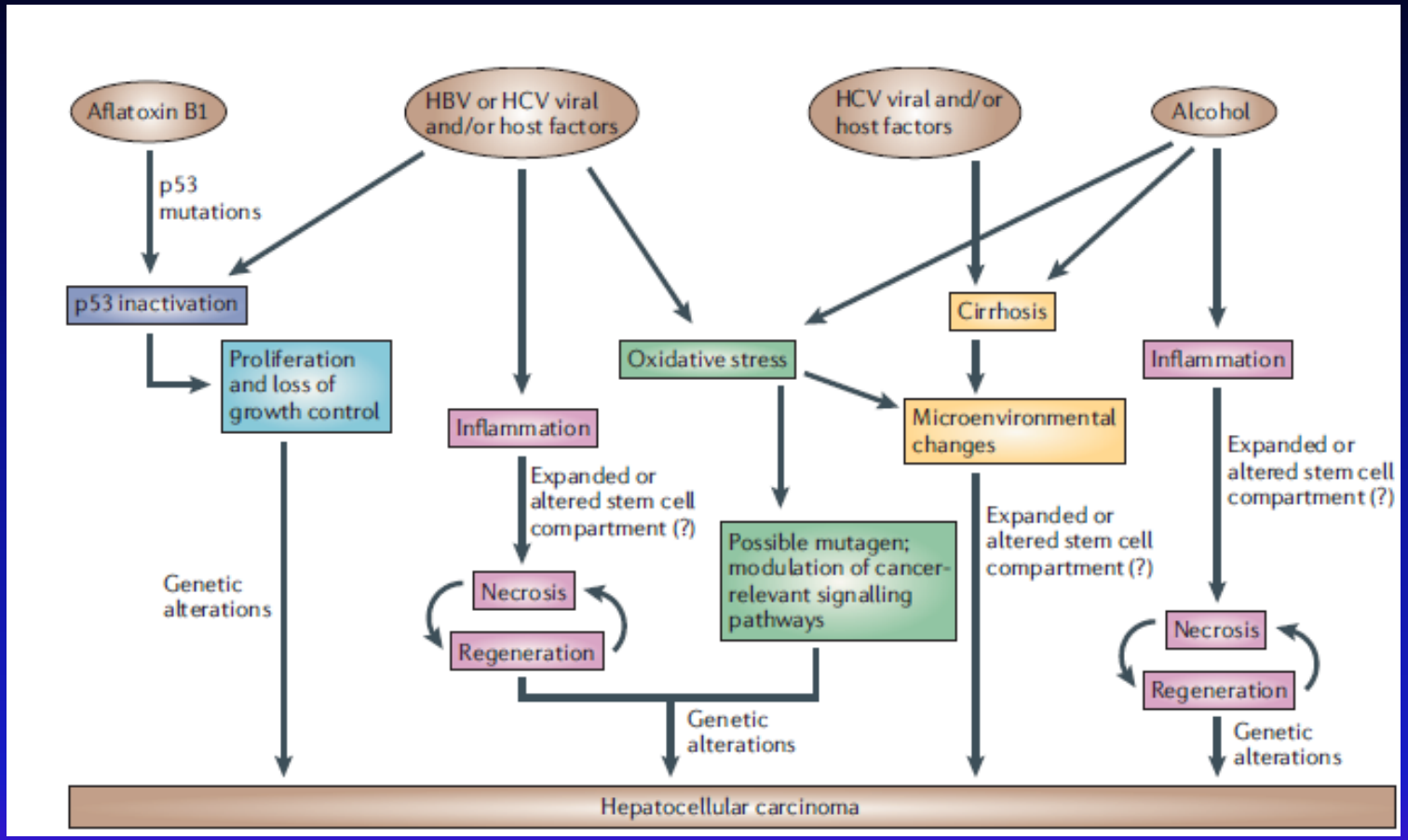
[a] Significantly different by Student's *t*-test. Necroinflammation: Groups B, C and D vs Group A, P < 0.001; B vs C, D, ns; C vs D, ns. Fibrosis: Group A vs Group B, ns; A or B vs C, P<0,01; A, B vs D, P < 0,01; C vs D, ns.

[b] Significantly different by X^2 test. Risk of cirrhosis: Group A vs Group B, C or D, P < 0,001; B vs C or D, P < 0,01. ns, not significant.

Alcohol and Alcoholism, 2006, 35: 286

Variables	Progressive fibrosis ($n = 44$)	Non-progressive fibrosis ($n = 34$)	
Sex (M/F)	28/16	16/18	
Transmission route (IDU/BT/SEX/HCW/unknown)	16/12/3/2/1	16/10/1/2/5	
Genotype (1/2/3/unknown)	19/11/12/2	18/4/10/2	
Age at initial biopsy (years)	36.8 (27.1–44.3)	34.0 (28.1–43.5)	
Age at follow-up biopsy (years)	43.7 (38.5–50.6)	39.0 (35.4–46.0)	
Time between first and follow-up biopsy (years)	6.5(3.9–10.6)	5.5 (2.5–7.7)	
Total amount of alcohol (g ethanol)	15 400 (3300–36 600)	3900 (900–14 500)	$P = 0.007$*
Alcohol per day (g ethanol)	5.7 (2.0–16.0)	2.6 (1.1–7.7)	$P = 0.03$*
Drinking frequency (drinking days/year)	34.5 (21.0–75.0)	8.2 (6.0–25.0)	$P = 0.006$*
Quantity consumed on each occasion (drinks/occasion)	4.0 (3.0–8.0)	3.0 (2.0–6.0)	

Westin et al, J Viral Hep 2002

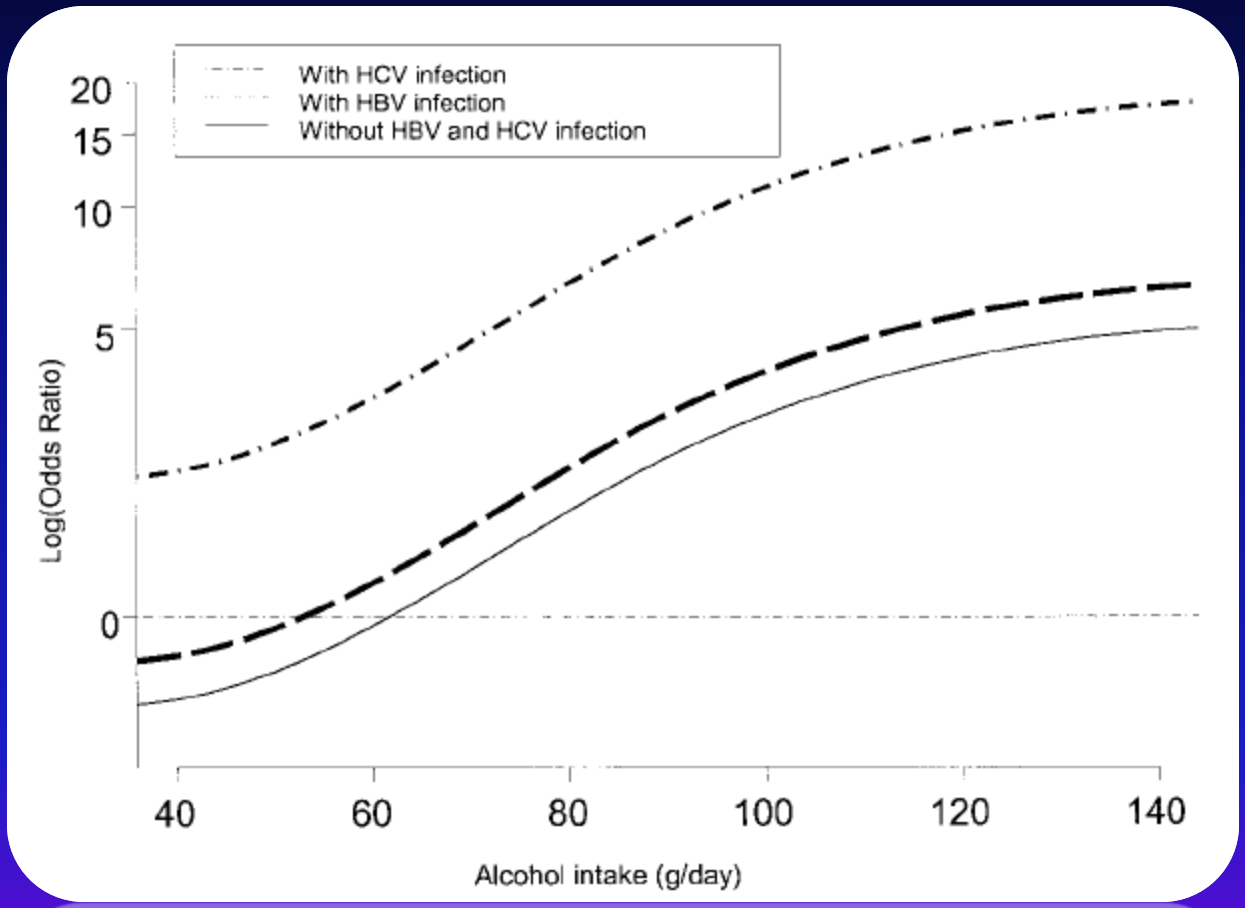


Farazi et al, Nature 2006

Distribution of cases and controls and odds ratios and their 95% confidence intervals according to alcohol intake and the presence of HCV and HBV infection

