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Farmaci ed ormoni

ETANOLO

NADPH

MEOS

NADP

NAD

ADH

NADH

IDROGENO

**ACETALDEIDE
(tossico)**

(ALDH)

Acetato

Piruvato

Glucosio ↓ (Ipoglicemia)

Lattato

Iperlattacidemia

Acidosi renale

Uricemia

Gotta

Collagene (?)

Sostituzione degli acidi grassi
come fonte energetica

Acidi grassi

Chetosi

Steatosi

Trigliceridi

Iperlipidemia

Metaboliti polari

Polimorfismi: ALDH2, ADH1B, ADH1C

GENDER DIFFERENCES IN ALCOHOL METABOLISM

Smaller volume of distribution of ethanol

Sex hormones

Decreased first-pass metabolism or more rapid absorption

Hepatic ADH activity reduced

Liver volume

Hepatic P450IIIE1 ?

STOMACO: FEMMINE

Cardia

**ALCOLDEIDROGENASI
Corpo-Fundica
Ridotta di circa 40-50%**

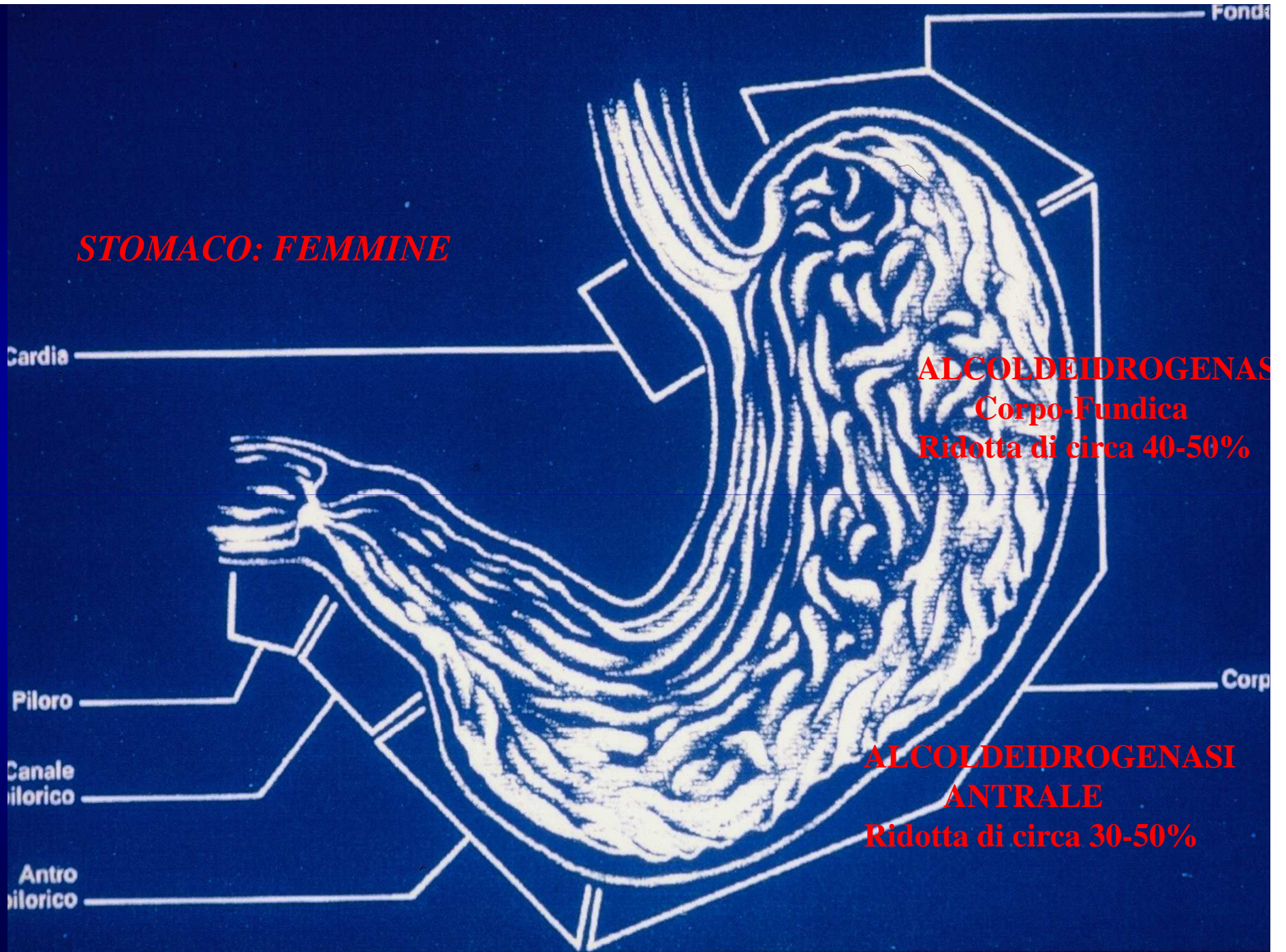
Piloro

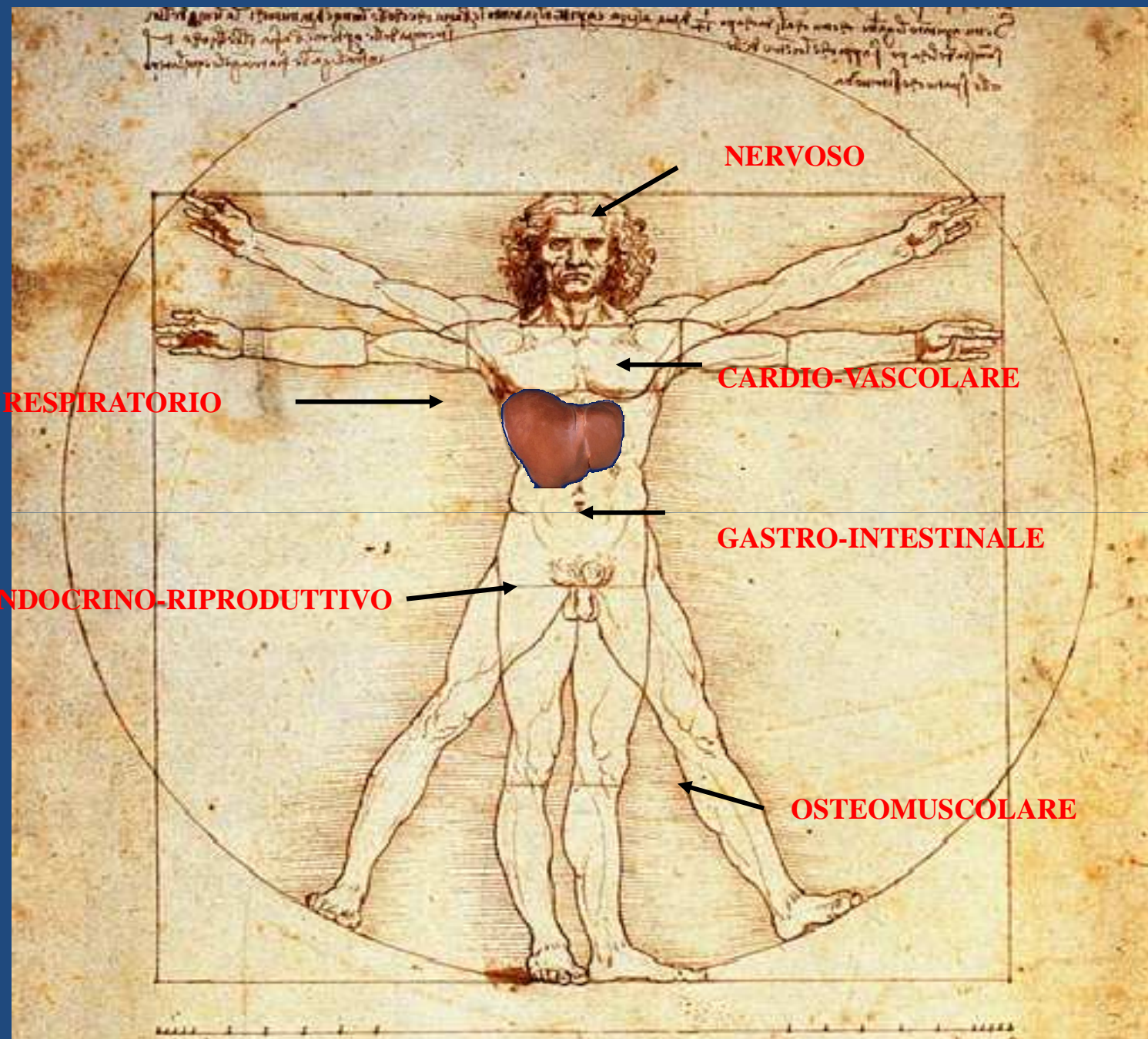
Canale
pilorico

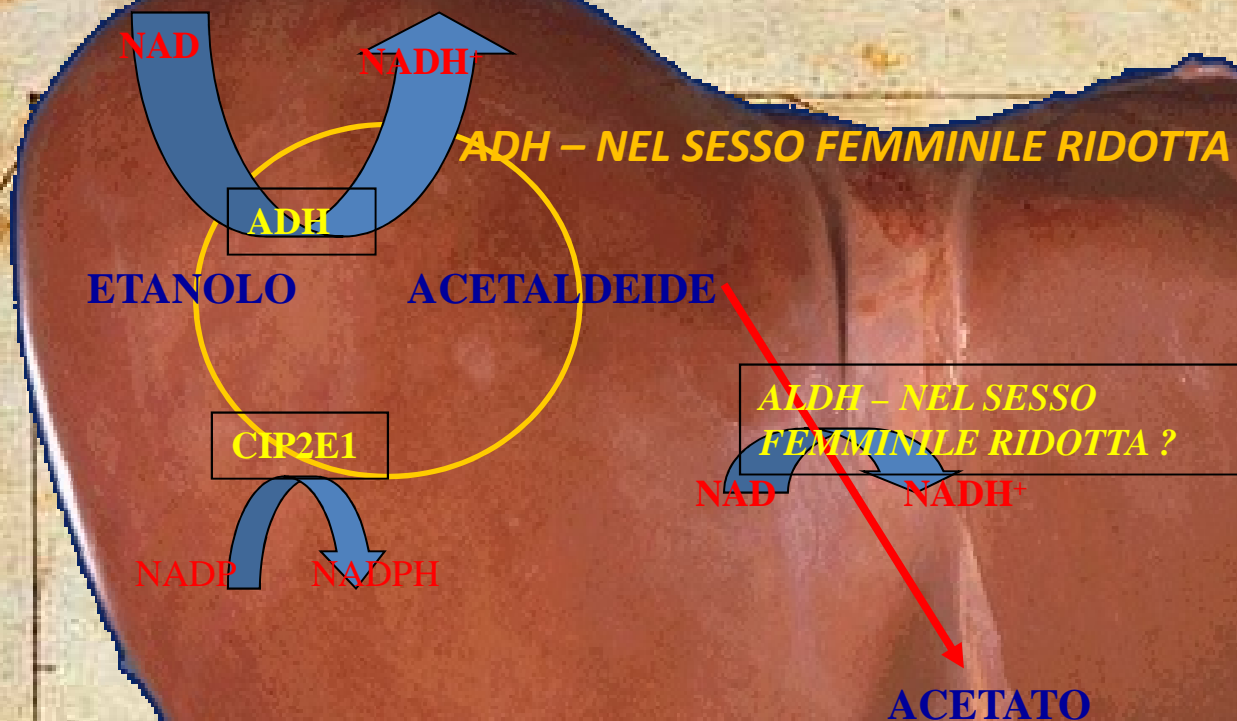
Antro
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Corpo

**ALCOLDEIDROGENASI
ANTRALE
Ridotta di circa 30-50%**





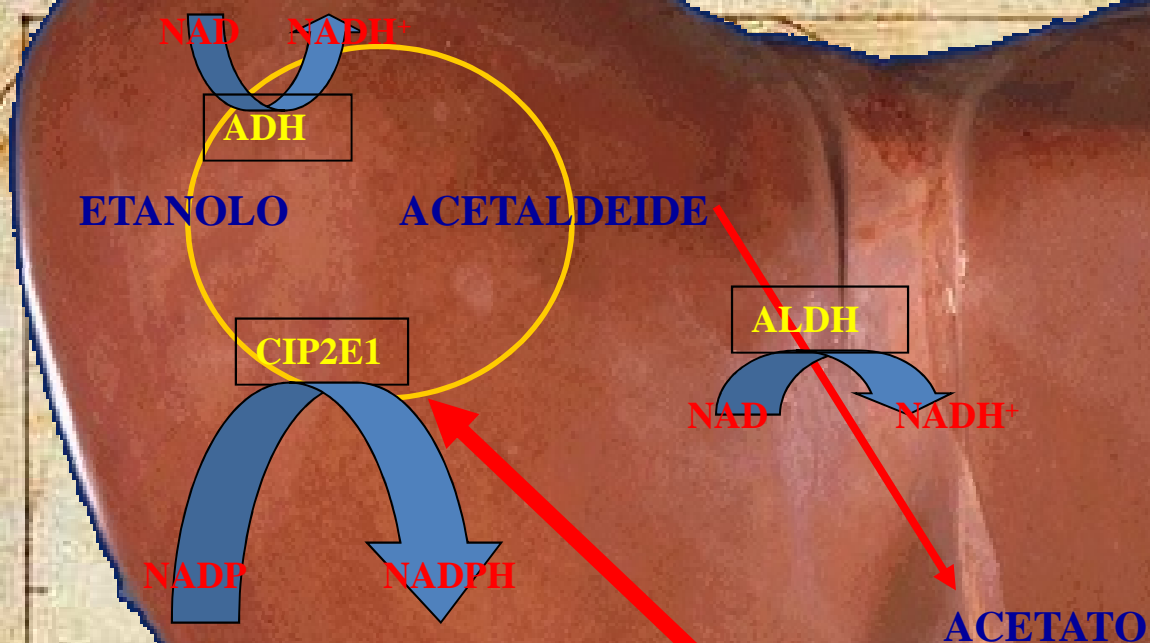


Social Drinker

ADH = Alcool deidrogenasi

CYP2E1 = Citocromo P-4502E1

ALDH = Aldeide deidrogenasi

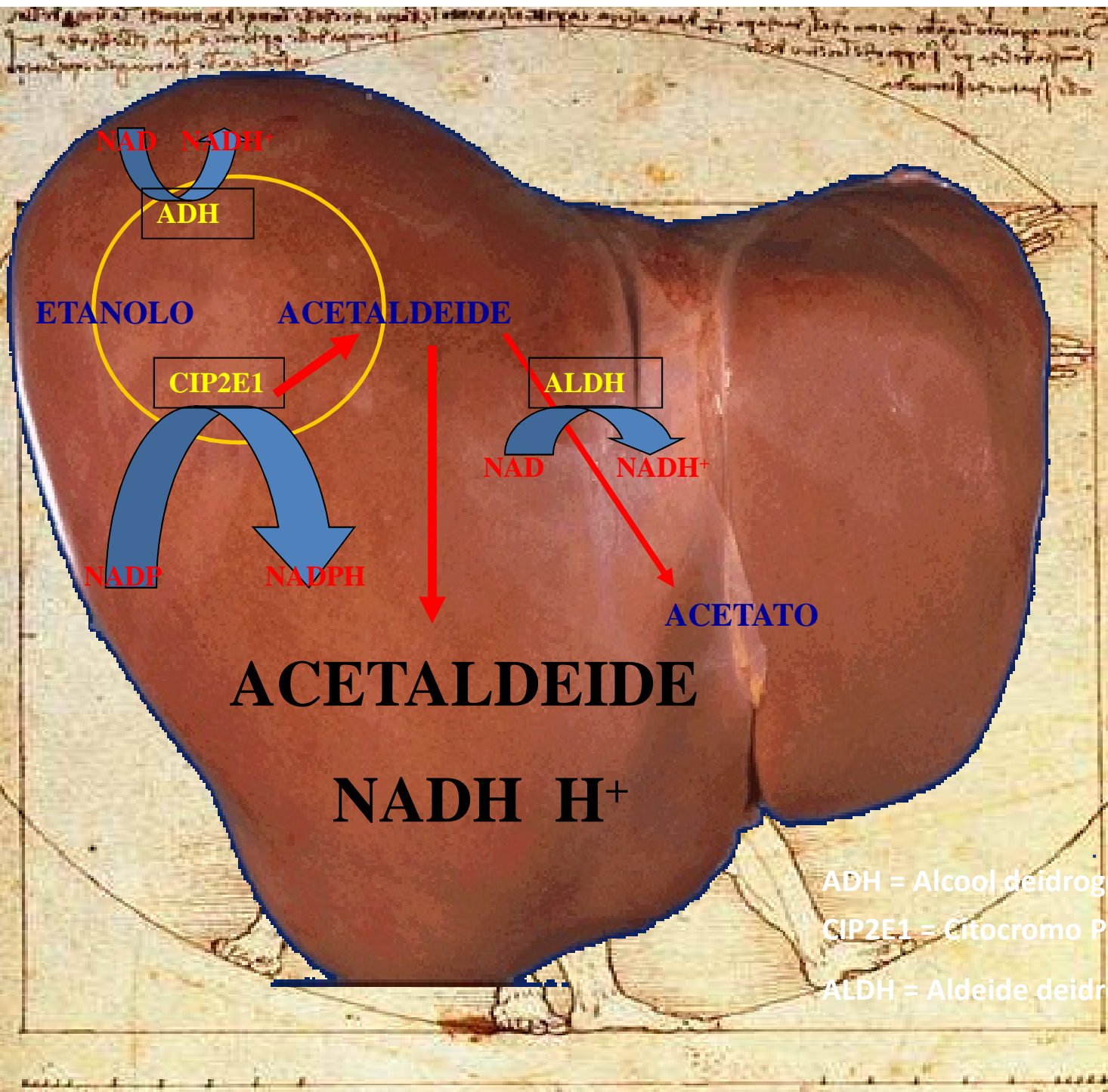


Alcoldipendenza

ADH = Alcool deidrogenasi

CYP2E1 = Citocromo P-450 2E1

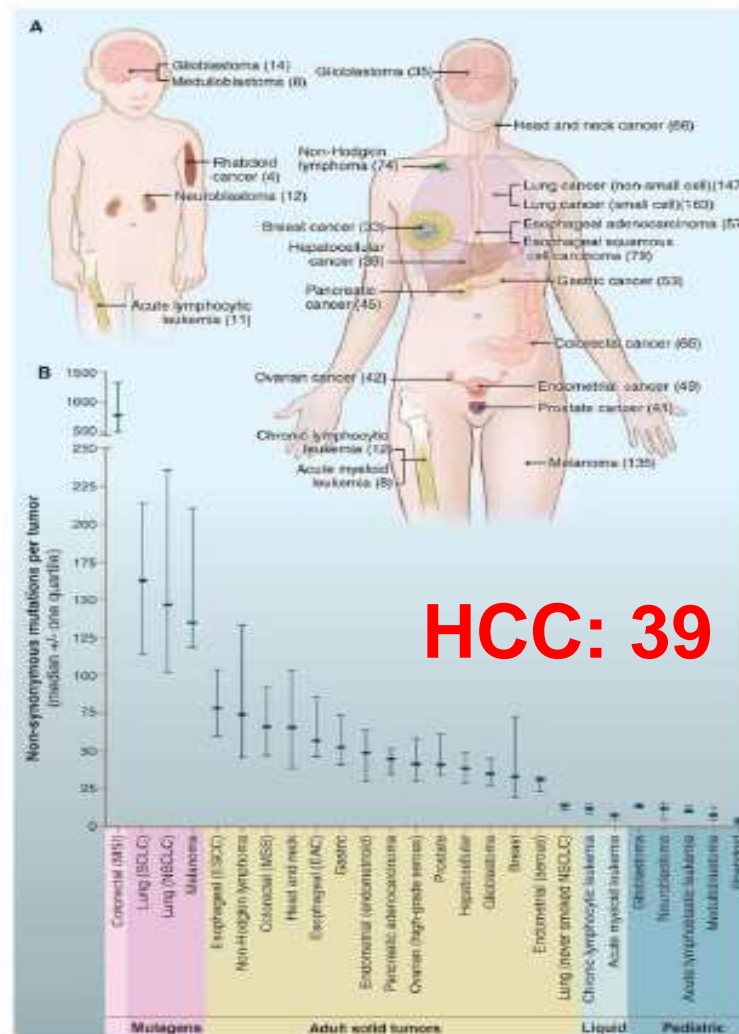
ALDH = Aldeide deidrogenasi



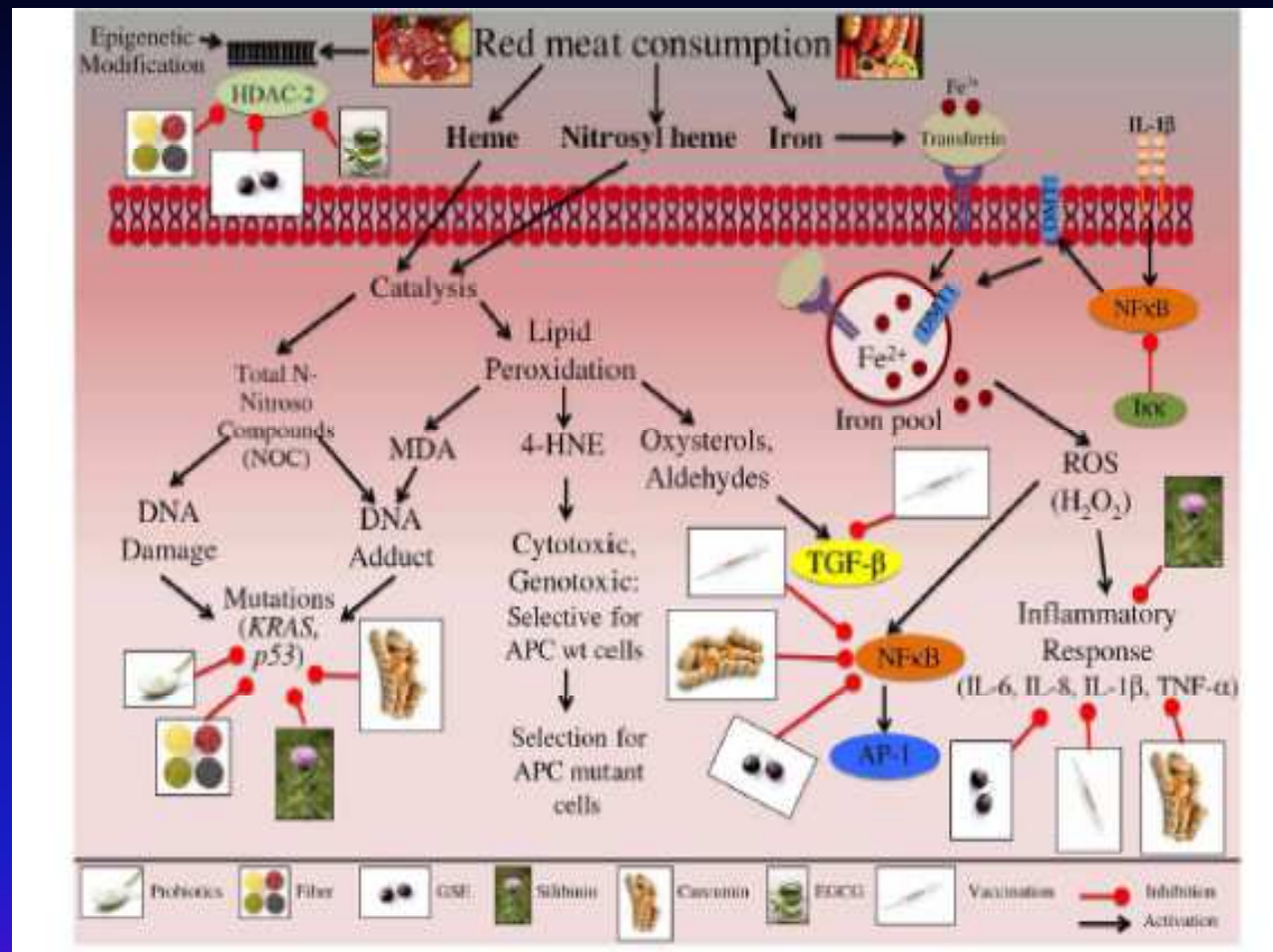
ADH = Alcool deidrogenasi

CIP2E1 = Citocromo P-4502E1

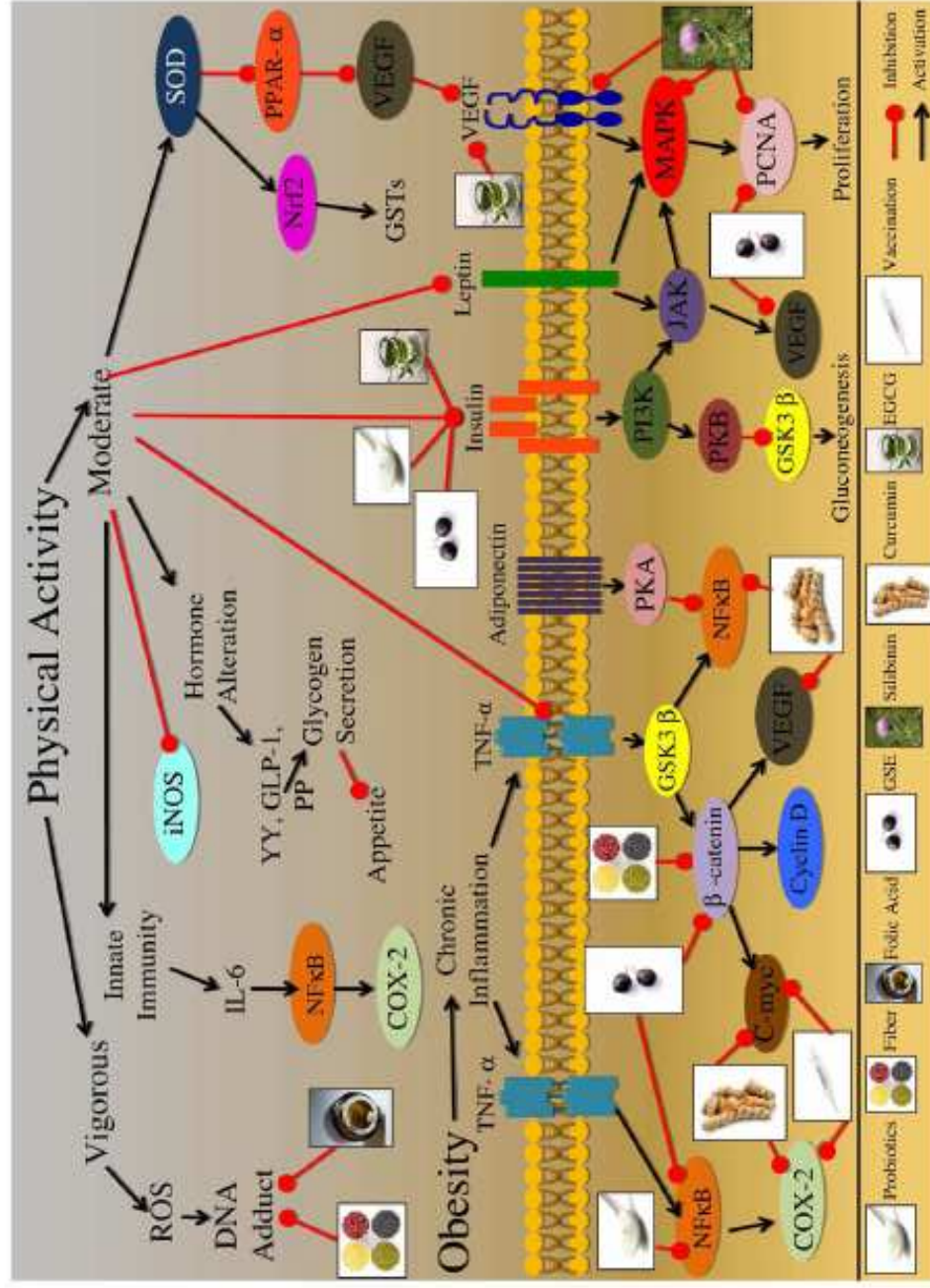
ALDH = Aldeide deidrogenasi

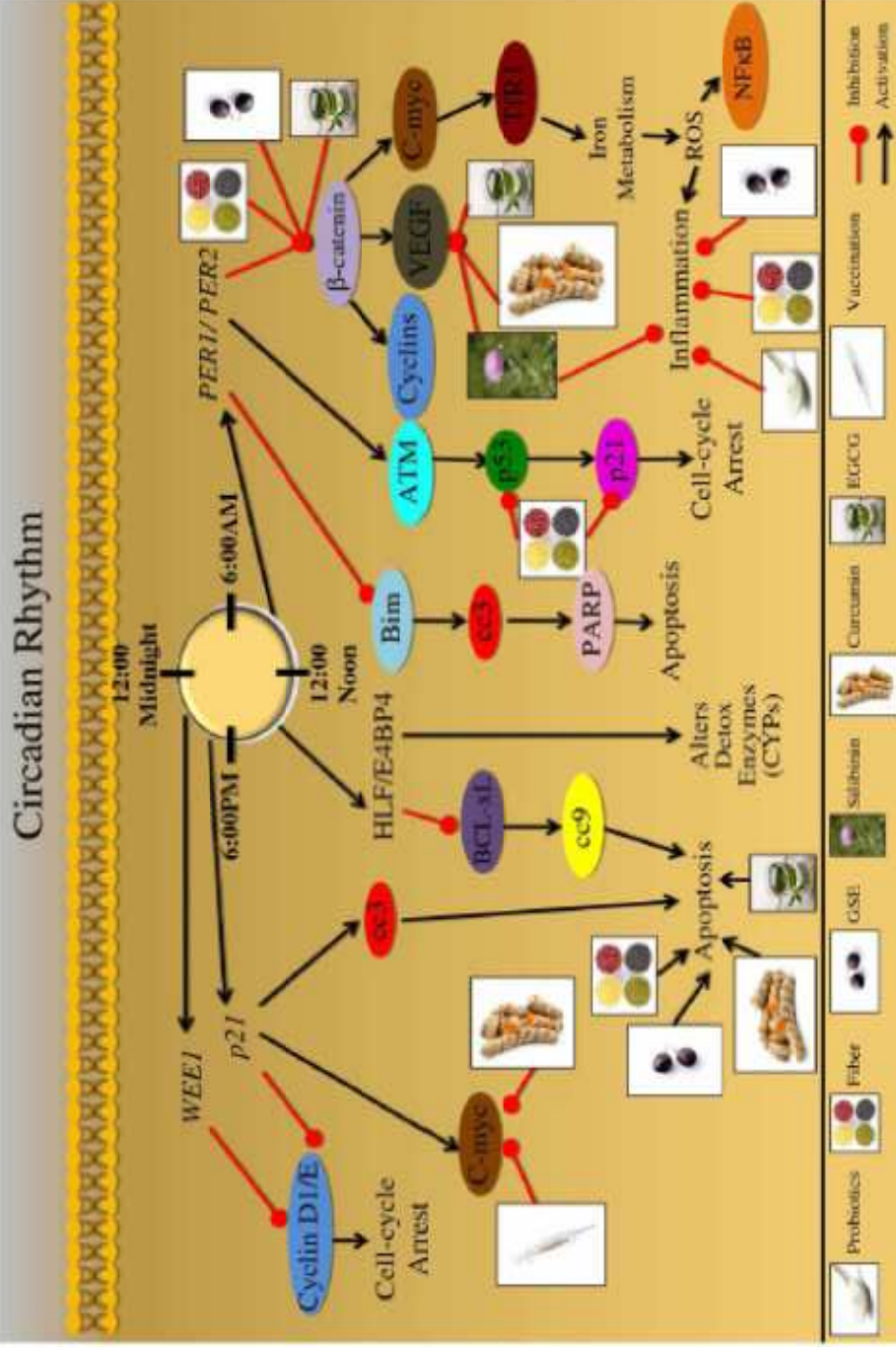


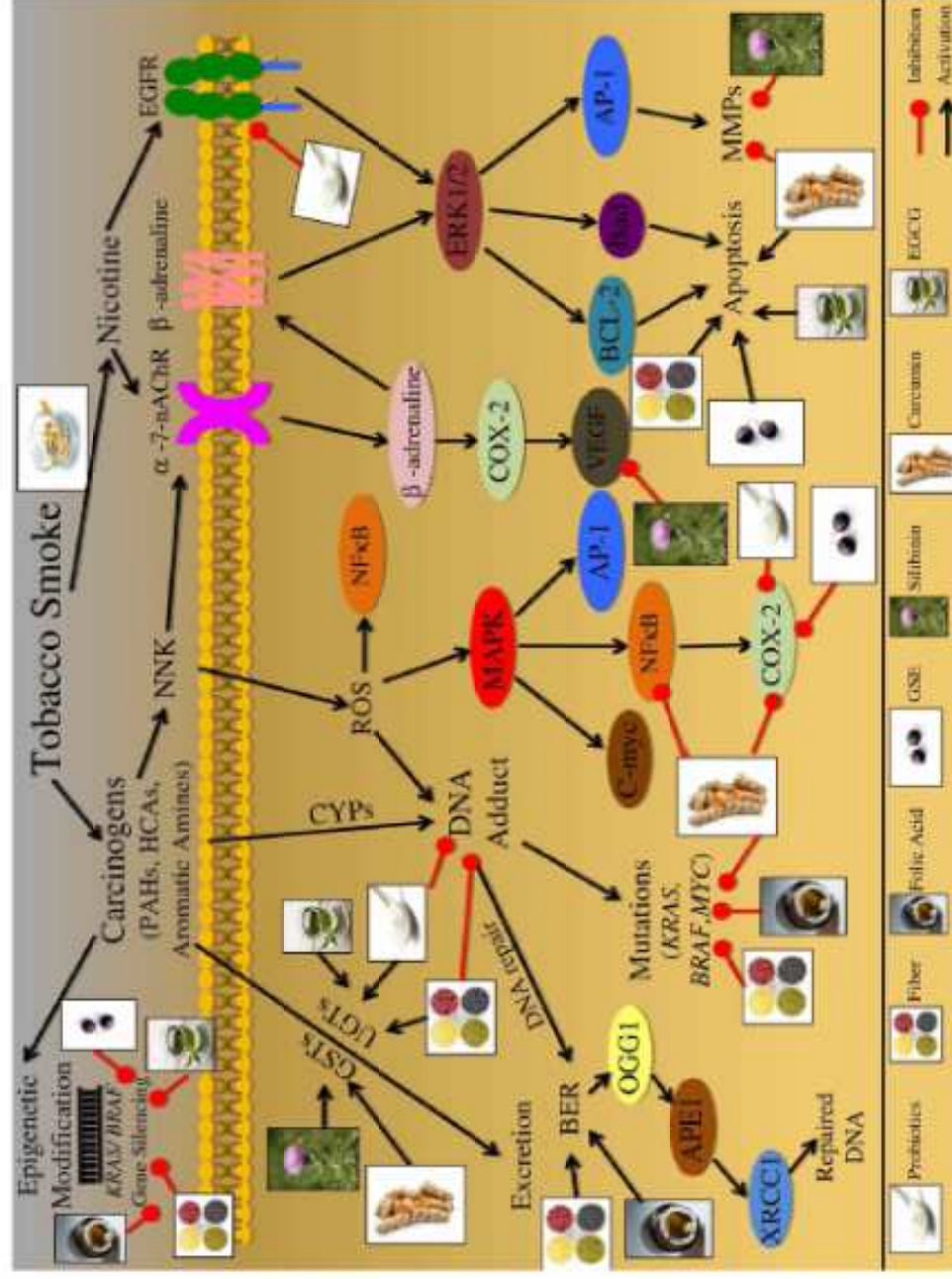
CANCER GENOME LANDSCAPES, www.sciencemag.org/special/cancergenomics, 2013



