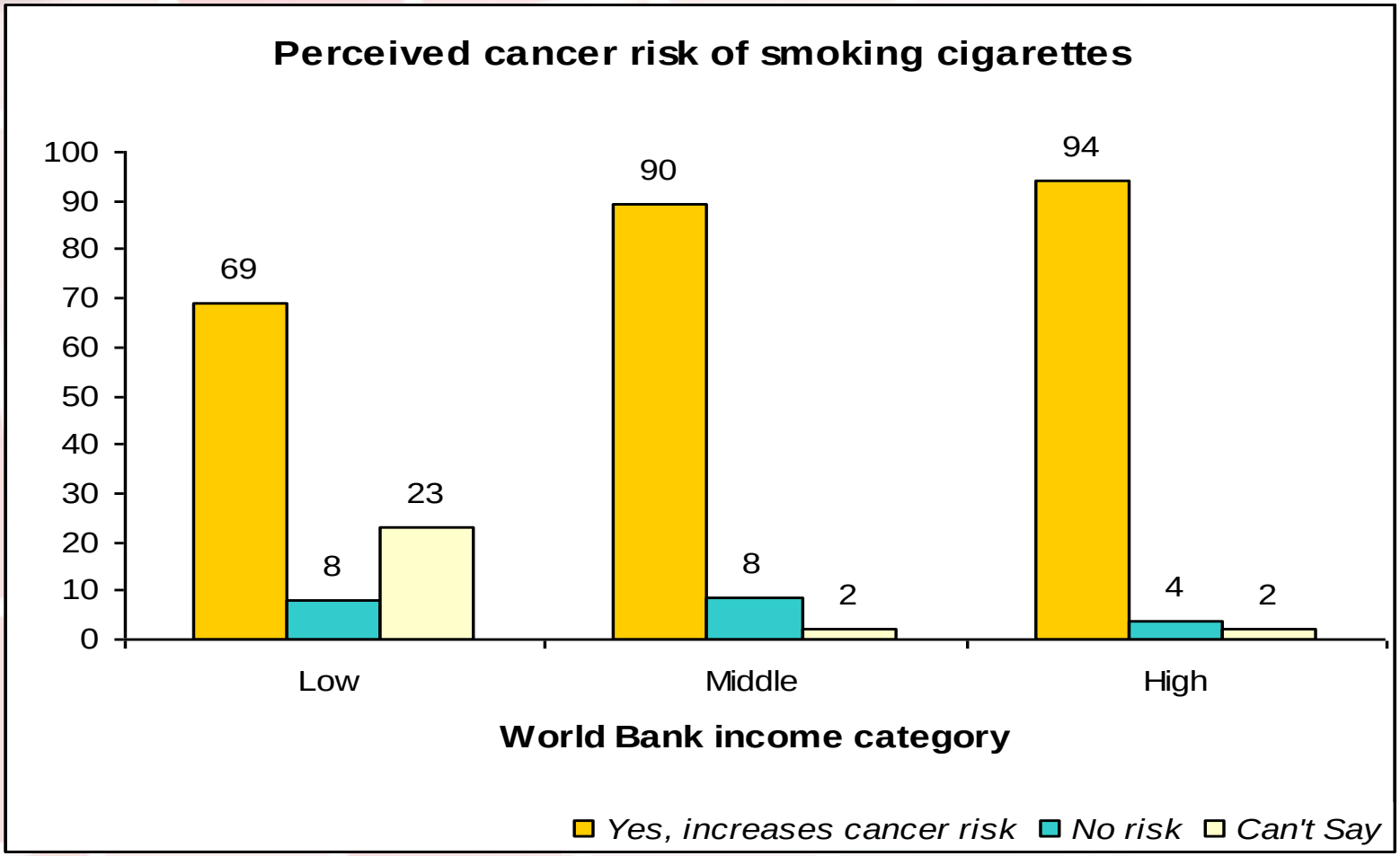
Perche' accettiamo i rischi evitabili delle bevande alcoliche?

Gianni Testino

Centro Alcologico Regionale
Regione Liguria
IRCCS AOU San Martino-IST, Genova

Perceived risk of smoking



Distribuzione percentuale del campione in base all'abitudine al fumo *(Analisi secondo il sesso)*

Non Fumatori:
35,1 milioni
67,1%

Uomini:	Donne:
14,7 milioni	20,4 milioni
58,7 %	74,8%

Ex Fumatori:
6,3 milioni
12,1%

Uomini:	Donne:
4,0 milioni	2,3 milioni
16,2%	8,3%

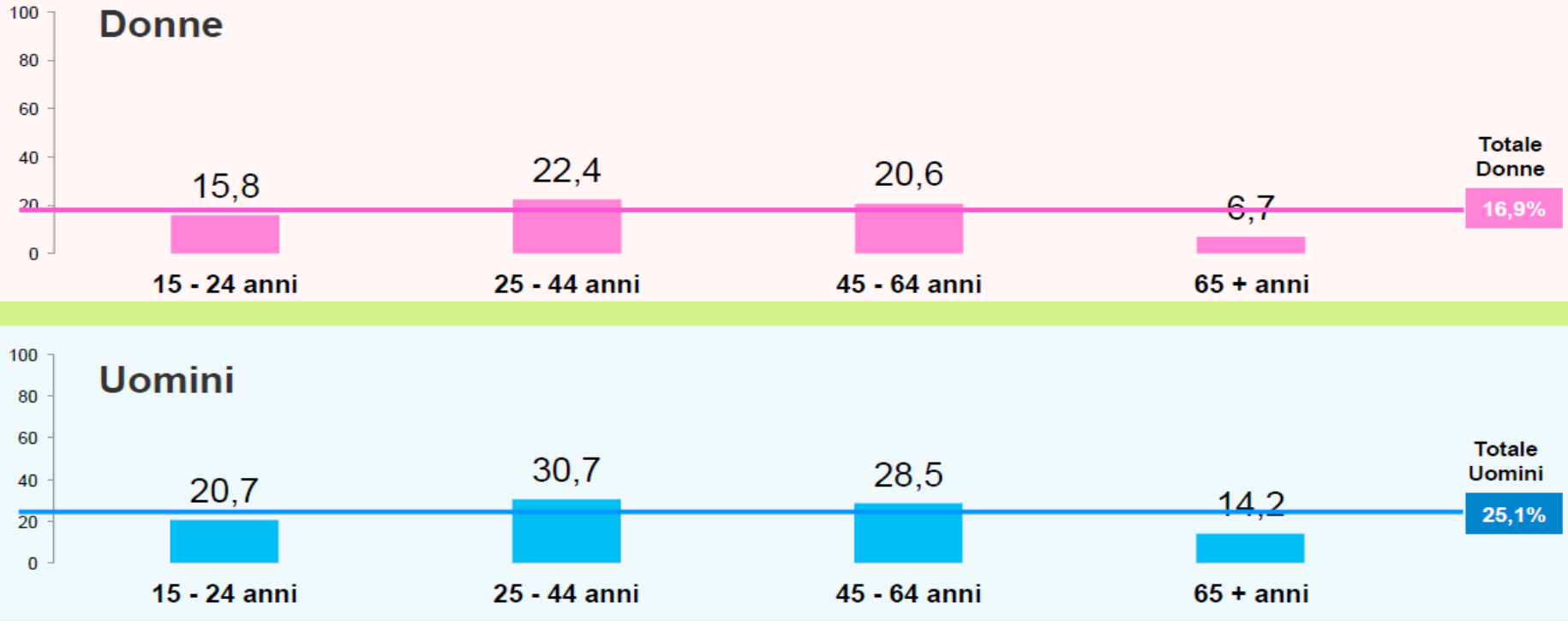
Fumatori:
10,9 milioni
20,8%

Uomini:	Donne:
6,3 milioni	4,6 milioni
25,1%	16,9%

OSSFAD – Indagine DOXA-ISS 2015

Rapporto ISS 2015

Prevalenza del fumo di sigarette fra gli uomini e le donne delle varie età



OSSFAD – Indagine DOXA-ISS 2015

Rapporto ISS 2015

DISTRIBUZIONE PERCENTUALE DEI FUMATORI IN BASE ALL'ABITUDINE AL FUMO (N.SIGARETTE/DIE) ED ALL'ETA'

Numero di sigarette fumate/die	Totale Fumatori	15-24 anni	25-44 anni	45-64 anni	65+ anni
Meno di 15 sigarette al giorno	53,7%	**82,8%**	58,0%	43,1%	48,6%
15-24 sigarette al giorno	41,8%	**15,0%**	38,3%	51,7%	44,6%
25 o più sigarette al giorno	3,3%	**0,0%**	3,6%	3,5%	4,7%

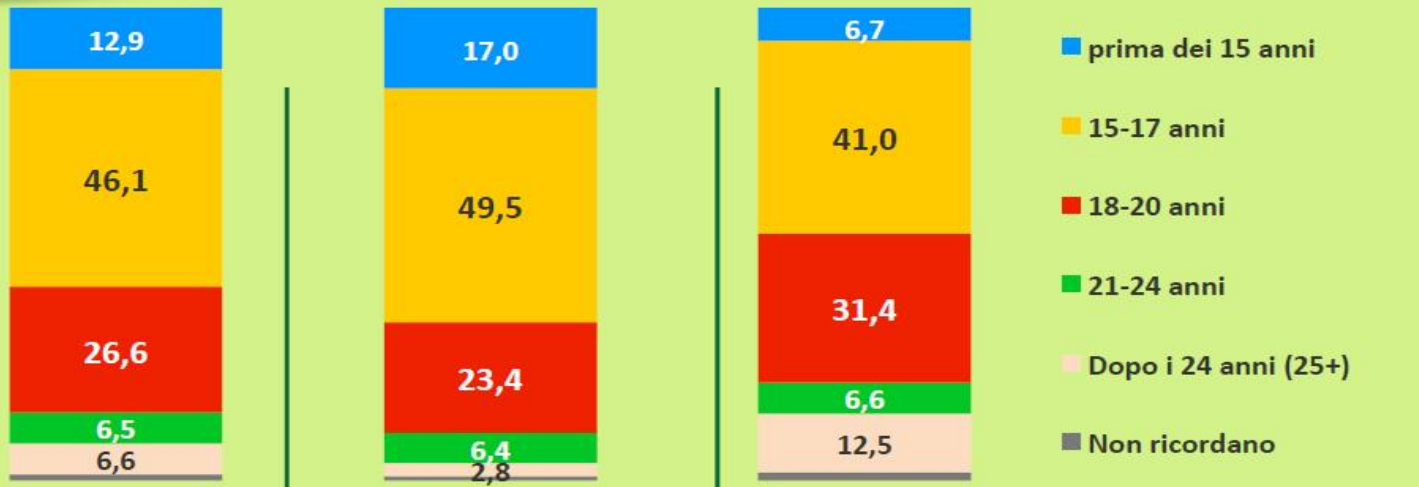
Anno 2014	
Meno di 15 sigarette al giorno	67,8%
15-24 sigarette al giorno	28,0%
25 o più sigarette al giorno	1,3

OSSFAD – Indagine DOXA-ISS 2015

Rapporto ISS 2015

A che età si inizia a fumare?

(Analisi secondo il sesso)

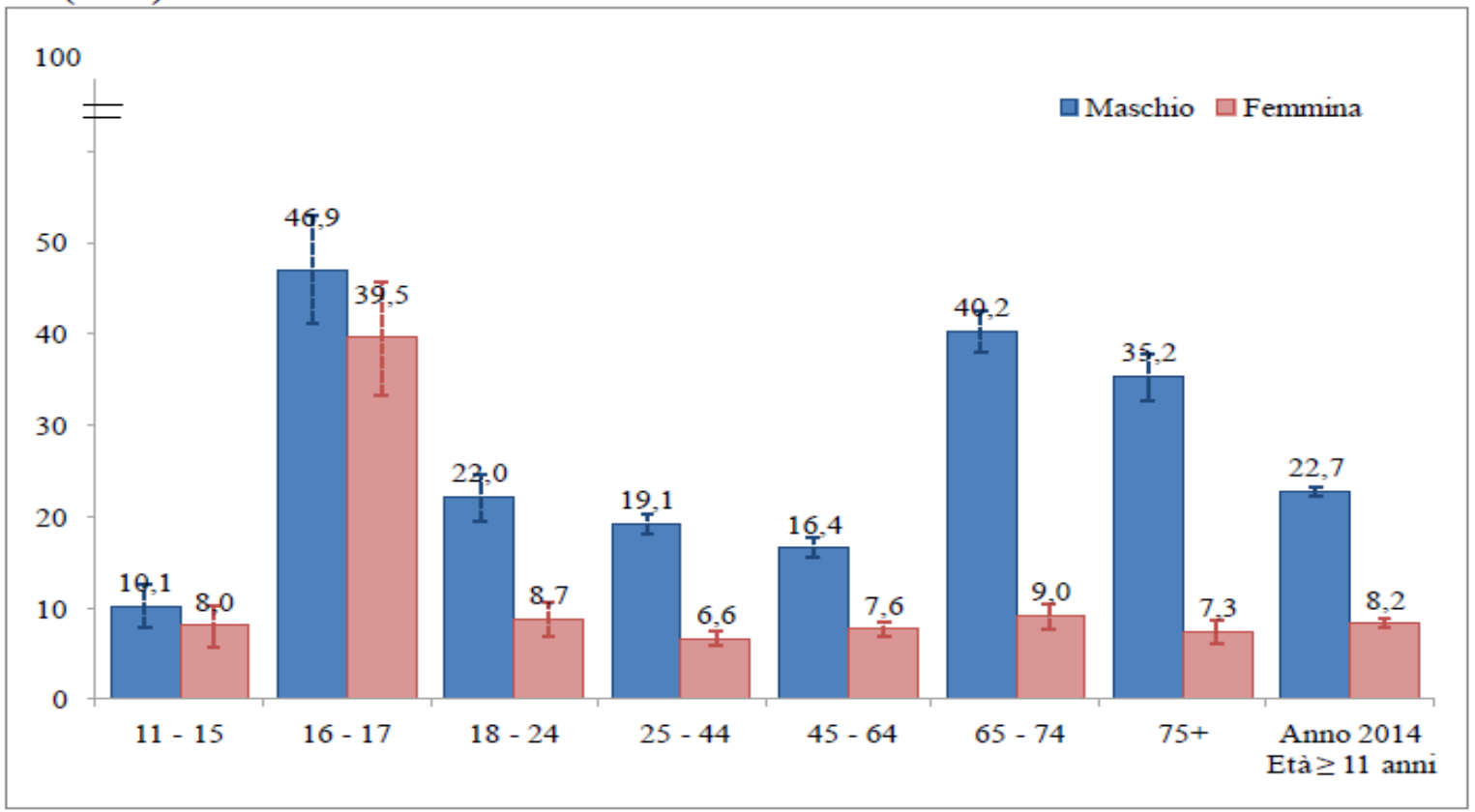


	totale	uomini	donne
Età media	17,9	17,0	19,1
% tra i 15 ed i 20 anni	72,7	72,9	72,4

