

Alcol ed Epatocarcinoma



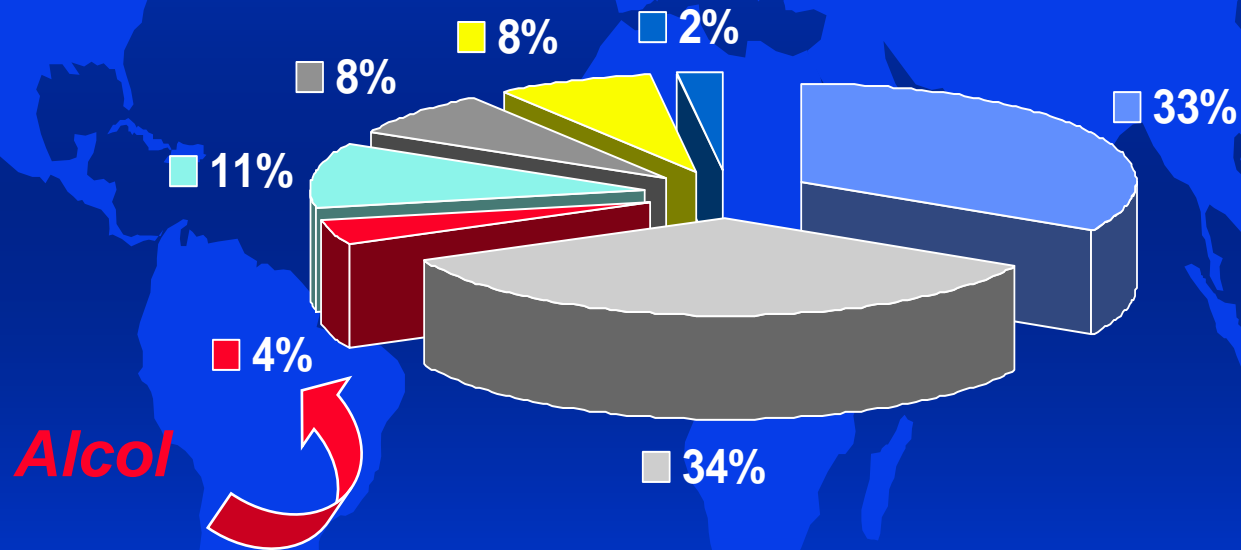
F. Farinati

Gastroenterologia, Padova

**ALCOL E VIRUS NELLA MALATTIE
DI FEGATO**



Alimentazione e cancro



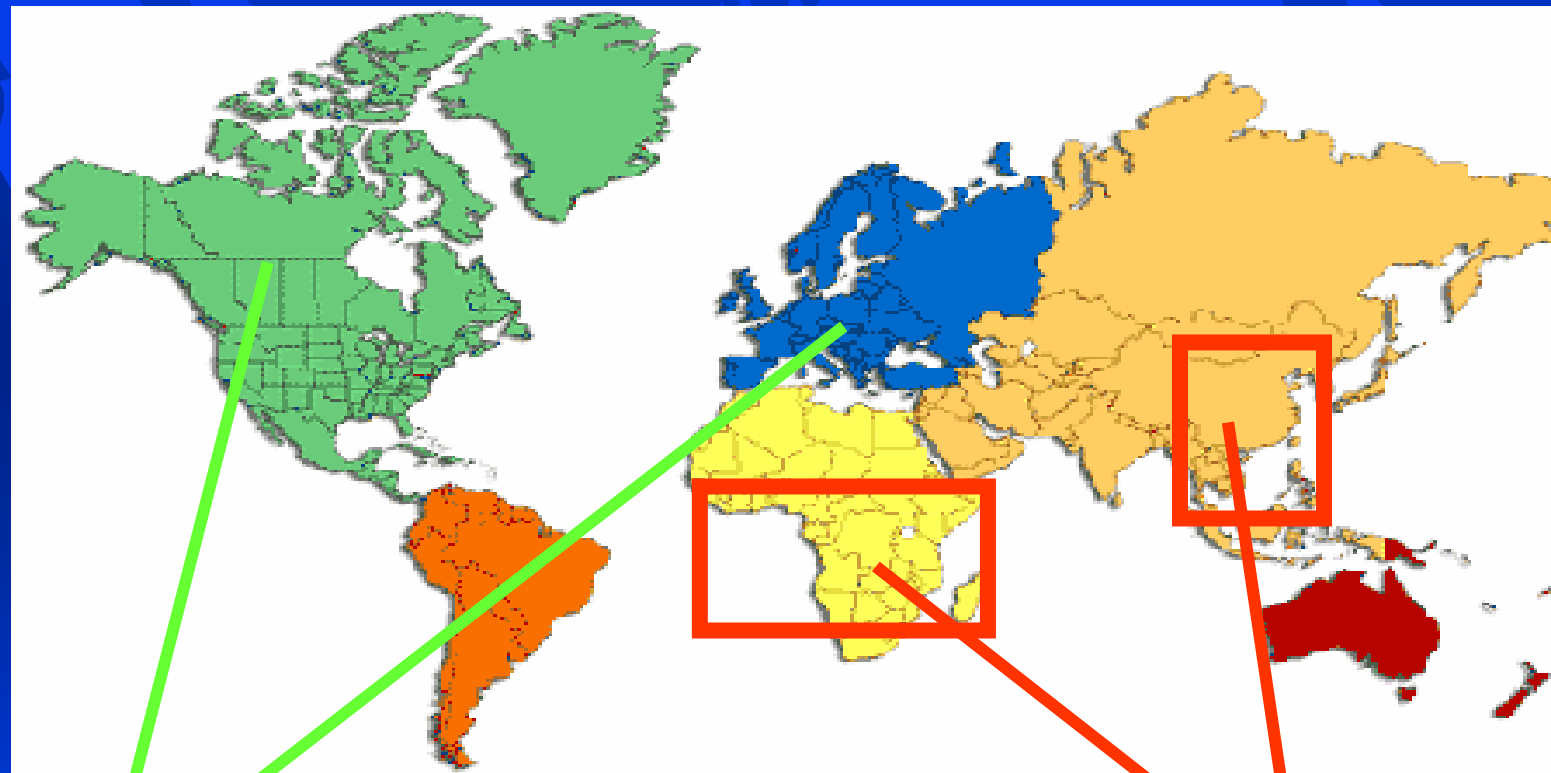
- | | | | |
|----------------|------------------|----------------|-------------|
| ■ Tabacco | ■ Aliment. | ■ Alcol | ■ Infezioni |
| ■ Inquinamento | ■ Fatt. sessuali | ■ Ereditarietà | |

Proc Nutr Soc. 2004
***Alcohol and cancer: genetic
and nutritional aspects.***

Poschl G, Stickel F, Wang XD, Seitz HK.

- ◆ *Chronic alcohol consumption is a major risk factor for cancer of oro-pharynx, hypopharynx, larynx and oesophagus, the liver, the colo-rectum and the breast*
- ◆ *Evidence is that acetaldehyde is responsible for alcohol-associated carcinogenesis. It is carcinogenic and mutagenic, binds to DNA and protein, destroys the folate molecule and results in secondary cellular hyper-regeneration.*

L'incidenza dell'HCC nel mondo



3-4/100.00

120/100.000

... più del 50%... su fegato sano !!!



... più dell'80% ...su fegato cirrotico!!!



Alcol



Tumore del fegato
ICD-IX: 155.0



Males

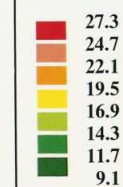
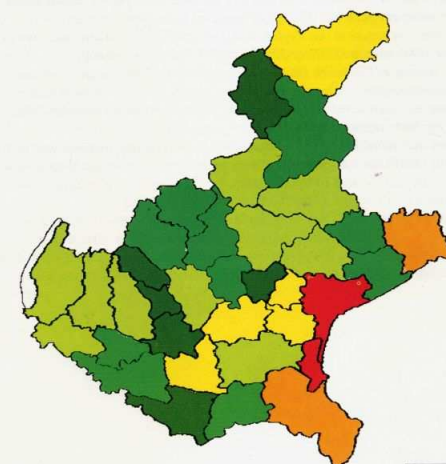
SMR (Italy = 100)