Derry et al, Frontiers in Oncology 2013

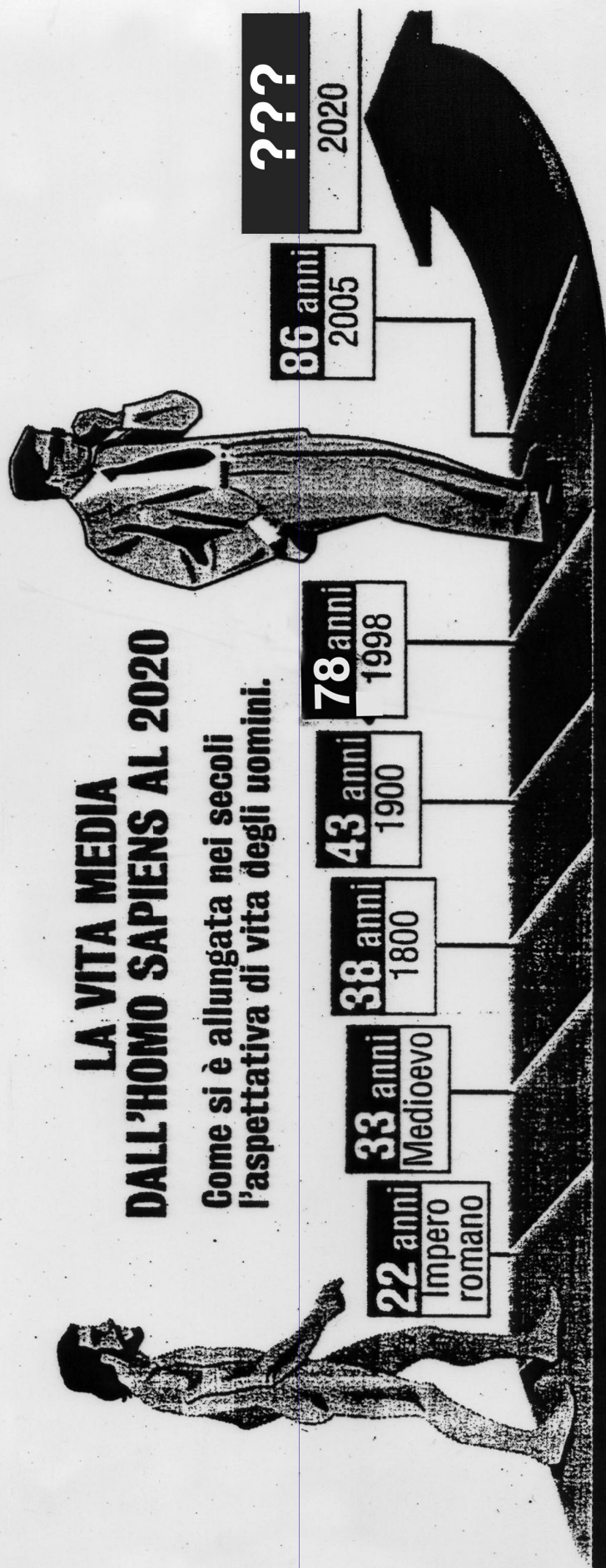


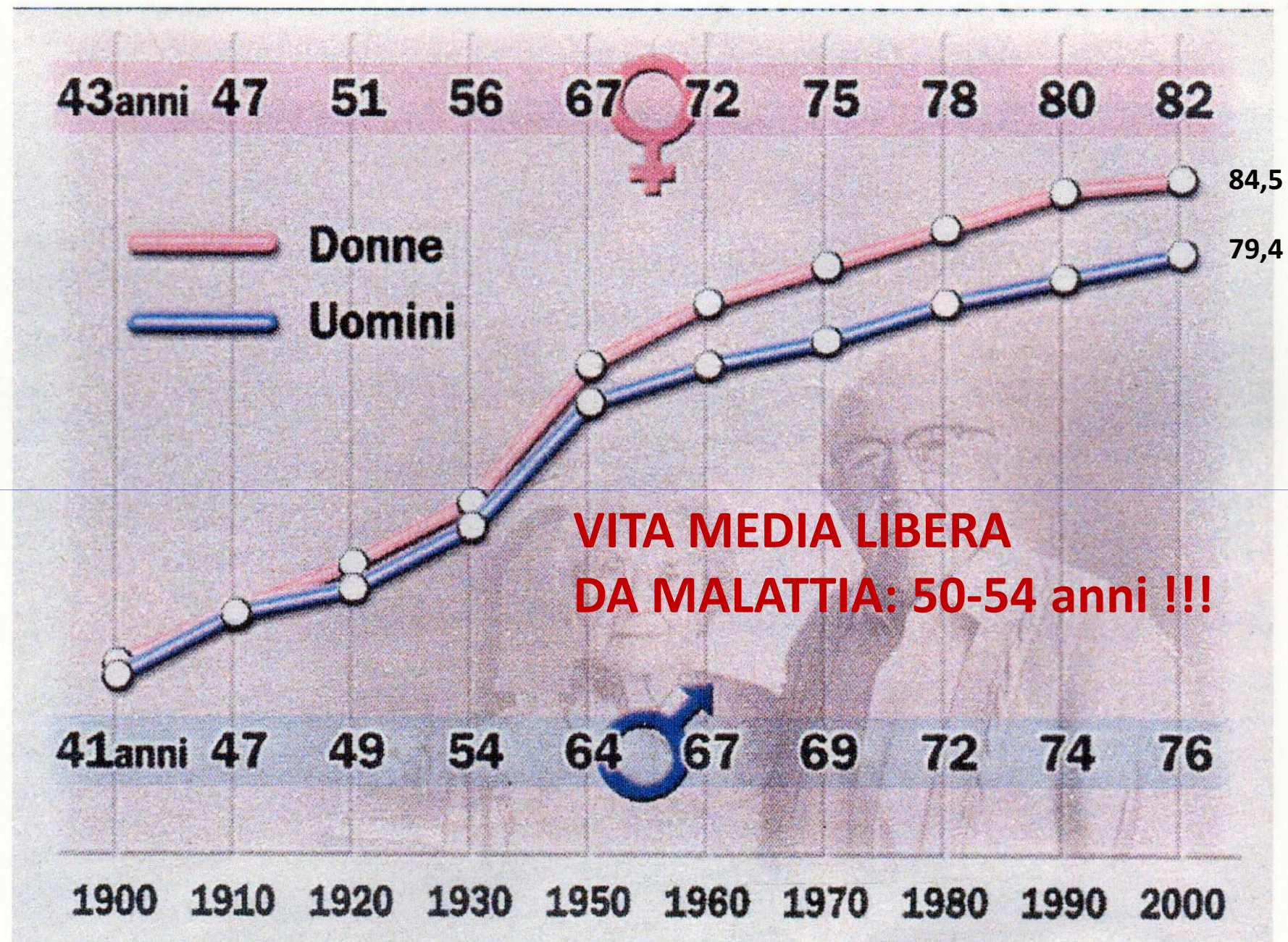


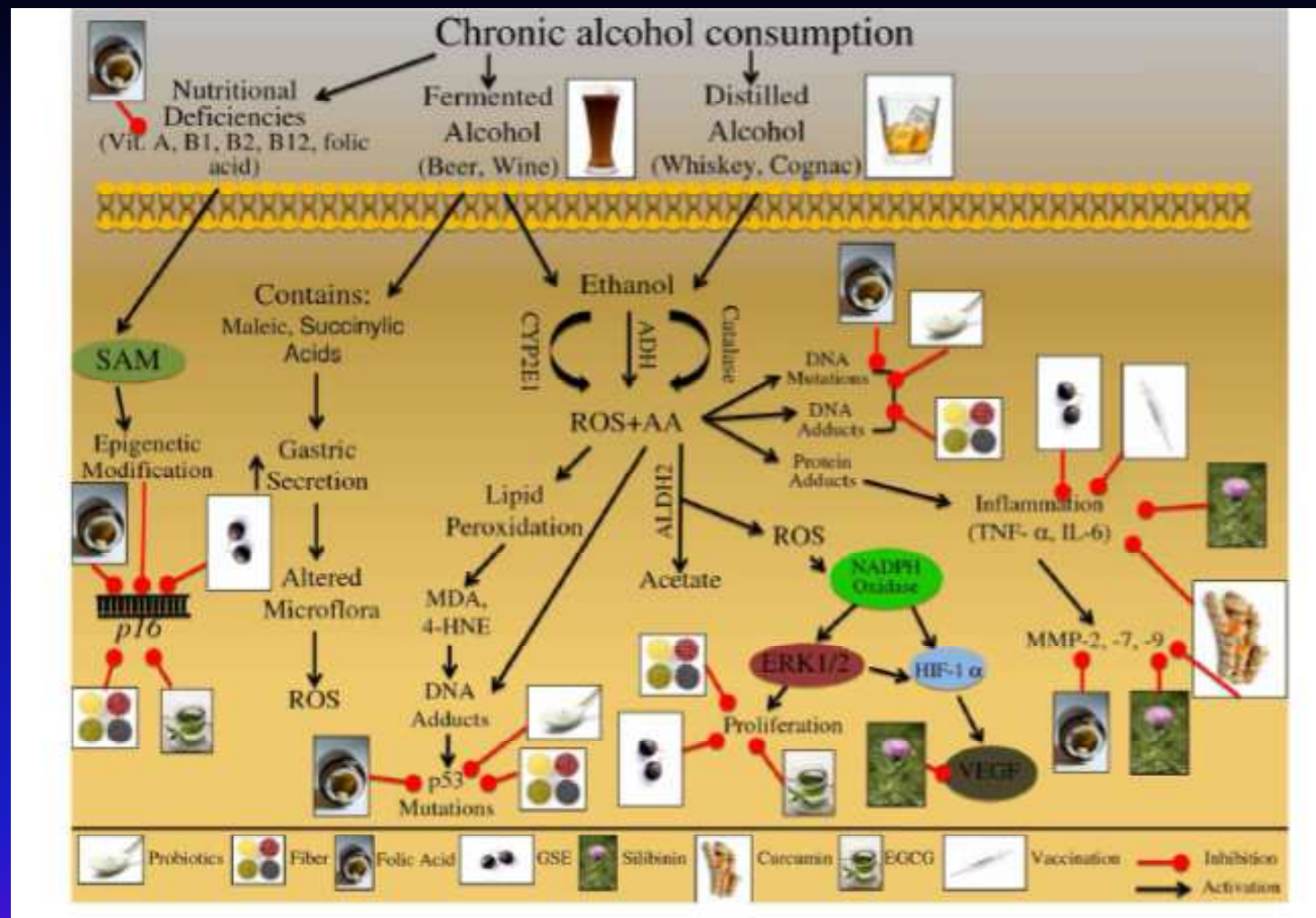


LA VITA MEDIA DALL'HOMO SAPIENS AL 2020

Come si è allungata nei secoli
l'aspettativa di vita degli uomini.







Decreased vitamin A levels result in decreased expression of the AP-1 gene, which is involved in cell cycle regulation and inflammation (TNF, NFkB.....) (Gianni Testino, Maedica 2011)

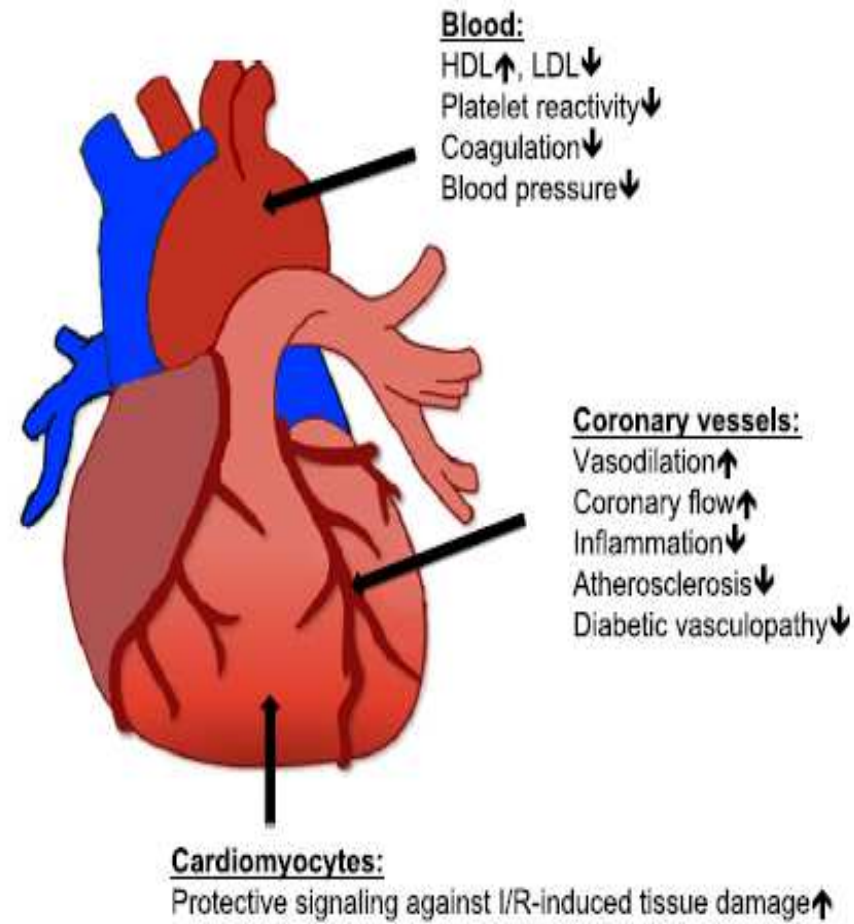
Derry et al, Frontiers in Oncology 2013

The use of expensive technologies instead of simple, sound and effective lifestyle interventions: a perpetual delusion

Silvia Carlos,^{1,2} Jokin de Irala,^{1,2,3} Matt Hanley,¹ Miguel Ángel Martínez-González^{1,3}

Journal of Epidemiology Community Health, 2014; 68: 897-904

The Spectrum of Cardioprotective Effects Induced by Antecedent Ethanol Ingestion



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

..... 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

... 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 exercise, 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

Testino G et al, Alcohol Alcohol 2013

Alcol, Ipertensione, Aritmie

Femmine

	0 gr	1-19 gr/die	20-39 gr/die
IPETENSIONE (RR)	1	1.4	2
ARITMIE (RR)*	1	1.5	2.2

*Sino al 30% delle FA da consumo
sociale di alcol

Scafato E., Istituto Superiore di Sanita', 2010

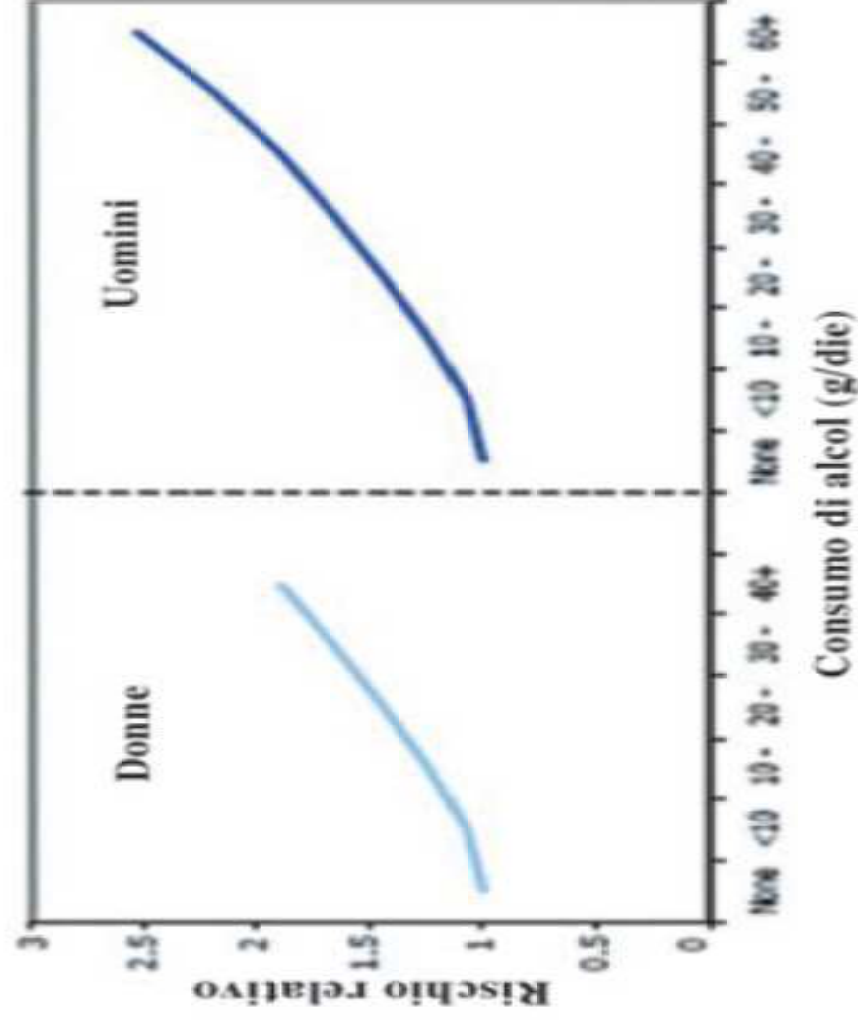


Figura 4.5. Rischio relativo di ipertensione per consumo alcolico.
Fonte: Strategy Unit (2003).

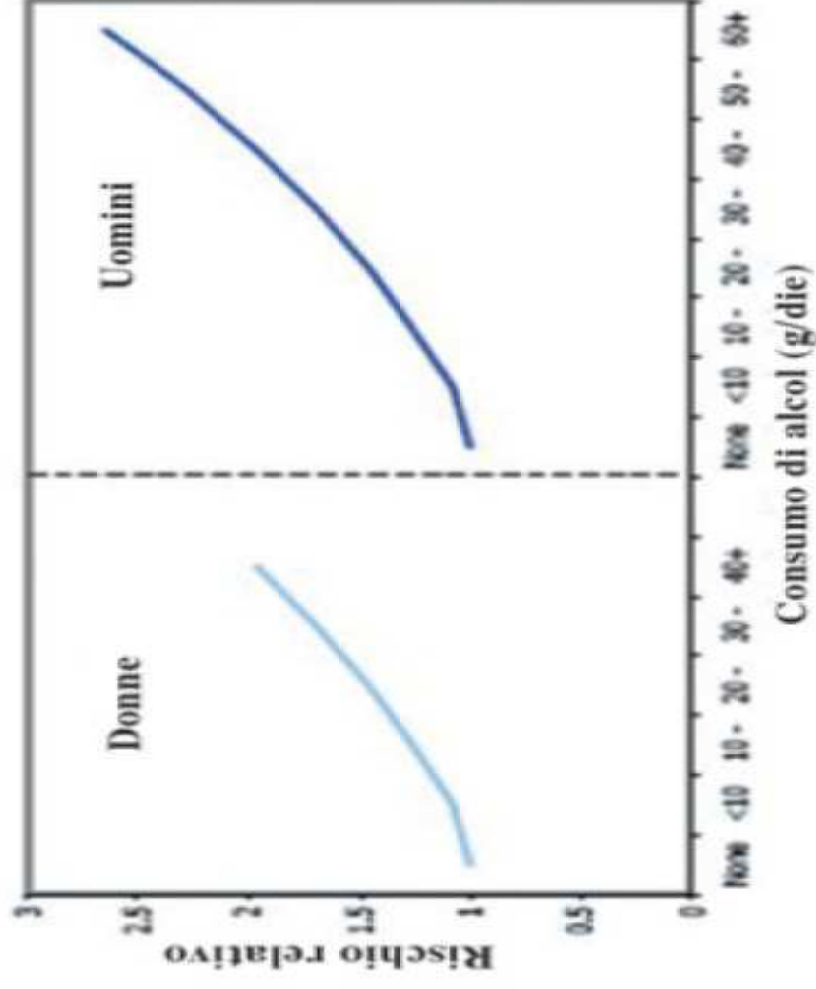


Figura 4.6. Rischio relativo di ictus emorragico per consumo alcolico. Fonte: Strategy Unit (2003).

LETTER TO THE EDITOR

Alcohol, Cardiovascular Disease and Cancer

Gianni Testino^{1,2,*}, Valentino Patussi^{2,3}, Emanuele Scutaro^{2,4}, Orre Ila Ancarani^{1,2} and Paolo Bono^{1,2}

¹Centro Alcolgico Regionale – Regione Liguria, UO Alcolgia e Patologie Correlate, Department of Internal and Specialistic Medicine, IRCCS AOI San Martino-National Institute for Cancer Research, Genova, Italy; ²World Health Organization – Collaborative Centre for Health Promotion, Research on Alcohol and Alcohol-related Health problems (Europe Region), Firenze, Italy; ³Centro Alcolgico Regionale – Regione Toscana, UO Alcolgia, Ospedale Careggi, Firenze, Italy and ⁴Istituto Superiore di Sanita', Roma, Italy

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(Received 21 May 2013; accepted 28 May 2013)

RESEARCH

Association between alcohol and cardiovascular disease: Mendelian randomisation analysis based on individual participant data

Conclusions Individuals with a genetic variant associated with non-drinking and lower alcohol consumption had a more favourable cardiovascular profile and a reduced risk of coronary heart disease than those without the genetic variant. This suggests that reduction of alcohol consumption, even for light to moderate drinkers, is beneficial for cardiovascular health.

Holmes MV et al, British Medical Journal 2014

PREVENZIONE ?

INSORGENZA DI DIABETE MELLITO TIPO II

ETANOLO E RISCHIO RELATIVO (RR)

Dosaggio protettivo ($RR < 1$):

- Uomini < 48 gr/die
- Donne < 30 gr/die

Incremento del Rischio ($RR > 1$):

- Uomini > 60 gr/die
- Donne > 30 gr/die

Binge Drinking: risk increase

Wei et al, Diabetes Care 2000; Carlsson et al, Diabetes Care 2003; Wannamethee et al, Arch Intern Med 2003; Koppes et al, Diabetes Care 2005; Djousse et al, Obesity 2007; Bantle et al, Metabolism 2008; Baliunas et al, Diabetes Care 2009; Joosten MM et al, Am J Clin Nutr 2010; Bonnet et al, Diabetologia 2012; Leite et al, World Journal of Gastroenterology 2014

Alcohol – Diabetes Mellitus

Diabetic control is significantly reduced by high alcohol consumption

Social drinker ?

Moderate amounts of ethanol may lead to hypoglycemia in type I diabetics

**Alcohol increase the risk of hypoglycemia in type II diabetes patients treated with sulfonylurea
hypoglycemic agents**

Chronic alcohol intake is associated with higher hemoglobin A1c values

Alcohol should be suspected in diabetics showing poor metabolic control

Odd Ratio for death of 4.38 in diabetic and alcohol consumption.....

CONSUMO DI BEVANDE ALCOLICHE IN SOGGETTI SANI

3 - 5 gr/die

Rischio minimo

Donna < 10 gr/die

Basso rischio

Uomo < 20 gr/die

Donna 11-40 gr/die

Consumo Rischioso

Uomo 21-60 gr/die

> 65 anni e fra i 16-18 anni >12/die

Donna > 40 gr/die

Consumo Dannoso

Uomo > 60 gr/die

Binge Drinking

Scafato E et al, Istituto Superiore Sanita' 2010
Testino G et al, Eur Rev Med Pharmacol Sci 2012
Testino G et al, BMJ.com 2014

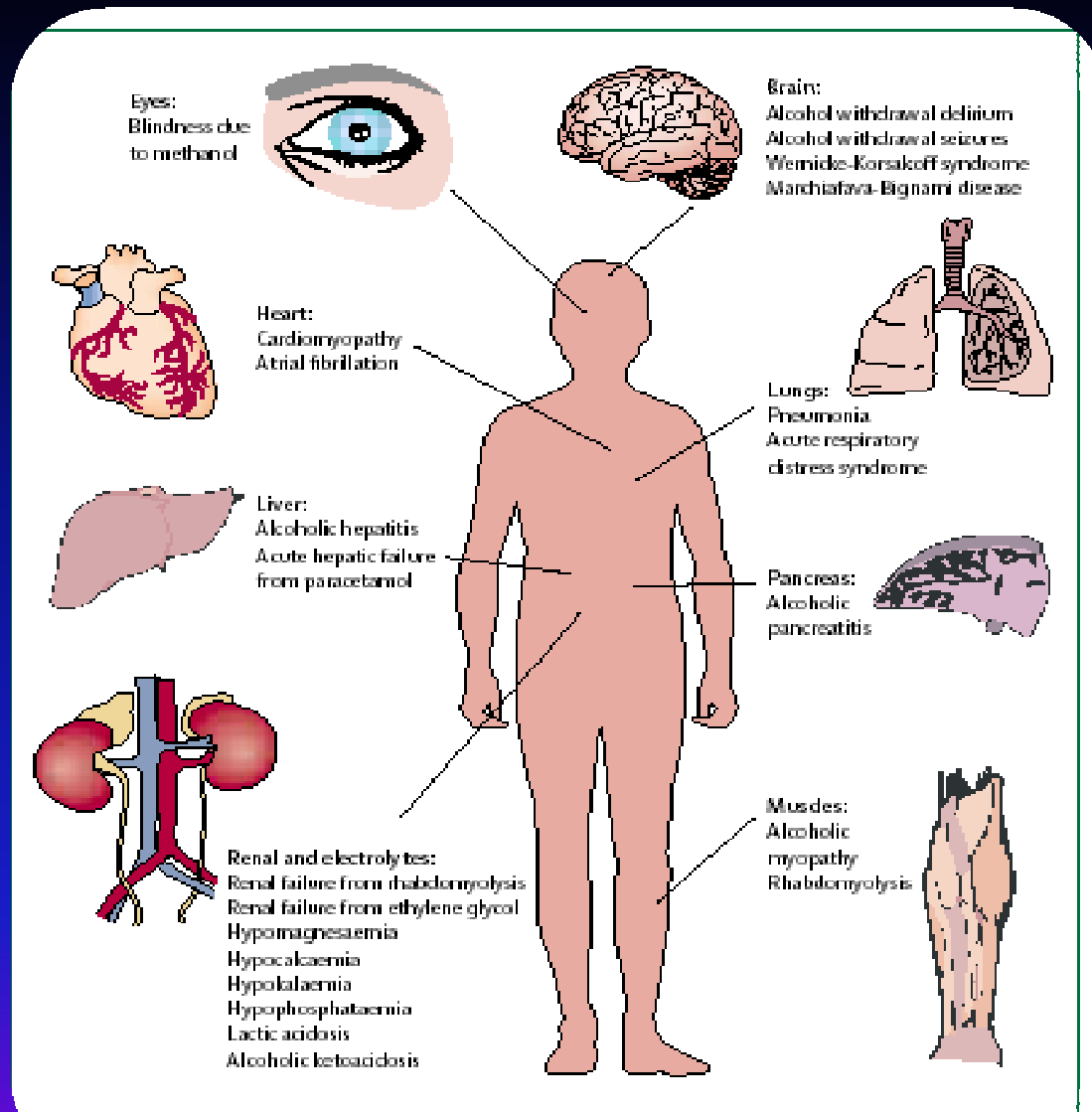


Figure 1: Disorders that can occur in critically ill patients as a result of alcohol abuse or dependence

Enrica Scafato (a), Silvia Giusti (a), Luca Casarino (b)
(a) Centro Nazionale di Epidemiologia, Sorveglianza e Promozione della salute, CNISPS, Centro
Organizzazione Mondiale della Sanità Ricerca sull'Alcol, Istituto Superiore di Sanità; (b) Lazio, Azienda 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

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

- Group 1** Carcinogenic to humans
(arsenic, asbestos, benzene, radionuclide, tobacco smoking)
- Group 2 A** Probably carcinogenic to humans
- Group 2B** Possibly carcinogenic to humans
(radio frequency electromagnetic 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*
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*New sites.

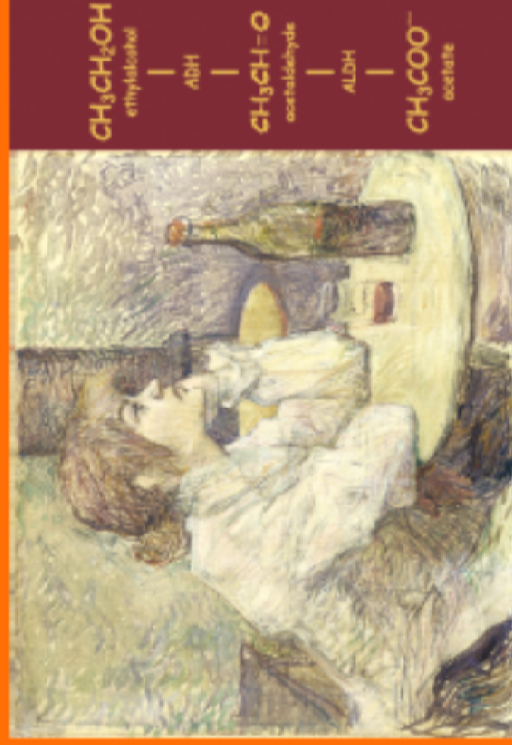
Table: Evidence for carcinogenicity in humans of Group 1 agents assessed

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
	Aristolochic acid			
000313-67-7	(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

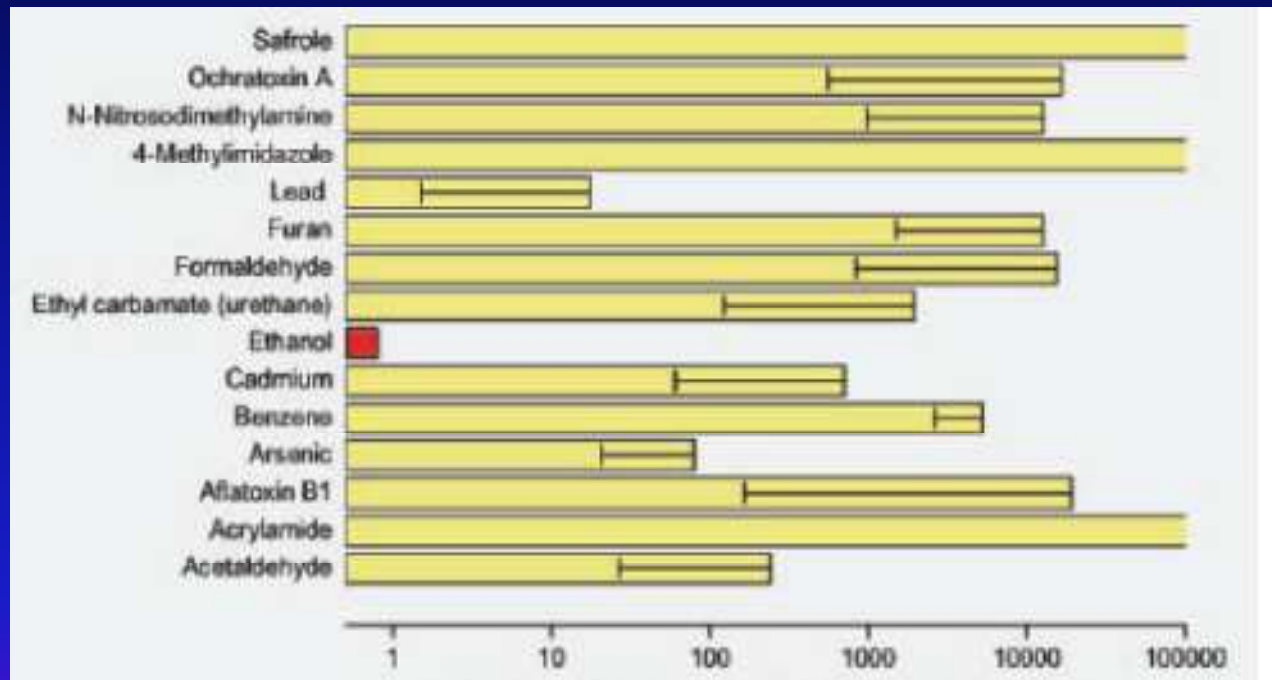
000064-17-5	Ethanol in alcoholic beverages	1	96, 100E	2012
	Ethylene oxide			
000075-21-8	(NB: Overall evaluation upgraded to Group 1 based on mechanistic and other relevant data)	1	97, 100F	2012
	Etoposide			
033419-42-0	(NB: Overall evaluation upgraded to Group 1 based on mechanistic and other relevant data)	1	76, 100A	2012
033419-42-0				
015663-27-1	Etoposide in combination with cisplatin and bleomycin	1	76, 100A	2012
011056-06-7				
	Fission products, including strontium-90	1	100D	2012
000050-00-0	Formaldehyde	1	88, 100F	2012

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 IARC¹)

Agent	IARC Monographs evaluation of Carcinogenicity			IARC Monographs (Volume Number)
	In animals	In humans	IARC group ¹	
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
Safrrole	Sufficient	Inadequate	2B	10, Sup 7

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

MARGIN OF EXPOSURE (MOE)



2.19 Synthesis

2.19.1 Oral cavity and pharynx

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 Larynx

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.