OSSFAD – Indagine DOXA-ISS 2015

Rapporto ISS 2015

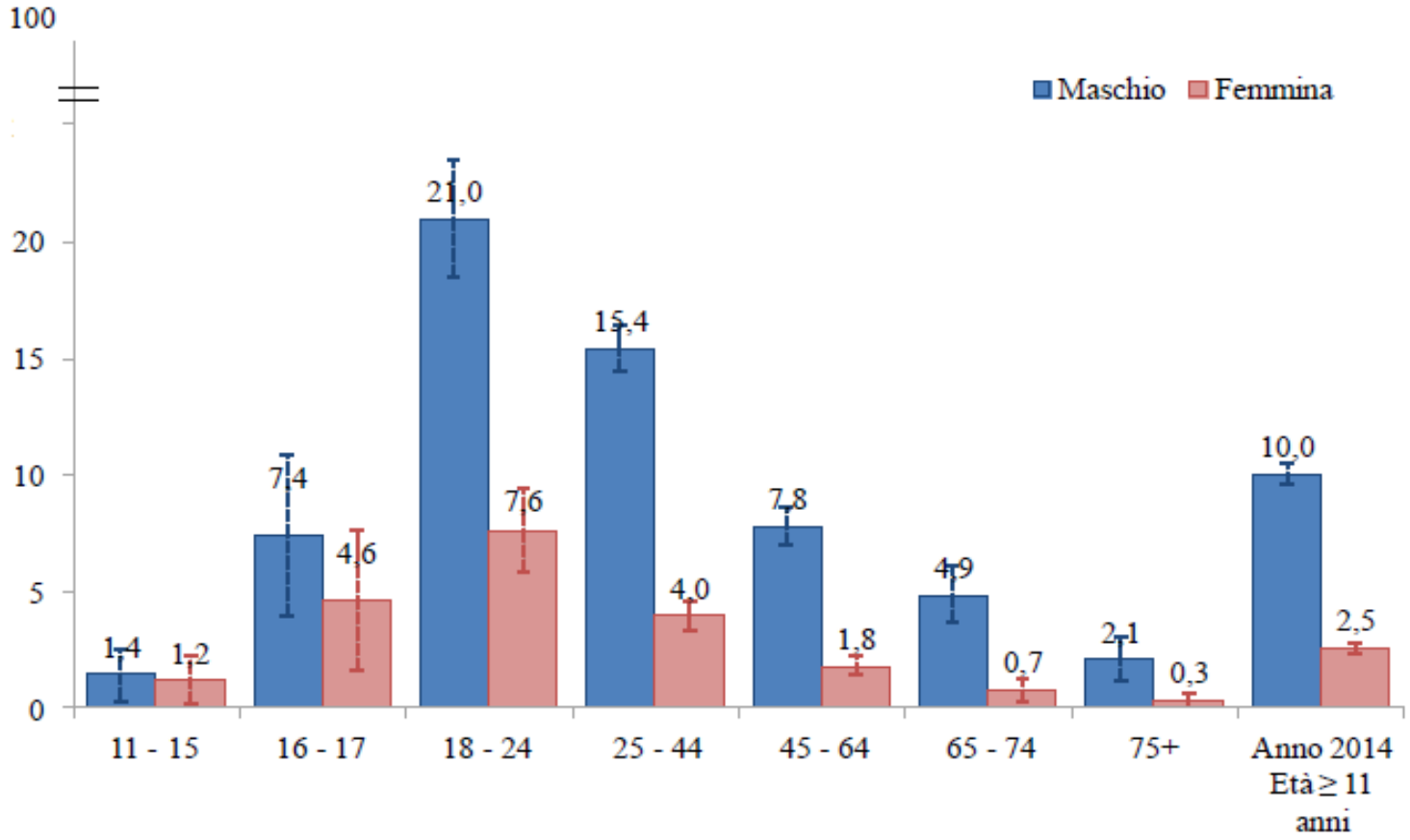
Figura 11. Prevalenza (%) di consumatori a rischio (criterio ISS)per genere e classi di età (2014)



Fonte: Elaborazioni ONA-CNESPS e WHO CC Research on Alcohol su dati dell'Indagine ISTAT Multiscopo sulle famiglie

Relazione al Parlamento, Ministero della Salute, 2015

Figura 9. Prevalenza (%) di consumatori *binge drinking* per genere e classe di età (2014)



Fonte: Elaborazioni ONA-CNESPS e *WHO CC Research on Alcohol* su dati dell'Indagine ISTAT Multiscopo sulle famiglie

Relazione al Parlamento, Ministero della Salute, 2015

Rehm *et al. BMC Medicine* 2014, **12**:189
http://www.biomedcentral.com/1741-7015/12/189

Medicine for Global Health

BMC Medicine

OPINION Open Access

Why does society accept a higher risk for alcohol than for other voluntary or involuntary risks?

Jürgen Rehm[1,2,3,4,5*], Dirk W Lachenmeier[5,6] and Robin Room[7,8,9]

Alcol, fumo e altre sostanze
Decessi - 2012

Fumo:	80000
Alcol:	20000
Eroina:	610
Morfina:	8
Cocaina:	2

Baleani e Scapellato, 2014

RISKS

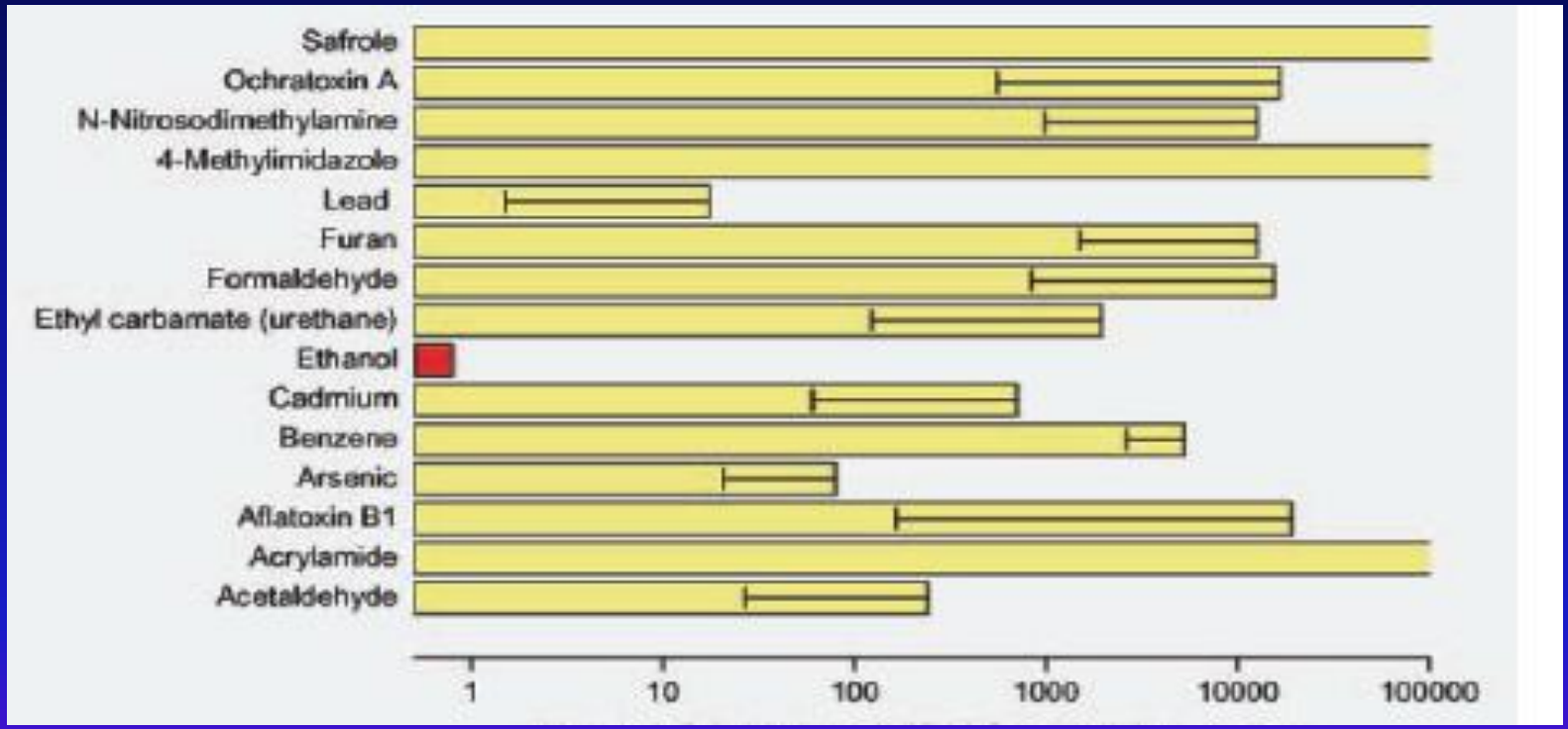
Involuntary risks are associated with activities, conditions or events to which individuals might be exposed without their consent.
Natural disaster (earthquakes, floods…), technology-related risks (bad air quality, contaminated water …)

Voluntary risk is associated with activities in which individuals participate by choice, and where they use their own value system and experience to determine if the risk of a voluntary activity is acceptable to them

… societies tend to accept much higher risks for voluntary behaviours than for involuntary exposure.

Rehm et al, BMC Medicine 2014; 12: 189

MARGIN OF EXPOSURE (MOE)



Lachenmeier and Rehm, Sci Rep 2015

Alcohol consumption (pure alcohol g/day)	Rate of alcohol attributable liver cirrhosis mortality for every 100 000 population	
	M	F
10	5.5	6.2
20	10.0	7.7
30	13.6	8.5
40	16.4	9.0
50	18.7	9.4
60	20.4	9.6
70	21.8	9.8
80	22.8	10.0
90	23.6	10.1
100	24.2	10.2
110	24.6	10.3
120	25.0	10.4
130	25.3	10.4
140	25.5	10.5

CI, confidence interval; M, male; F, female.

Lachenmeier et al, Int J Epidemiol 2011

ACCEPTABLE DAILY INTAKE (ADI) FOR LIVER CIRRHOSIS MORBIDITY AND MORTALITY

ADI= BMDL/UF

2.6 g/day

IPCS: international Programme on Chemical Safety
BMD: brenchmark dose
BMDL: lower one-sided confidence limit of BMD
UF: uncertainly factor

Lachenmeier et al, Int J Epidemiol, 2011

US Environmental Protection Agenct, 1995
EFSA. EFSA J 2005
Bi J, J Food Sci 2010

CONSUMO DI BEVANDE ALCOLICHE IN SOGGETTI SANI

Donna < 10 gr/die — ***Basso rischio***
Uomo < 20 gr/die

one in 1000 deaths *

Donna 11-40 gr/die — ***Consumo Rischioso***
Uomo 21-60 gr/die — **one in 100 deaths ***
> 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 et al, Alcohol Alcohol 2013
**Rehm et al, BMC 2014*

higher than the usually accepted involuntary risk of one in one million !!! *

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

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

TOBACCO, ALCOHOL AND CANCER

Tobacco	Tobacco/ Alcohol	Alcohol
Nasopharynx	Head	Breast
Lung	Oral Cavity	Galbladder
Stomach	Pharynx	Prostate
Kidney	Larynx	Melanoma
Bladder	Esophagus	
Cervix	Colorectum	
Leukemia	Liver	
	Pancreas	

Chin et al, Ann Global Health 2014
Praud et al, Int J Cancer 2016

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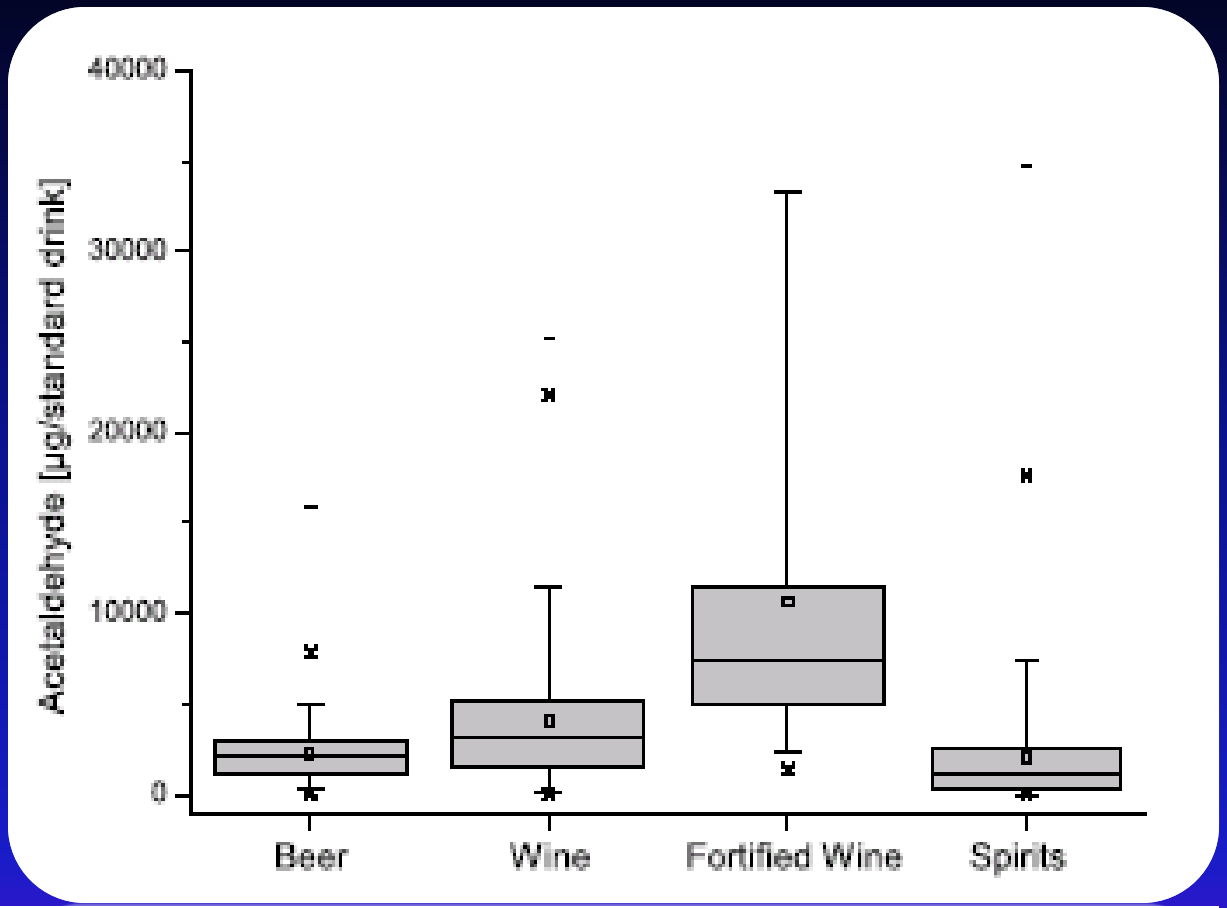
Table: Evidence for carcinogenicity in humans of Group 1 agents assessed



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

D.W. Lachenmeier, Food and Chemical Toxicology 2008

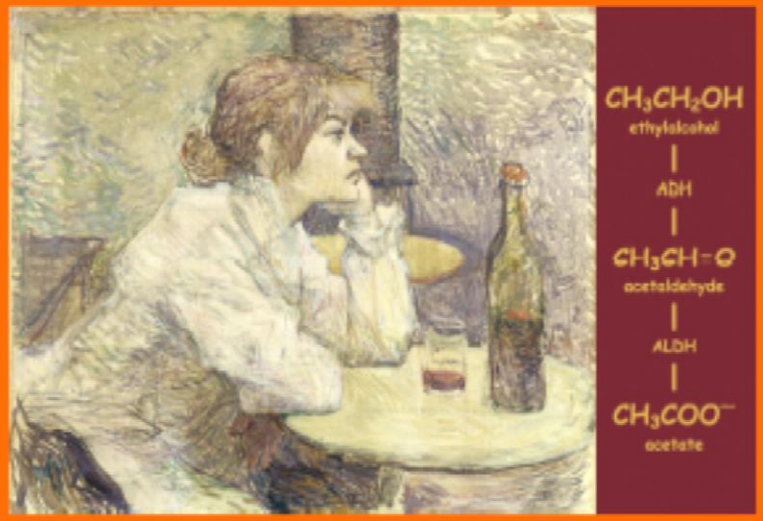
D.W Lachenmeier et al, Addiction 2009

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
	[illegible]			
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

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).

