

Stress oxydant et cancers

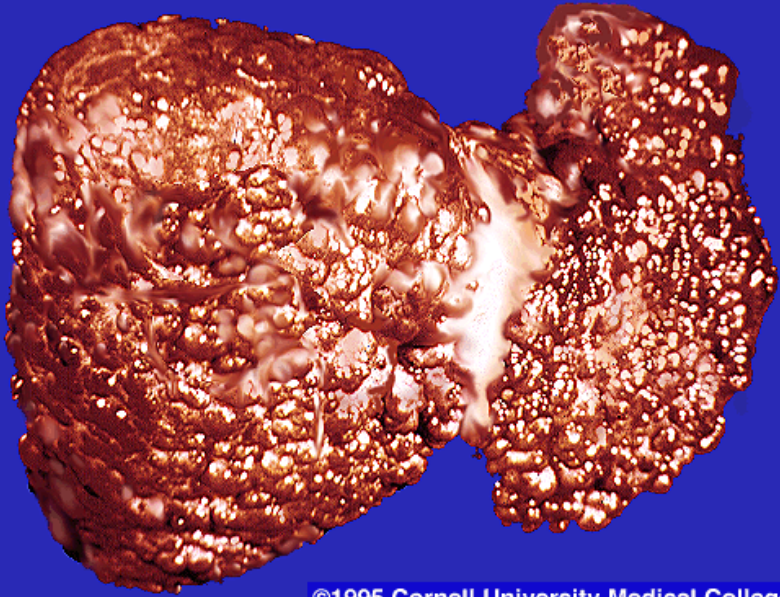
*L'exemple du lien entre
fer et cancer du foie*

Pierre Nahon

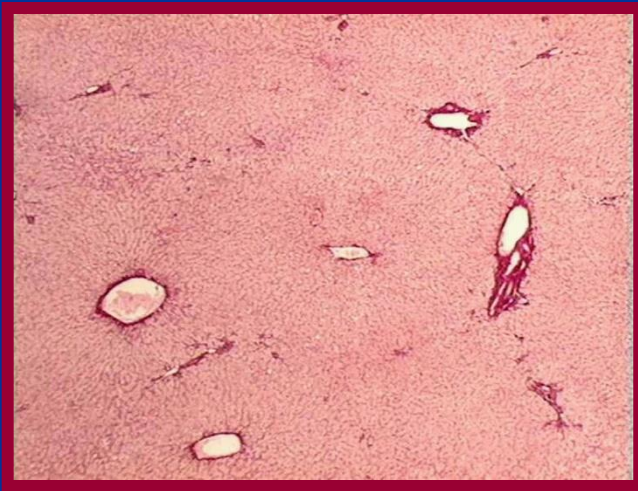
Service d'Hépatologie
Hôpital Jean Verdier
Bondy – Université Paris 13

INSERM U773 - Paris 7

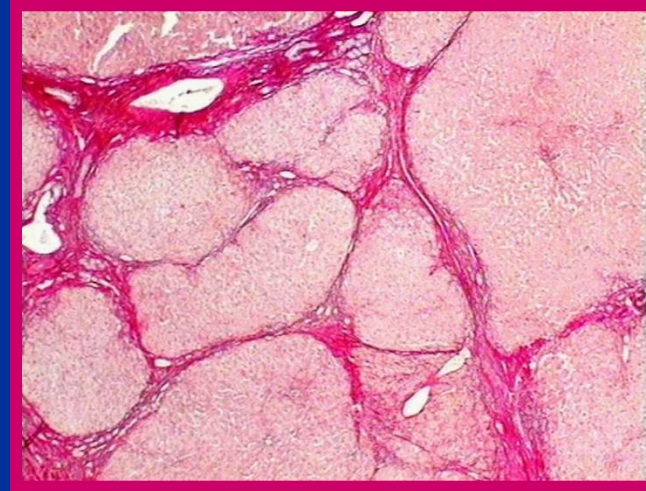
**La cirrhose: évolution ultime
de toutes les maladies
chroniques du foie**



©1995 Cornell University Medical College

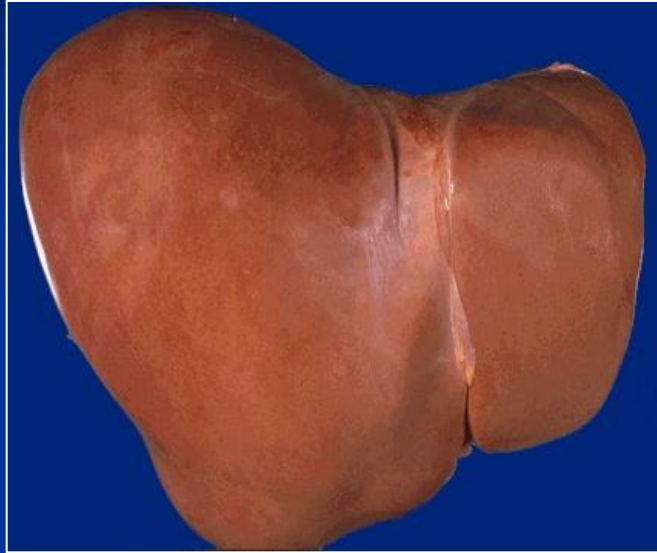


Foie normal

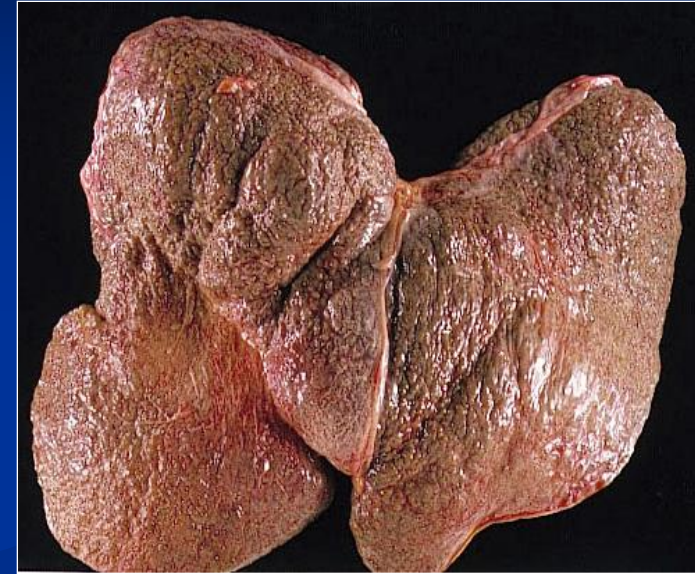


Cirrhose

Du foie normal à la cirrhose



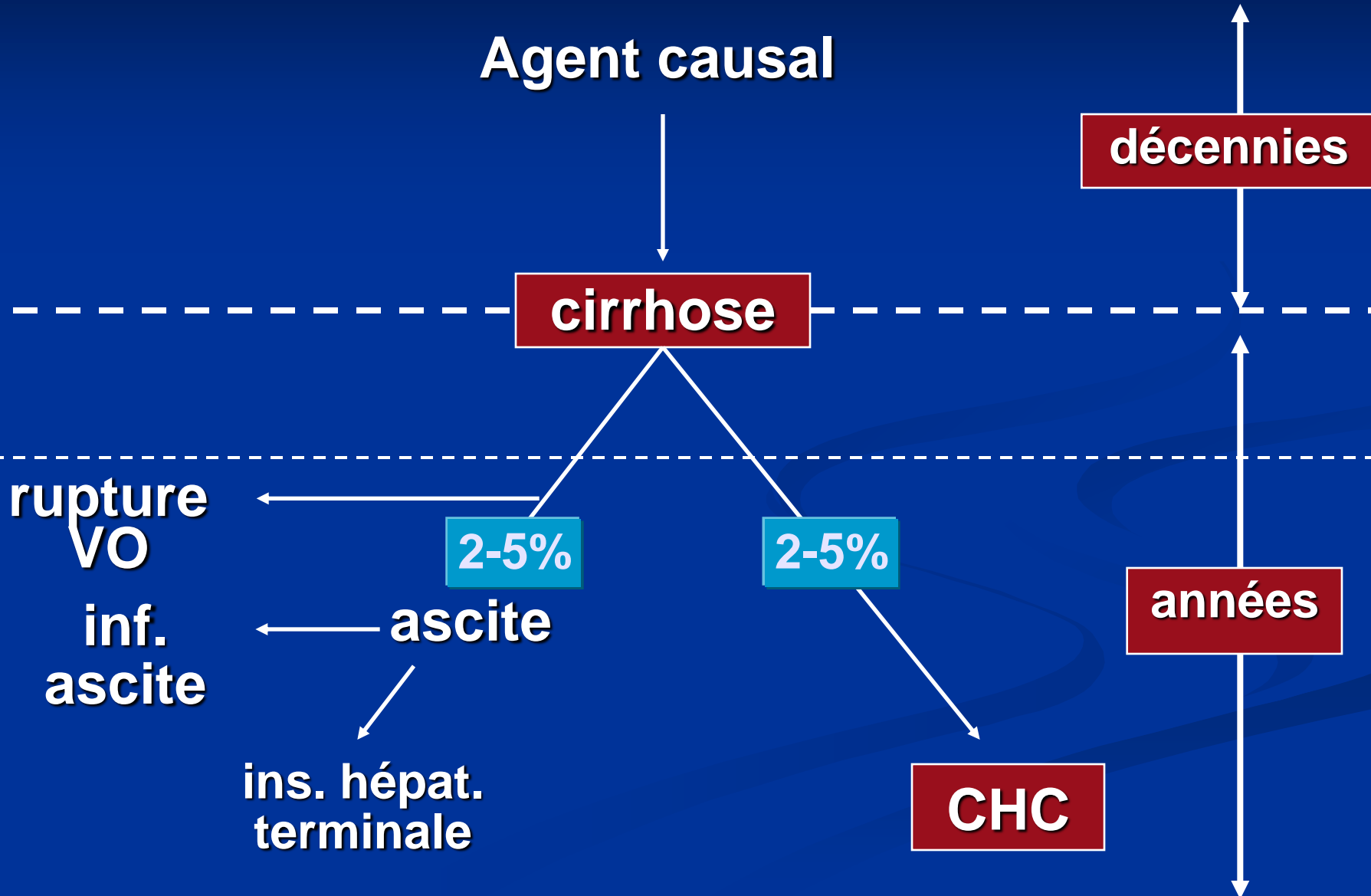
- Alcool
- VHC
- VHB
- NASH

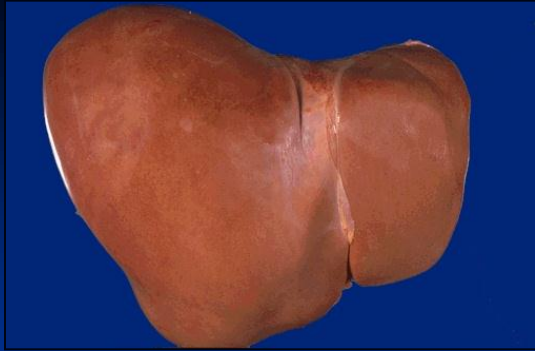


Causes de cirrhose en France

■ Alcool	60 - 85 %
■ Virus de l'hépatite C	10 - 20 %
■ Stéatose et NASH	?
■ Virus de l'hépatite B	2 - 5 %
■ Hémochromatose	< 5 %
■ CBP, HAI, etc.	rare

Maladies chroniques du foie

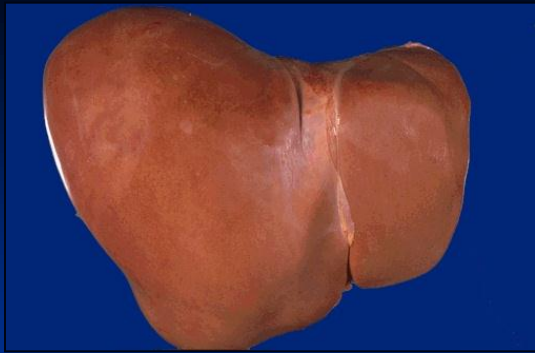




Foie normal

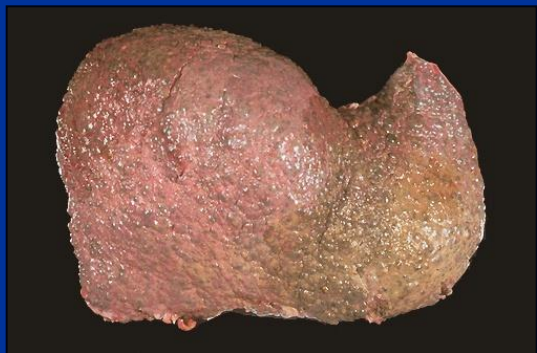


Foie cirrhotique

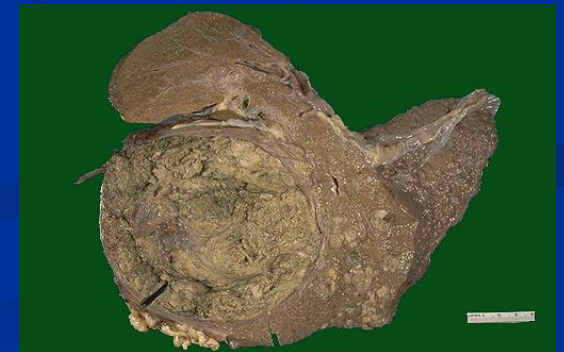


Foie normal

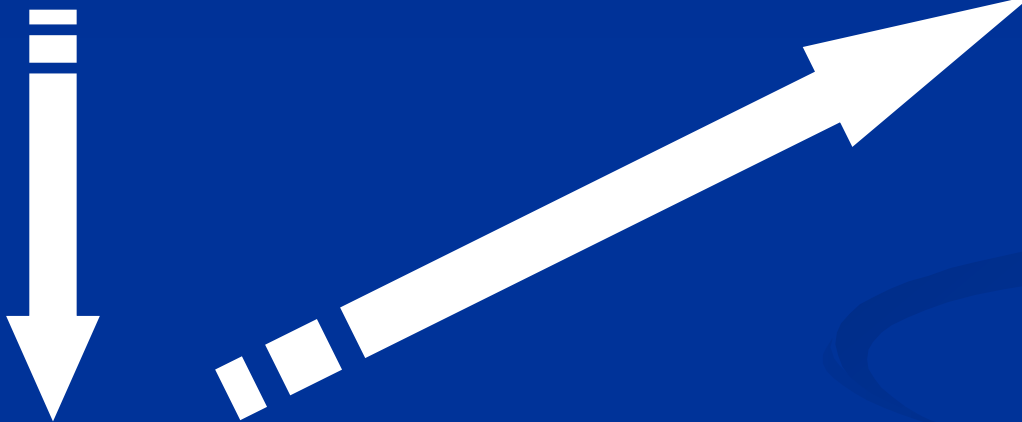
**Mortalité non liée
Au CHC
(hémorragies,
insuffisance hépatique...)**



Foie cirrhotique



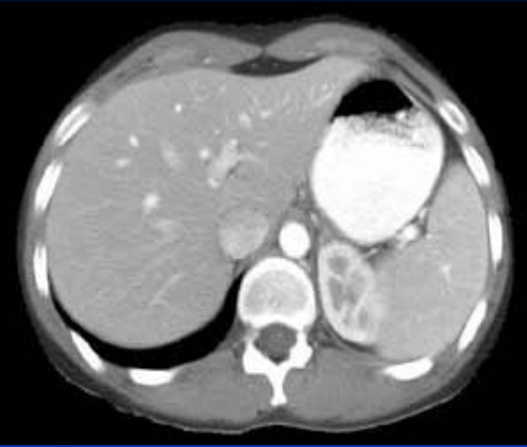
Foie tumoral



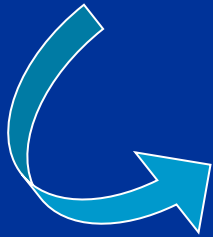
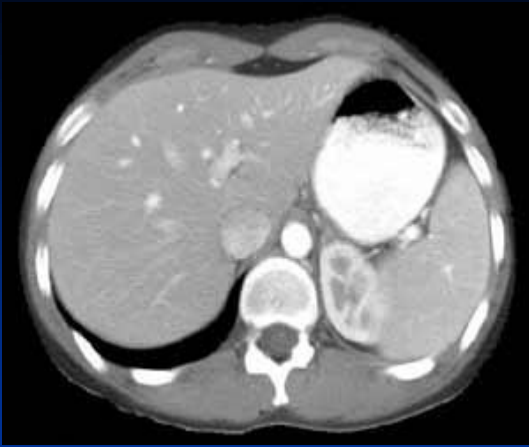
Carcinome hépatocellulaire