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

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, MHSoc, Yu Ye, MA, and Timothy S. Naimi, MD, MPH

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.²⁻⁴ 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 2007.²⁻⁷ In addition to confirming earlier research for the previously mentioned cancers, they con-

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)

Daily consumption of up to 20 grams of alcohol accounted for 26% to 35% of alcohol-attributable cancer death

Applying the Precautionary Principle to Nutrition and Cancer
Journal of the American College of Nutrition, 2014

SOGGETTO SANO

Cancro bocca, faringe e laringe:
un drink/settimana → incremento rischio del 24%

Carcinoma Squamo-Cellulare del tratto aereo-digestivo
superiore: 10 grammi etanolo/die → incremento rischio 10-15%

Carcinoma Esofago:
un drink/settimana → aumento rischio del 4%

Cancro Coloretale:
10 grammi di etanolo/die → incremento del rischio del 9%

Cancro Mammella:
10 grammi di etanolo/die → incremento del rischio del 10%

Gonzales et al, J Am College Nutr 2014

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)	–	–	–	–

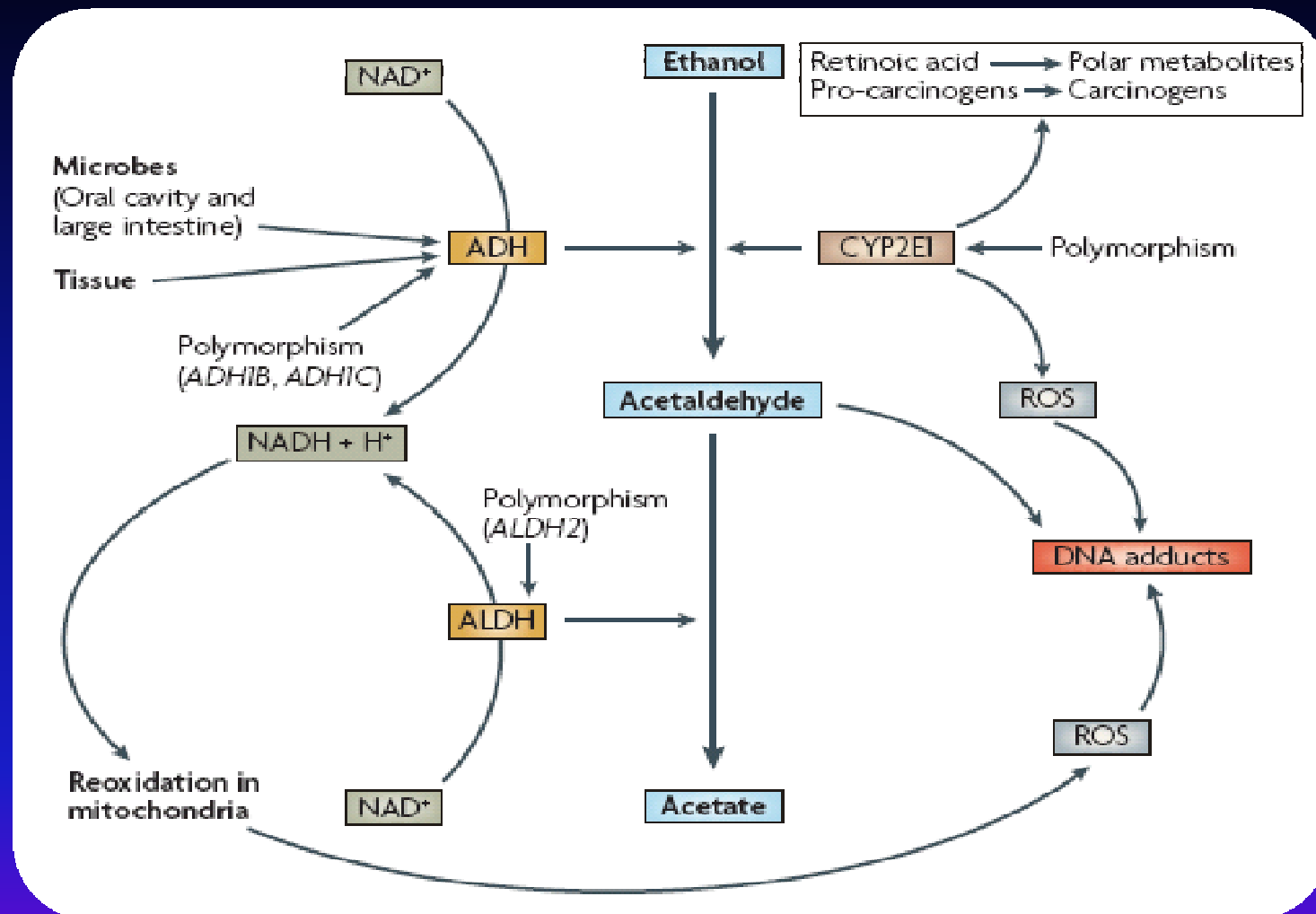
* $P < 0.05$.

** $P < 0.001$.

Thygesen et al, Alcohol and Alcoholism 2009

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**



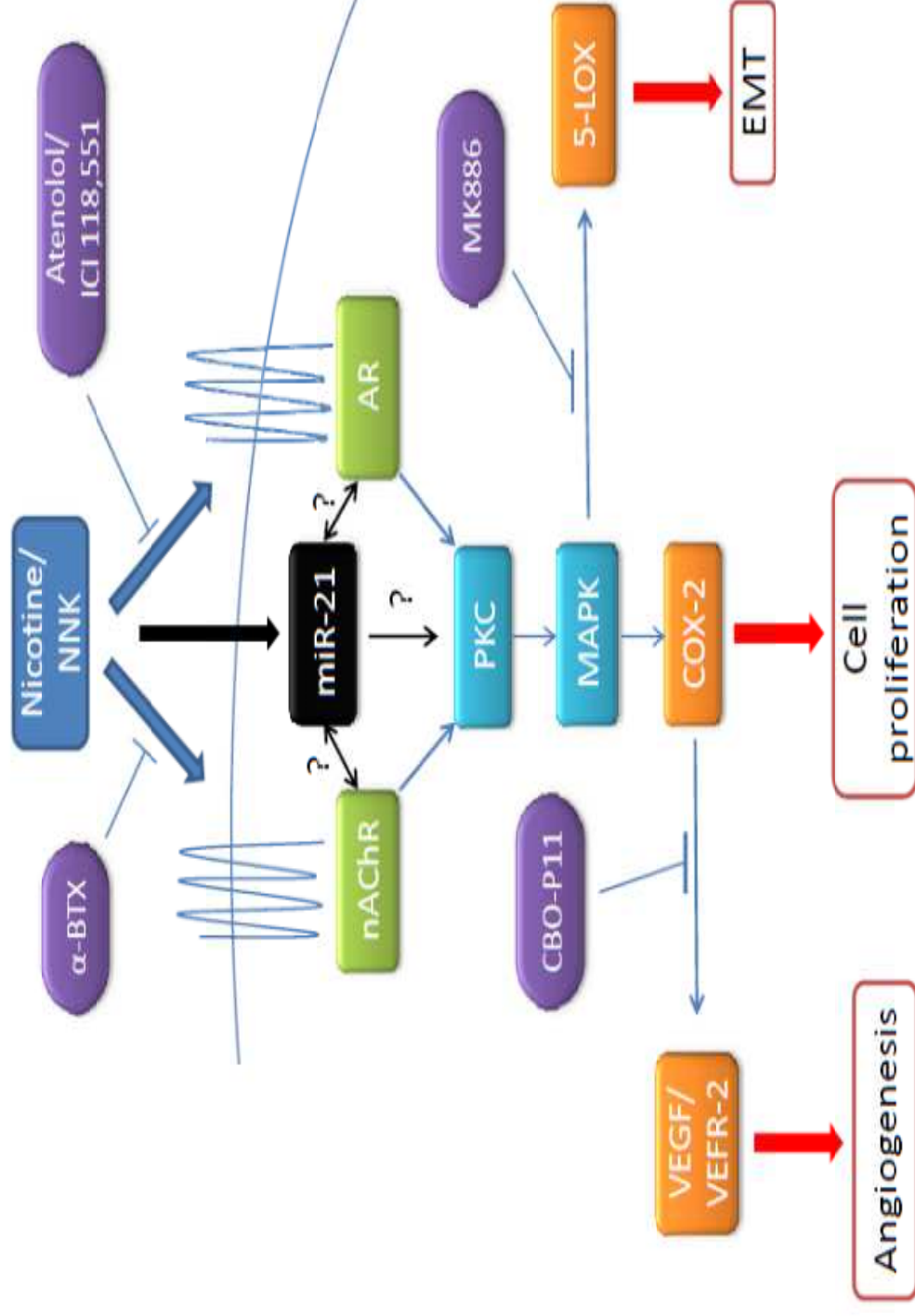
Seitz and Stickel, Nat Rev Cancer 2007

CIGARETTE SMOKING

- Cardiovascular diseases*, cancers, lung diseases, chronic renal disorders
- Lung cancer: 90% of small cell lung cancer; 70% of non-small cell lung cancer
- Gastrointestinal disorders: «abdominal discomfort», ulcers, IBD, **cancers**
- 5000 ingredients
- 150 carcinogenic activities
- Alkaloids, phenolic compounds, volatile aldehydes, polycyclic aromatic hydrocarbons, tobacco-specific nitrosamines, heavy metals

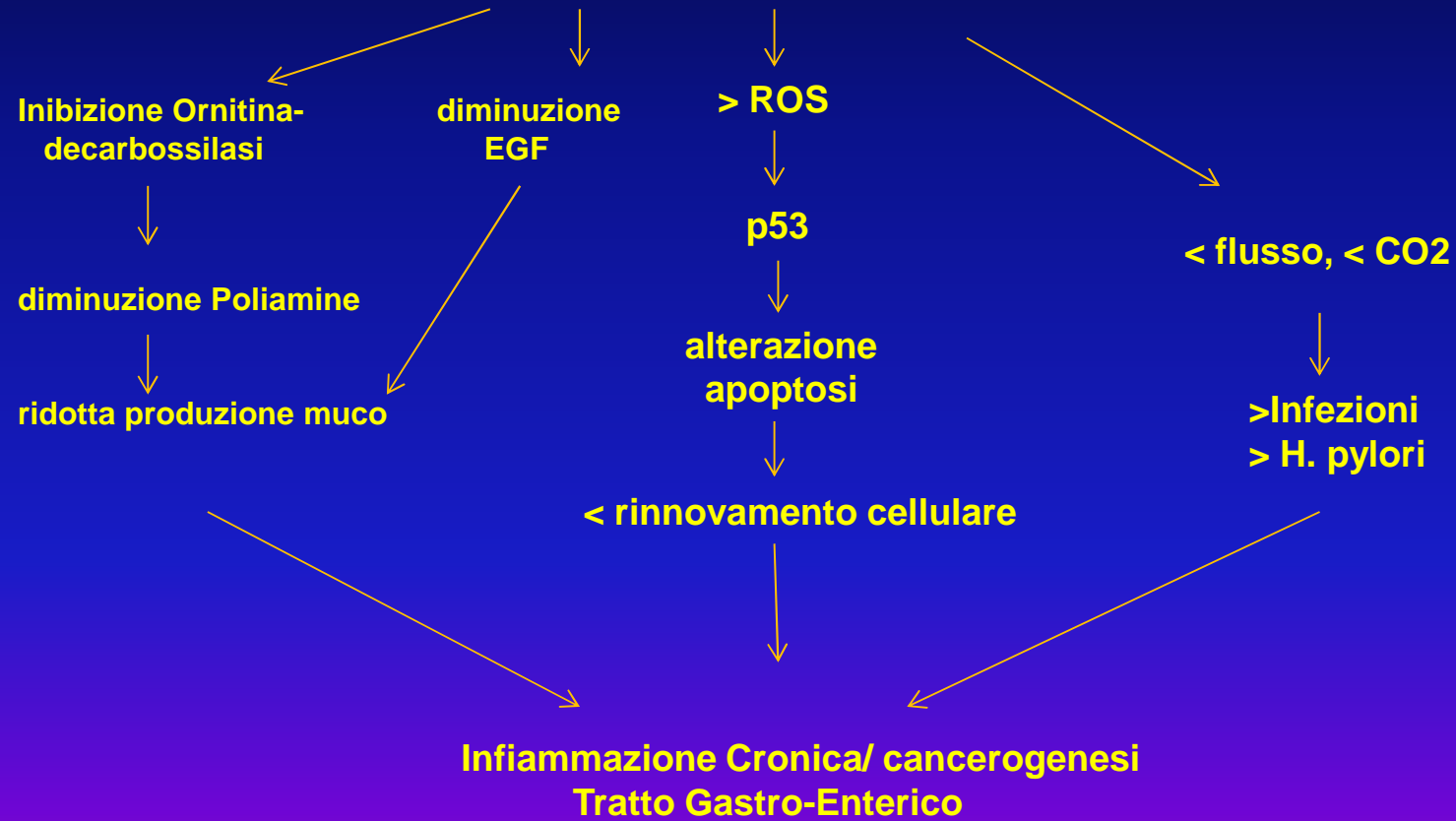
** Oxidative stress → lipid peroxidation → low density lipoprotein (LDL) oxidation →*

→ Atherosclerosis



A schematic representation showing the interaction of nAChR and AR in the nicotine/NNK-stimulated gastric carcinogenesis.

CIGARETTE SMOKING



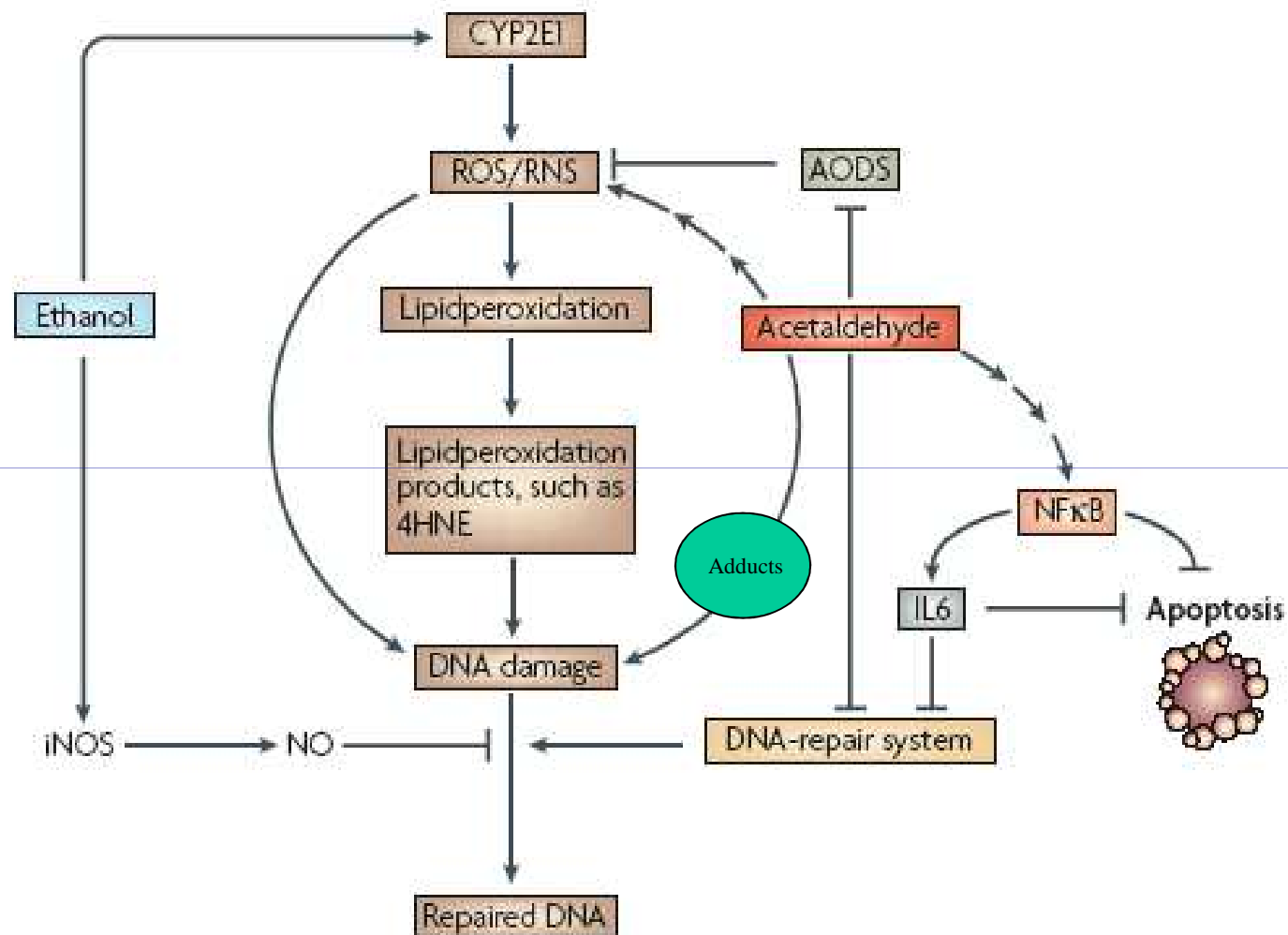


TABLEAU 1 : **POLYMORPHISMES GÉNÉTIQUES ASSOCIÉS AUX ENZYMES
QUI MÉTABOLISENT L'ALCOOL**

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

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

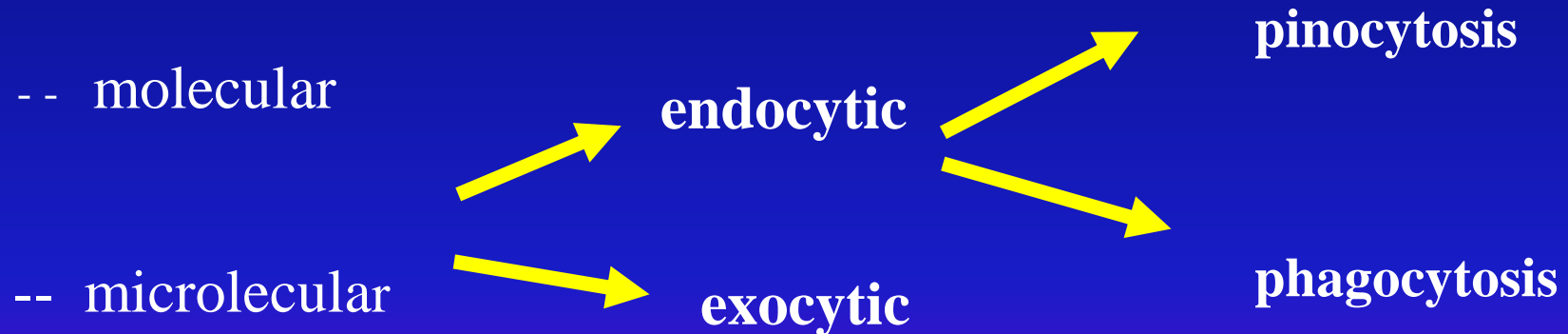
Genes/polymorphisms	Alcohol 1-30 g/day	Alcohol > 30/ g/day
ALDH2-active	OR 7.2	
ALDH2-deficiency	OR 14.5	OR 102.5
Slow ADH1B + ALDH2-deficiency	OR 37.5	OR 382.3

Salaspuro M, Scand J Gastroenterol 2009

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

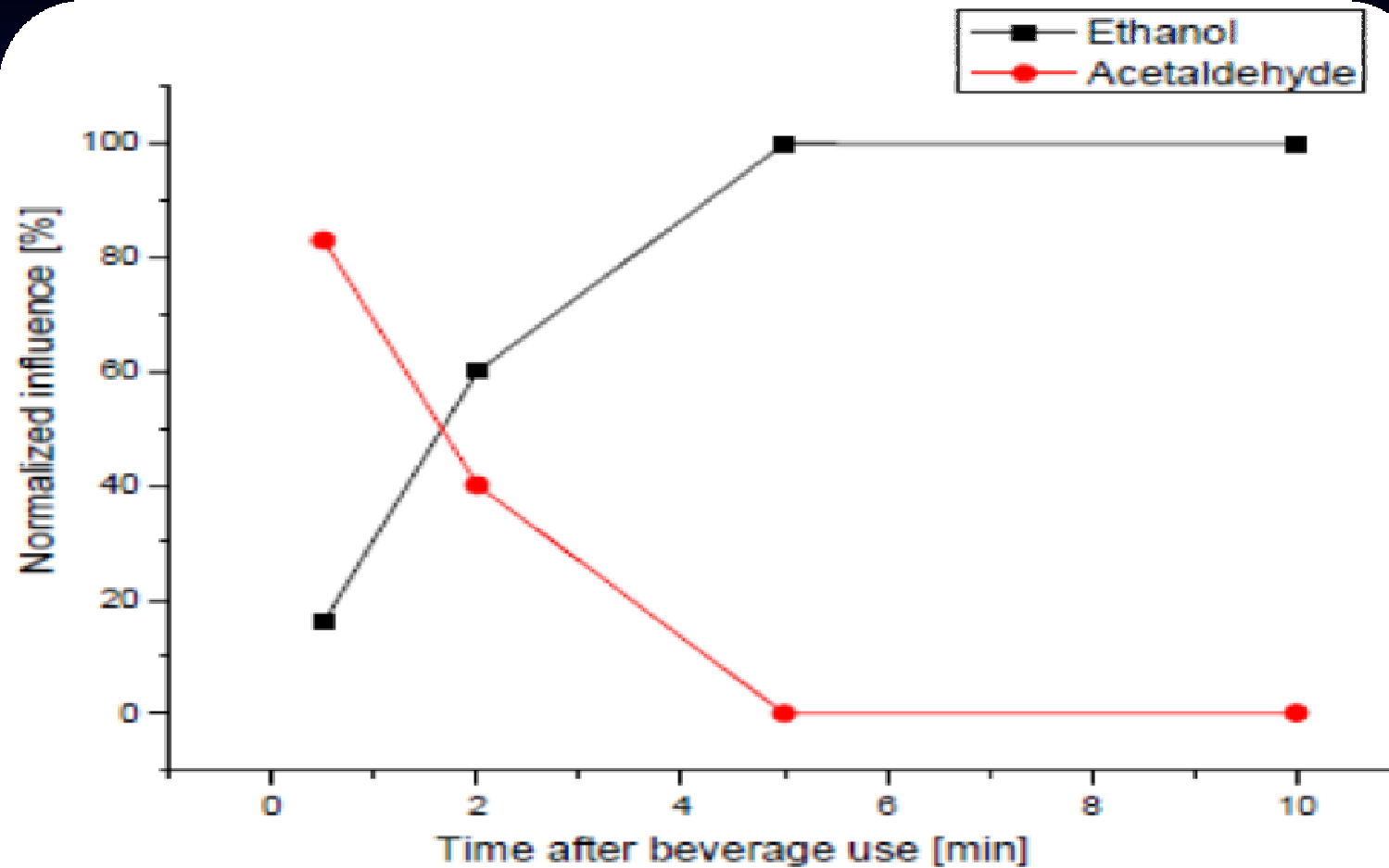


Figure 2 Influence of ethanol and acetaldehyde content of the beverages on the salivary acetaldehyde concentration.

Lachenmeier and Monakhova, J Exp Clin Cancer Res 2011

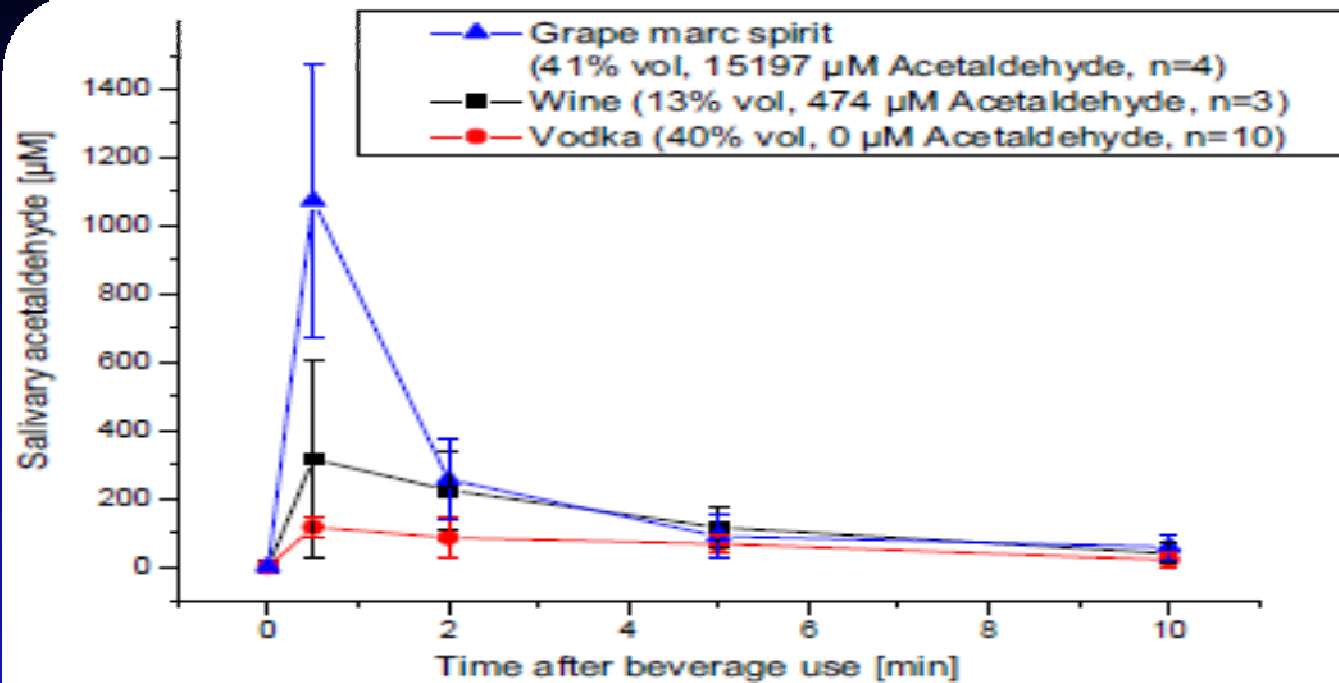


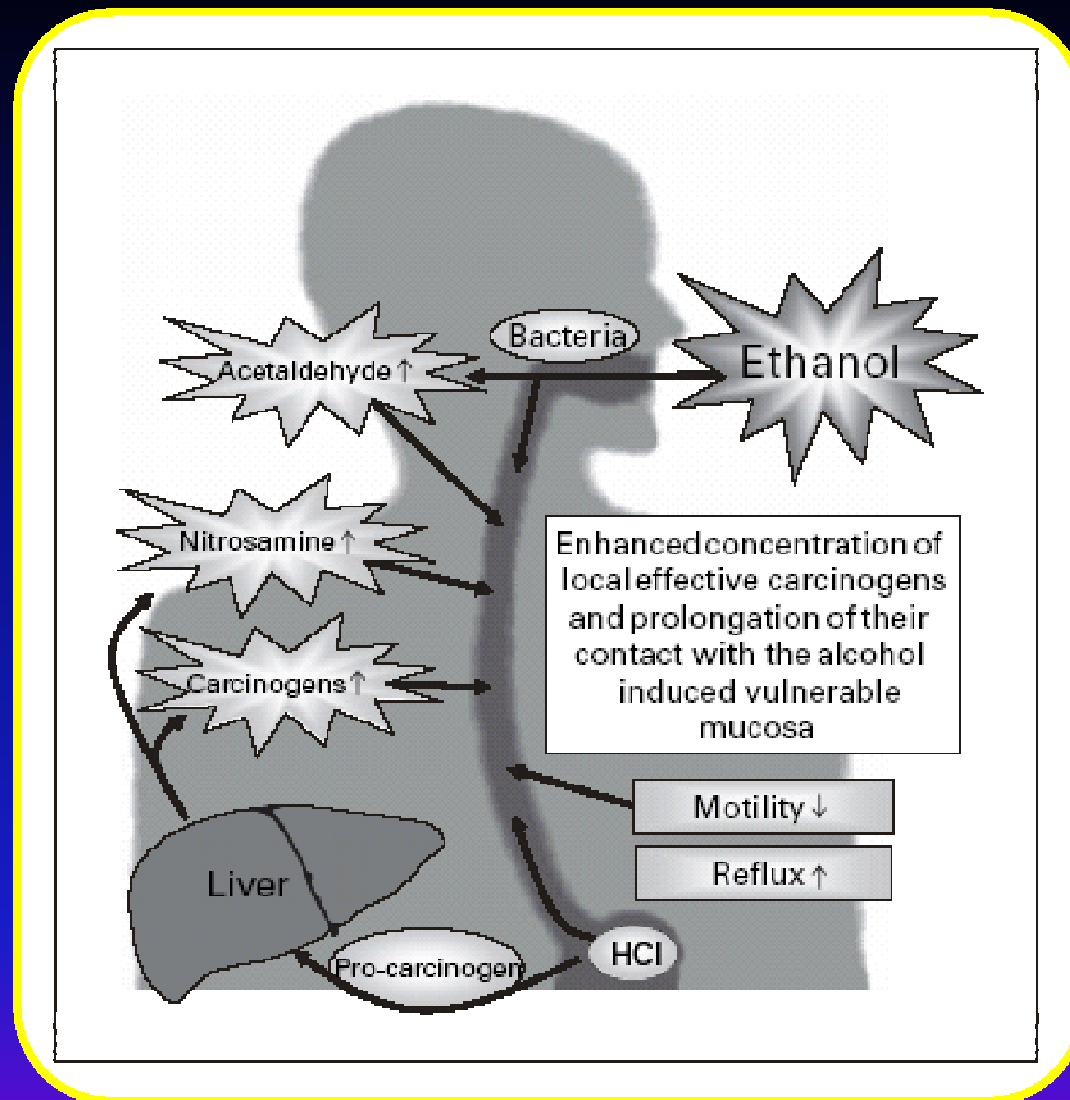
Figure 1 Salivary acetaldehyde concentrations after alcoholic beverage use in three different samples. The values are average and standard deviation of all assessors. The figure legend states the alcoholic strength (in % vol) and the acetaldehyde content (in μM) in the beverages, as well as the number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

[Lachenmeier and Monakhova, J Exp Clin Cancer Res 2011](#)

..... mutagenic amount of acetaldehyde in saliva falls between 50 and 150 micronM/L