Lachenmeier et al, Int J Cancer 2012; 131: E995-E1003

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 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.

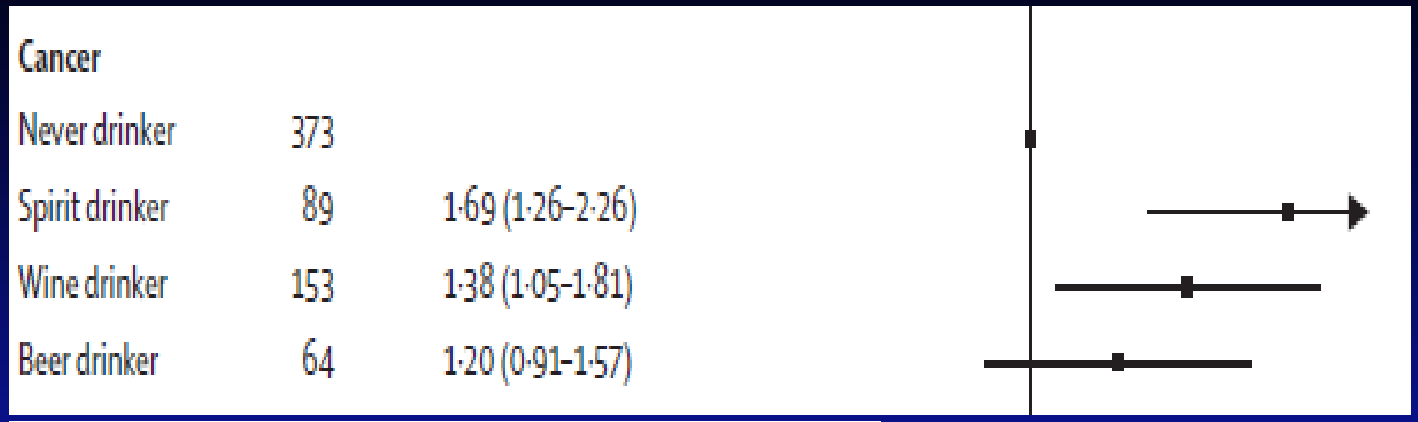
Conclusions. Alcohol remains a major contributor to cancer mortality and YPLL. Higher consumption increases risk but there is no safe threshold for alcohol and cancer risk. Reducing alcohol consumption is an important and underemphasized cancer prevention strategy. (*Am J Public Health.* Published online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

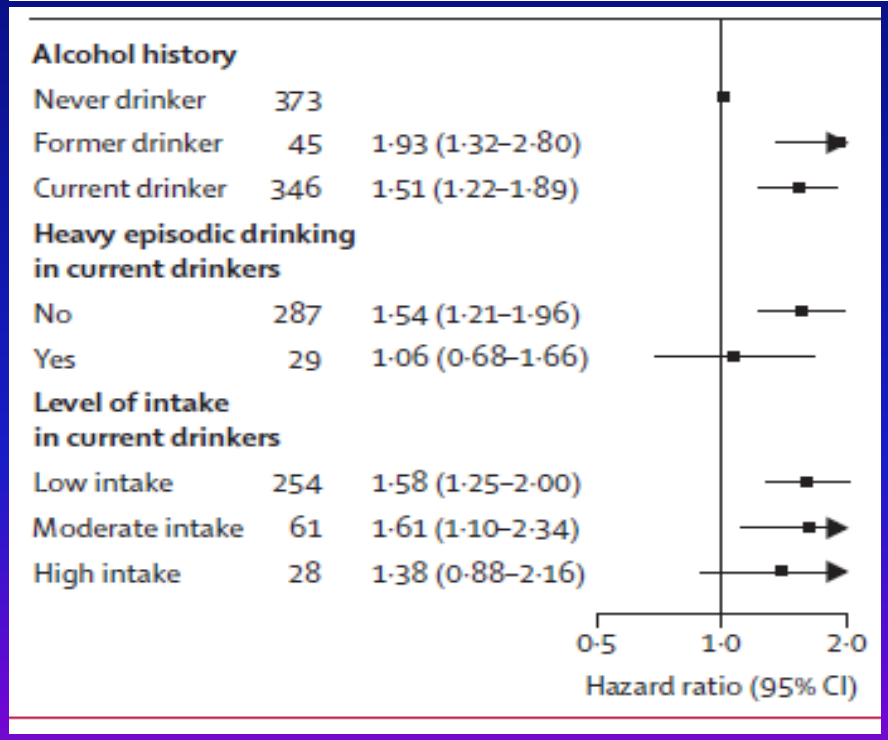
Alcohol use is estimated to account for about 4% of all deaths worldwide.[1] Research over several decades has consistently shown that alcohol increases the risk for cancers of the oral cavity and pharynx, larynx, esophagus, and liver.[2–5] The biological mechanisms by which alcohol induces cancer are 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-

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

ALCOHOL AND CANCER





Smyth et al, Lancet 2015
Rehm, BMJ 2015
Cao et al, BMJ 2015

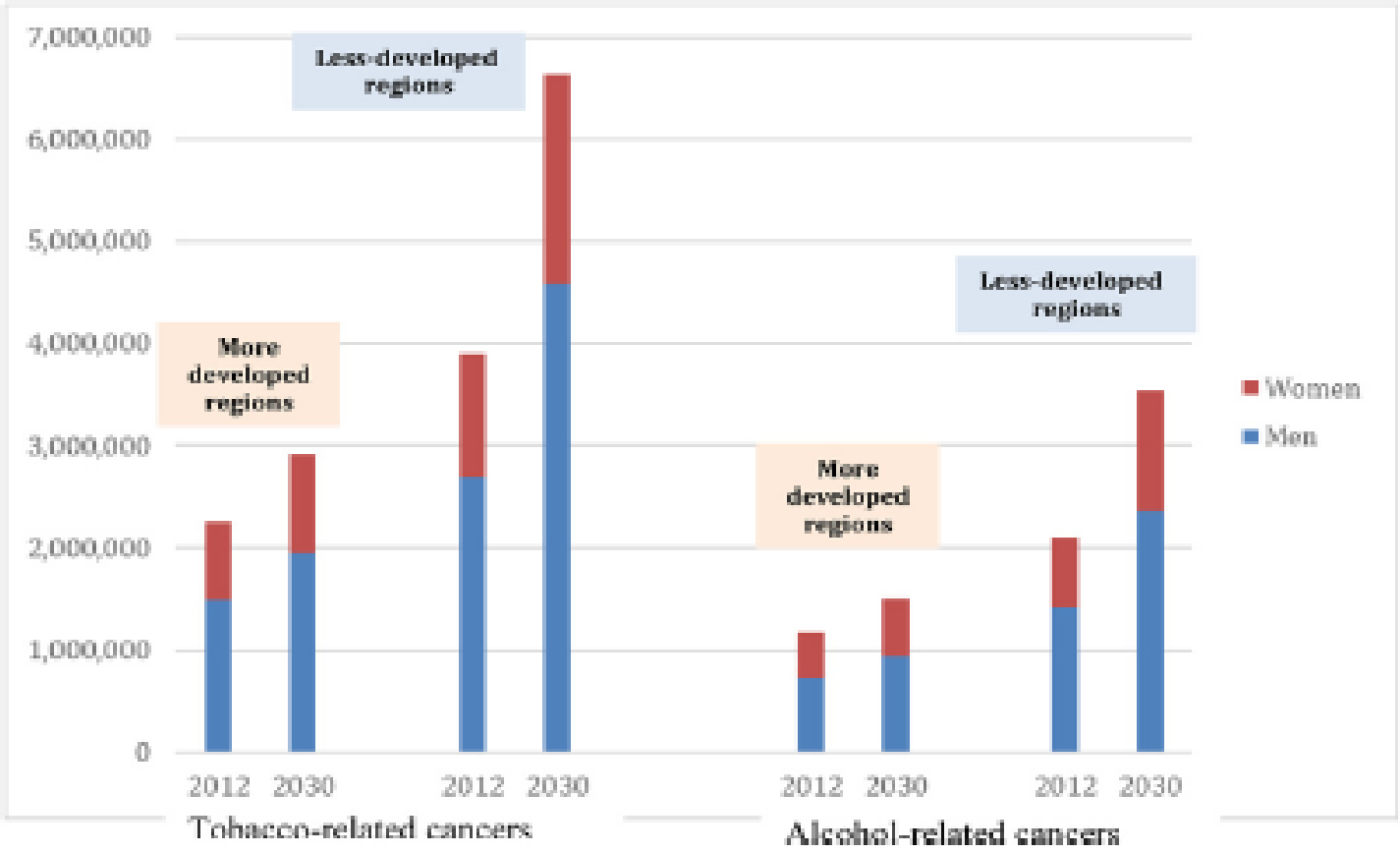


Figure 5. Projections of tobacco- and alcohol-related cancer cases for 2030 for more developed versus less-developed regions.[2]

Lee and Hashibe, Annals of Global Health 2014

ALCOL, STILI DI VITA, CULTURA

DISINFORMAZIONE
IGNORANZA

INFORMAZIONI
ESEMPI

tradizioni/costumi
natura umana

CULTURA
NATURA UMANA

CULTURA
natura umana

Tradizioni/ abitudini tramandate per inerzia. Opinioni accolte acriticamente.

Liberazione dai costumi dannosi.
Si accede ad un corretto funzionamento del ragionamento.
Comportamenti maturi

Protezione che permette un miglioramento globale/ psico-fisico a 360°

Comportamenti affidabili non sopraffatti dalle emozioni e da abitudini magari piacevoli ma dannose

possibile opera incompleta, difettosa

essere umano modellato come un capolavoro.
Da estetica dell'arte a estetica della salute

Modificato da Remotti F., Fare Umanita', Ed. Laterza, Roma 2013

L'estetica della salute: Gianni Testino, Silvia Testino, 2016

ETANOLO: tossico, cancerogeno, teratogeno, droga

CULTURA o TRADIZIONE?

- **Alimento**
- **Normalizzazione**
- **Successo**
- **Benessere** ***(sovrastima del consumo moderato-sociale)***
- **Lobbies**
- **Influenza politica**
- **Mancanza di un linguaggio comune fra i professionisti della salute** ***(non attivazione universitaria insegnamento di alcologia)***

L'estetica della salute, Gianni Testino, Silvia Testino, 2016

… 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

…… moderate drinking (12.5 g ethanol per day for women and 25 g ethanol per day for men) is associated with lower rates of cardiovascular disease but is not uniformly protective for other cardio-vascular conditions and *cancer*

Ronksley et al; BMJ 2011

Alcohol: less is better

Fernandez-Sola, Nature Cardiol 2015

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……

PRUDENCE !!!

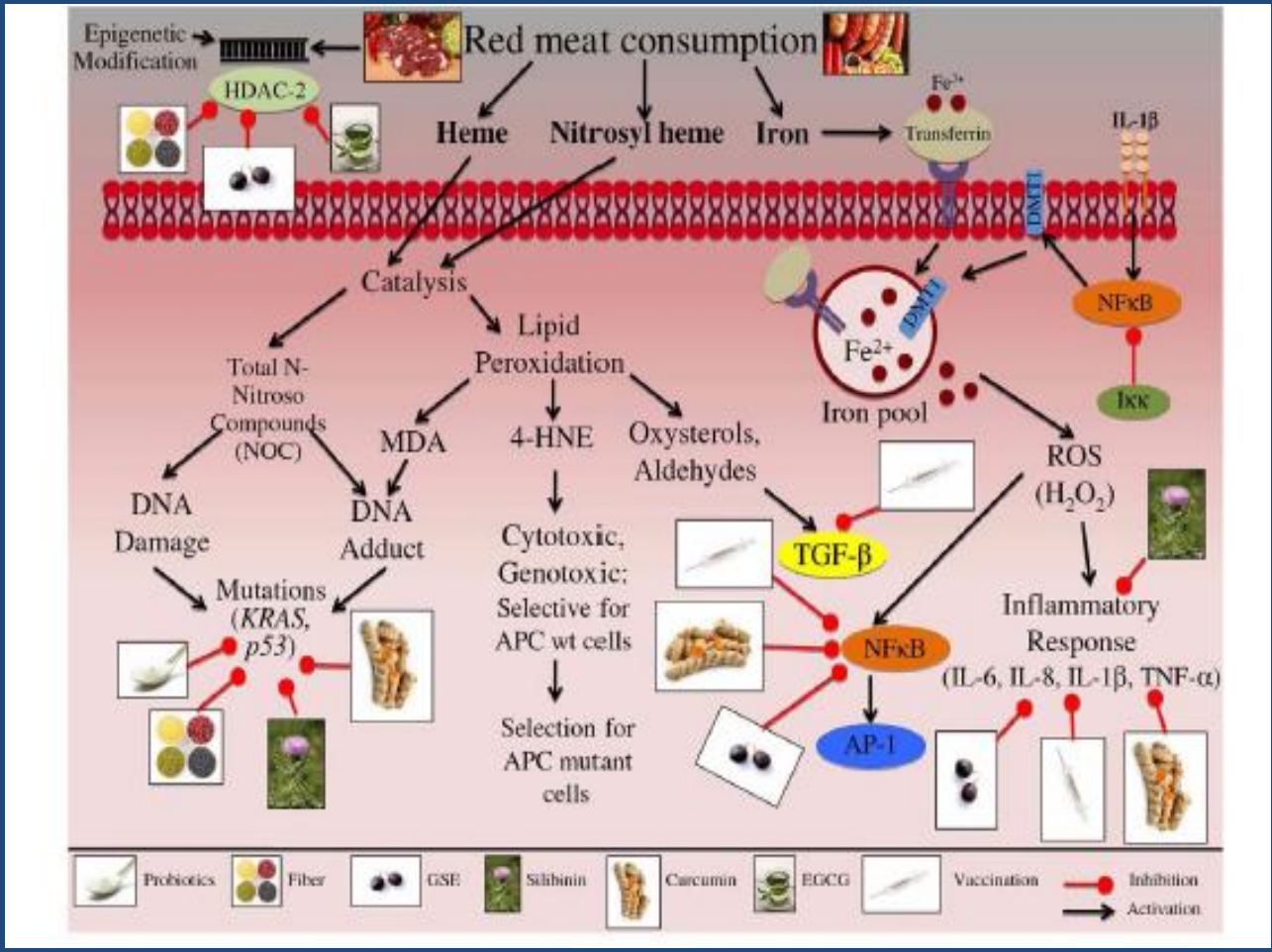
THE IMPACT OF MODERATE ALCOHOL CONSUMPTION ON HEALTH: PRUDENCE

GIANNI TESTINO, SILVIA LONE, ALESSANDRO SUMBERAZ, PAOLO BORRO
Centro Alcologico Regionale - Regione Liguria, Dept. of Internal Medicine, IRCCS AOU San Martino-IST, Genova, Italy

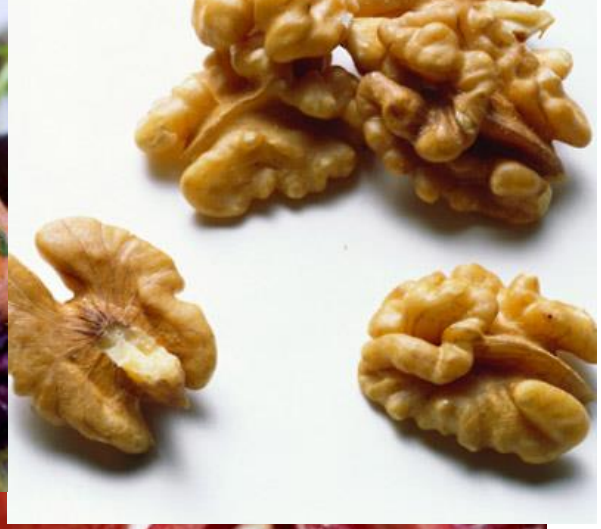
The prudent physician or cardiologist should update the patient with these scientific data. Moderate doses of ethanol (the so called "protective doses") increase the risk of neoplasia[21, 22].