HCV or HBV infection	Alcohol intake (g/day) 0 - 60			> 60		
	Cases /control s (no)	OR	95%CI	Cases / control (no)	OR	95%CI
Neither	30 / 412	Reference		157/ 335	7.0	4.5, 11.1
HCV infection	95/ 21	55.0	29.9, 10.0	76/ 11	109	50.9, 233.0
HBV infection	41 / 27	22.8	12.1, 42.8	51/ 17	48.6	24.1, 98.0

Donato et al , 2002

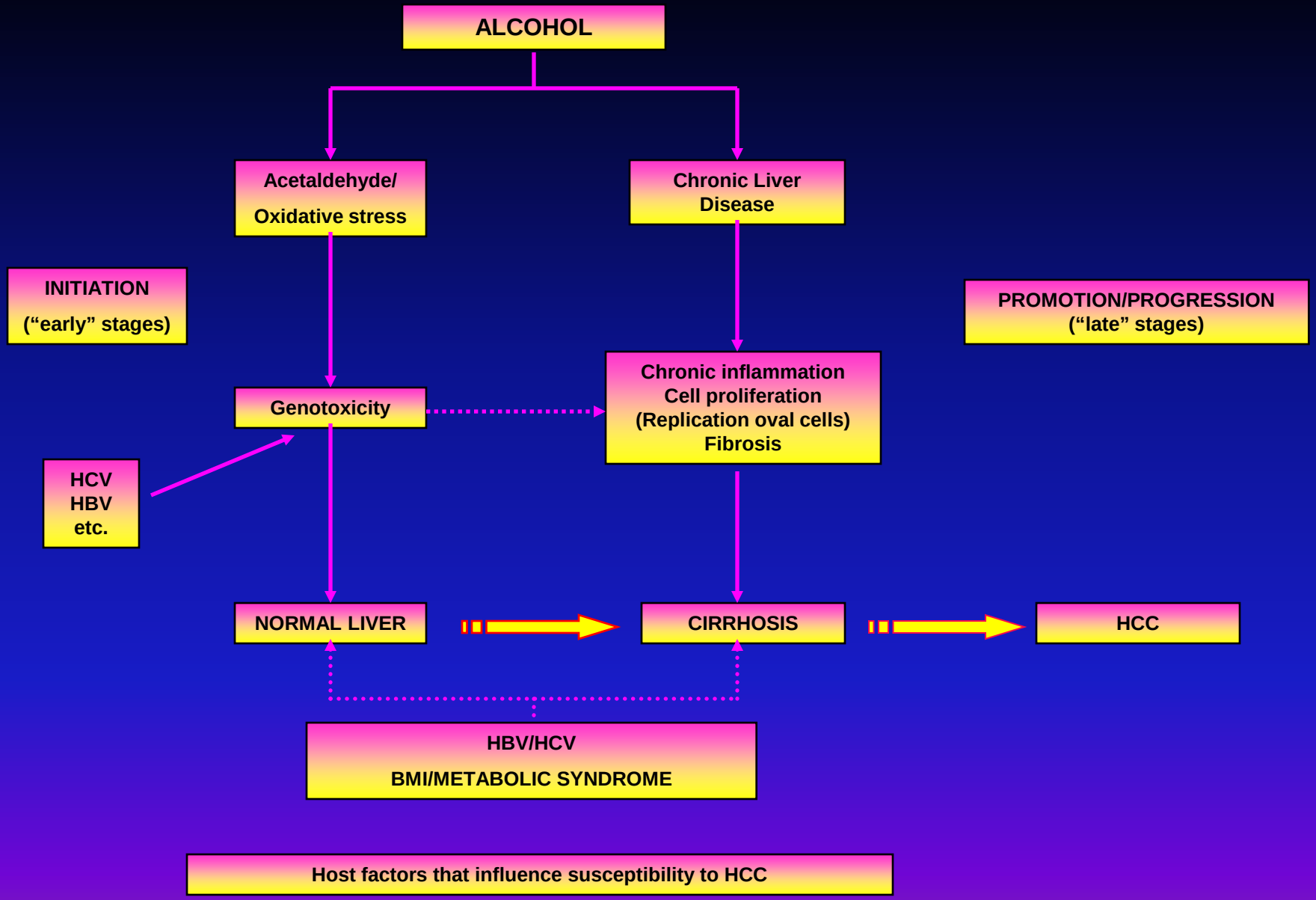


Donato et al., 2002

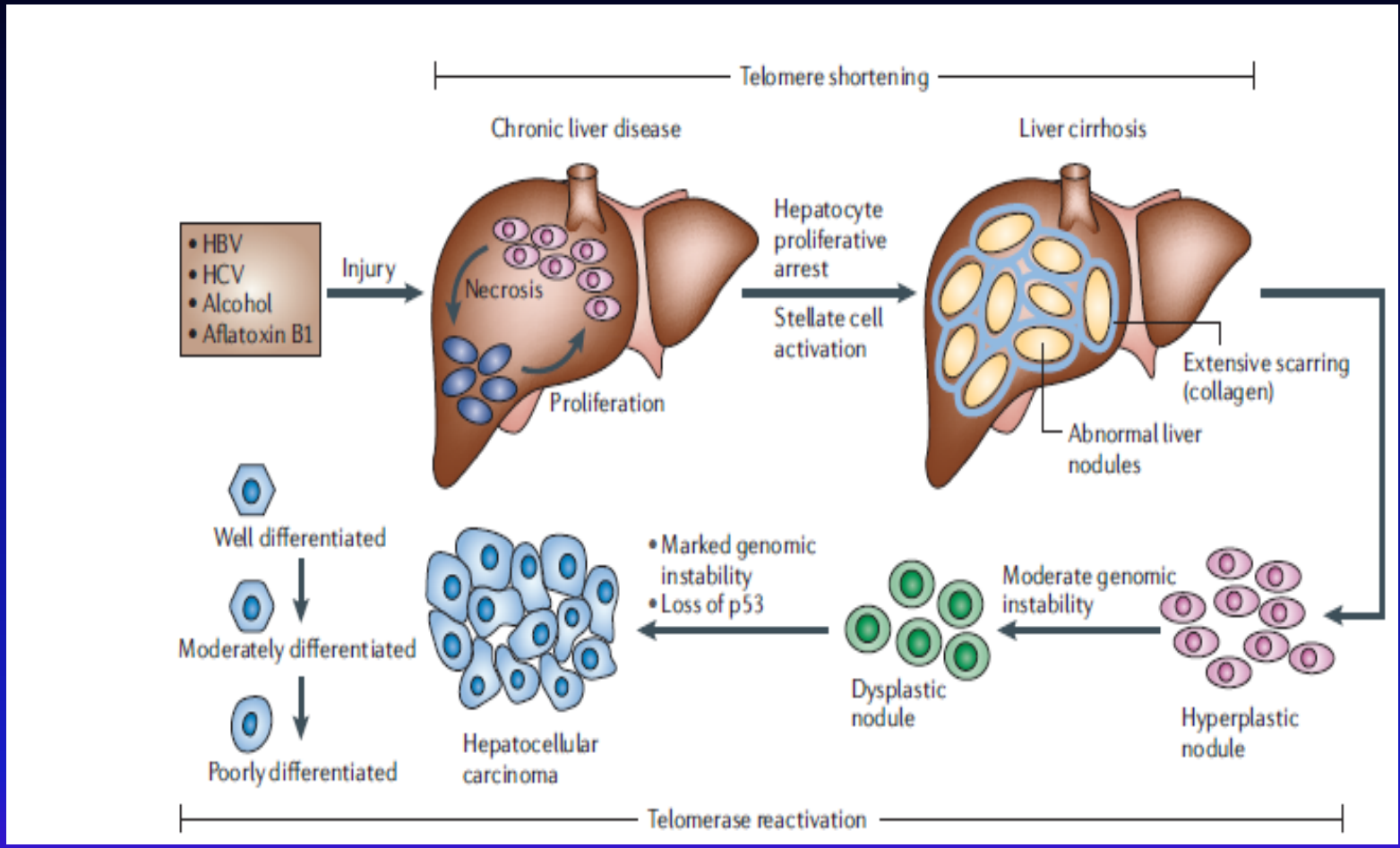
Interaction of Heavy Alcohol Consumption (> 80 mL ethanol/d) With Chronic Hepatitis Virus Infection (HBV or HCV) and Diabetes Mellitus: Logistic Regression Analysis With Adjusted OR