Salaspuro M, Novartis Found Symp 2007

Lachenmeier and Monakhova, 2011



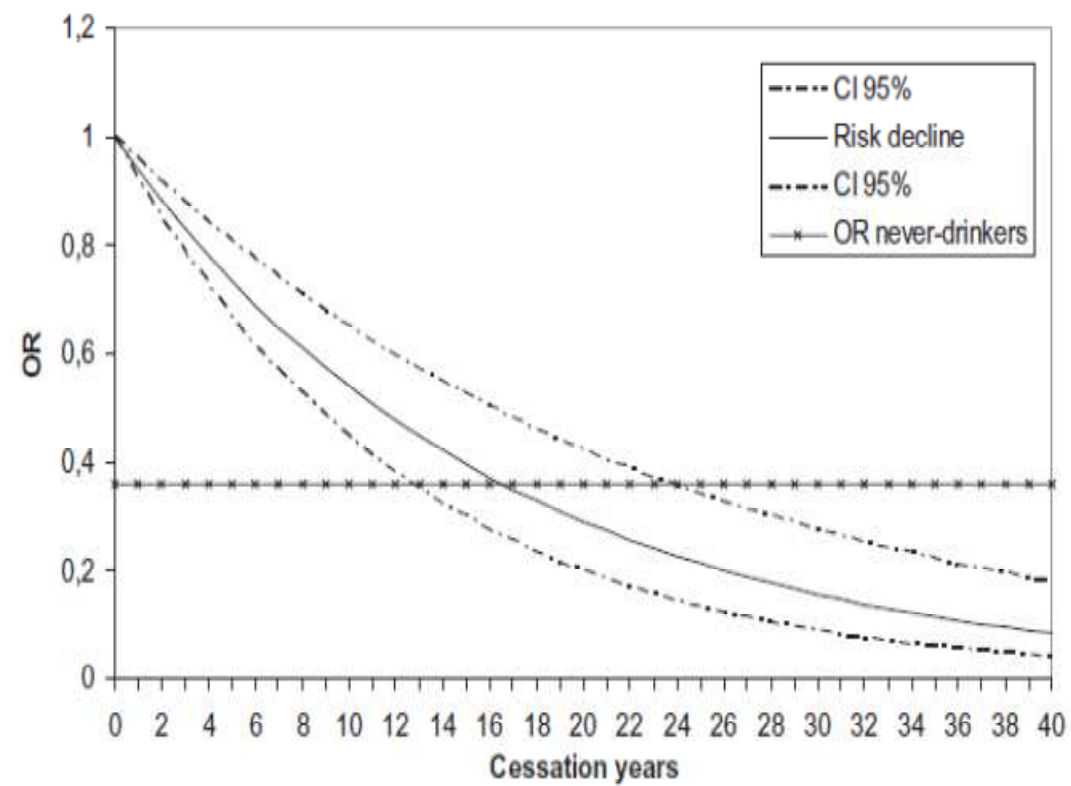


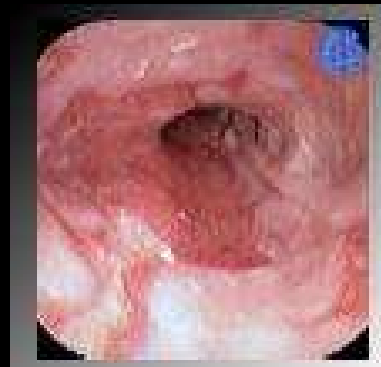
Figure 3 Estimated temporal characteristics of decline in risk of oesophageal cancer after drinking cessation; OR: odds ratio; CI: confidence interval

acido (Hcl)

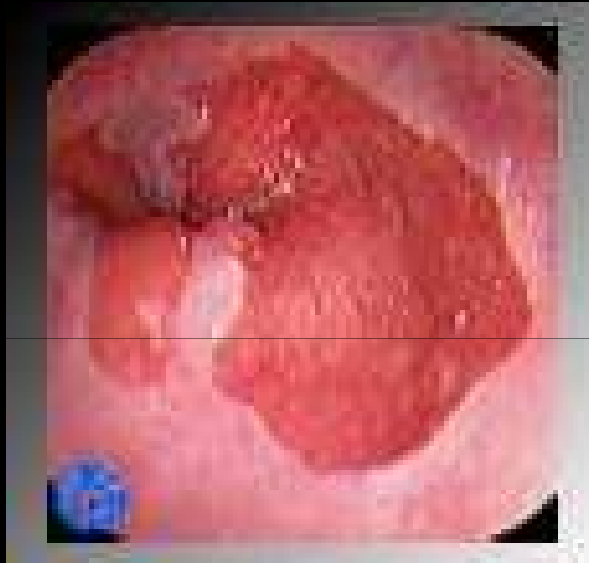
pepsina

bile

esofagite

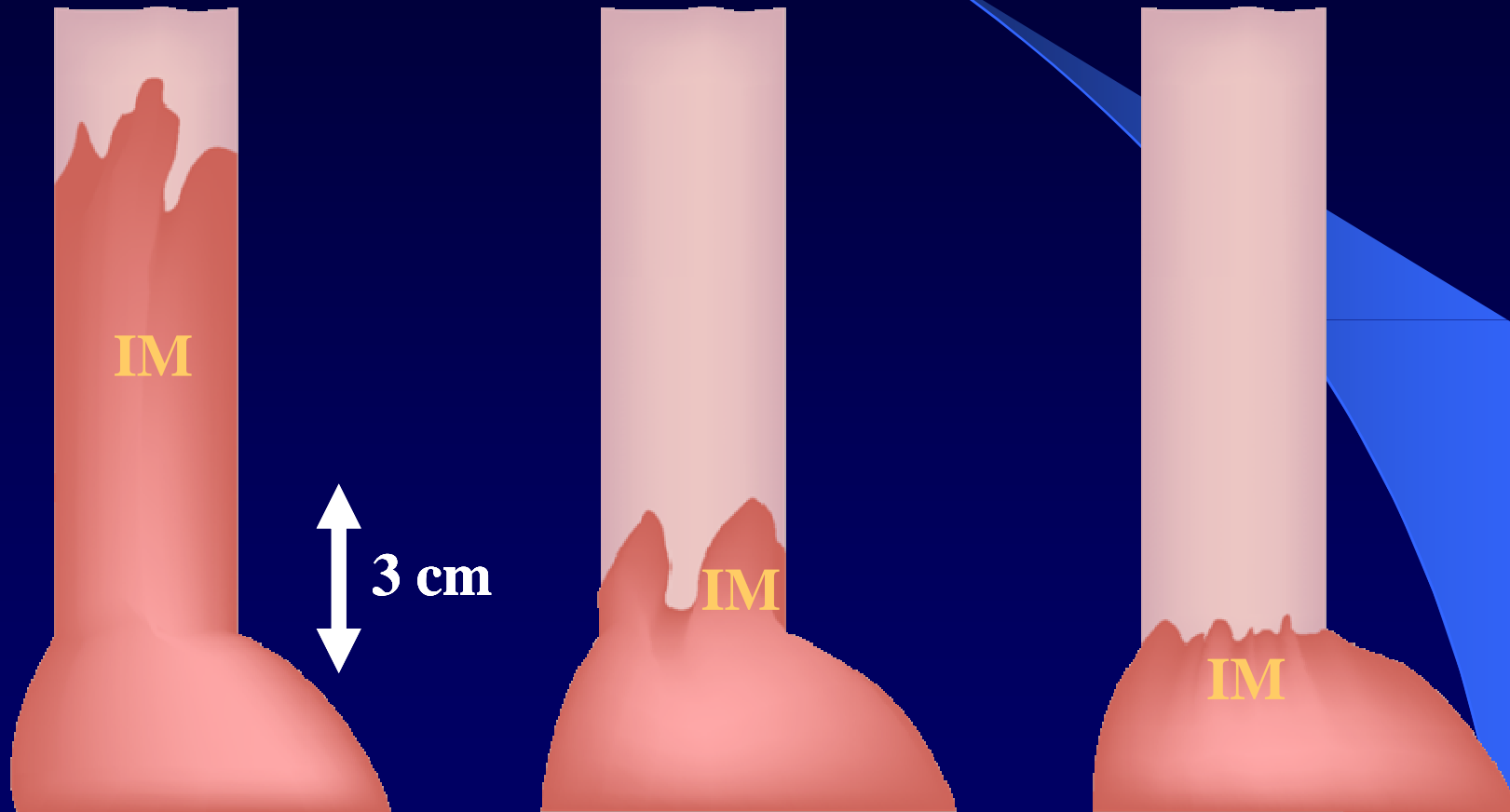


Esofago di Barrett



Sostituzione dell'epitelio squamoso dell'esofago da parte di un epitelio colonnare specializzato caratterizzato da "goblet cells" e strutture villose (metaplasia intestinale)

Long and Short Barrett's Esophagus and Intestinal Metaplasia of the Cardia

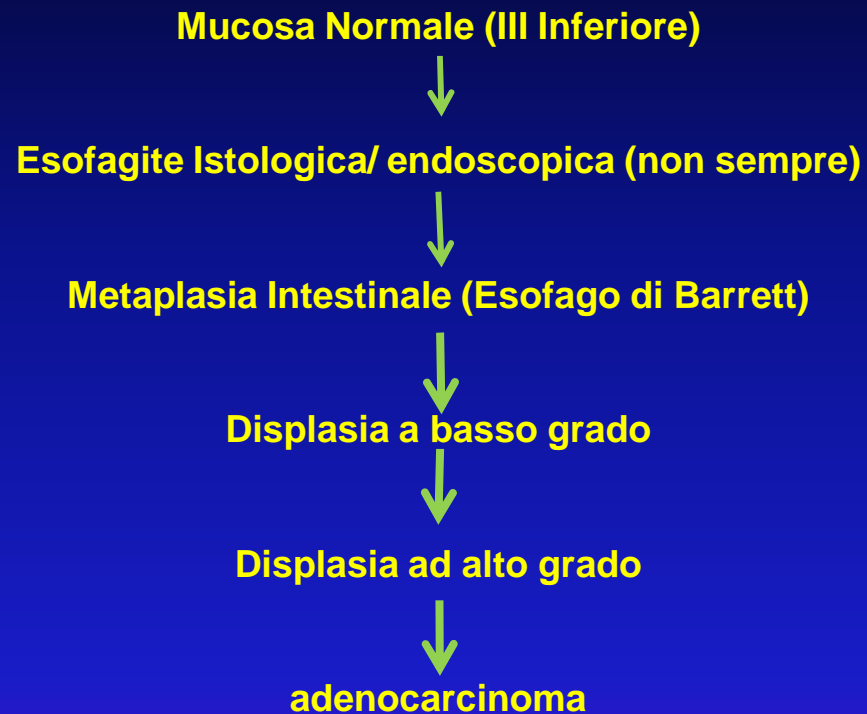


Long BE

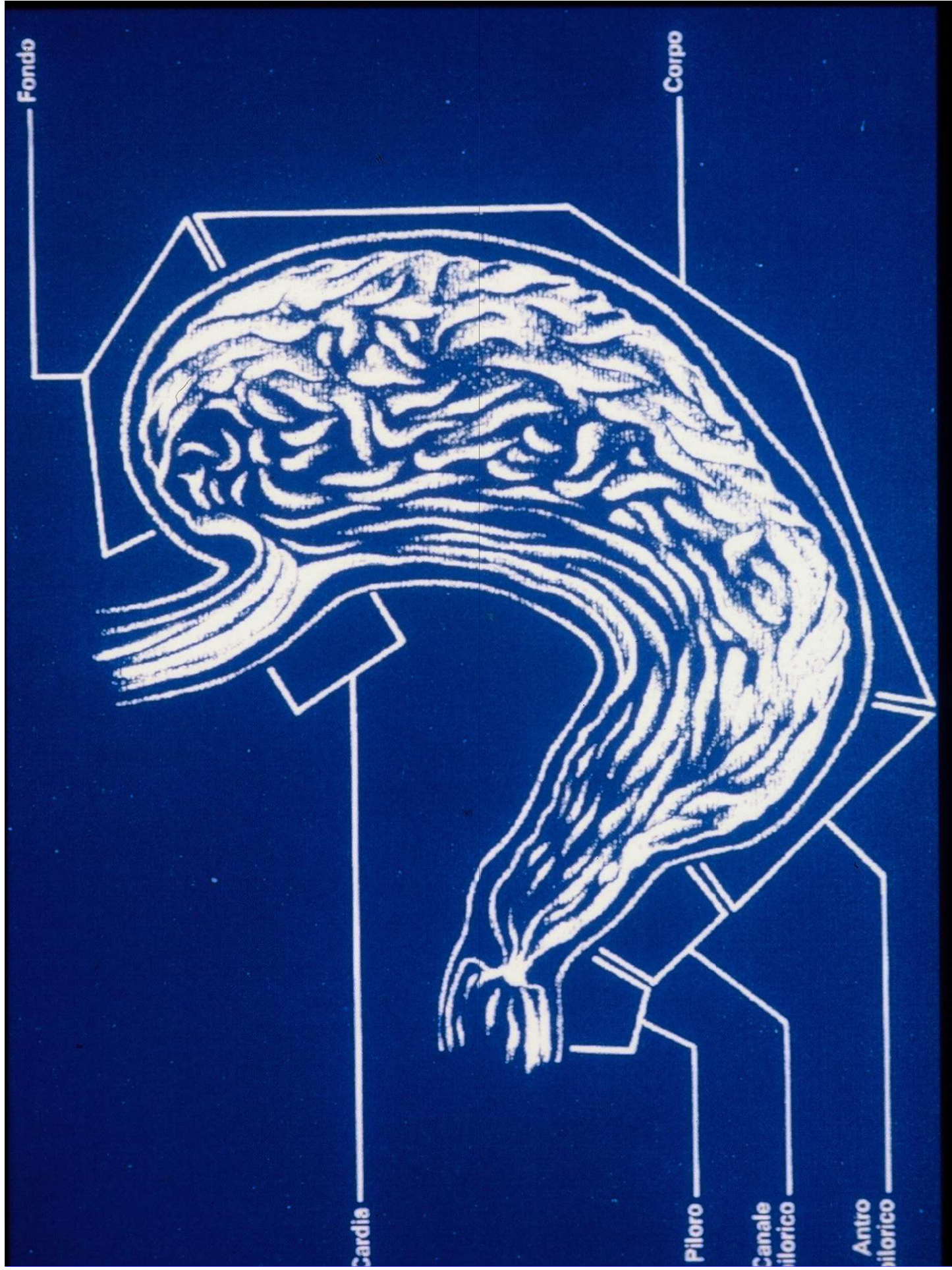
Short BE

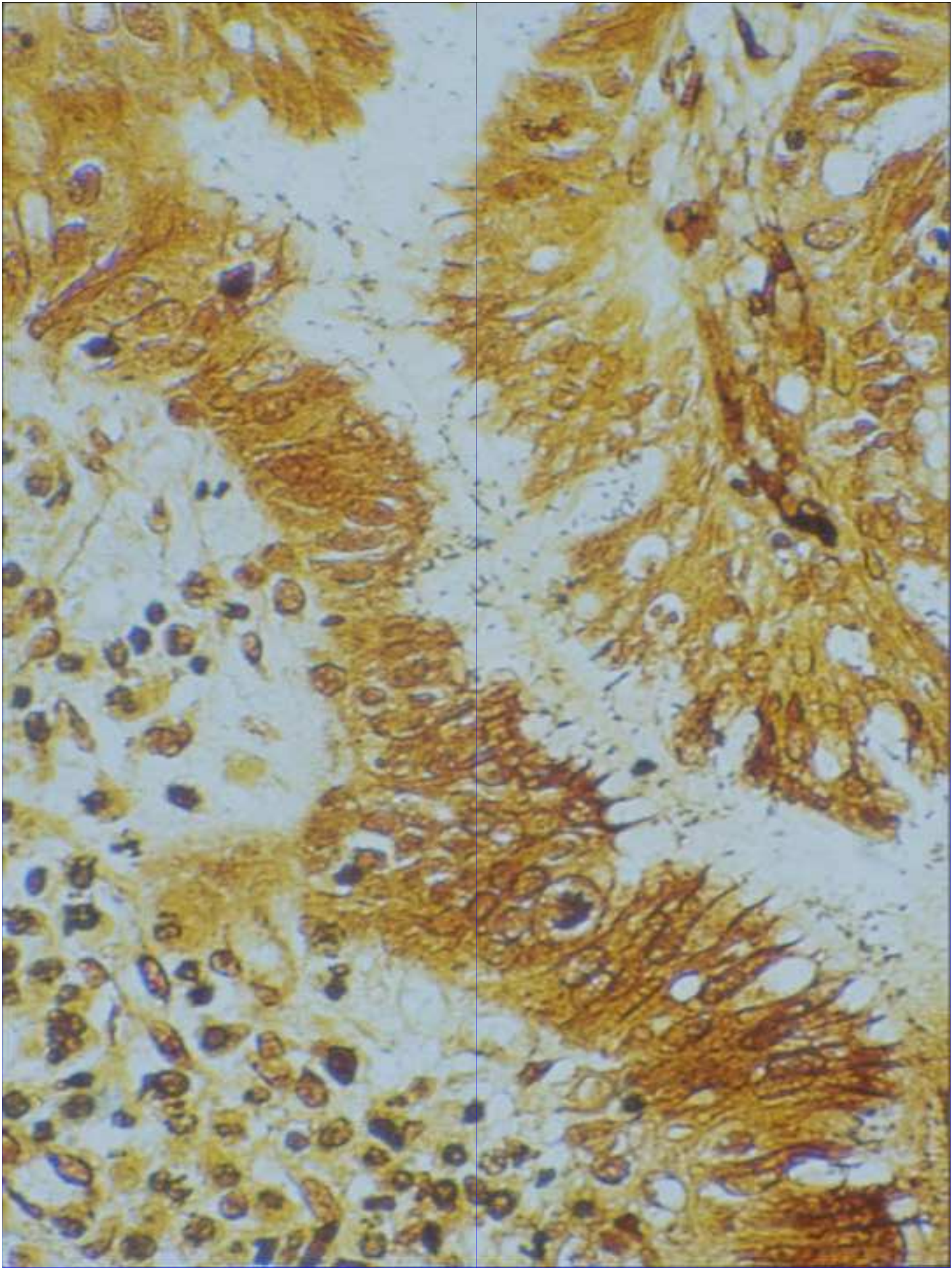
IM-Cardia

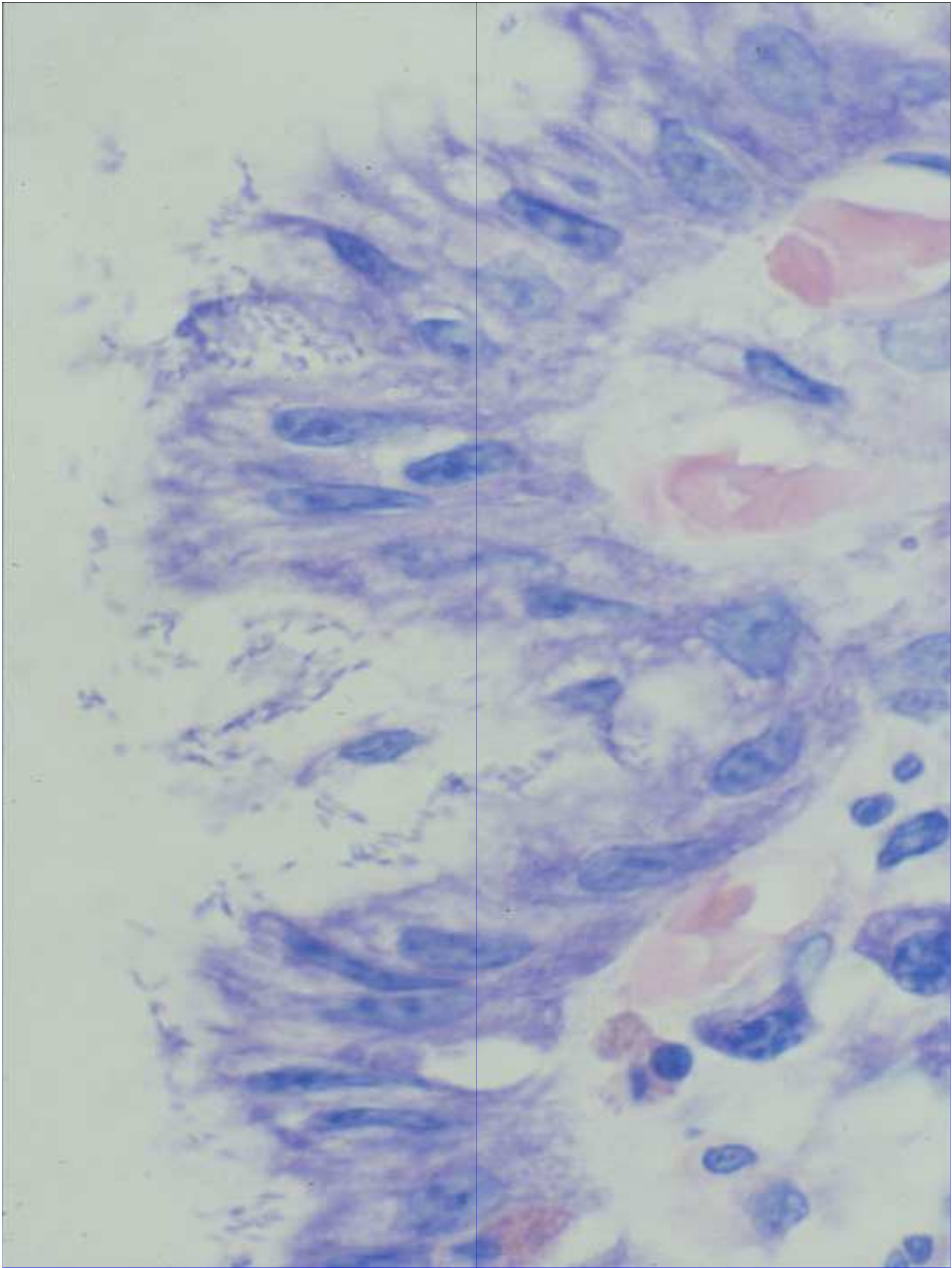
ALCOL/ ESOFAGO: PREVENZIONE SECONDARIA

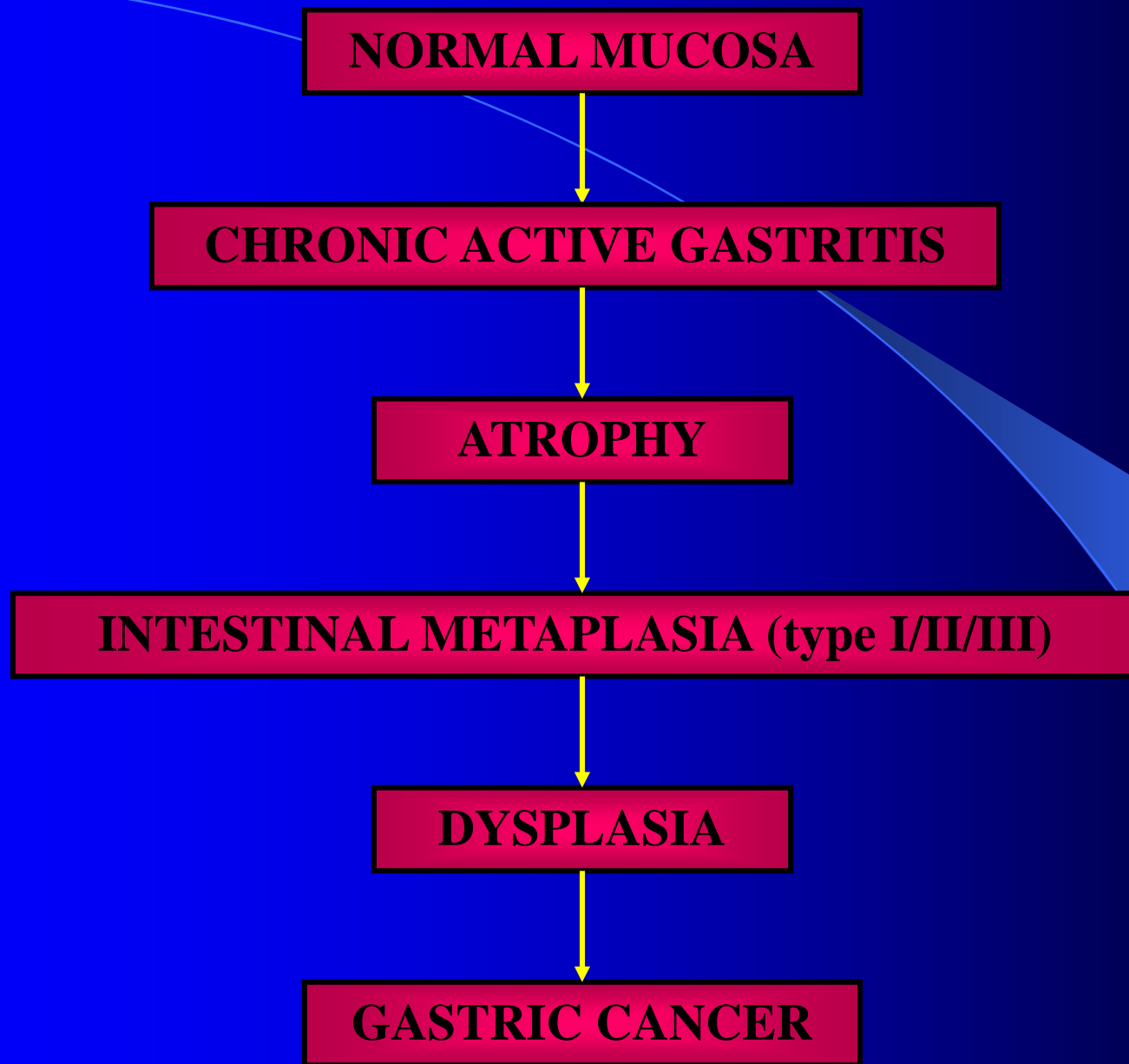


Biopsie multiple anche al III medio e superiore per prevenzione
Carcinoma Squamo-Cellulare (il piu' frequente) !!!









Testino G, Am J Gastroenterol 1995

CARCINOGENESIS NUTRITIONAL FACTORS

Ethanol and Retinoid Metabolism

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

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

↓
expression AP1 (JUN and FOS) transcriptional complex

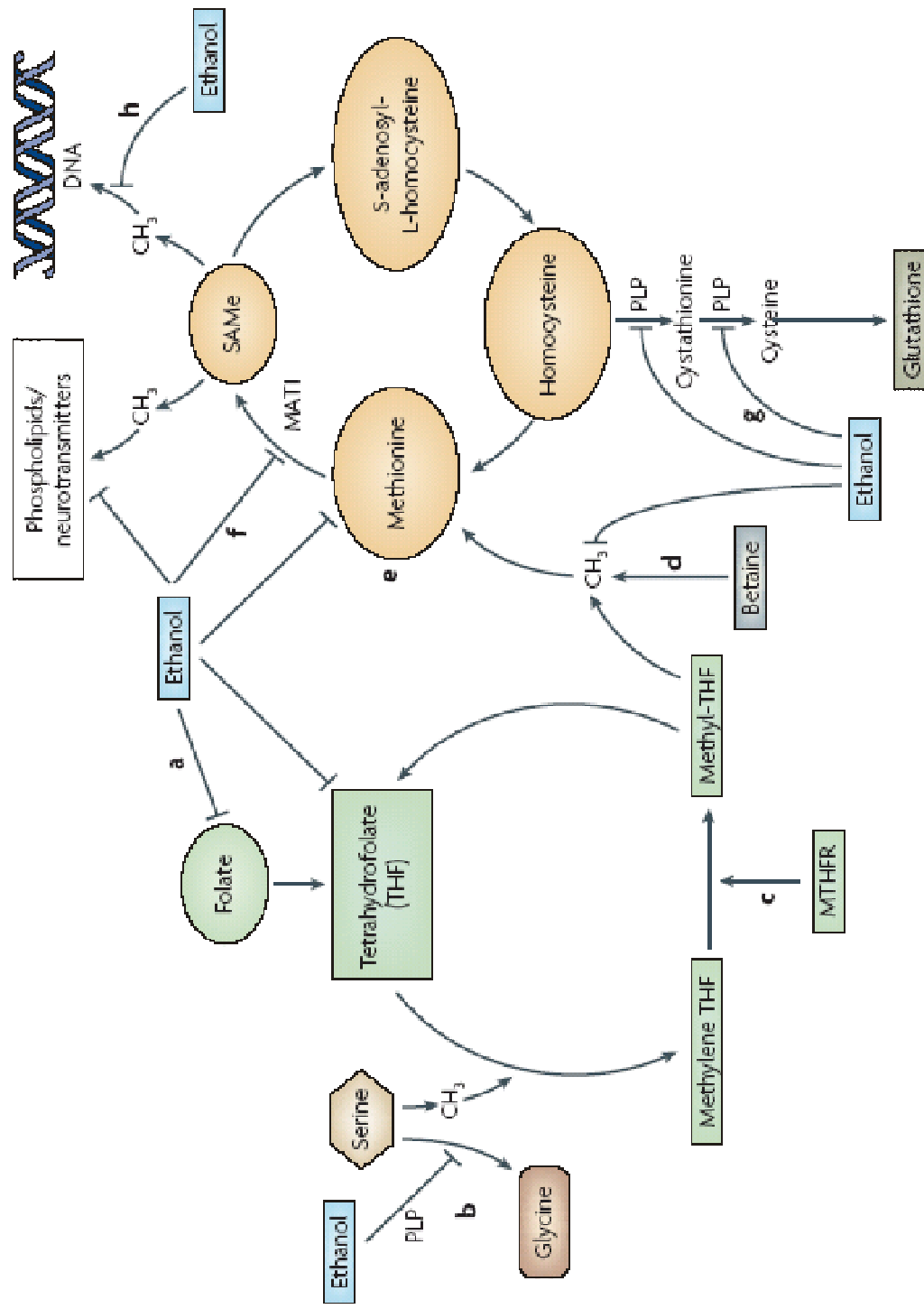
↓
> cell hyperproliferation/ < apoptosis

Liu et al, Gastroenterology 2001; Chung et al Carcinogenesis 2001;

Liu et al , Alcoholism Clin Exp Res 2002; Napoli JL 2011

Szabo et al, Advances Exp Med Biol 2015

Ethanol and Altered Methyl Group Transfer (Thompson et al, Liver Int 2011)





Alcohol
(homocysteine,SAM)



Folate
(depletion)



Selenium
(depletion)

Alcohol

promoting -
(APC1, p 14 ,p 16 , h MLH1)



Folate

p53/MTHFR
Polymorphism



Selenium
p53.p16



Phytoestrogens

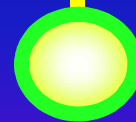
(H-ras , OR binding?)