<60 60-89 90-109 110-139 ≥140



Dati Registro Tumori Veneto

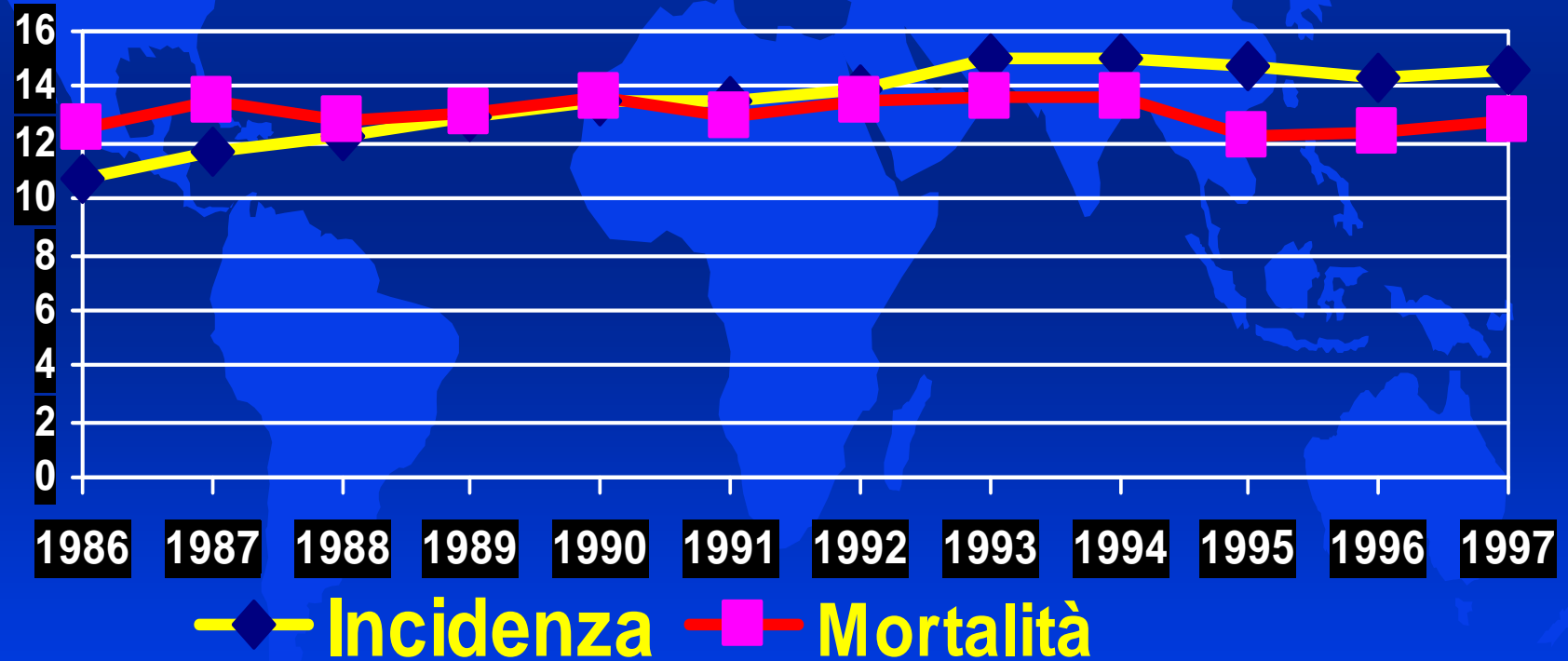
TUMORE DEL FEGATO, MASCHI
NEOPLASM OF LIVER, MALES
(155)



Dati Istat di Mortalità 1994

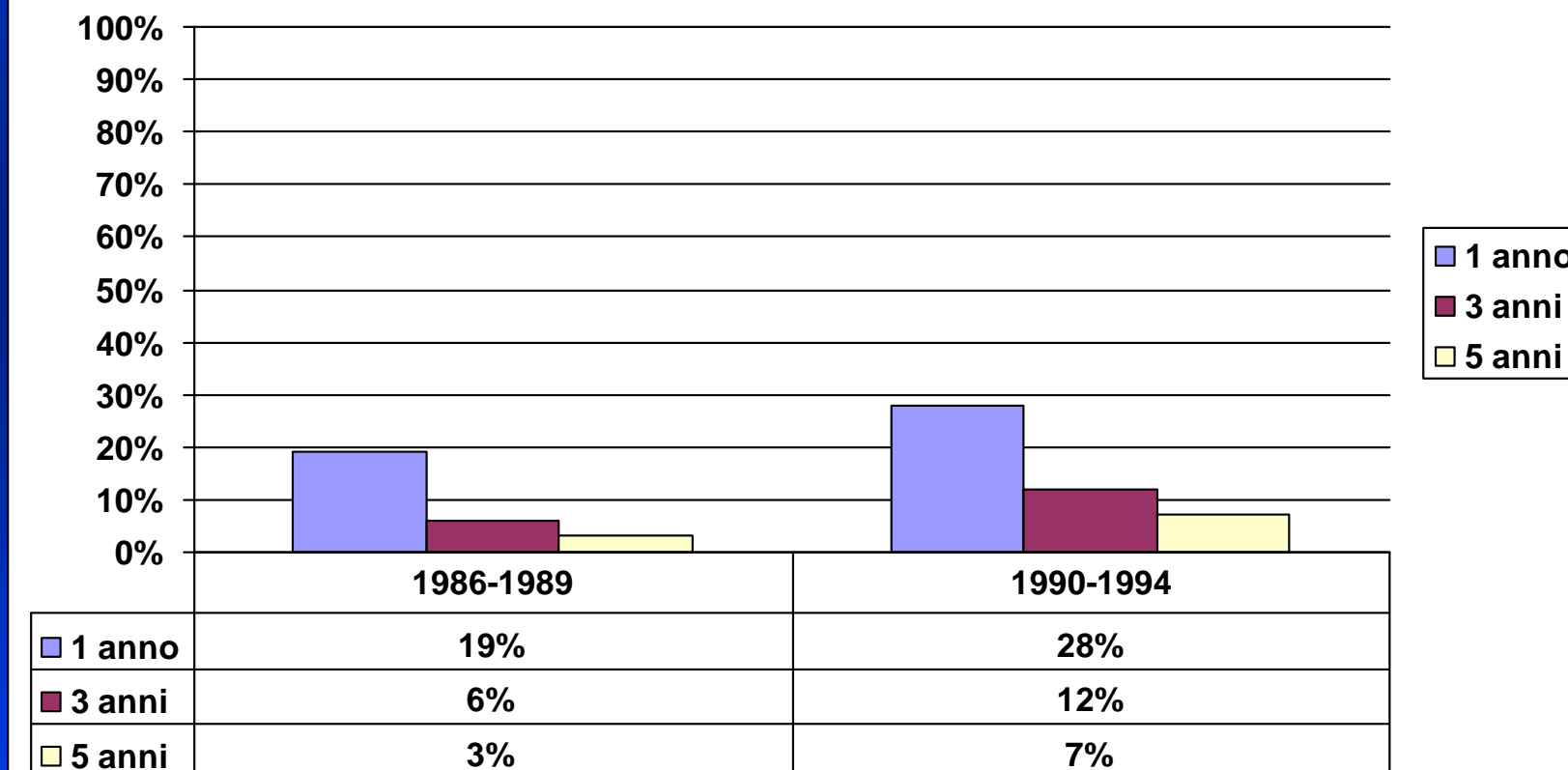
Epatocarcinoma

Airt - tassi standardizzati



Epatocarcinoma: sopravvivenza

Airt - sopravvivenza relativa % per periodo di diagnosi



HCV, ETOH and HCC

Factor	Comparison	P-value (log-rank test)
Age at the start of IFN treatment (years)	≥ 65 vs < 65	0.026
Sex	Male vs female	0.059
Alcohol intake	≥ 27 g/day vs < 27 g/day	0.015
	≥ 80 g/day vs < 80 g/day	0.447
Laboratory data before IFN treatment		
AST (IU/L)	≥ 80 vs < 80	0.446
ALT (IU/L)	≥ 80 vs < 80	0.890
Platelet count ($\times 10^4/\mu\text{L}$)	≥ 15.0 vs < 15.0	0.326
HCV genotype	Genotype 1 vs genotype 2	0.428
Positive for anti-HBc	Positive vs negative	0.097
Positive for anti-HBc (diluted at 1:200)	Positive vs negative	0.646
Liver histology before IFN treatment	F0, F1 and F2 vs F3 and F4	0.007

Tokita H

Journal of Gastroenterology and Hepatology (2005) 20, 752–758

HCV, HBV, ETOH and HCC

FATTOVICH ET AL

GASTROENTEROLOGY Vol. 127, No. 5

Table 3. Factors Affecting Progression to Hepatocellular Carcinoma in Compensated Cirrhosis Because of Hepatitis C

Factors	Comment
Host related	
Age at diagnosis	Important
Age at infection	Important
Male sex	Important
Severity of liver disease at presentation	Important
Comorbidity	
Porphyria cutanea tarda	Important (Southern Europe and United States)
Iron overload	Controversial
Liver steatosis	Growing evidence
Diabetes mellitus	Growing evidence
Viral related	
HCV genotype	Controversial
HCV load	Insufficient evidence
Overt HBV coinfection	Important
Occult HBV coinfection	Growing evidence
HIV coinfection	Growing evidence
External	
Alcohol intake	Important
Smoking	Controversial

Table 5. Factors Affecting Progression to Hepatocellular Carcinoma in Compensated Cirrhosis Because of Hepatitis B

Factors	Comment
Host related	
Age at diagnosis	Important
Male sex	Important
Severity of liver disease at presentation	Important
Viral related	
HBV replication status during follow-up	Important
HBV genotype/HBV mutant	More research needed
HDV coinfection	Important
HCV coinfection	Important
HIV coinfection	More research needed
External	
Alcohol intake	Important
Smoking	Controversial
Environmental contaminants (aflatoxins)	Important in HBV endemic regions

HCV, HBV, ETOH and HCC

Synergism of Alcohol, Diabetes, and Viral Hepatitis on the Risk of Hepatocellular Carcinoma in Blacks and Whites in the U.S.

