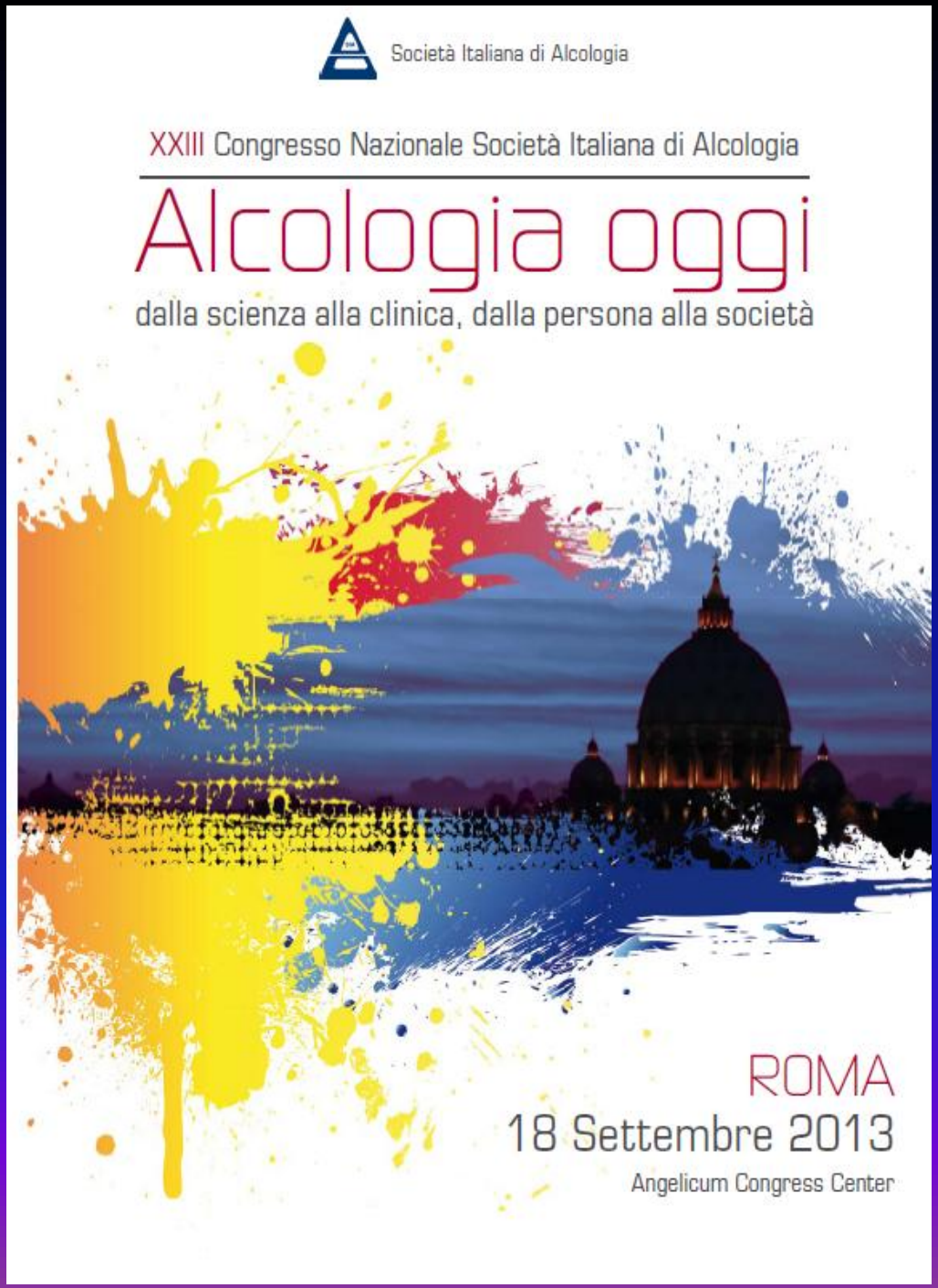


Gianni Testino

Centro Alcologico Regionale – Regione Liguria

UO Alcologia e Patologie Correlate

Dip. Medicina Interna e Specialistica

IRCCS AOU San Martino-Istituto Nazionale per la Ricerca sul Cancro, Genova

Emanuele Scafato (a), Silvia Ghirini (a), Luca Casertano (b)
(a) Centro Nazionale di Epidemiologia, Sorveglianza e Promozione della salute, CNESPS; Centro Organizzazione Mondiale della Sanità Ricerca sull'Alcol, Istituto Superiore di Sanità; (b) Lazioanità, Agenzia di Sanità Pubblica della Regione Lazio

L'assunzione acuta di alcol comporta

- *conseguenze organiche*
  - epatiti
  - esofagite
  - dispepsia
  - gastrite
  - uricemia
  - pancreatite
  - aritmie cardiache
  - traumi
  - reazioni con altre sostanze
  - danni al feto
  - reazioni con i farmaci
- *conseguenze psicologiche*
  - riduzione delle capacità cognitive
  - depressione
  - ansia
  - tentati suicidi
  - problemi psicologici dei figli
  - insonnia
- *conseguenze sociali*
  - violenze familiari
  - disgregazione familiare
  - abuso sui minori
  - incidenti domestici
  - incidenti sul lavoro
  - difficoltà sul lavoro
  - problemi di ordine pubblico
  - gravidanze indesiderate

L'assunzione cronica di alcol comporta per l'

- *conseguenze organiche*
  - steatosi epatica
  - cirrosi
  - demenza
  - epatocarcinoma
  - varici esofagee
  - gastroduodeniti
  - pancreatiti
  - carcinoma bocca, laringite, esofago, fe;
  - danni al sistema nervoso
  - obesità
  - diabete
  - miopatie
  - neuropatie
  - deficienze nutrizionali
  - disfunzioni sessuali
  - impotenza
  - ipogonadismo
  - alterazioni mestruali
  - alterazioni del sistema immunitario
  - patologie oculari
  - patologie dermatologiche
  - danni ai reni
  - ipertensione arteriosa
  - gotta
- *conseguenze psicologiche*
  - insonnia
  - disturbi di personalità
  - amnesie
  - tentati suicidi
  - allucinazioni
- *conseguenze sociali*
  - problemi familiari
  - senza fissa dimora
  - difficoltà sul lavoro
  - instabilità lavorativa
  - incidenti sul lavoro
  - disoccupazione
  - problemi giudiziari
  - problemi finanziari
  - gioco d'azzardo
  - assunzione di altre sostanze
  - poliassunzioni di sostanze nei figli

Scafato et al. Alcol e Salute,

ISS – Centro Collaboratore OMS 2012

ALCOHOL

Fatty Liver **Chronic Pancreatitis** **Parotid Hypertrophy** **Carcinogenesis***

Alcohol Hepatitis/Fibrosis

Cirrhosis

Hepatocellular Carcinoma

Glossitis

Stomatitis

Gastro-Esophageal Reflux

Mallory-Weiss Syndrome

Chronic Gastritis

Erosive Hemorrhagic Gastritis

Delayed Gastric Emptyimg

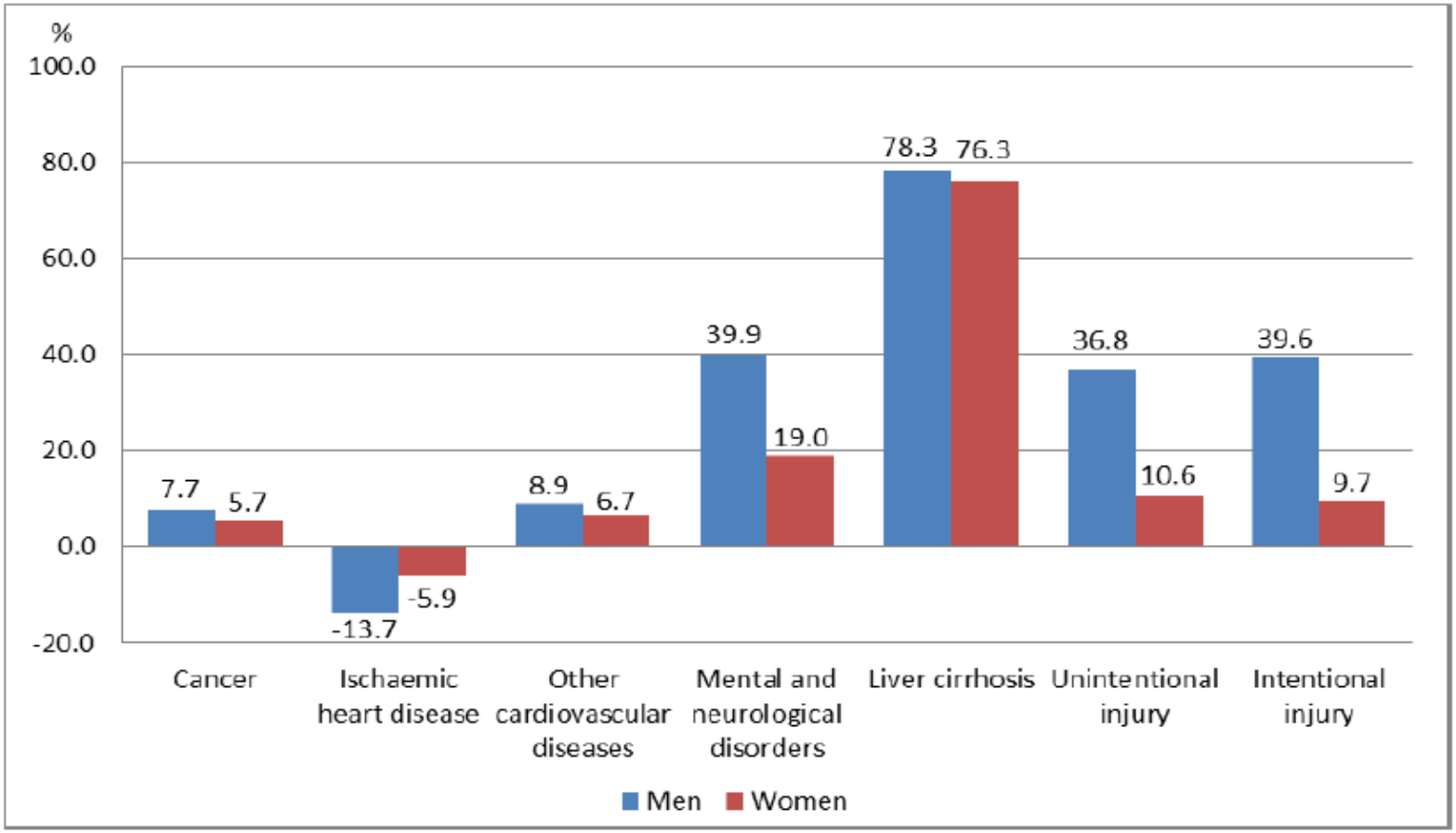
Malabsorption

Reduce Transit Time

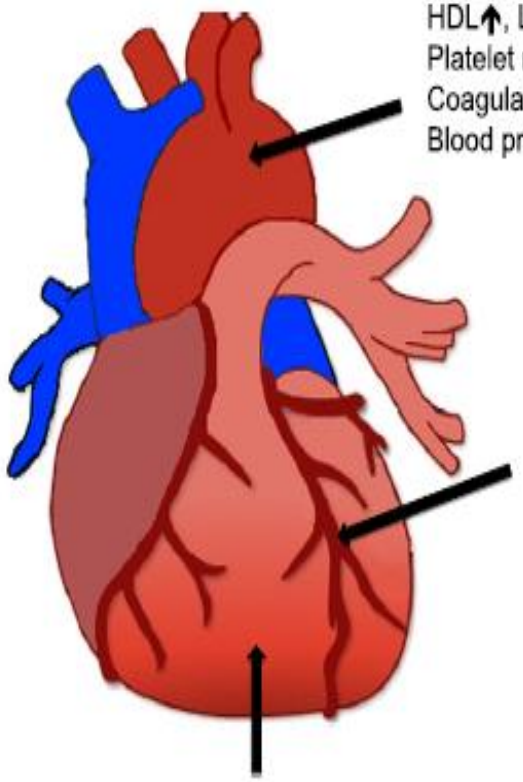
***Upper Aero-Digestive Tract, Colon, Rectum, Breast, Liver, Pancreas**

Testino G.
Hepatogasroenterology 2008

Proportion of deaths for major disease categories attributable to alcohol



The Spectrum of Cardioprotective Effects Induced by Antecedent Ethanol Ingestion



Blood:
HDL↑, LDL↓
Platelet reactivity↓
Coagulation↓
Blood pressure↓

Coronary vessels:
Vasodilation↑
Coronary flow↑
Inflammation↓
Atherosclerosis↓
Diabetic vasculopathy↓

Cardiomyocytes:
Protective signaling against I/R-induced tissue damage↑

Krenz and Korthuis; Journal of Molecular and Cellular Cardiology, 2012

ALCOHOL
and HEART DISEASE

….from both the public health and clinical viewpoints, there is no merit in promoting alcohol consumption as a preventive strategy

World Health Organization, 2007

World Health Organization
REGIONAL OFFICE FOR Europe

Alcohol in the European Union

Consumption, harm and policy approaches

Cardiovascular disease

Alcohol use is related overwhelmingly detrimentally to many cardiovascular outcomes, including hypertensive disease (Taylor et al., 2009), haemorrhagic stroke (Patra et al., 2010) and atrial fibrillation (Samokhvalov, Irving & Rehm, 2010). For ischaemic heart disease and ischaemic stroke, the relationship is more complex. Chronic heavy alcohol use has been associated uniformly with adverse cardiovascular outcomes (Rehm & Roerecke, 2011). But, on average, light to moderate drinking has a protective effect on ischaemic diseases (Roerecke & Rehm, in press).This effect is found to be equal for people who just drink beer or who just drink wine (Di Castelnuovo et al., 2002). More and more, however, it is being understood that a large part of this effect is due to confounders (Roerecke & Rehm, 2010), with low to moderate alcohol use being a proxy for better health and social capital (Hansel et al., 2010). In any case, the protective effect totally disappears when drinkers report at least one heavy drinking occasion per month (Roerecke & Rehm, 2010); there is no protective effect for younger people, for whom any dose of alcohol increases the risk of ischaemic events (Juonala et al., 2009); and, in older people, a greater reduction in death from ischaemic heart disease can be more effectively obtained by being physically active and eating a healthier diet than by drinking a low dose of alcohol (Mukamal et al., 2006).The detrimental effects of heavy drinking occasions on ischaemic diseases are consistent with the physiological mechanisms of increased clotting and a reduced threshold for ventricular fibrillation which occur following heavy drinking (Rehm et al., 2010).

World Health Organization, 2012

Pooled Relative Risks for Ischemic Heart Disease
in former Drinkers Compared With
Long-Tem Abstainers, by Sex and EndPoint,1980-2010

Sex,EndPoint,and Model	No.of Studies	Pooled relative Risk
Men		
Mortality		
All available estimates (combined sex or endpoint incluted)	27	1.21
Stratified by sex and endpoint	14	1.25
Woman		
Mortality		
All available estimates (combined sex or endpoint incluted)	18	1.36
Stratified by sex and endpoint	10	1.54

Roerecke M and Rehm J, American Journal of Epidemiology 2010

NATIONAL HEART FOUNDATION: POSITION STATEMENT

In Australia, the National Heart Foundation explicity advises against the consumption of red wine and other types of alcoholic drinks for the preventig or treatment of heart disease

National Heart Foundation of Australia, 2010

Drinking alcohol is well known to be positively associated with the development of hypertension.

Alcohol consumption is linearly related to increased blood pressure.

Okubo et al; Alcohol 2001

Wakabayashi and Araki; Alcohol Clin Exp Res 2010

Scafato et al; ISS 2010

Higashiyama et al, Hypertension Research 2013

WORLD HEALTH ORGANIZATION
International Agency for Research on Cancer
(IARC)
Evaluation of Carcinogenic Risks to Humans

Group 1 Carcinogenic to humans
(arsenic, asbesto, benzene, radionuclide, tobacco smoking …..)

Group 2 A Probably carcinogenic to humans

Group 2B Possibly carcinogenic to humans
(radio frequency elettromagnetic fields from wireless phones ….)

Group 3 Unclassifiable as to carcinogenicity in humans

Group 4 Probably not carcinogenic to humans

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

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.

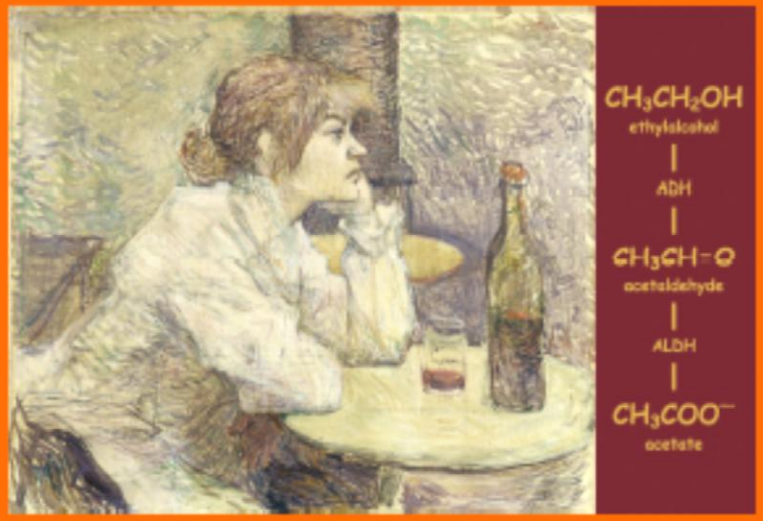
Table: Evidence for carcinogenicity in humans of Group 1 agents assessed

WORLD HEALTH ORGANIZATION
INTERNATIONAL AGENCY FOR RESEARCH ON CANCER

IARC Monographs on the Evaluation of Carcinogenic Risks to Humans

VOLUME 96

Alcohol Consumption and Ethyl Carbamate



LYON, FRANCE
2010

WORLD HEALTH ORGANIZATION
INTERNATIONAL AGENCY FOR RESEARCH ON CANCER

IARC Monographs on the Evaluation of Carcinogenic Risks to Humans

VOLUME 100

A Review of Human Carcinogens

Part E: Personal Habits and Indoor Combustions

LYON, FRANCE

2012

Agents Classified by the *IARC Monographs*, Volumes 1–104

CAS No	Agent	Group	Volume	Year
000075-07-0	Acetaldehyde associated with consumption of alcoholic beverages	1	100E	2012
	Acid mists, strong inorganic	1	54, 100F	2012
001402-68-2	Aflatoxins	1	56, 82, 100F	2012
	Alcoholic beverages	1	44, 96, 100E	2012
	Aluminium production	1	34, Sup 7, 100F	2012
000092-67-1	4-Aminobiphenyl	1	1, Sup 7, 99, 100F	2012
	Areca nut	1	85, 100E	2012
000313-67-7	Aristolochic acid (NB: Overall evaluation upgraded to Group 1 based on mechanistic and other relevant data)	1	82, 100A	2012
000313-67-7	Aristolochic acid, plants containing	1	82, 100A	2012
007440-38-2	Arsenic and inorganic arsenic compounds	1	23, Sup 7, 100C	2012
000064-17-5	Ethanol in alcoholic beverages	1	96, 100E	2012
000075-21-8	Ethylene oxide (NB: Overall evaluation upgraded to Group 1 based on mechanistic and other relevant data)	1	97, 100F	2012
033419-42-0	Etoposide (NB: Overall evaluation upgraded to Group 1 based on mechanistic and other relevant data)	1	76, 100A	2012
033419-42-0 015663-27-1 011056-06-7	Etoposide in combination with cisplatin and bleomycin	1	76, 100A	2012
	Fission products, including strontium-90	1	100D	2012
000050-00-0	Formaldehyde	1	88, 100F	2012

OMS, IARC 2012

2.19 Synthesis

2.19.1 Oral cavity and pharnyx

Data published since the previous *IARC monograph* (IARC, 2010) support the conclusion that consumption of alcoholic beverages is causally related to cancer of the oral cavity and pharynx. Increasing alcohol consumption increases risk in a dose-dependent manner, does not vary materially by beverage type or sex and the association is not due to chance, bias or confounding.

2.19.2 Larnynx

Data published since the previous *IARC Monograph* (IARC 2010) supports the conclusion that consumption of alcoholic beverages is causally related to cancer of the larynx. Increasing alcohol consumption increases risk in a dose-dependent manner, does not vary materially by beverage type or sex, and chance, bias and confounding can be ruled out.

2.19.3 Oesophagus

Data published since the previous *IARC Monograph* (IARC, 2010) supports the conclusion that consumption of alcoholic beverages is causally related to squamous cell carcinoma of the oesophagus. Increasing alcohol consumption increases risk in a dose-dependent manner, does not vary materially by beverage type or sex, and chance, bias and confounding can be ruled out. There is now a substantial body of evidence that alcoholic beverage consumption is not associated with adenocarcinoma of the oesophagus.

2.19.4 Upper aerodigestive tract

There is evidence that consumption of alcoholic beverages is causally related to cancer of the upper aerodigestive tract, as it is for cancer of the oral cavity and pharynx, larynx and oesophagus separately. Increasing alcohol consumption increases risk in a dose-dependent manner, does not vary materially by beverage type or sex and chance, bias and confounding can be ruled out.

2.19.5 Colon and rectum

Overall, the data published since the previous *IARC Monograph* (IARC, 2010) supports the conclusion that consumption of alcoholic beverages is causally related to cancer of the colorectum. Most of the evidence suggests that consumption of alcoholic beverages is positively associated with both cancer of the colon and cancer of the rectum, and is similar in men and women, although the data are not entirely consistent. Similarly, there is some evidence that risk may only be increased at relatively high levels of intake (i.e. > 30 g/d). There is consistent evidence that risk does not differ by beverage type; whether the risk associated with consumption of alcoholic beverages differs by smoking status or intake of dietary folate is inconsistent.

2.19.6 Liver

The new studies support the previous conclusion that the risk for hepatocellular carcinoma is causally related to the consumption of alcoholic beverages. It is not possible to draw any conclusion concerning consumption of alcoholic beverages and risk of cholangiocarcinoma.

OMS, IARC Volume 100 E, pag 450, 2012

2.19.8 Pancreas

There is accumulating evidence that high alcohol intake (i.e. ≥ 30 g/d) is associated with a small increased risk of cancer for the pancreas. However, the possibility that residual confounding by smoking may partly explain this association cannot be excluded. Whether the risk associated with heavy alcohol consumption differs by beverage type, smoking status or body mass index requires further investigation.