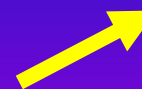
CARCINOGENESIS
Genome
Hypomethylation



oncogenes



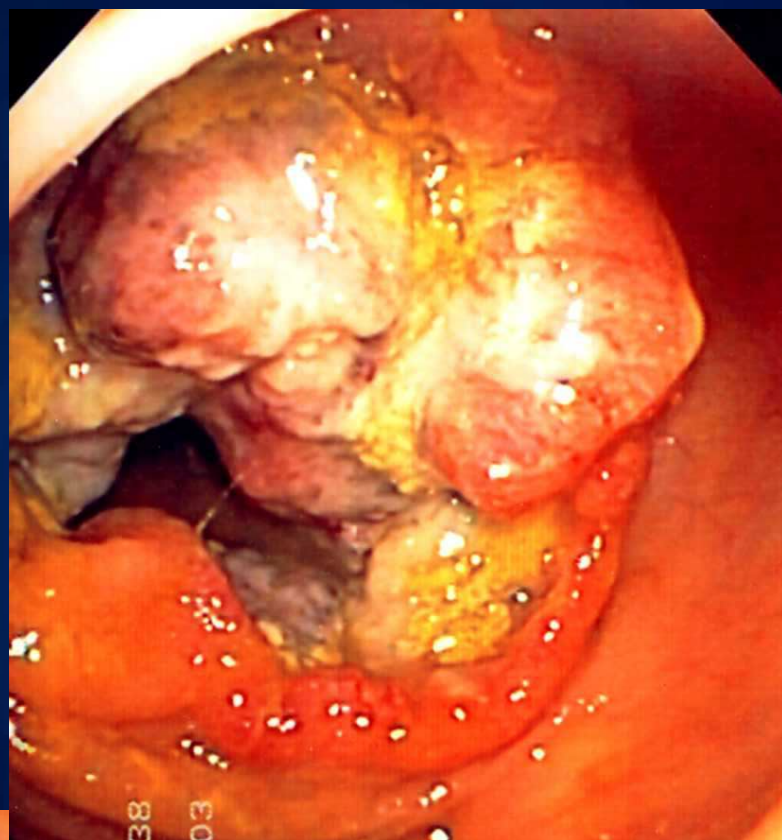
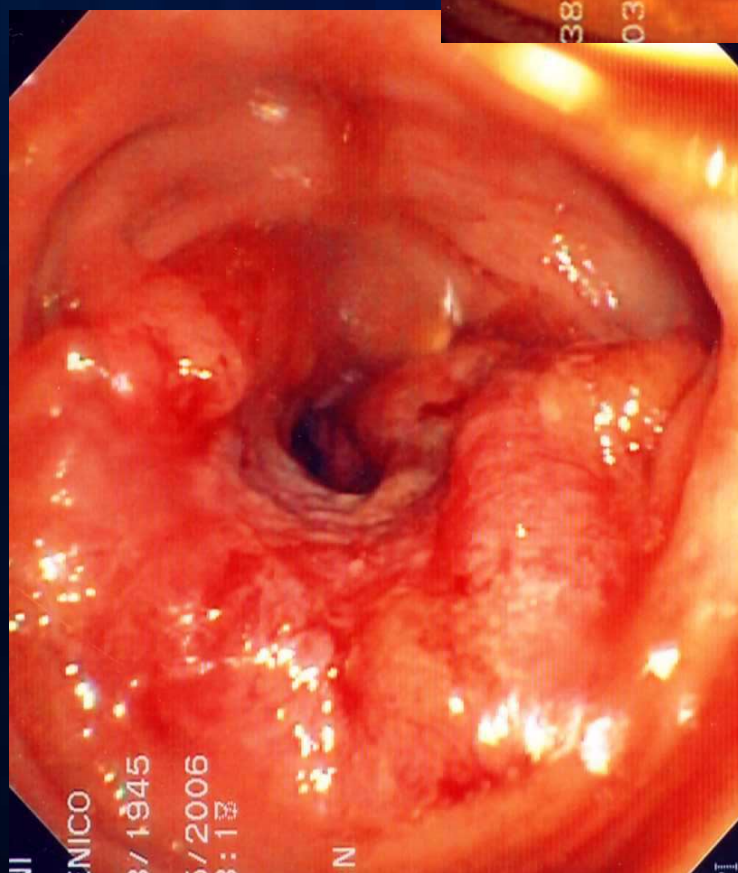
Health
Phenotype
Age



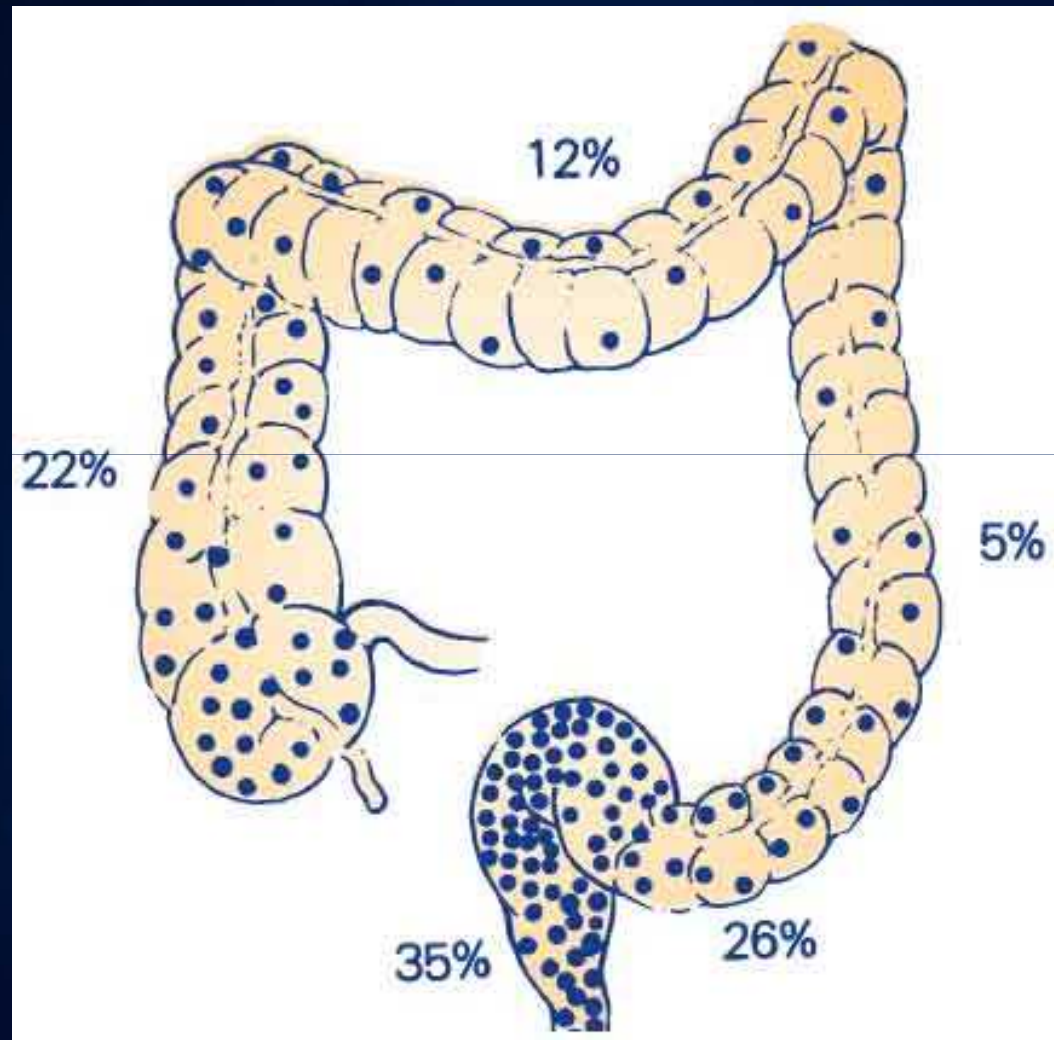
CARCINOGENESIS
Gene Promoter
Hypermethylation

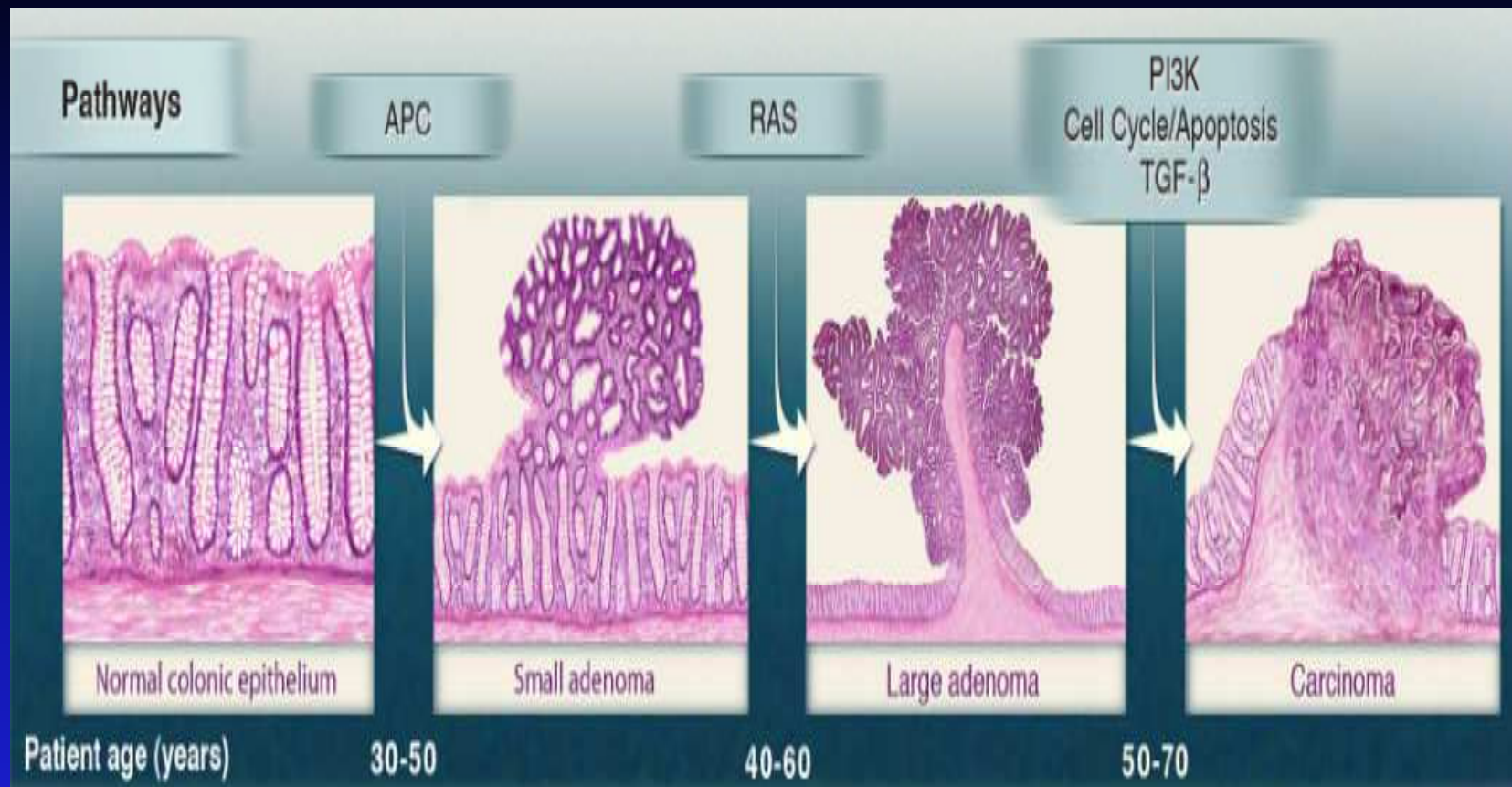
Thompson et al, Liver Int 2011

Seitz and Mueller, Adv Exp Med Biol 2015



Localizzazione del cancro coloretta





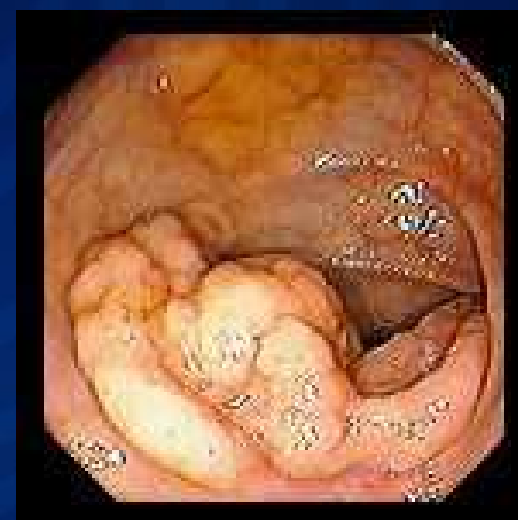
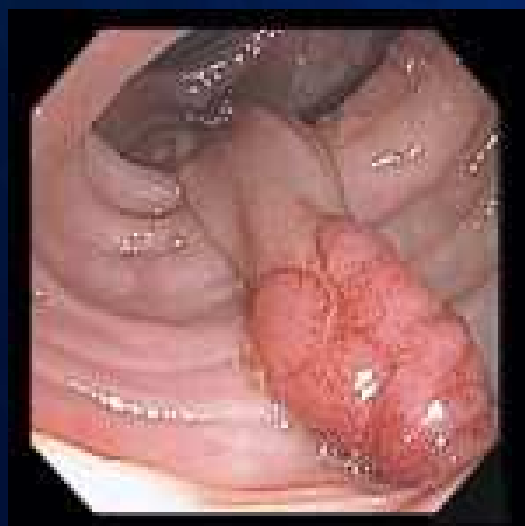
Social Consumption

10 gr/die

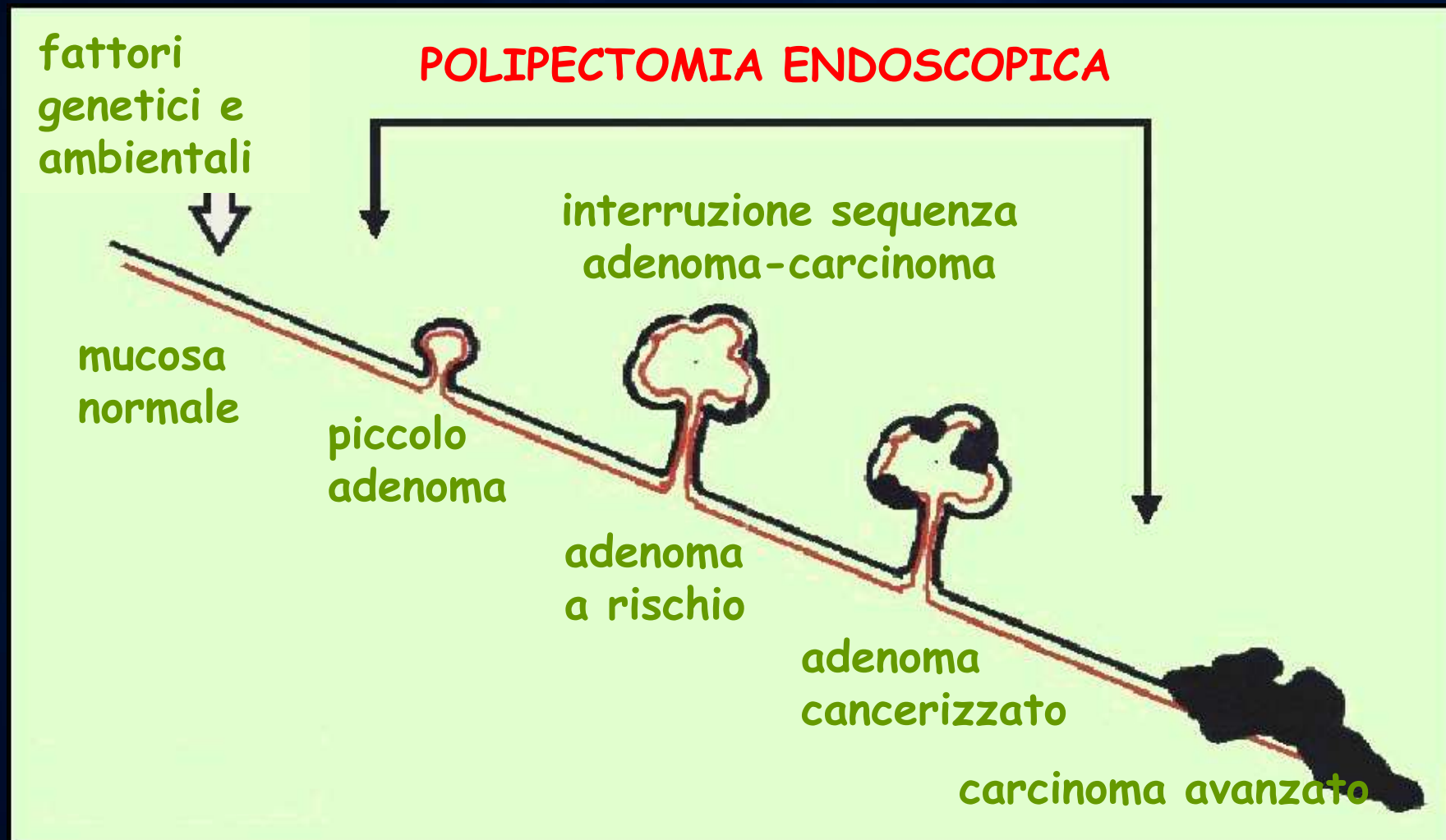
Testino, 2011

Volgelstein et al, Science 2013

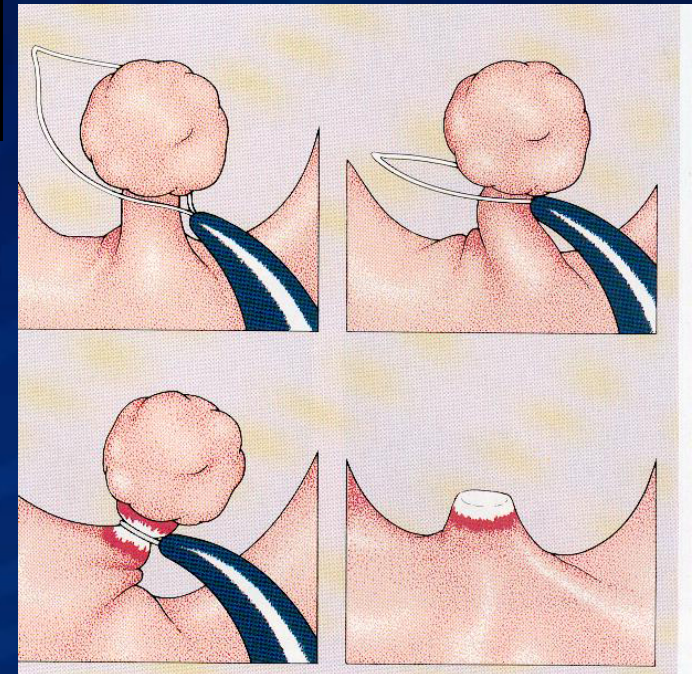
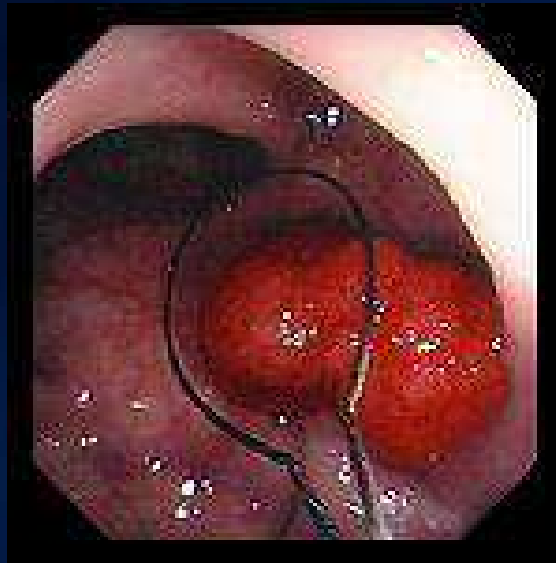
Polipi adenomatosi



Storia naturale del cancro coloretta



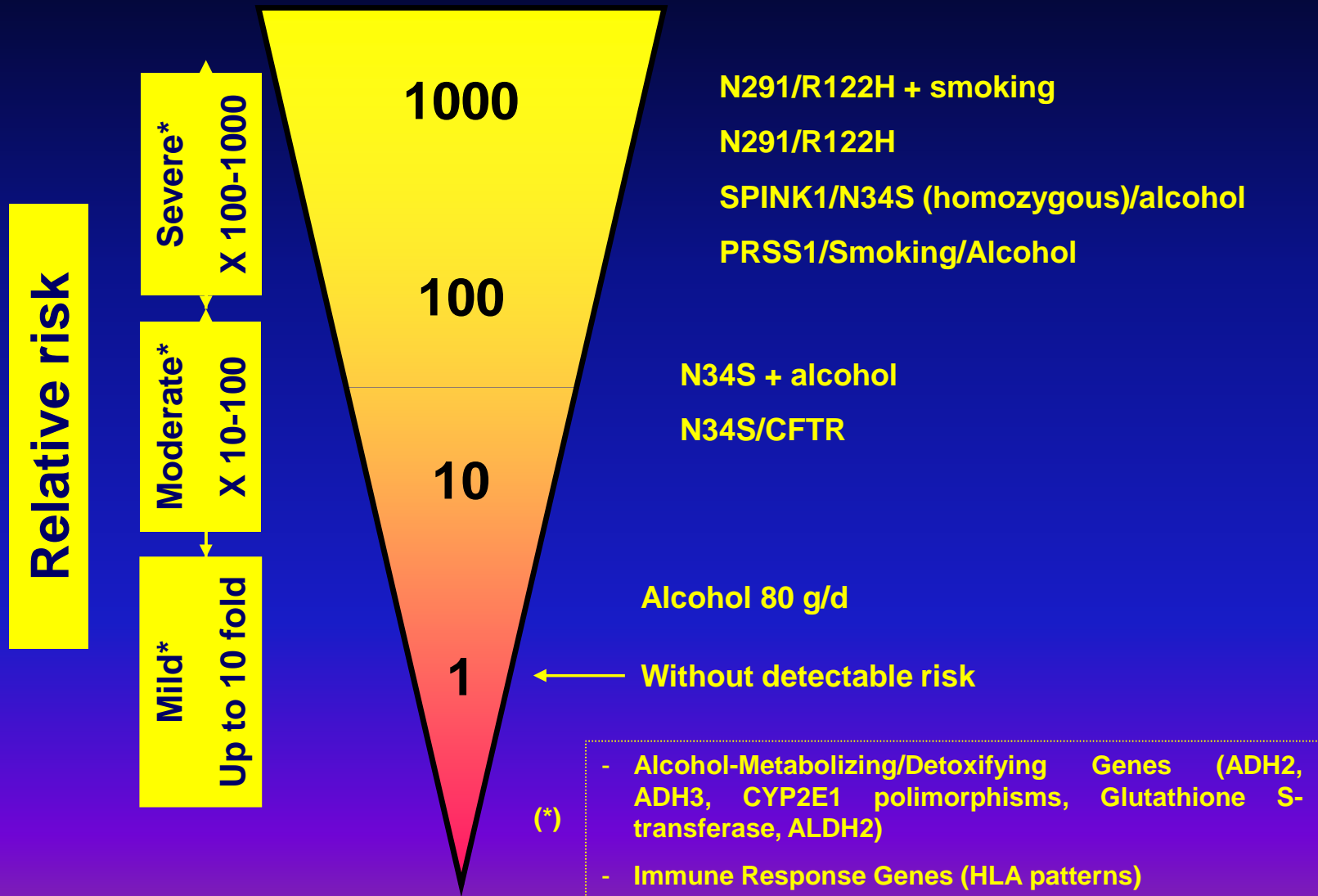
Polipectomia endoscópica



N° e TIPO POLIPO/I	1° CONTROLLO	CONTROLLI SUCCESSIVI
Polipo iperplastico	FOBT a 5 aa	
Poliposi iperplastica	Colonscopia a 5 aa	Se negativa FOBT a 5 aa
Adenoma a basso rischio: <ul style="list-style-type: none"> ▪ ≤ 2 polipi ▪ < 1 cm ▪ tubulare 	Colonscopia dopo 5 aa	Se negativa FOBT a 5 aa
Adenoma ad alto rischio. <ul style="list-style-type: none"> ▪ Displasia di alto grado ▪ ≥ 1 cm ▪ Componente villosa $> 25\%$ Adenomi multipli: <ul style="list-style-type: none"> ▪ tra 3 e 10 polipi 	Colonscopia a 3 aa	Se negativa ripetere dopo 3 aa, se negativa FOBT a 5 aa
<ul style="list-style-type: none"> ▪ Polipo sessile ≥ 2 cm ▪ Polipectomia incompleta o "piecemeal" 	Colonscopia a 3-6 mesi e sino a clearance della lesione e verifica di clean colon	Se negativa ripetere dopo 3 aa; se ancora negativa FOBT a 5 aa
Più di 10 adenomi	<ul style="list-style-type: none"> ▪ Considerare ipotesi di sindrome poliposica ▪ Management individuale 	
Adenoma con ca intramucoso	Come adenoma ad alto rischio	

Note:

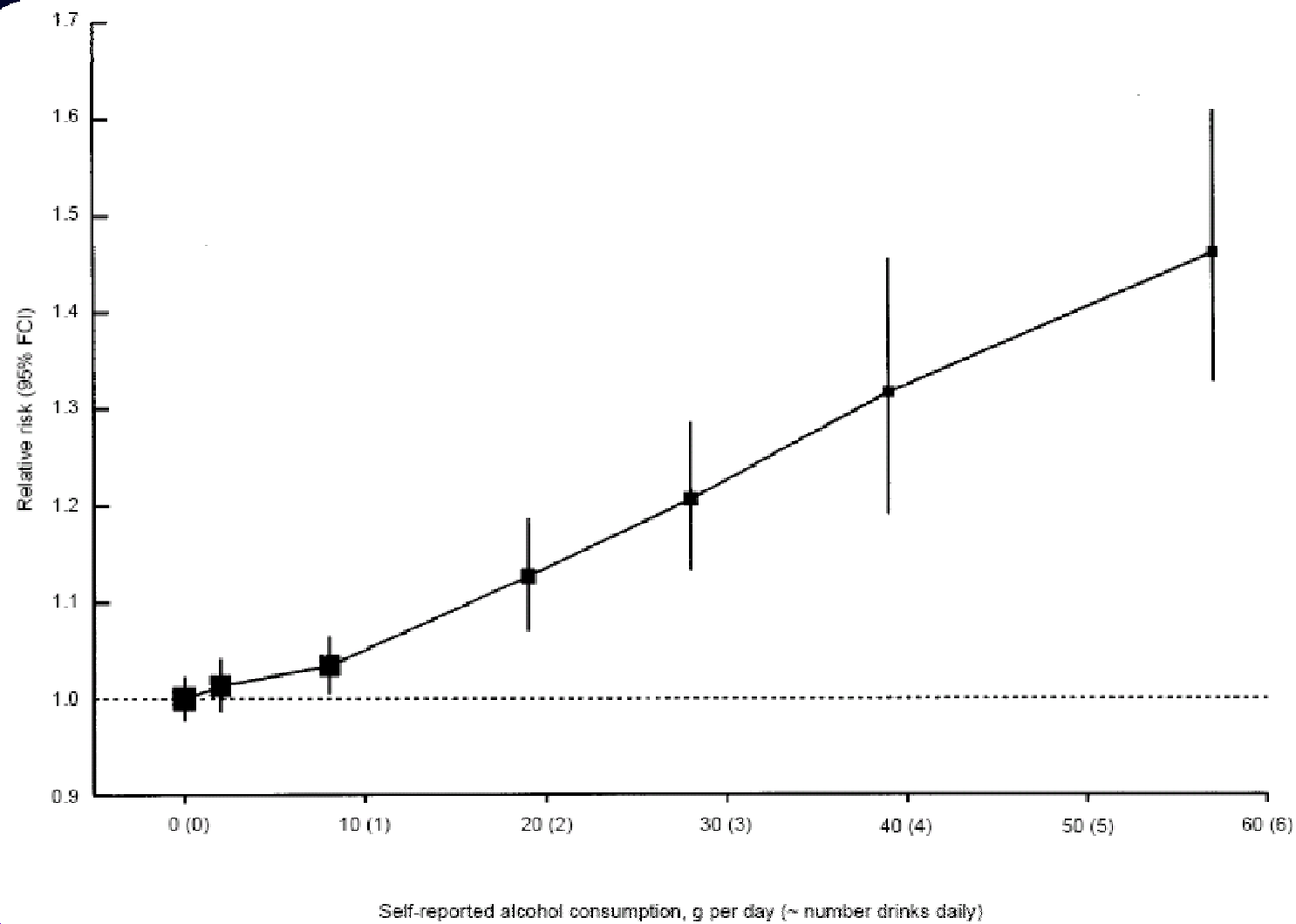
Strenght of genetic and environmental risk factors of chronic pancreatitis



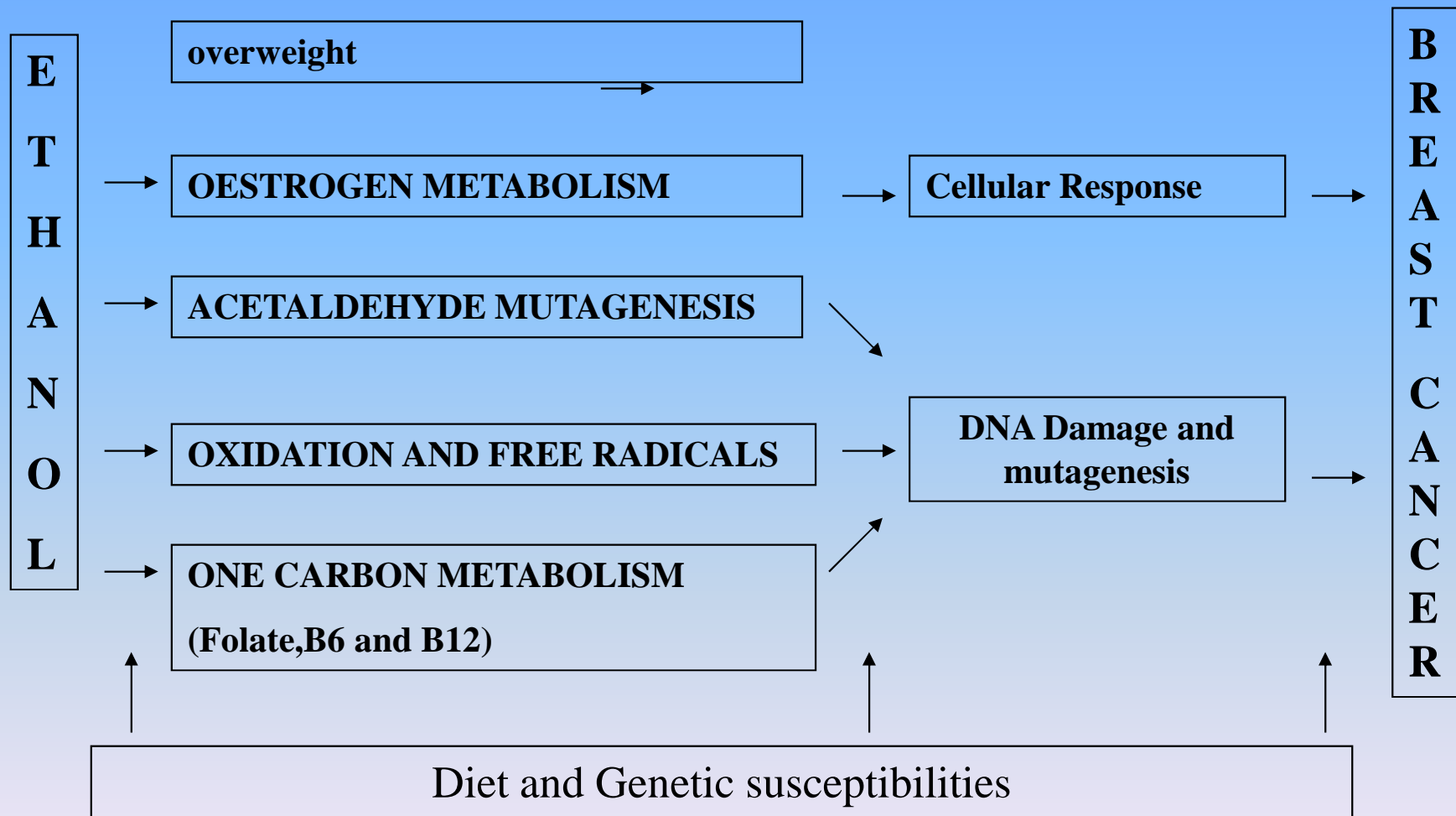
ASSOCIATION OF ALCOHOL INTAKE WITH PANCREATIC CANCER MORTALITY

Alcohol Intake, Drinks per Day	No. of Deaths	Relative Risk (95% CI)
Nondrinker	1792	1.00
Occasional	469	1.08
1	141	1.06
2	92	1.02
> 3	131	1.36

Gapstur et al, Arch Intern Med 2011



Br J of Cancer, 2002



ALCOHOL PROMOTES MAMMARY TUMOR DEVELOPMENT

Increased expression of aromatase (converts androgens to estrogens)

Increased systemic estrogen levels

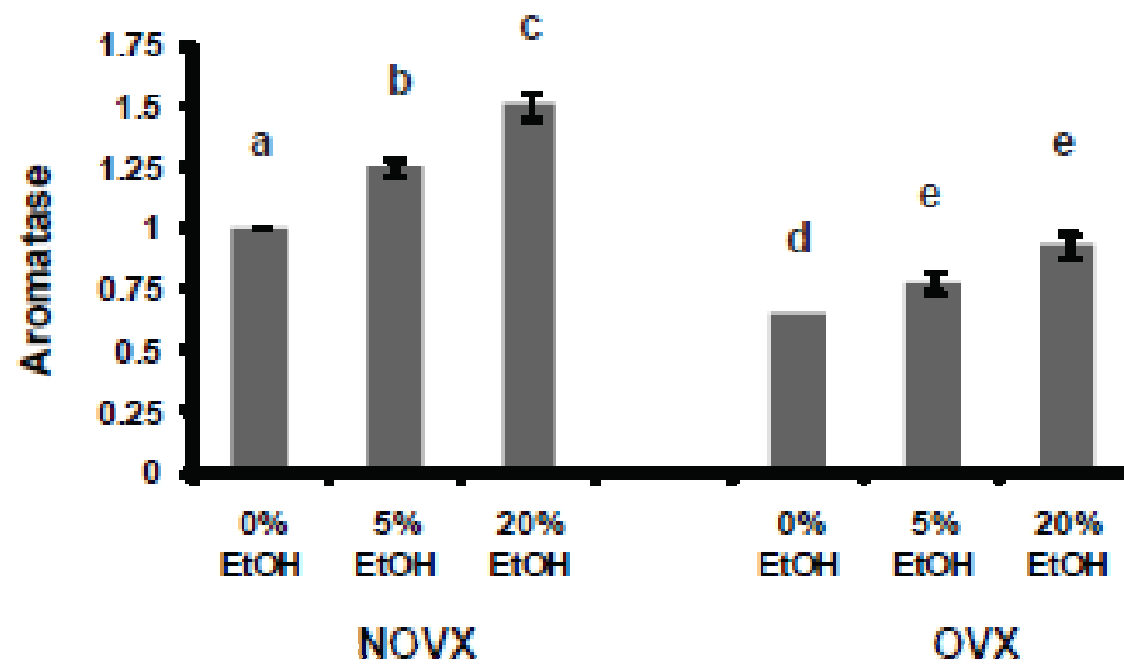
Increased expression Estrogen Receptor alpha

Wong et al., Alcoholism: Clinical and Experimental Research 2011

Alcohol increases insulin sensitivity
and promotes mammary tumorigenesis

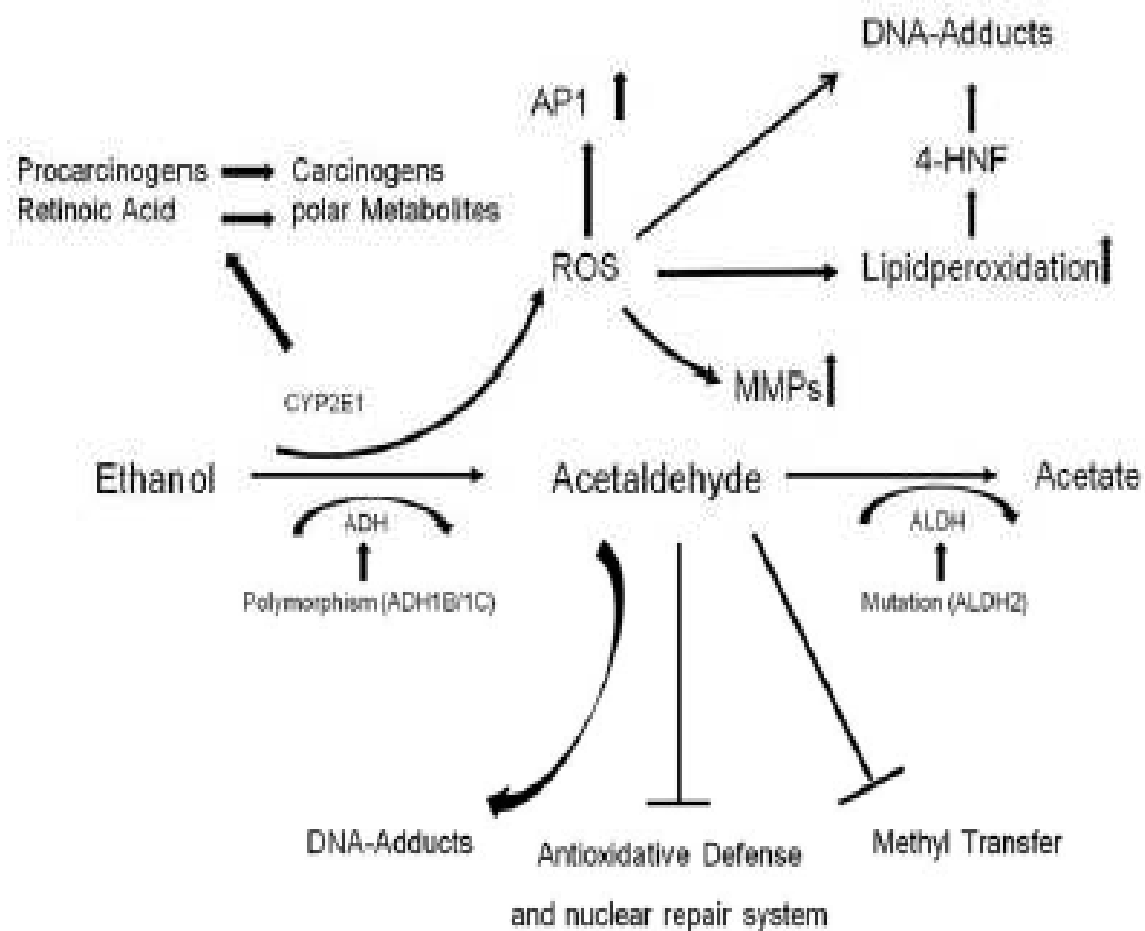
Hong et al, Cancer Letters 2010

Tumor Aromatase Level



Wong AW, 2011

Alcohol and breast cancer



Seitz HK et al, Alcohol and Alcoholism 2012

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

Table 3. Risk of Biopsy-Confirmed BBD in Young Females With Family History of BC, Family History of Maternal BBD
Family History

	BC in Affected Family Member			BDD in Mother
	Mother or Aunt	Grandmother	Any Family Member (Mother, Aunt, Grandmother)	
GUTS girls, No.	477	749	1157	1264
GUTS BBD cases, No.	10	10	19	18
Risk factor, OR (P)				
Adolescent alcohol, daily drink	3.80 (.02)	2.29 (.04)	2.28 (.01)	1.96 (.02)
PHV, in./y	1.82 (.05)	0.71 (.51)	1.21 (.49)	1.31 (.44)
Menarche age, y	1.21 (.47)	1.08 (.77)	1.05 (.78)	1.00 (.99)
Young adult height, in.	0.95 (.67)	0.93 (.54)	0.96 (.64)	1.07 (.44)
Childhood BMI, kg/m ²	1.00 (.97)	0.83 (.16)	0.93 (.37)	0.99 (.90)
BMI change, kg/m ²	1.03 (.72)	1.06 (.59)	1.04 (.58)	1.05 (.44)
Young adult BMI, kg/m ²	1.02 (.81)	0.94 (.51)	0.99 (.80)	1.02 (.63)
Adolescent waist circumference, in.	0.92 (.51)	0.90 (.37)	0.91 (.27)	1.08 (.30)

6888

18-27 years

< 7 drinks/wk

Berkey CS et al, Cancer 2012

**AMERICAN SOCIETY OF CLINICAL ONCOLOGY
CLINICAL PRACTICE GUIDELINES
JULY 2013**

PREVENTION BREAST CANCER

- Chemoprevention
- Surgery
- Lifestyle Changes

CHEMOPREVENTION

- Tamoxifen (35 years older)
- Raloxifene (post-menopausal women)
- Aromatase inhibitors
- -- MAP.3 and IBIS-II studies: incidence of ER-positive Invasive Breast Cancer
- was decreased by the Ais exemestane and anastrozole

SURGERY

- Salpingo-oophorectomy
- Bilateraly risk reduction mastectomy

LIFESTYLE CHANGES

.....the role of chemopreventive agents in patients
with hereditary predisposition to breast cancer is not well established

Advani and Moreno-Aspita, Breast Cancer: Targets and Therapy 2014

....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 (LOW RISK).