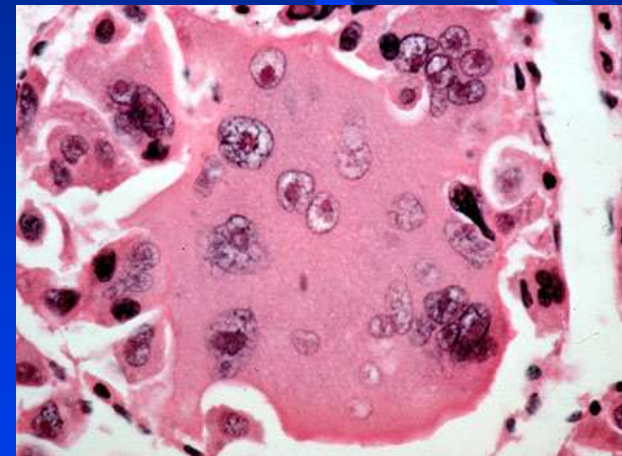
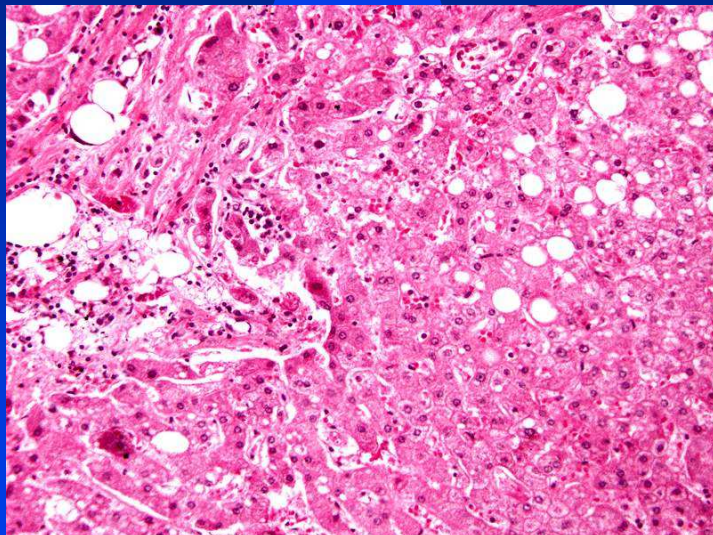
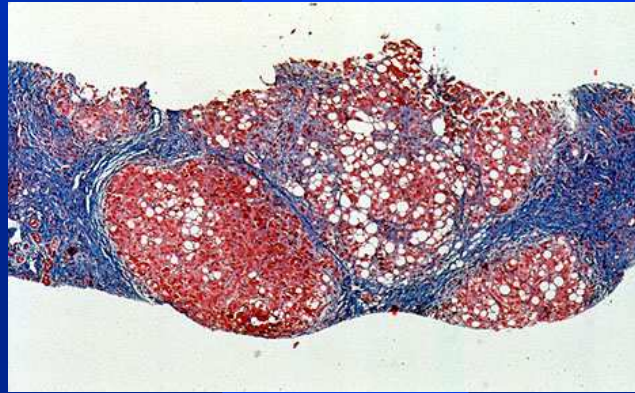
TABLE 4
Interactions of HBV/HCV Infection with Diabetes, Alcohol Drinking, and Cigarette Smoking on Risk of Hepatocellular Carcinoma among Non-Asians in Los Angeles County, California

HBV/HCV markers	Alcohol drinking			
Negative	≤ 4 drinks per day	80	173	1.0
Negative	> 4 drinks per day	29	22	2.6 (1.3-5.1)
Positive	≤ 4 drinks per day	85	23	8.1 (4.6-14.4)
Positive	> 4 drinks per day	51	2	48.3 (11.0-212.1)

Alcol ed Epatocarcinoma



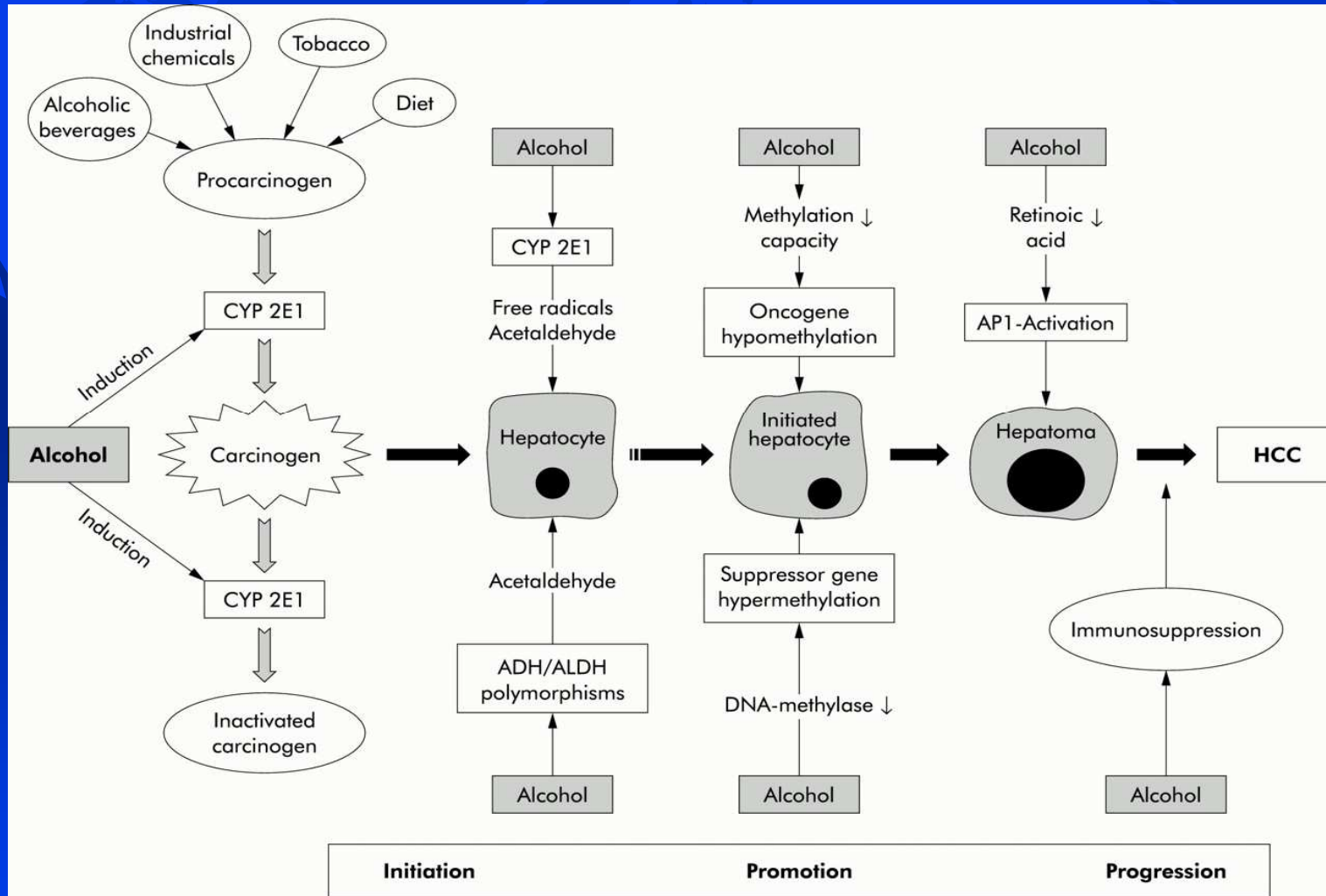
Alcol e carcinogenesi



- ◆ **Induzione di fibrosi/cirrosi**
- ◆ **Aumentata attivazione di xenobiotici altamente reattivi → danno genomico**
- ◆ **↑ Assorbimento intestinale di ferro e ↑ accumulo epatico**
- ◆ **↓ Concentrazioni epatiche di vit. A**
- ◆ **Interferenza nella metilazione di oncogeni**
- ◆ **Inibizione del DNA repair**
- ◆ **↓ Immunosorveglianza (cellule NK)**
- ◆



Alcol e cancerogenesi epatica



Alcol ed attivazione di carcinogeni

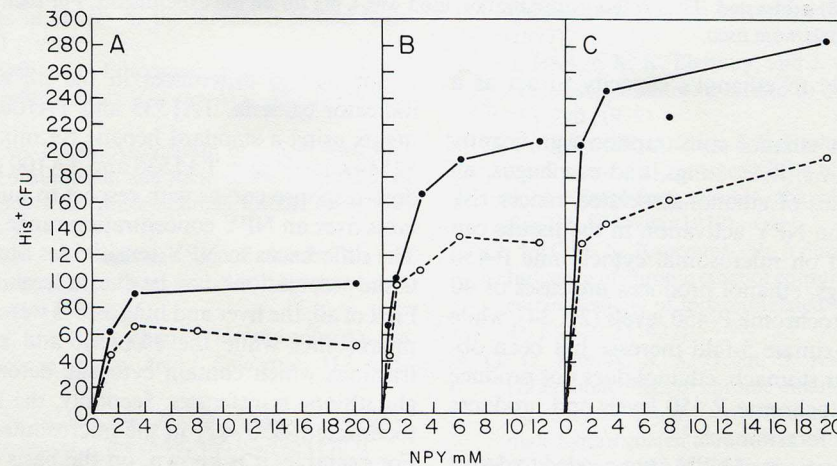


FIG. 1. NPY activation by liver microsomes of ethanol-fed (●) and control (○) animals.