Testino et al, Acta Mediterranea Medica 2015

COLORECTAL CANCER



Derry et al, Frontiers in Oncology 2013

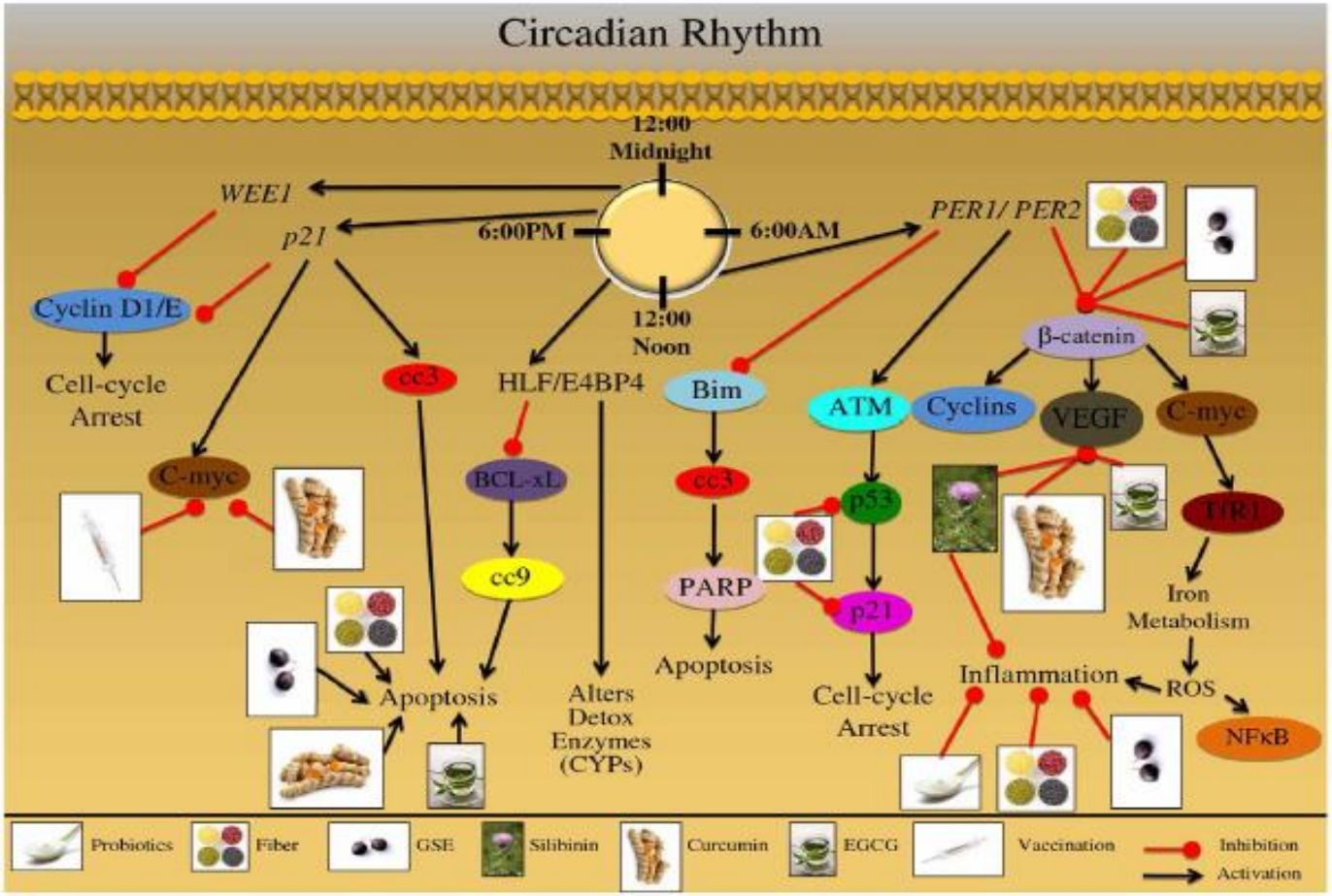





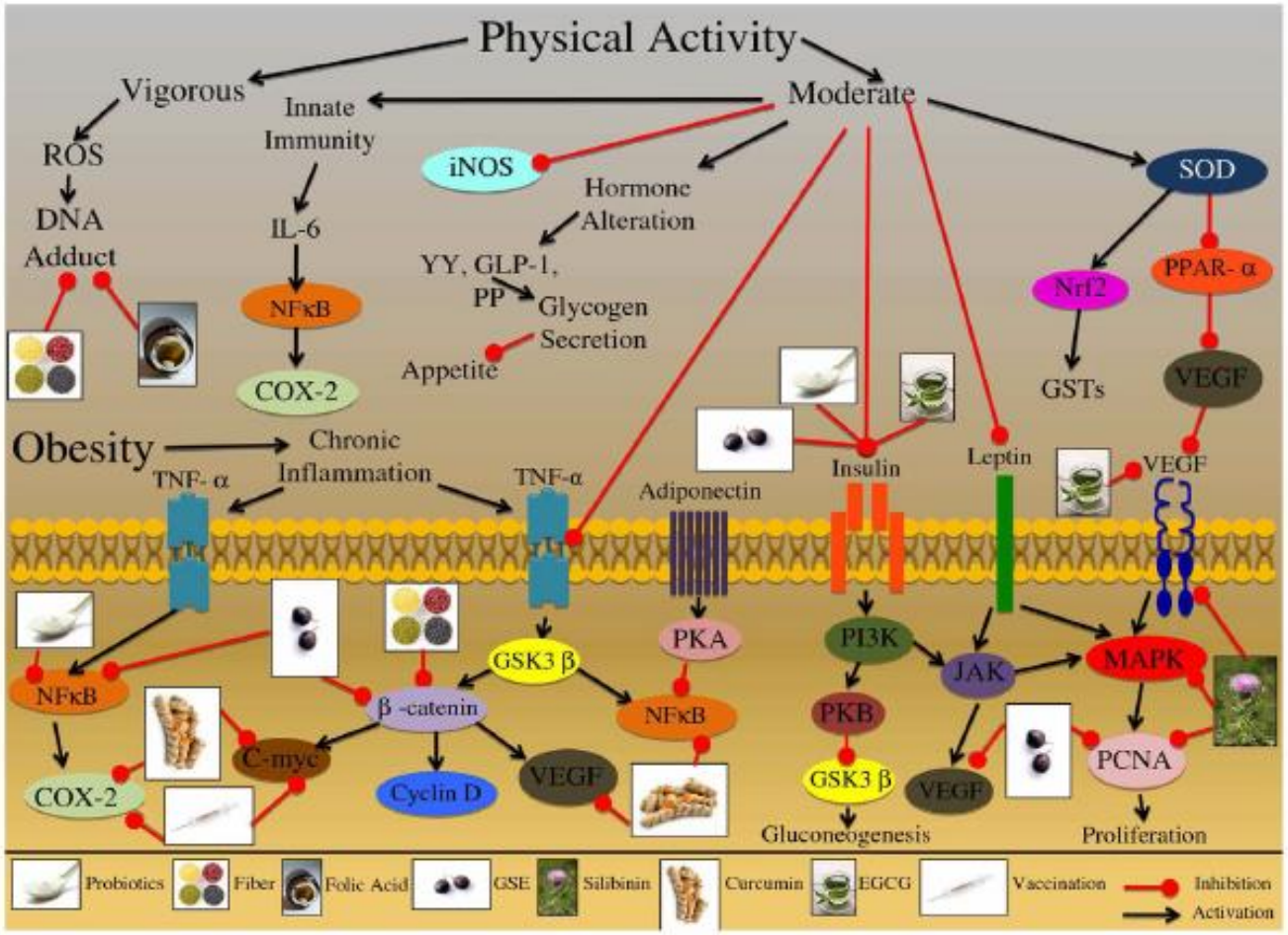




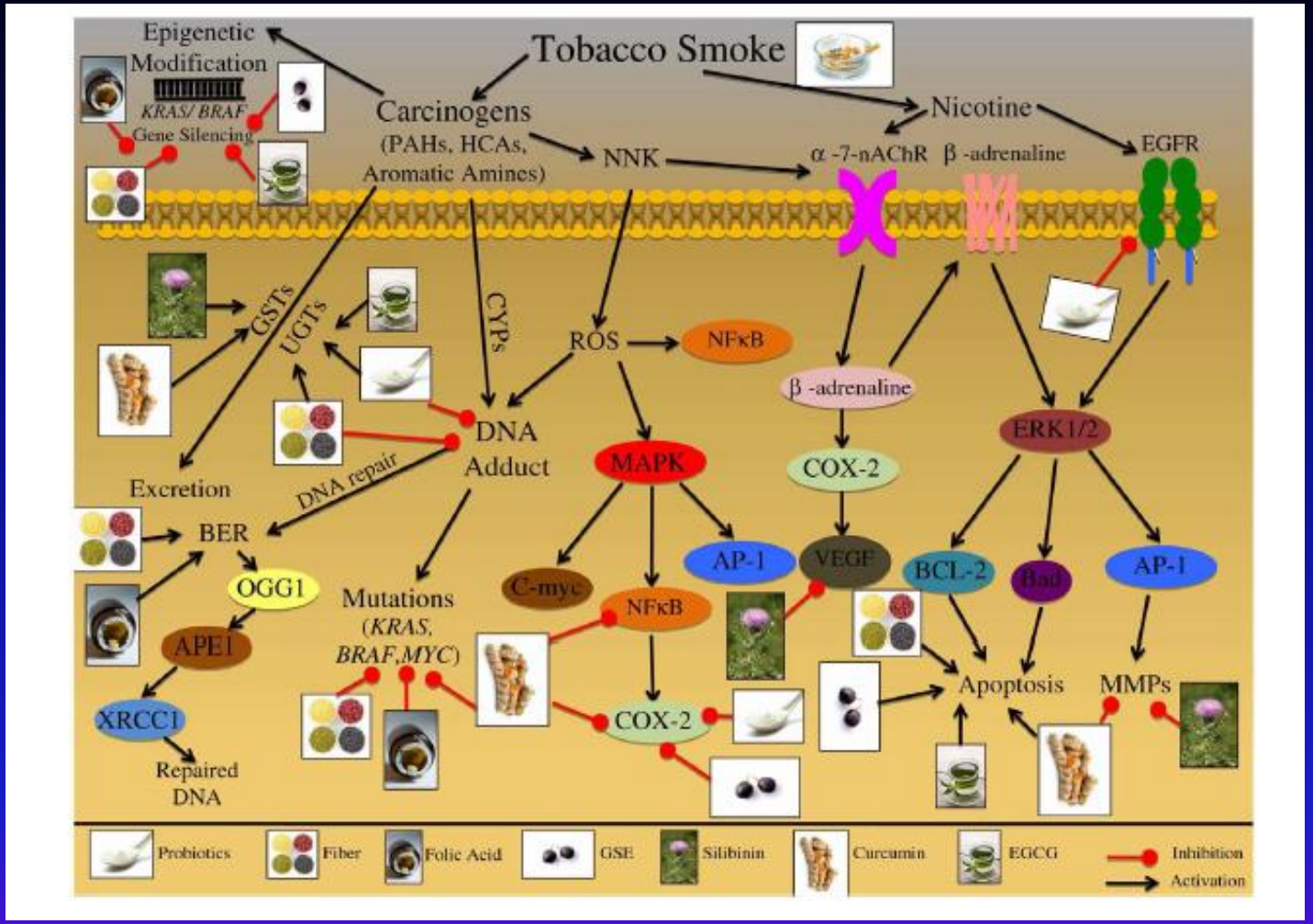

GS Sukkar, Corso Aziendale San Martino-IST, Genova, 05/04/2016



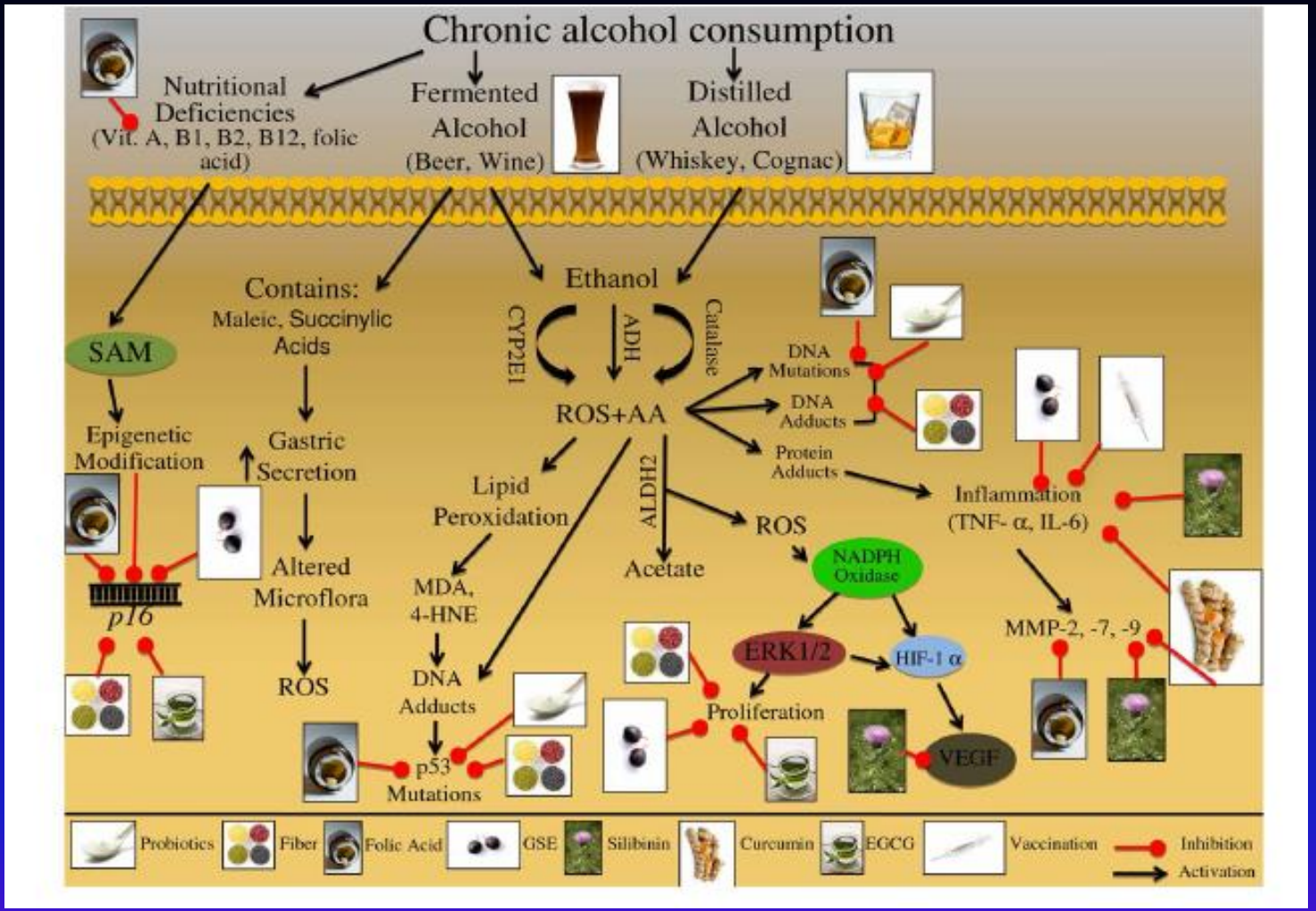
Derry et al, Frontiers in Oncology 2015



Derry et al, Frontiers in Oncology 2015

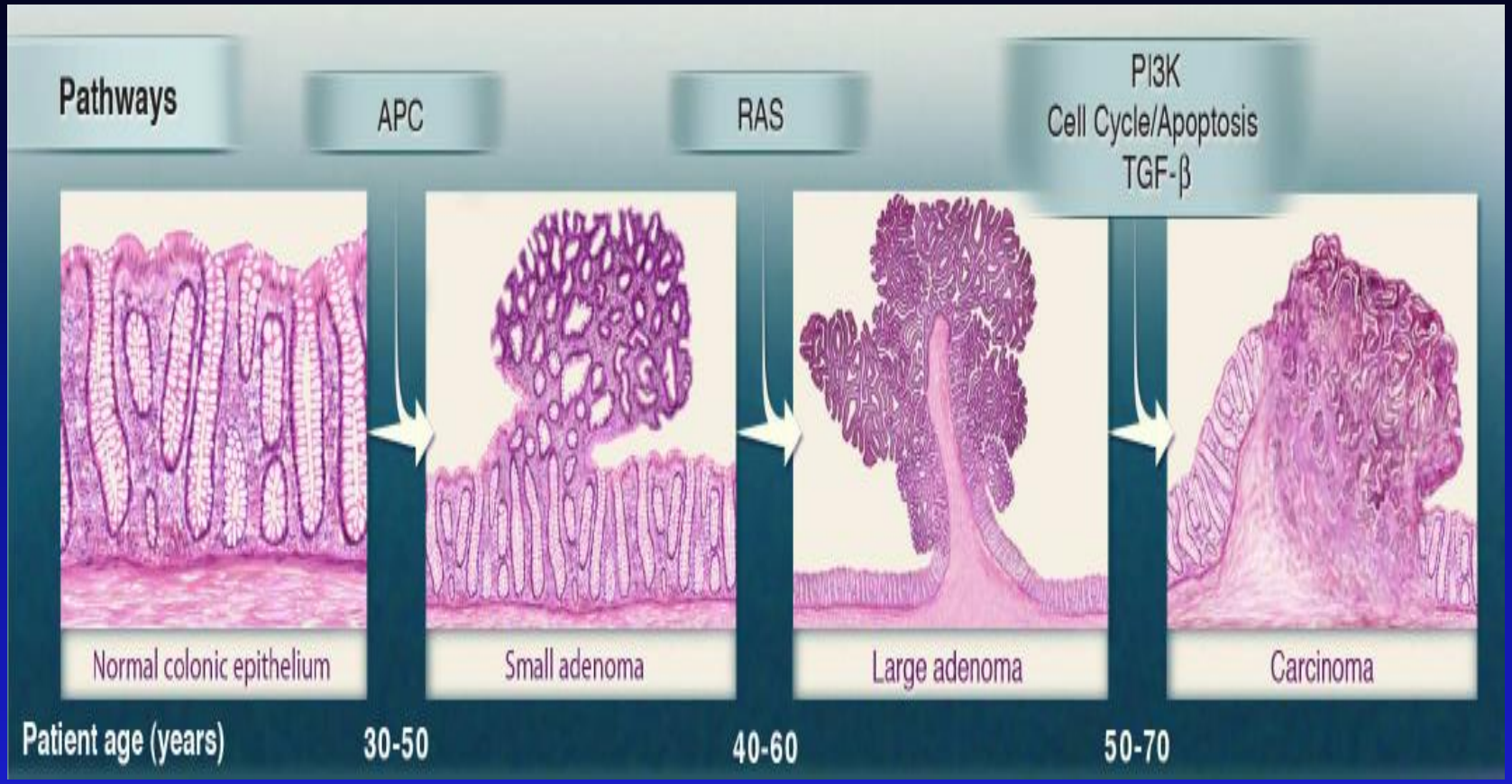


Derry et al, Frontiers in Oncology 2015



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

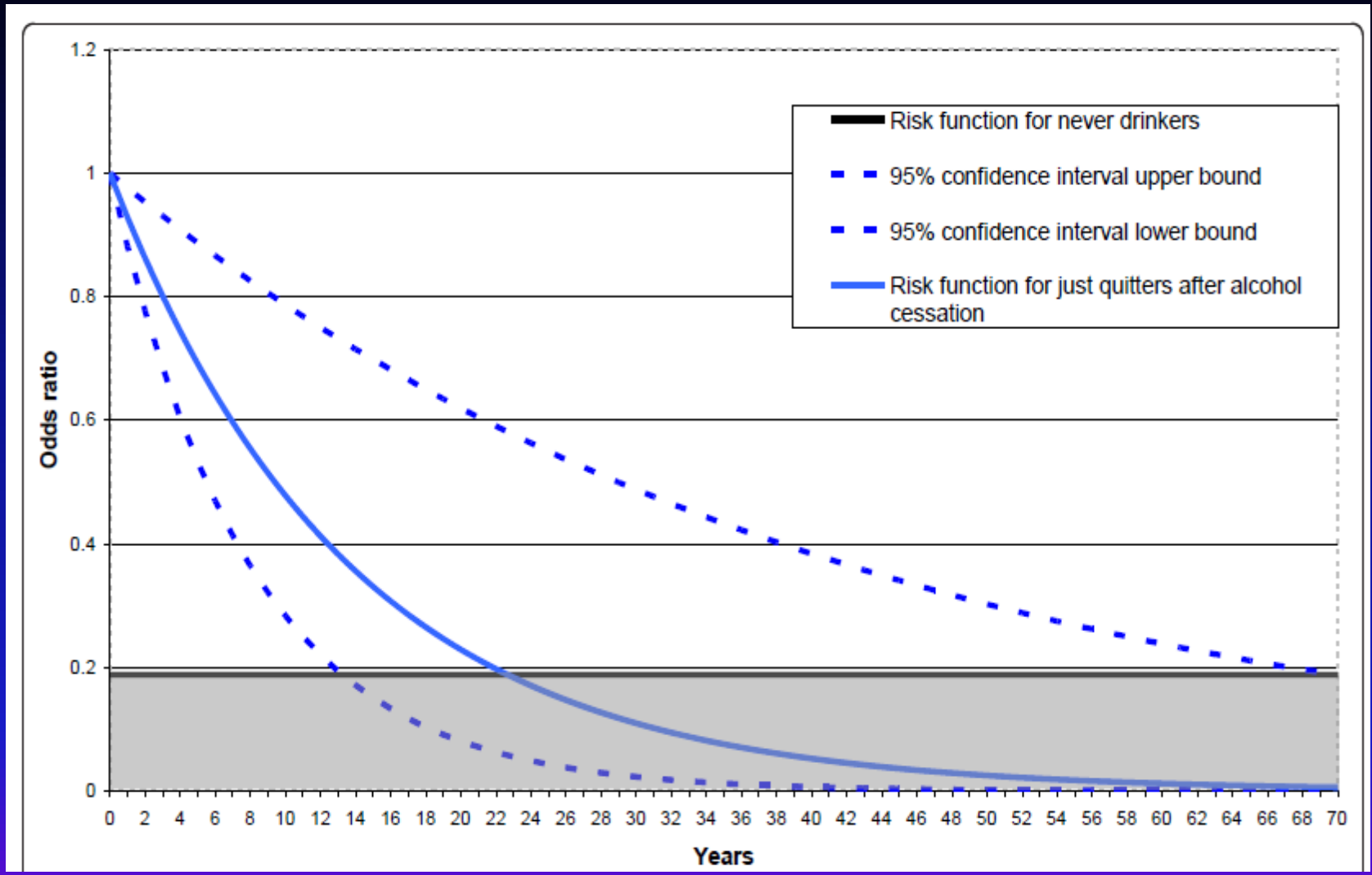


Volgelstein et al, Science 2013

Social Consumption (20-30 gr/die)

Testino, 2011