Alcohol intake is one of the few modifiable breast cancer risk factors yet
identified

Singletary and Gapstur, JAMA 2001

Testino G, Maedica 2011

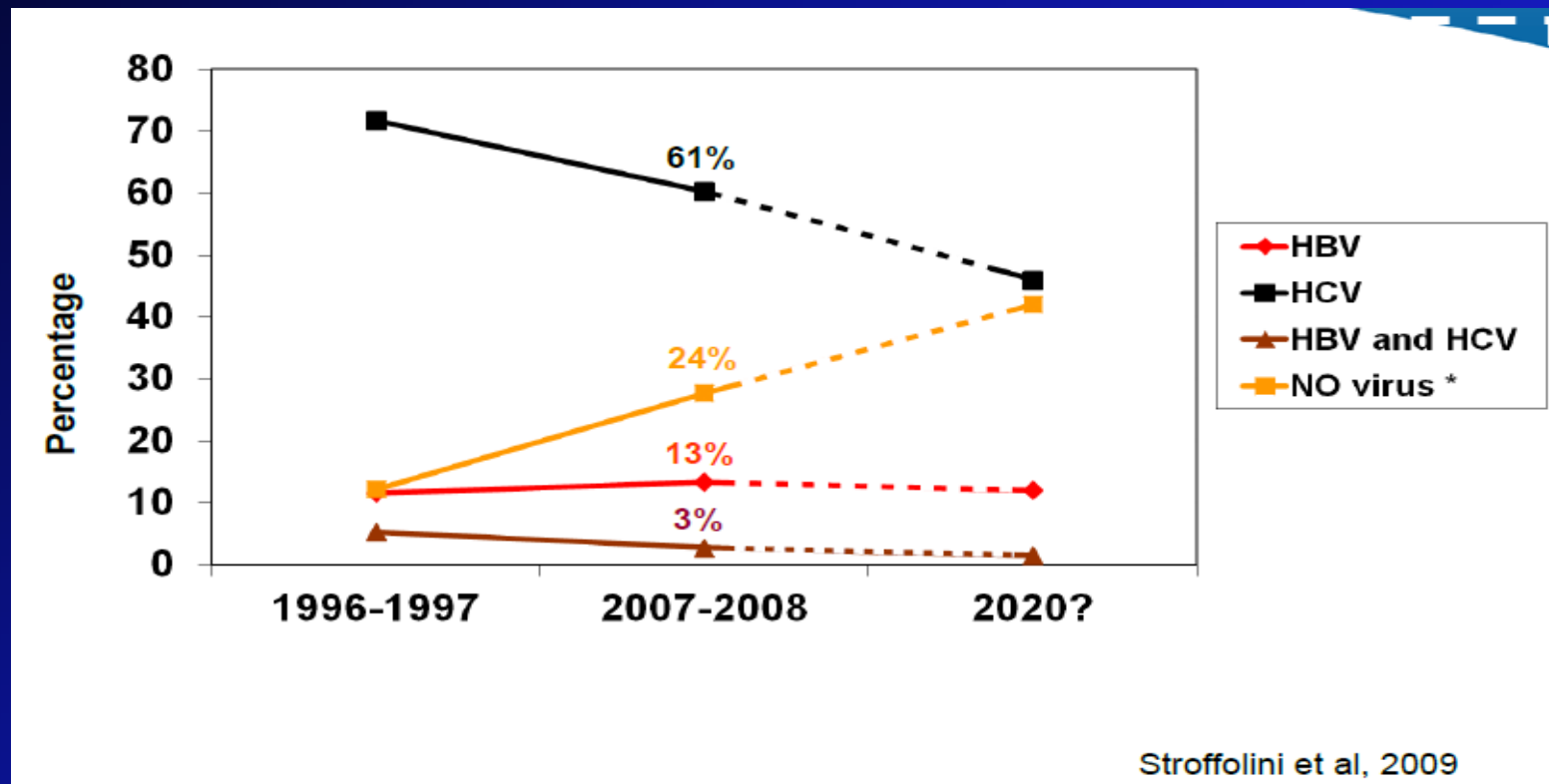
Dumalaon-Canaria et al, Cancer Causes Control 2014

Zakhari and Hoek, Adv Exp Med Biol 2015

Overweight - obesity

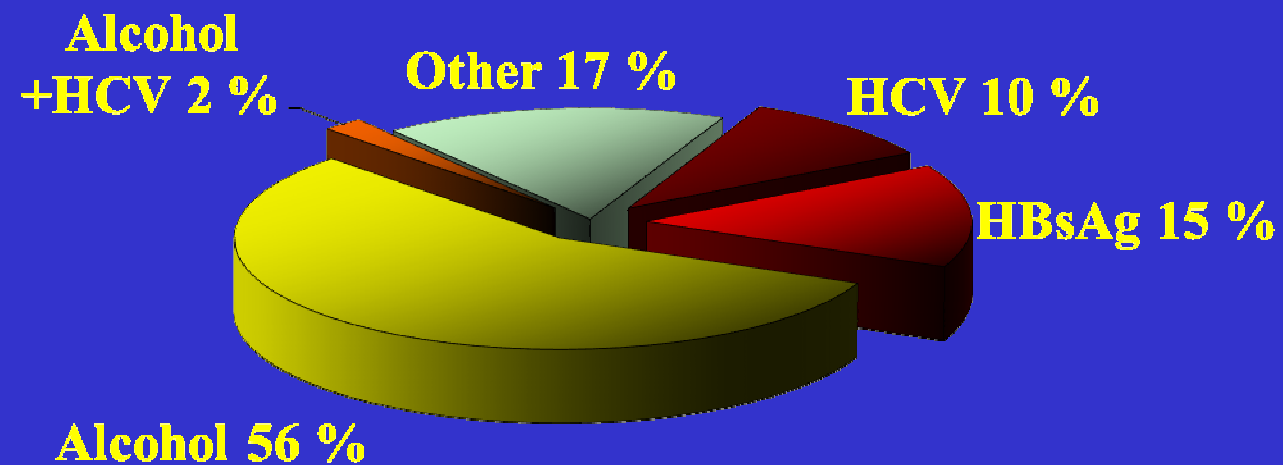
Epidemiologia: il futuro ?

ETIOLOGY OF HCC IN ITALY : OBSERVED AND EXPECTED TEMPORAL TRENDS (23 CENTRES : 1733 HCC)



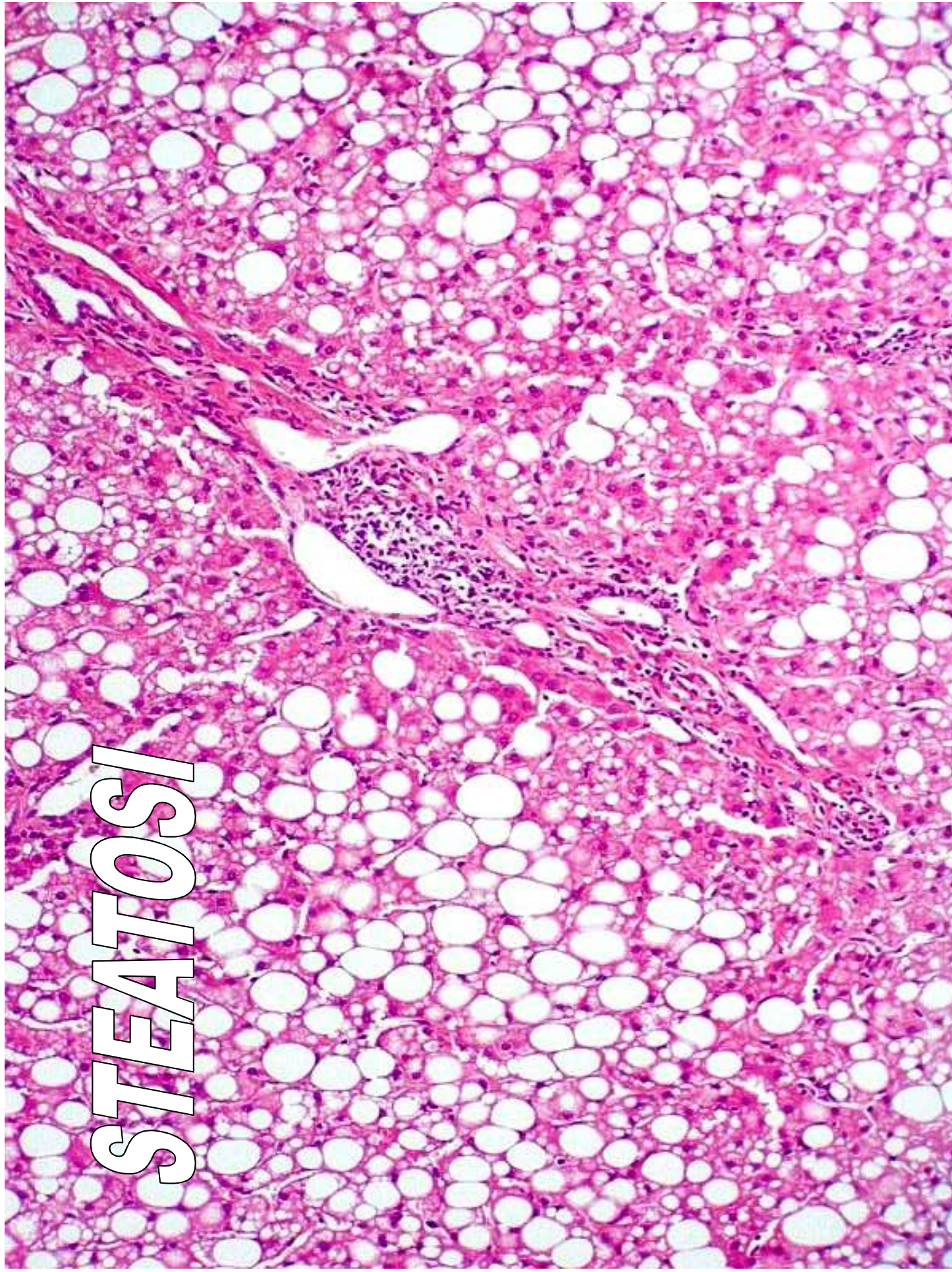
Epidemiologia: il futuro dopo i nuovi farmaci antivirali ? Un ipotesi

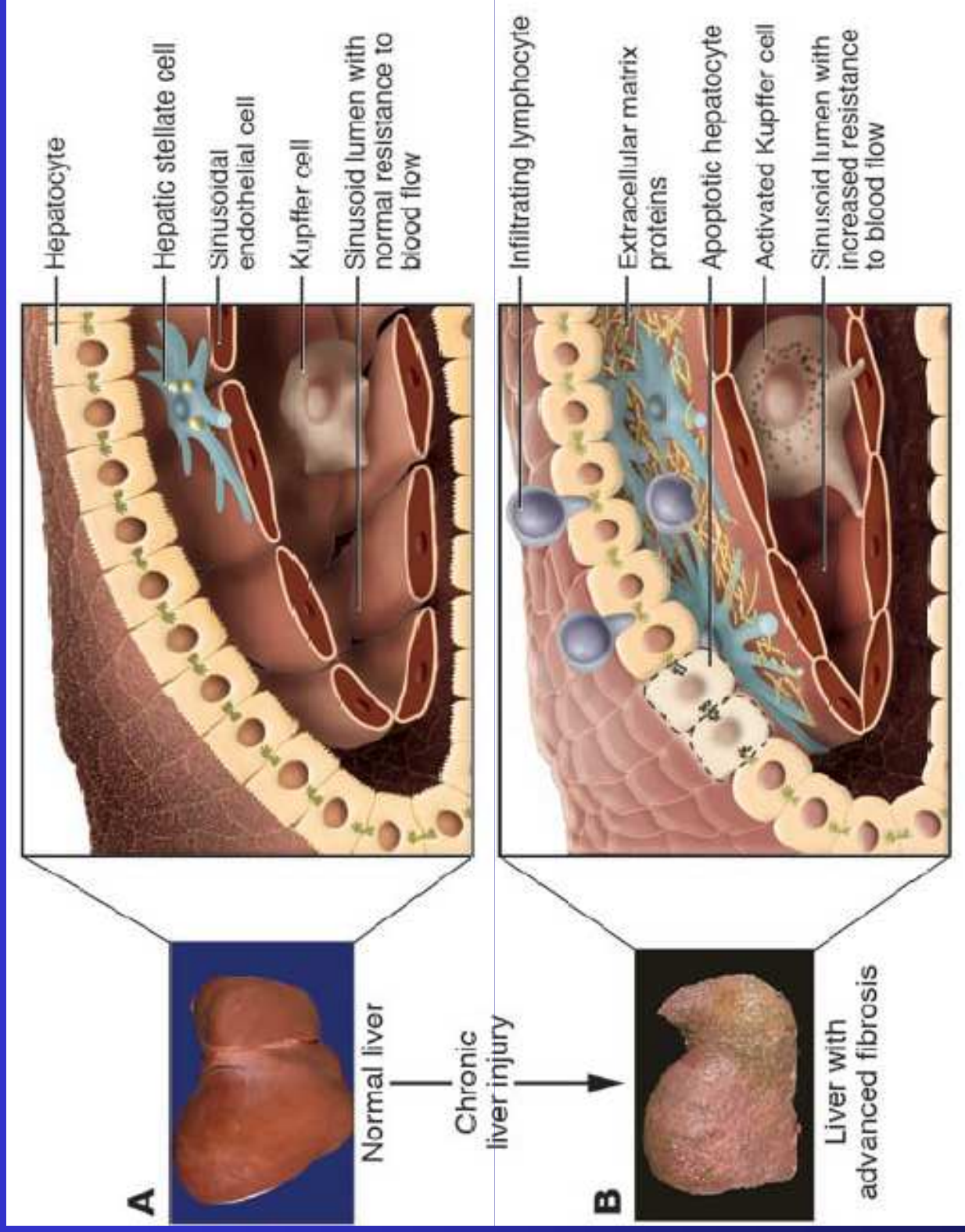
CHRONIC LIVER DISEASE



Borro and Testino, 2014

STEATOSIS





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

HCV PATIENTS

CIRROSI



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)	<i>P</i> = 0.007*
Alcohol per day (g ethanol)	5.7 (2.0–16.0)	2.6 (1.1–7.7)	<i>P</i> = 0.03*
Drinking frequency (drinking days/year)	34.5 (21.0–75.0)	8.2 (6.0–25.0)	<i>P</i> = 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

Tokushige et al, J Gastroenterol 2011

THE SEARCH FOR GENETIC RISK FACTORS FOR ALCOHOLIC LIVER DISEASE

Genetic variation modulating addiction to alcohol

Genetic variation of alcohol-metabolising enzymes

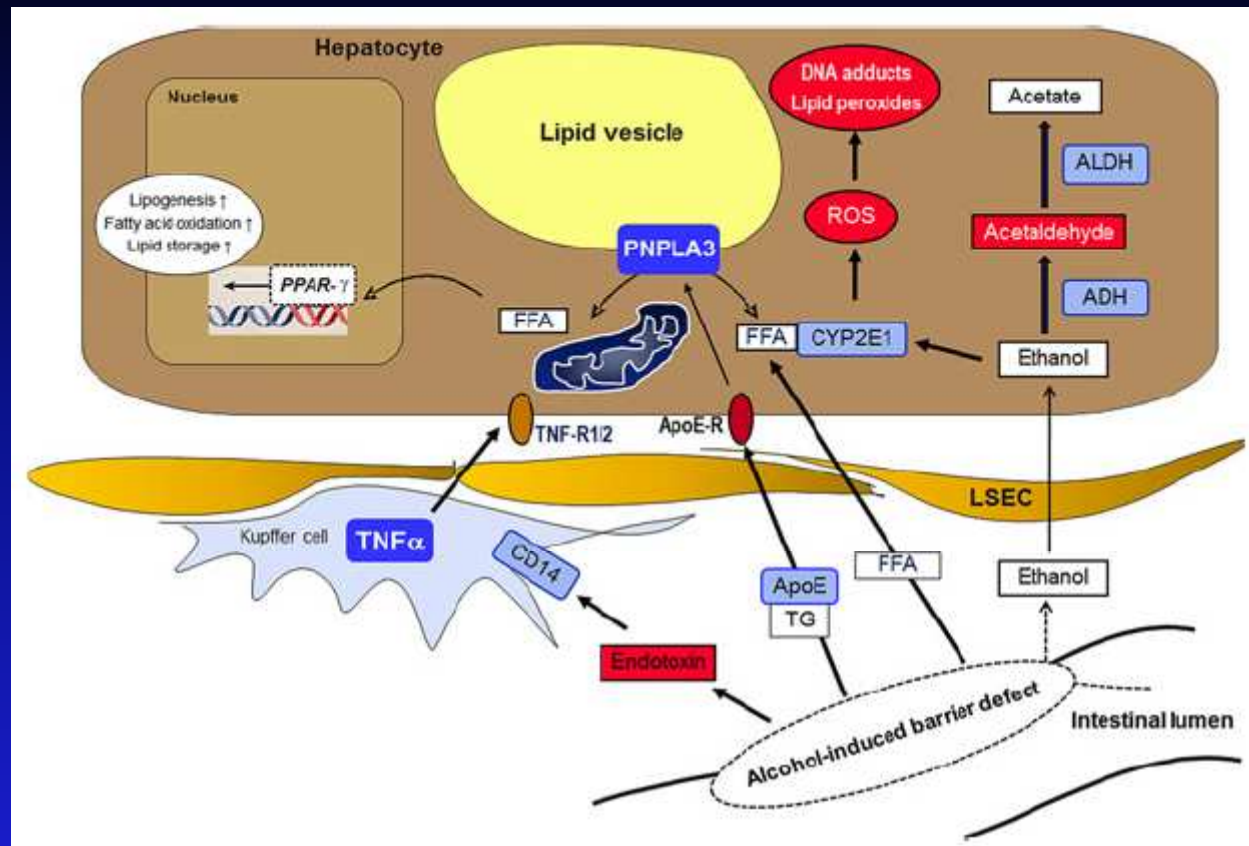
Genetic variations involved in oxidative stress

Genetic variations controlling hepatic lipid storage

**Genetic polymorphisms modulating endotoxin
inflammation**

Polymorphic variants of fibrosis-associated genes

Stickel and Hampe, Gut 2011

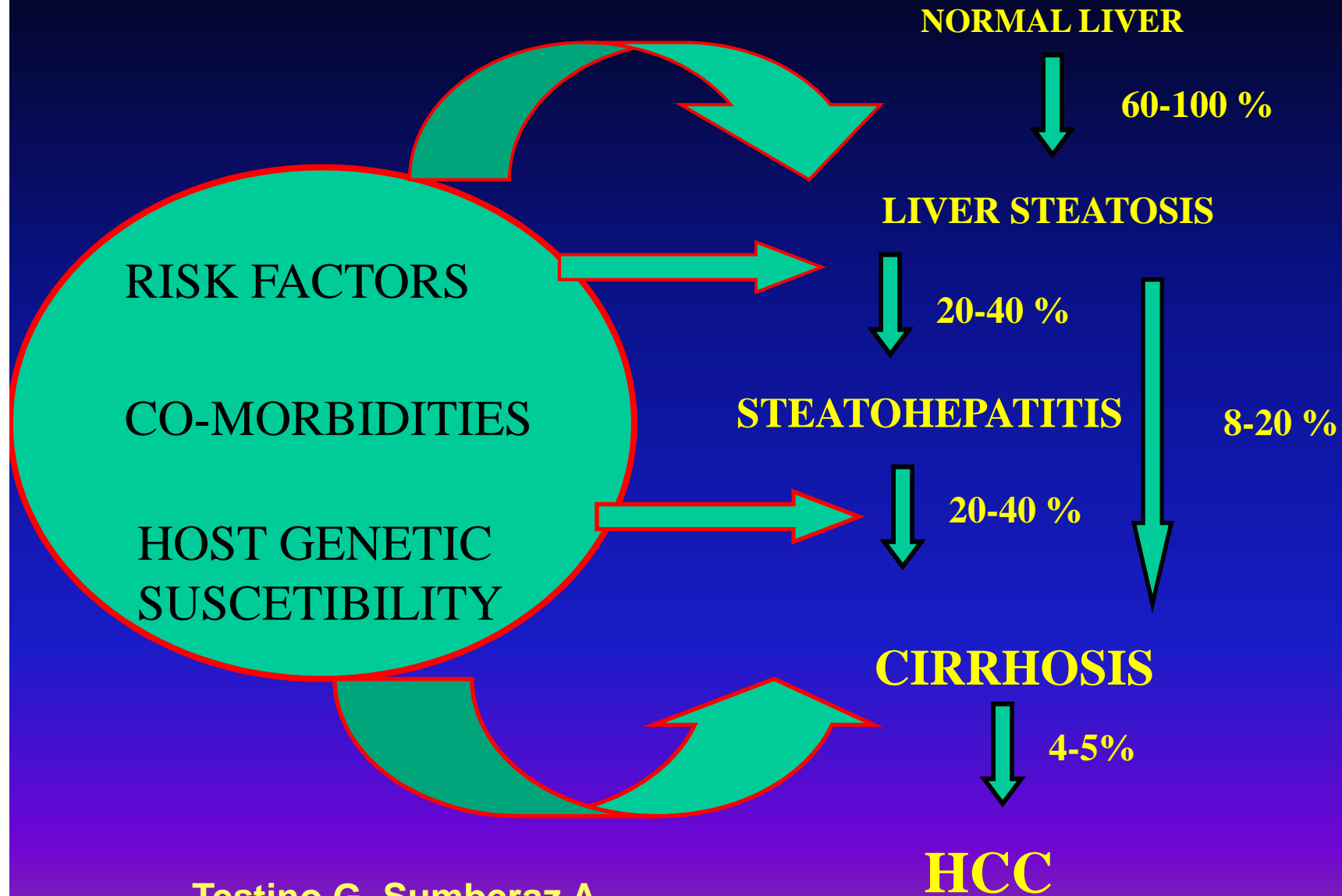


Tumor Necrosis Factor alpha – 238A

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

Sookoian S et al, Hepatology 2011

CHRONIC ALCOHOL DRINKER



Testino G, Sumberaz A
Hepatogastroenterol, 2008

**ALCOHOL CONSUMPTION AND ISOLATED NON ALCOHOLIC STEATOSIS
OR ASSOCIATED TO DIABETES MELLITUS TIPE II**

Binge Drinking (1 time month): progression fibrosis

20 gr/day: progression fibrosis

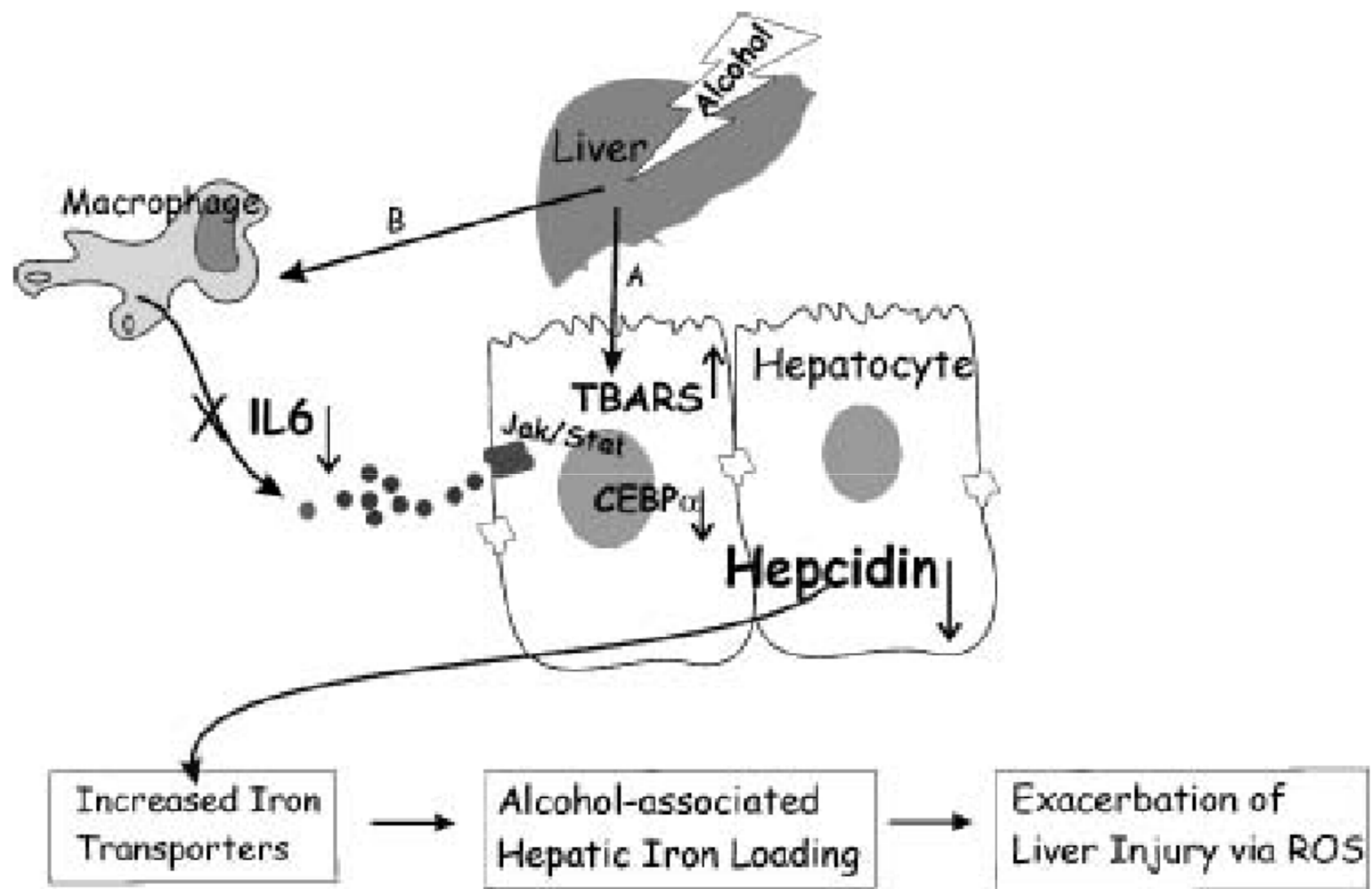
Ekstedt et al, Scand J Gastroenterol 2009

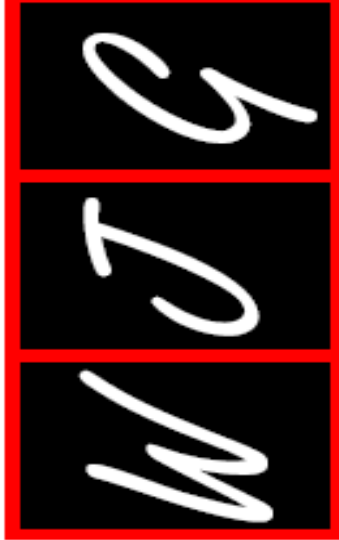
Lee and Kowdley, Clin Liver Dis 2012

**In presenza di steatosi non alcolica/ diabete non si assiste ad una influenza
sulla resistenza insulinica !**

Si assiste ad un peggioramento della fibrosi (evoluzione cirrotica piu' rapida)

**La transizione istopatologica fra «pura» steatosi non alcolica e steatosi
alcolica si fa sempre piu' sfumata con il progredire del tempo**





*World Journal of
Gastroenterology*

Submit a Manuscript: <http://www.wjgnet.com/esps/>
Help Desk: <http://www.wjgnet.com/esps/helpdesk.aspx>
DOI: 10.3748/wjg.v20.i43.15943

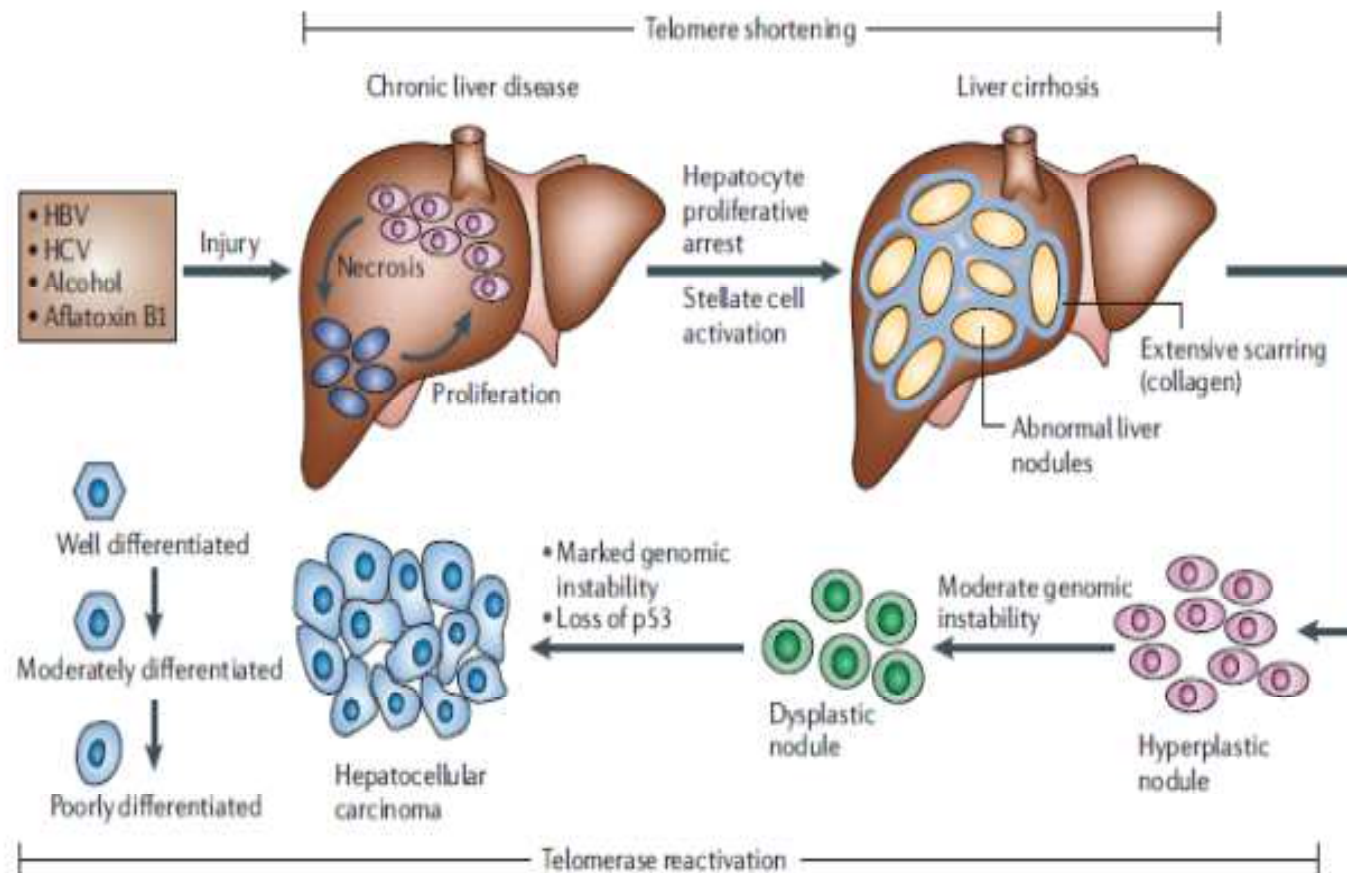
World J Gastroenterol 2014 November 21; 20(43): 15943-15954
ISSN 1007-9327 (print) ISSN 2219-2840 (online)
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TOPIC HIGHLIGHT