Interaction Variables		β Coefficient (± SE)	P	OR (95% CI)	S (95% CI)*
Virus	Alcohol				
Negative	Negative			1	
Positive	Negative	2.9 (0.79)	0.0001	19.1 (4.1-89.1)	
Negative	Positive	0.87 (0.32)	0.006	2.4 (1.3-4.4)	
Positive	Positive	3.9 (1.04)	0.0001	53.9 (7.0-415.7)	2.7 (1.1-5.2)
Diabetes	Alcohol				
Negative	Negative			1	
Positive	Negative	0.87 (0.33)	0.008	2.4 (1.3-4.5)	
Negative	Positive	0.95 (0.34)	0.004	2.6 (1.4-4.9)	
Positive	Positive	2.3 (0.69)	0.001	9.9 (2.5-39.3)	2.9 (1.3-4.6)

Hassan et al., 2002



Donato et al., 2002



Farazi et al, Nature 2006

TELOMERE LENGHT ACCORDING TO USUAL DRINKING CATEGORIES

	Geometric mean	95% CI	P-value	P-trend
0-1 drink-units/day	0.67	(0.63-0.72)	Ref.	
2-4 drink-units/day	0.61	(0.56-0.68)	0.14	
>4 drink-units/day	0.48	(0.39-0.59)	0.002	0.003

Pavanello et al, International Journal of Cancer 2011

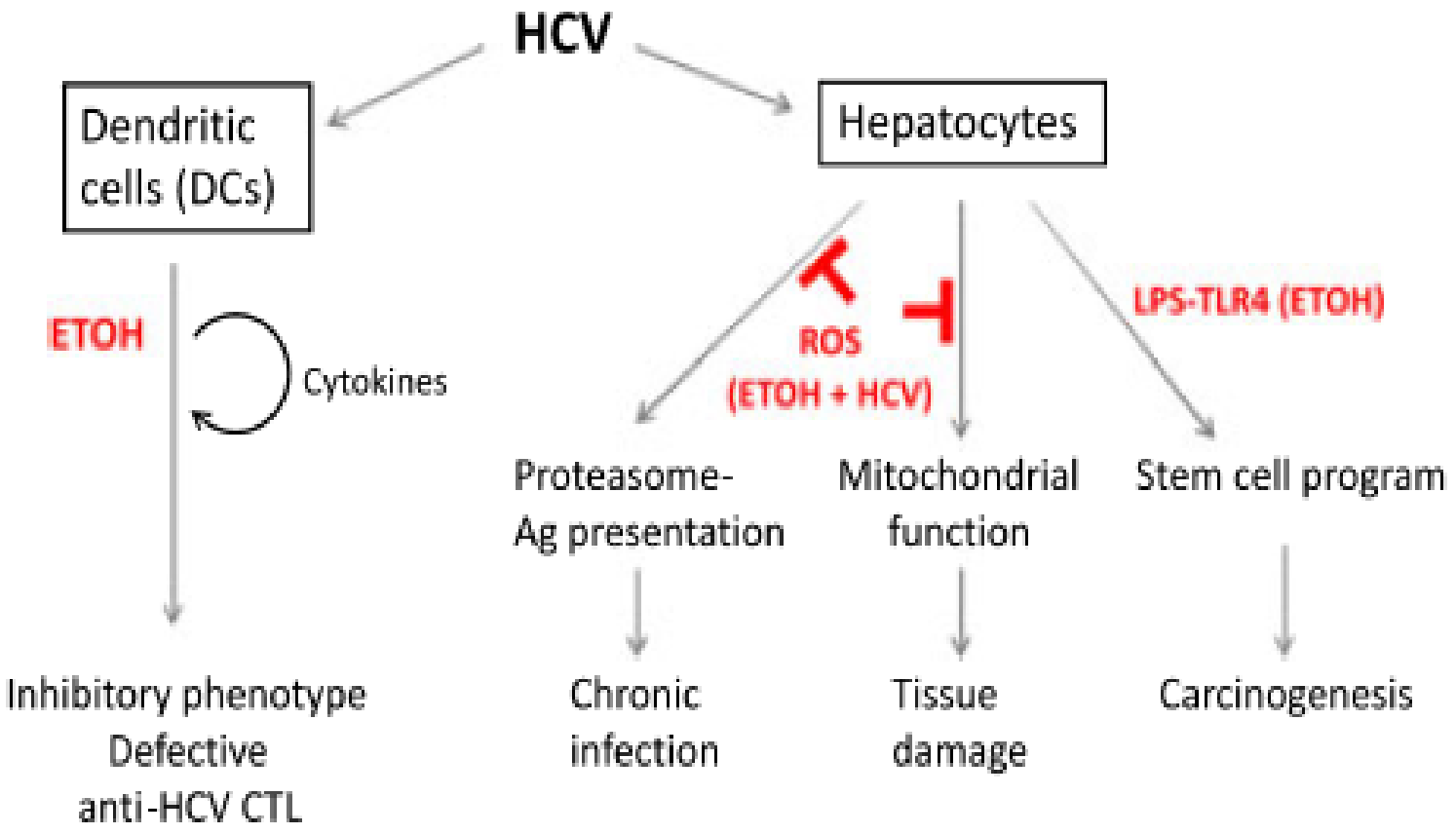
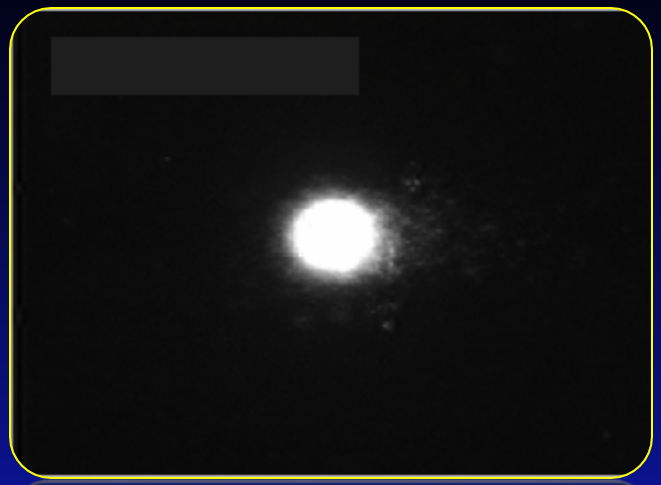
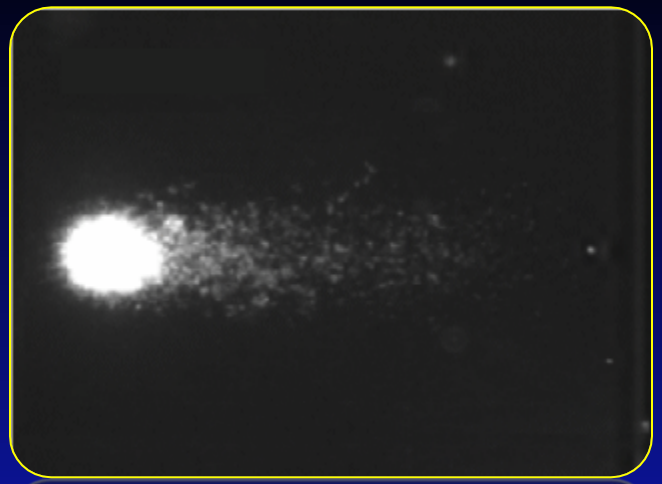


Fig. 1. A schematic of the interactions between alcohol and HCV and their impact on immune cells and liver cells. Ag, antigen.

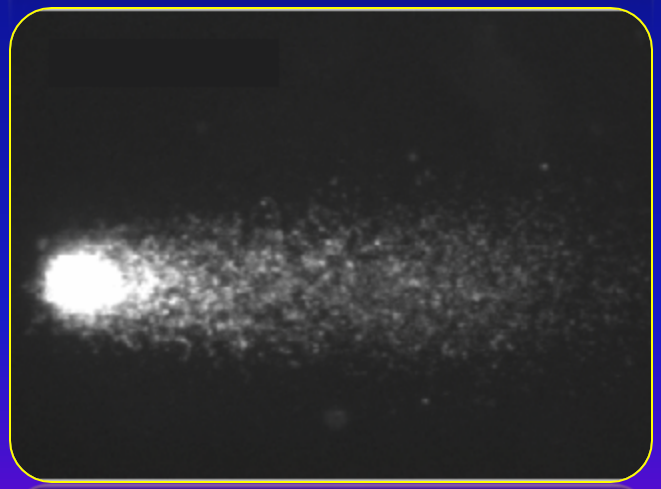
Szabo et al, Alcohol Clin Exp Res 2010



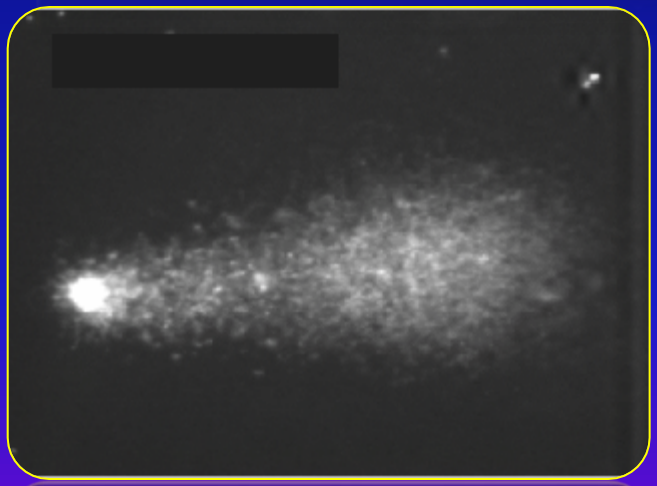
controllo



1



2



3

1,2,3 = diversi gradi di danno

A. Martelli, F. Mattioli, G. Testino et al – European J Gastroenterol Hepatol 2008

FREQUENCY OF DNA HYPERMETHYLATION IN HCC AND THEIR ASSOCIATION WITH ALCOHOL

Gene	Percentage of hypermethylated tumor samples
RASSF1A	67%
GSTP1	44%
P14 ARF	0%
GNMT	30%
DOK1	60%
MGMT	22%
CHRNA3	33%