2.19.10 Breast

Occurrence of cancer of the female breast is causally associated with the consumption of alcoholic beverages. Cancer risk increases proportionately according to the amount of alcohol consumed, with an increase in risk of up to 12% for each additional drink consumed regularly each day (equivalent to about 10 g/d). The risk does not appear to vary significantly by beverage type or smoking status. It remains

World Health Organization, IARC, Volume 100 E, pag. 451 2012

There is *sufficient evidence* in humans for the carcinogenicity of alcohol consumption. Alcohol consumption causes cancers of the oral cavity, pharynx, larynx, oesophagus, colorectum, liver (hepatocellular carcinoma) and female breast. Also, an association has been observed between alcohol consumption and cancer of the pancreas.

For cancer of the kidney and non-Hodgkin lymphoma, there is *evidence suggesting lack of carcinogenicity.*

There is *sufficient evidence* in humans for the carcinogenicity of acetaldehyde associated with the consumption of alcoholic beverages. Acetaldehyde associated with the consumption of alcoholic beverages causes cancer of the oesophagus and of the upper aerodigestive tract combined.

There is *sufficient evidence* in experimental animals for the carcinogenicity of ethanol.

There is *sufficient evidence* in experimental animals for the carcinogenicity of acetaldehyde.

Alcohol consumption is *carcinogenic to humans (Group 1).*

Ethanol in alcoholic beverages is *carcinogenic to humans (Group 1).*

Acetaldehyde associated with the consumption of alcoholic beverages is *carcinogenic to humans (Group 1).*

World Health Organization, International Agency for Cancer Research,

Volume 100 E, pag. 476 – Lyon, France 2012

Alcohol Attributable Burden of Incidence of Cancer in Eight European Countries* Based on Results from Prospective Cohort Study

* Denmark, France, Germany, Greece, Italy, the Netherlands, Spain, UK

…among men and women, 10% (95% confidence interval 7 to 13%) and 3% (1 to 5%) of the incidence of total cancer was attributable to former and current alcohol consumption……

Alcohol Attributable Fractions:

upper aerodigestive tract	44% for men and 25% for women
liver	33% for men and 18% for women
colorectal	17% for men and 4% for women
female breast	5%

BMJ 2011; 342: d1564

Alcohol-Attributable Cancer Deaths and Years of Potential Life Lost in the United States

David E. Nelson, MD, MPH, Dwayne W. Jarman, DVM, MPH, Jürgen Rehm, PhD, Thomas K. Greenfield, PhD, Grégoire Rey, PhD, William C. Kerr, PhD, Paige Miller, PhD, MPH, Kevin D. Shield, MHSc, Yu Ye, MA, and Timothy S. Naimi, MD, MPH

Objectives. Our goal was to provide current estimates of alcohol-attributable cancer mortality and years of potential life lost (YPLL) in the United States.

Methods. We used 2 methods to calculate population-attributable fractions. We based relative risks on meta-analyses published since 2000, and adult alcohol consumption on data from the 2009 Alcohol Epidemiologic Data System, 2009 Behavioral Risk Factor Surveillance System, and 2009–2010 National Alcohol Survey.

Results. Alcohol consumption resulted in an estimated 18 200 to 21 300 cancer deaths, or 3.2% to 3.7% of all US cancer deaths. The majority of alcohol-attributable female cancer deaths were from breast cancer (56% to 66%), whereas upper airway and esophageal cancer deaths were more common among men (53% to 71%). Alcohol-attributable cancers resulted in 17.0 to 19.1 YPLL for each death. Daily consumption of up to 20 grams of alcohol (≤ 1.5 drinks) accounted for 26% to 35% of alcohol-attributable cancer deaths.

Conclusions. Alcohol remains a major contributor to cancer mortality and YPLL. Higher consumption increases risk but there is no safe threshold for alcohol and cancer risk. Reducing alcohol consumption is an important and underemphasized cancer prevention strategy. (*Am J Public Health.* Published online ahead of print February 14, 2013: e1–e8. doi:10.2105/AJPH.2012.301199)

Alcohol use is estimated to account for about 4% of all deaths worldwide.[1] Research over several decades has consistently shown that alcohol increases the risk for cancers of the oral cavity and pharynx, larynx, esophagus, and liver.[2–5] The biological mechanisms by which alcohol induces cancer are not fully understood, but may include genotoxic effects of acetaldehyde, production of reactive oxygen or nitrogen species, changes in folate metabolism, increased estrogen concentration, or serving as a solvent for tobacco metabolites.[5]

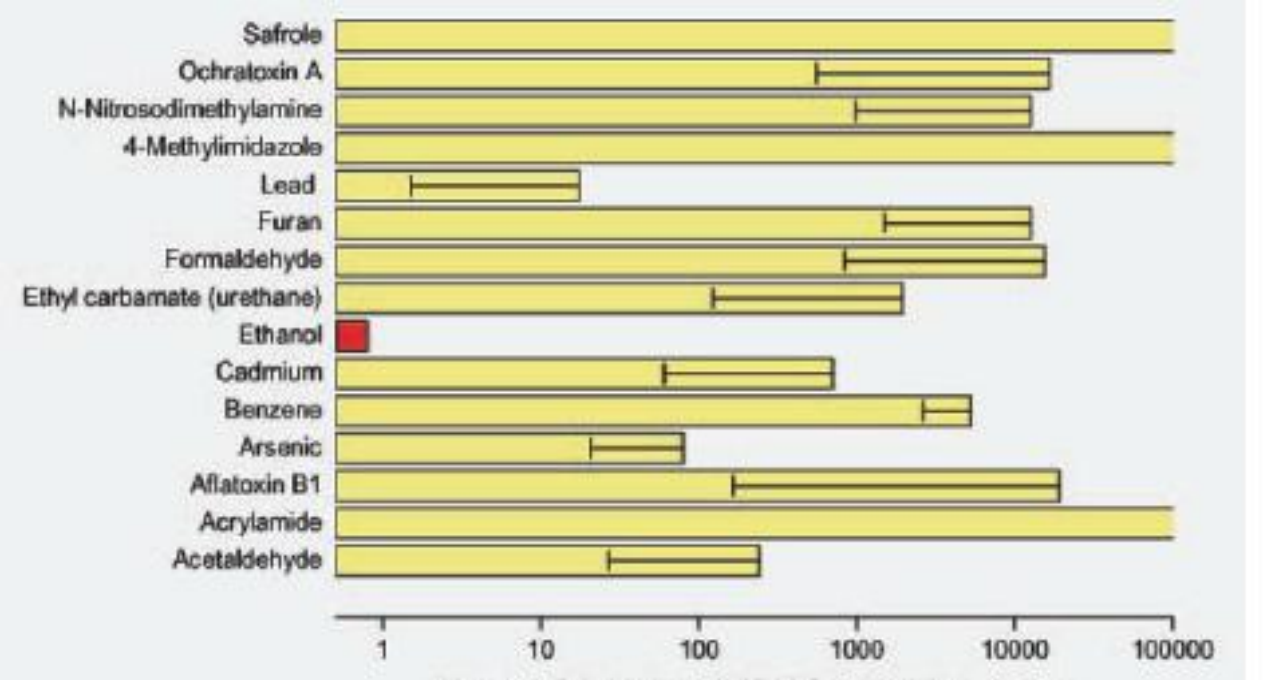
The International Agency for Research on Cancer (IARC) and the World Cancer Research Fund/American Institute for Cancer Research (WCRF/AICR) both published comprehensive reviews of the scientific literature on alcohol and cancer risk in 2007.[5–7] In addition to confirming earlier research for the previously mentioned cancers, they con-

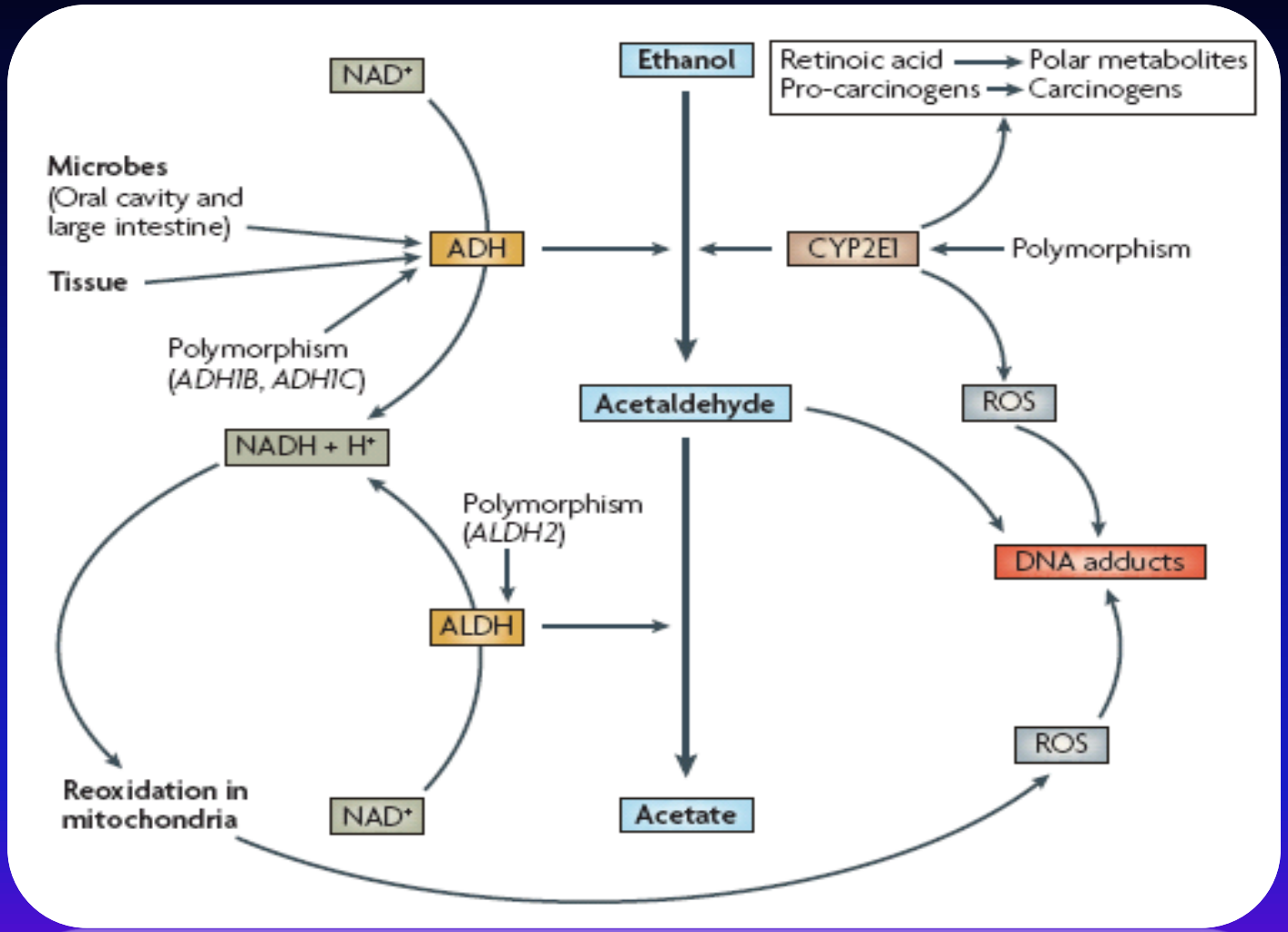
Table 1. Summary of WHO International Agency for Research on Cancer (IARC) evaluation of carcinogenicity of substances that may be present in alcoholic beverages (updated from IARC[2])

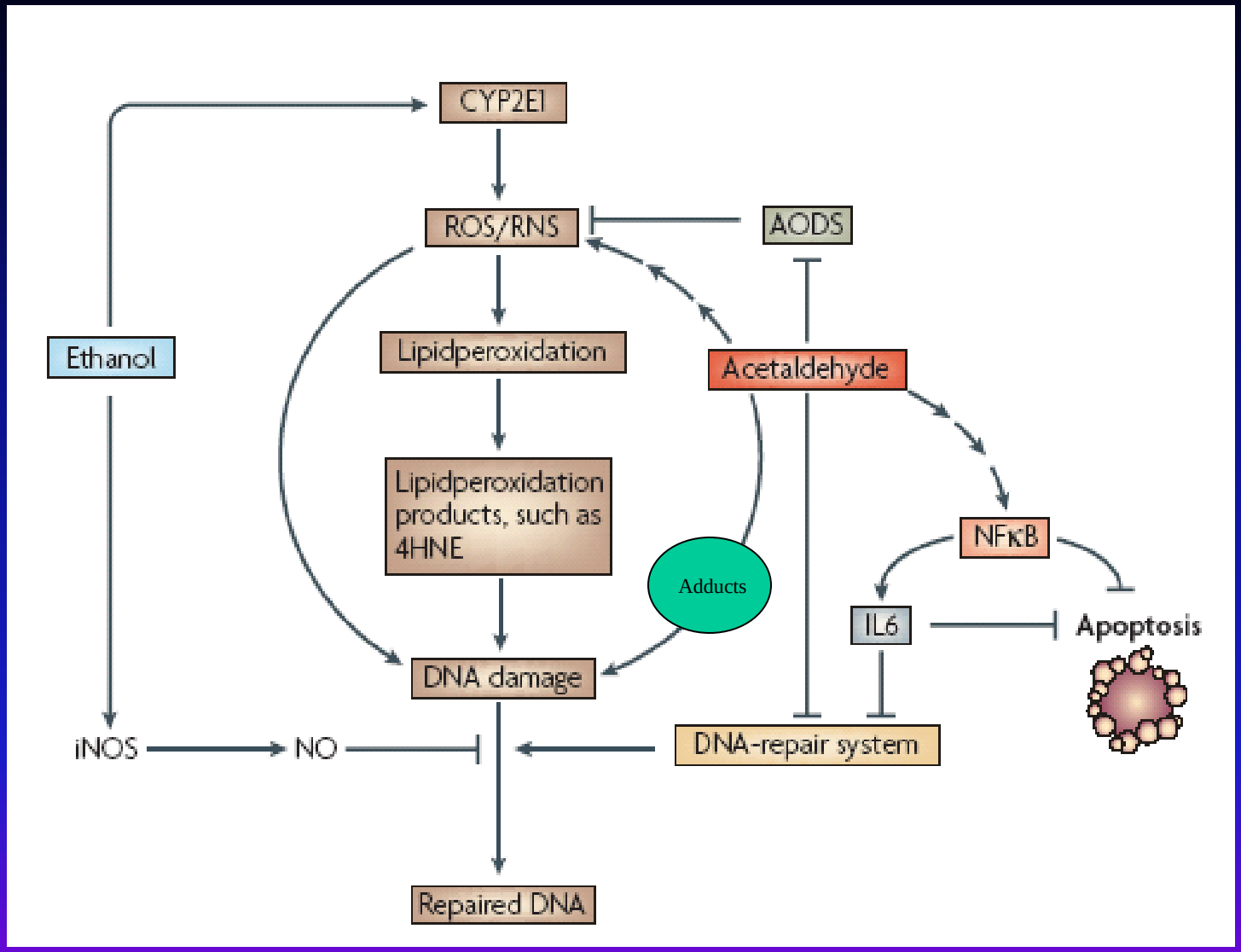
Agent	*IARC Monographs* evaluation of Carcinogenicity			
	In animals	In humans	IARC group[1]	*IARC Monographs* (Volume Number)
Acetaldehyde associated with consumption of alcoholic beverages	Sufficient	Sufficient	1	36, Sup 7, 71, 100E
Acrylamide	Sufficient	Inadequate	2A	60
Aflatoxins	Sufficient	Sufficient	1	56, 82, 100F
Arsenic	Sufficient	Sufficient	1	23, Sup 7, 100C
Benzene	Sufficient	Sufficient	1	29, Sup 7, 100F
Cadmium	Sufficient	Sufficient	1	58, 100C
Ethanol in alcoholic beverages	Sufficient	Sufficient	1	44, 96, 100E
Ethyl carbamate (urethane)	Sufficient	Inadequate	2A	7, Sup 7, 96
Formaldehyde	Sufficient	Sufficient	1	88, 100F
Furan	Sufficient	Inadequate	2B	63
Lead compounds, inorganic	Sufficient	Limited	2A	87
4-Methylimidazole	Sufficient	Inadequate	2B	101
N-Nitrosodimethylamine	Sufficient	Inadequate	2A	17, Sup 7
Ochratoxin A	Sufficient	Inadequate	2B	56
Safrole	Sufficient	Inadequate	2B	10, Sup 7

[1]Group 1: Carcinogenic to humans; Group 2A: Probably carcinogenic to humans; Group 2B: Possibly carcinogenic to humans (for definitions of groups, see monographs.iarc.fr).

MARGINE OF EXPOSURE (MOE)




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

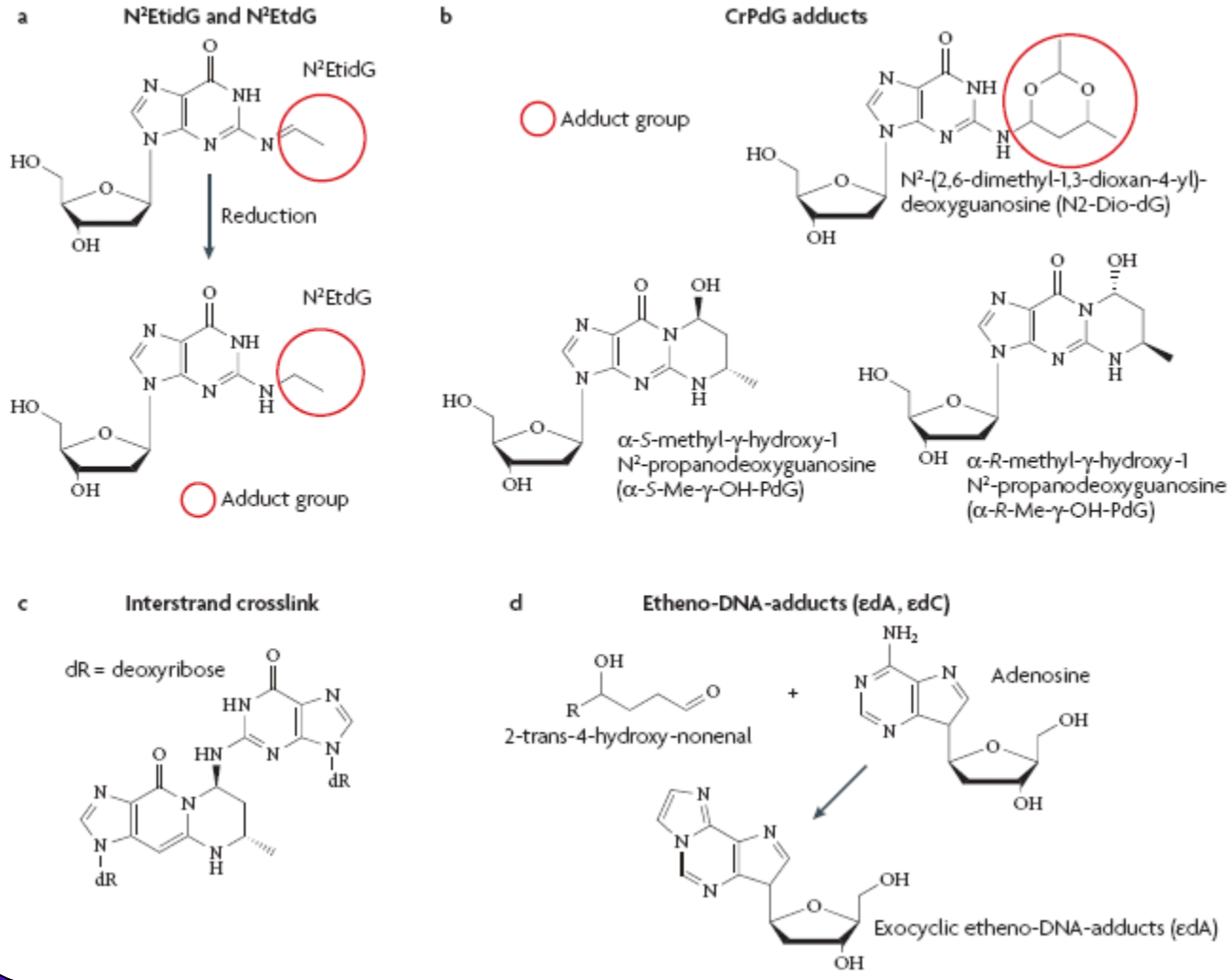
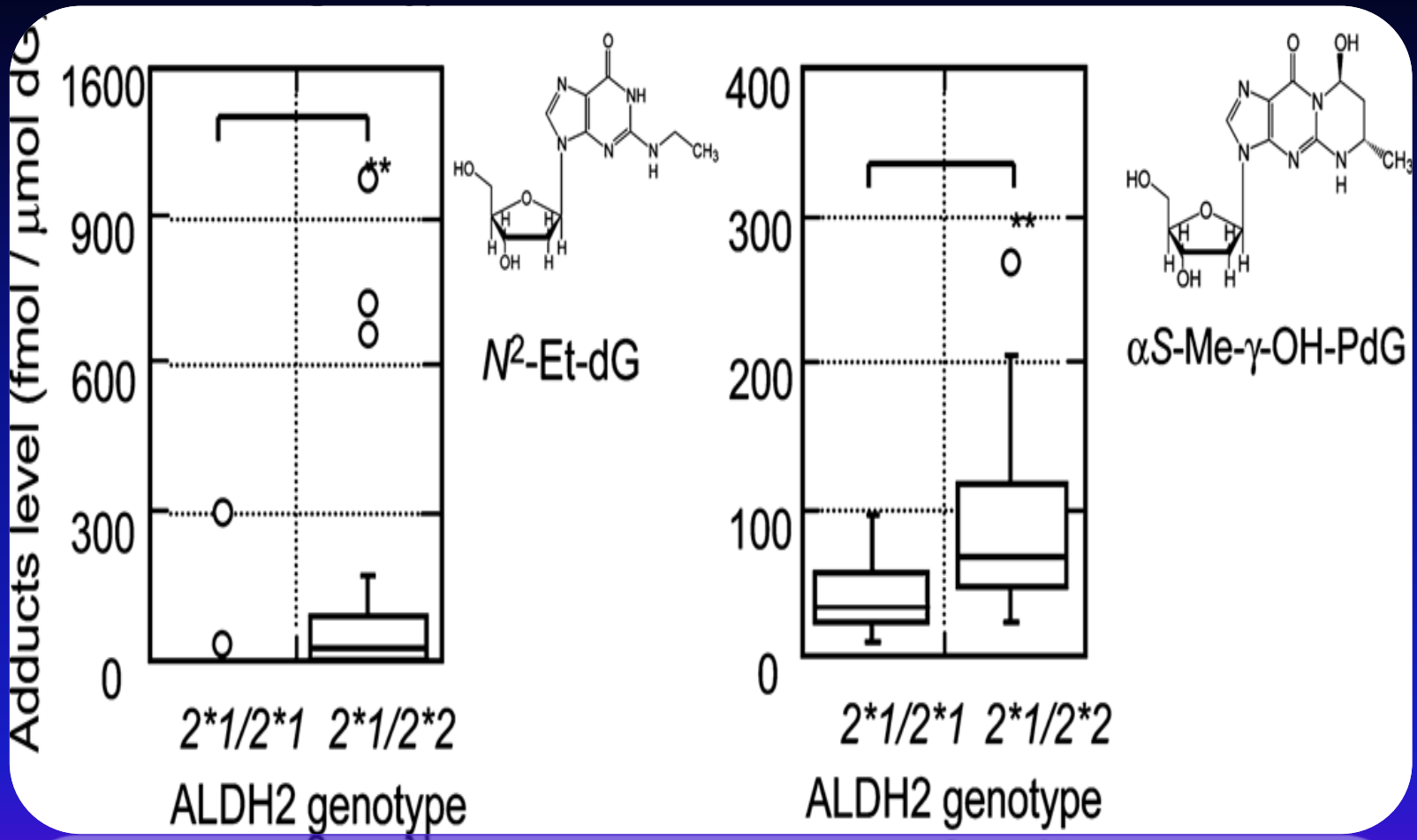

a
N²EtidG and N²EtdG
N²EtidG
Reduction
N²EtdG
Adduct group
b
CrPdG adducts
Adduct group
N²-(2,6-dimethyl-1,3-dioxan-4-yl)-deoxyguanosine (N2-Dio-dG)
α-S-methyl-γ-hydroxy-1 N²-propanodeoxyguanosine (α-S-Me-γ-OH-PdG)
α-R-methyl-γ-hydroxy-1 N²-propanodeoxyguanosine (α-R-Me-γ-OH-PdG)
c
Interstrand crosslink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

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

Table II. Relative risk (odds ratios) of digestive tract cancers among Japanese alcoholics after adjustment for confounders among ALDH2-deficient subjects compared with those with the normal ALDH2 enzyme.