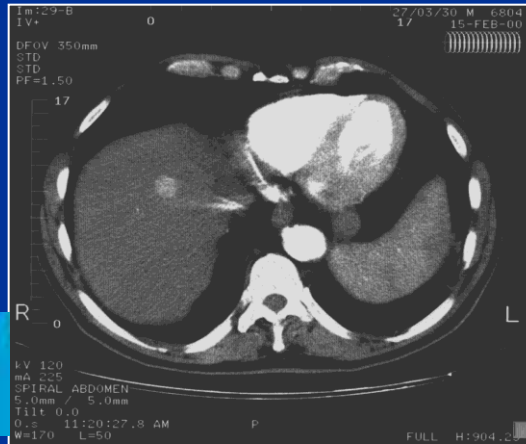
Cirrhose = état pré-cancéreux



Cirrhose = état pré-cancéreux

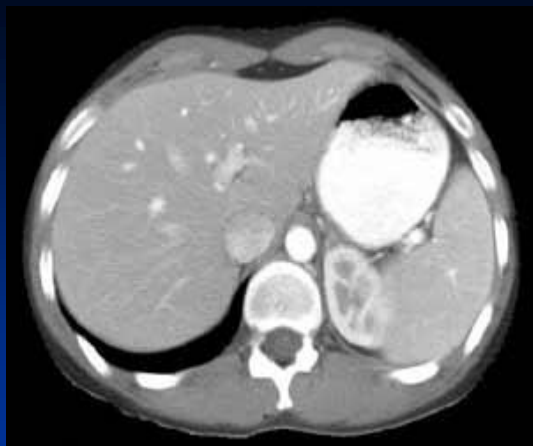


DEPISTAGE

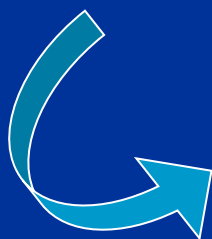


« Petit CHC »

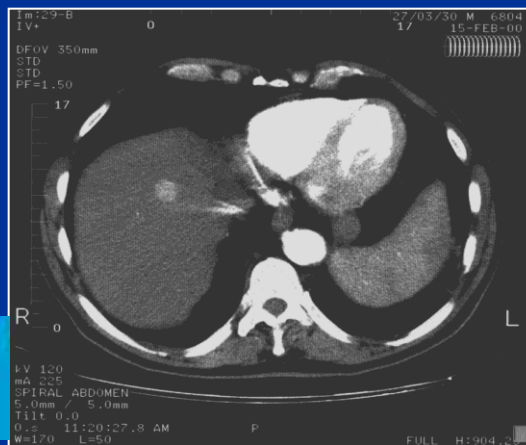
Cirrhose = état pré-cancéreux



TRAITEMENT CURATEUR

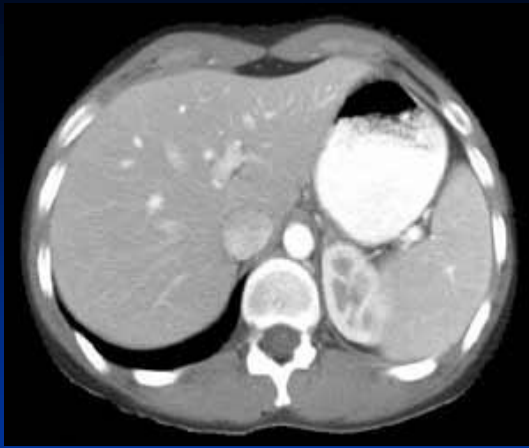


DEPISTAGE



« Petit CHC »

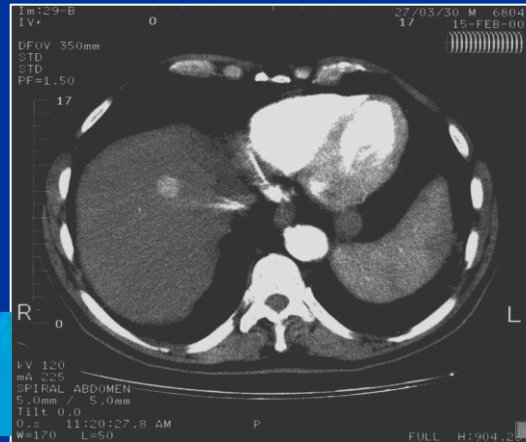
Cirrhose = état pré-cancéreux



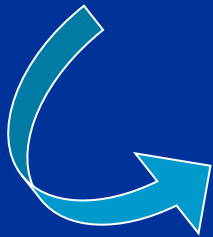
TRAITEMENT CURATEUR



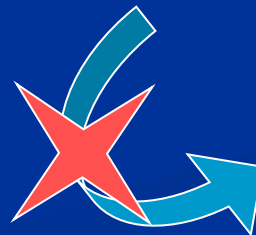
« Petit CHC »

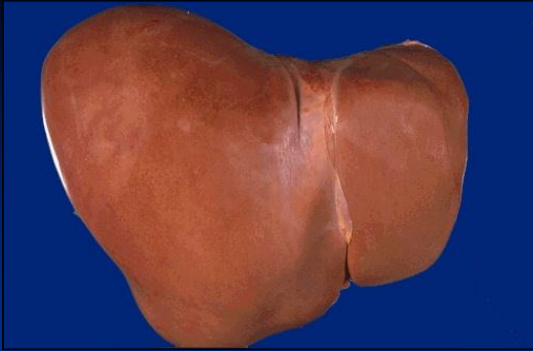


DEPISTAGE



« Gros CHC »





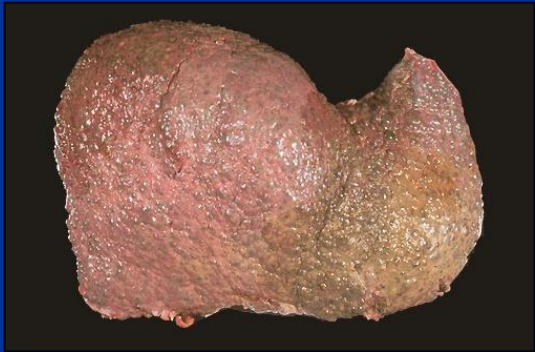
Foie normal

VHC

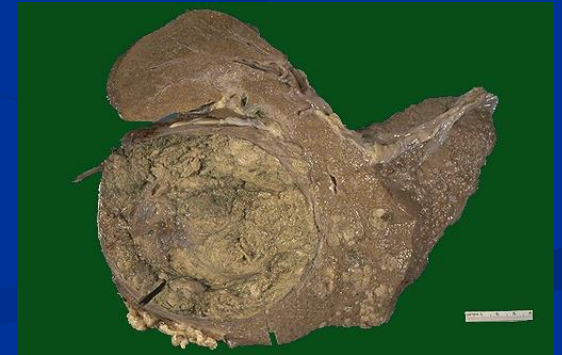
ALCOOL

VHB

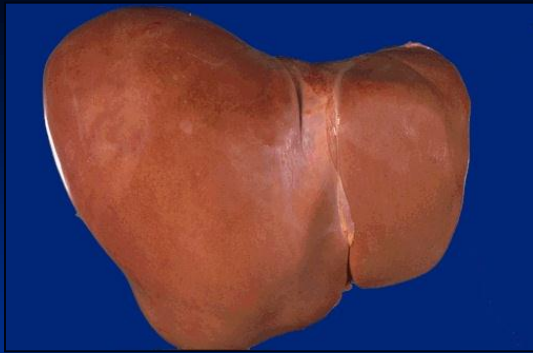
**SYNDROME
METABOLIQUE**



Foie cirrhotique

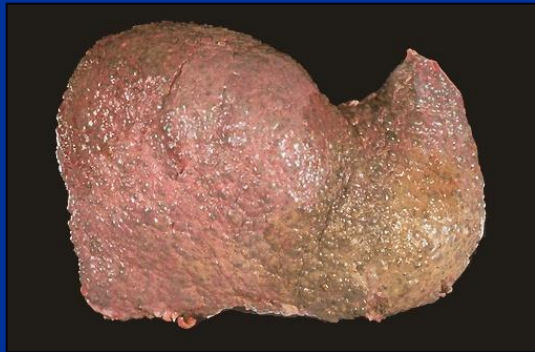
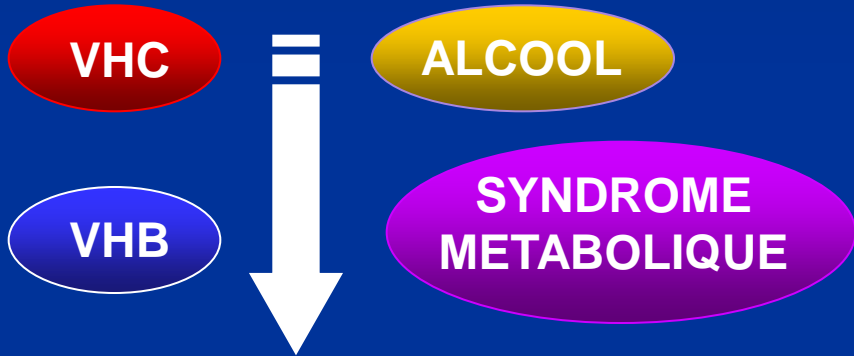


Foie tumoral

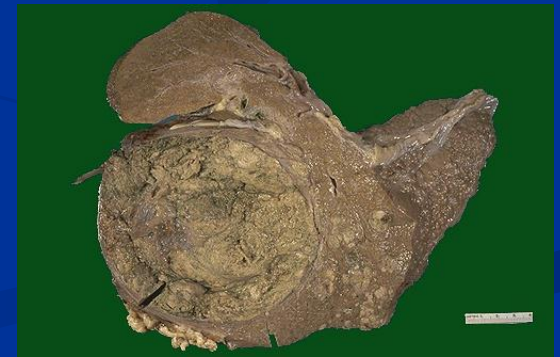


Foie normal

IDENTIFICATION DE FACTEURS DE RISQUE

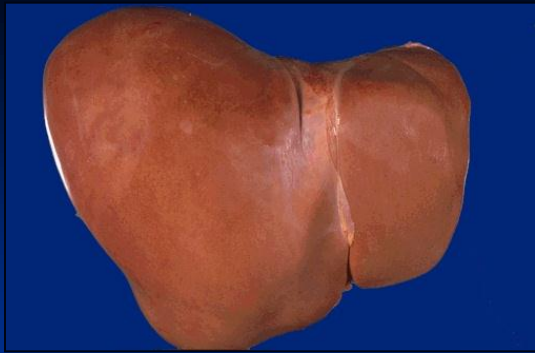


Foie cirrhotique

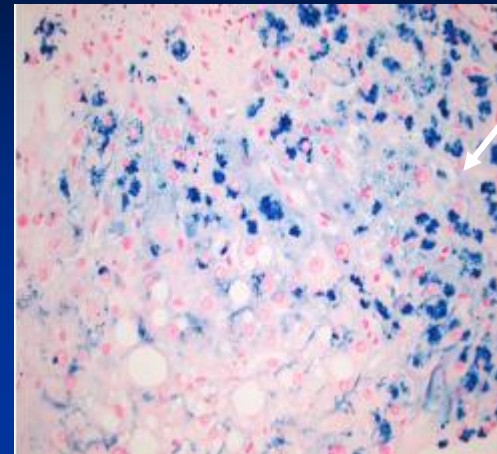


Foie tumoral

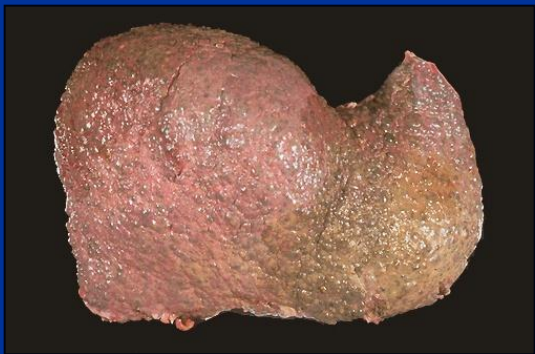
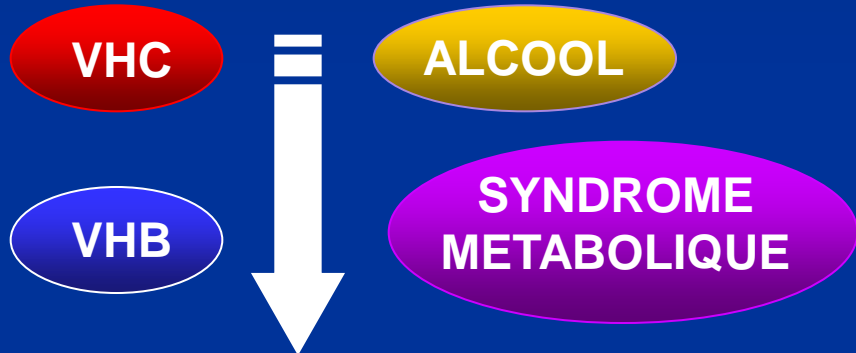




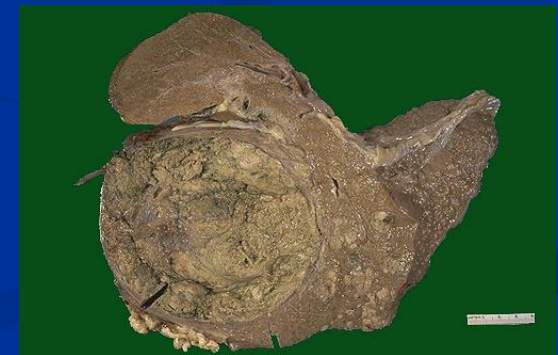
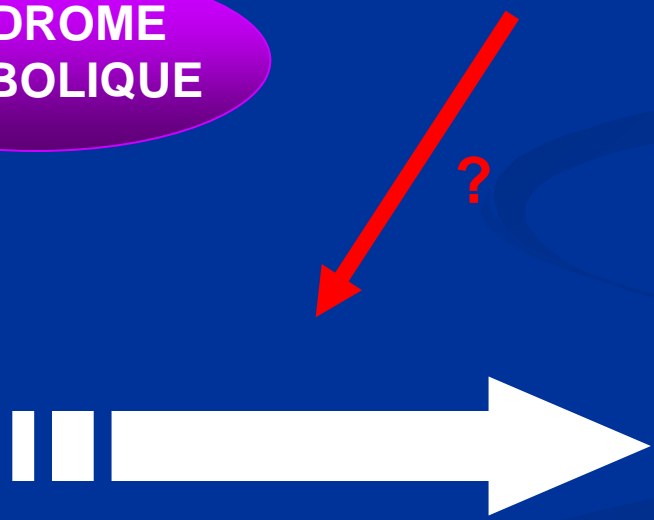
Foie normal



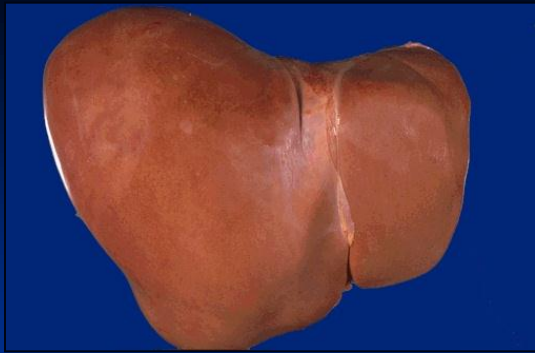
Surcharge Hépatique en fer (Perls)



Foie cirrhotique



Foie tumoral



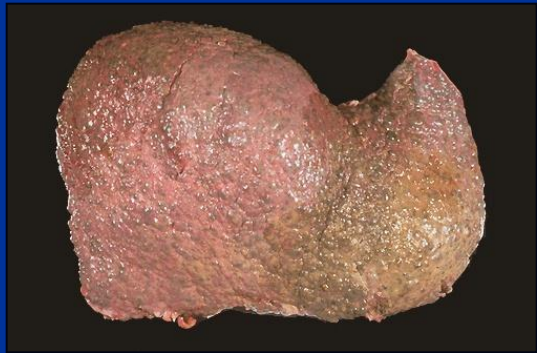
Foie normal

VHC

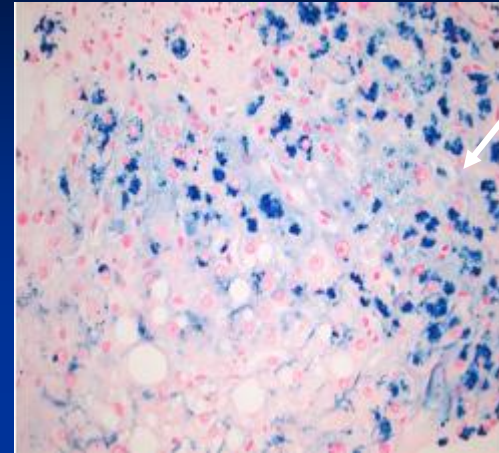
ALCOOL

VHB

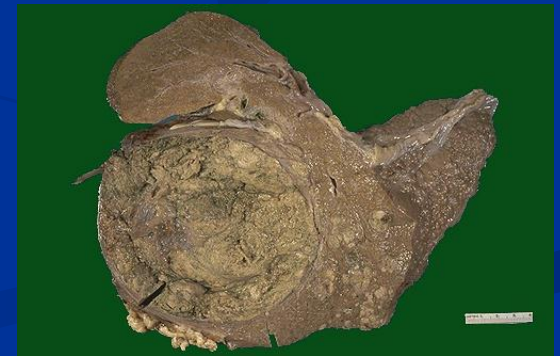
SYNDROME METABOLIQUE



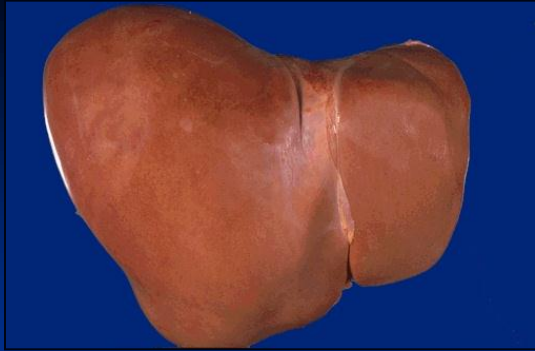
Foie cirrhotique



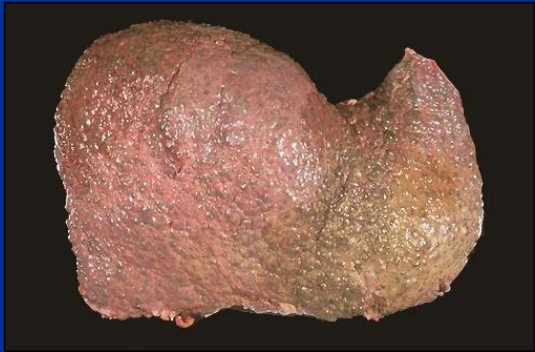
Surcharge Hépatique en fer (Perls)