RASSF1A: Ras signalling

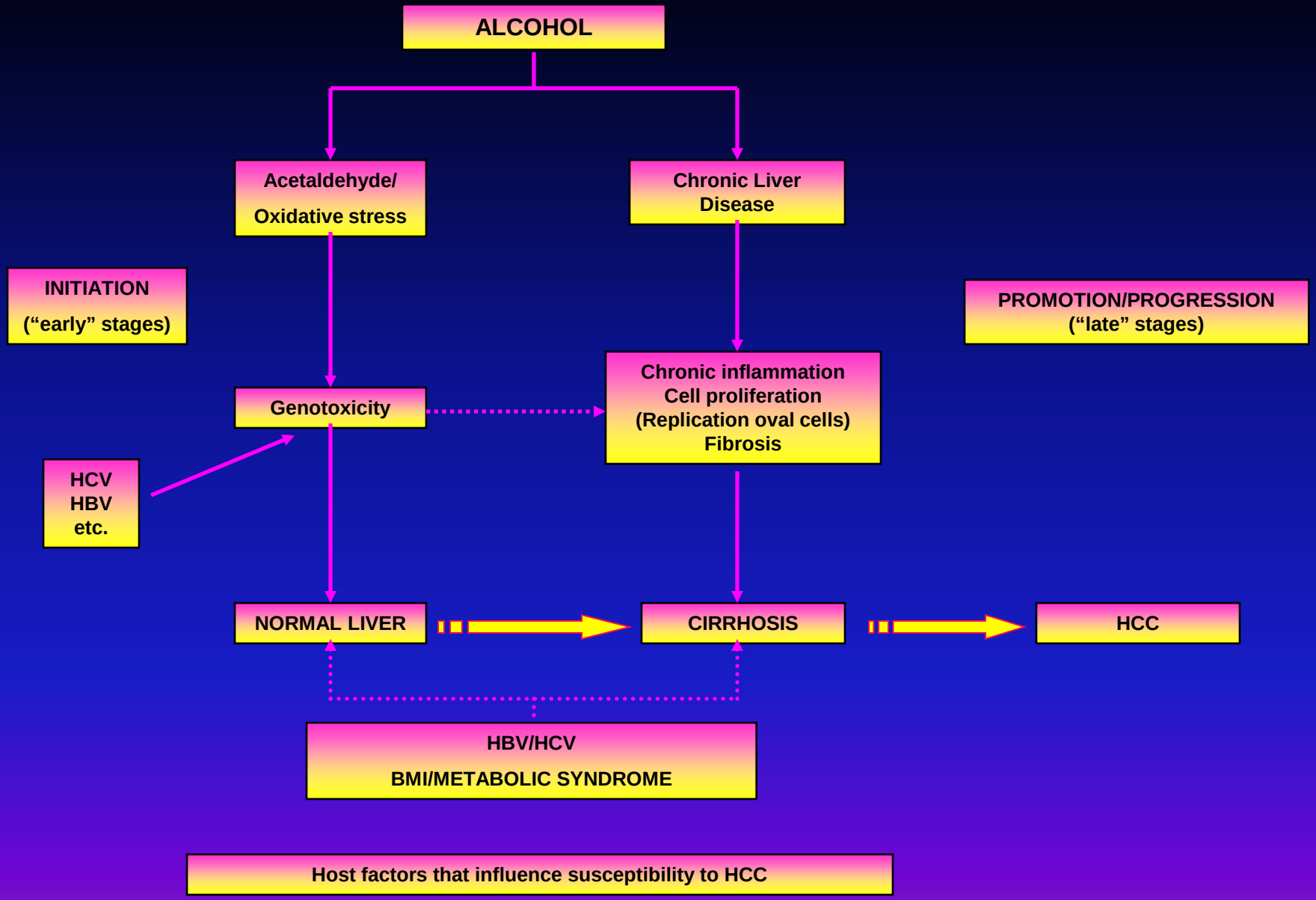
GSTP1: detoxification of carcinogens

DOK1: response to interferon

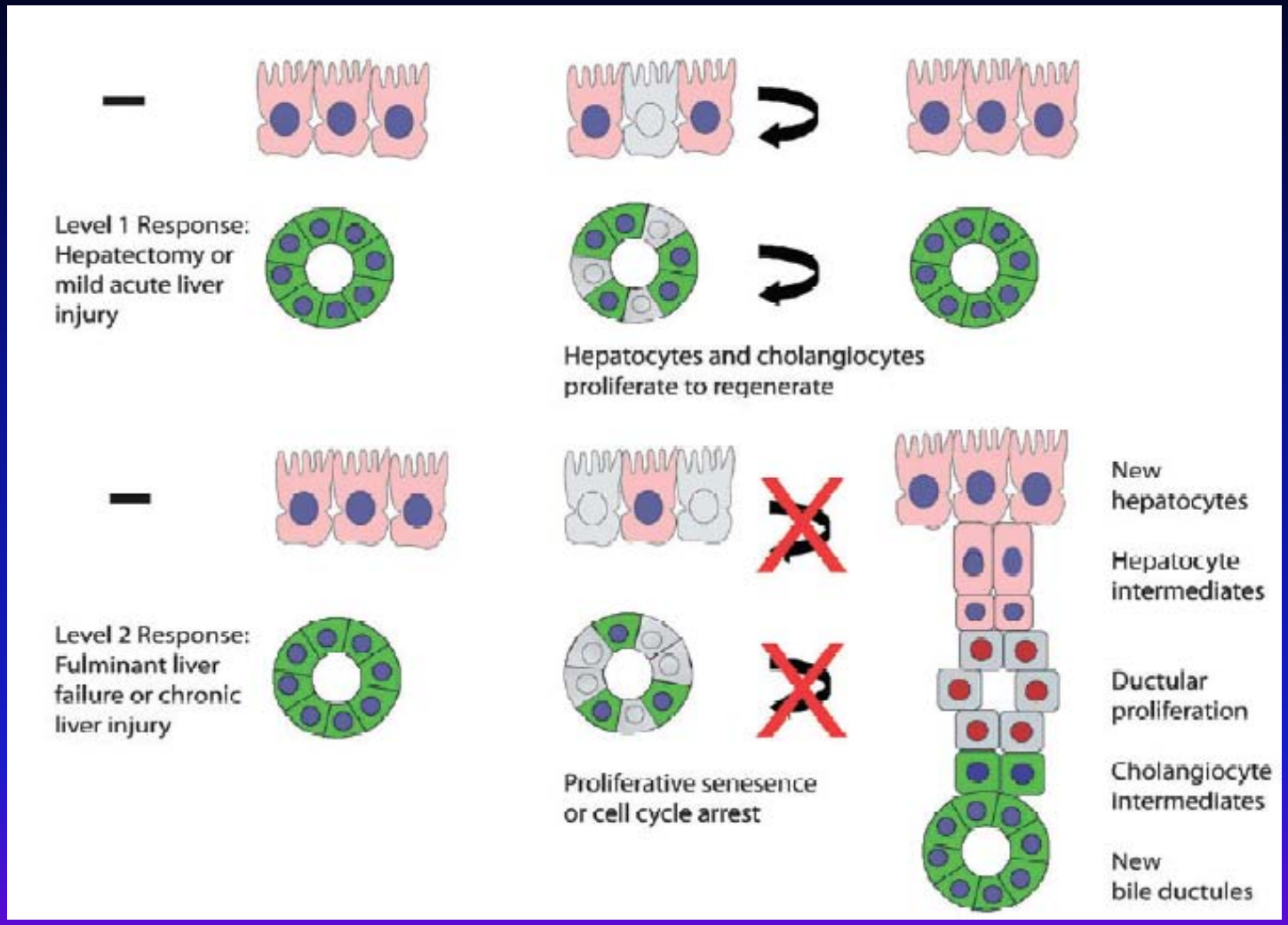
CHRNA3: angiogenic growth

MGMT: DNA repair

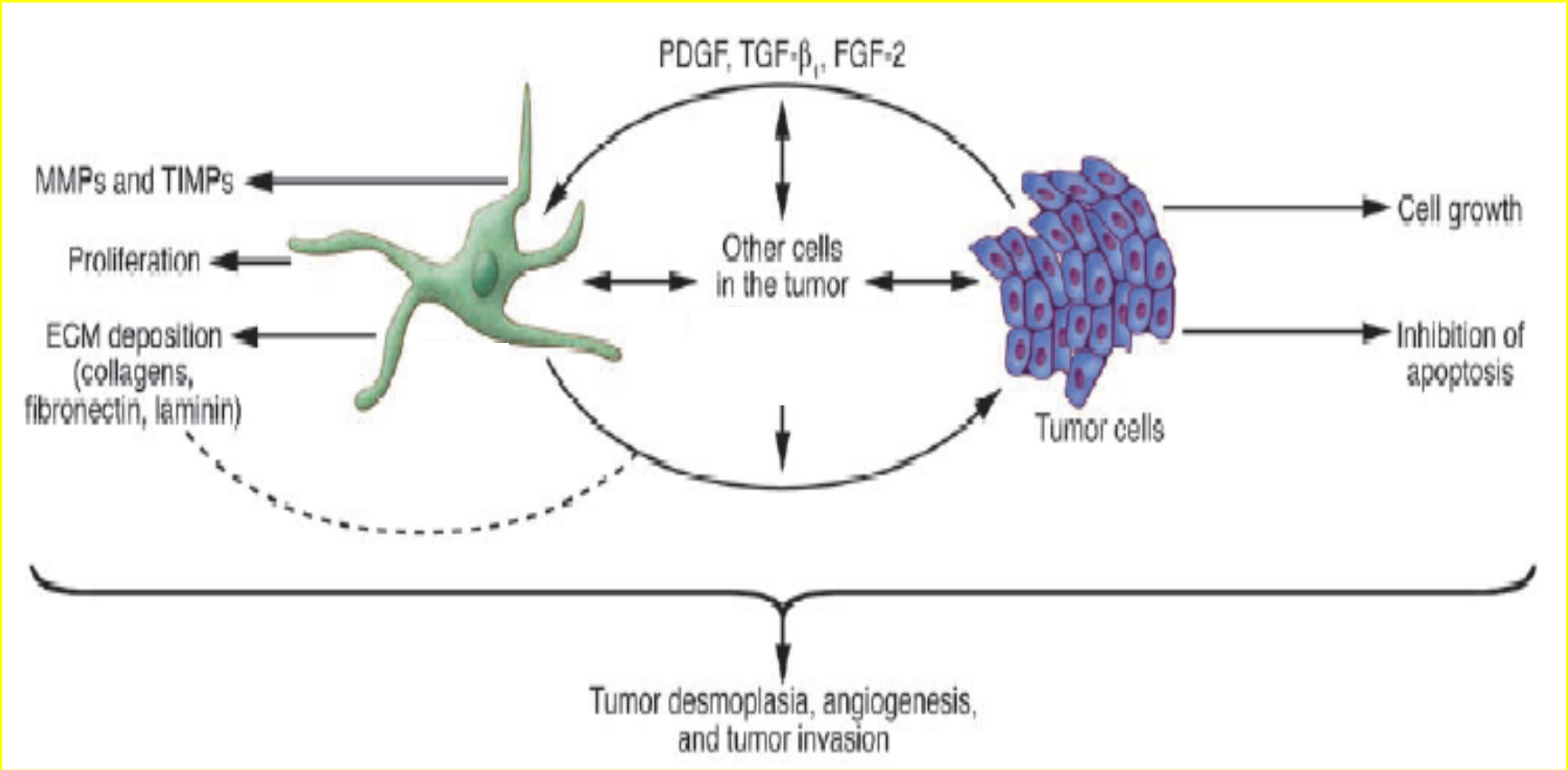
LAMBERT et al, J HEPATOL 2010

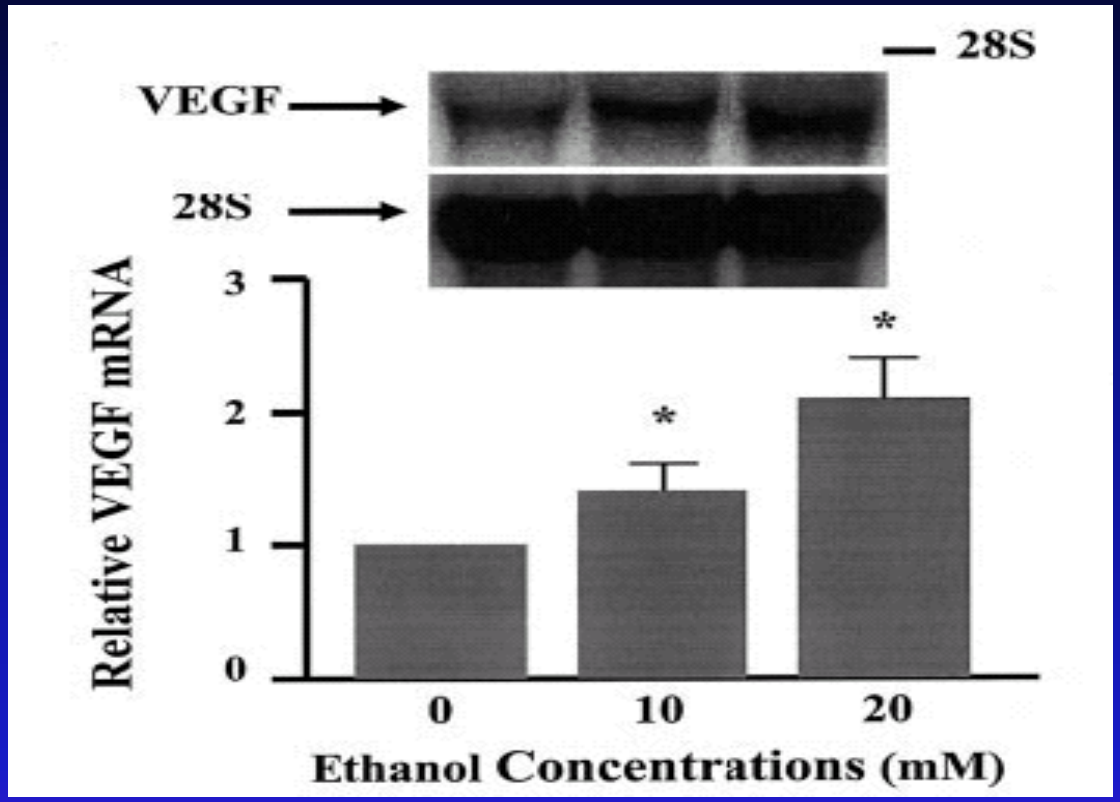


Donato et al., 2002