Each point represents the average number of His⁺ colony-forming units (CFU) of *Salmonella* TA1535, scored on duplicate plates. The background CFU which are seen in the absence of NPY (35 ± 5) have been subtracted. The microsomal protein concentrations used in A, B, and C were 0.8, 1.5, and 2 mg/ml, respectively. The experiments reported in each panel were carried out using different pooled liver samples from six pairs of pair-fed animals.

Table 3. Effect of Dietary Ethanol on Hepatic O^6 -MeGT Activity

Diet group*	O^6 -Methylguanine removed
	<i>fmol/min/mg protein</i>
Control	4.42 ± 0.17
Ethanol	2.52 ± 0.31

See Ref. 57. Results are expressed as means ± SE and are significantly different with a $p < 0.01$.

* Five pairs of rats were pair-fed isocaloric ethanol-containing (36% of total calories as ethanol) or dextrimaltose control diets for a period of 4 weeks; 18 hr prior to deaths the ethanol-containing diet was removed and both groups of animals were fed the control diet.

Table 4. Direct Effect of Ethanol and Methanol on O^6 -MeGT Activity

	O^6 -Methylguanine removed
	<i>pmol/30 min</i>
Liver extract	2.85 ± 0.36
+ 50 mM ethanol	1.74 ± 0.41*
+ 50 mM methanol	1.36 ± 0.35†

See Ref. 56. O^6 -MeGT was partially purified by ammonium sulfate fractionation of liver homogenates prepared from three hepatectomized rats.^{48,49} Enzyme activity was assayed in 50 mM Tris-HCl, pH 8.3, 1 mM dithiothreitol, 0.1 mM EDTA. The DNA substrate contained 10 pmol of O^6 -methylguanine and 5 mg of liver homogenate protein were used in the assays.

* $p < 0.05$.

† $p < 0.01$.

**Alcohol DNA
repair**

**Alc.Clin.Exp.Res,
1986**

Vitamine, cancro ed alcol

- ◆ ***L'alcol riduce i livelli di Vit A***
- ◆ ***Vitamina A***
 - *sopprime la trasformazione*
 - *inibisce la carcinogenesi*
 - *riduce le lesioni preneoplastiche*
 - *inibisce i secondi tumori*
 - *ridotti livelli o ridotta espressione del recettore in vari tumori*
- ◆ ***Deficit di Folati***
 - *ipometilazione del DNA (evento precoce carcinogenesi)*



FERRO ed HCC

- ◆ *Alcol induce accumulo di ferro*
- ◆ *Il ferro induce fibrosi - cirrosi*
- ◆ *Cellule tumorali in vitro crescono e sopravvivono meglio in medium ricco di ferro*
- ◆ *il ferro determina \uparrow radicali liberi \rightarrow mutazioni genetiche (8OHdG)*
- ◆ *eccesso di ferro favorisce la persistenza dell'infezione da HBV-HCV e riduce risposta a IFN.*