HEPATOCELLULAR CARCINOMA



Heckley GA et al, BMC Cancer 2011

DELAYED DIAGNOSIS OF HCC WITH ALCOHOLIC LIVER DISEASE

Table 3. Tumor stage at diagnosis of HCC with respect to chronic liver disease etiology (p = 0.186)

	Alcoholic liver disease		Viral hepatitis	
BCLC class	n	%	n	%
A	44	14.6	20	22.0
B	92	30.5	32	35.2
C	132	43.7%	31	34.1
D	34	11.3	8	8.8

Schutte et al, Liver Cancer 2012

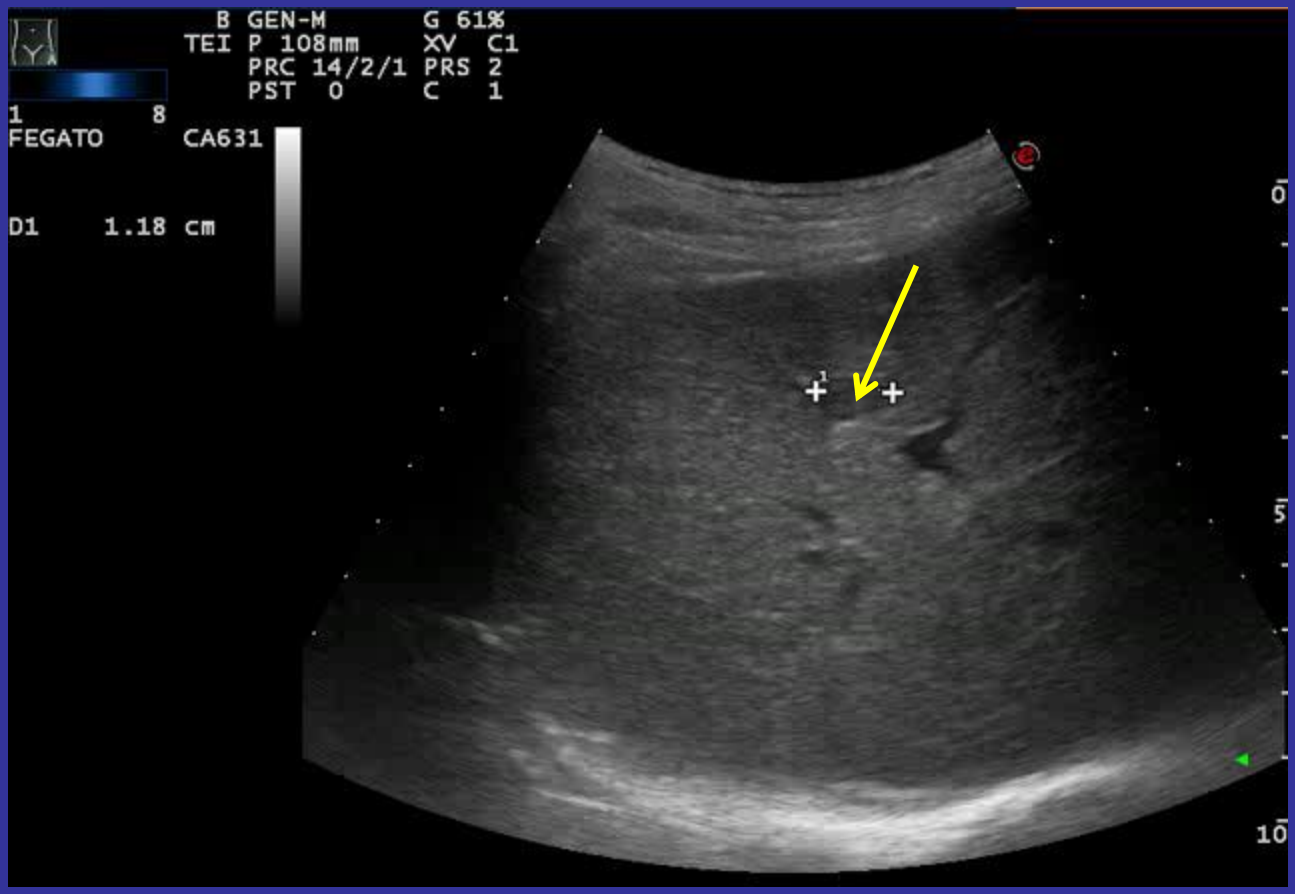
Application of hepatocellular carcinoma surveillance in a European setting. What can we learn from clinical practice ?

In a European setting, only 22% of HCCs were diagnosed by surveillance, and in more than one-third of cases, surveillance was indicated but missed.