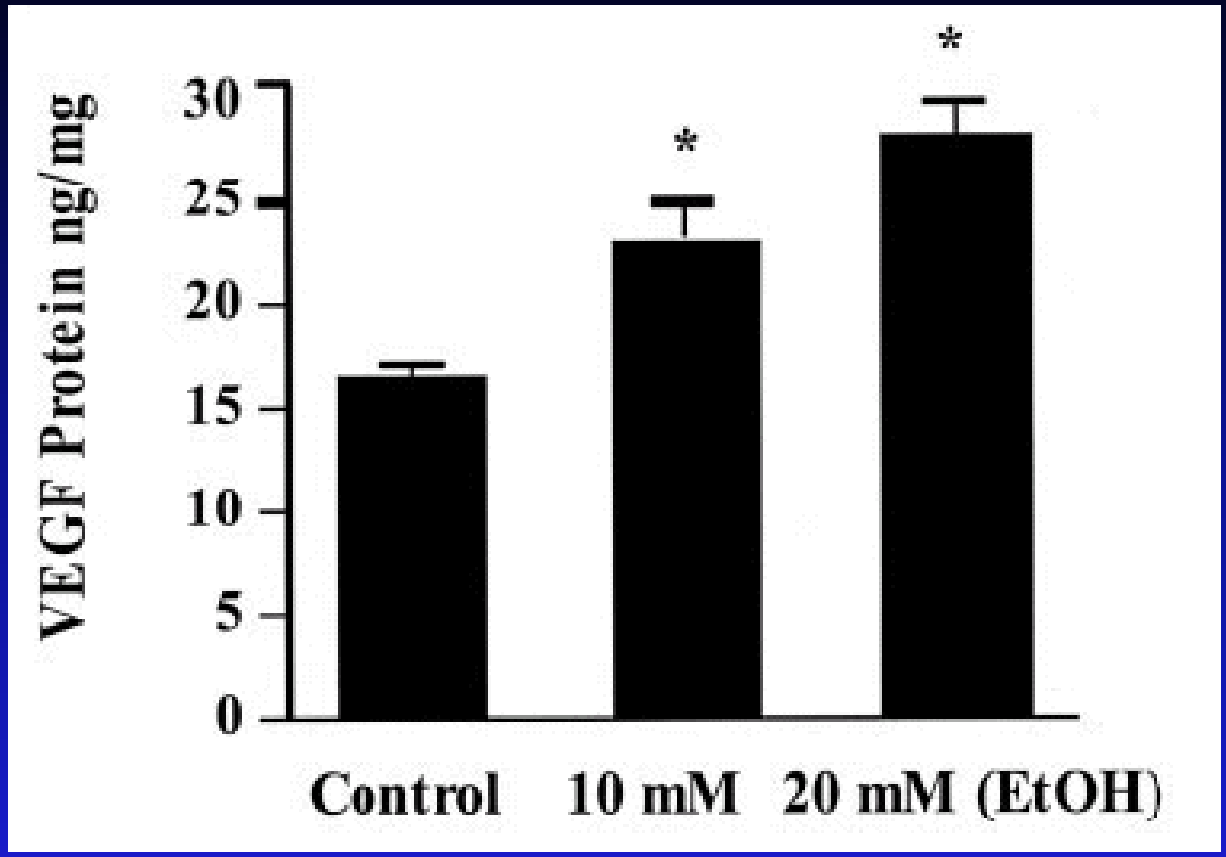


Riehle KJ et al, J Gastroenterol Hepatol 2011

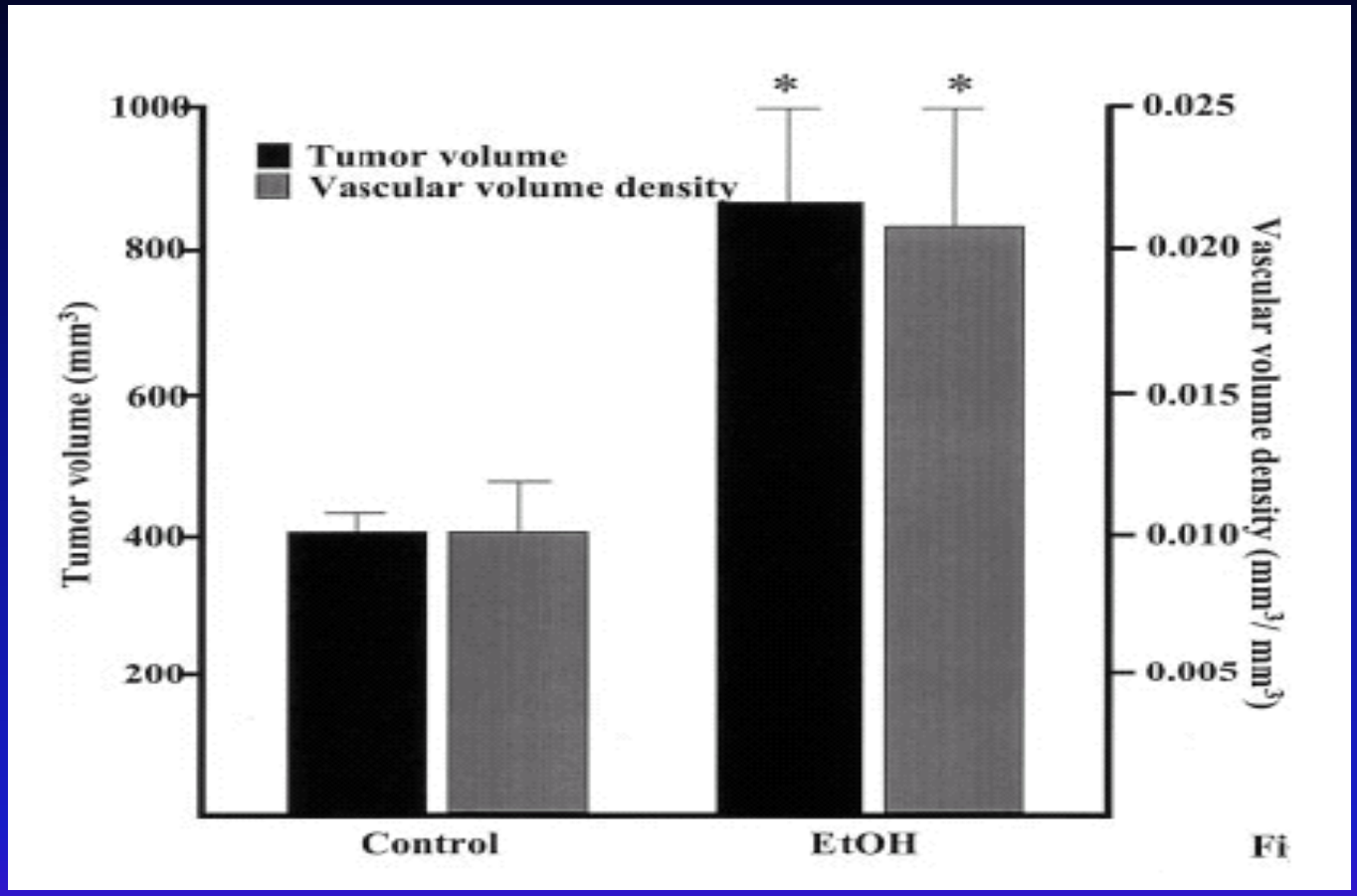

PDGF, TGF-β1, FGF-2
MMPs and TIMPs
Proliferation
ECM deposition
(collagens,
fibronectin, laminin)
Other cells
in the tumor
Tumor cells
Cell growth
Inhibition of
apoptosis
Tumor desmoplasia, angiogenesis,
and tumor invasion



Gu JW et al, Cancer 2005