Type of cancer	Odds ratios
Oropharyngolaryngeal	11.1
Oesophageal	12.5
Stomach	3.5
Colon	3.4
Oesophageal cancer concomitant with oropharyngolaryngeal and/or stomach cancer	54.2

Abbreviation: ALDH2 =mitochondrial aldehyde dehydrogenase.
Source: Yokyama et al. [20].

Yokoyama et al, Carcinogenesis 1998

IMPACT OF ALDH2-DEFICIENCY GENES ON THE RISK FOR OESOPHAGEAL CANCER

Genes/polymorphisms	Alcohol 1-30 g/day	Alcohol > 30/ g/day
ALDH2-active	OR <7.2	
ALDH2-deficiency	OR 14.5	OR 102.5
Slow ADH1B + ALDH2-deficiency	OR 37.5	OR 382.3

Salaspuro M, Scand J Gastroenterol 2009

vino e salute
Osservatorio Nazionale sul Consumo Consapevole del Vino

Wine in Moderation
Art de Vivre

Wine, food and cancer prevention

International Symposium of the European Cancer Prevention Organization (ECP)

Castle of Grinzane Cavour (Piedmont, Italy)
25th -26th of november 2011

L' "**International Congress on wine, food and cancer prevention**" si svolgerà il **25 e 26 novembre 2011**. Si tratta di un congresso internazionale sotto l'egida dell'**ECP** (**European Cancer Prevention Organization**), una delle più prestigiose Istituzioni di ricerca scientifica in Europa. L'ECP ha sede in Belgio e costituisce un network di ricerca con affiliazioni in tutti i Paesi europei. Pubblica una rivista scientifica assai quotata: l'EJCP (European Journal of Cancer Prevention) e coordina progetti di ricerca in vari settori della prevenzione oncologica incluso quello dei rapporti fra alimentazione e cancro.
L'obiettivo è quello di far luce su un tema di rilevante significato scientifico e sociale qual è il rapporto tra il consumo di alcuni cibi, il vino e la prevenzione. Porrà in evidenza come il consumo corretto e consapevole di alcuni alimenti e di vino sia fondamentale per prevenire rischi di carattere oncologico.

Fotogallery
workshop 5-7 Febbraio 2010

citazioni celebri

Chi beve solo acqua ha un segreto da nascondere.
(Charles Baudelaire, 1821- 1867).

Login
Nome utente
Password
Ricordami
Login

Password dimenticata?
Nome utente dimenticato?

Chi è online
3 visitatori online

Alcohol and Alcoholism Vol. 48, No. 5, pp. 627–628, 2013
Advance Access Publication 6 July 2013

doi: 10.1093/alcalc/agt064

LETTER TO THE EDITOR

Alcohol, Cardiovascular Disease and Cancer

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… the data on alcohol and cardiovascular disease are still correlative,
whereas the toxic effects of alcohol are well established.
Perhaps that is why some studies show a reduction in cardiovascular disease,
but not overall mortality, in patients who drink alcoholic beverages.

Substitution of one disease for another is not a medical advance.

……with respect to the prevention of cardiovascular disease, since a number of preventive therapies, such as exrcise, smoking cessation, and lowering of cholesterol levels and blood pressure, do not have undesirable effects of alcohol*.

Goldberg IJ, The New England Journal of Medicine, 2006

* 10 gr/die: increased risk of several common cancers

Lauer and Sorlier, J Natl Cancer Inst 2009

…… moderate drinking (12.5 g alcohol per day for women and 25 g alcohol per day for men) is associated with lower rates of cardiovascular disease but is not uniformly protective for other conditions, such as cancer.

Ronksley et al; BMJ 2011

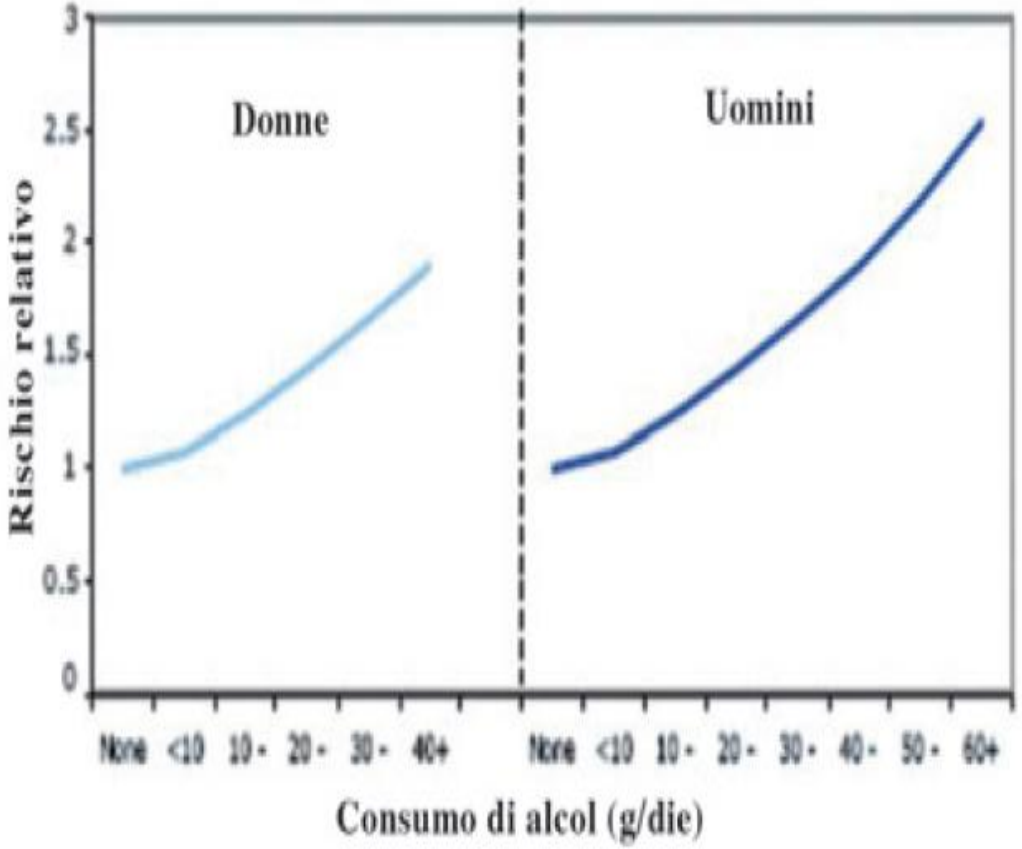


Figura 4.5. Rischio relativo di ipertensione per consumo alcolico.
Fonte: Strategy Unit (2003).

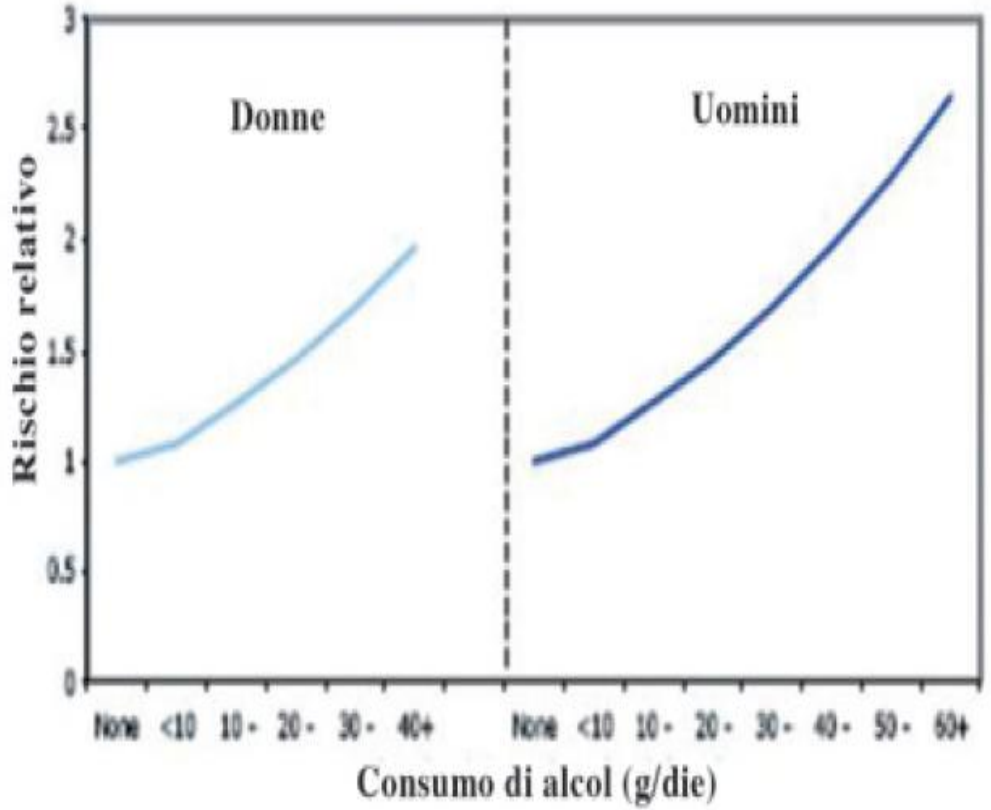


Figura 4.6. Rischio relativo di ictus emorragico per consumo alcolico. Fonte: Strategy Unit (2003).

Low doses of alcohol are associated with the risk of breast cancer

- **up to one drink per day***
- **3-6 drinks/ week****

*** Giacosa et al, Eur J Cancer Prev 2011**

**** Pelucchi et al, Nutr Cancer 2011**

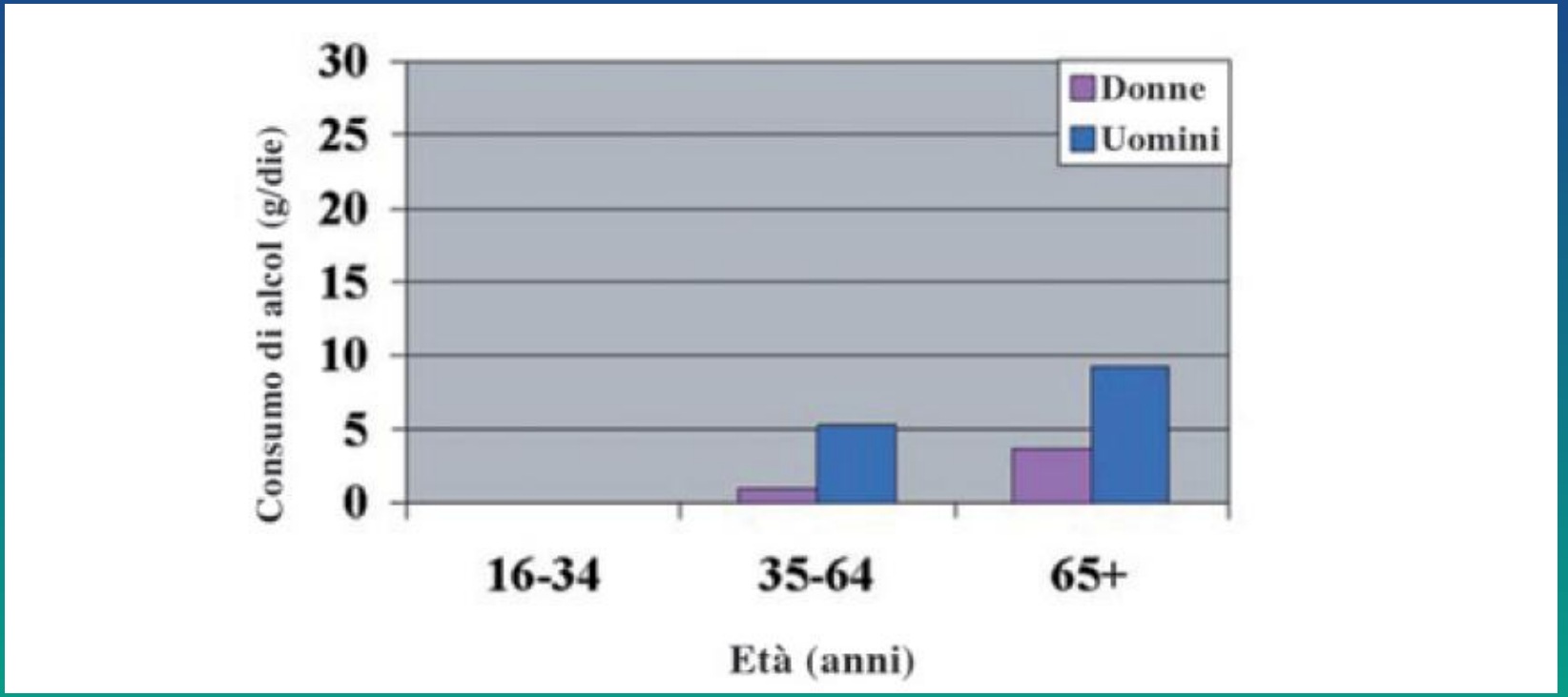
Prospective Study of Adolescent Alcohol Consumption and Risk of Benign Breast Disease in Young Women

Drinking Frequency	OR
Never to less than weekly	1.00 (referent)
1-2 U/ wk	1.72
3-5 U/ wk	3.34
6-7 U/ wk	5.94

Berkey CS et al, Pediatrics 2010

Printz C, Cancer 2010

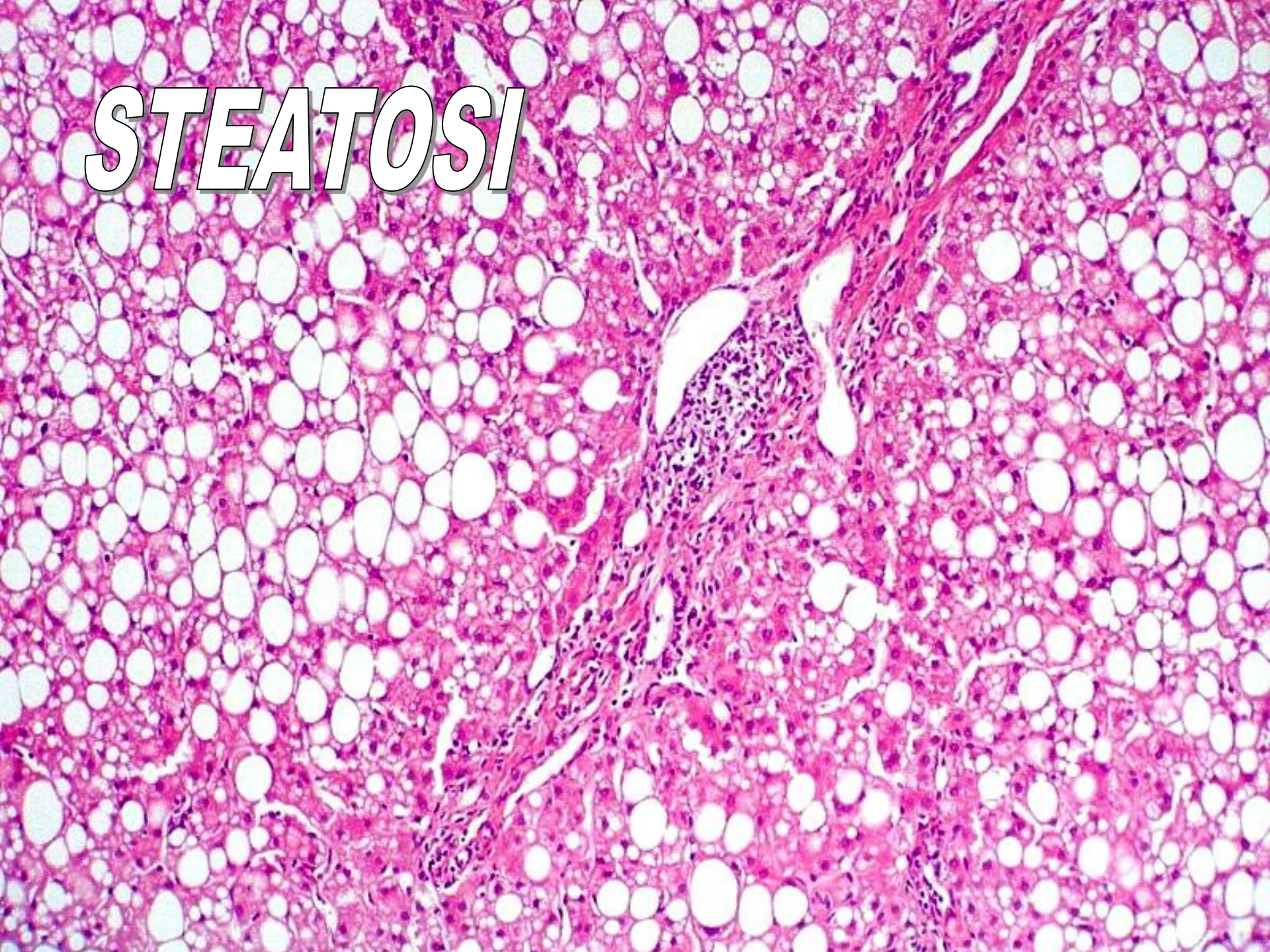
Livello di Consumo di Alcol associato al minor rischio di morte