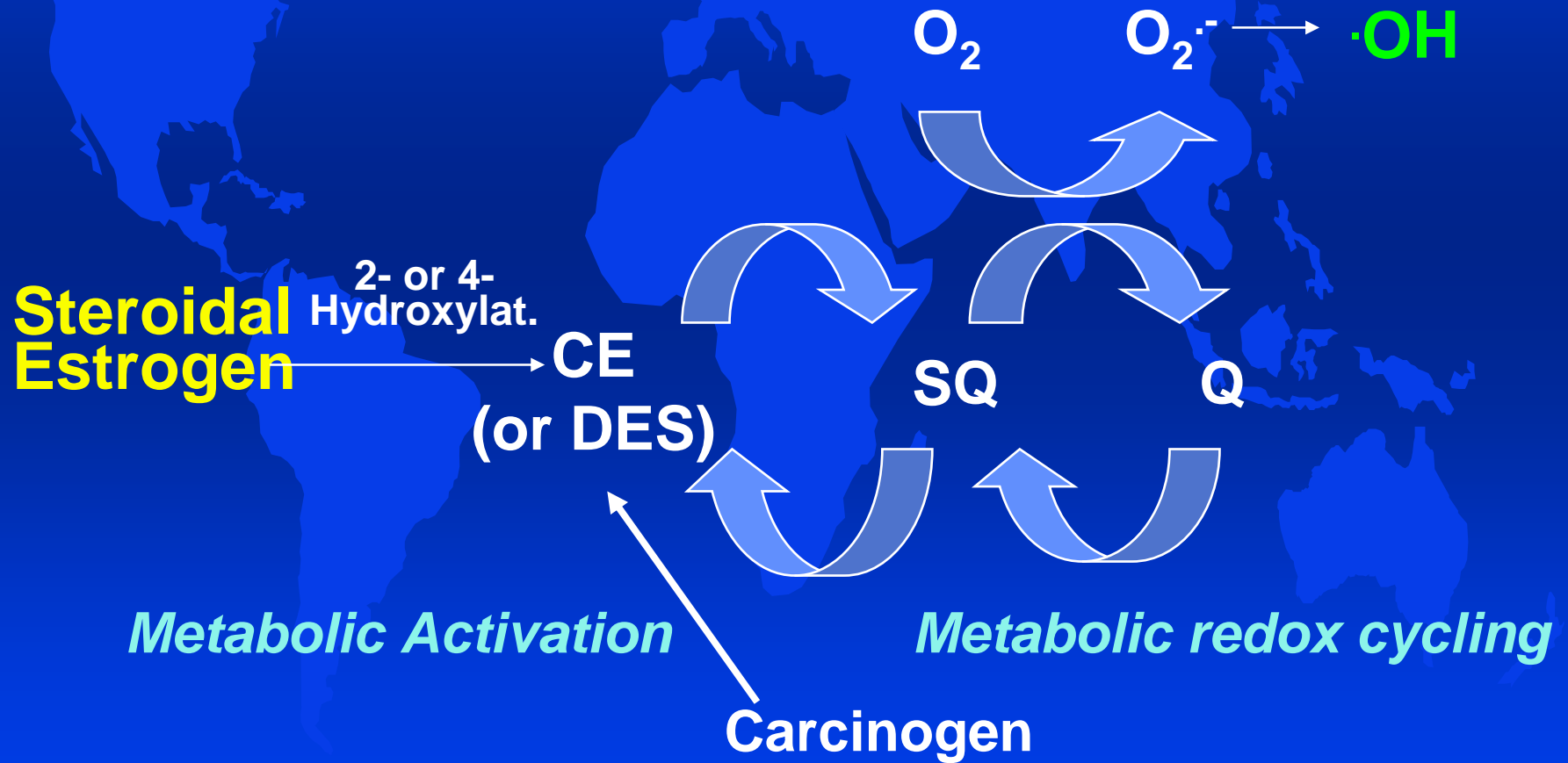


Alcol ed estrogeni

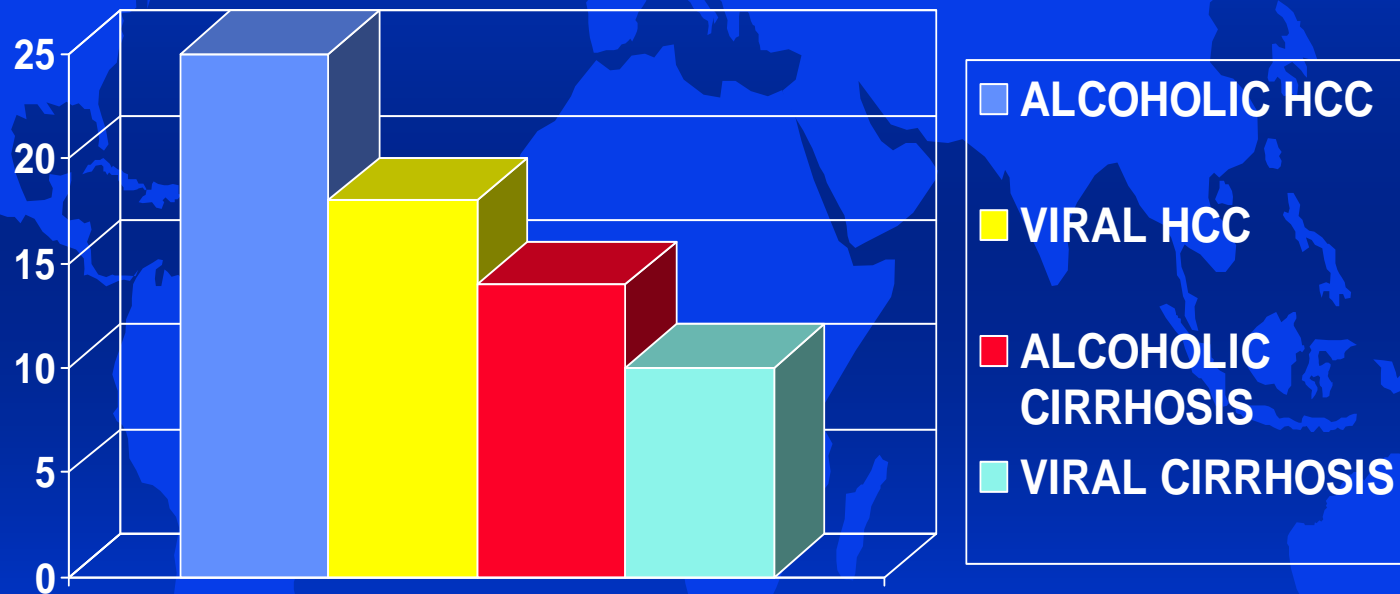
Un uso moderato di alcol aumenta i livelli di estrogeni endogeni, che controllano la rigenerazione epatica e aumentano la produzione di radicali liberi.

Il paziente con cirrosi, in particolare se alcolica è notoriamente femminilizzato.

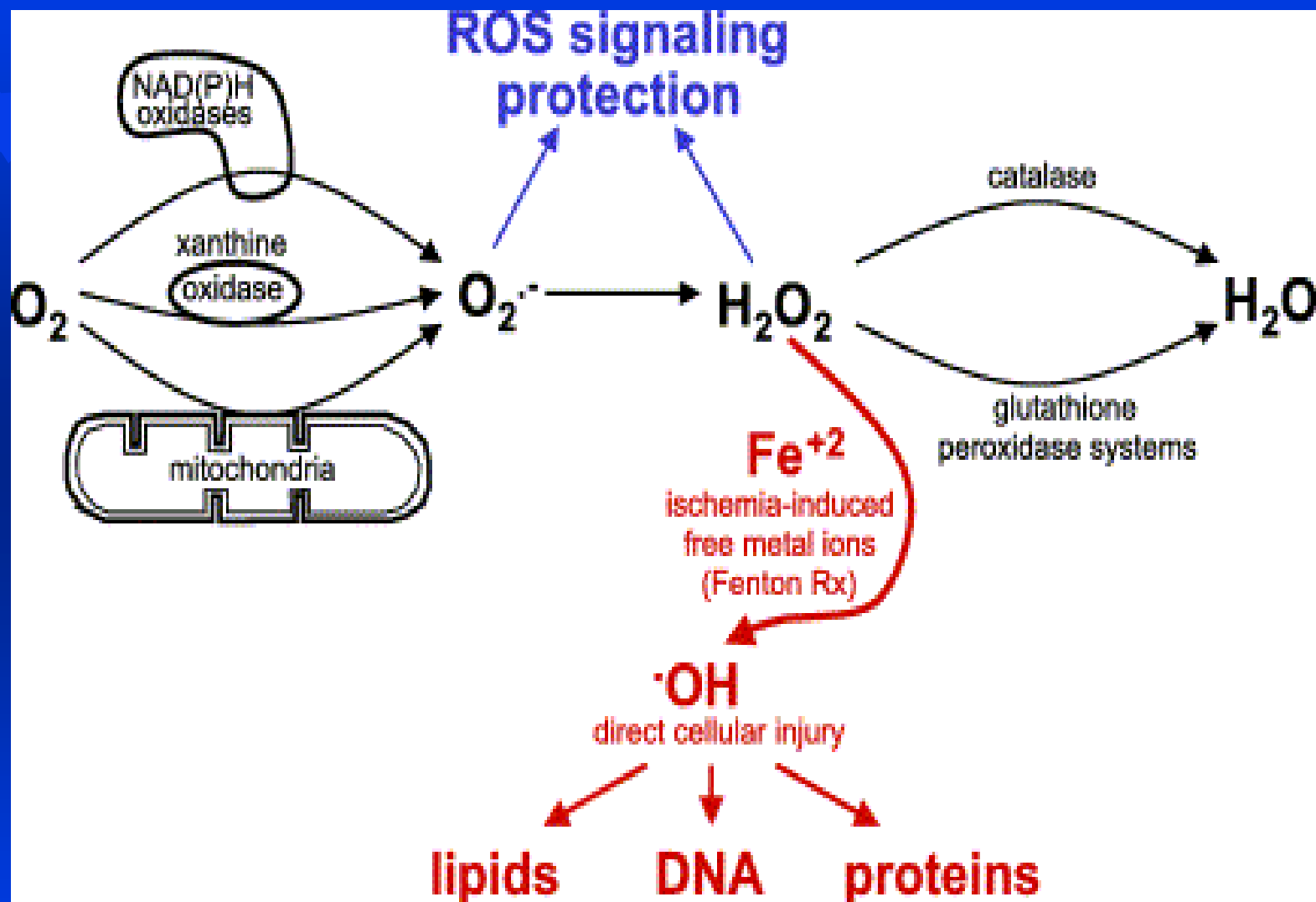
Induction of free radicals by estrogens



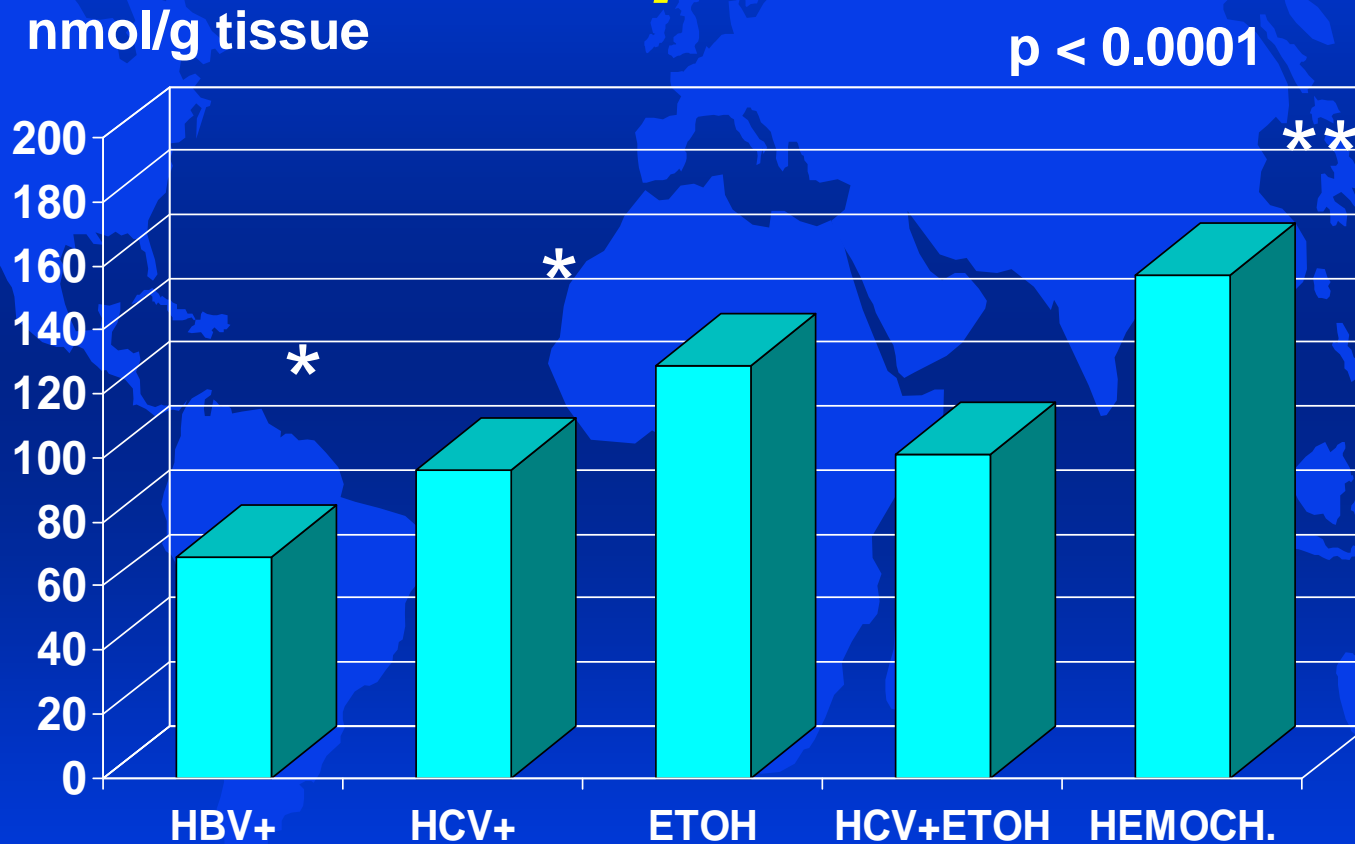
Estradiol/testosterone ratio in cirrhosis and HCC