Gu JW et al, Cancer 2005



Gu JW et al, Cancer 2005

Correlation between Liver Metastasis and Alcohol Consumption

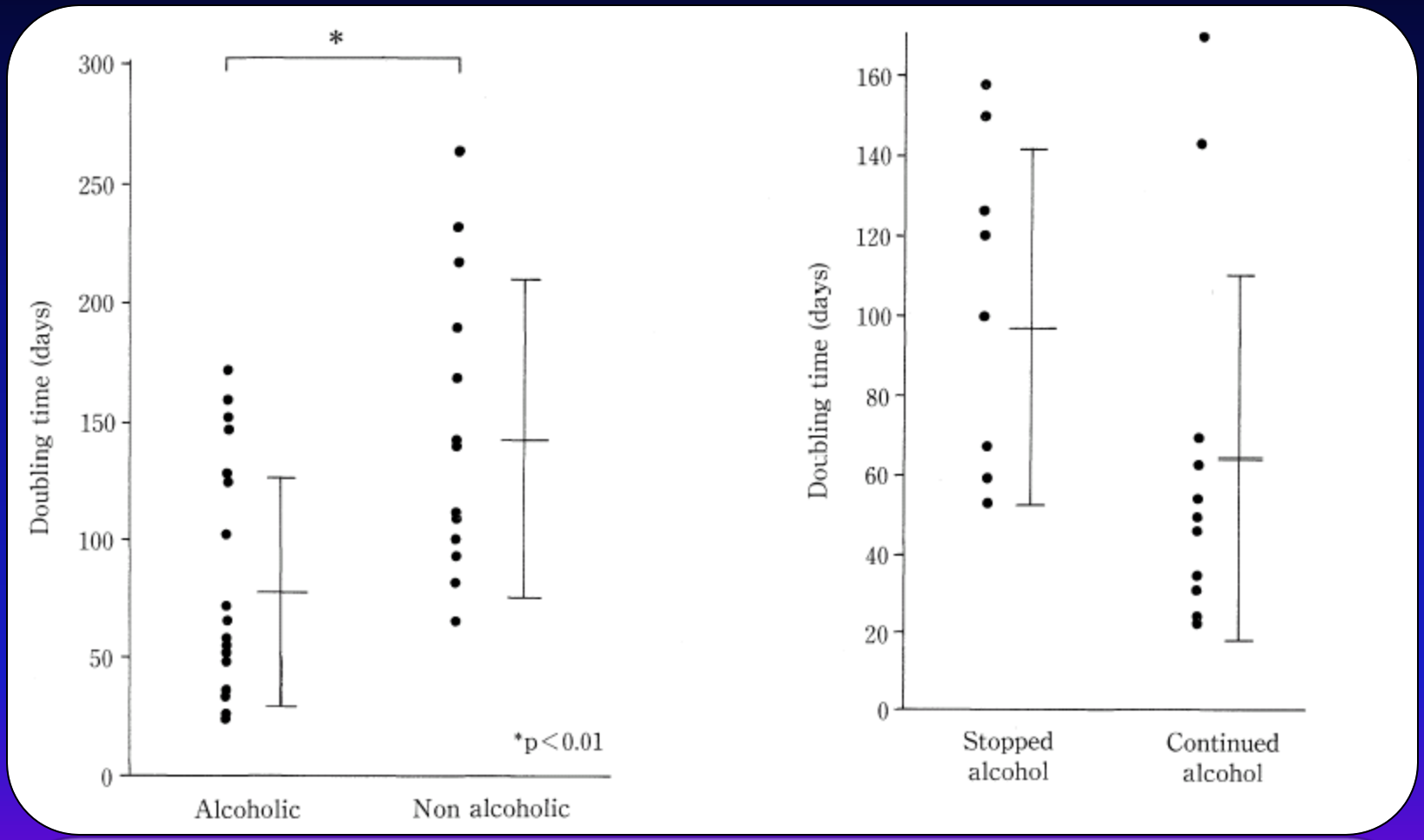
	Liver metastasis cases/total cases		
	NACG	ACG	*P* value[a]
Total	17/95	17/38	0.0021
Synchronous	7/95	9/38	0.0201
Metachronous[b]	10/88	8/29	0.0714

NACG: Nonalcohol-consuming group; ACG: alcohol-consuming group.