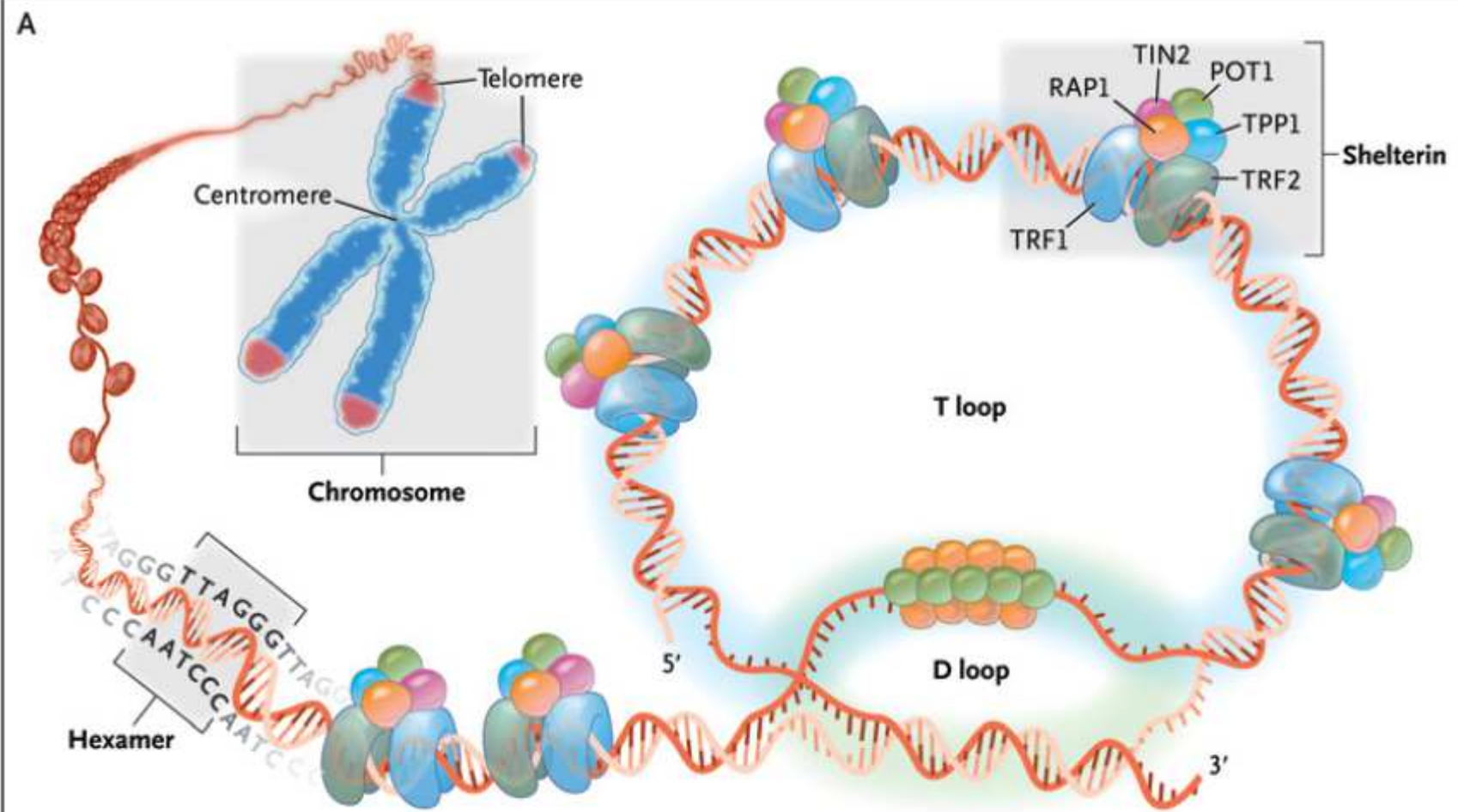
WJG 20th Anniversary Special Issues (1): Hepatocellular carcinoma

Alcohol and hepatocellular carcinoma: A review and a point of view

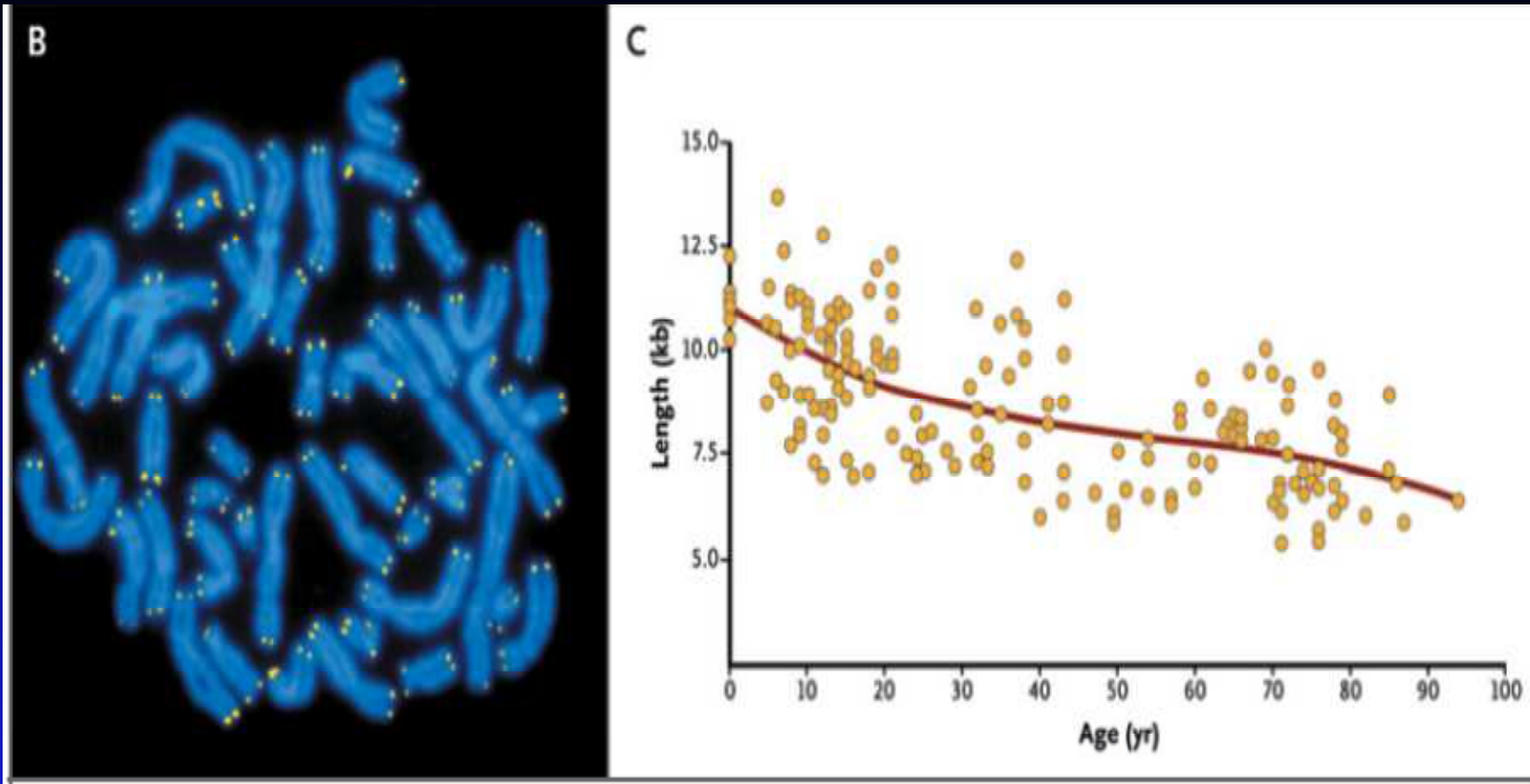
Gianni Testino, Silvia Leone, Paolo Borro



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

Percentage of hypermethylated tumor samples

Gene	
RASSF1A	67%
GSTP1	44%
P14 ^{ARF}	0%
GNMT	30%
DOK1	60%
MGMT	22%
CHRNA3	33%

RASSF1A: Ras signalling

GSTP1: detoxification of carcinogens

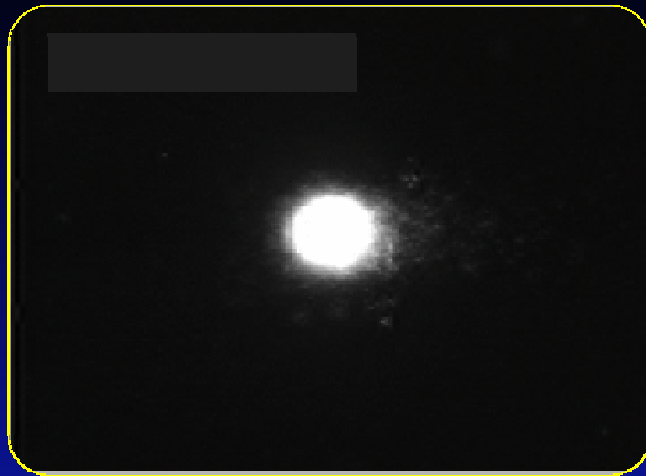
DOK1: response to interferon

CHRNA3: angiogenic growth

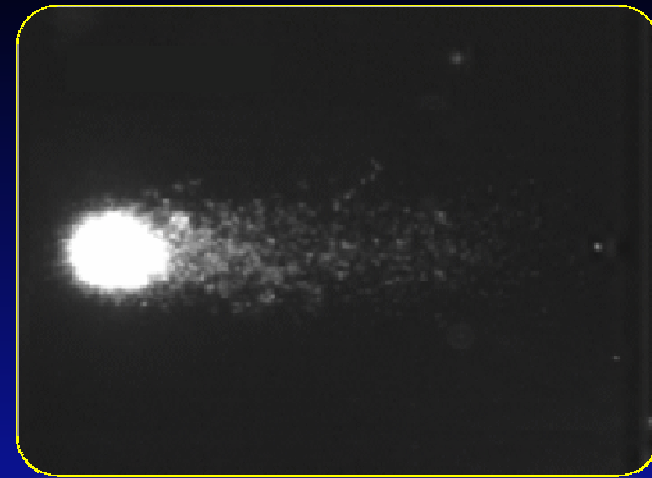
MGMT: DNA repair

LAMBERT et al, J HEPATOL 2010

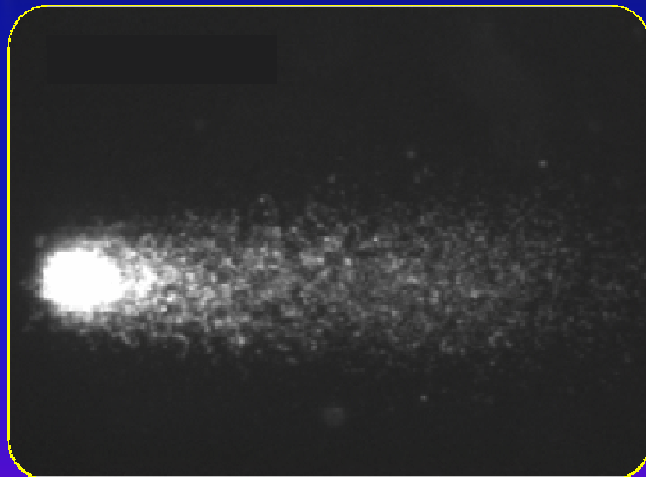
Seitz and Mueller, Biological Basis of
Alcohol Induced Cancer 2015



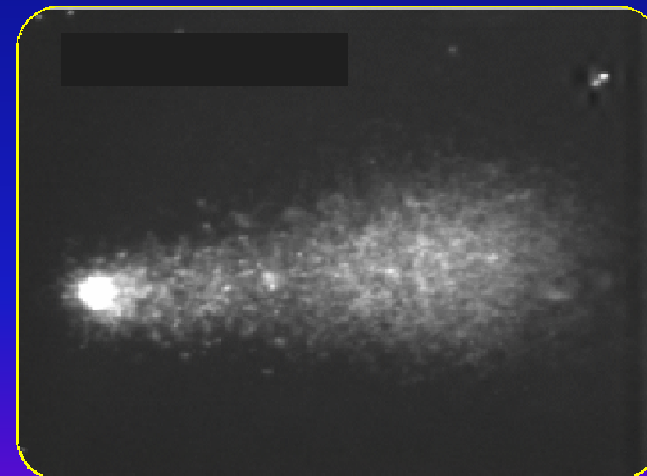
controllo



1

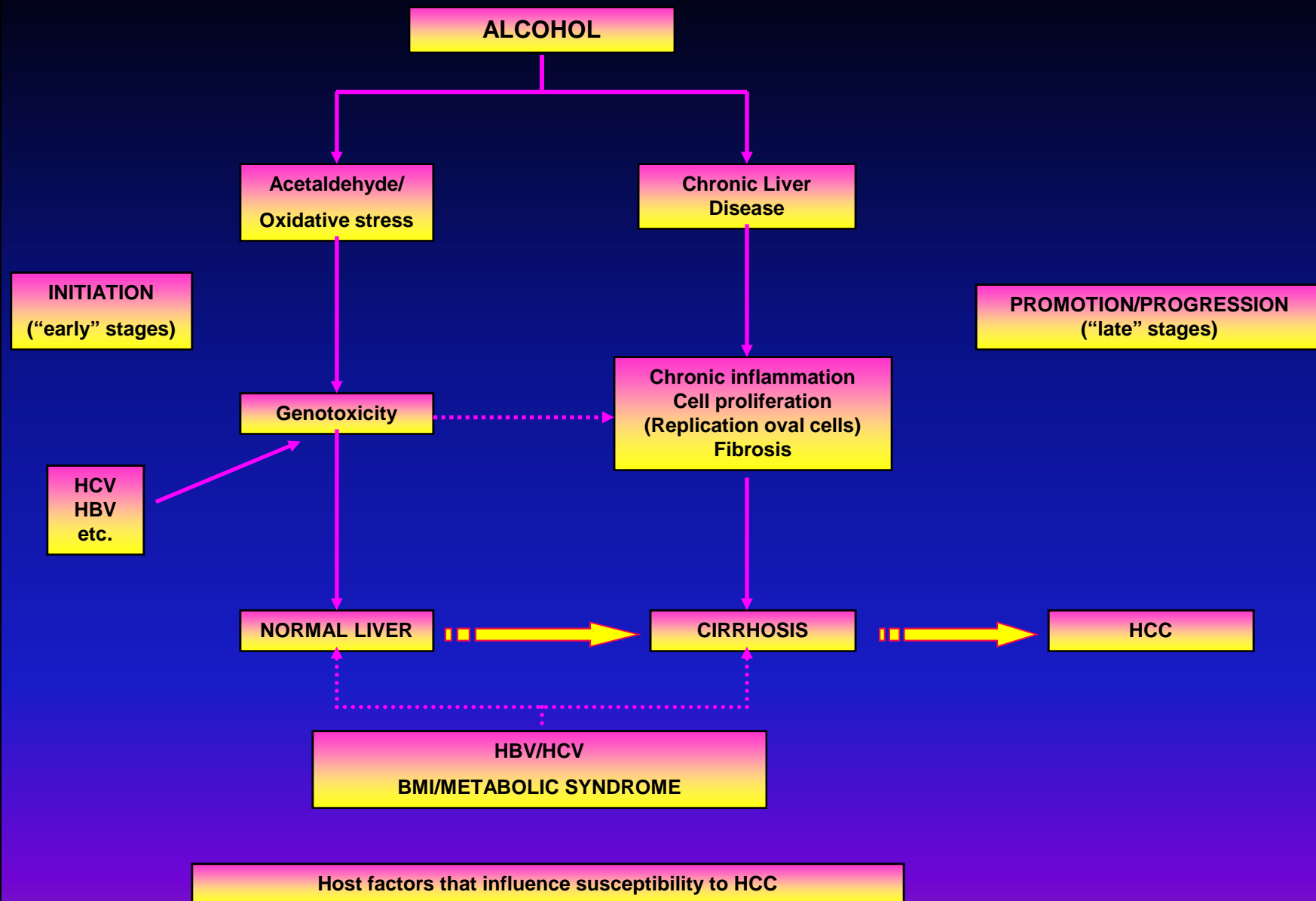


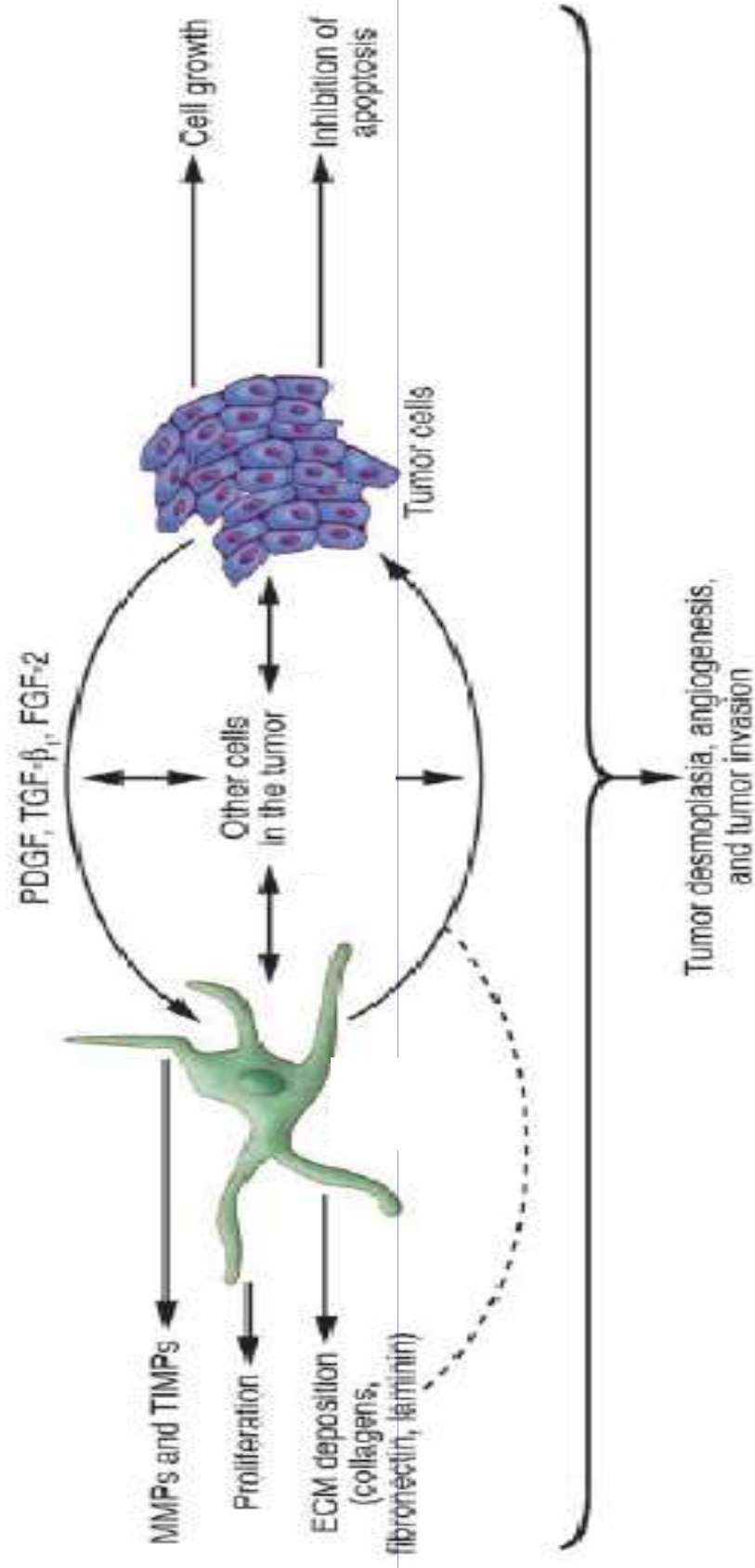
2

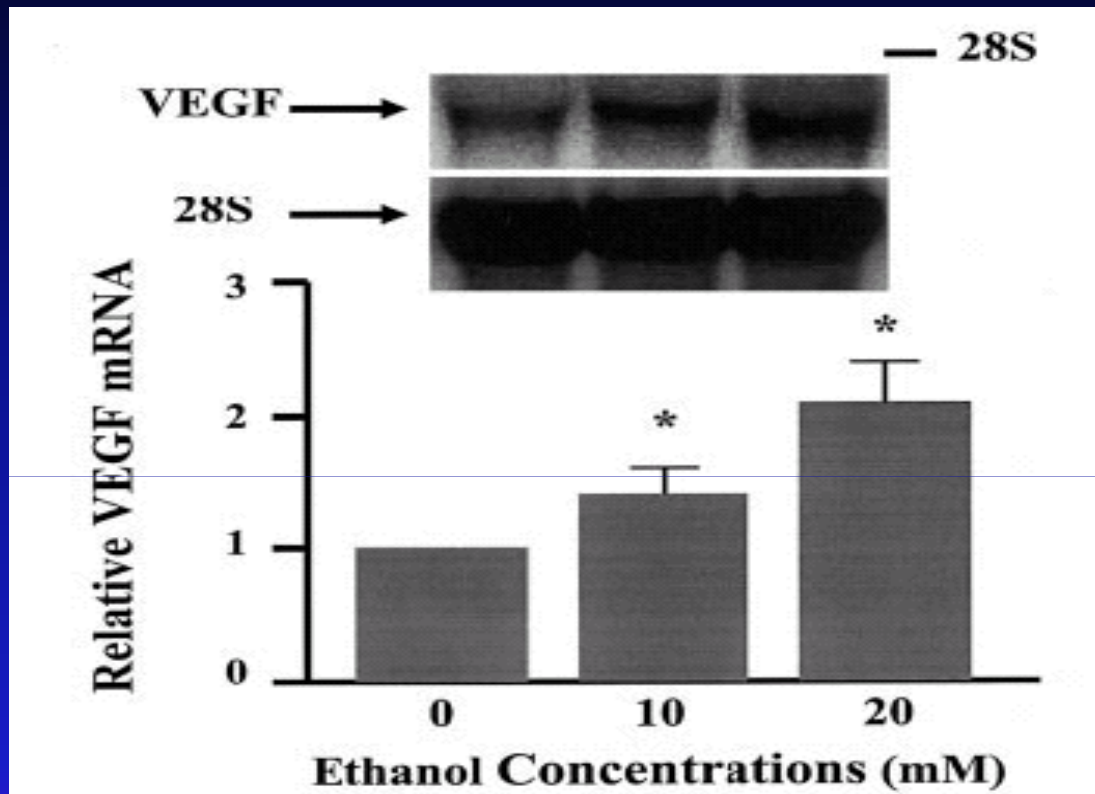


3

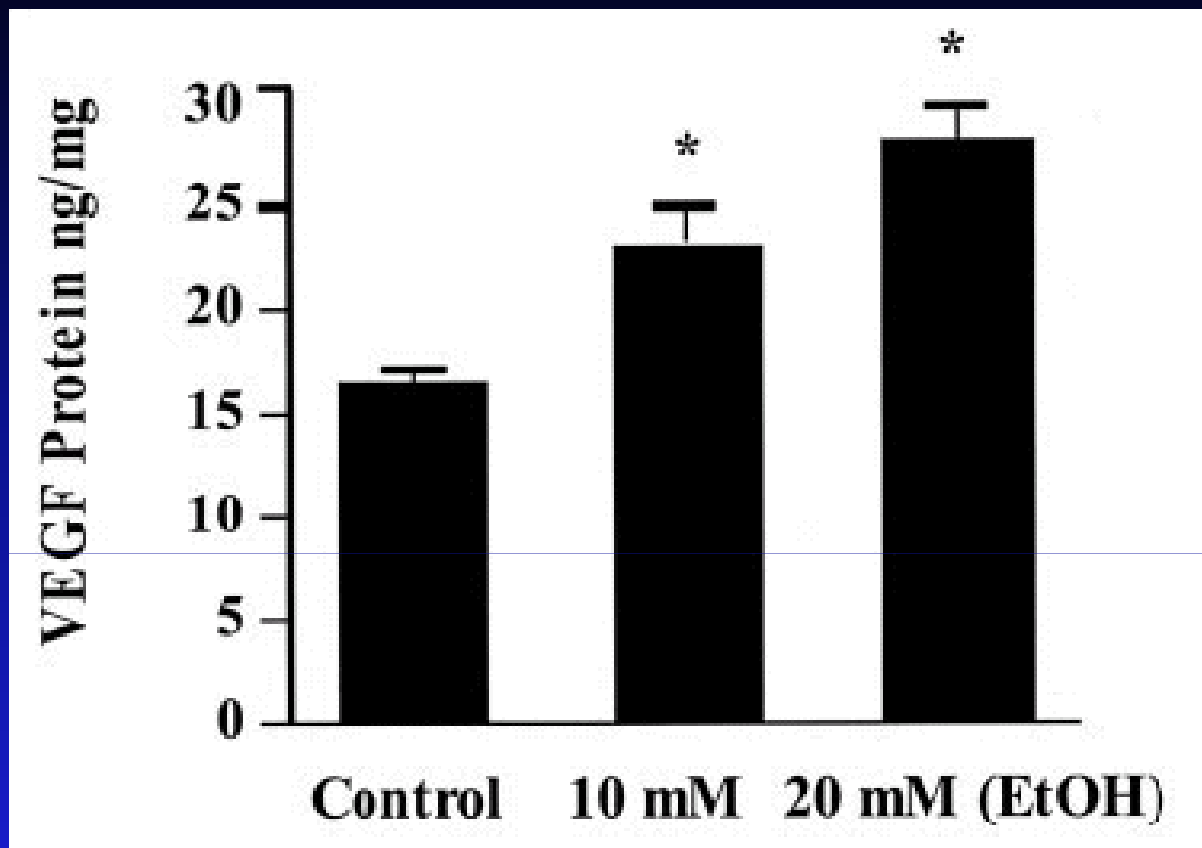
1,2,3 = diversi gradi di danno



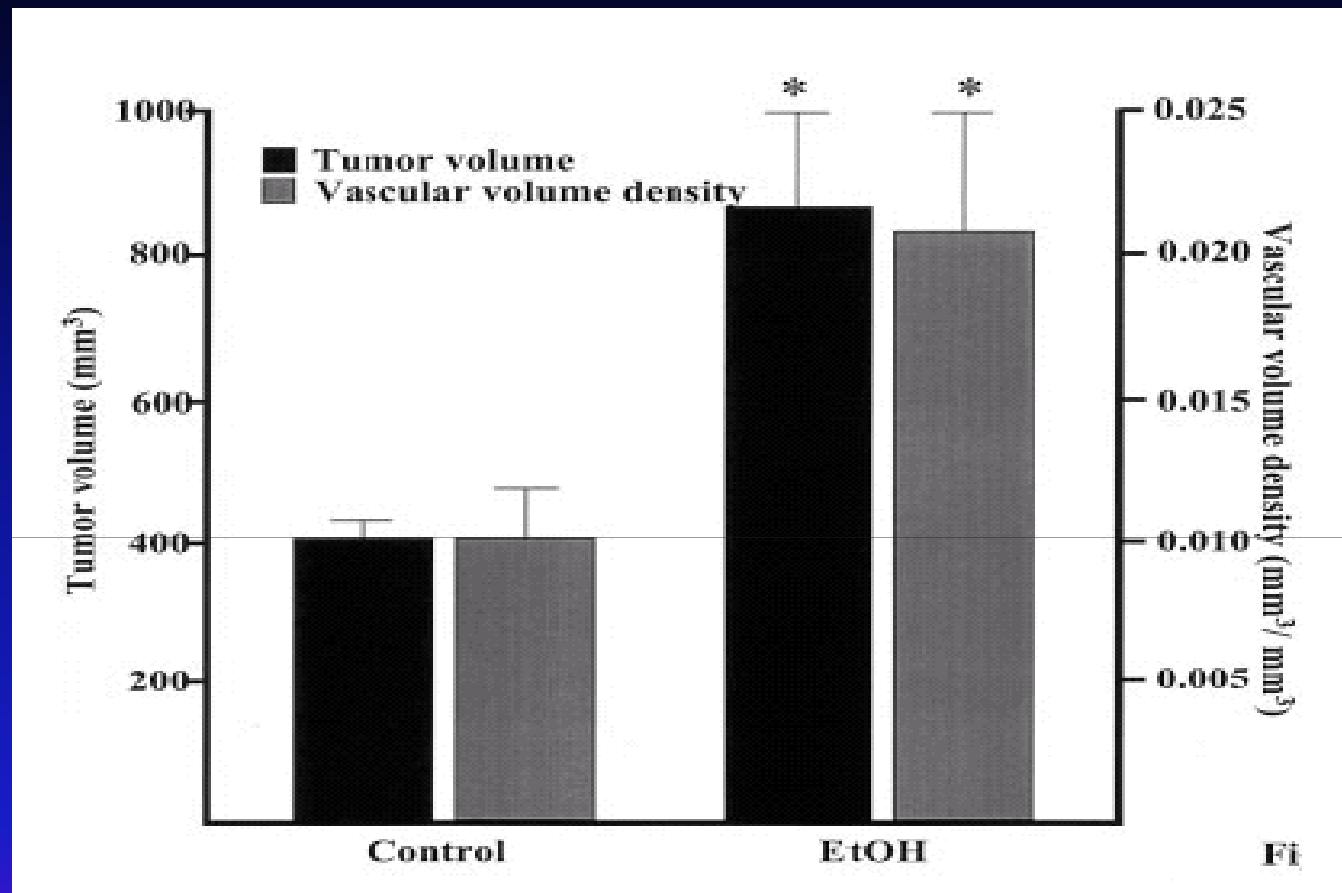




Gu JW et al, Cancer 2005



Gu JW et al, Cancer 2005



Gu JW et al, Cancer 2005

Correlation between Liver Metastasis and Alcohol Consumption

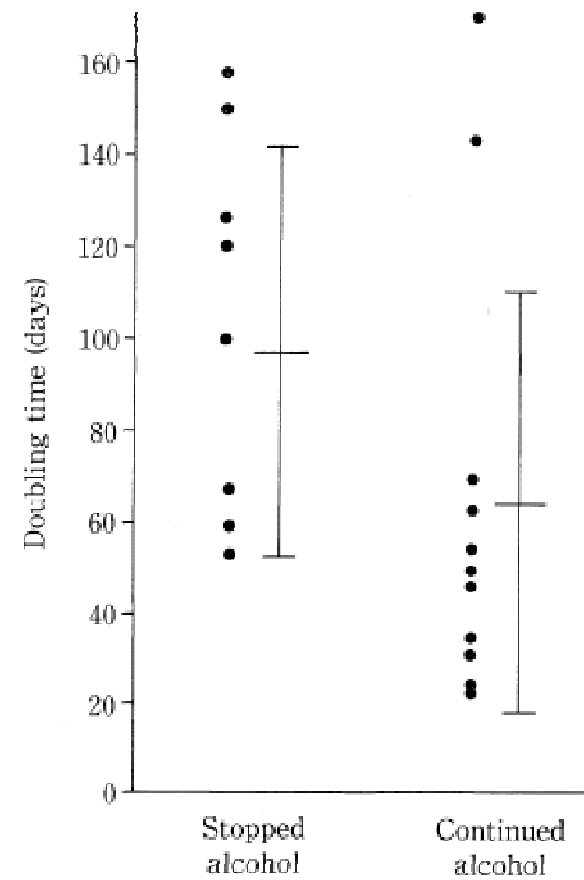
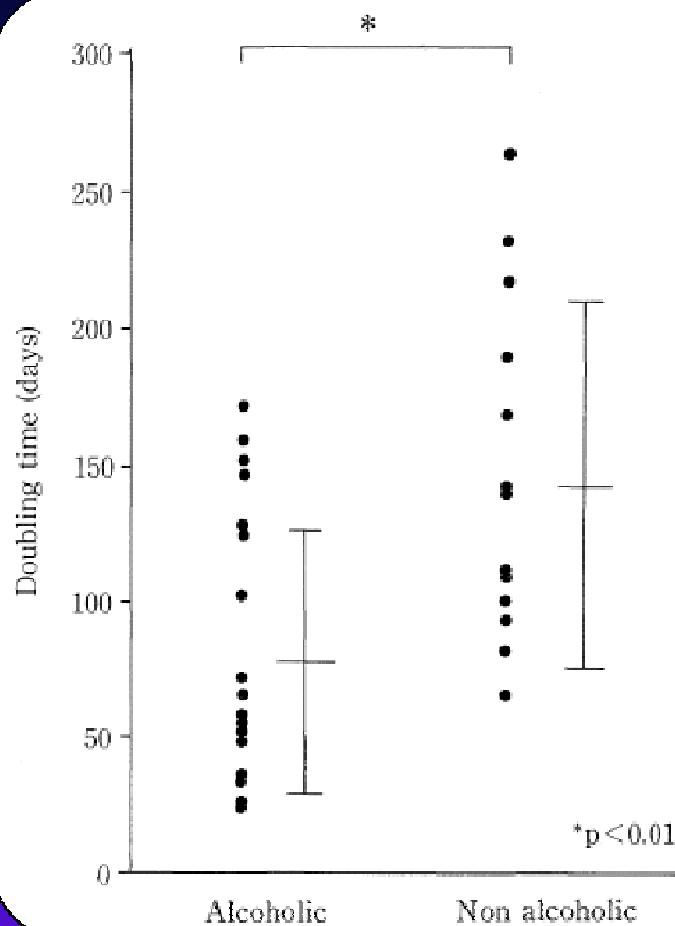
	Liver metastasis cases/total cases		<i>P</i> value ^a
	NACG	ACG	
Total	17/95	17/38	0.0021
Synchronous	7/95	9/38	0.0201
Metachronous ^b	10/88	8/29	0.0714