Eur.J.Gastroenterol. Hepatol, 1995

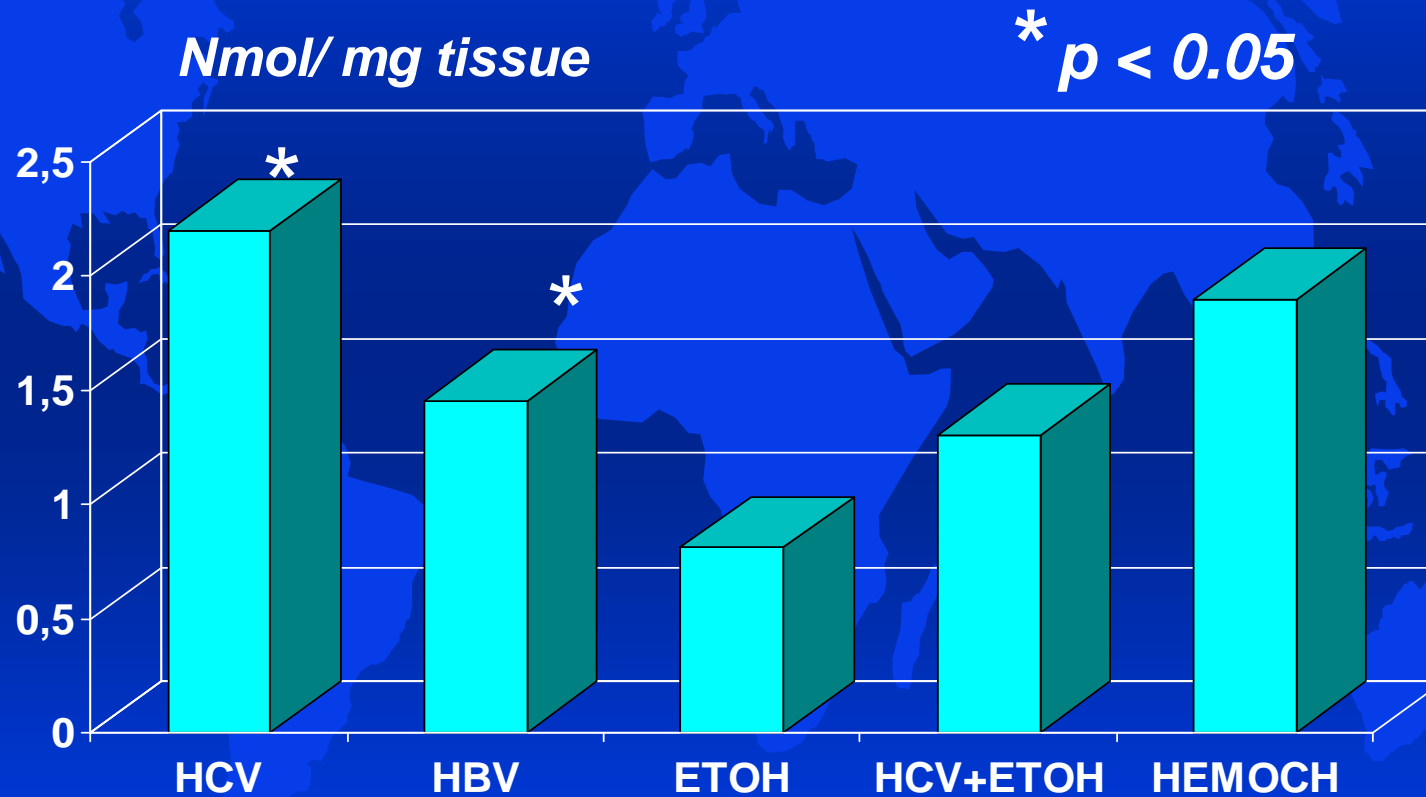


MDA tissue levels in chronic hepatitis



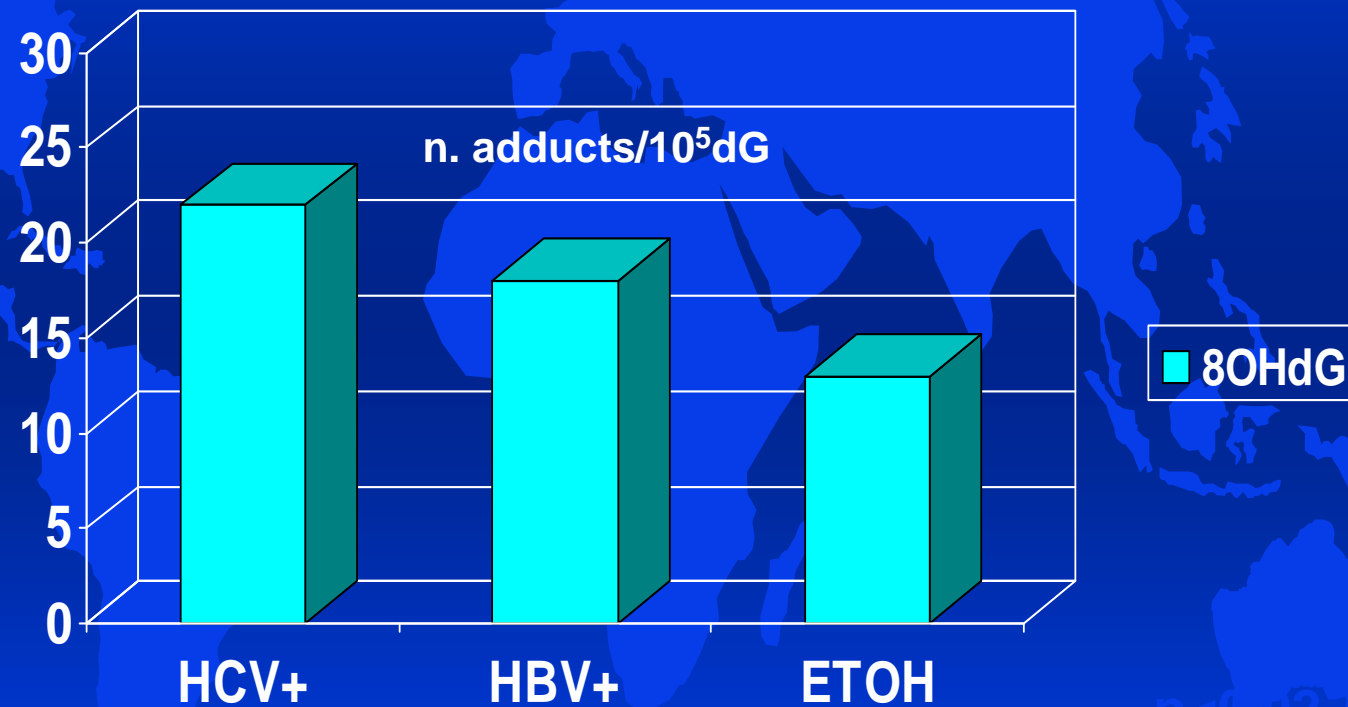
J.Hepatol, 1995

GSH tissue levels in chronic hepatitis



J.Hepatol, 1995

8OHdG LEVELS IN TUMOR TISSUE IN PATIENTS WITH HCC OF DIFFERENT ETIOLOGY



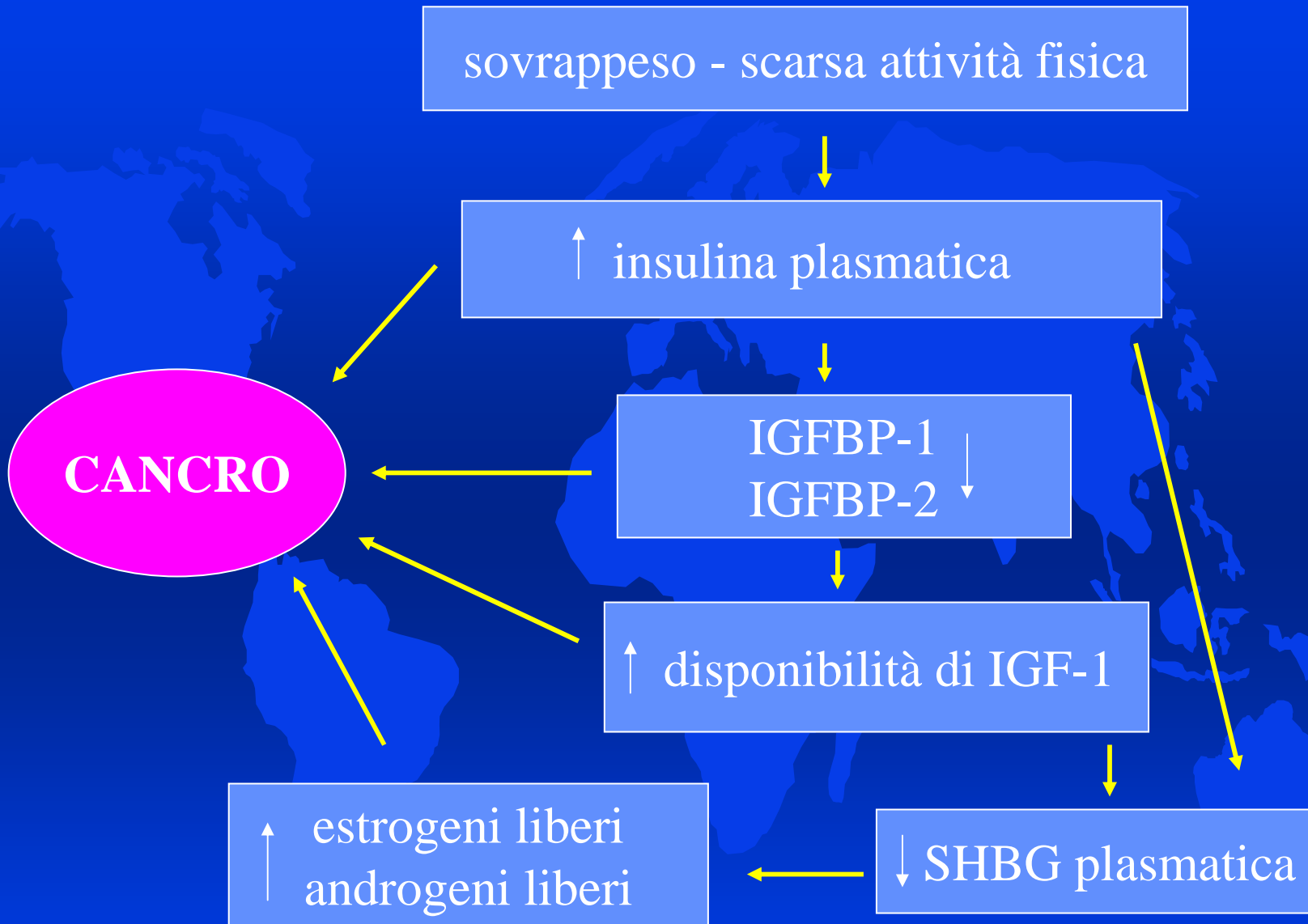
J.Hepatol, 2001

Alcol, Sovrappeso, obesità e cancro

- ◆ *alcohol consumption, especially daily , should be regarded as a risk factor for an increased body weight and obesity.*
- ◆ *In Europa il 50% circa della popolazione maschile ed il 35% di quella femminile è sovrappeso o obesa*
- ◆ *L'obesità aumenta il rischio di cancro per **colon**, mammella, endometrio, **esofago** e rene.....*
 - *alterazione ormoni endogeni*
 - ☞ *insulina*
 - ☞ *insulin-like growth factor*
 - ☞ *estrogeni*
 - ☞ *androgeni*
 - *alterazione bilancio citoproliferazione/apoptosi, differenziazione*

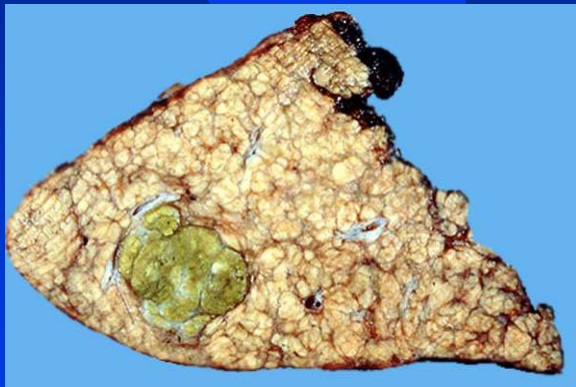
Bianchini F, 2002





Alcol, BMI e HCC

- ◆ ***19.271 biopsie di pz. con cirrosi epatica sottoposti a OLTx***
- ◆ ***incidenza dell'HCC (3.4%; n = 659) in relazione a BMI ed eziologia della cirrosi***
- ◆ ***analisi multivariata per controllare fattori confondenti come età e sesso***



Nair S. et al. Hepatology 2002

L'obesità rappresentava un fattore di rischio indipendente per HCC solo nei pz. con:

- epatopatia alcolica (OR 3.2; 95% CI 1.5-6.6; P=.002)***
- cirrosi criptogenetica (OR 11.1; 95%CI 1.5-87.4; P=.02)***

Interazioni “gene-enviroment”

- ◆ ***Amine eterocicliche e gene APC***
- ◆ ***Carcinogeni indiretti e stato acetilatore***
- ◆ ***Polimorfismi glutatione transferasi***
- ◆ ***Alcol e attività cit P450 E2***
- ◆ ***Espressione di geni codificanti per le mucine gastriche***
- ◆ ***Polimorfismi genetici per le interleukine***
- ◆ ***.....***
- ◆ ***.....***



Ann N Y Acad Sci. 2004 Nov;1025:472-80.

Influence of genetic variations of ethanol-metabolizing enzymes on phenotypes of alcohol-related disorders.

Higuchi S, Matsushita S, Masaki T, Yokoyama A, Kimura M, Suzuki G, Mochizuki H. Institute of Clinical Research, National Alcoholism Center Kurihama Hospital, 5-3-1 Nobi, Yokosuka, Kanagawa, 239-0841, Japan.