[a] Fisher's exact test.

[b] Synchronous liver metastasis cases were excluded.

Maeda M et al, Cancer 1998



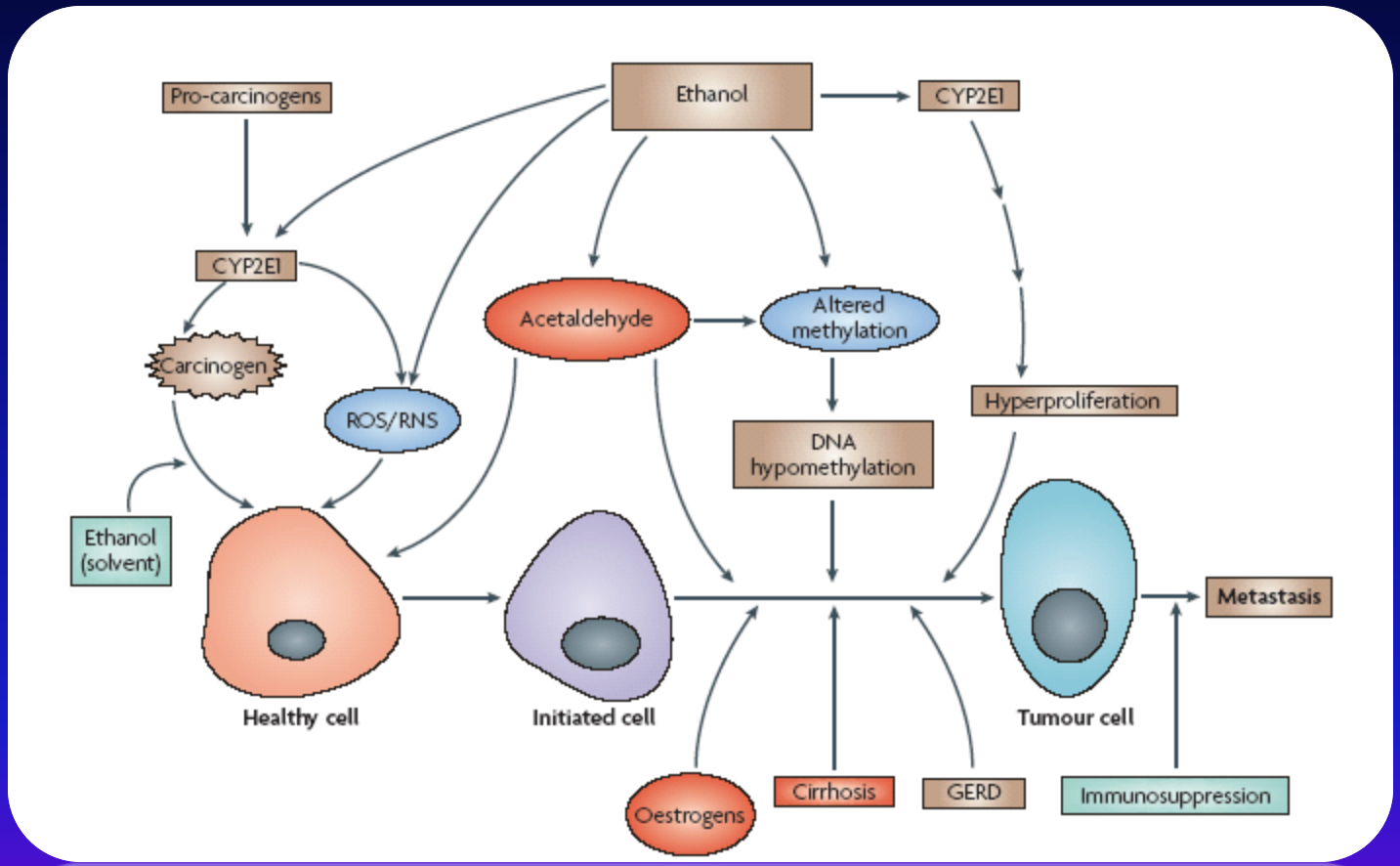
After detection HCC 20-80 gr/day

Matsuhashi et al, Internal Medicine 1996

	5 5– year HCC incidence rate	5 – year death incidence rate
Group 1	0/20 (0%)	1/20 (5%)
Group 2 and 3	4/77 (5.1%)	9/77 (11.6%)
Group 4	32/93 (34.4%)	35/93 (37.6%)

1) N. Polymorphisms
2) 1–2 ALA –SOD 2 ALLELES
3) 2 GMPO ALLESSES
4) 2 GMPO ALLELES + 1-2 ALA – SOD 2 ALLESES

Nathon et al, Hepatology 2009


Pro-carcinogens
Ethanol
CYP2E1
CYP2E1
Acetaldehyde
Altered methylation
Carcinogen
ROS/RNS
Hyperproliferation
DNA hypomethylation
Ethanol (solvent)
Metastasis
Healthy cell
Initiated cell
Tumour cell
Oestrogens
Cirrhosis
GERD
Immunosuppression

RISK FACTORS FOR ALCOHOL ASSOCIATED CARCINOGENESIS

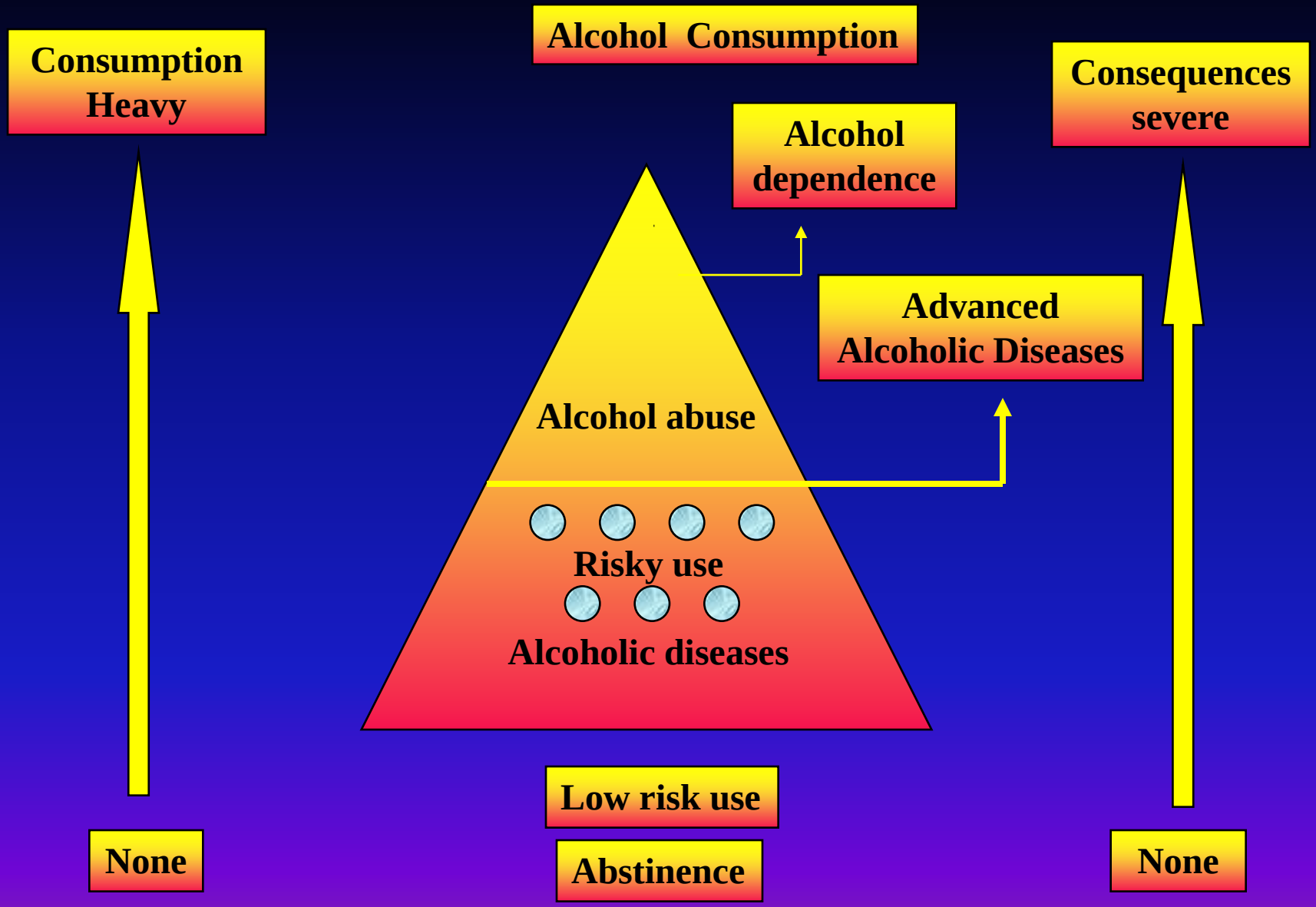
1) **Upper aerodigestive tract**: smoking, poor oral hygiene and poor dental status, highly concentrated alcoholic beverages, additional supplementation of vitamin A an d β-carotene, ADH1C*1,1 homozygocity, ALDH 2*2,2-mutation, precancerous conditions such as Barret's oesophagus and gastro-oesophagus and gastro-oesophagus reflux, atrophic gastritis, Helicobacter pylori infection