Foie tumoral



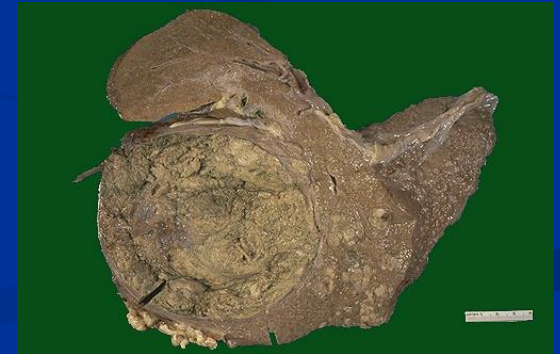
Foie normal



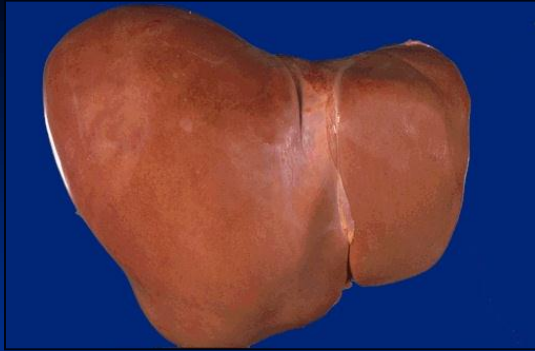
Foie cirrhotique

**STRESS
OXYDANT**

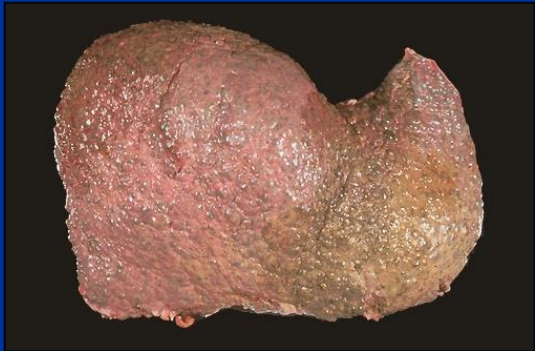
**SURCHARGE
HEPATIQUE
EN FER**



Foie tumoral



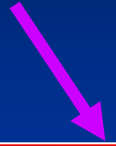
Foie normal



Foie cirrhotique



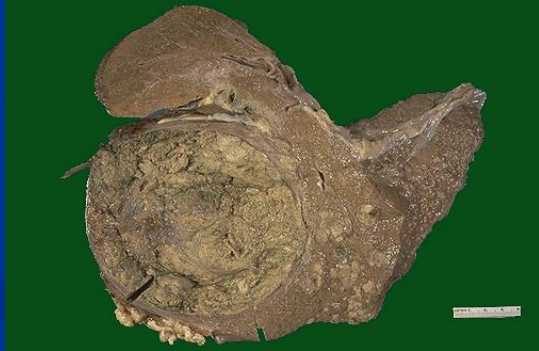
POLYMORPHISMES GENETIQUES



**STRESS
OXYDANT**



**SURCHARGE
HEPATIQUE
EN FER**



Foie tumoral

DEFINITIONS

- Radical libre: espèce chimique ayant un ou plusieurs électrons célibataires
- Stress oxydant: accumulation de d'espèces réactives de l'oxygène (RL ayant un e- libre sur un atome d'oxygène)

Génération des ERO par le fer



Espèces réactives de l'oxygène



Protéines

Lipides

ADN



Oxydation...



**Péroxydation
lipidique...**



**Bases modifiées : bases hydroxylées
(8-OH guanine...),
Simple et doubles cassures de
l'ADN,
Modification des sucres et des
protéines de l'ADN.**



**Altérations des
transports ioniques
Systèmes enzymatiques...**



**Altération
Membranaire...**



**Altération de l'expression des
gènes ...**

ATTEINTE CELLULAIRE

Espèces réactives de l'oxygène



Réponse cellulaire



Activation de facteurs de transcription



Induction de gènes de réponse au stress oxydant

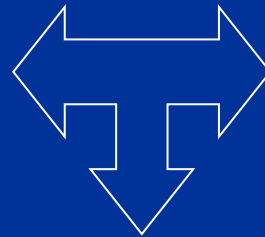
Anti-oxydants

Enzymes de Réparation de l'ADN

Enzymes de Réparation des lipides

Protéases, cytokines, protéines de choc thermique...

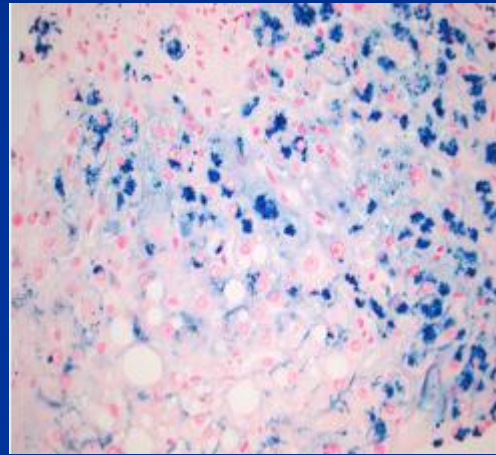
Prolifération
cellulaire
abérrante



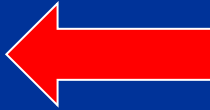
Apoptose
Nécrose

Adaptation
au Stress oxydant

PROLIFERATION CELLULAIRE



**STRESS
OXYDANT**



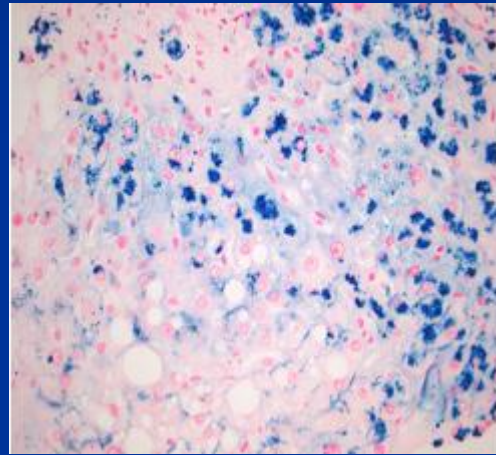
**DIMINUTION DES
DEFENSES
ANTI-TUMORALES**



**ATTEINTES STRUCTURALES DIRECTES
ET MUTATIONS DE L'ADN**



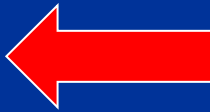
PROLIFERATION CELLULAIRE



**DIMINUTION DES
DEFENSES
ANTI-TUMORALES**



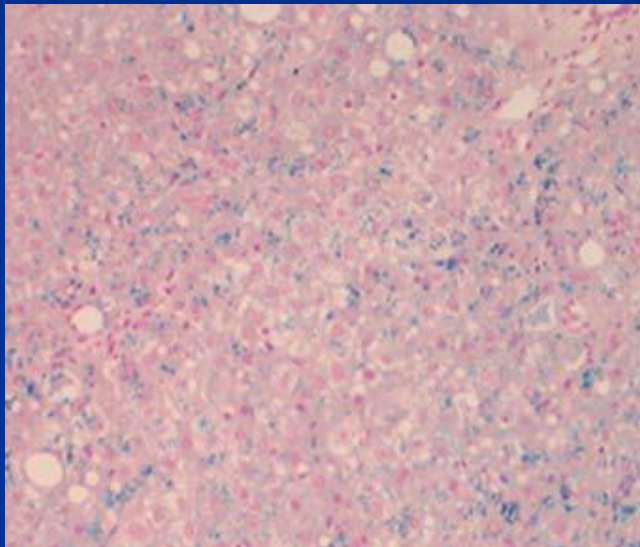
**STRESS
OXYDANT**



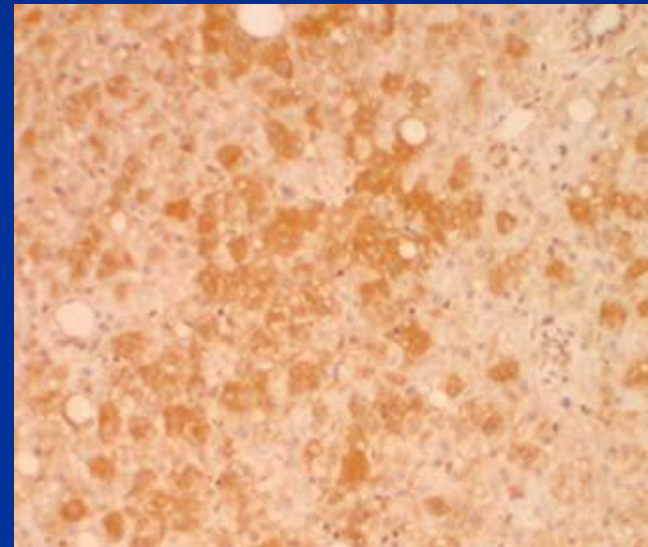
**ATTEINTES STRUCTURALES DIRECTES
ET MUTATIONS DE L'ADN**

Surcharge hépatique en fer et stress oxydant

Ohhira et al, Alcohol Clin Exp Res 1998



Coloration de Perls



Protéine HNE

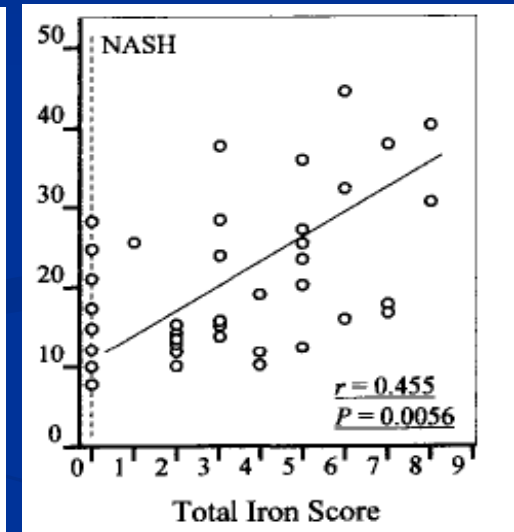
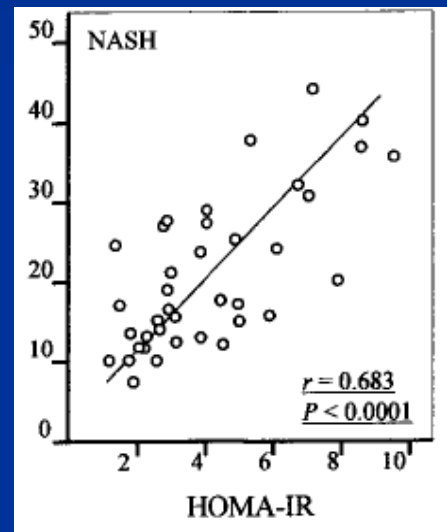
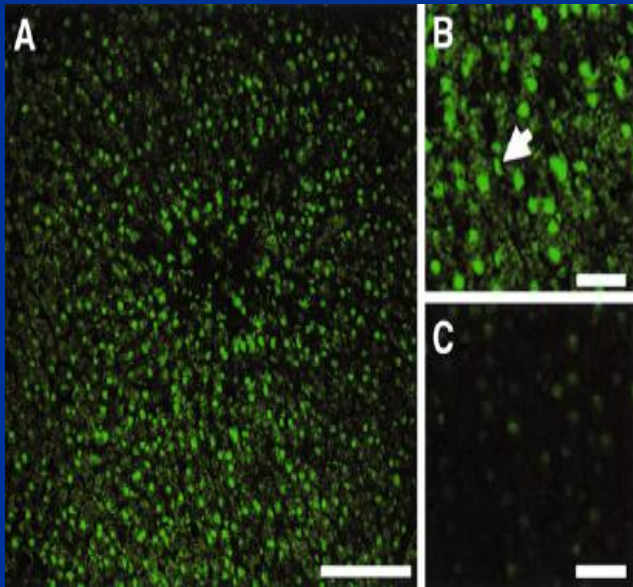


SHF et stress oxydant IH
au cours de la maladie alcoolique du foie

Iron Overload Is Associated with Hepatic Oxidative Damage to DNA in Nonalcoholic Steatohepatitis

Cancer Biomarkers 2009

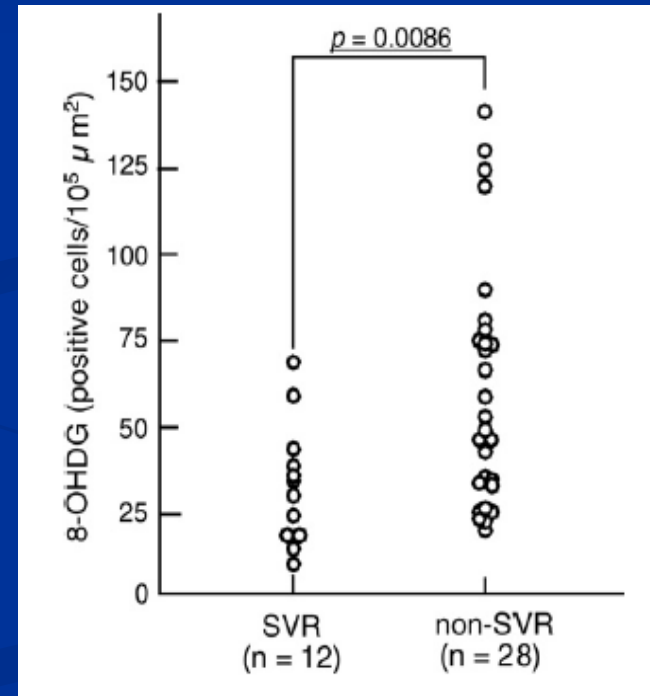
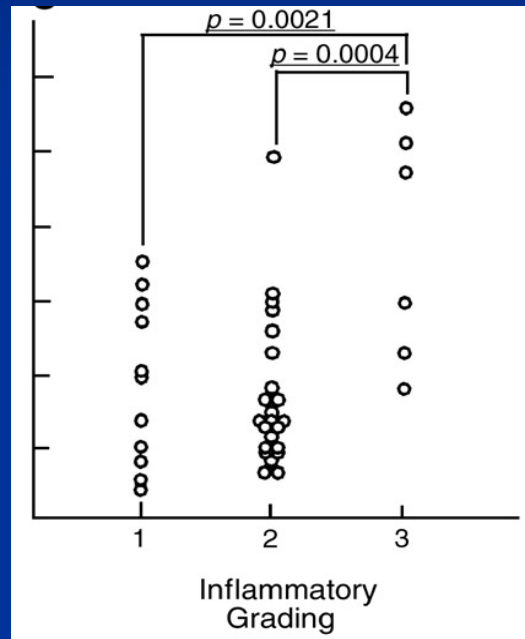
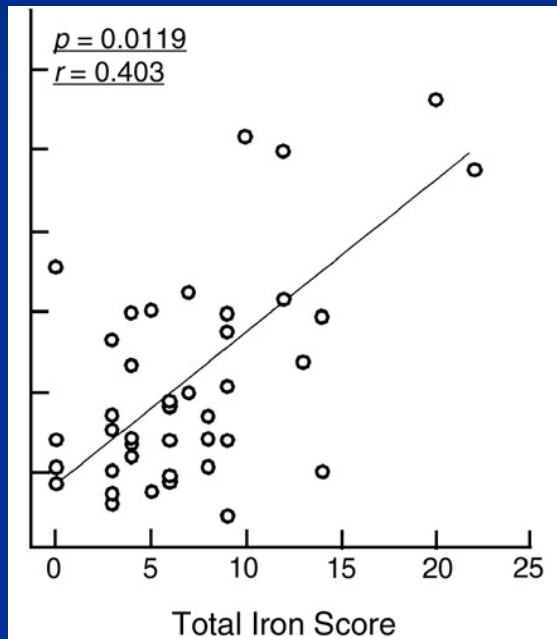
Immuno-marquage au 8-OHdG