.....the less active allele of the ADH2 gene (ADH2*1) is associated with an increased risk for alcohol dependence, alcohol-induced persistent amnestic disorder, alcohol withdrawal syndrome, and cancer.

Dieta e Cancro

***Scuola della Sanità Pubblica di Harvard,
dipartimento di Epidemiologia e Nutrizione.***

Alcol e bevande contenenti caffeina

Alti consumi di alcol sono una causa accertata di cancro alla cavità orale, laringe, esofago e fegato. Una o due dosi al giorno di alcol aumentano il rischio di cancro al seno. Consumi più alti di alcol sembrano associati col rischio di cancro al colon e del retto.

CODICE EUROPEO CONTRO IL CANCRO

Adottando uno stile di vita più sano è possibile evitare taluni tipi di cancro e migliorare lo stato di salute.

- 1. Non fumare. Se fumi, smetti il più presto possibile e non fumare in presenza di altri. Se non fumi, non provare a farlo.***
- 2. Se bevi alcolici, birra, vino o liquori, moderane il consumo.***


Vino rosso e cancro

- ◆ **Polifenoli ad azione anticarcinogenetica**

- quercetina
- catechina
- trans resveratrolo
- acido gallico

- ◆ **Effetti:**

- aumentata apoptosi
- arresto di crescita
- inibizione sintesi DNA
- modulazione “signal transduction”



Abuso:
Ca esofago
Ca retto
Ca pancreas
EpatoCa

Soleas GJ, 2002

Moderato consumo di Alcol e rischio di morte

Table 2. Cox Proportional Hazard Ratios for Dietary Pattern and 3 Lifestyle Factors for 10-Year All-Cause and Cause-Specific Mortality in Elderly Europeans

Variables	Causes of Death, Hazard Ratio (95% Confidence Interval) ^a				
	All Causes	Coronary Heart Disease	Cardiovascular Disease	Cancer	Other Causes
No. at risk	2339	2152	2152	2152	2145
No. of events	935	122	371	233	145
Protective factors [†]					
Mediterranean diet	0.77 (0.68-0.88)	0.61 (0.43-0.88)	0.71 (0.58-0.88)	0.90 (0.70-1.17)	0.61 (0.44-0.85)
Moderate alcohol consumption	0.78 (0.67-0.91)	0.60 (0.40-0.88)	0.74 (0.59-0.93)	0.73 (0.54-0.98)	0.63 (0.44-0.90)
Physical activity	0.63 (0.55-0.72)	0.72 (0.48-1.07)	0.65 (0.52-0.81)	0.64 (0.48-0.84)	0.52 (0.37-0.74)
Nonsmoking	0.66 (0.57-0.75)	0.60 (0.54-1.17)	0.68 (0.54-0.85)	0.47 (0.36-0.62)	0.92 (0.59-1.24)

^aModel adjusted for the other dietary and lifestyle factors, age, sex, number of years of education, body mass index, and study.