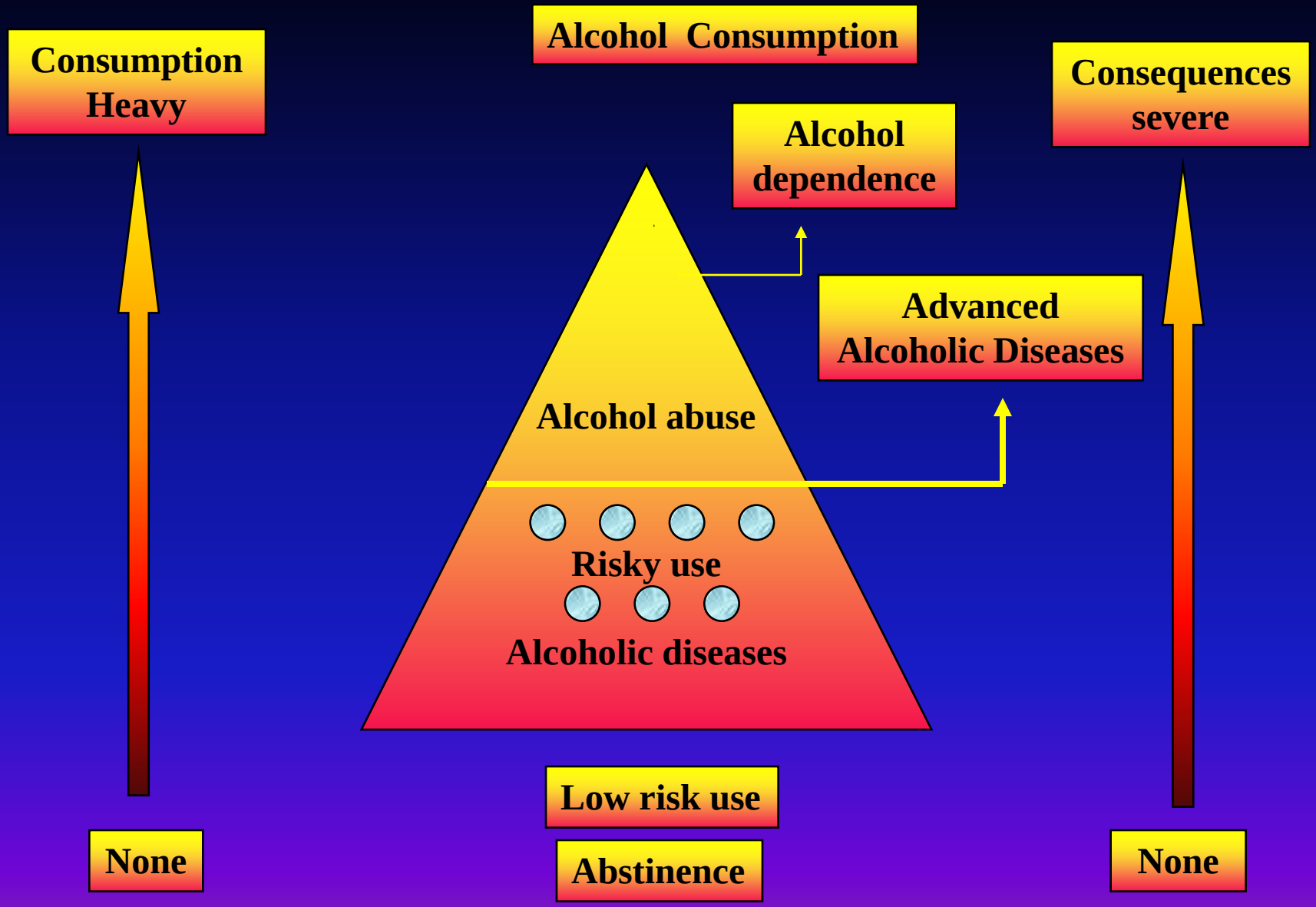
2) **Liver:** cirrhosis, hepatitis B- and C infection, haemochromatosis, exposure to aflotoxins and vinylchloride

3) **Pancreas:** smoke, N291/R122H, SPINK1/N34S, PRSS1

4) **Colorectum**: chronic inflammatory bowel disease, polyps, deficiency of folate, ADH1C*1 homozygocity, ALDH2*2 mutation

5) **Breast**: high oestradiol concentrations (expecially in midcycle), ADH1C*1 genotype? Family history


Consumption
Heavy
None
Alcohol Consumption
Alcohol
dependence
Advanced
Alcoholic Diseases
Alcohol abuse
Risky use
Alcoholic diseases
Low risk use
Abstinence
Consequences
severe
None


Alcohol Consumption
Consumption
Heavy
None
Alcohol
dependence
Advanced
Alcoholic Diseases
Consequences
severe
Alcohol abuse
Risky use
Alcoholic diseases
Low risk use
Abstinence
None

ALCOHOL AND CANCER RECOMMENDATION

“no safe level” - “low risk”

20 – 30 gr/day in healthy man

10 gr/day in healthy women

European Code Against Cancer,
Boyle et al; Ann Oncol 2003

28 gr /day in healthy man

14 gr / day in healthy women

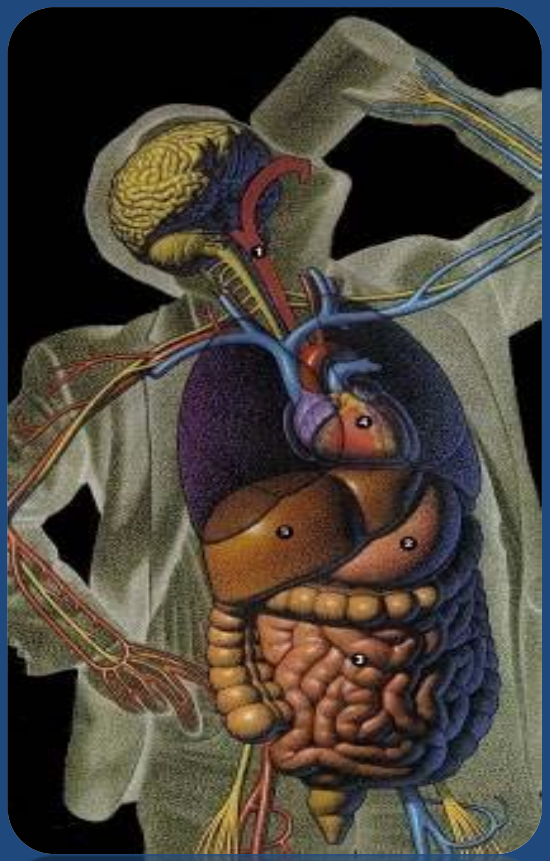
US Departments of Agricolture and Health and Human Services; July 2009

ALCOHOL CONSUMPTION AND CANCER

"THE ANALYSIS WAS UNABLE TO IDENTIFY A THRESHOLD LEVEL OF ALCOHOL CONSUMPTION BELOW WHICH NO INCREASE RISK FOR CANCER IS EVIDENT "

Bagnardi et al, Alcohol Research and Health 2001

Institute National du cancer, Paris 2007
World Cancer Research Fund, American Institute for Cancer Research, 2010
IARC, 2010
Association of European Cancer Leagues, 2011



GRAZIE

PER

L’ATTENZIONE !