*Diminution des lésions oxydatives
de l'ADN après phlébotomies*

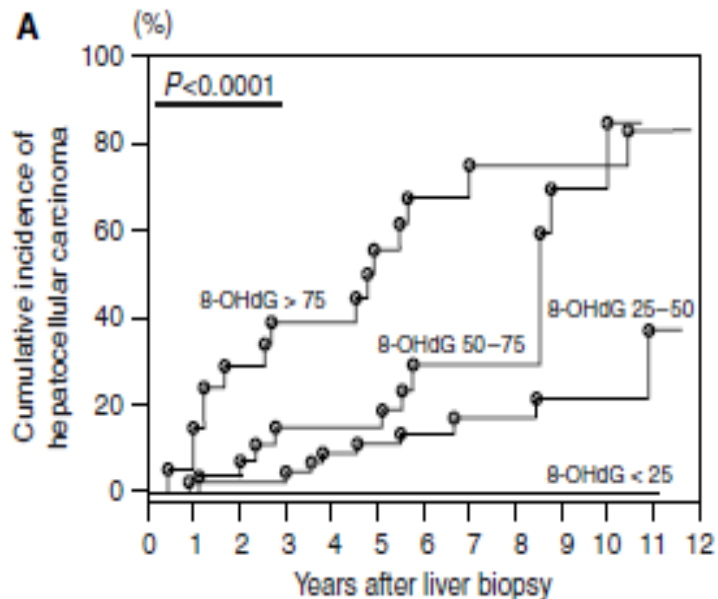
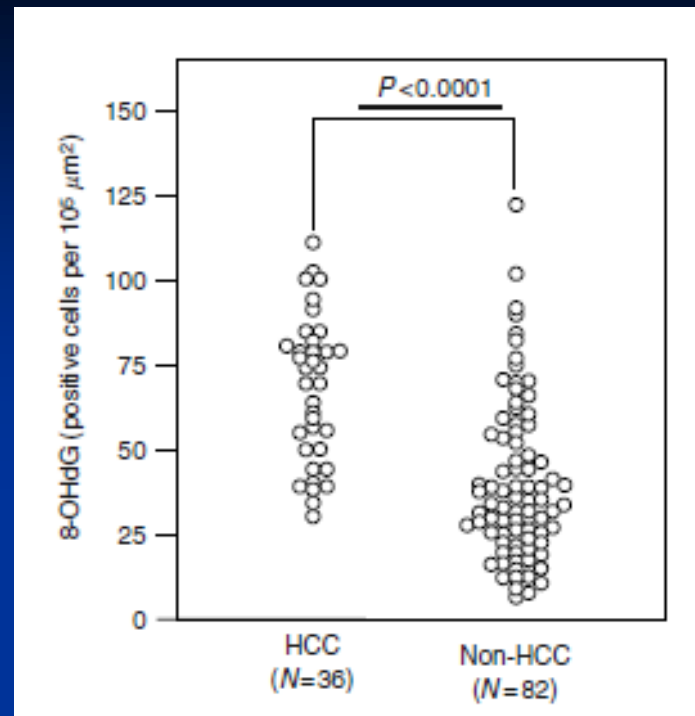
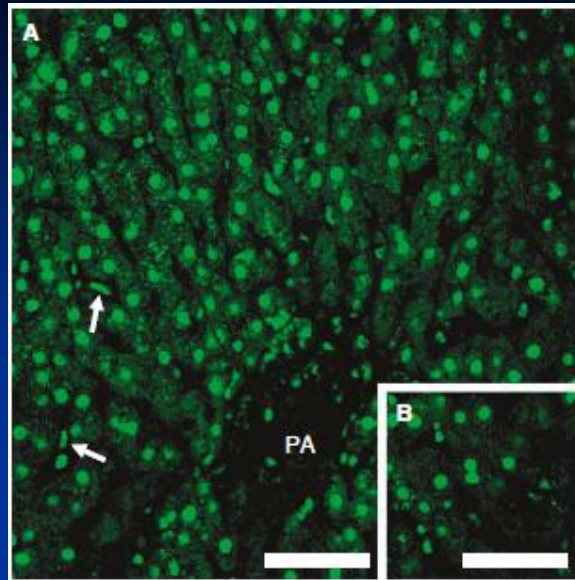
Hepatic oxidative DNA damage correlates with iron overload in chronic hepatitis C patients

Free Radic Biol Med 2007



**Fer et stress oxydant IH:
marqueurs de sévérité au cours
des infections virales ???**

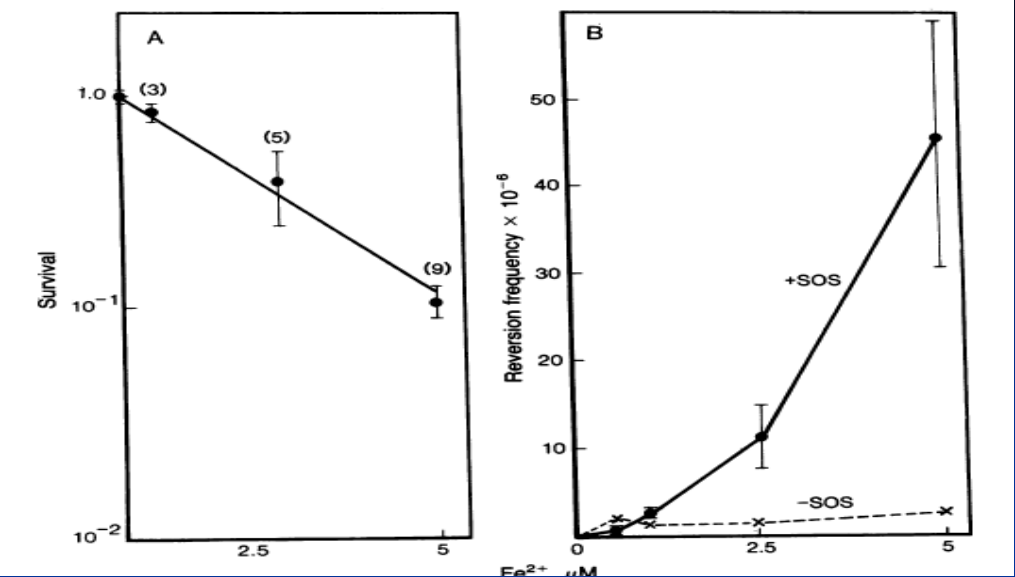
Immuno-marquage au 8-OHdG



**Stress oxydant intra-hépatique,
marqueur du risque de CHC**

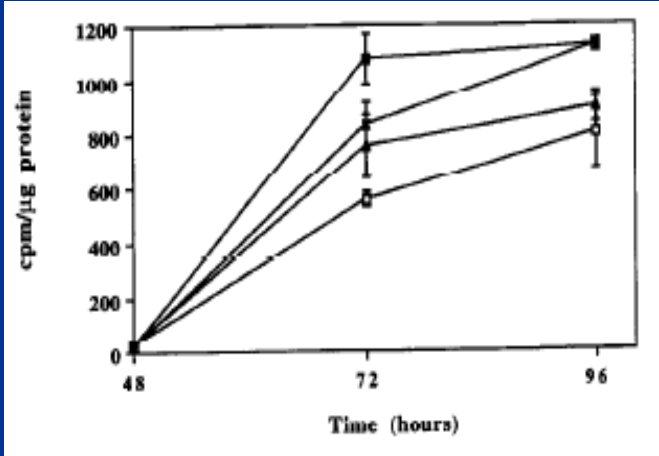
Tanaka et al, Br J Cancer 2008

Survie

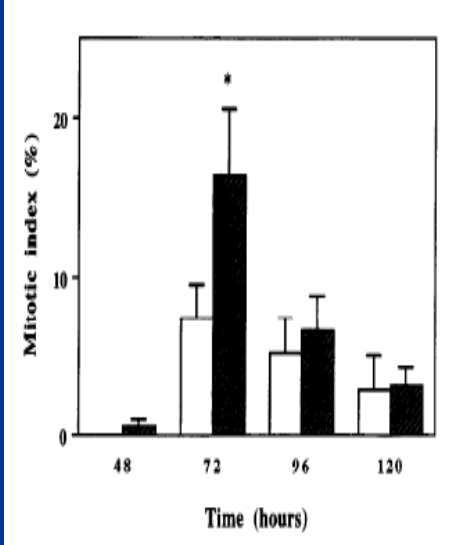


Acquisition de mutations

Prolifération cellulaire

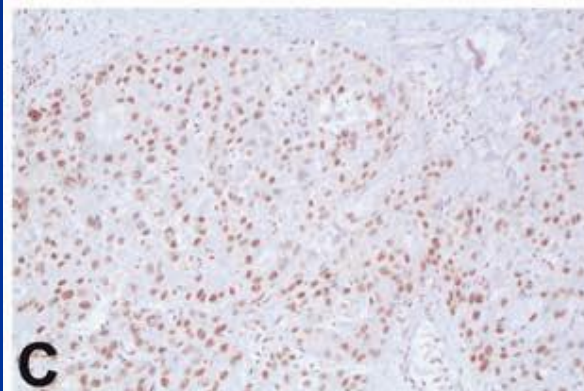
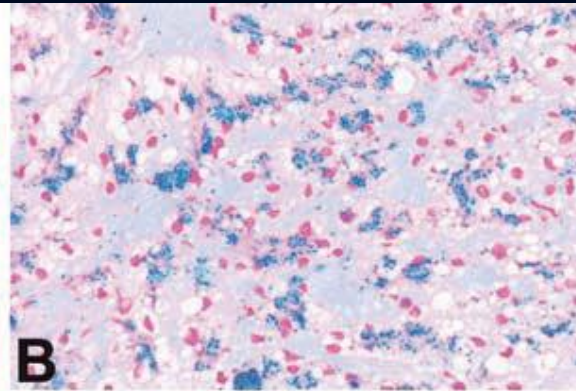
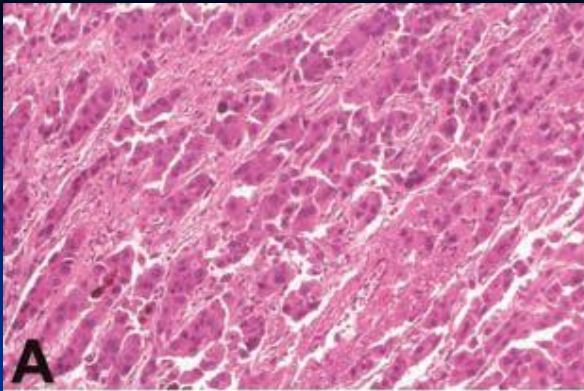


Synthèse d'ADN

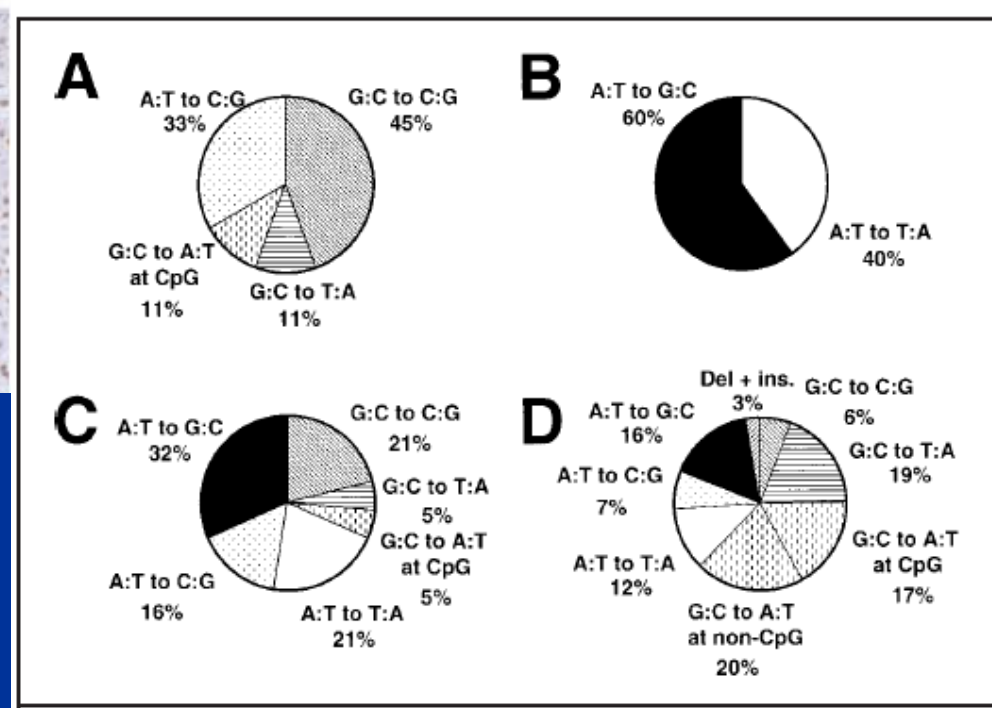


Effets du fer sur l'ADN

Loeb et al, PNAS 1988
Chenoufi et al, J Hepatol 1997



Immuno-marquage p53



SHF et mutations de p53

LE FER: CO-FACTEUR DE CARCINOGENESE

Furutani et al, Gastroenterology 2006



Contrôles (non TgM-C)



Contrôles (non TgM-Fe) + Fer



VHC (TgM-C)