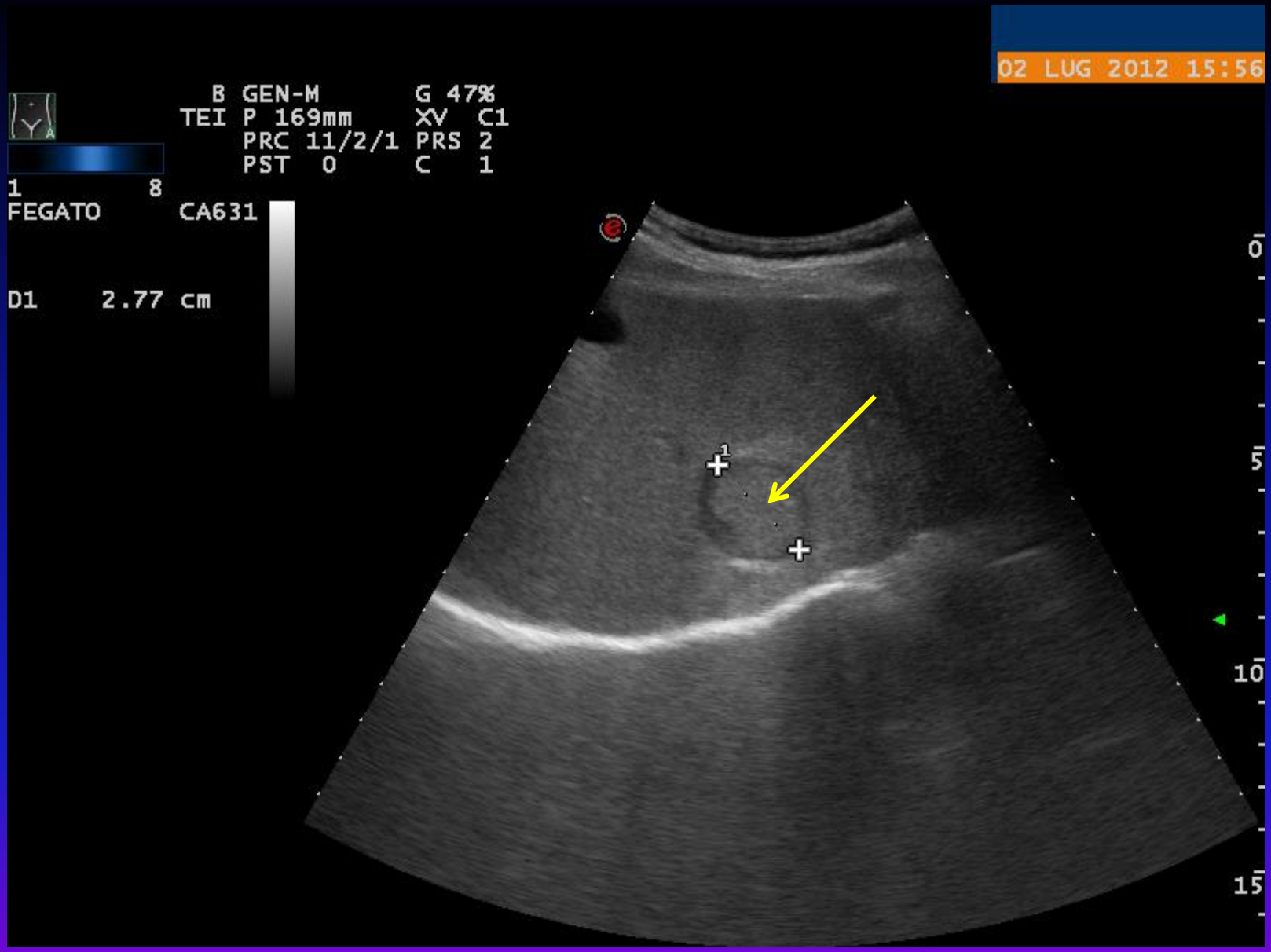
NAFLD and alcoholic liver disease were associated with deficient surveillance.

Survival was significantly better in patients who underwent surveillance compared with those in whom surveillance was missed although indicated.

Edenvik P et al, Liver Int 2015



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



Paolo Borro – Centro Alcologico Regionale Ligure, IRCCS Ospedale 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

ETANOLO: tossico, cancerogeno, teratogeno, droga

CULTURA o TRADIZIONE?

- Alimento
- Normalizzazione
- Successo
- Sport

PUBBLICITA'/ GIOVANI

- Benessere *(sovrastima del consumo moderato-sociale)*
- Lobbies
- Influenza politica
- Mancanza di un linguaggio comune fra i professionisti della salute *(non attivazione universitaria insegnamento di alcologia)*

L'estetica della salute: Gianni Testino, Silvia Testino 2016

BRAIN MATURATION (I)

Adolescent brain undergoes extensive morphometric and functional maturation involving decreases in gray matter and increases in white matter volume

Pfefferbaum et al, Arch Neurol 1994; Giedd, Ann New York Ac Sci 2004

Cross-sectional studies have shown that cortical gray matter volume reduction begins during preadolescence.
Related to pruning of excess neurons, changes in the extracellular matrix and white matter encroachment (posterior brain region → anterior regions)

Paus, Trends in Cognitive Science; Gogtay et al, Proc Nat Ac Sci 2004

Cortical gray matter decreases in dorsal prefrontal cortical volume continuing into early adulthood (mid-20s)

Sowell et al, J Neurosci 2001

White matter volume increases over adolescent, due to in part to myelinization of white matter tracts and axonal extension for connectivy

Giedd et al, Nature Neuroscience 1999

BRAIN MATURATION (II)

….neural processes are integral components of functional development, creating localized and enhanced efficient information processing required for mature complex cognitive and motor abilities

Squeglia et al, J Intern Neuropsychol Society 2013

-Deleterious effects of exogenous agents, including alcohol

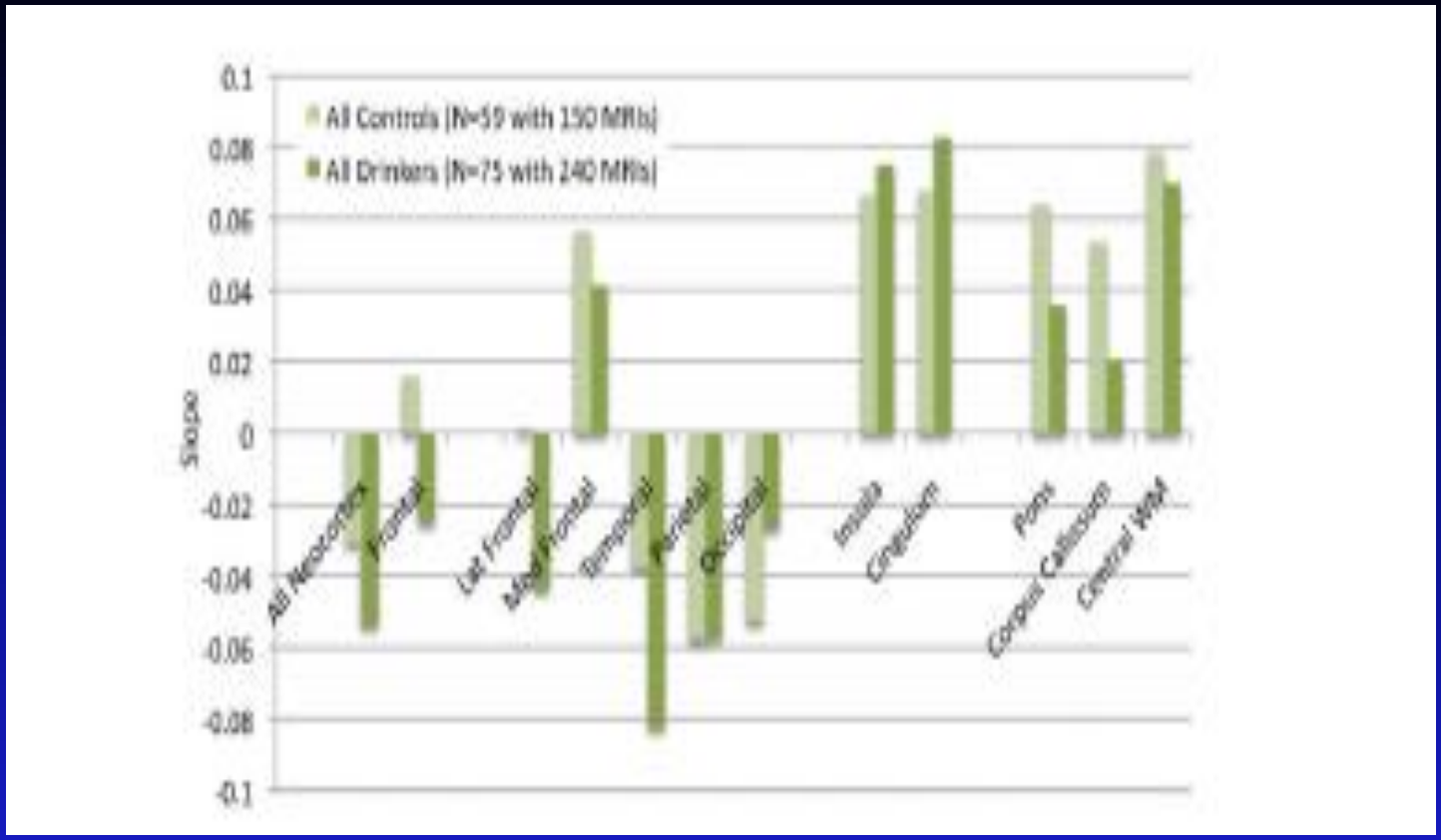
Jacobus and Tapert, Ann Rev Clin Psychol 2013

Controlled longitudinal study (dynamic neural events, 17 → 19 years): accelerated cortical thinning of right middle frontal gyrus and decreased white matter volume subjacent to precentral gyral and middle temporal gyral cortices (Luciana et al, Am J Drug Alcohol Abuse 2013)

-15 → 18: greater volume reduction in the left ventral diencephalon, left inferior and middle temporal gyrus, and left caudate

Squeglia et al, Developmental and Cognitive Neuroscience 2014

alcohol drinking alters the traiectories ?



I volumi neocorticali si riducono fisiologicamente nei non bevitori e nei bevitori. Nei bevitori questo decremento e' significativamente accentuato.
L'accrescimento del corpo calloso e CWM e' ridotto significativamente rispetto ai non bevitori.

Squeglia et al, Am J Psychiatry 2015

dispensano piacere → **ricordo proteina resistente Cpeb (ippocampo) ***

attivazione apparato muscolo-scheletrico → ci si procura sostanza

consentire/ negare aurorizzazione

riattivato da stimoli ambientali: questa memoria vive dentro di noi, ma e' indipendente da noi. Ubbidisce unicamente a se stessa (Marcel Proust)

→ *I ricordi da sostanze non naturali sono straordinariamente intensi / traduzione chimica molto resistente → irrazionalita' comportamentale (impossibile opporsi)* (*L. Gallimberti, 2013*)

L. Gallimberti, Morire di Piacere, BUR Rizzoli, Milano 2012

IN RAPPORTO ALLO SVILUPPO NEUROLOGICO

STRATEGIA: POSTICIPARE IL PIU' POSSIBILE IL PRIMO CONTATTO CON IL CERVELLO DEI GIOVANI CON ETANOLO E NICOTINA

SE IL CONSUMO AVVENISSE DOPO I 20 ANNI (meglio dopo i 25 anni):

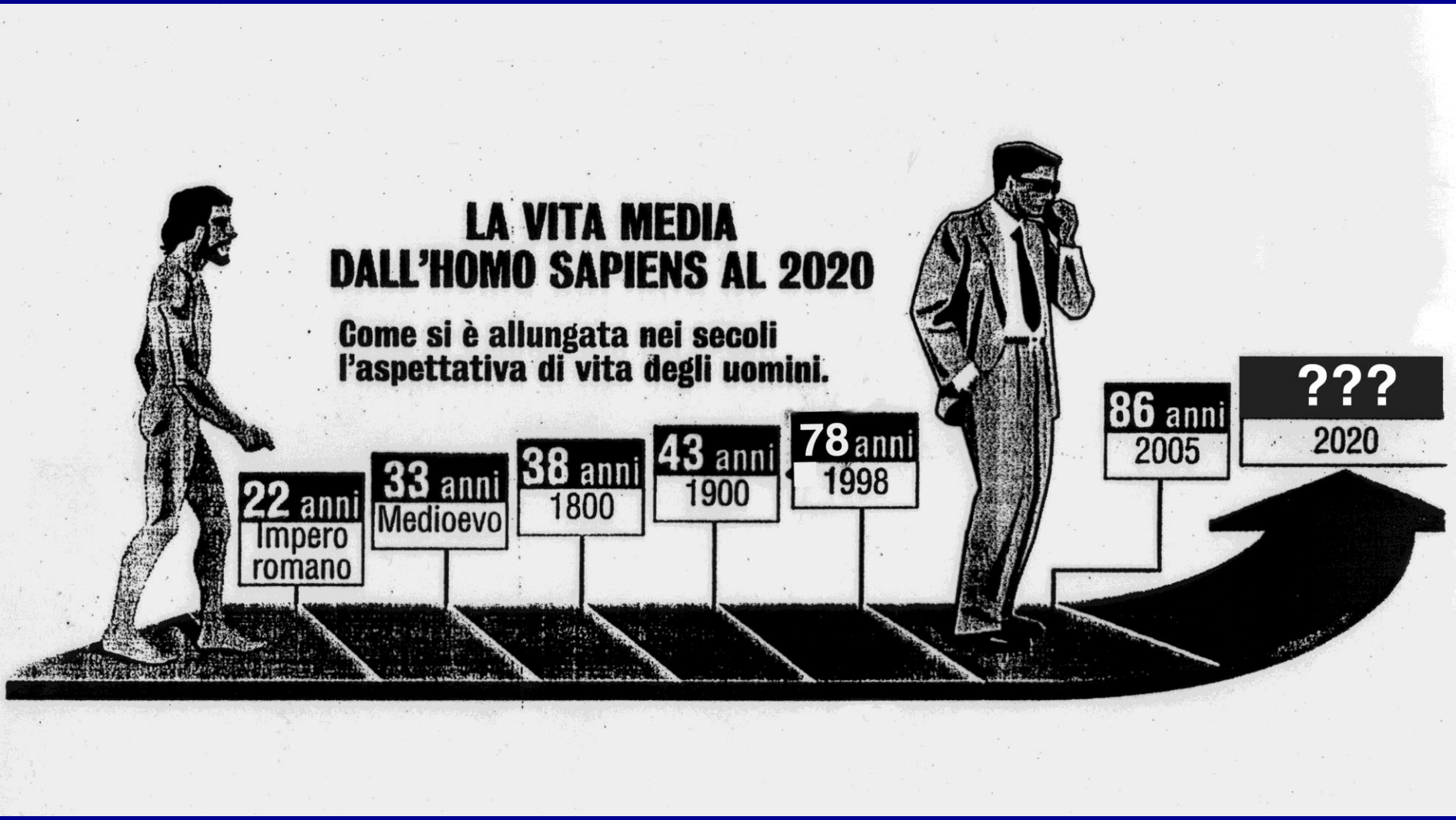
- *Dipendenza «rara»*
- Minori danni organici
- Anni di vita vissuti liberi da malattia aumentati in modo significativo