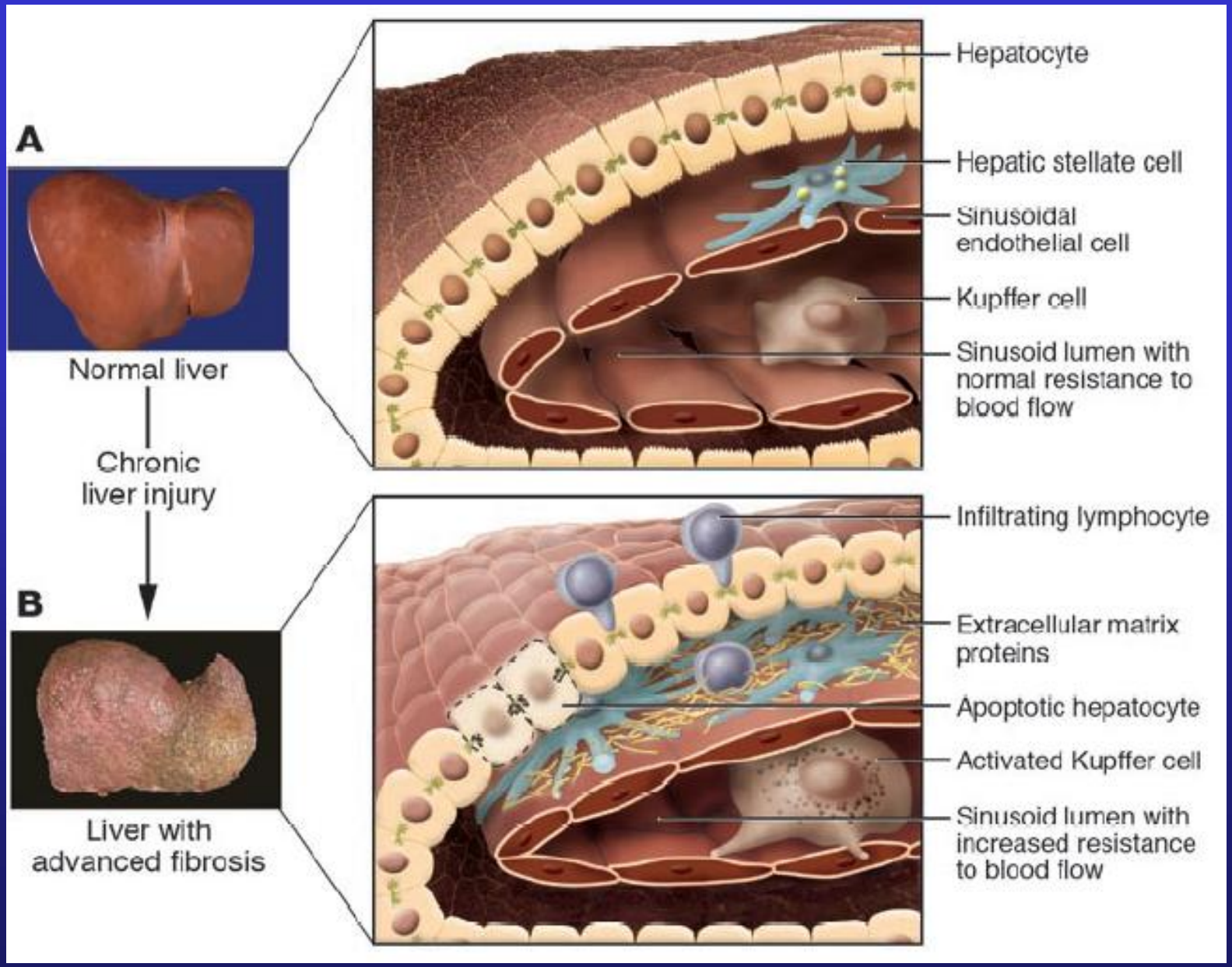


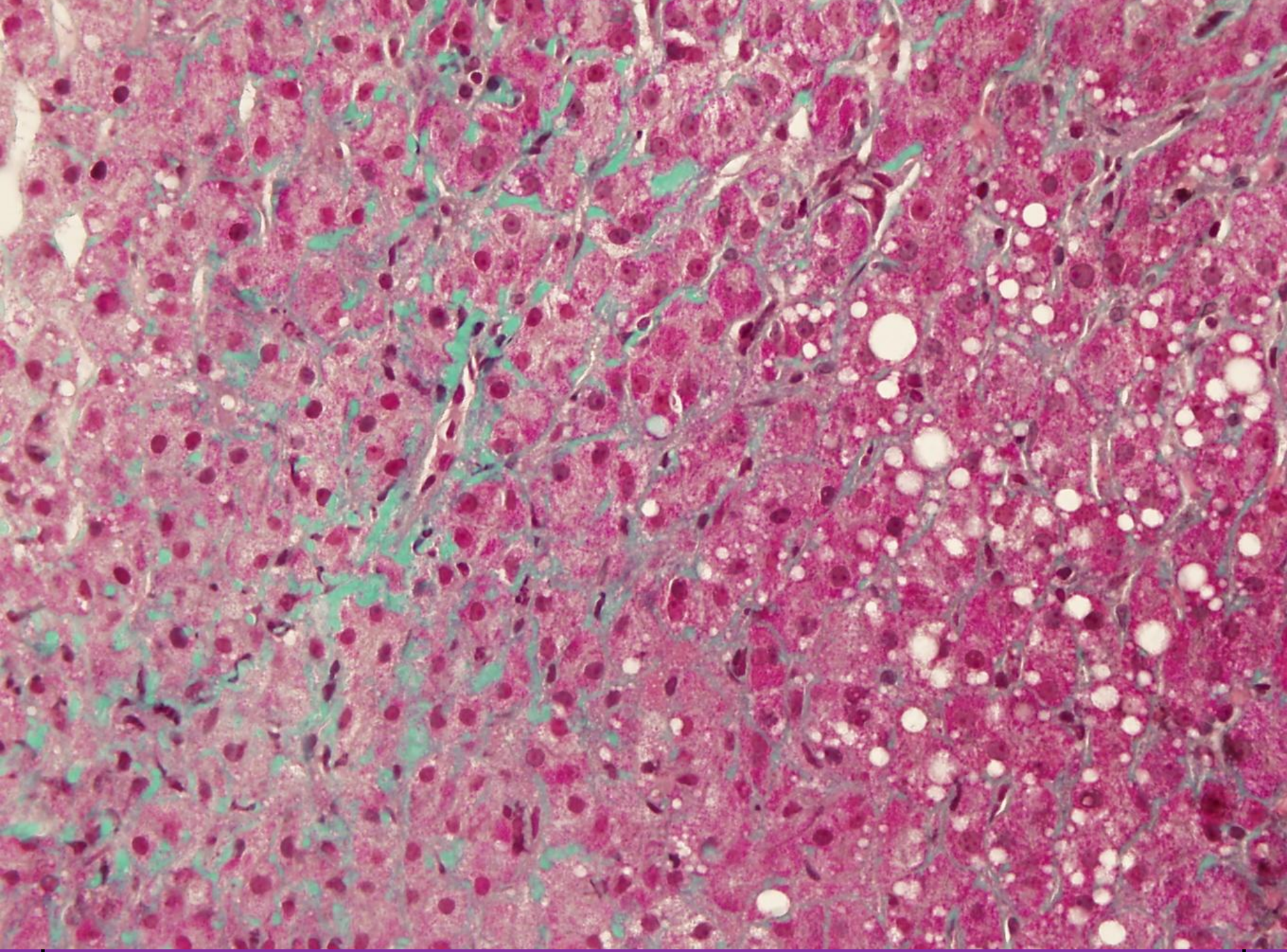
White et al, 2002

Scafato et al, 2012

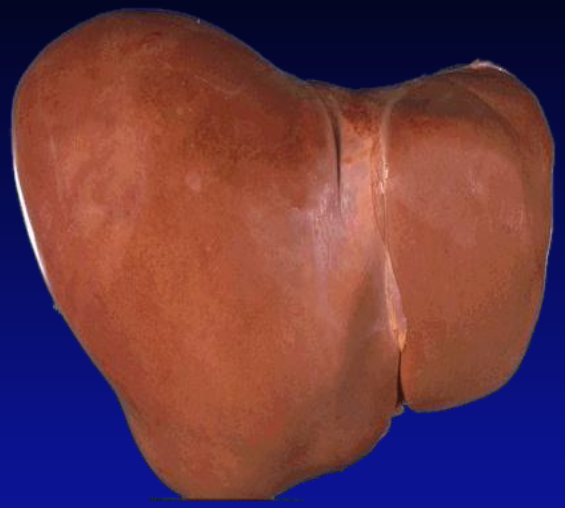
STEATOSI




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

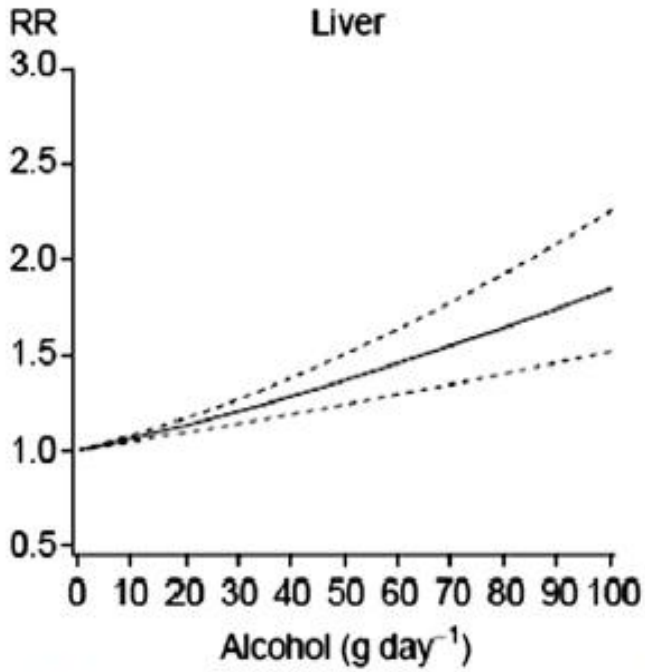


Fig. 1. RR functions and 95% CIs showing the dose-response relationship between alcohol consumption and the risk of liver cancer.

Grewal and Viswanathen, Clin Liver Dis 2012

THE SEARCH FOR GENETIC RISK FACTORS FOR ALCOHOLIC LIVER DISEASE

Genetic variation modulating addiction to alcohol

Genetic variation of alcohol-metabolising enzymes

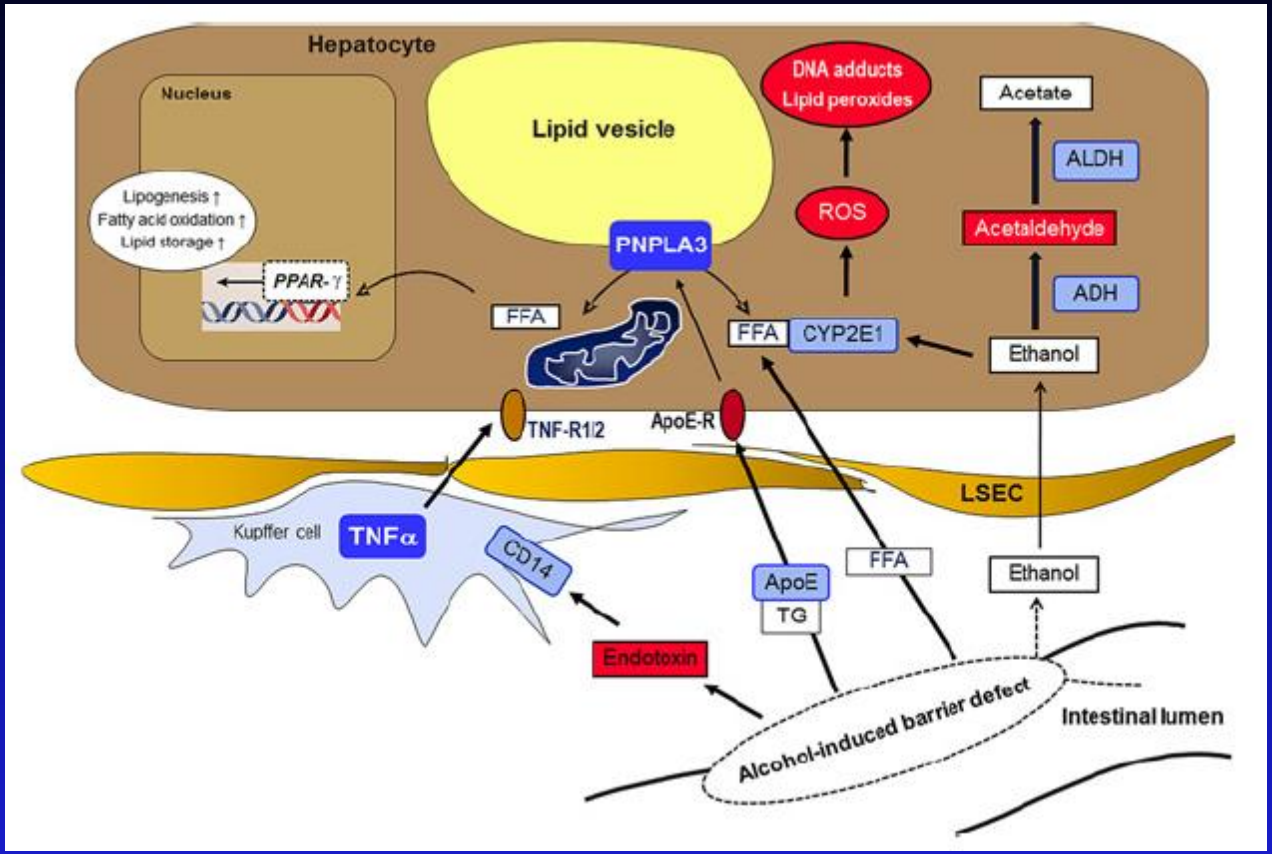
Genetic variations involved in oxidative stress

Genetic variations controlling hepatic lipid storage

Genetic polymorphisms modulating endotoxin inflammation

Polymorphic variants of fibrosis-associated genes

Stickel and Hampe, Gut 2011

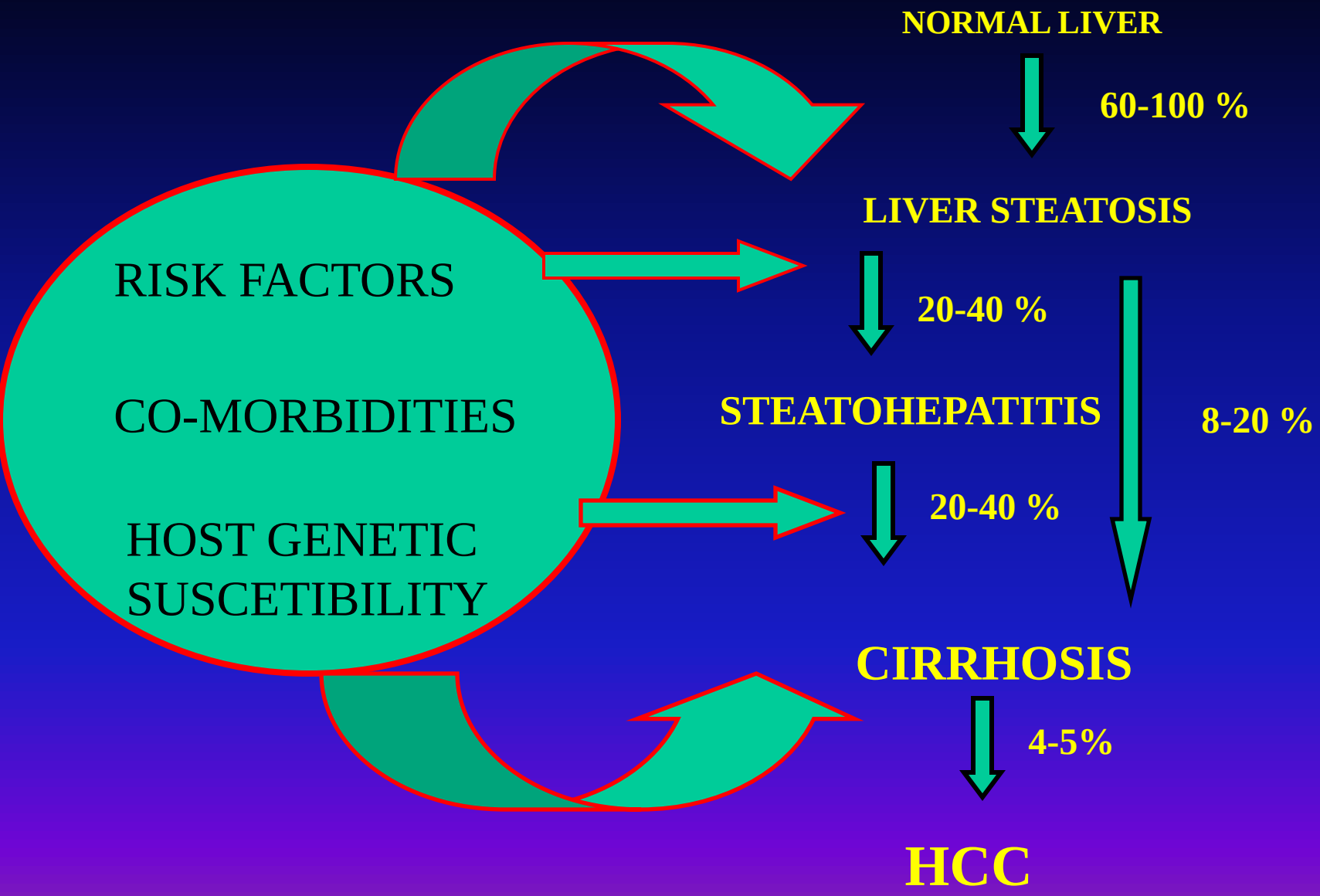


Tumor Necrosis Factor alpha – 238A

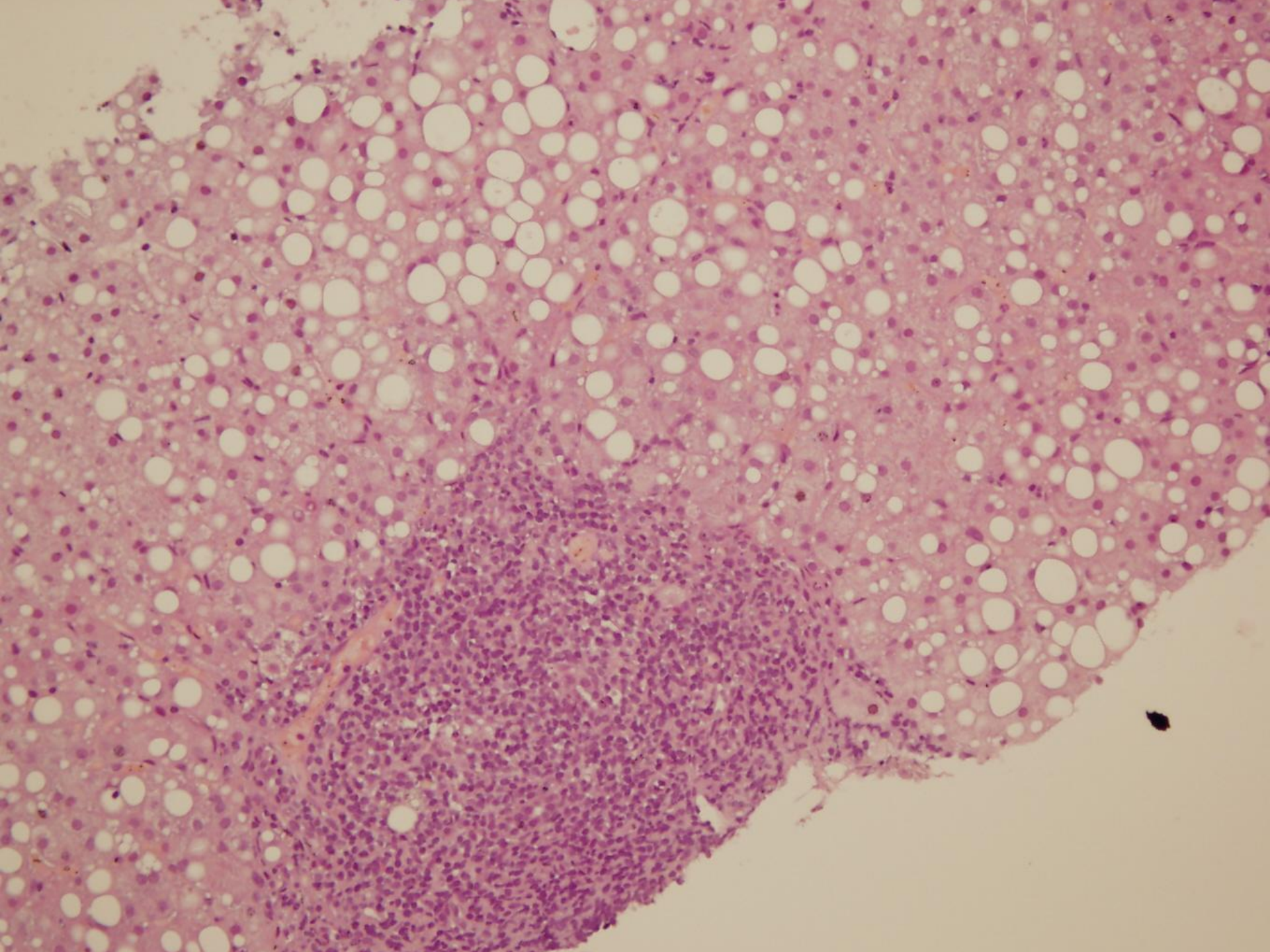
PNPLA3 rs738409 G: patatin-like phospholipase domain-containing 3

Sookoian S et al, Hepatology 2011

CHRONIC ALCOHOL DRINKER



Testino G, 2008



Alcol – HCV : Epidemiologia

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

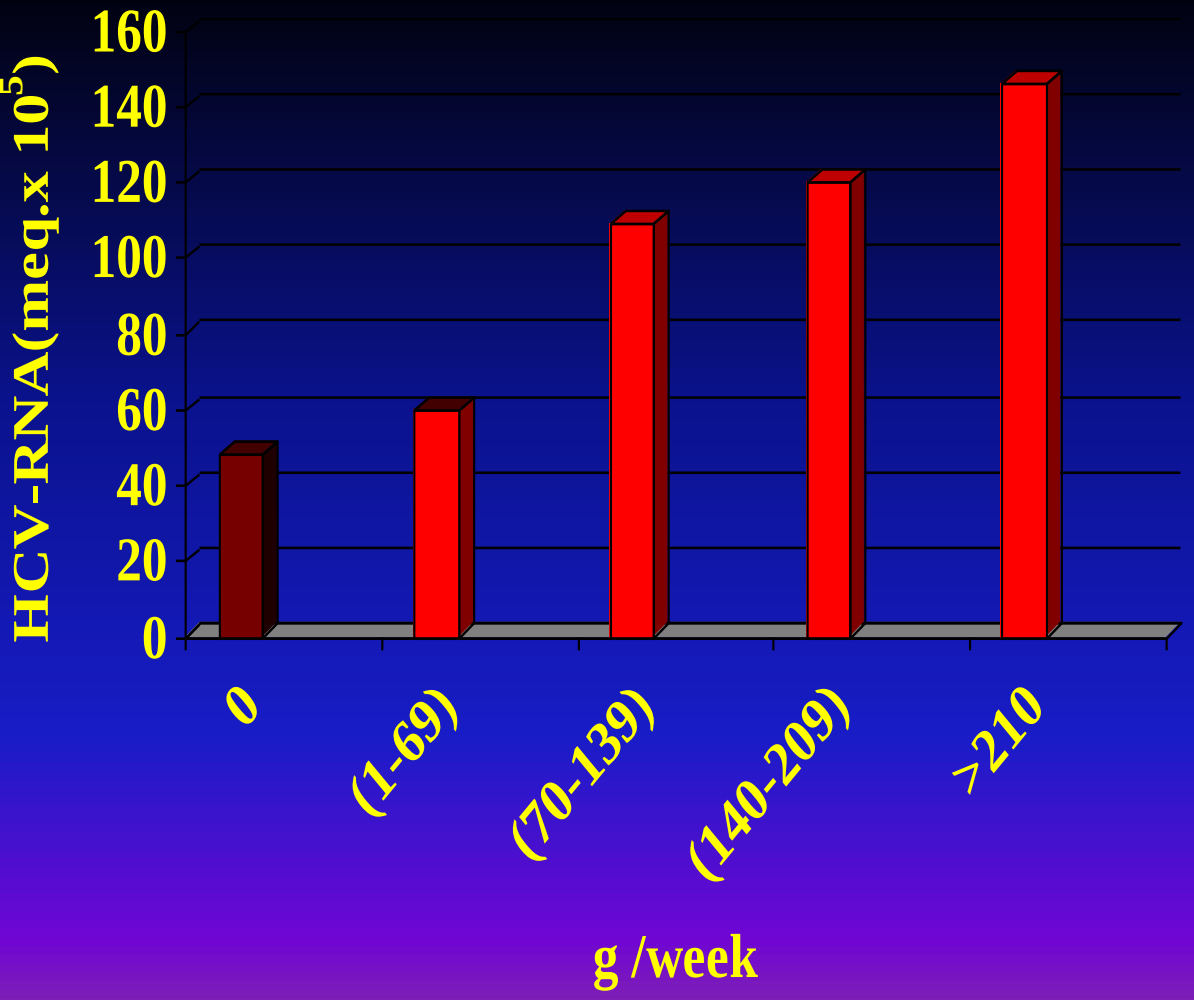
(Sata J Viral Hepat 1996; Kwon 2000 J Gastroenterol Hepatol; Ashwani J Clin Gastroenterol 2007)

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

HCV –RNA POSITIVO / EPATOPATIA ALCOLICA : 30%

(Testino G et al, 2009)