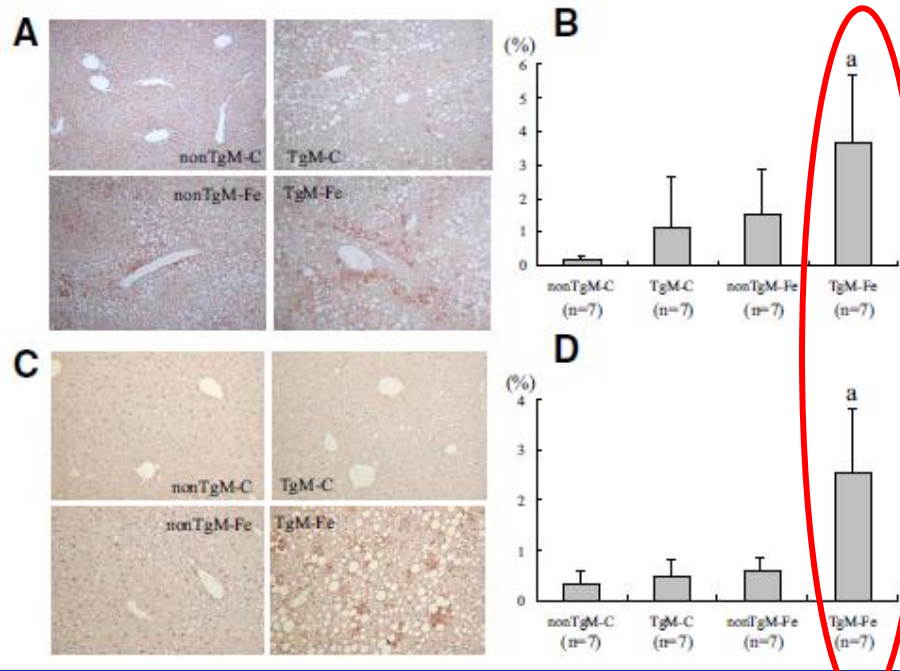


VHC (TgM-Fe) + Fer

SUIVI 2 ANS

HHE

PEROXYDATION LIPIDIQUE



HNE

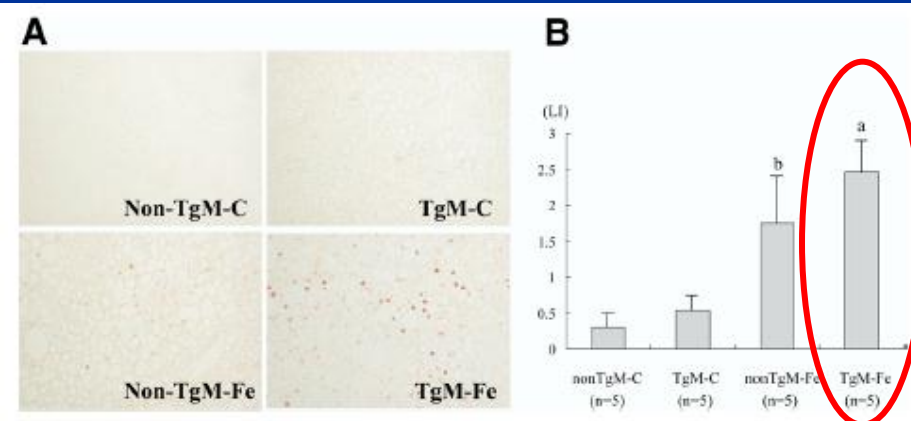
CONTROLES

CONTROLES + FER

VHC

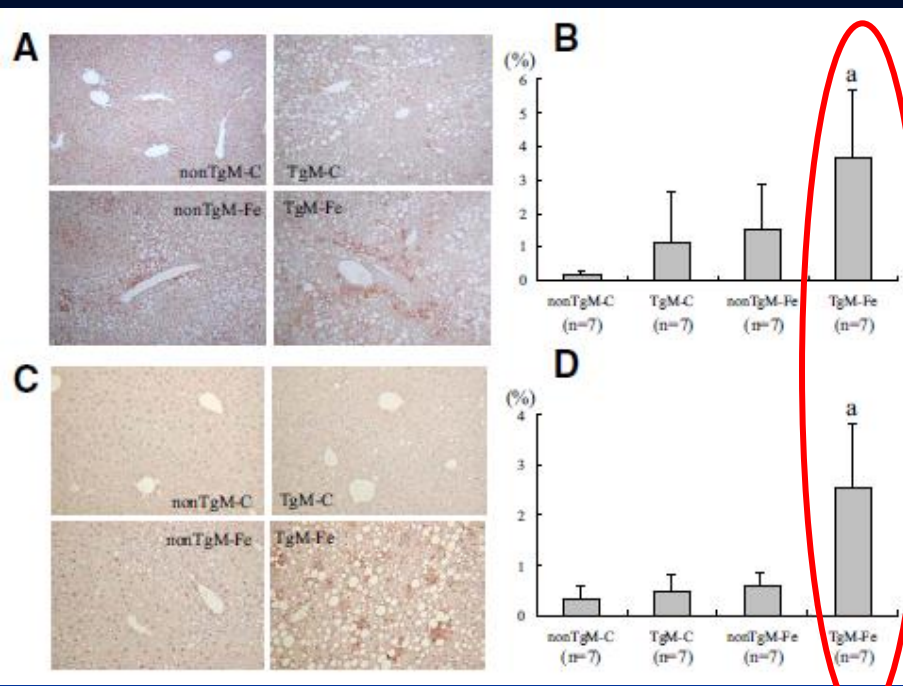
VHC + FER

PROLIFERATION



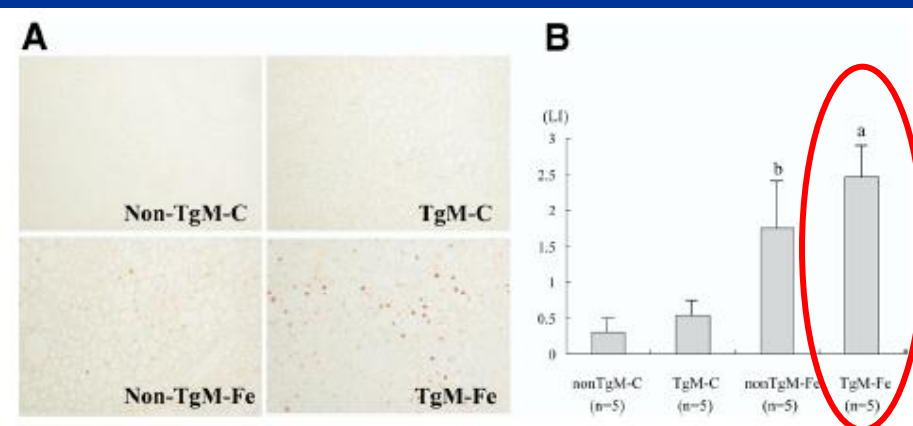
HHE

PEROXYDATION LIPIDIQUE

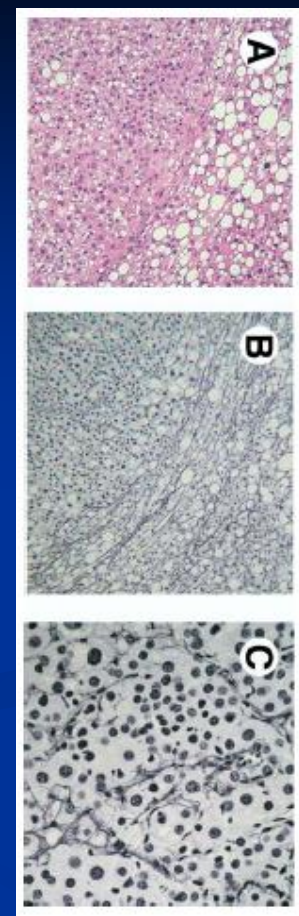


HNE

PROLIFERATION

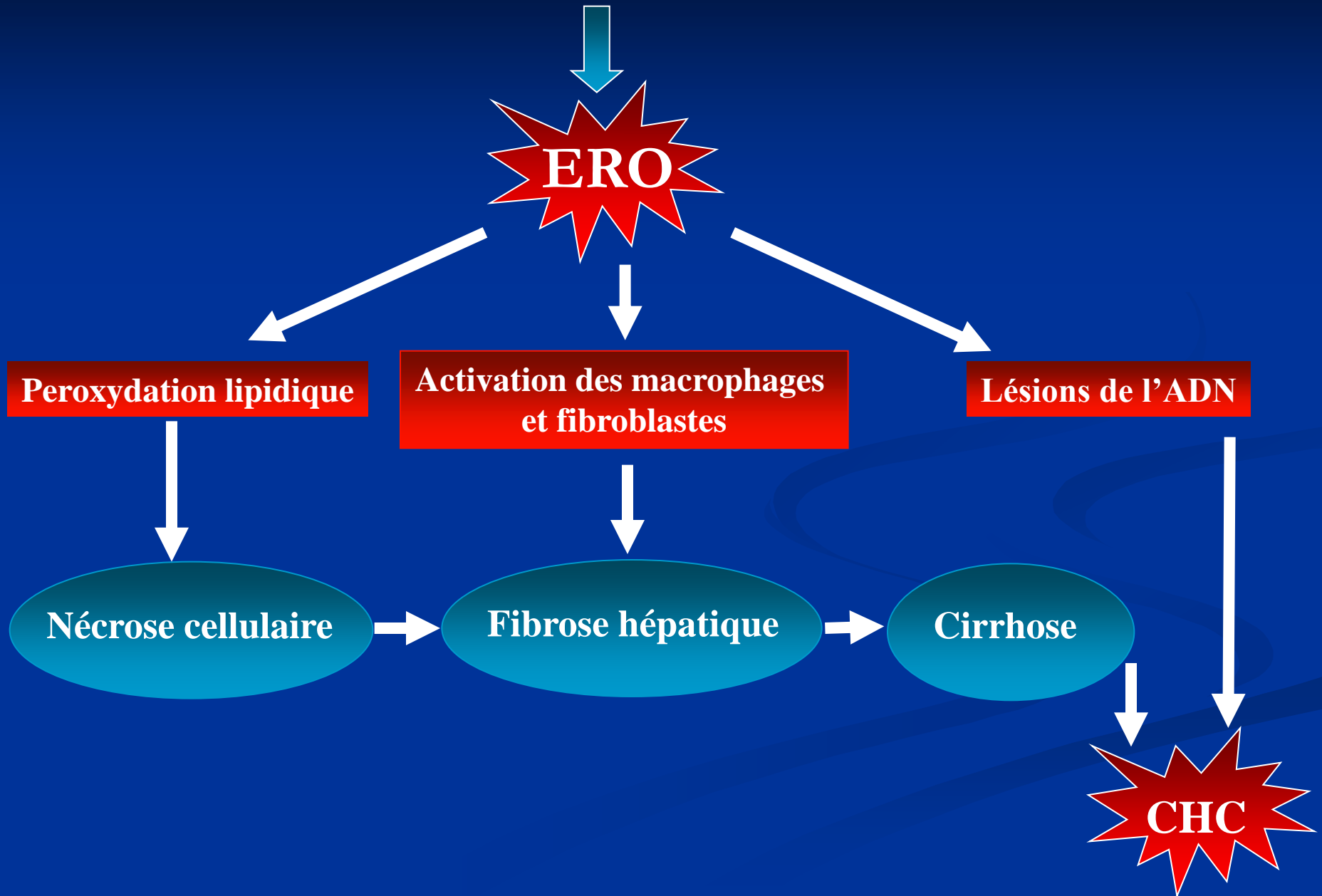


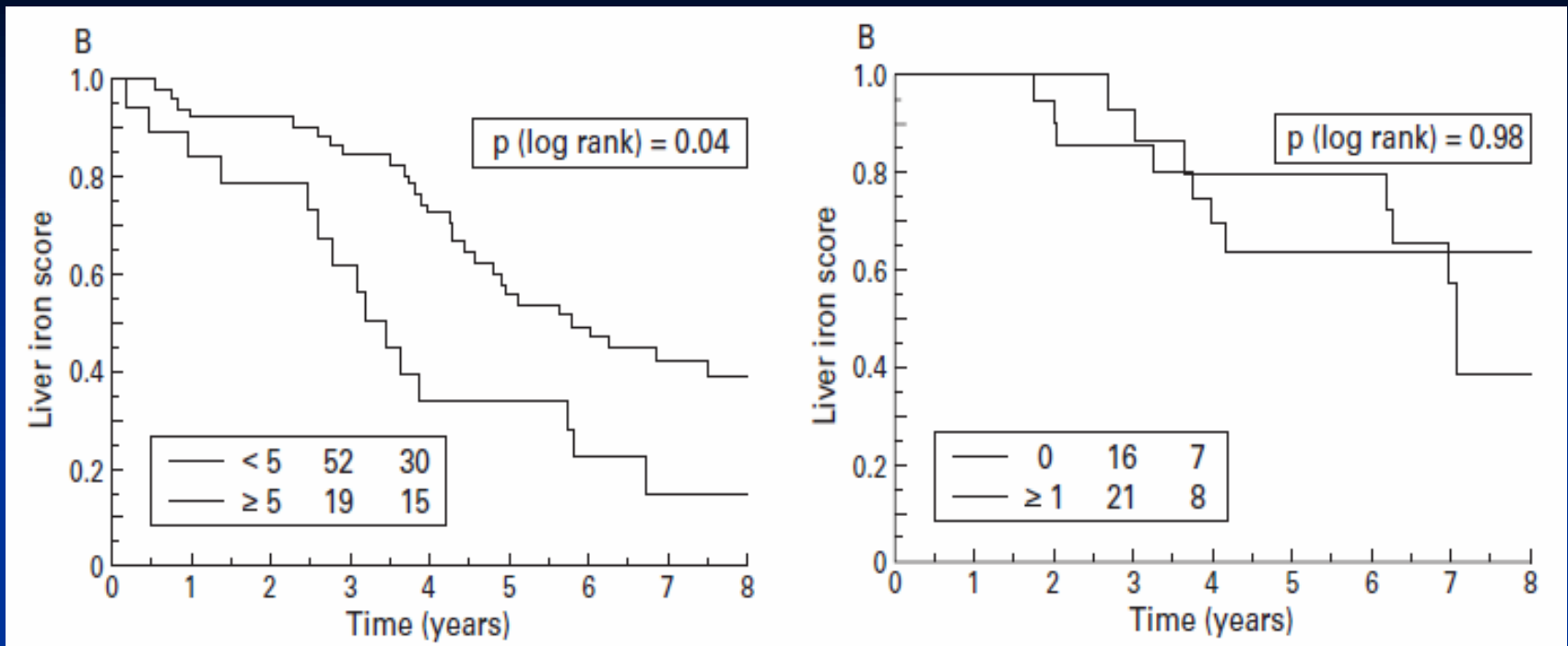
CONTROLES
CONTROLES + FER
VHC
VHC + FER



45% DE CHC
vs 0% DANS
LES AUTRES
GROUPES

Surcharge hépatique en fer



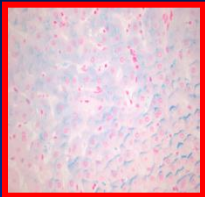


ALCOOL

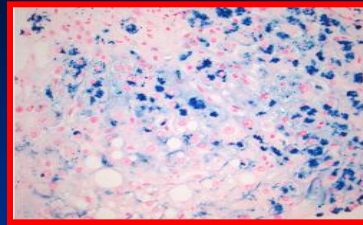
VHC

**SHF et décès au cours
de la cirrhose**

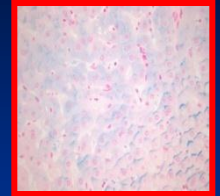
VIRUS



ALCOOL



NASH



**SURCHARGE EN FER
HEPATIQUE**

MALADIE DE WILSON

GENETIQUE

Hémochromatose

- Mutations HFE
- Mutations TfR2
- Mutations Hémojuveline

Non hémochromatose

- Mutations ferroportine
- Aceruloplasminémie
- Surcharge africaine

**SYNDROME
INFLAMMATOIRE**

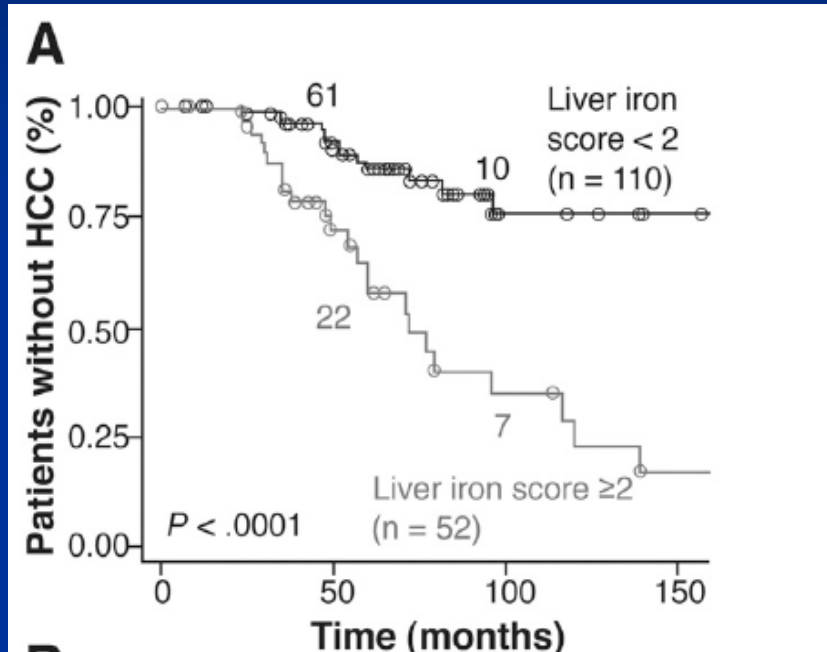
APPORTS EXCESSIFS

DESORDRES HEMATOLOGIQUES

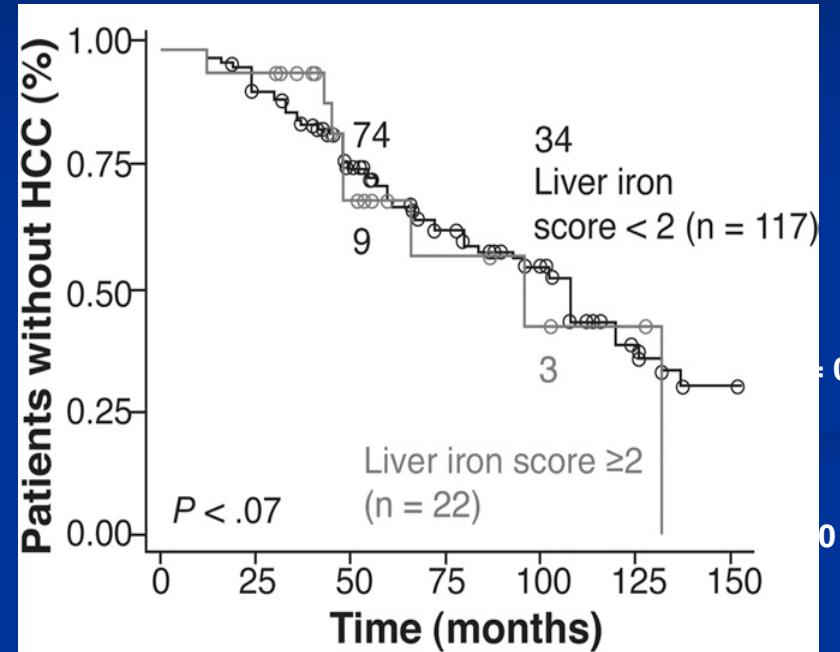
- Porphyrie cutanée tardive
- Dysérythropoïèse