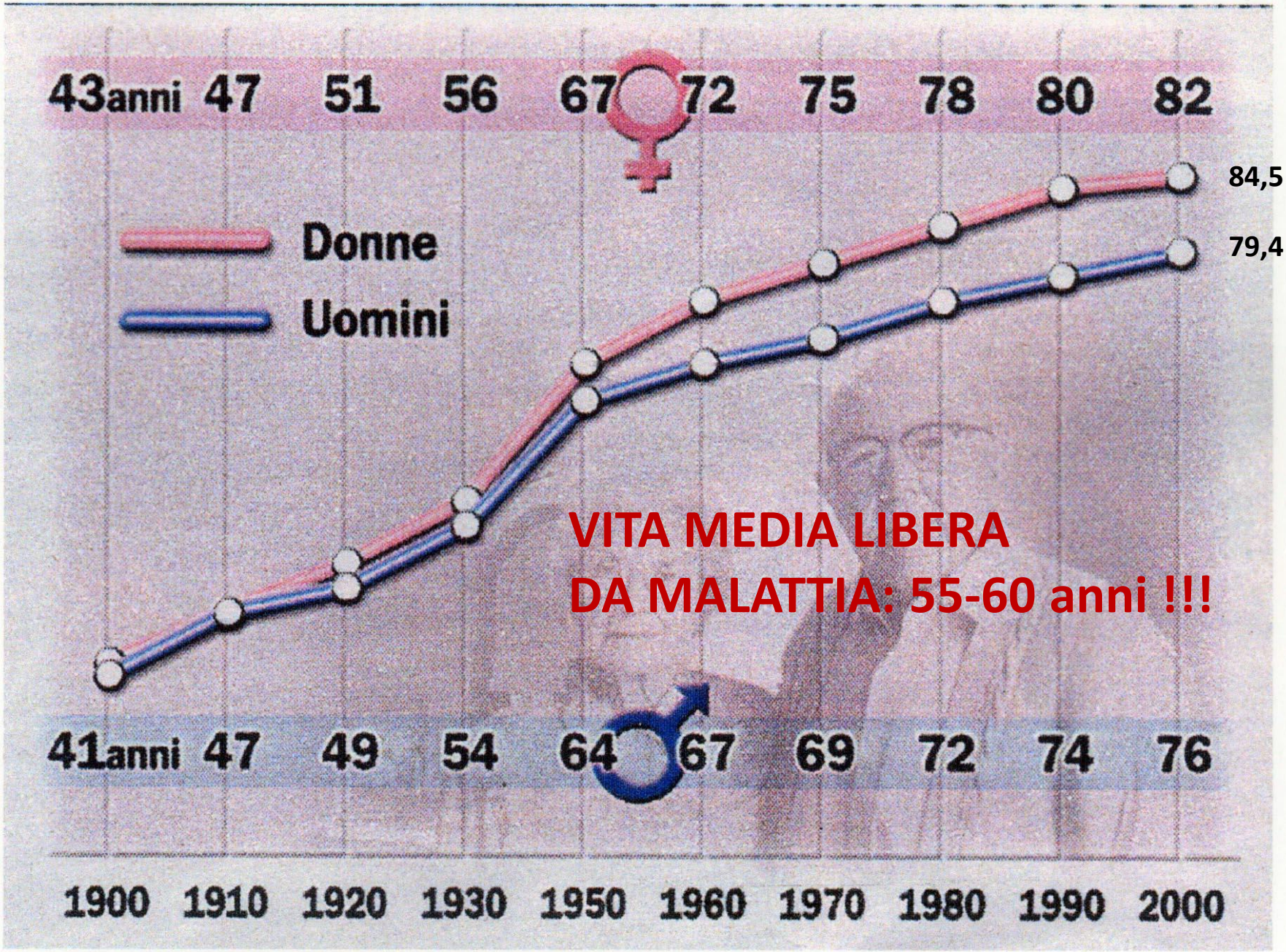
P. Shaw et al, 2008; L. Gallimberti, 2013

Se primo consumo sotto i 15 anni 38% di rischio di evolvere in dipendenza →

rischio cala al 10% all'eta' di 21 anni ed e' sotto il 10% dopo i 25 anni

Silveri MM, Pharmacol Ther 2014; 143: 197-216


LA VITA MEDIA
DALL'HOMO SAPIENS AL 2020
Come si è allungata nei secoli
l'aspettativa di vita degli uomini.
22 anni
Impero romano
33 anni
Medioevo
38 anni
1800
43 anni
1900
78 anni
1998
86 anni
2005
???
2020


43anni 47 51 56 67 72 75 78 80 82
84,5
79,4
Donne
Uomini
VITA MEDIA LIBERA
DA MALATTIA: 55-60 anni !!!
41anni 47 49 54 64 67 69 72 74 76
1900 1910 1920 1930 1950 1960 1970 1980 1990 2000

PROMOZIONE DELLA SALUTE

La promozione della salute è la Scienza che, attraverso il coinvolgimento consapevole e responsabile del cittadino, favorisce scelte utili al massimo potenziamento della salute del singolo e della collettività.

EDUCAZIONE ALLA SALUTE

Consiste in un processo educativo permanente nei confronti della salute, che da un lato richiede la conoscenza dei rischi, dall'altro necessita della consapevolezza delle responsabilità nella difesa del proprio equilibrio psicofisico considerato come un diritto-dovere dell'individuo e di tutta la collettività.

Drug and Alcohol Review (July 2009), 28, 426–435
DOI: 10.1111/j.1465-3362.2009.00055.x

REVIEW

Warnings on alcohol containers and advertisements: International experience and evidence on effects

CLAIRE WILKINSON[1] & ROBIN ROOM[1,2]

[1]*AER Centre for Alcohol Policy Research, Turning Point Alcohol and Drug Centre, Melbourne, Australia, and* [2]*School of Population Health, University of Melbourne, Melbourne, Australia*

2 Evaluations of the effect of alcohol warning labels are limited to the US experience with labels implemented in 1989. Although there is some limited evidence of effects on knowledge and attitudes, there is only slight evidence of any effects on drinking behaviour. In contrast to this, the tobacco labelling experience offers strong evidence that warning labels can be effective not only in increasing information and changing attitudes, but also in affecting behaviour.

3 Unlike current cigarette warnings, alcohol warning labels have been extremely limited in scope. To use the terms of Ferrence *et al.* [29], warnings are often 'vague and equivocal' rather than 'specific and unambiguous'. Alcohol warnings have not been presented 'in a vivid manner that evokes an emotional reaction'. The Swedish warning labels on advertisements seem to be the single example in the alcohol field of rotating warnings; otherwise a single warning has been used, which will not continue to catch attention. It is not surprising in these circumstances that no effectiveness in changing behaviour has been showed for alcohol warning labels.

SciMedCentral

Annals of Public Health and Research

Review Article

Alcohol Consumption and Cancer: A Literature Search and a Proposal

Gianni Testino[1,2]*, Silvia Leone[3], Valentino Patussi[2,4], Patrizia Balbinot[1,2], Tiziana Fanucchi[2,4], Alessandro Sumberaz[1,2], Emanuele Scafato[2,5] and Paolo Borro[1,2]

[1]Centro Alcologico Regionale – Regione Liguria, IRCCS AOU San Martino-IST, Italy
[2]World Health Organization Collaborating Centre for Research and Health Promotion on Alcohol and Alcohol-related Health Problems, Istituto Superiore di Sanita, Italy
[3]School of Toxicology, University of Genoa, Italy
[4]Centro Alcologico Regionale Toscano, AOU Careggi, Italy
[5]National Institute of Health, Italy

***Corresponding author**
Gianni Testino, Centro Alcologico Regionale – Regione Liguria, Padiglione 10, IRCCS AOU San Martino-IST (National Institute for Research on Cancer), Piazzale R. Benzi 10, 16132 Genova, Email: gianni.testino@hsanmartino.it

Submitted: 01 December 2015

Accepted: 18 January 2016

Published: 19 January 2016

Keywords

- Alcohol
- Cancer
- Carcinogenesis
- Prevention

Like tobacco and asbestos …… alcohol could cause cancer.
The more you drink and the more often you drink….. The more you increase your risk (UK TV).

There was general consensus in the scientific and medical communities that the consumption of alcohol could increase an individual's risk of developing particular cancer, such as cancer of the breast, larynx and oesophagus.

Crowe et al, BMJ 2011; Gornall, BMJ 2015

Miller et al. BMC Public Health (2016) 16:139
DOI 10.1186/s12889-016-2812-8

BMC Public Health

RESEARCH ARTICLE Open Access

Message on a bottle: are alcohol warning labels about cancer appropriate?

Emma R. Miller[1*], Imogen J. Ramsey[1], Genevieve Y. Baratiny[2] and Ian N. Olver[3]

…. the wider literature and our own findings suggest they might produce only limited effects on drinking behaviour on their own.

To maximise impact, warning labels should be considered for use in conjunction with other avenues for prevention, and incorporated into *multi-faceted health campaigns.*

BMC Public Health 2016

The effect of cancer warning statements on alcohol consumption intentions

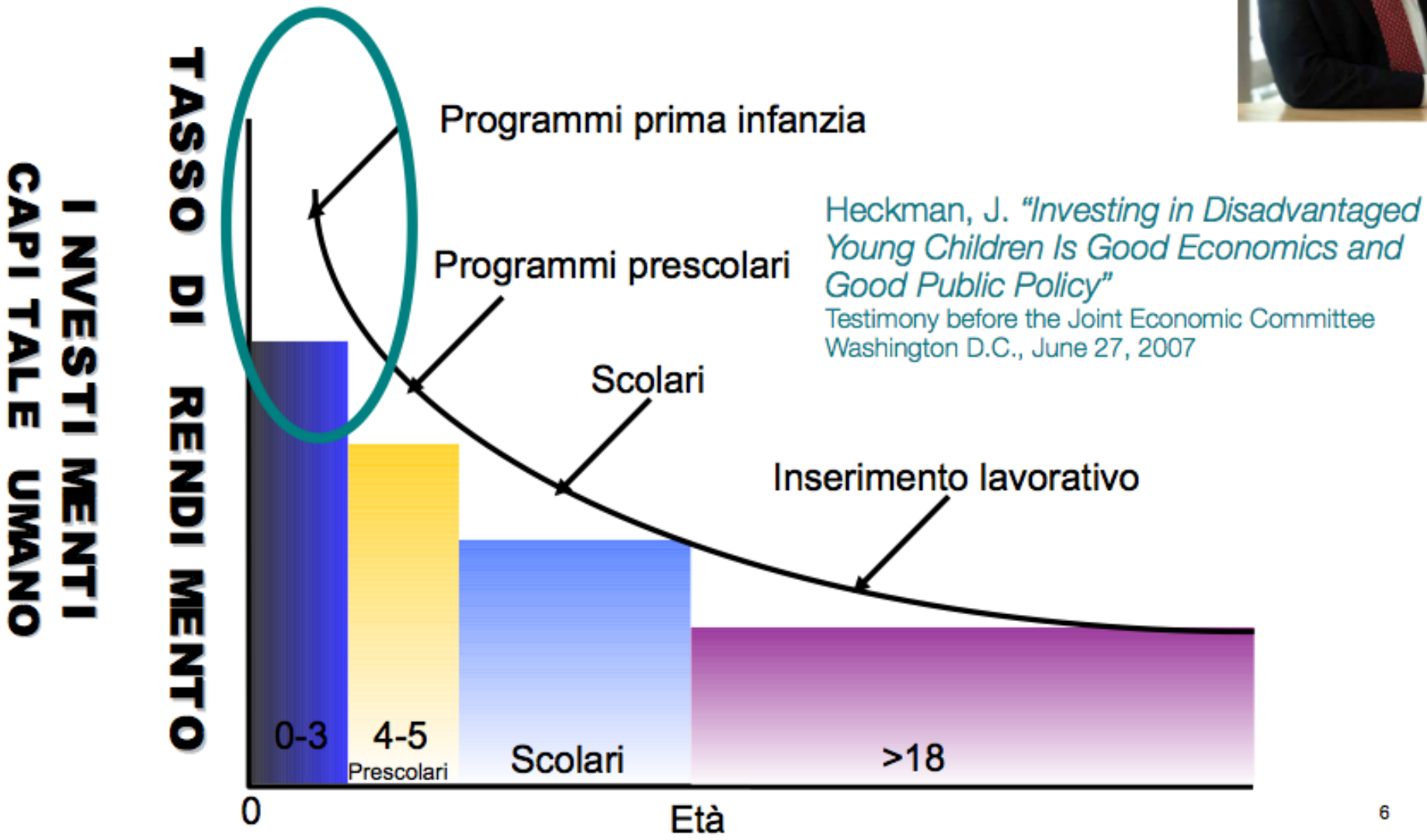
Simone Pettigrew[1]*, Michelle I. Jongenelis[1], David Glance[2], Tanya Chikritzhs[3], Iain S. Pratt[1,4], Terry Slevin[1,4], Wenbin Liang[3]and Melanie Wakefield[5]

… warning statements in isolation cannot be expected to result in substantial changes in behaviour and instead require reinforcement via other forms of information, such as via general practitioners and education …..

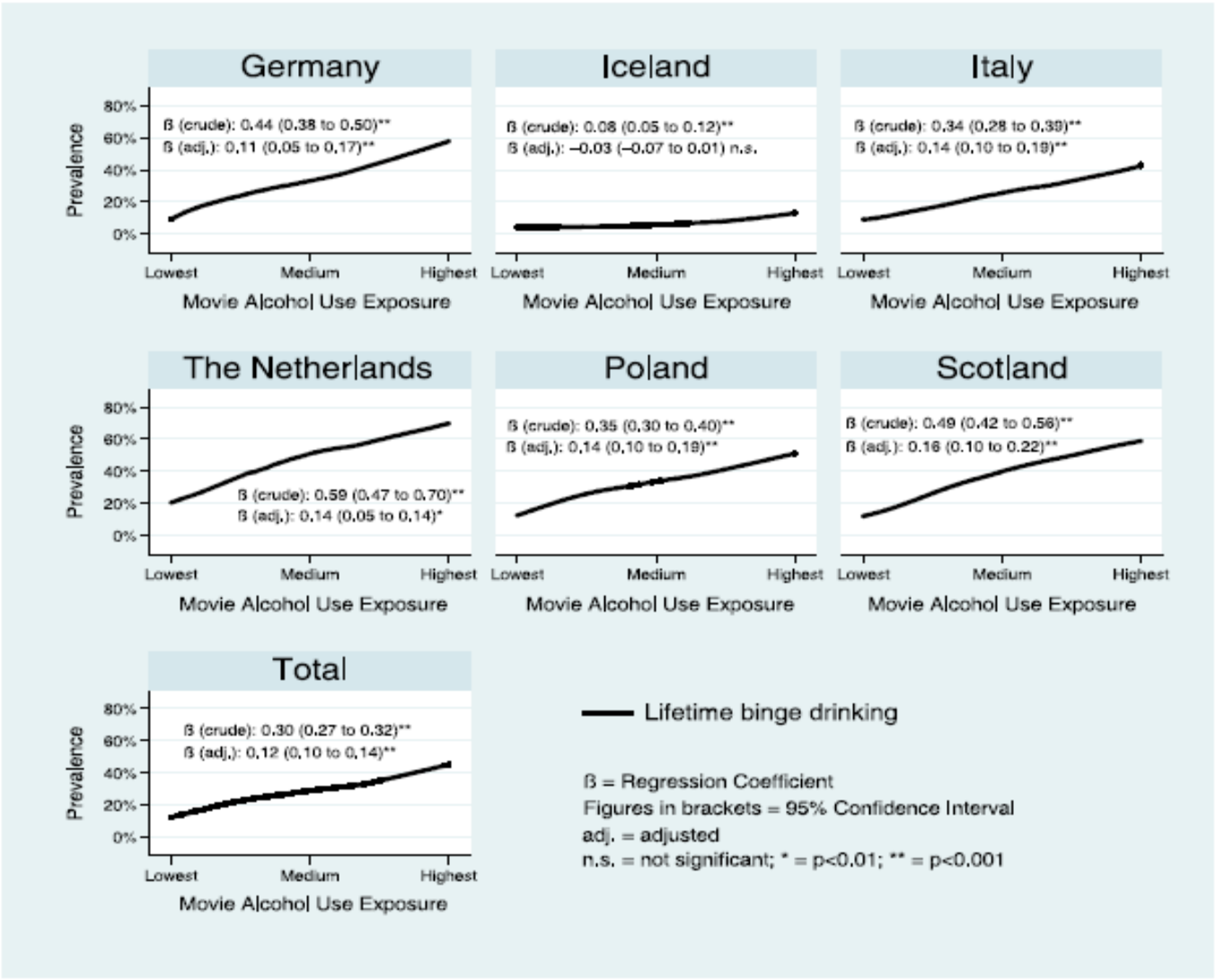
… cancer warning statements have the potential to play an important role in public *education programs* designed to inform drinkers of the long-terms harms associated with alcohol consumption and encourage behavioral change.