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

Matsushashi et al, Internal Medicine 1996

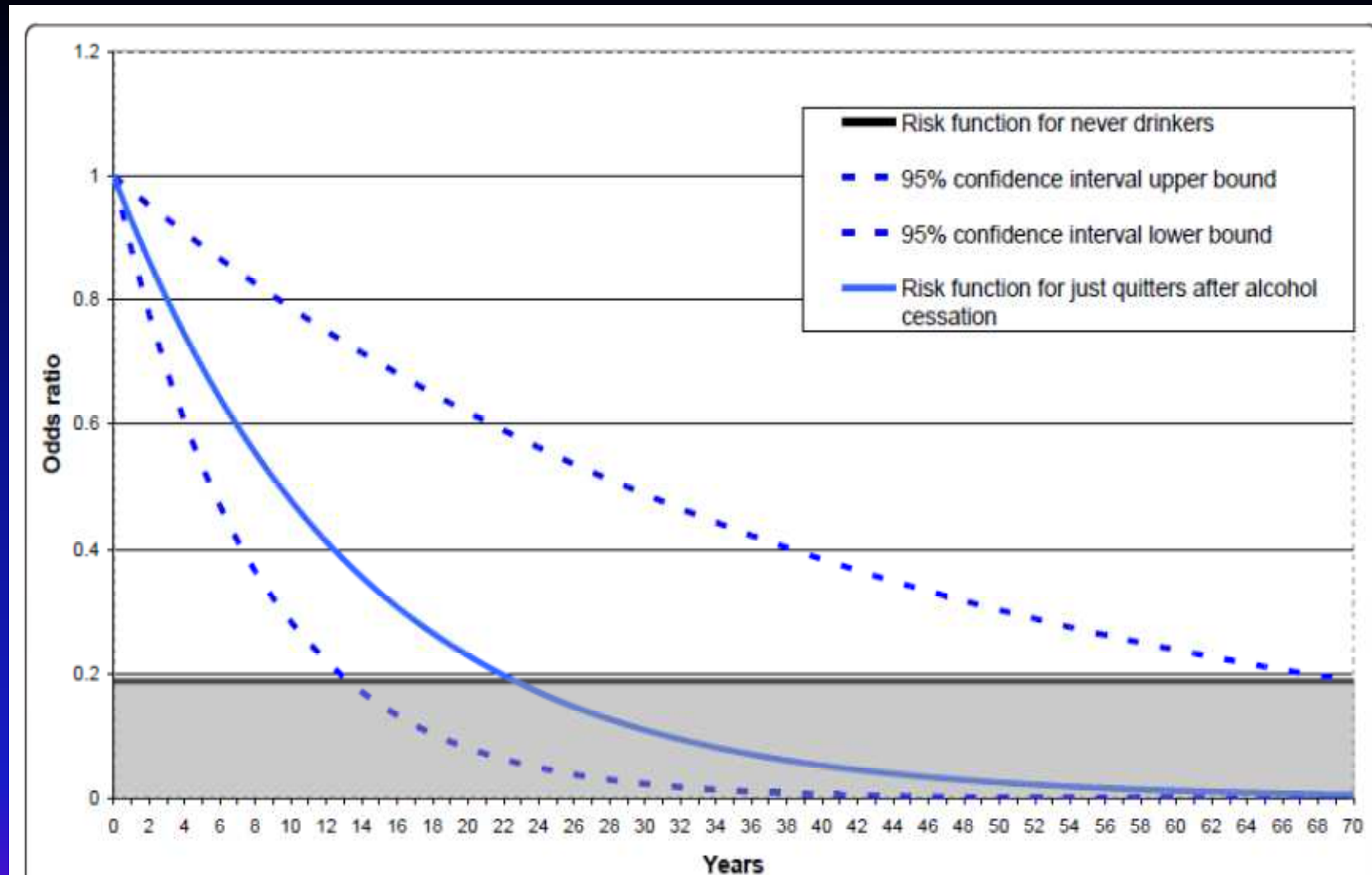
**5– year HCC incidence
rate**

**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

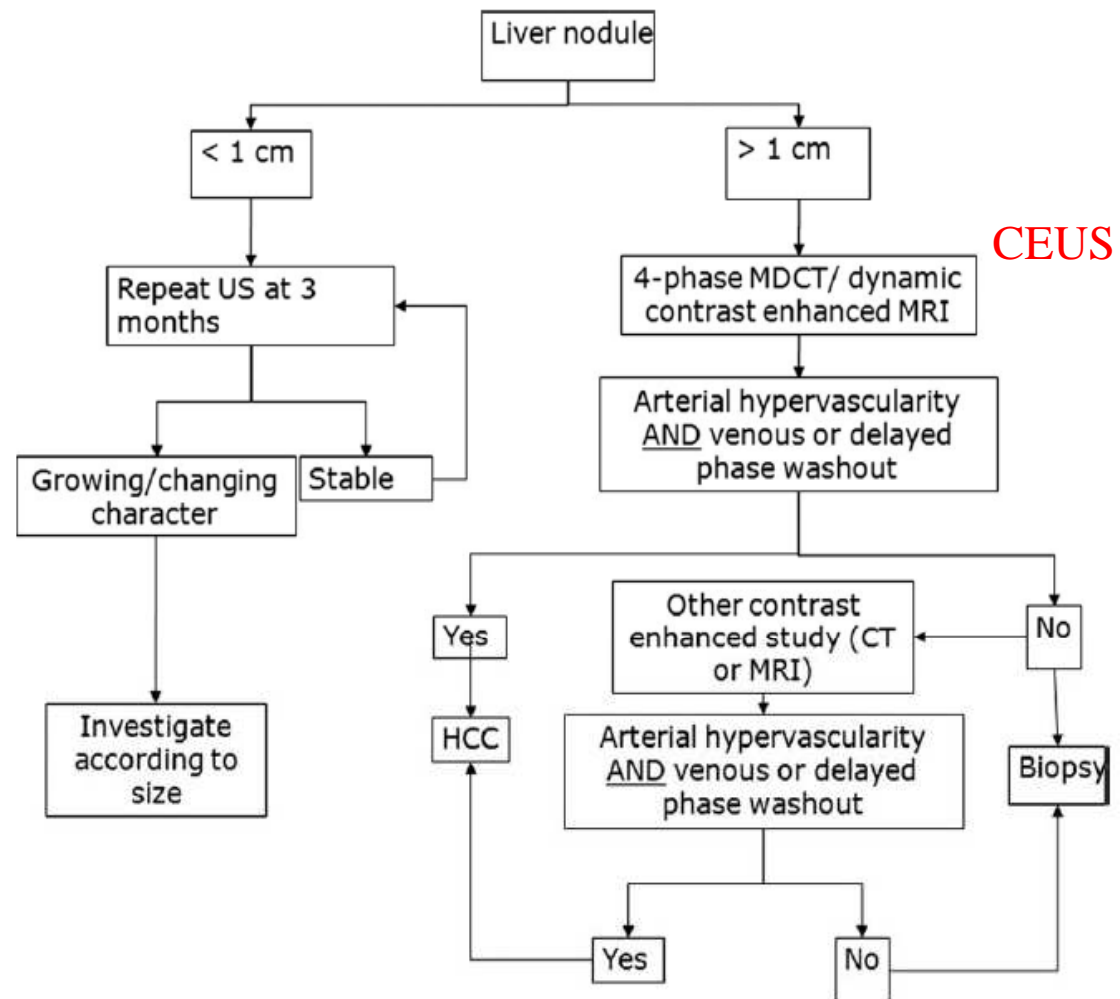
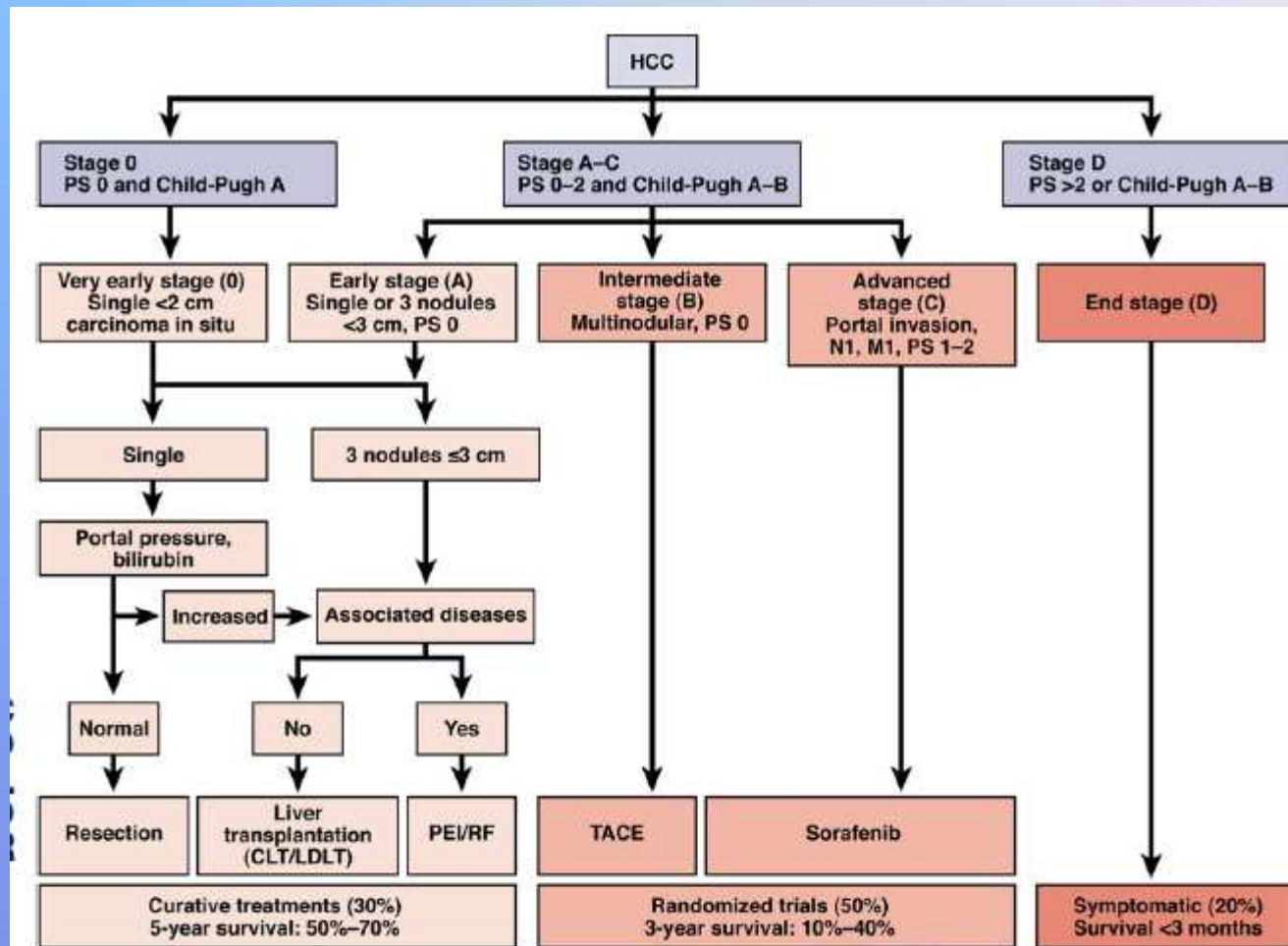


Fig. 1. Diagnostic algorithm for suspected HCC. CT, computed tomography; MDCT, multidetector CT; MRI, magnetic resonance imaging; US, ultrasound.

AASLD, Hepatology 2010

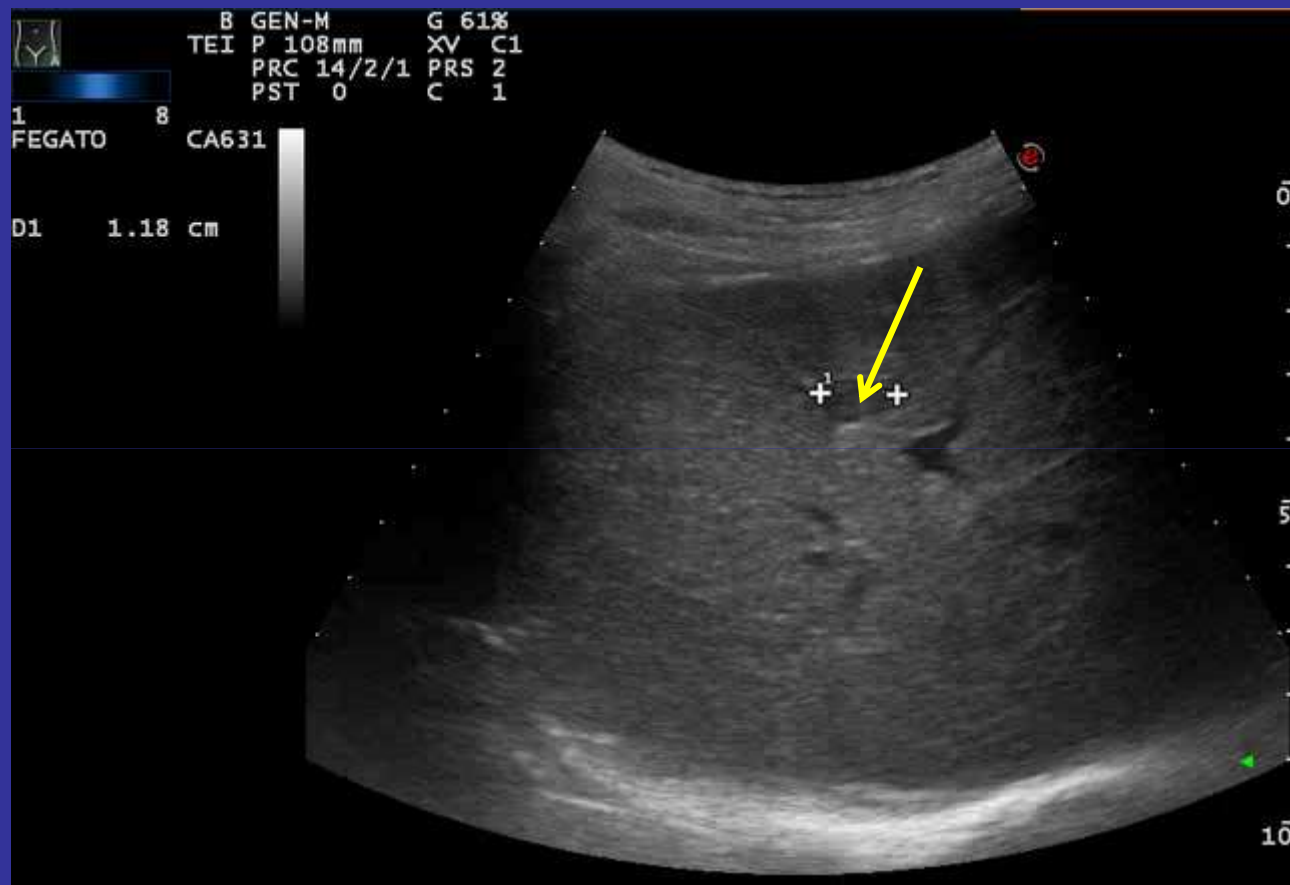
CEUS: Contrast-Enhanced Ultrasound

Minami et al, World J Radiol 2009; Omata et al, Hepatol Int 2010; Minami and Kudo, World J Gastroenterol 2010; Giorgio et al, Anticancer Res 2011

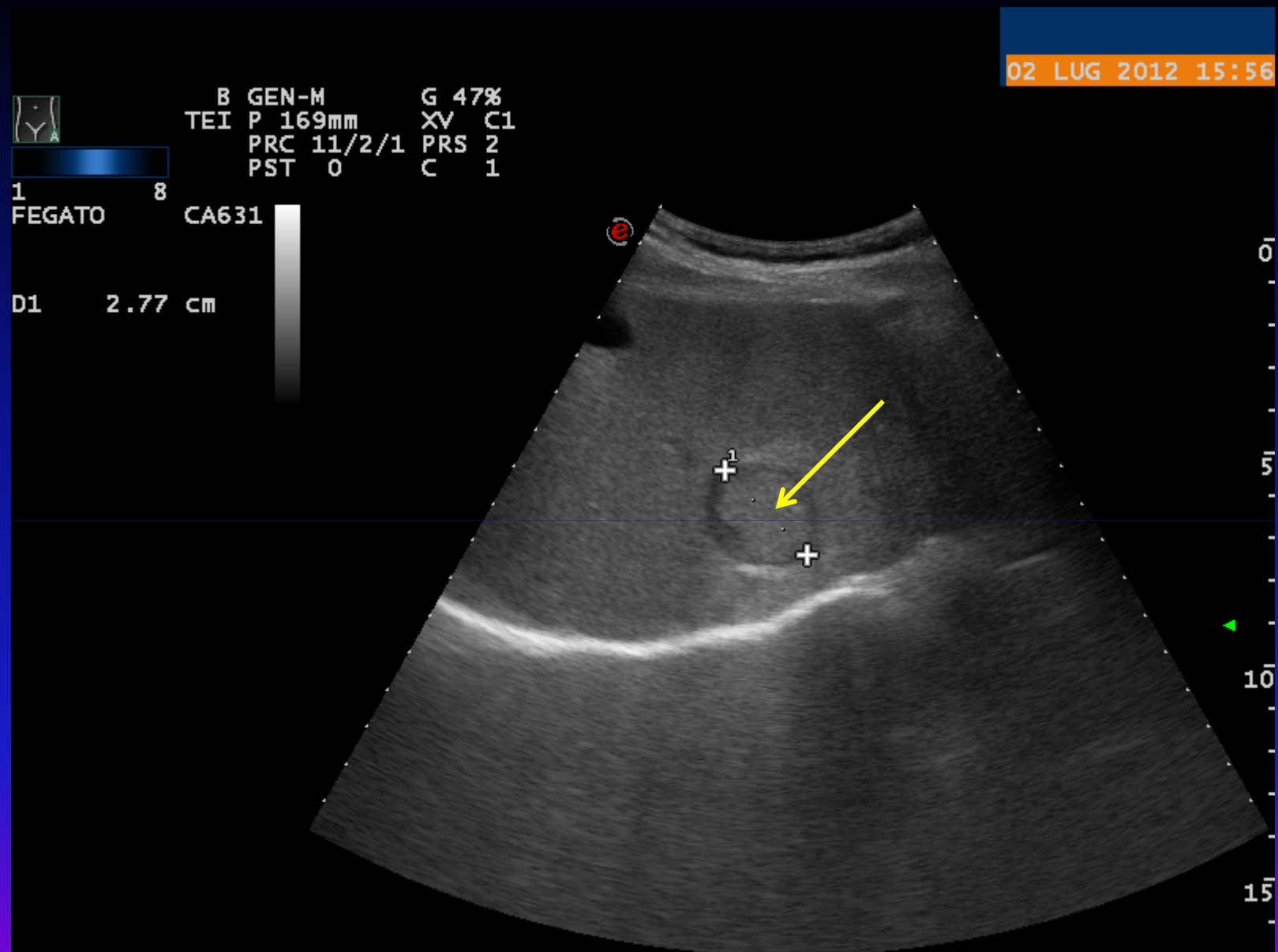


Barcelona Clinic Liver Cancer Staging System (BCLC-SS)

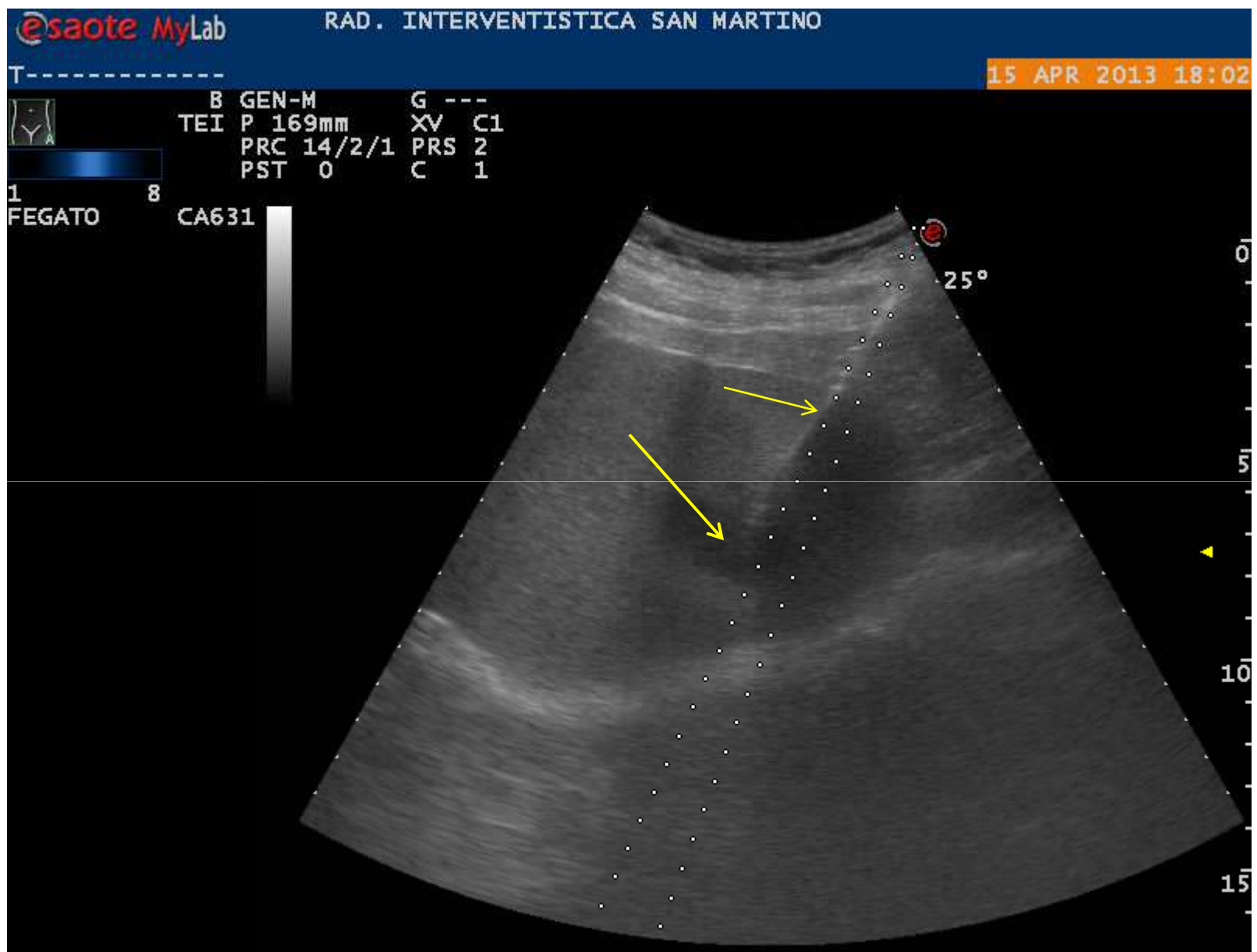
Llovet et al, Semin Liver Dis 1999; Bruix and Llovet, Lancet 2009



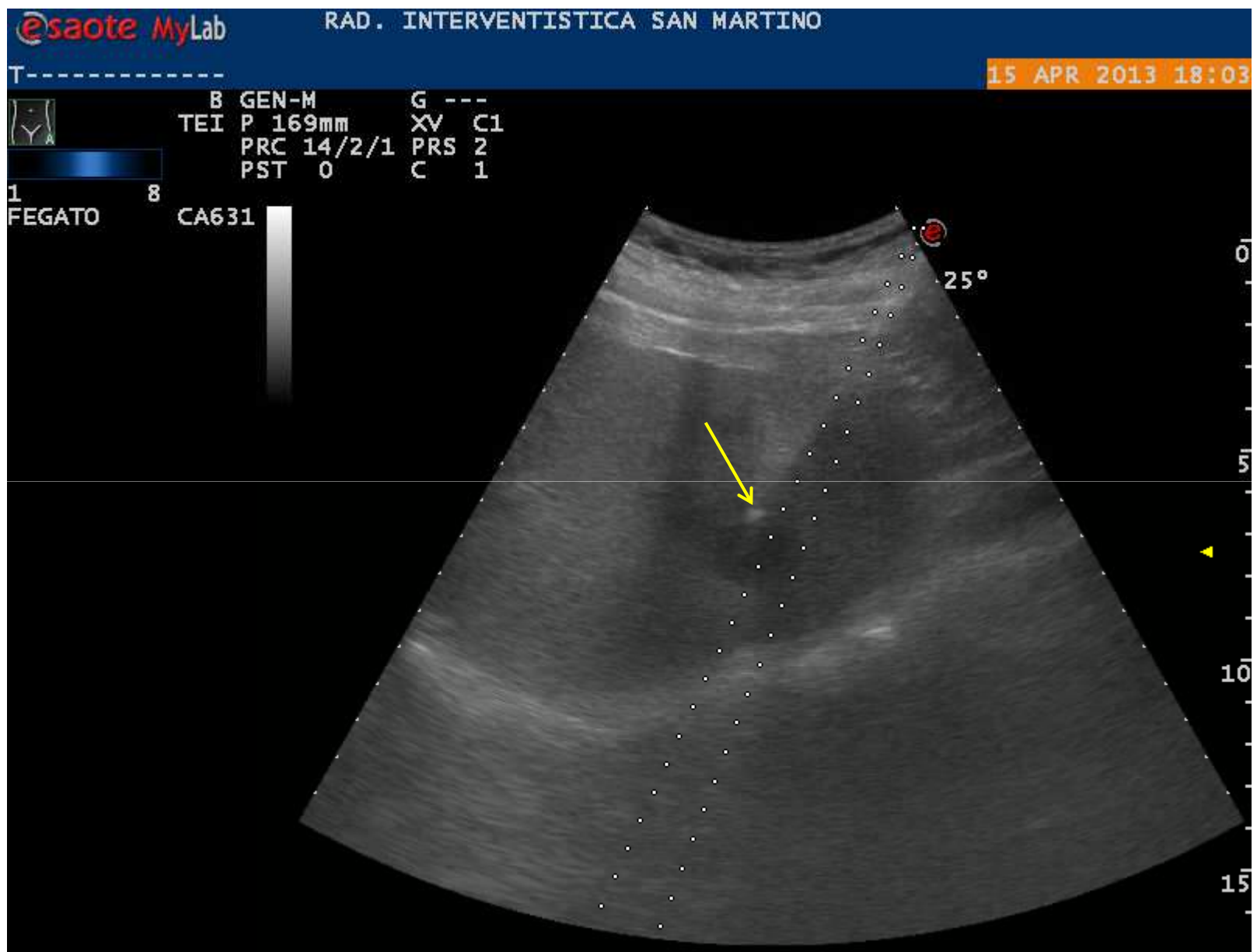
Paolo Borro – Centro Alcológico Regionale Ligure, IRCCS San Martino-IST, Genova



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



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



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



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

Hepatocellular Carcinoma (HCC)



Small HCC of 2 cm in size of an alcoholic patient (BCLC 0 stage) treated by surgical resection of S VI. Pathology examination: microscopic vascular invasion (High risk of recurrence → Indication of liver transplantation (« *ab initio* » indication)

An International Consensus for Medical Leadership on Alcohol

..... Medical professionalism includes the responsibility to speak out, to lead, and to voice advocacy. It is every clinician's responsibility 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.

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 e 2013

Union for the International Cancer Control, 2010

Association of European Cancer Leagues, 2011

Cancer Council Australia, 2011

Public Health, 2011

OMS (IARC), 2010 e 2012

Istituto Superiore di Sanita', Italy; 2013

CC – OMS (Europe Region, ISS); World Cancer Report (OMS), 2014

SOGGETTI CON CONSUMO RISCHIOSO/DANNOSO E ALCOLDIPENDENTI

PRIMA VALUTAZIONE – PREVENZIONE SECONDARIA

Migliorare anamnesi alcolica/ 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 Se assenza di cirrosi ETG ogni 12 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

**Consumption
Heavy**

Alcohol Consumption

**Consequences
severe**

**Alcohol
dependence**

**Advanced
Alcoholic Diseases**

Harmful

Risky use

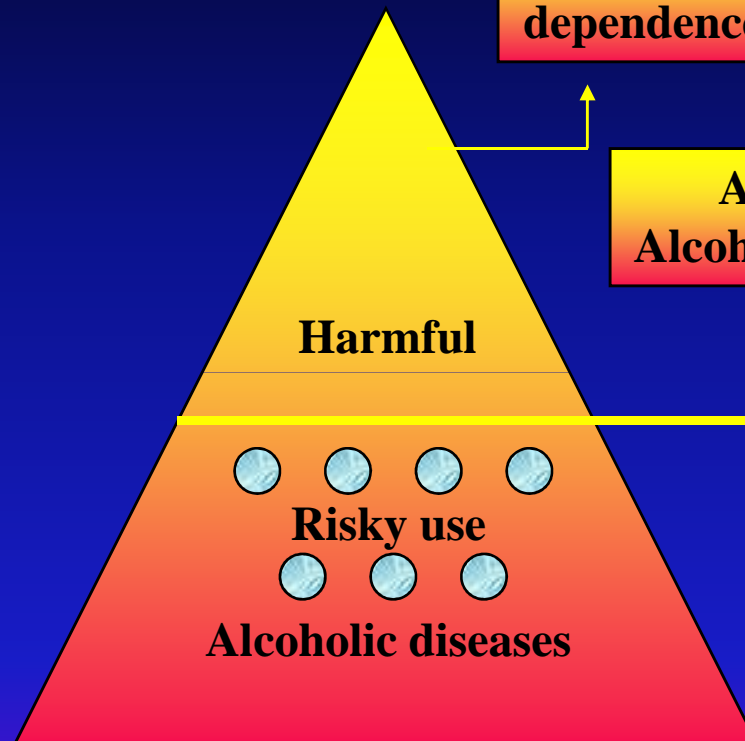
Alcoholic diseases

None

Low risk use

Abstinence

None



**Consumption
Heavy**

Alcohol Consumption

**Consequences
severe**

**Alcohol
dependence**

**Advanced
Alcoholic Diseases**

Harmful

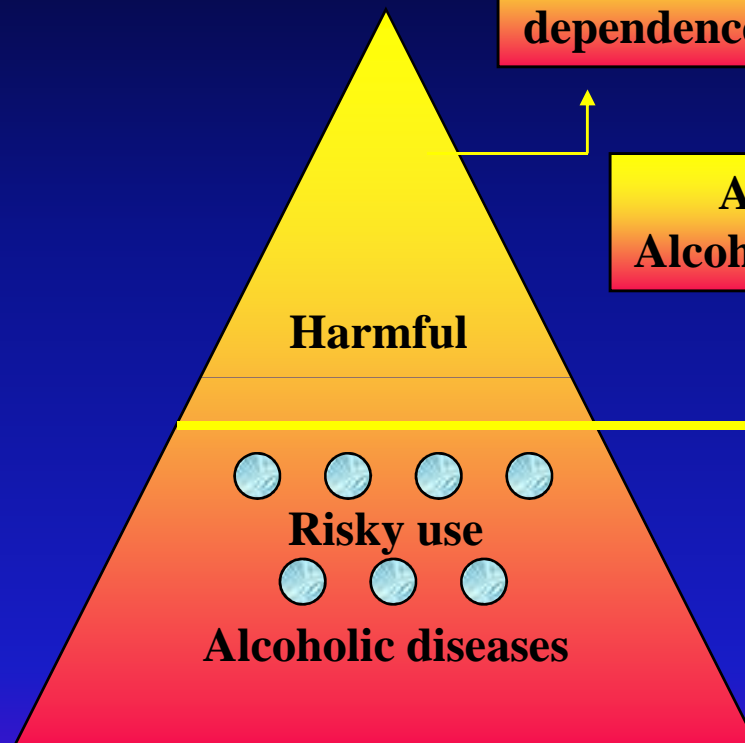
Risky use
Alcoholic diseases

Low risk use

Abstinence

None

None



Gracie