Fer hépatique et survenue du CHC

Malades sans CHC



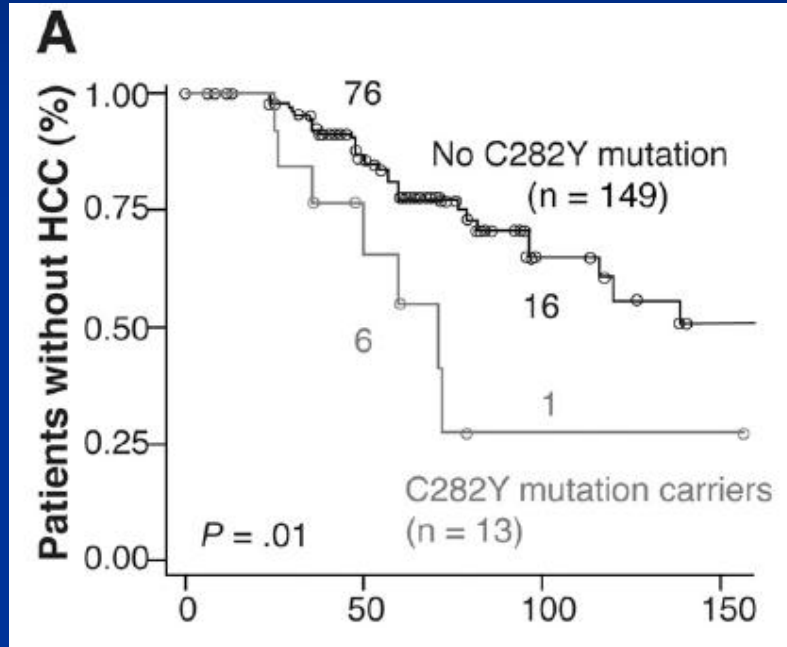
Cirrhose alcoolique



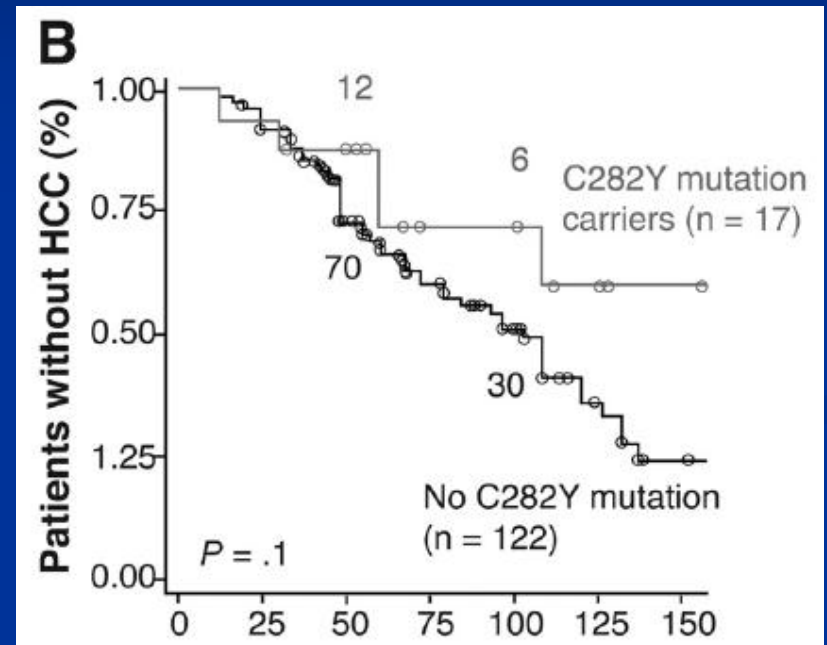
Cirrhose virale C

Mutation HFE C282Y et survenue du CHC

Malades sans CHC



Cirrhose alcoolique



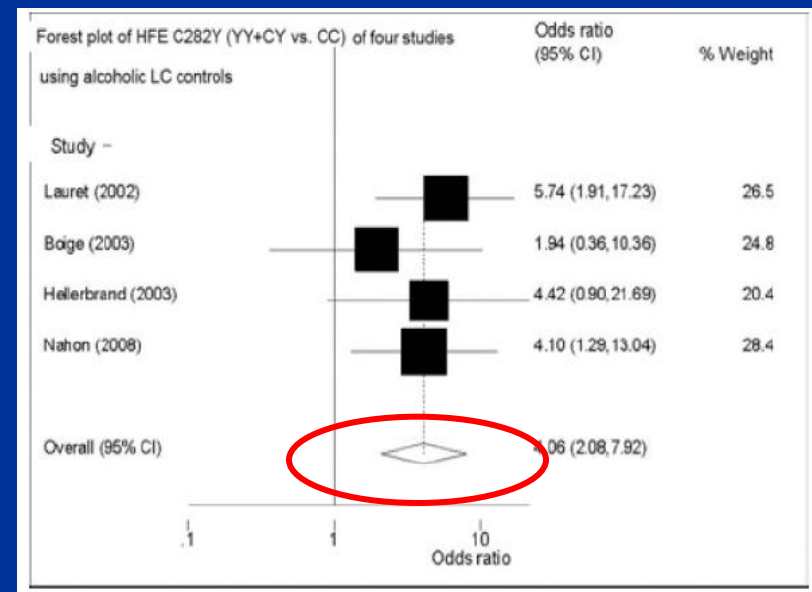
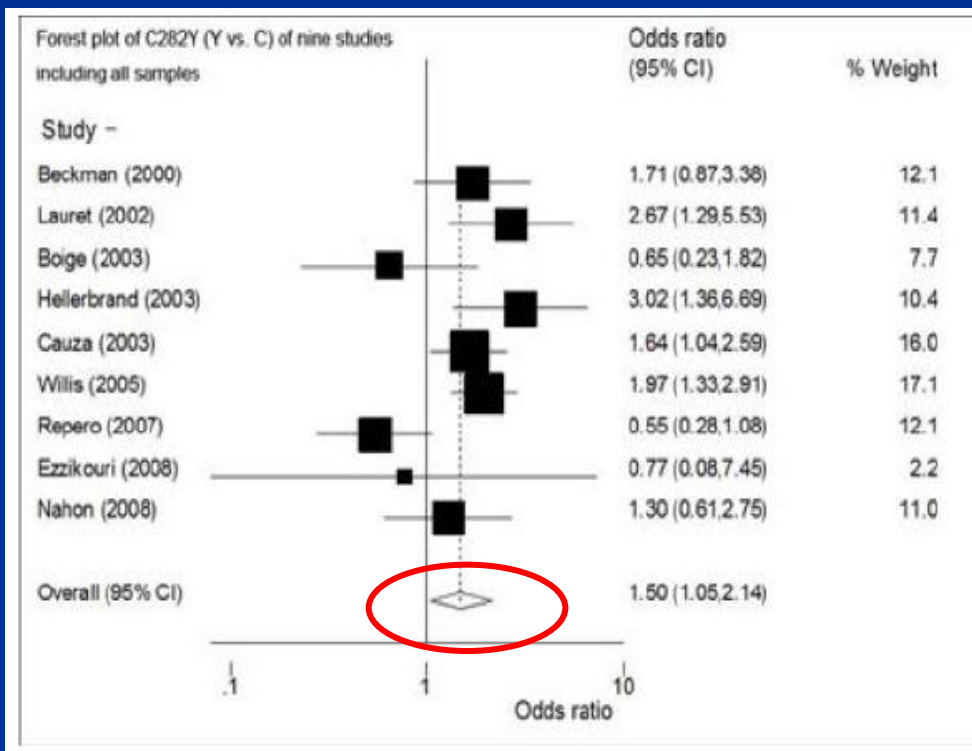
Cirrhose virale C

Mois

Association between C282Y and H63D mutations of the HFE gene with hepatocellular carcinoma in European populations: a meta-analysis

Journal of Experimental & Clinical Cancer Research 2010, **29**:18

Cas: 1102
Ctr: 3766
Etudes: 9



TOUTES CAUSES

ALCOOL

Liver iron excess in patients with hepatocellular carcinoma developed on non-alcoholic steato-hepatitis[☆]

Table 3
Significance of variables for prediction of hepatocellular carcinoma.
Multivariate analysis.

Variable	Odds ratio	95% Confidence interval	<i>p</i> Value
Ferritin (>500 mg/L)	1.36	0.78–3.14	0.136
Steatosis grade (>2)	1.02	0.51–2.77	0.811
Necroinflammation (>1)	1.89	0.86–4.17	0.169
Body mass index (>30)	0.89	0.51–1.86	0.643
Large liver cell dysplasia (presence)	1.33	0.56–3.17	0.667
cTIS (0 or >0).	7.08	2.77–18.07	0.0001
Diabetes-mellitus (presence)	6.04	2.29–15.91	0.0009

cTIS, corrected total iron score.

Sorrentino et al, J Hepatol 2009

SHF et CHC au cours de la cirrhose dysmétabolique

**TRAITEMENTS
ANTI-OXYDANTS
ET PREVENTION DU CHC**

Mortality in Randomized Trials of Antioxidant Supplements for Primary and Secondary Prevention

Systematic Review and Meta-analysis

JAMA, February 28, 2007—Vol 297, No. 8

Participants: 232 606
Essais contrôlés: 68

Conclusions Treatment with beta carotene, vitamin A, and vitamin E may increase mortality. The potential roles of vitamin C and selenium on mortality need further study.

Rationnel

■ Travaux expérimentaux

- ERO \longrightarrow carcinogenèse et maladies vasculaires
- Antioxydants pourraient lutter contre les effets biologiques des ERO

■ Epidémiologie observationnelle

- Régimes pauvres en antioxydants
- Faibles taux sériques d'antioxydants

\longrightarrow *Risques accrus de cancers et maladies CV*

*Epidémiologie interventionnelle: essais randomisés
Antioxydants vs placebo*

Essais de prévention primaire

Etude Linxian (1994)	Population carencée	Doses nutritionnelles BC, Vit E, selenium
Etude ATBC (1994)	Fumeurs	« Hautes doses » BC, Vit E
Etude CARET (1996)	Fumeurs	« Hautes doses » BC, Vit A
Etude PHS (1996)	Médecins	« Hautes doses » BC, aspirine
Etude Women's health (1999)	Population générale	« Hautes doses » BC, aspirine
Etude Women's health (2005)	Population générale	« Hautes doses » Vit E
Etude SUVIMAX (2005)	Population générale	« Doses nutritionnelles » BC, Vit E, selenium

Essais de prévention primaire

Etude Linxian (1994)	Population carencée	Doses nutritionnelles BC, Vit E, selenium	↘ CANCERS
Etude ATBC (1994)	Fumeurs	« Hautes doses » BC, Vit E	
Etude CARET (1996)	Fumeurs	« Hautes doses » BC, Vit A	
Etude PHS (1996)	Médecins	« Hautes doses » BC, aspirine	
Etude Women's health (1999)	Population générale	« Hautes doses » BC, aspirine	
Etude Women's health (2005)	Population générale	« Hautes doses » Vit E	
Etude SUVIMAX (2005)	Population générale	« Doses nutritionnelles » BC, Vit E, selenium	↘ CANCERS

Essais de prévention primaire

Etude Linxian (1994)	Population carencée	Doses nutritionnelles BC, Vit E, selenium	↘ CANCERS
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Etude PHS (1996)	Médecins	« Hautes doses » BC, aspirine	PAS D'EFFET
Etude Women's health (1999)	Population générale	« Hautes doses » BC, aspirine	PAS D'EFFET
Etude Women's health (2005)	Population générale	« Hautes doses » Vit E	PAS D'EFFET
Etude SUVIMAX (2005)	Population générale	« Doses nutritionnelles » BC, Vit E, selenium	↘ CANCERS

Essais de prévention primaire

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Etude Women's health (2005)	Population générale	« Hautes doses » Vit E	PAS D'EFFET
Etude SUVIMAX (2005)	Population générale	« Doses nutritionnelles » BC, Vit E, selenium	↘ CANCERS

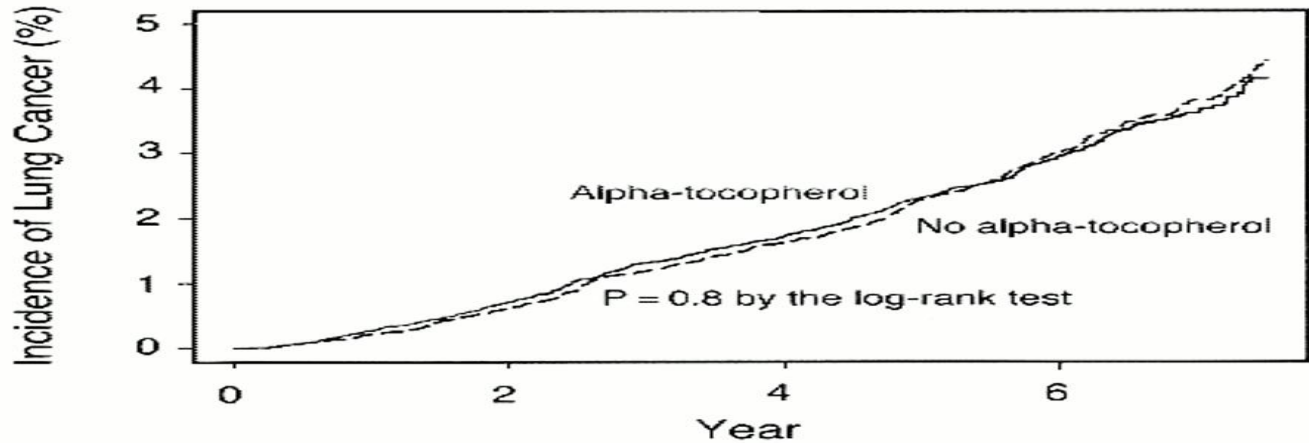
Essais de prévention primaire

Pas d'effet CV

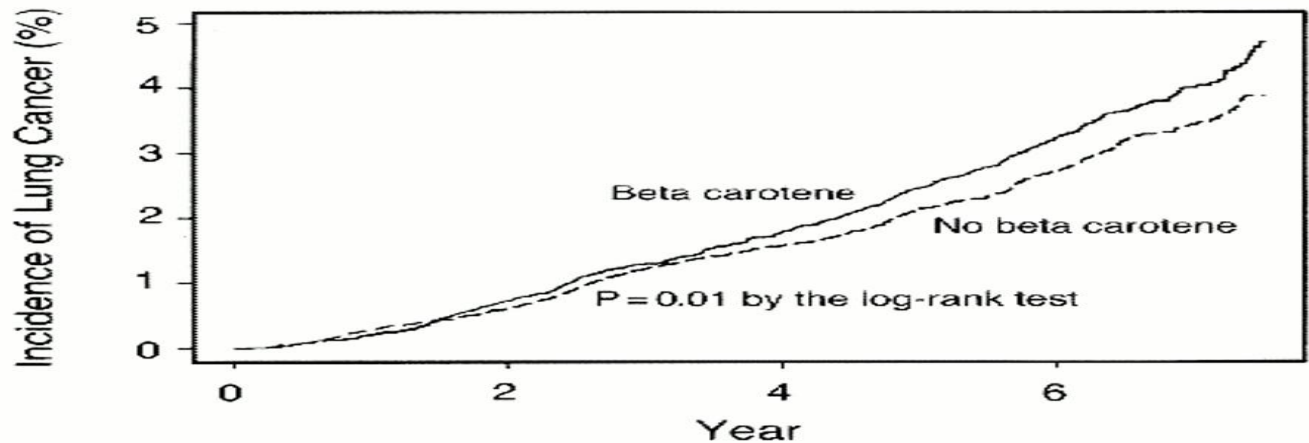
Etude Linxian (1994)	Population carencée	Doses nutritionnelles BC, Vit E, selenium	↘ CANCERS
Etude ATBC (1994)	Fumeurs	« Hautes doses » BC, Vit E	↗ CANCERS
Etude CARET (1996)	Fumeurs	« Hautes doses » BC, Vit A	↗ CANCERS
Etude PHS (1996)	Médecins	« Hautes doses » BC, aspirine	PAS D'EFFET
Etude Women's health (1999)	Population générale	« Hautes doses » BC, aspirine	PAS D'EFFET
Etude Women's health (2005)	Population générale	« Hautes doses » Vit E	PAS D'EFFET
Etude SUVIMAX (2005)	Population générale	« Doses nutritionnelles » BC, Vit E, selenium	↘ CANCERS