Health Education Research 2016; 31: 60-9

POLITICHE SOCIALI



Heckman, J. *"Investing in Disadvantaged Young Children Is Good Economics and Good Public Policy"*
Testimony before the Joint Economic Committee
Washington D.C., June 27, 2007



Hanewinkel et al, Pediatrics 2012

Table 1. **Whole School, Whole Community, and Whole Child (WSCC) Components by Category**

WSCC Components	Categories
• Physical education and physical activity • Nutrition environment and services • Health education	Supporting healthy student behaviors
• Health services • Counseling, psychological, and social services • Employee wellness	Supporting school health services
• Social and emotional school climate • Physical environment	Supporting safe and positive school environments
• Family engagement • Community involvement	Supporting the engagement of family and community

ASCD, Centers for Disease Control and Prevention. Available at: http://www.ascd.org/ASCD/pdf/siteASCD/publications/wholechild/wscc-a-collaborative-approach.pdf Accessed on July 7, 2015

WHOLE SCHOOL, WHOLE COMMUNITY, WHOLE CHILD MODEL
ACADEMIC ACHIEVEMENT

→ **eta' 3-18 anni**

Physical education/ physical activity
(4 meta-analyses, 15 systematic review, 9 unstructured literature reviews)

Nutrition
(2 meta-analyses, 9 systematic review, 3 unstructured literature reviews)

Health education
(6 systematic reviews, 2 unstructured literature reviews)

Pro-social behaviour **(Rasberry et al, Prev Med 2011)**

ACADEMIC ACHIEVEMENT: academic performance, educational behaviour, cognitive ability and attitude (attention, memory, mood …)

Hawkins et al, Arch Pediatr Adolesc Med 2008

PHYSICAL EDUCATION AND PHYSICAL ACTIVITY
(improved academic achievement, better concentration and attention, higher achievement tests score …)

PRO-SOCIAL BEHAVIORS
(improved cognitive performance, positive classroom behaviors)

NUTRITION ENVIRONMENT AND SERVICES (National School Lunch Program and School Breakfast Program)
(improved cognitive performance and attendance, increased academic grades, increased standardized tests score …)

HEALTH EDUCATION (health education curricula and instruction)
(nutrition, physical activity, tobacco, alcohol, drugs, sexual health, sleep, violence prevention, mental and emotional health)
(increased academic grades and test scores ….)

Low et al, Can Med Assoc J 2013; Busch et al, Rev Educ Res 2014; Esteban-Cornejo et al, J Sci Med Sport 2014; Shochat et al, Sleep Med Rev 2014; Michael et al, J School Health 2015

LIFESTYLE RISK FACTORS AND RESIDUAL LIFE EXPECTANCY AT AGE 40: A GERMAN COHORT STUDY

RESIDUAL LIFE EXPECTANCY (RLE)

The combined loss of RLE for smoking, obesity, alcohol drinking,

red meat consumption versus never smoking, optimal BMI, no/light alcohol drinking

and low processed/ read meat consumption was 17 years for men and 13.9 for women

Li K et al, BMC Medicine 2014

…… cancer deaths can be reduced by more than 75% in the coming decades, but than this reduction will only come about if greater efforts are made towards early detection and prevention

Vogelstein et al, Cancer Genomics 2014

Colditz GA, American Society of Clinical Oncology 2014

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

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 ???

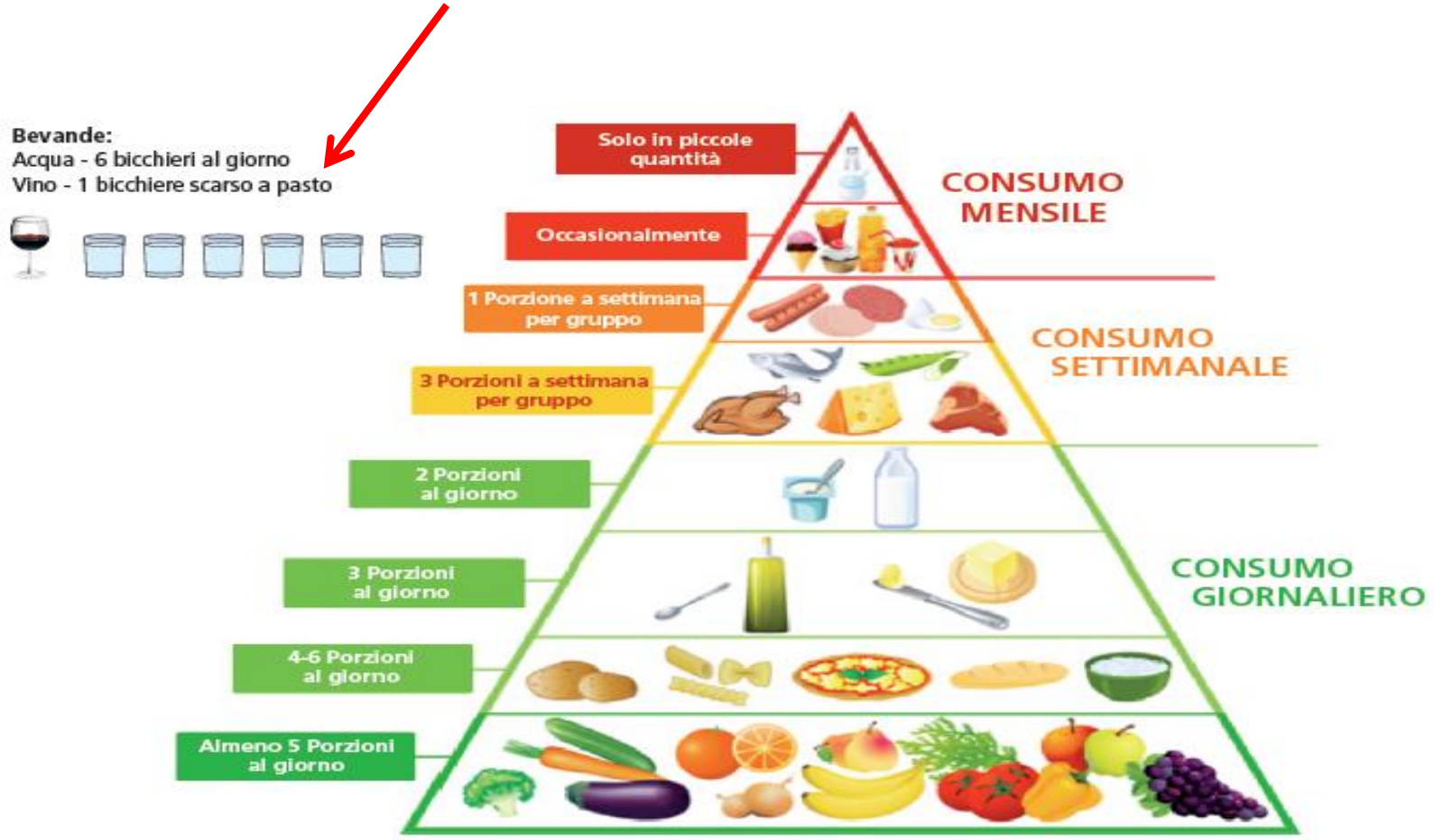


Figura 11.1 "Piramide alimentare".

EXPO, 2015

Cultural Change in not easy

best way to market a drug is the marketing of a disease

A) Cardio-vascular disease (CVD)

1) **Today, it is becoming more obvious that it is not LDL-cholesterol that is directly implicated in CVD but small, dense, type B particles generated after a high intake of sugar and processed carbohydrates**
   (Malhotra, BMJ 2013; Sinatra et al, J Am Coll Nutr 2014; Singh et al, PLoS One 2013)

2) **A stronger focus on nutrition instead of the global oversimplification to massive statin use would have been the most sensible approach**
(Ioannidis et al, JAMA 2014; Pencina et al, N Engl J Med 2014; Anonimous, Lancet 2014, 383: 669)

3) **80% of CVD events can be prevented with simple dietary and non-dietary lyfestyle measures**
(Reiner et al; J Epidemiol Community Health 2013; Perlemutter et al, Altern Ther Health Med 2013; WHO, CVD, updated March 2013; Mascitelli and Goldstein, Lancet 2013)

4) **Virgin olive oil obtained a 30% relative reduction in major CV events (stroke, myocardial, infarction, CV death)** **(Martinez-Gonzales, Int J Epidemiol 2012; Estruch et al, N Engl J Med 2013)**

5) **Alcohol and CVD prevention: «a nonsense» !** **(Testino et al, Nutr Metab Cardiovasc Dis 2014)**

B) Medication versus lifestyle in diabetes prevention

T2D will affect more than 10% of the adult population in many countries during the next two decades, with a projected increase of 55% by 2035.
T2D is also increasing in youth ***(Shaw et al, Diabetes Res Clin Pract 2010; Beagley et al, Res Clin Pract 2014; Zimmet et al, Lancet Diabetes Endocrinol 2014)***

1) T2D largely preventable. Up to 91% of T2D cases could be prevented by relatively modest lifestyle changes: global growing rates of T2D represent a *profound humiliation* for public health ***(Carlos et al, J Epidemiol Community Health 2014; Ley et al, Lancet 2014)***

2) Metformin efficacy was only limited to subjects with a body mass index > 35 kg/m2 (Knowler et al, N Engl J Med 2002)

3) Randomized controlled trials and longitudinal observational studies have confirmed that dietary changes combined with non-dietary lifestyle modification can have a long-term effect on T2D prevention (Danaei et al, Epidemiology 2013; Salas-Salvado et al, AnnIntern Med 2014)

C) The Mirage of Antiobesity drugs !!! «eat less»

Anonimous. The catastrophic failures of public health, Lancet 2004; 363: 745)

1) In the USA, Europe and Canada less than 4% of the public budget is spent on prevention (< 0.5% in Italy)
(Sullivan et al, Eur J Cancer 2012; OCSE, 2014)

2) A culture based on alcohol consumption, ultra-processed food, low physical activity, and long periods spent in front of a computer is now widespread, albeit with strong socioeconomics differentials
(Moodie et al, Lancet 2013)

3) Global styles of consumption fostered by changes in the economy are not counteracted by global preventive initiatives.

The benefit of prevention take time to manifest, and prevention needs ***LEADERSHIP*** and vision from policy makers *(Vineis and Wild, Lancet 2014)*

LEADERSHIP OSPEDALIERA

- I professionisti della salute ospedalieri possono esercitare una profonda influenza sull'atteggiamento dei pazienti e dei loro familiari, in quanto maggiormente sensibili alle indicazioni sanitarie

- Influenza le scelte e le decisioni politiche dei livelli superiori dell' organizzazione della societa'

V. Patussi, CAR Toscana 2007

AREE DI AZIONE (I)

- **PROMUOVERE LA SALUTE DEL PAZIENTE (identificazione precoce, informazioni, distribuzione materiale informativo ….)**

- **PROMUOVERE LA SALUTE DEL PERSONALE OSPEDALIERO**

- **AZIONI DI COMUNITA' (Medici di famiglia, Scuola, Municipi ……)**

V Patussi, CAR Toscana, 2007

AREE DI AZIONE (II)

- **PROMUOVERE LA SALUTE DEL PAZIENTE (identificazione precoce, informazioni, distribuzione materiale informativo ….)**
- **PROMUOVERE LA SALUTE DEL PERSONALE OSPEDALIERO**

- **AZIONI DI COMUNITA' (Medici di famiglia, Scuola, Municipi ……)**

-- implementare i nodi della rete collaborando con i servizi territoriali (integrazione ospedale-territorio/ dipartimenti inter aziendali): PREVENZIONE SECONDARIA

-- promozione del paziente esperto/ integrazione con le associazioni di autotutela e promozione della salute

V Patussi, CAR Toscana 2007

« SCHOOL HEALTH PROGRAMS ARE ESSENTIAL IF WE ARE

TO ATTAIN BOTH NATIONAL EDUCATION GOALS AND NATIONAL HEALTH

OBJECTIVES BY THE YEAR 2020»

Michael et al. Journal of School Health 2015

TAKE HOME MESSAGE…

SCELTE CHE AIUTANO IN PREVENZIONE ONCOLOGICA
Previeni sovrappeso e obesità … *Senza improvvisare!*
Limita carne rossa ed evita la processata (insaccati, würstel, hamburger…)
Mangia almeno 2-3 porzioni tra frutta/verdura al giorno di vari tipi e colori
Scegli metodiche di cottura semplici
Preferisci cereali integrali, anziché raffinati
Limita alimenti ad alto contenuto calorico ed evita le bevande zuccherate
Non esagerare con il sale (NaCl)
Scopri e valorizza l'uso delle spezie e delle erbe aromatiche
Segui una dieta varia, bilanciata, preferendo le fonti naturali dei nutrienti
Evita l'uso di bevande alcoliche (anche in gravidanza)
Non fumare
Svolgi regolarmente attività fisica, evita la sedentarietà

Ufficio Scolastico Regionale (MIUR) Ligure – CAR, IRCCS AOU San Martino-IST, Genova
patrizia.balbinot@hsanmartino.it

La città e la salute

PER SAPERNE DI PIÙ
www.hsanmartino.it
www.gaslini.org

I ragazzi a scuola a San Martino "Alcol e droghe vi distruggono"

Invitati 200 studenti delle medie Sukkar, Alloisio, Testino e Viotti illustrano i pericoli per la salute

I PUNTI

L'ALCOL
È considerato uno dei principali fattori di rischio per alcune malattie. Ed è pericoloso alla guida

LE DROGHE
Vene sono alcune di nuova generazione ancora più devastanti. I danni possono essere irreparabili

LA COLLABORAZIONE
Tra IRCCS San Martino e l'Ufficio scolastico regionale la sinergia per coinvolgere i ragazzi delle scuole

ELEONORA ROSSI

L'EDUCAZIONE a corretti stili di vita potrebbe diventare una materia di studio a scuola, per adesso un progetto, poi si vedrà.

Intanto ieri mattina al Centro Congressi del San Martino davanti a una platea di circa duecento ragazzi delle medie inferiori c'erano Samir Sukkar, direttore di dietetica e nutrizione, Antonella Alloisio, dirigente della chirurgia toracica, Gianni Testino, epatologo e coordinatore del Centro

IL MESSAGGIO
I corretti stili di vita in età adolescenziale prevengono i tumori in età adulta e avanzata
GIANNI TESTINO EPATOLOGO

...nitaria Patrizia Balbinot: «Se ... un video presentato da Suk- ... Altri tre incontri previsti ... no 12 grammi di etanolo al ... molecolari modificate da sof-


Grazie