EFFETTI DELL'ALCOOL SU HCV-RNA



Pessione, hepatology 1998

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)	

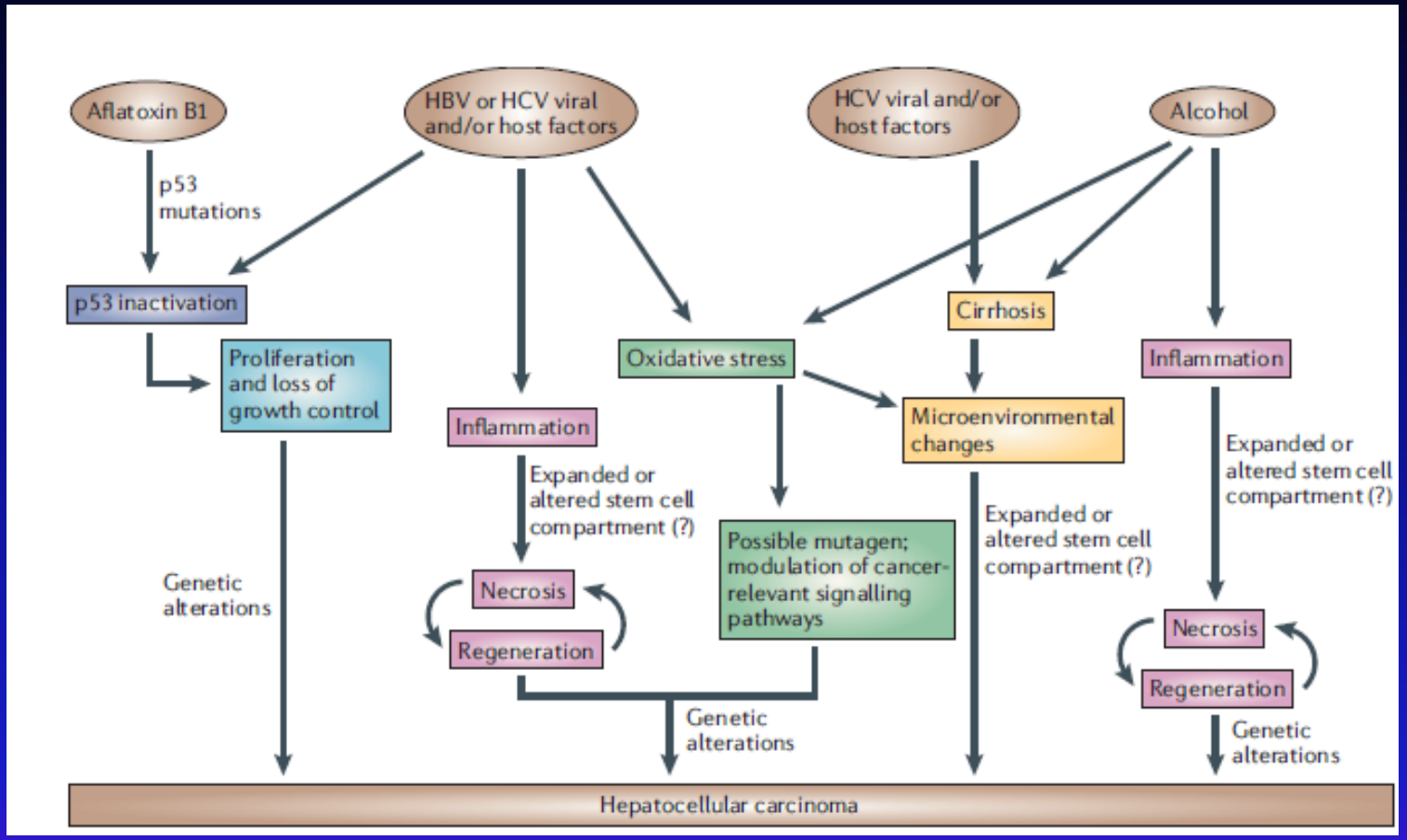
Westin et al, J Viral Hep 2002

HCV, ALCOL, MORTALITY

	All-cause mortality HR	Cardiovascular mortality HR	Liver-related mortality HR
HCV + ALCOL > 20 gr/die	5.12 (1.97-13.28)	3.34 (0.55-20.5)	183.74 (15.98-infinity)
HCV + ALCOL < 20 gr/ die	2.44 (1.59-3.75)	0.71 (0.23-2.21)	74.25 (19.62-280.92)

Third National Health and Nutrition Examination Survey

Younossi ZM et al, Aliment Pharmacol Ther 2013



Farazi et al, Nature 2006

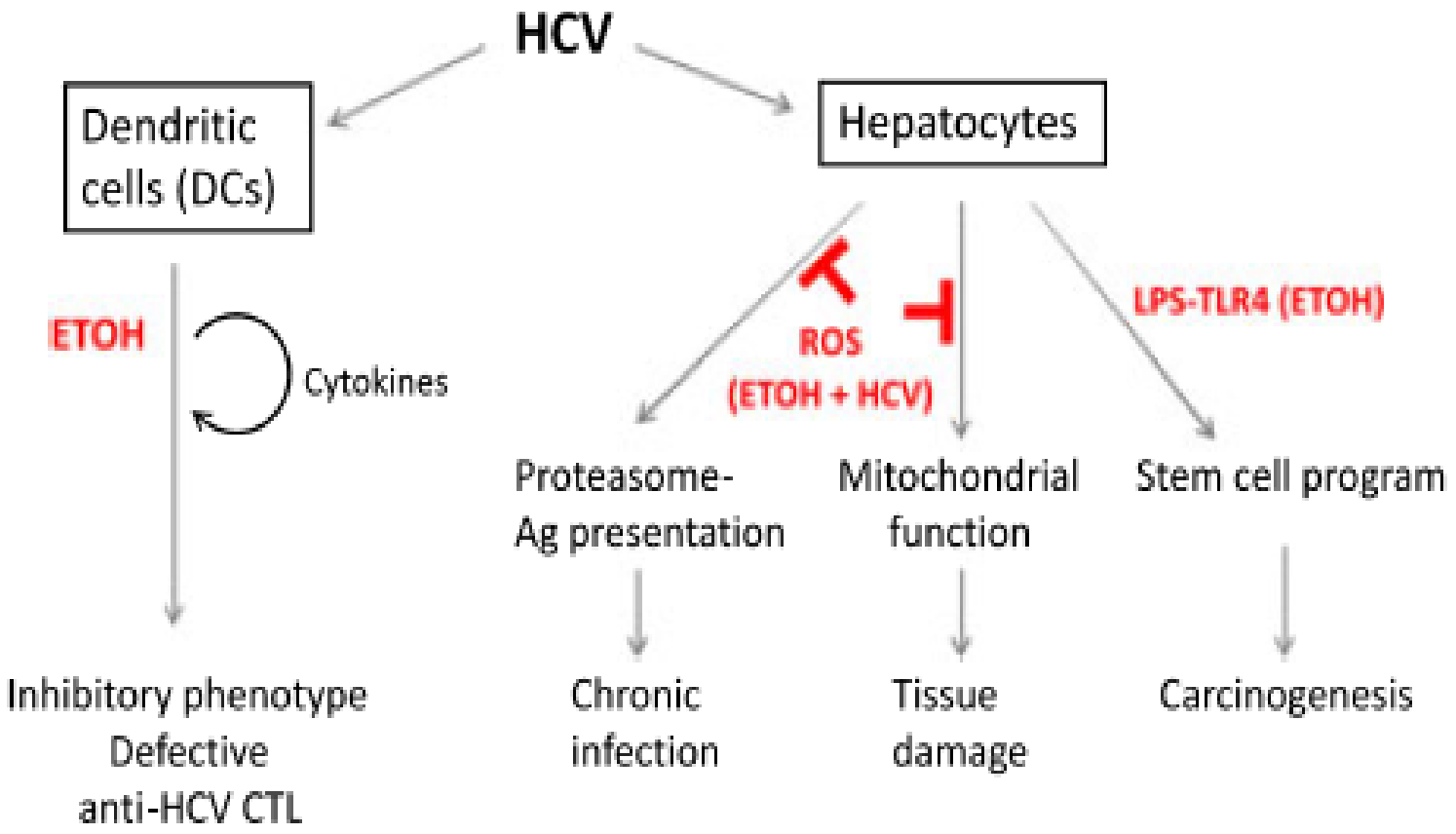


Fig. 1. A schematic of the interactions between alcohol and HCV and their impact on immune cells and liver cells. Ag, antigen.

Szabo et al, Alcohol Clin Exp Res 2010

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

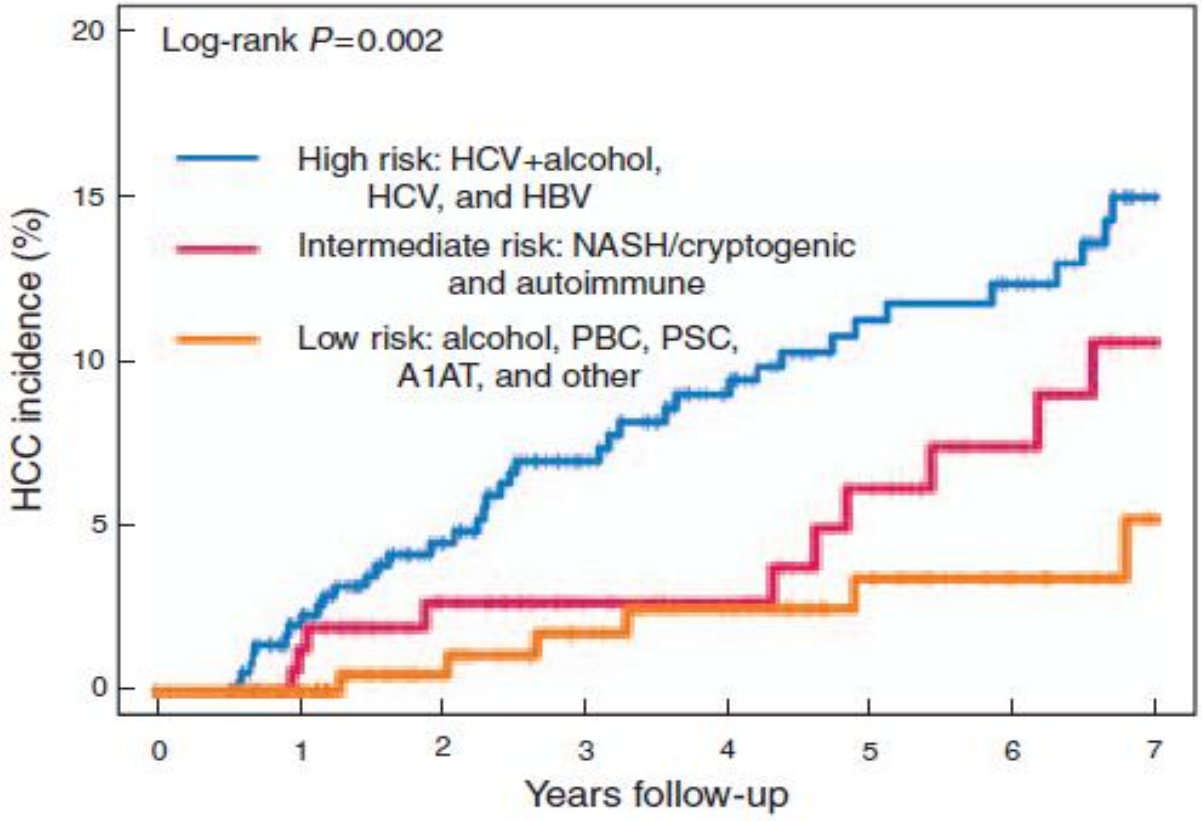
HCV or HBV infection	Alcohol intake (g/day) 0 - 60			> 60		
	Cases /controls (no)	OR	95%CI	Cases / control (no)	OR	95%CI
Neither	30 / 412	Reference		157/ 335	7.0	4.5, 11.1
HCV infection	95/ 21	55.0	29.9, 10.0	76/ 11	109	50.9, 233.0
HBV infection	41 / 27	22.8	12.1, 42.8	51/ 17	48.6	24.1, 98.0

Donato et al , 2002

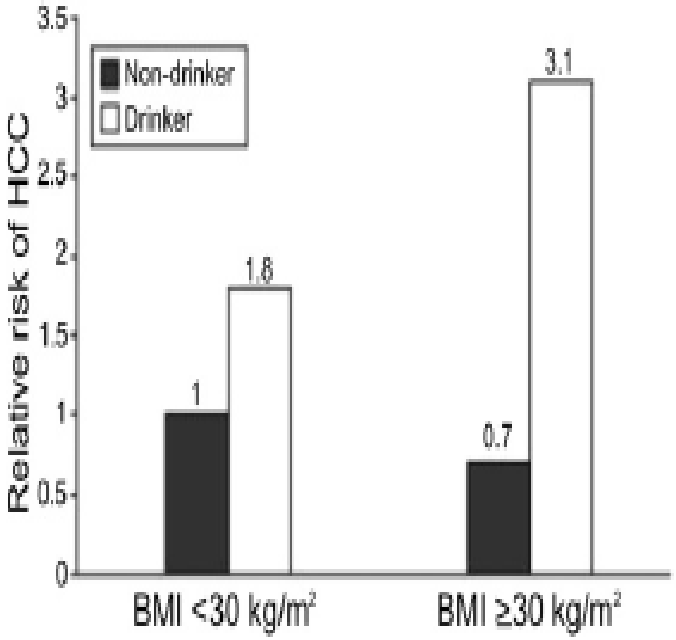
Interaction of Heavy Alcohol Consumption (> 80 mL ethanol/d) With Chronic Hepatitis Virus Infection (HBV or HCV) and Diabetes Mellitus: Logistic Regression Analysis With Adjusted OR

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)

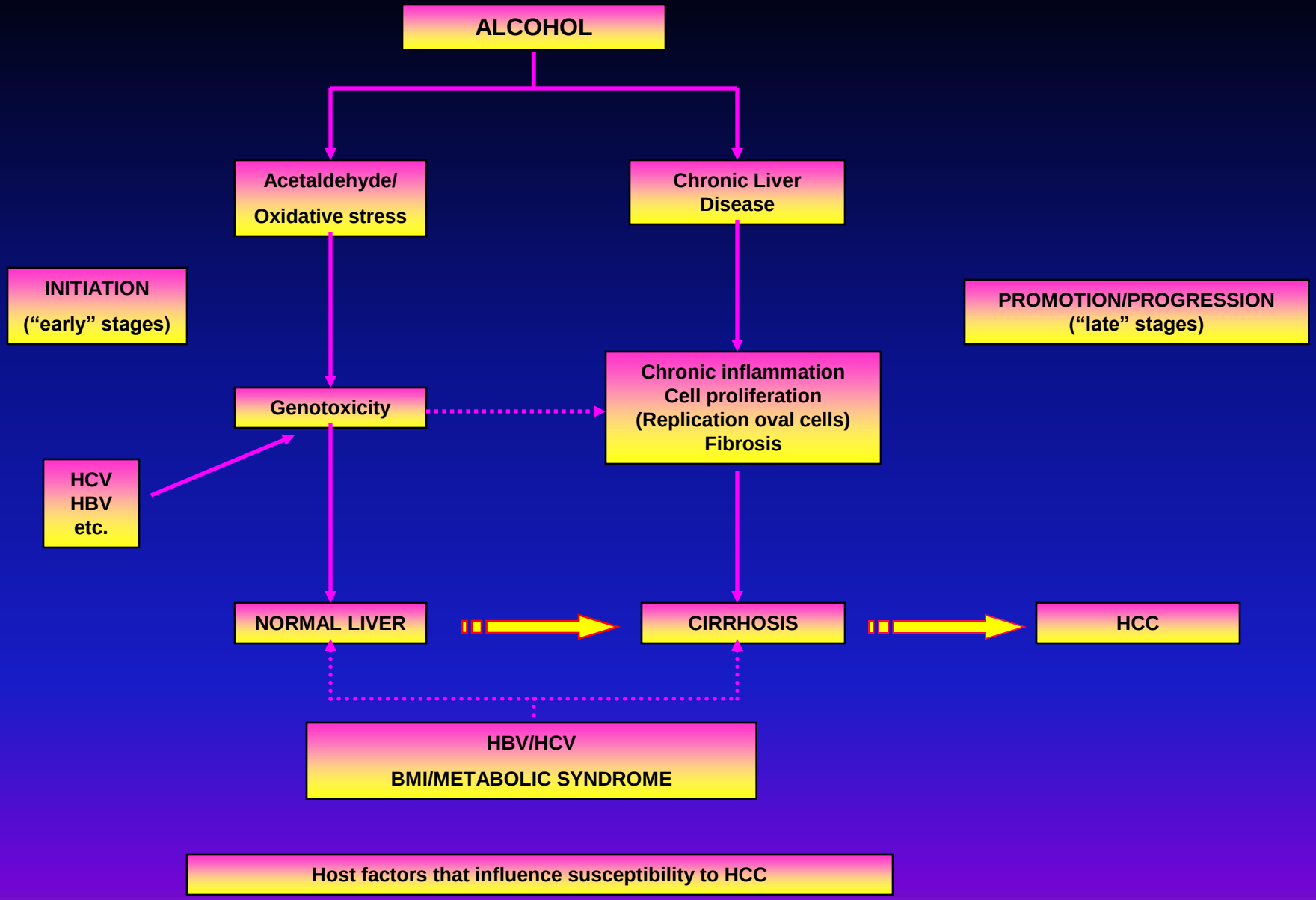
Hassan et al., 2002



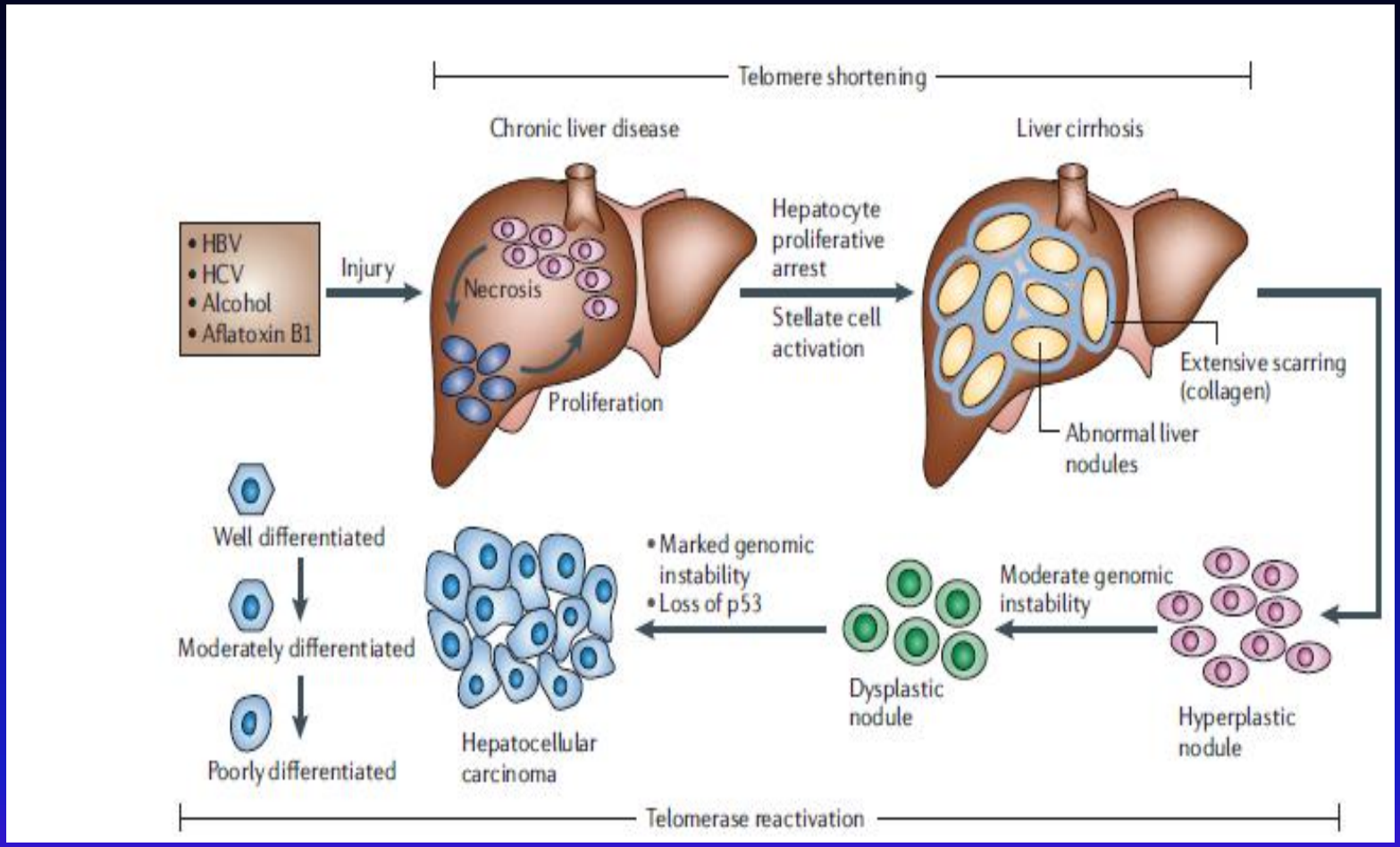
Berman et al, Am J Gastroenterol 2011



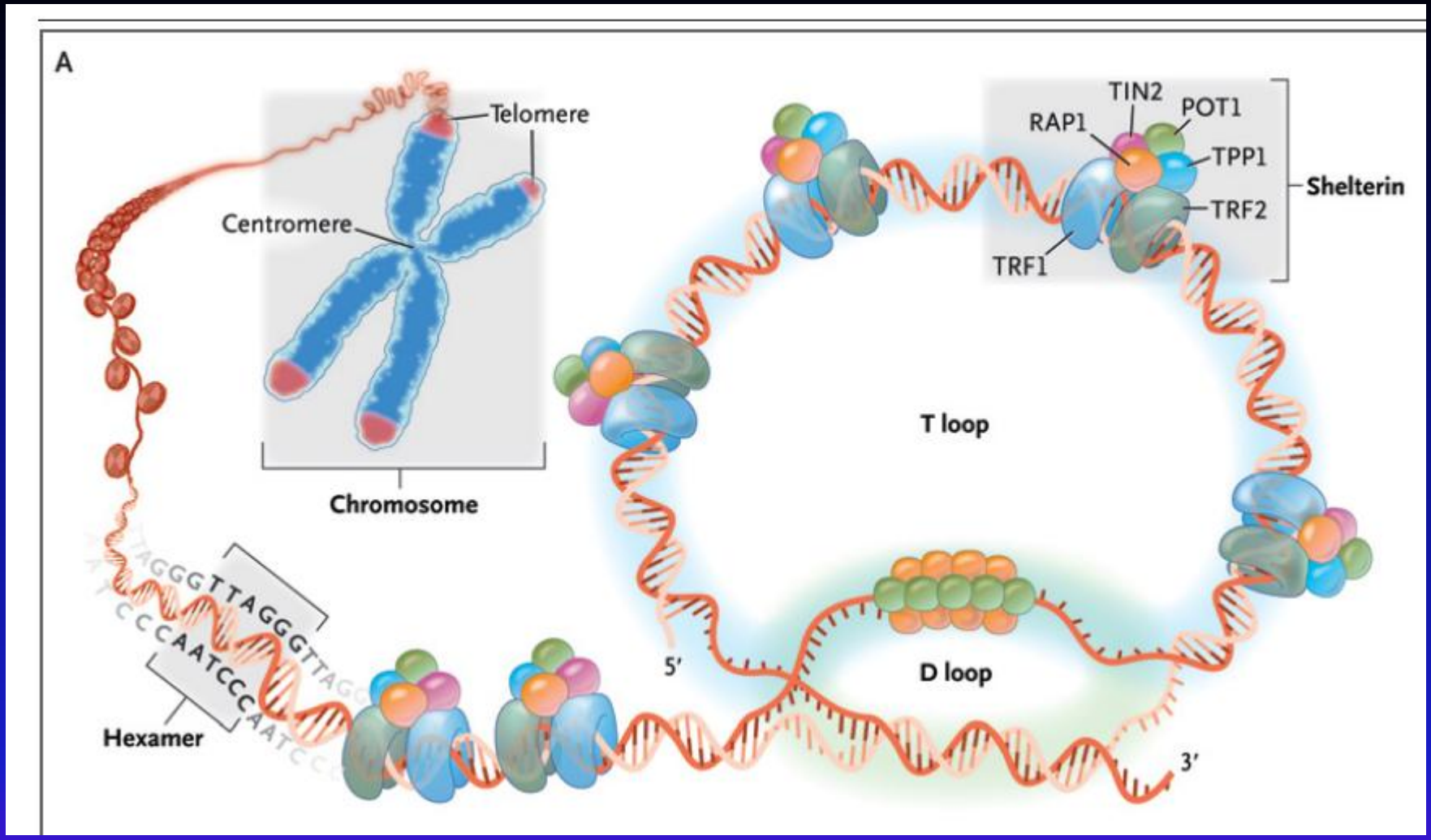
Grewal and Viswanathen, Clin Liver Dis 2012