[†]To achieve protective factors in each category, participants must have scored at least 4 points for the Mediterranean diet score, consumed more than 0 g of alcohol a day, scored in the intermediate or highest tertile for either the Voormits or Morris questionnaires, and were nonsmokers or had quit smoking for at least 15 years.

Ann Epidemiol. 2005

***The influence of duration of follow-up on the association between alcohol and cause-specific mortality in a prospective cohort study.
Nielsen NR et al., Denmark (G.J.)***



The apparent protective effect of a moderate alcohol consumption on coronary heart disease attenuated during prolonged follow-up, whereas moderate alcohol consumption became associated with higher risk of death from cancer with longer follow-up.

National Institute on Alcohol Abuse and Alcoholism Report on Moderate Drinking

- ◆ ***Alcohol is associated with an increase risk of breast cancer; the relative risk for moderate intake is small but relevant in females with family history***
- ◆ ***Moderate alcohol intake may potentiate other hepato-toxins with respect to HCC***

Alcoholism Clin.Ex.Res, 2004

And that's it for moderate!



***L'alcol non è un
carcinogeno diretto !***

***Agisce da promotore del
processo carcinogenetico***

Biochem Biophys Res Commun. 2004 Dec.

Abrogation of hepatocyte apoptosis and early appearance of liver dysplasia in ethanol-fed p53-deficient mice.

Pani G et al. Institute of General Pathology, Catholic University Rome, Italy.

....marked and widespread dysplasia.... heralding malignant transformation were scored in all the mutant mice exposed to ethanol, but not in the control-fed littermates nor in ethanol-fed normal mice.

These observations suggest that p53-dependent apoptosis restrains the tumorigenic effect of ethanol on liver cells.... and reveal an unexpected carcinogenic potential of alcohol which appears to be independent from the induction of cirrhosis and hepatocyte regeneration

Cancer Gene Therapy (2004), 1-8

© 2004 Nature Publishing Group All rights reserved 0929-1903/04 \$30.00



www.nature.com/cgt

Suicide gene therapy: conversion of ethanol to acetaldehyde mediated by human beta 2 alcohol dehydrogenase

Philip Savage,¹ Pam Cowburn,¹ Dahn Clemens,² Thomas Hurley,³ Bim Laguda,⁴ Pilar Martin-Duque,⁴ Georges Vassaux,⁵ and Nick R Lemoine⁵

***GOOD NEWS FROM
ALCOHOL !***

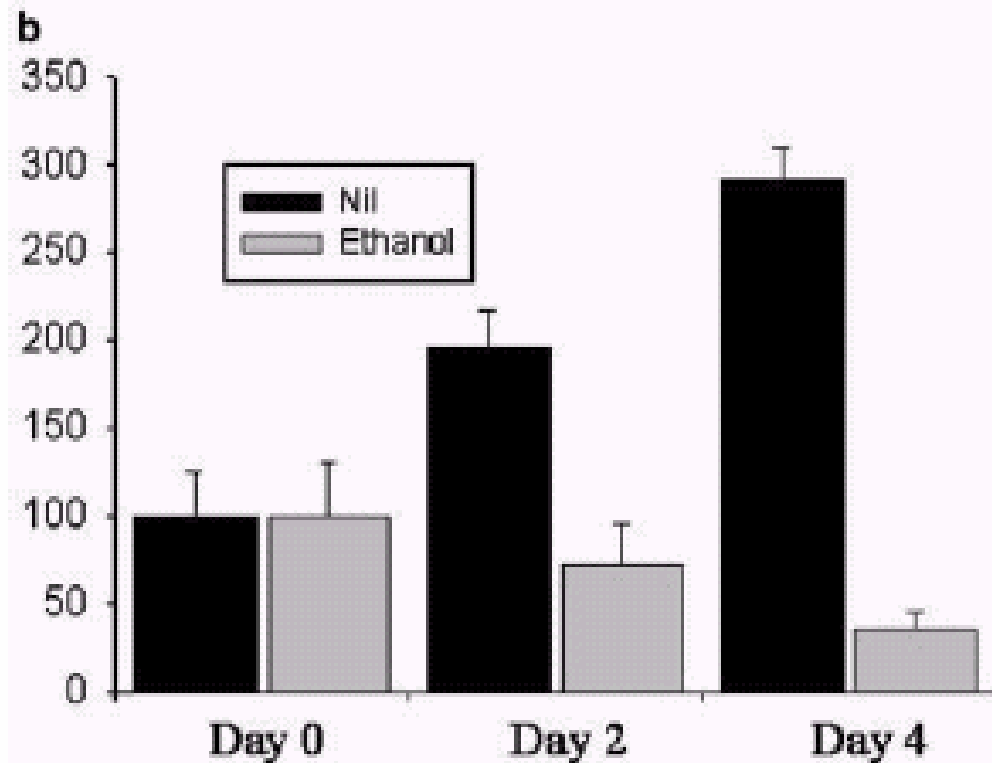
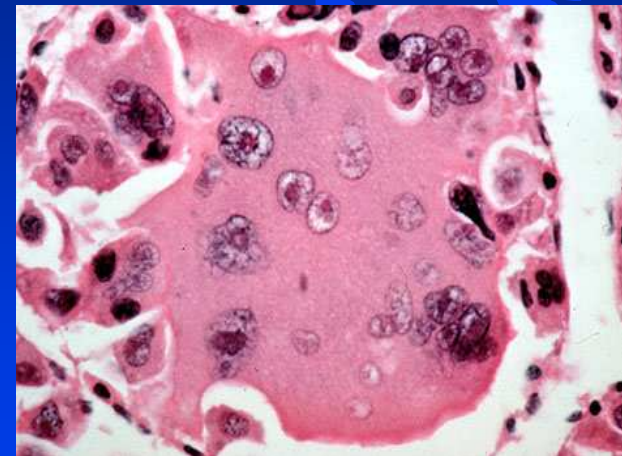
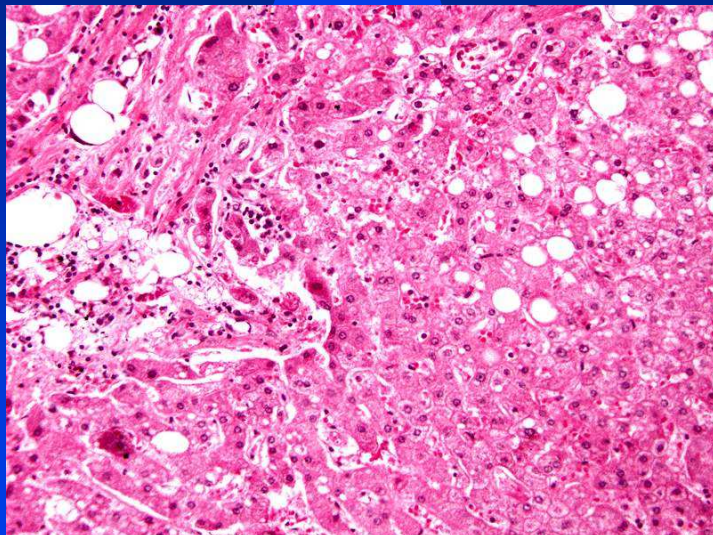
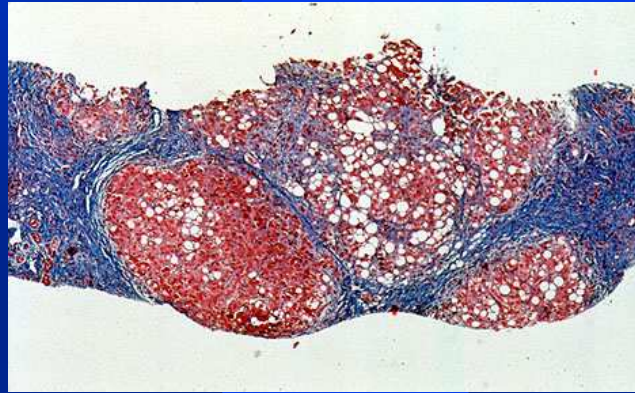


Figure 3 (a) Effects of ethanol exposure on native CMT-64, Ad-ADH-transduced CMT-64 cells and ADH-transfected VA-13 cells. The addition of ethanol resulted in changes to cell numbers to 184% for CMT-64 (500:1), 74% for CMT-64 (1000:1) and 75% for VA-13.

The ability to selectively express ADH and thus produce acetaldehyde within malignant, infected or other diseased cells may allow selective cytotoxicity to be produced with an economic, simple and well-tolerated system as either a monotherapy or in combination with conventional cytotoxic agents. This system should allow

Alcol e carcinogenesi





***"Ogni piacere dei mortali è mortale."
(Montaigne)***