Alpha-Tocopherol Beta Carotene Cancer (ATBC) Study - Lung cancer

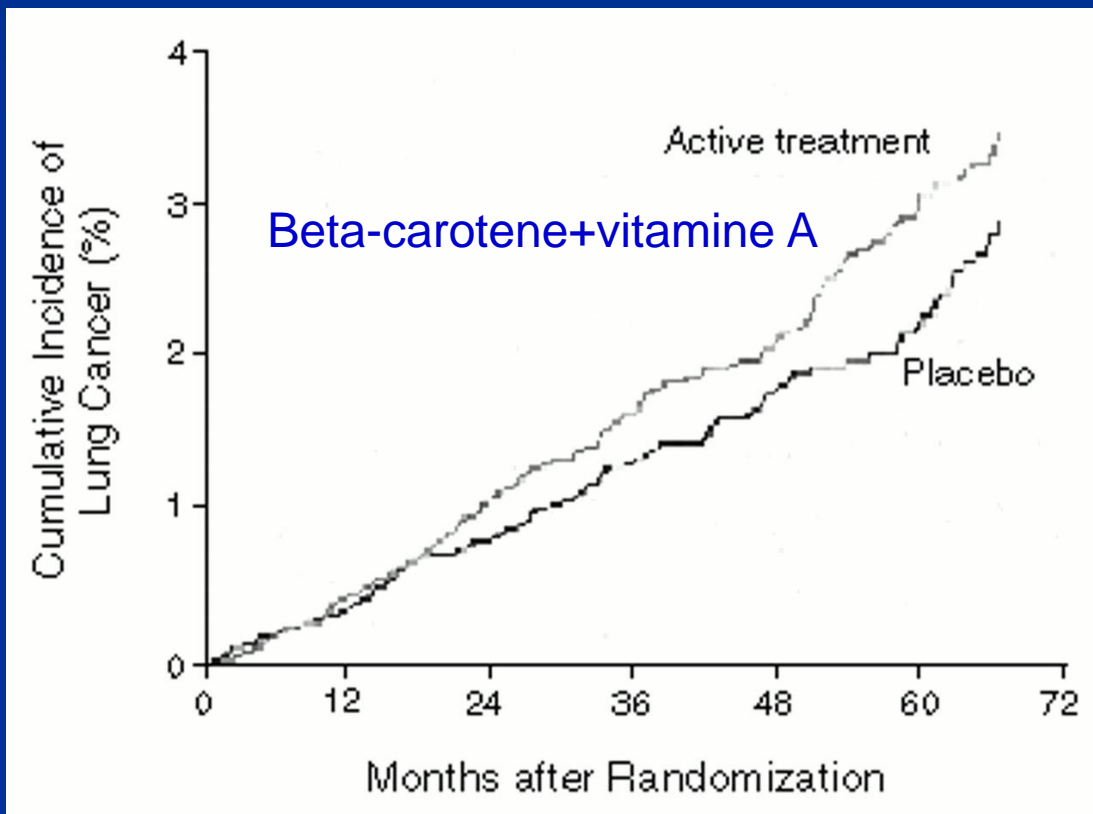
Vitamine E



Beta-carotene

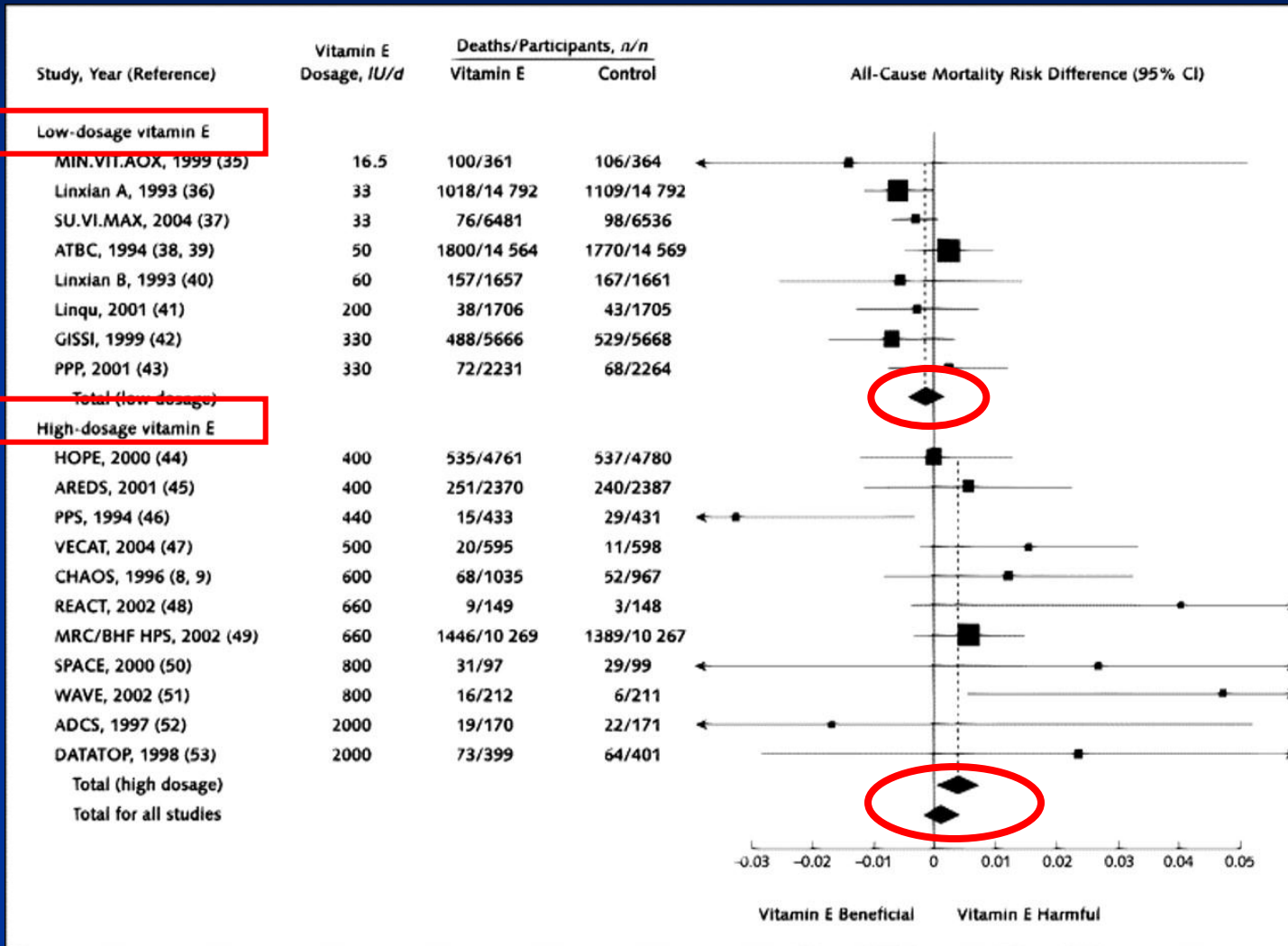


Carotene and Retinol Efficacy Trial (CARET) - Lung cancer



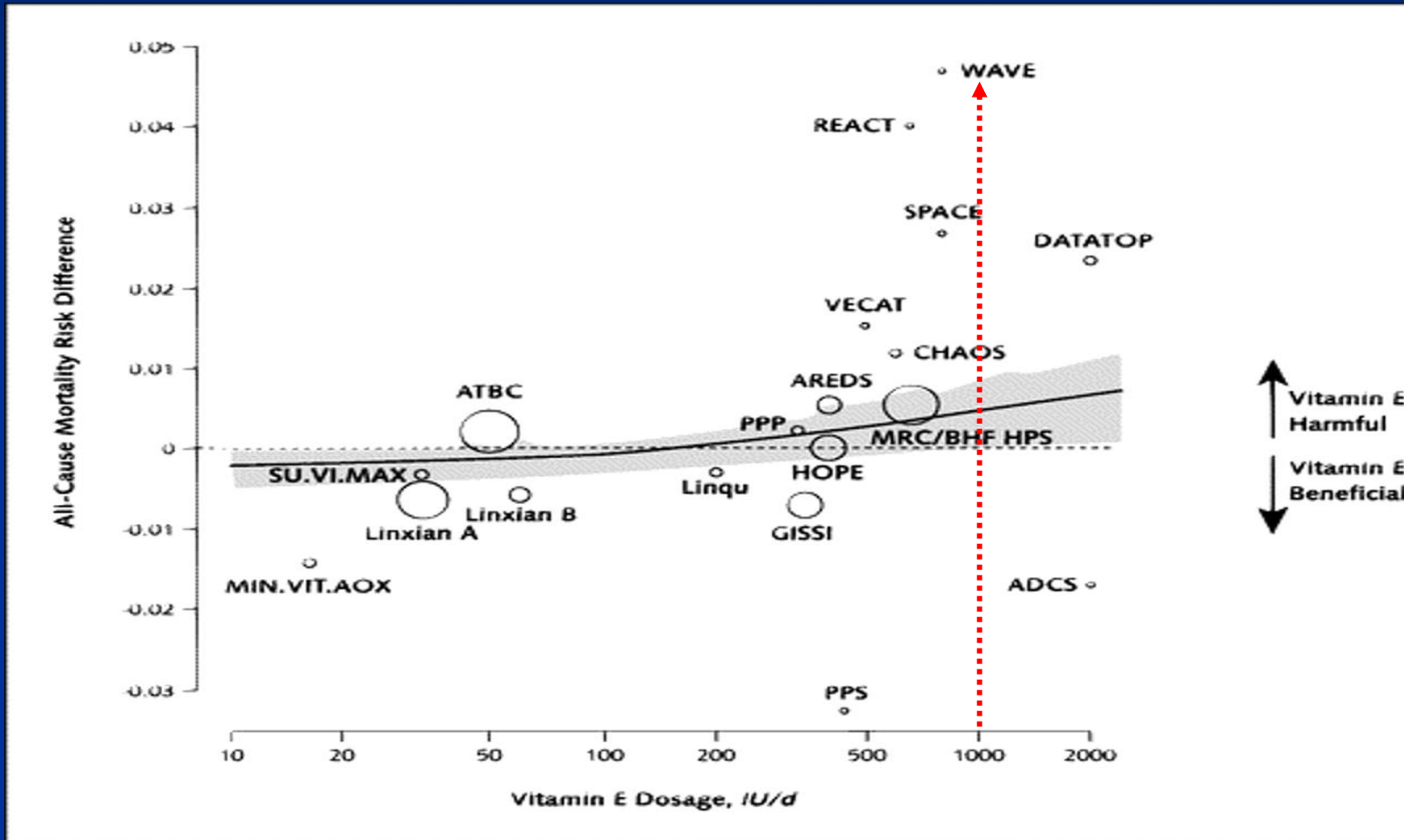
- n=18,314
- Asbestose ou fumeurs
- RR=1.28 (1.04-1.57)

Vitamine E & mortalité



- n=135,967
- Essais=19

Vitamine E & mortalité: association dose-effet ???





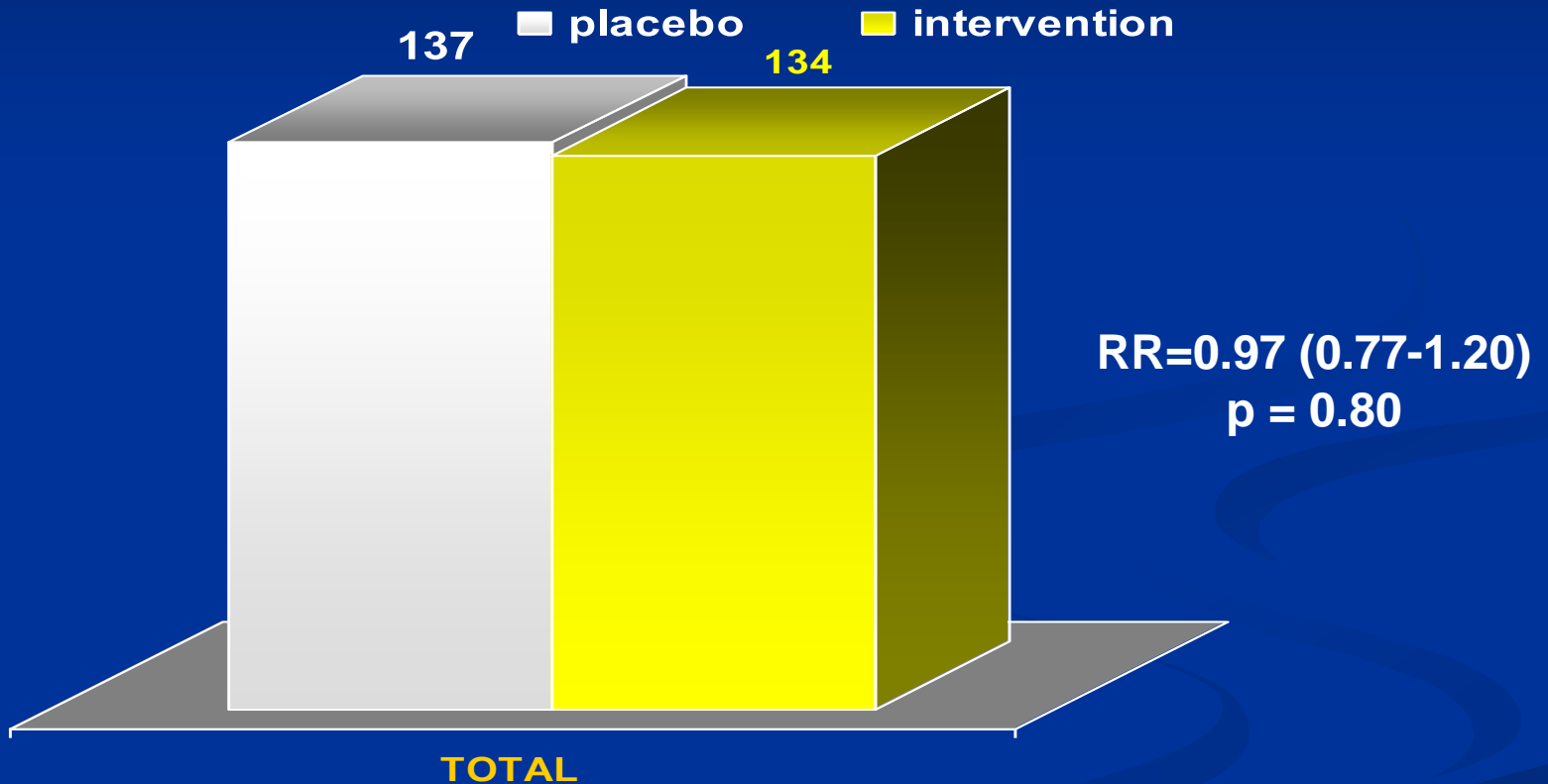
Blackmores Vitamin E 1000 IU

...helps reduce oxidation of LDL chol...is a powerful antioxidant and free radical scavenger **Price: \$39.95**