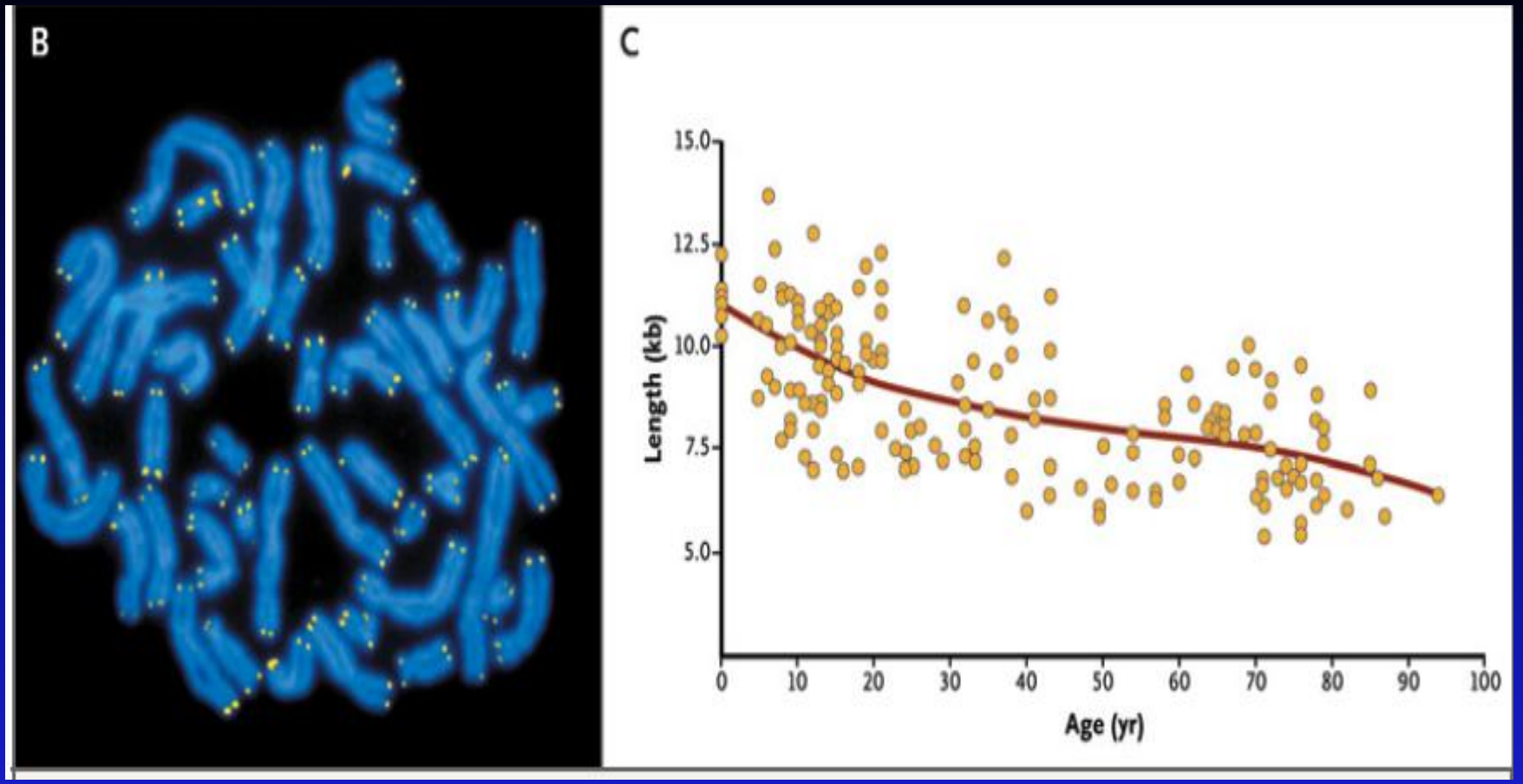
Donato et al., 2002



Farazi et al, Nature 2006



Calado and Young, N Engl J Med 2009



Calado and Young, N Engl J Med 2009

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

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

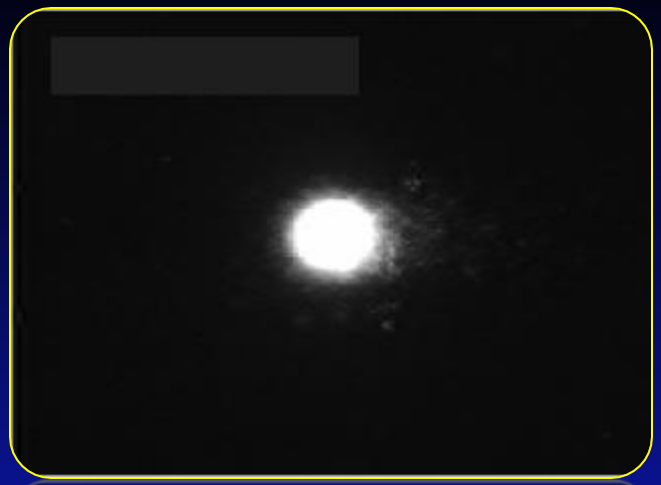
GSTP1: detoxification of carcinogens

DOK1: response to interferon

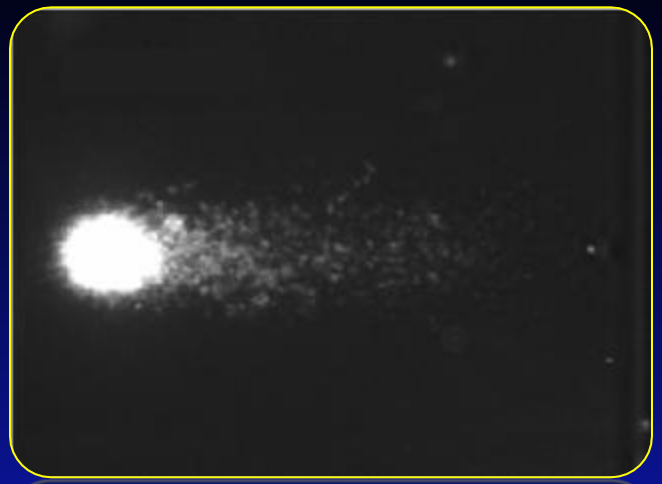
CHRNA3: angiogenic growth

MGMT: DNA repair

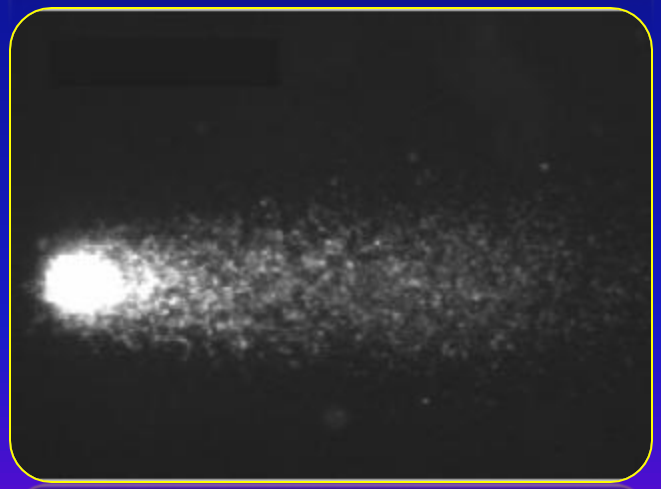
LAMBERT et al, J HEPATOL 2010



controllo



1



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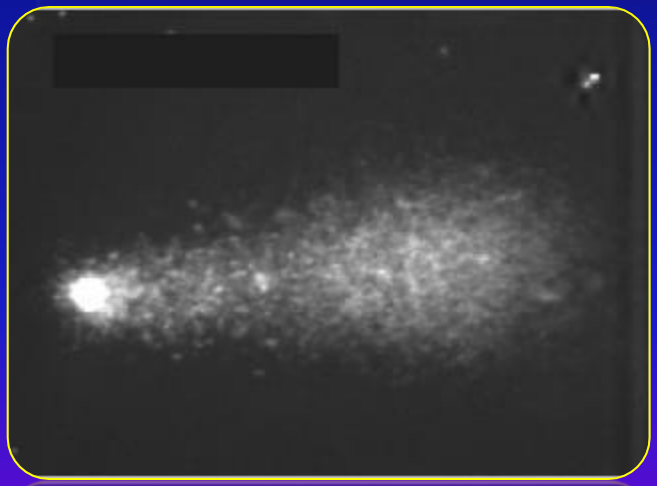
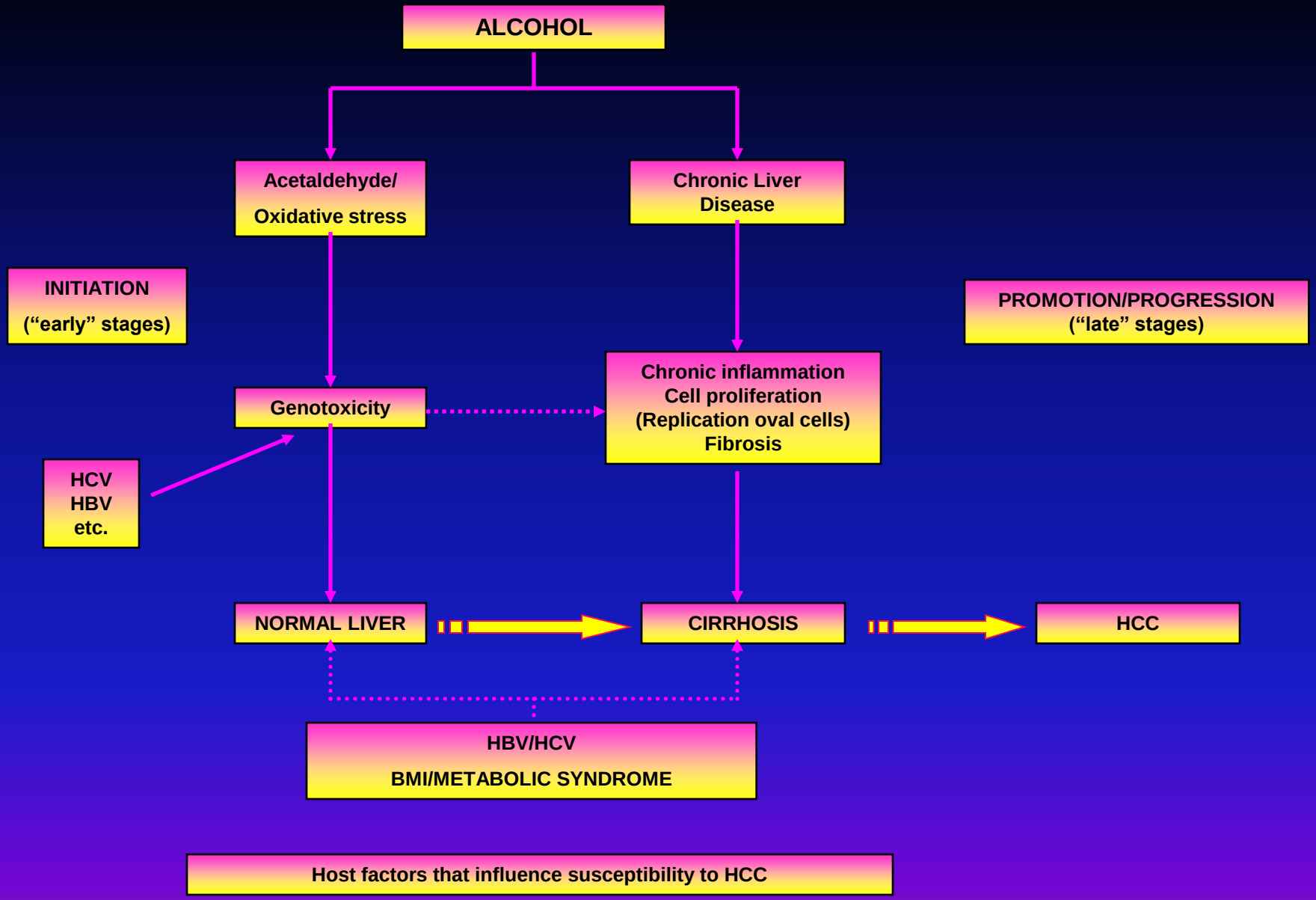


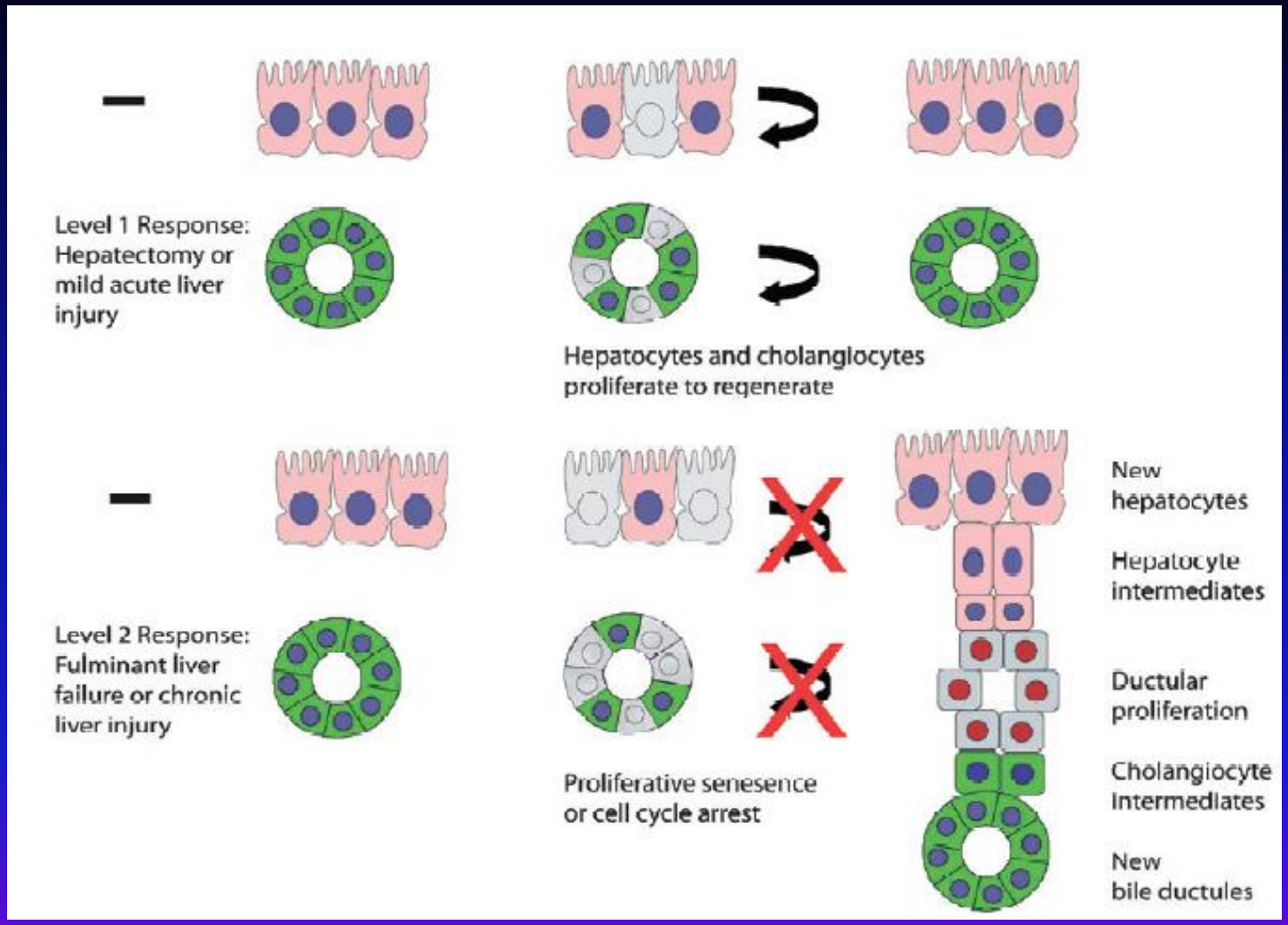
3

1,2,3 = diversi gradi di danno

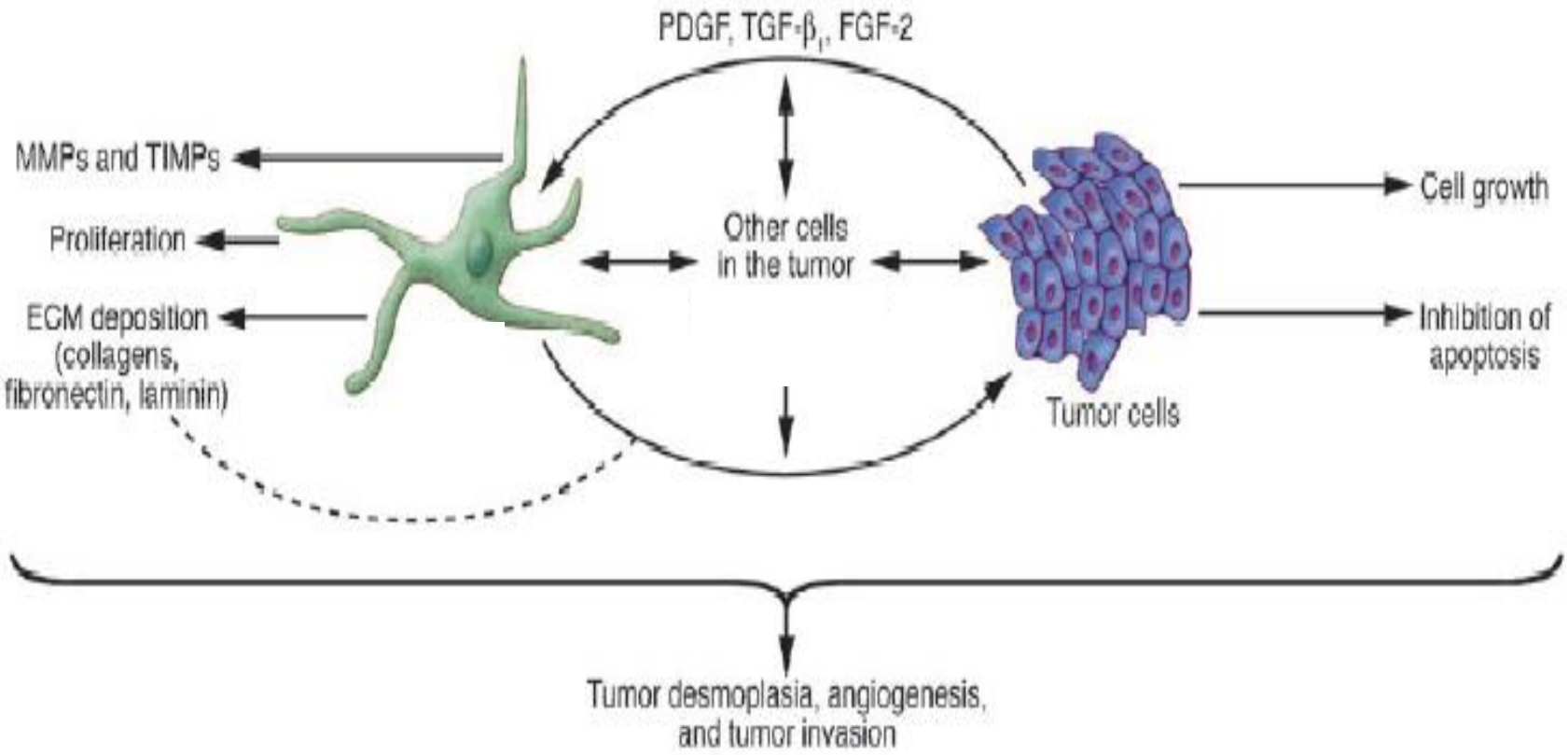
Martelli, Sumberaz, Testino – European J Gastroenterol Hepatol 2008

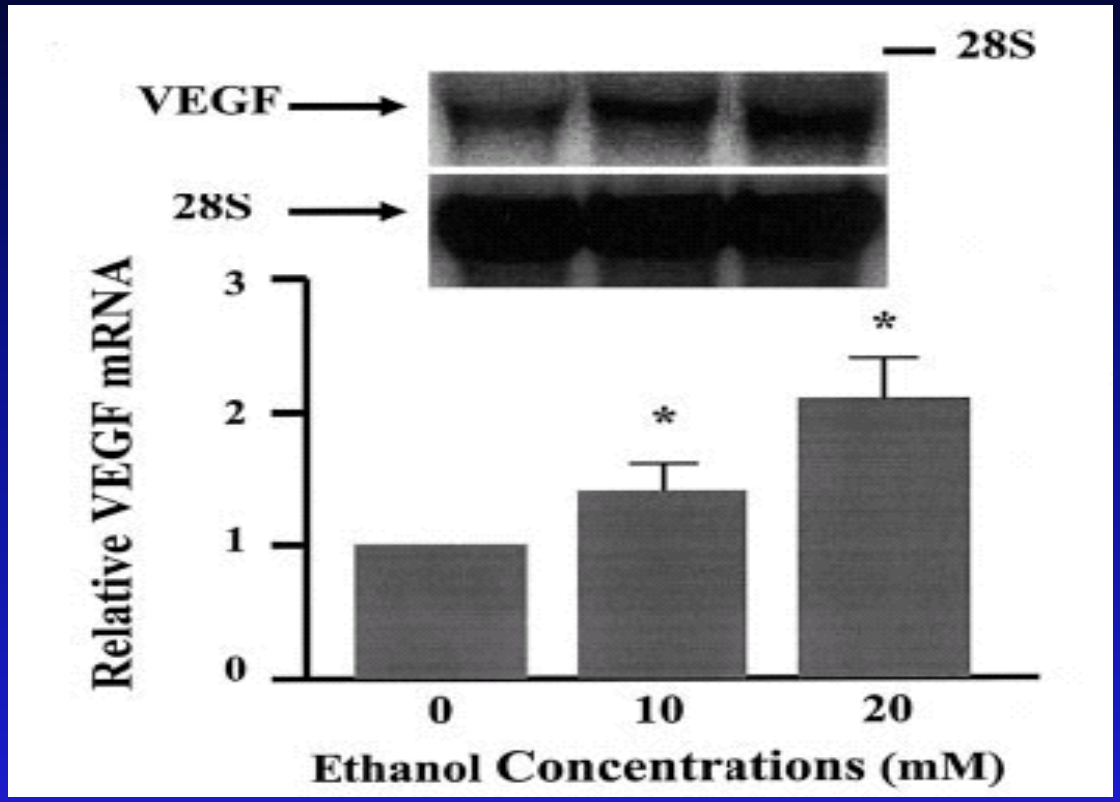


Donato et al., 2002

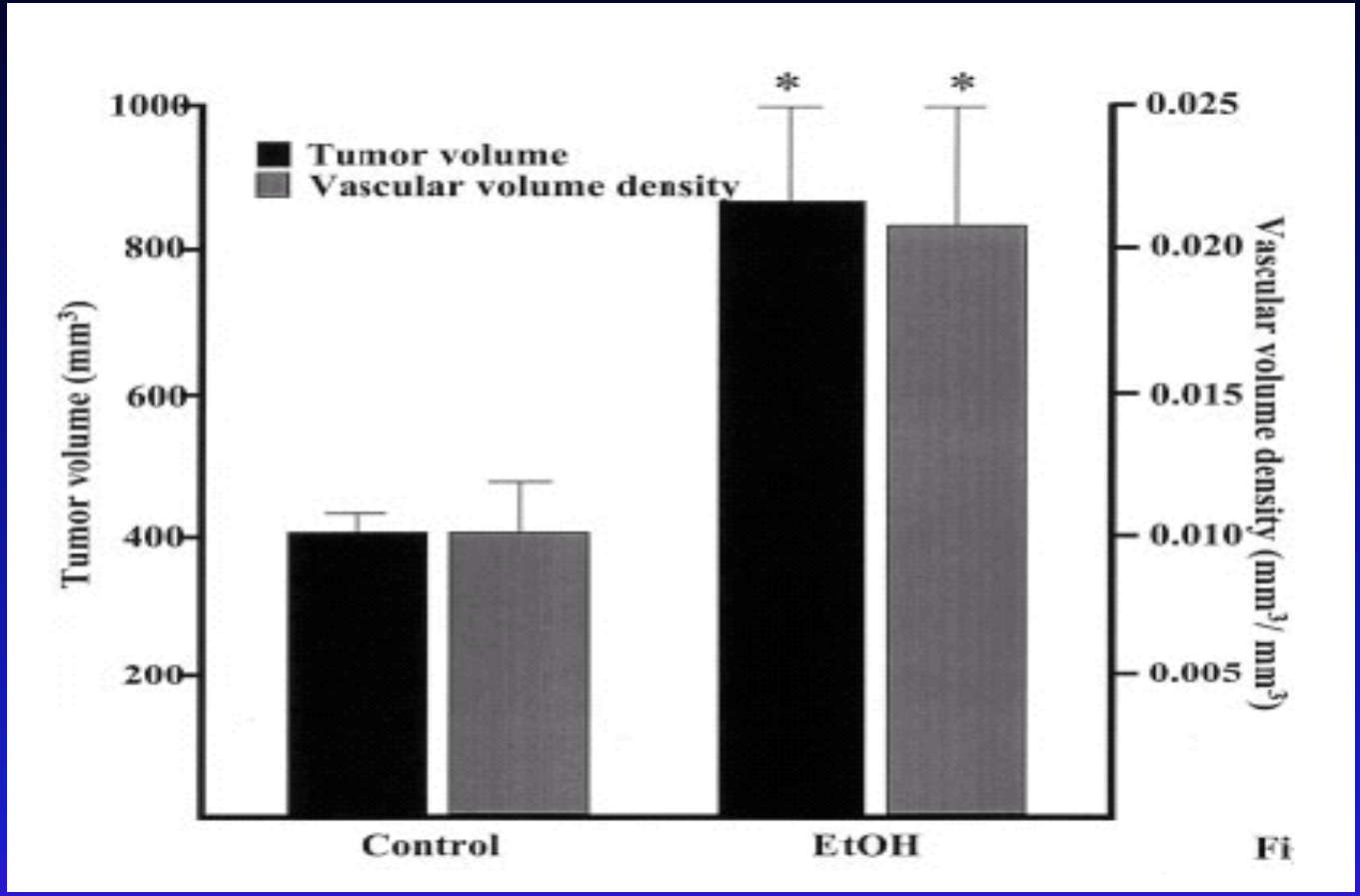


Riehle KJ et al, J Gastroenterol Hepatol 2011


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



Gu JW et al, Cancer 2005

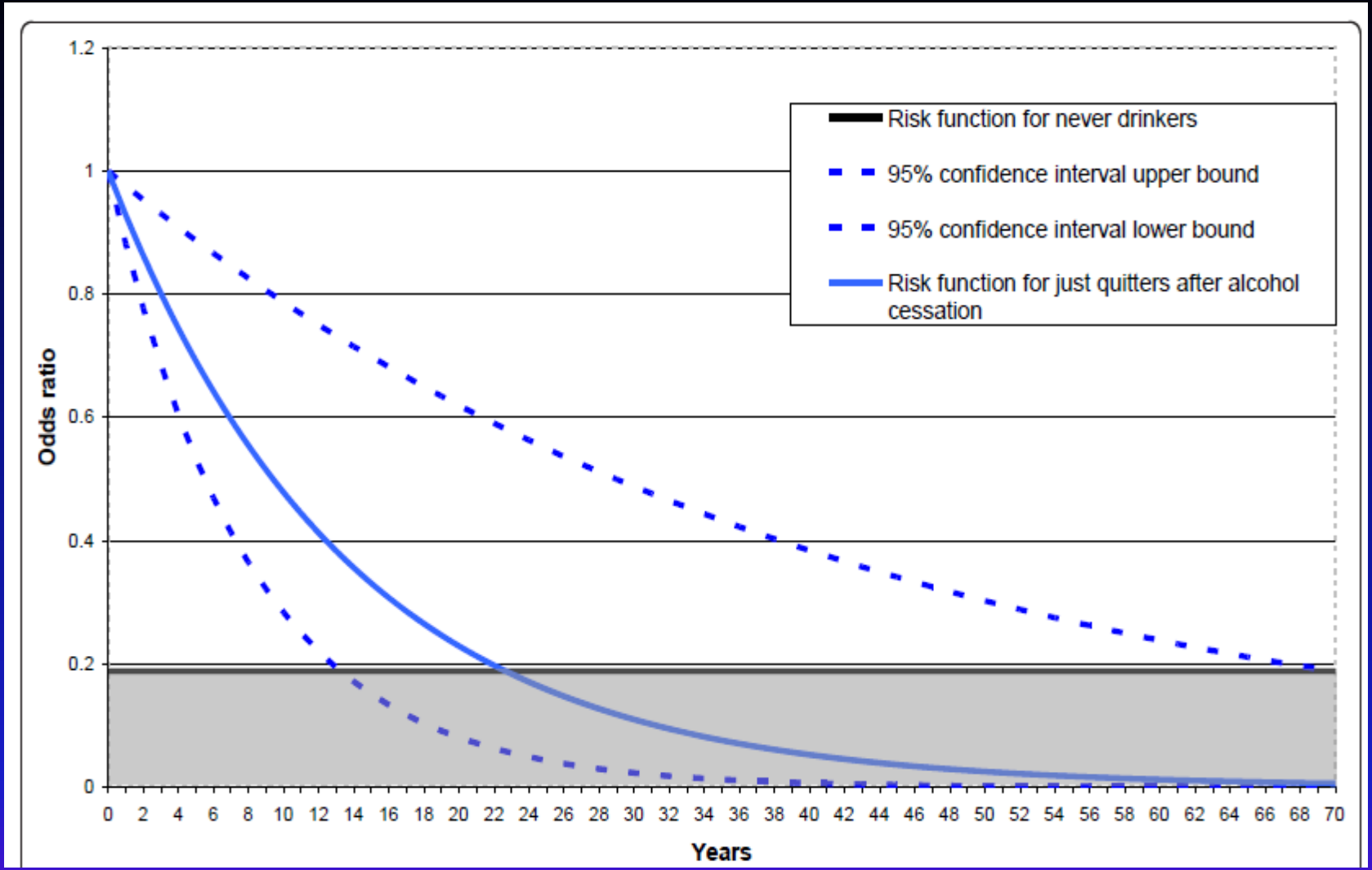


Gu JW et al, Cancer 2005

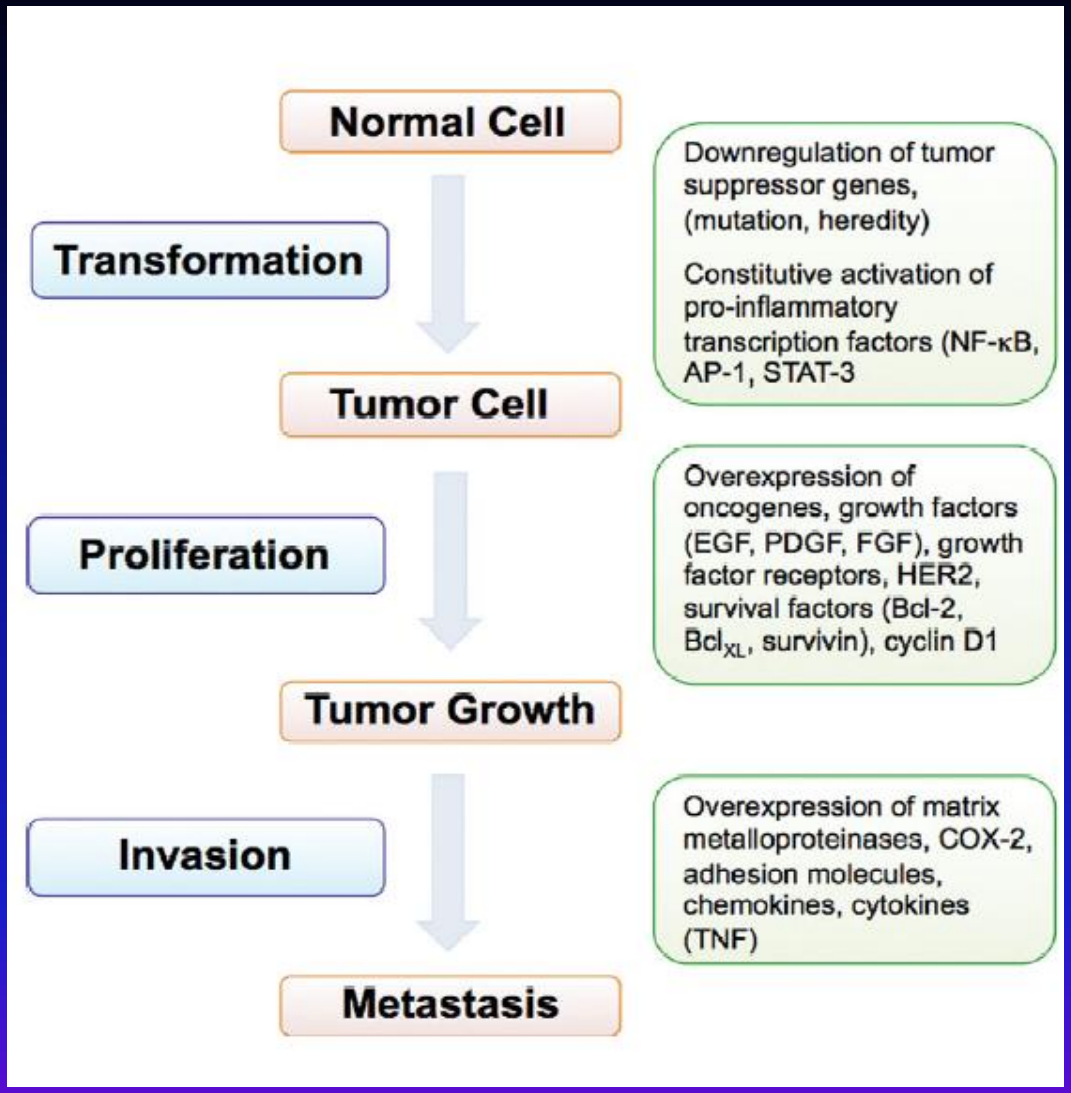
	5– year HCC incidence rate	5 – year death incidence rate
Group 1	0/20 (0%)	1/20 (5%)
Group 2 and 3	4/77 (5.1%)	9/77 (11.6%)
Group 4	32/93 (34.4%)	35/93 (37.6%)