Equivalent intake of 4 kg of butter/d

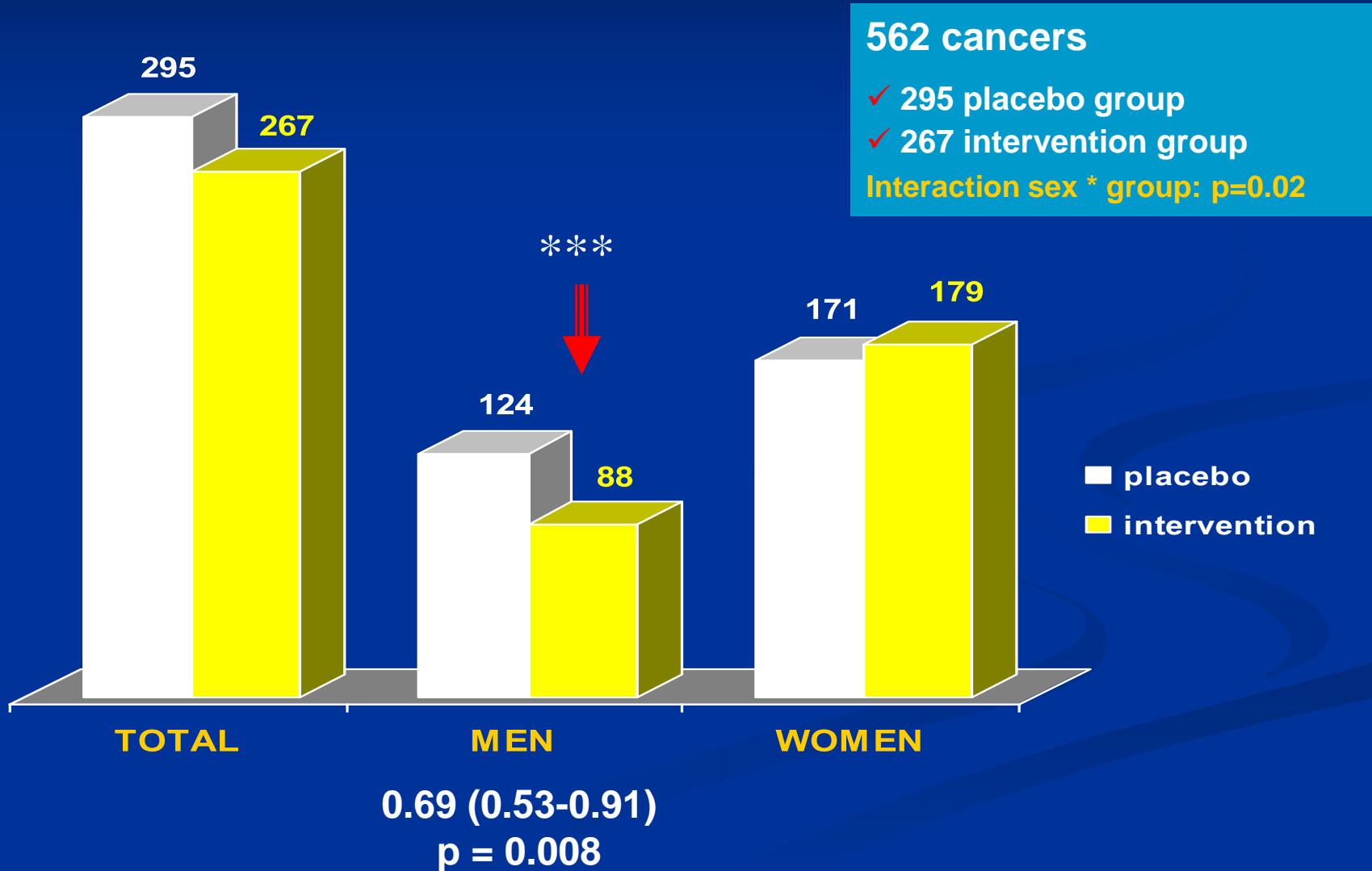


SUVIMAX: évènements ischémiques

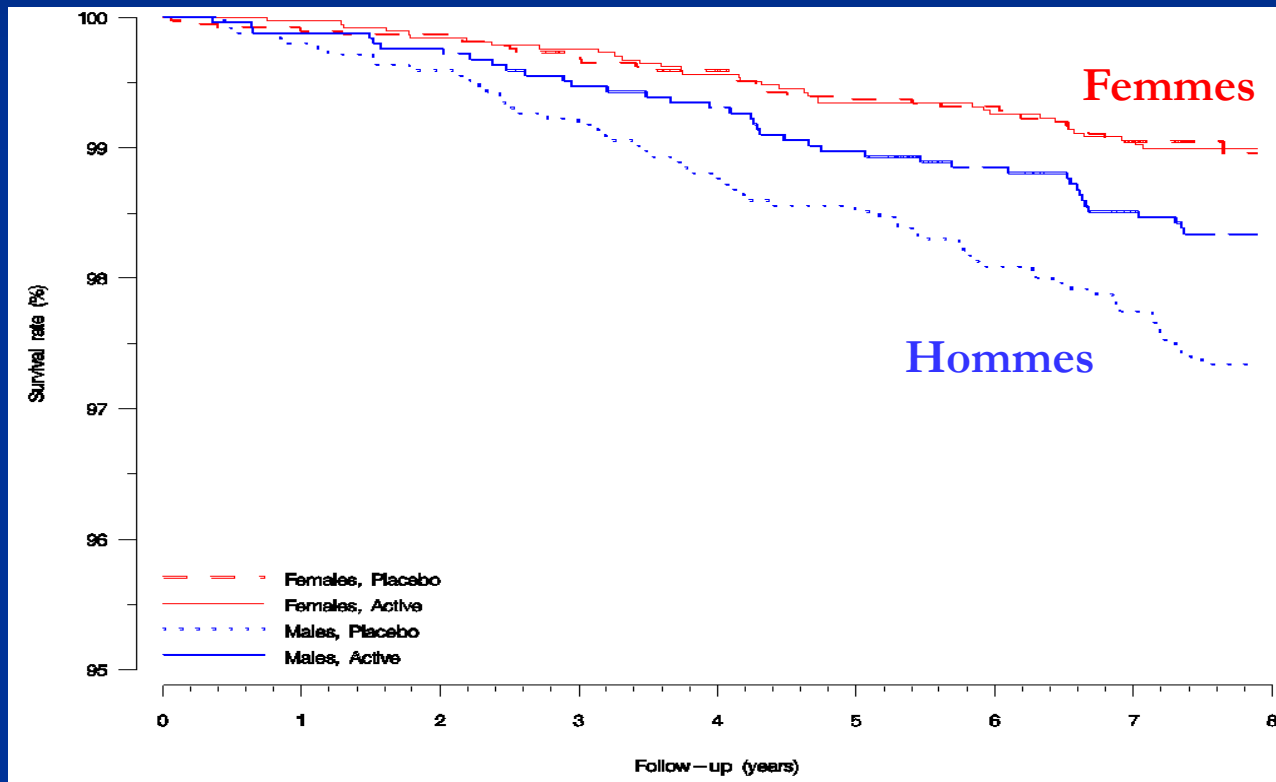


271 events
No sex X group interaction

SUVIMAX: cancers



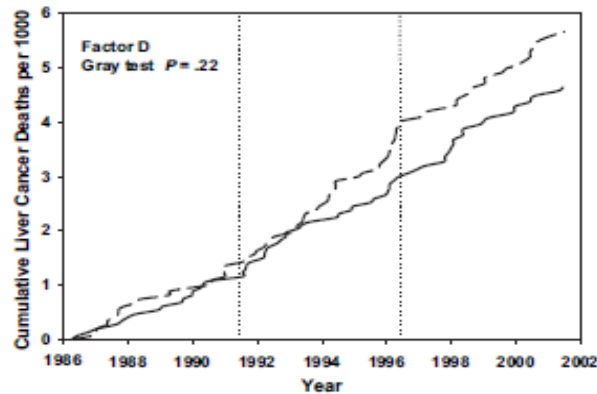
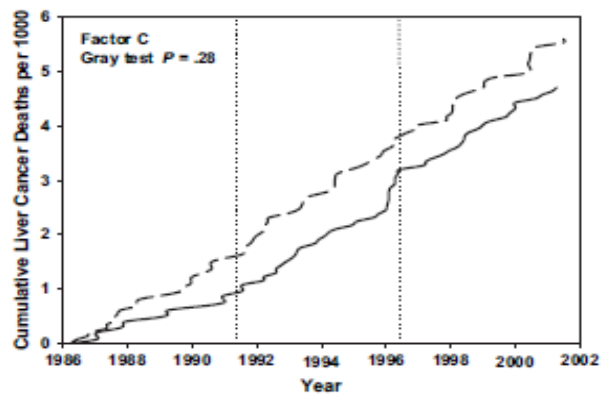
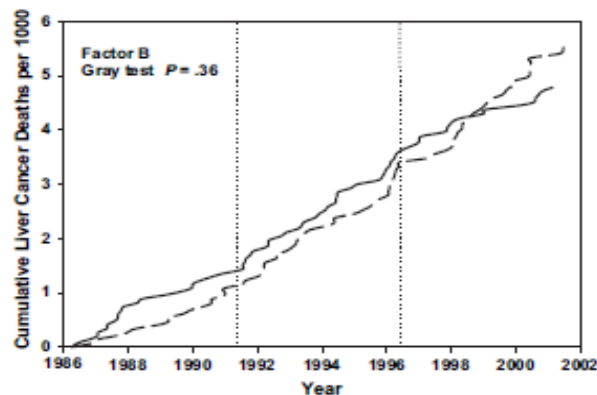
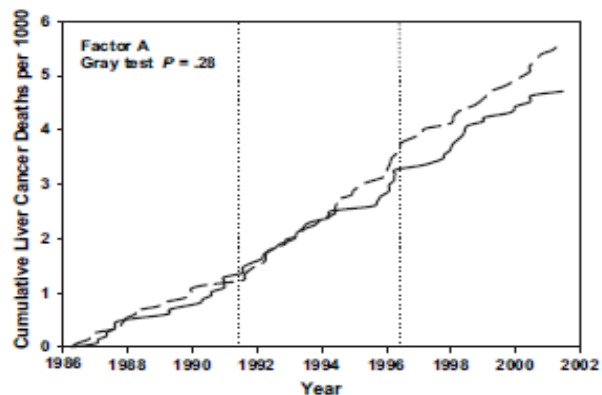
SUVIMAX: survie



Chemoprevention of Primary Liver Cancer: A Randomized, Double-Blind Trial in Linxian, China

JNCI 2007

Mortalité liée au CHC



4 Combinaisons
d'antioxydants

Conclusion None of the factors tested reduced overall liver cancer mortality. However, three factors reduced liver cancer mortality in certain subgroups.

Selenium in the Prevention and Treatment of Hepatocellular Carcinoma

Anti-Cancer Agents in Medicinal Chemistry, 2010

Resveratrol in the chemoprevention and treatment of hepatocellular carcinoma

Cancer Treatment Reviews, 2010

→ *Phase pré-clinique*

→ *Quels types d'essais ?*

Population générale



Population
générale



Population
exposée



Cirrhose

Population générale



Population exposée



Cirrhose

Contexte biologique



Alcool

VHB

VHC

Population générale



Population exposée



Cirrhose

Contexte biologique



Alcool



VHB



VHC



Prise en compte des variations individuelles

**CONCLUSIONS
ET
PERSPECTIVES**

**SURCHARGE HEPATIQUE
EN FER**

STRESS OXYDANT



**SURCHARGE HEPATIQUE
EN FER**

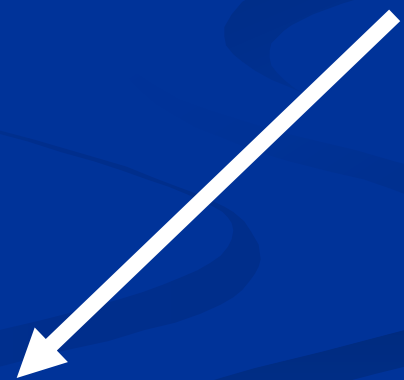
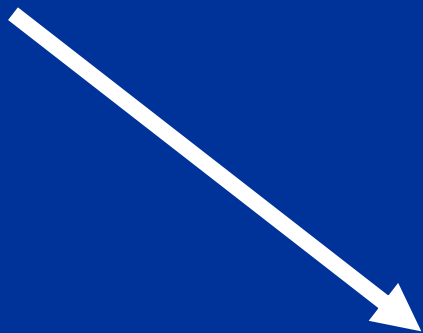
STRESS OXYDANT



**SURCHARGE HEPATIQUE
EN FER**

STRESS OXYDANT

CHC



**FACTEURS
GENETIQUES**

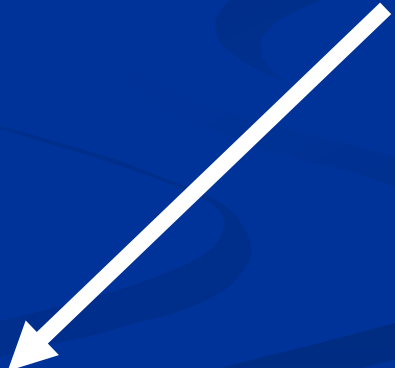
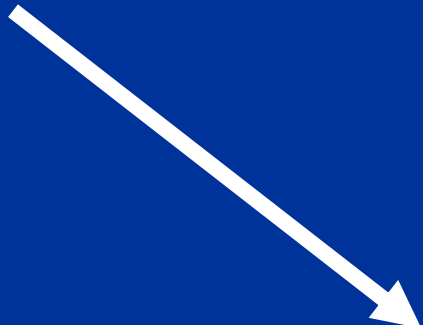
**FACTEURS
ENVIRONNEMENTAUX**

- Syndrome dysmétabolique
- Alcool
 - Dose
 - Type
 - Mode
- Facteurs nutritionnels
 - Aliments riches en fer
 - Oxydants/anti-oxydants



**SURCHARGE HEPATIQUE
EN FER**

STRESS OXYDANT



CHC

**FACTEURS
GENETIQUES**

**FACTEURS
ENVIRONNEMENTAUX**

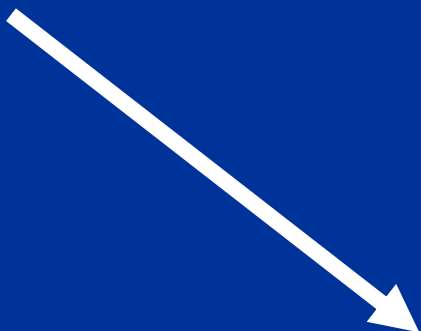
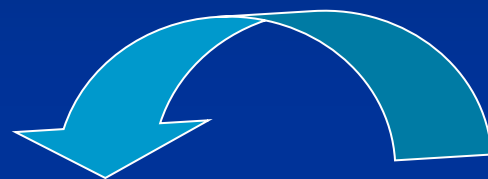
- Syndrome dysmétabolique
- Alcool
 - Dose
 - Type
 - Mode
- Facteurs nutritionnels
 - Aliments riches en fer
 - Oxydants/anti-oxydants

**SURCHARGE HEPATIQUE
EN FER**

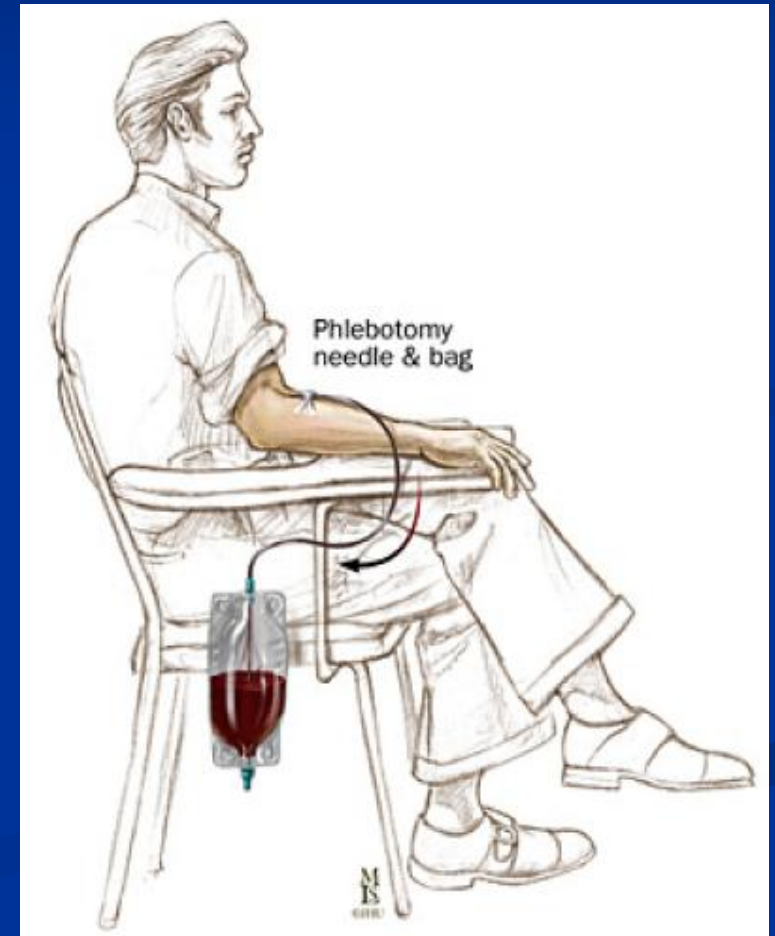
**CAUSE DE
LA MALADIE HEPATIQUE
SOUS-JACENTE**

STRESS OXYDANT

CHC



Saignées



EASL clinical practice guidelines for HFE hemochromatosis

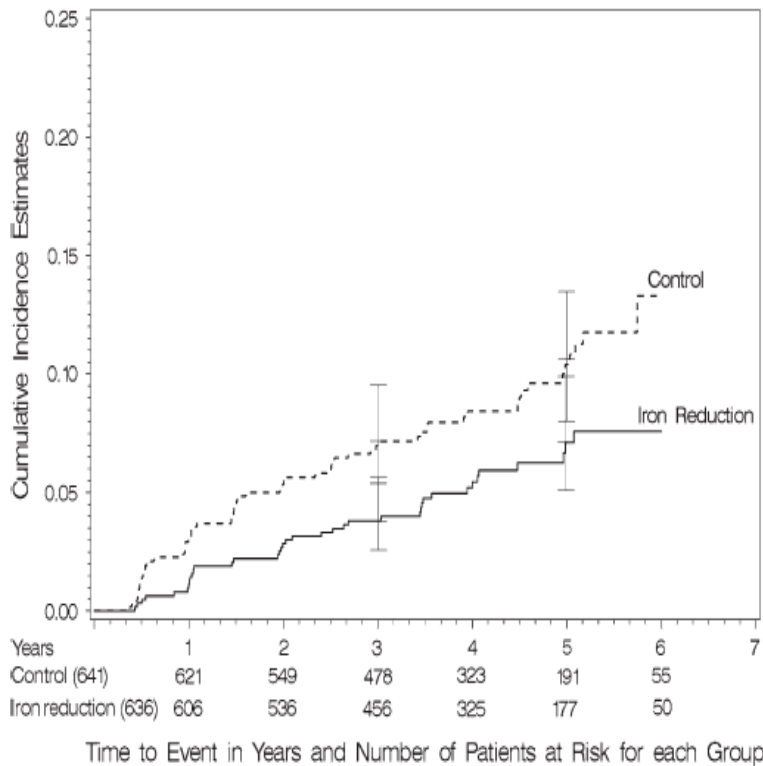
European Association for the Study of the Liver*

Decreased Cancer Risk After Iron Reduction in Patients With Peripheral Arterial Disease: Results From a Randomized Trial

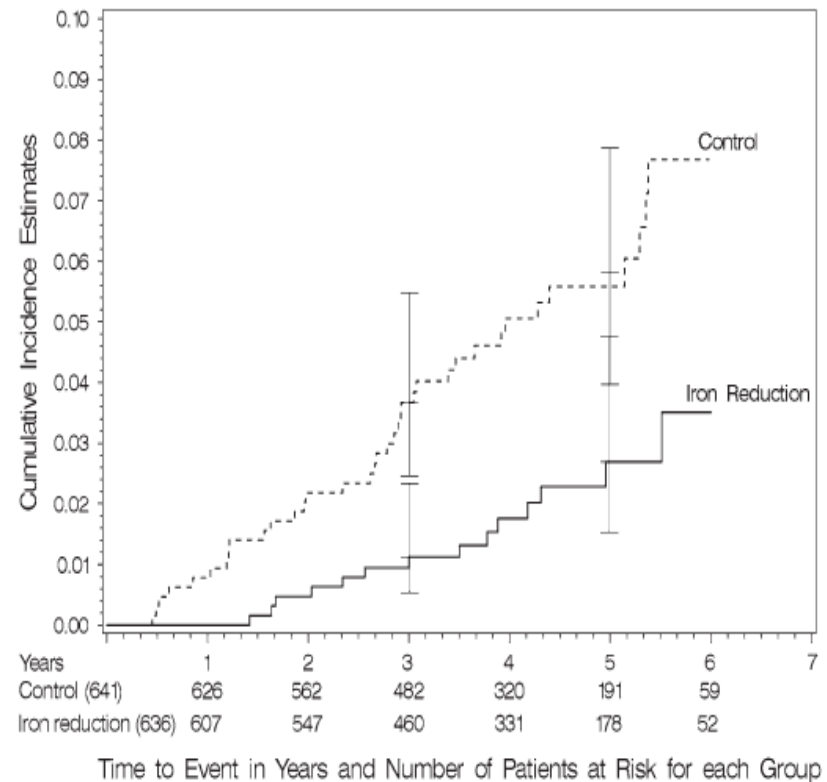
Zacharski et al, JNCI 2008

Essai FeAST

CANCER INCIDENCE



CANCER-RELATED DEATH



La déplétion en fer réduit le risque de survenue de cancers