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



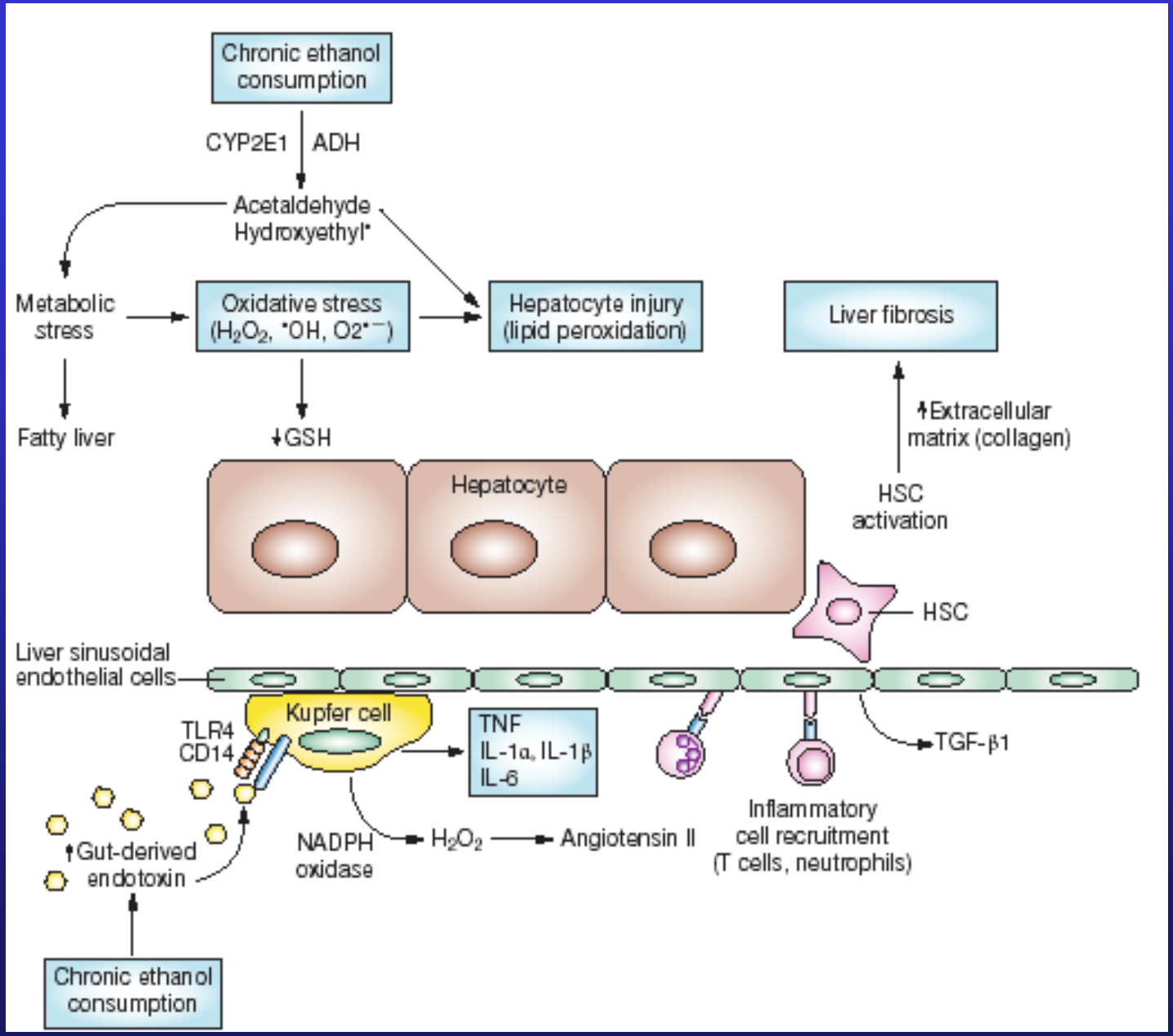
Heckley GA et al, BMC Cancer 2011



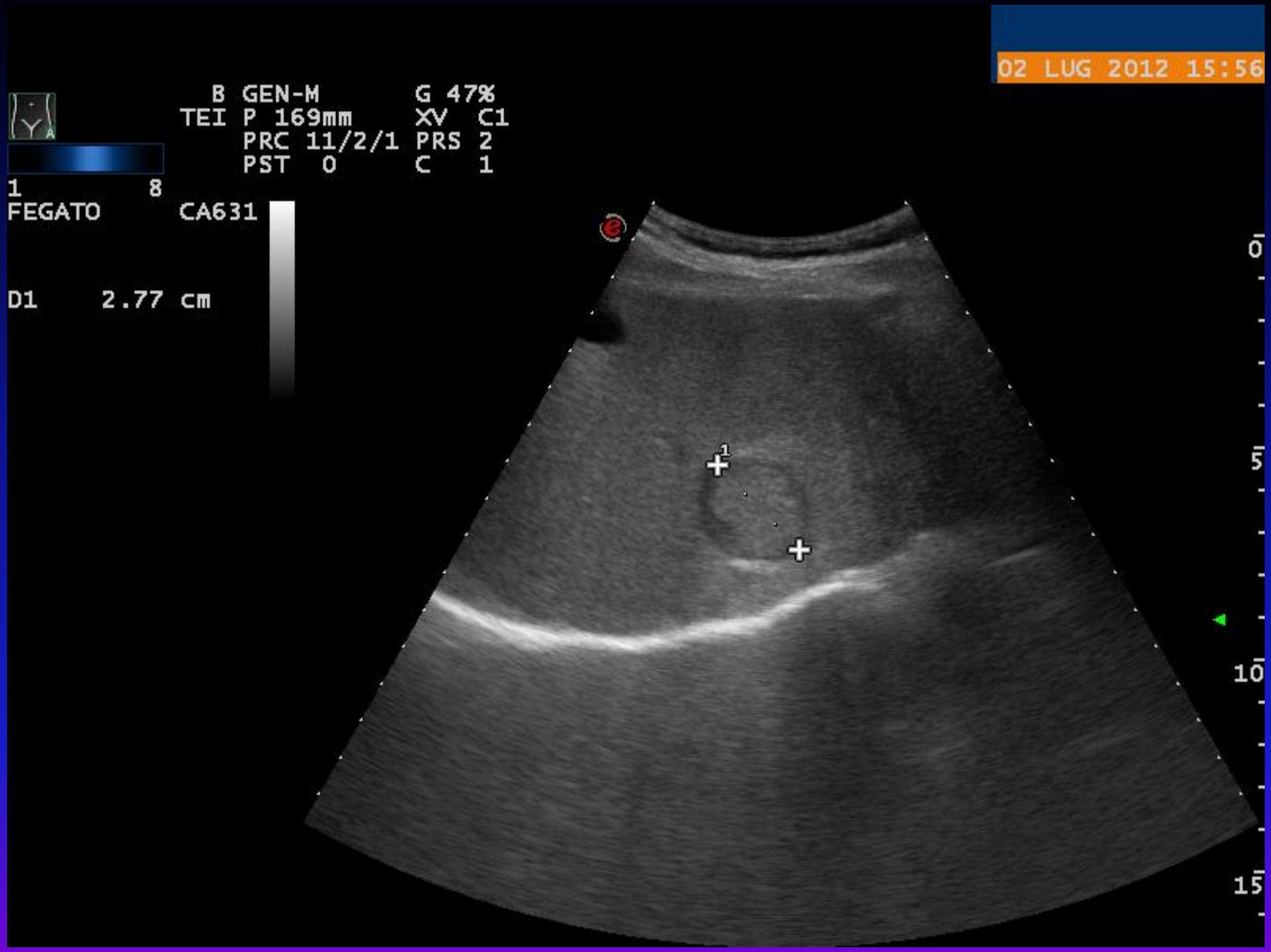
Curcumina

Silibina

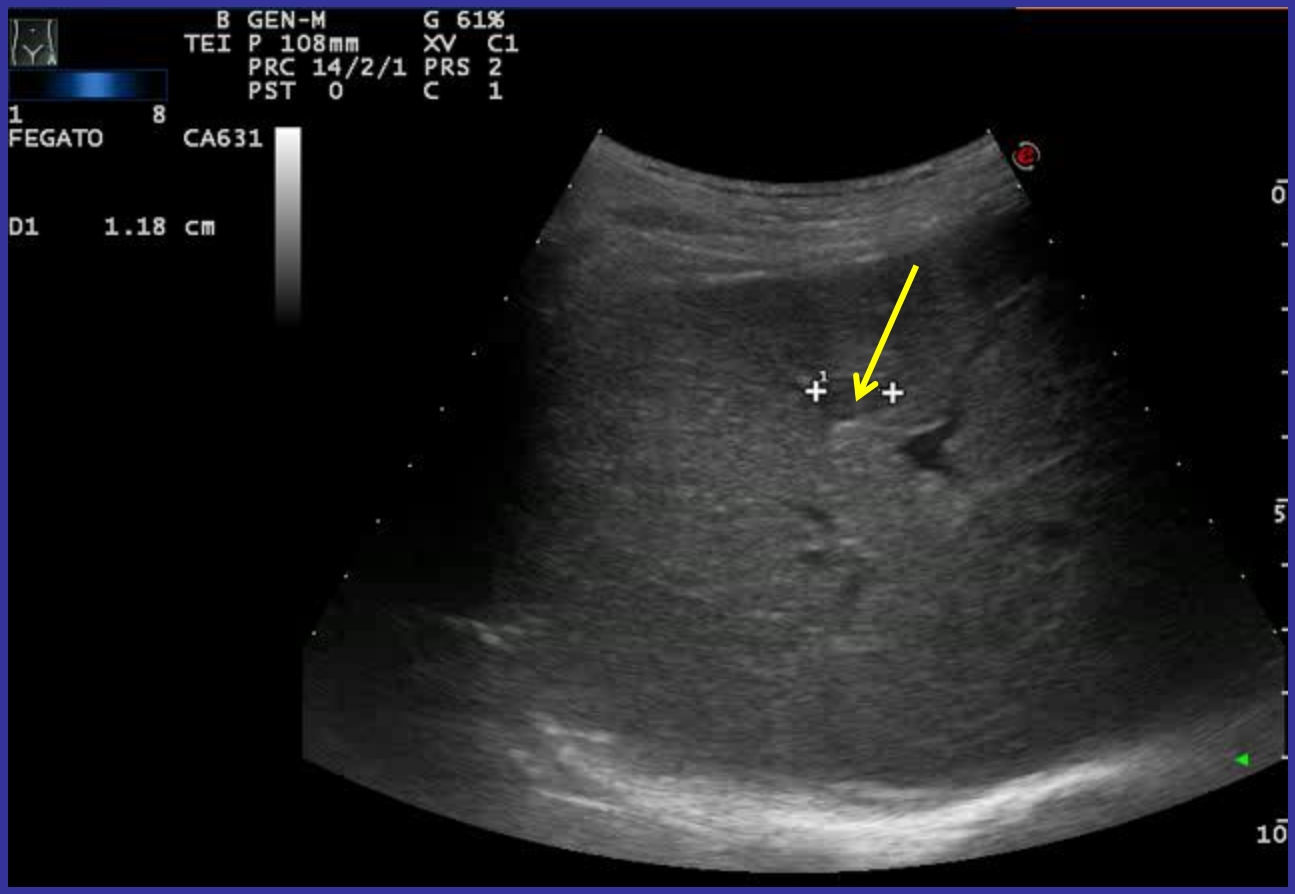
SAMe


Chronic ethanol consumption
CYP2E1
ADH
Acetaldehyde
Hydroxyethyl•
Metabolic stress
Oxidative stress (H_2O_2, •OH, $O2^{\bullet -}$)
Hepatocyte injury (lipid peroxidation)
Liver fibrosis
Fatty liver
↓GSH
↑Extracellular matrix (collagen)
Hepatocyte
HSC activation
HSC
Liver sinusoidal endothelial cells
Kupfer cell
TLR4
CD14
TNF
IL-1α, IL-1β
IL-6
TGF-β1
Inflammatory cell recruitment (T cells, neutrophils)
↑Gut-derived endotoxin
NADPH oxidase
H_2O_2
Angiotensin II
Chronic ethanol consumption

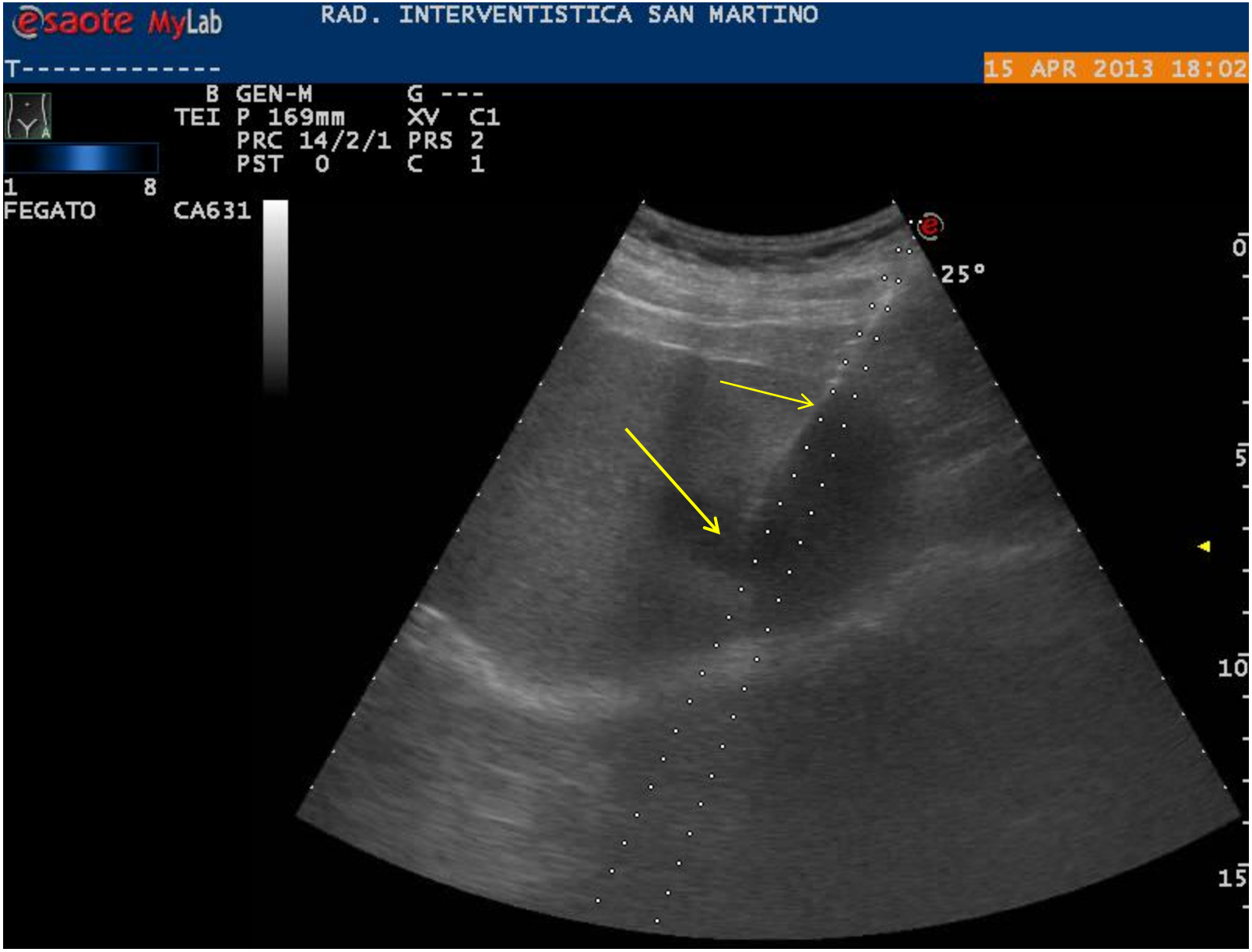
Tilg H., 2007



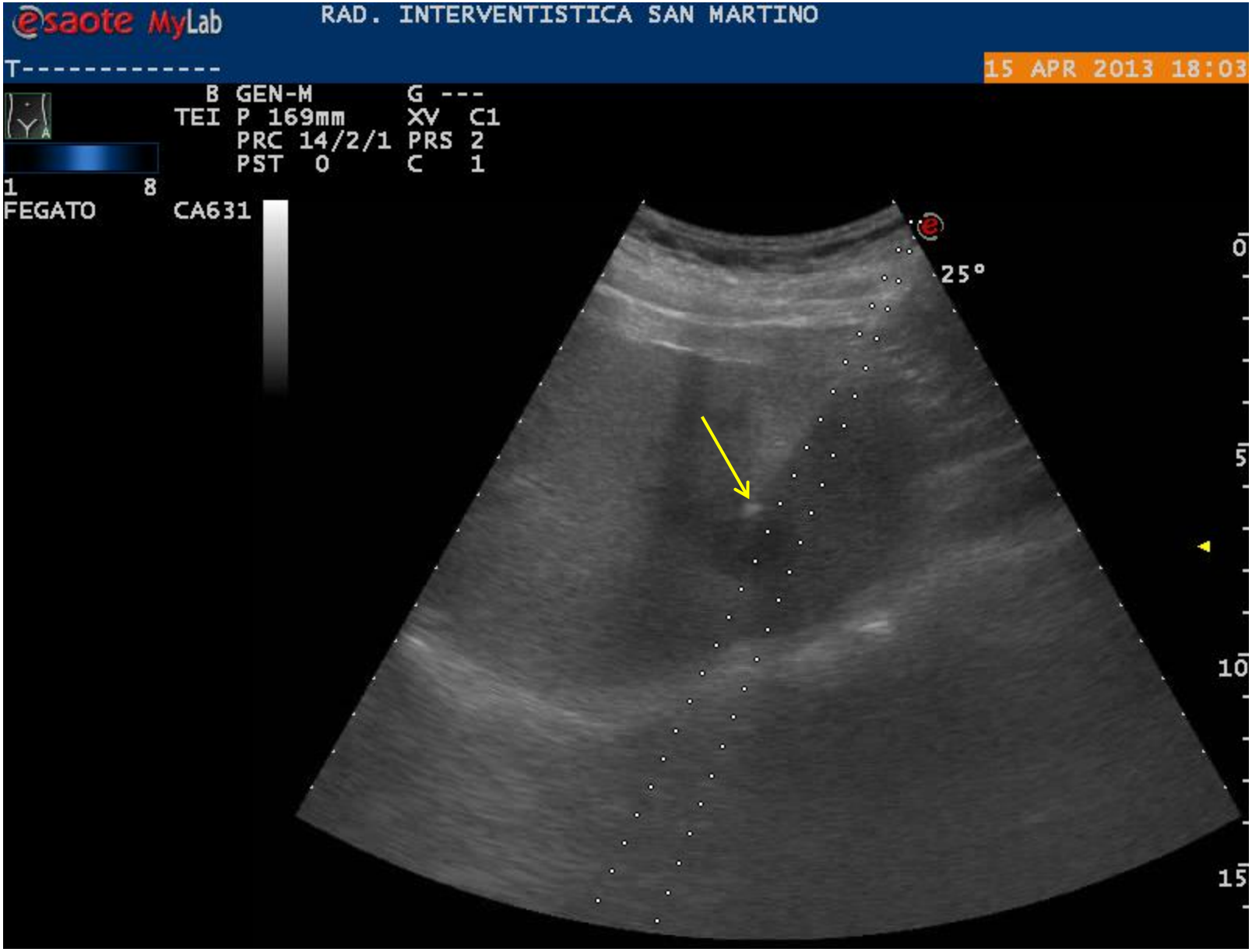
Borro and Testino, Liver Int 2013



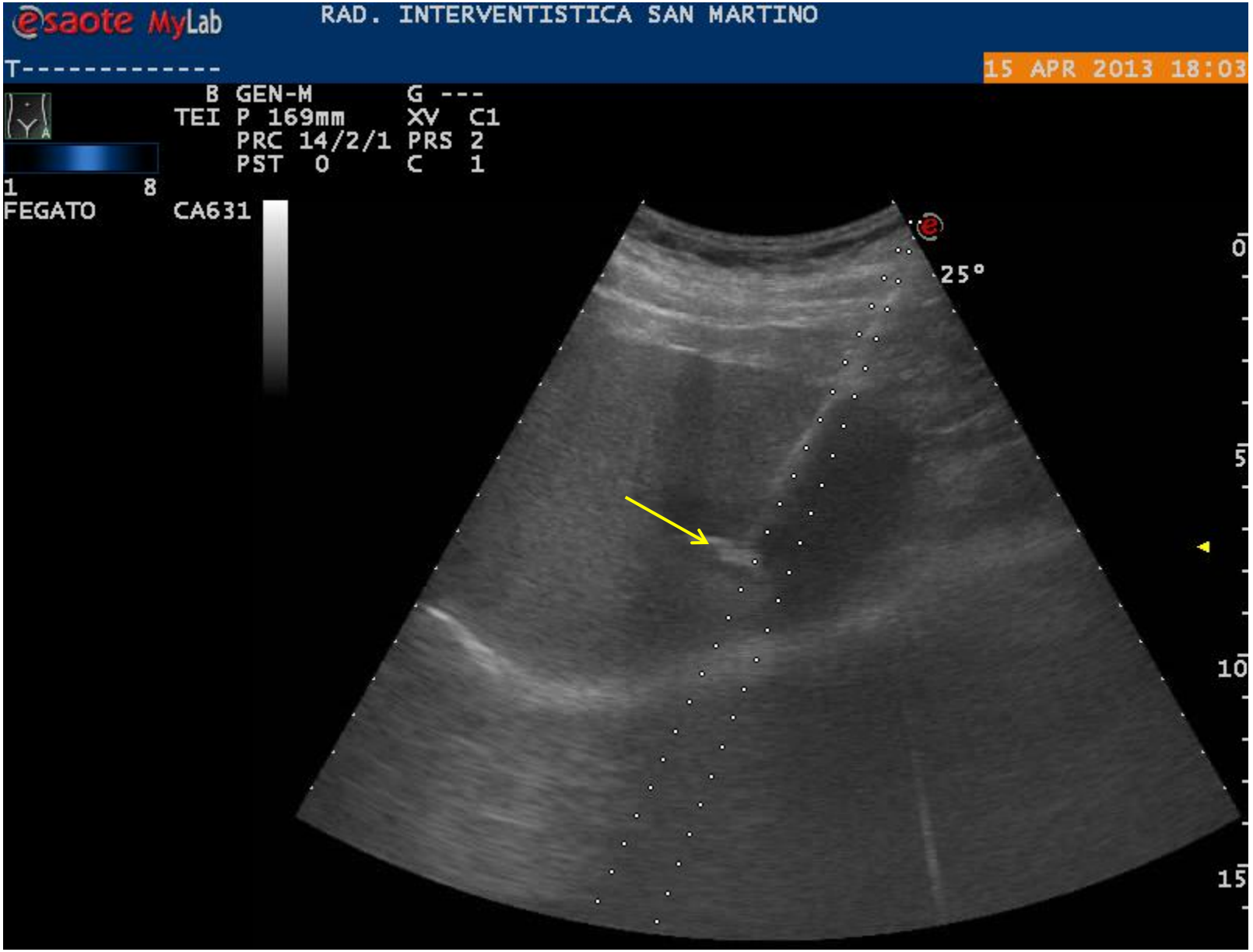
Paolo Borro – Centro Alcologico Regionale Ligure (Direttore: G. Testino), IRCCS San Martino-IST, Genova



Paolo Borro – Centro Alcologico Regionale Ligure, IRCCS San Martino-IST, Genova



Paolo Borro – Centro Alcologico Regionale Ligure, IRCCS San Martino-IST, Genova



Paolo Borro – Centro Alcologico Regionale Ligure, IRCCS San Martino-IST, Genova

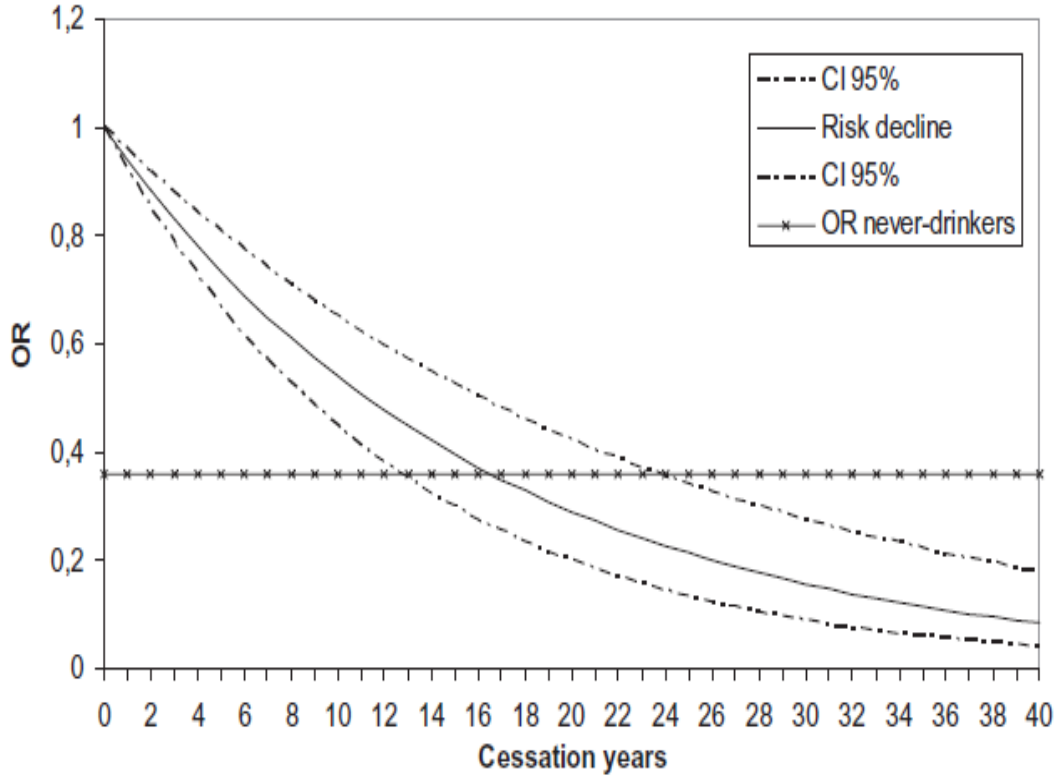


Figure 3 Estimated temporal characteristics of decline in risk of oesophageal cancer after drinking cessation; OR: odds ratio; CI: confidence interval

Jarl and Gerdtham, Addiction 2011

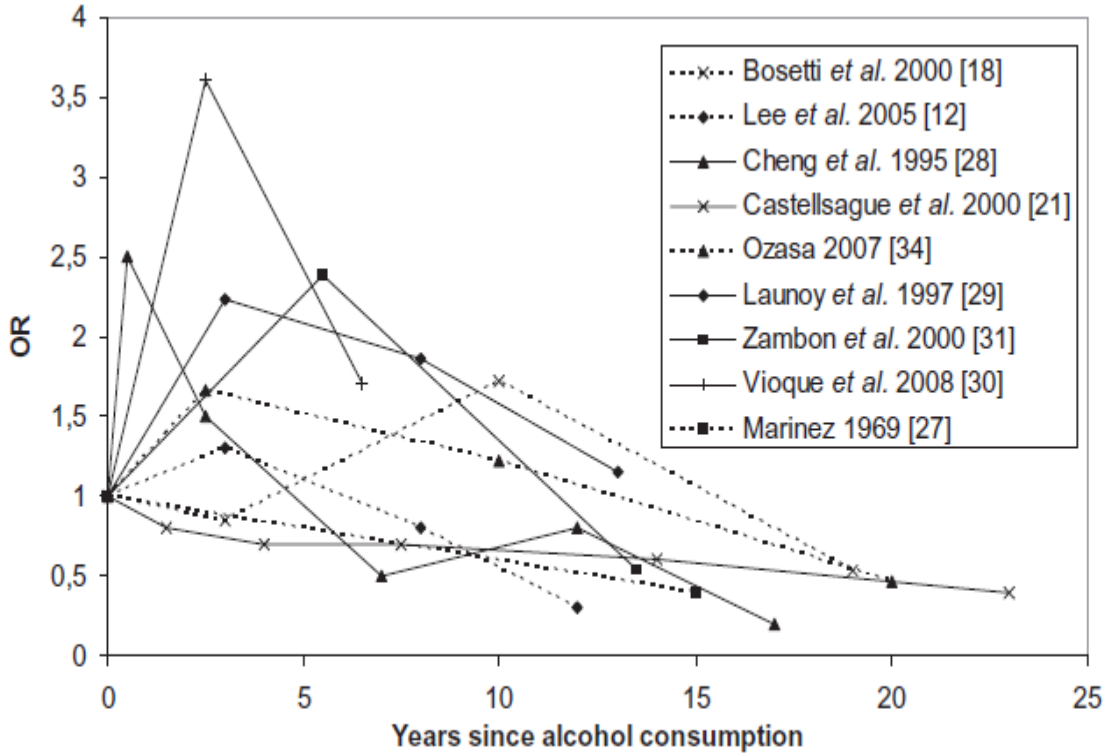


Figure 1 Risk of oesophageal cancer following drinking cessation, studies included in the meta-analysis; OR: odds ratio

Jarl and Gerdtham, Addiction 2011

SOGGETTI CON CONSUMO RISCHIOSO/DANNOSO E ALCOLDIPENDENTI

PRIMA VALUTAZIONE – PREVENZIONE SECONDARIA

Migliorare anamnesi alcologica/ Esame Obiettivo

Testa-Collo	Visita Neurologica/ETG Collo
Cavita' Orale, Faringe, Laringe	ORL (Laringoscopia)
Esofago-Stomaco	Infezione da Hp/ Endoscopia con biopsie
Colon-Retto	Sangue occulto feci/colonscopia (clisma TAC colon/ colonscopia virtuale)
Fegato e regione bilio-pancreatica	Valutazione HBV/ HCB/ HIV - ETG ogni 6 mesi
Polmone	Rx Torace
Prostata	PSA tot. e libero con rapporto (tot/libero) al di sotto dei 70 anni
Mammella	ETG se sotto i 40 anni Mammografia e/o ETG se oltre i 40 anni

An International Consensus for Medical Leadership on Alcohol

. . . . . Medical professionalism includes the responsability to speak out, to lead, and to voice advocacy. It is every clinician's responsability to address alcohol harm, both on a daily basis with individual patients and in the wider context of health harms and inequalities at the population level.

The voice of doctors is valued and trusted within societies, and therefore we call on all doctors to show effective leadership by holding ministries of health accountable for their lack of action in the face of such robust evidence.

We ask governments to act urgently and to champion evidence-based initiatives for the implementation of effective alcohol strategies at all levels to improve the health of populations worldwide.

Coltard C et al, Lancet 2011; vol 378: 1215


Grazie