L'Epatite C come modello dinamico della disparità di genere nelle malattie di fegato

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UNIVERSITÀ DEGLI STUDI
DI MODENA E REGGIO EMILIA

Summary

- Reason for gender differences
- The HCV model
  - Menopause
  - Fertility
- HCC

Evidence of the presence of ER alfa and AR in the liver

Characterization of estrogen receptor from human liver. Gastroenterology 1989

Ethanol-induced increase in cytosolic estrogen receptors in human male liver: a possible explanation for biochemical feminization in chronic liver disease due to alcohol. Hepatology1989

Type of estrogen receptor determines response to antiestrogen therapy. Cancer Research 1996

Variant liver estrogen receptor transcripts already occur at an early stage of chronic liver disease. Hepatology 1998

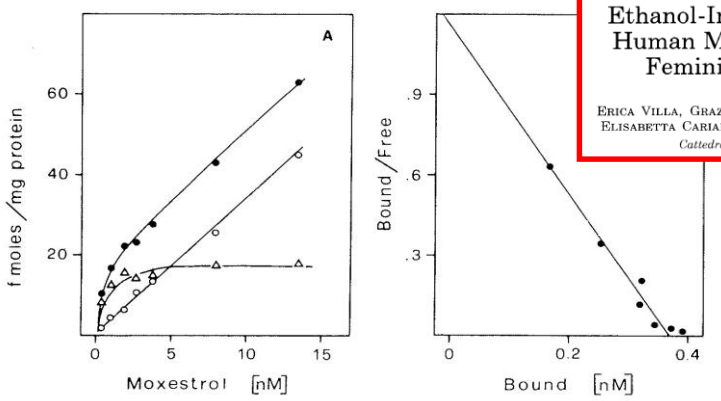
Natural history of inoperable hepatocellular carcinoma: estrogen receptors' status in the tumor is the strongest prognostic factor for survival. Hepatology 1998

Hormonal therapy with megestrol in inoperable hepatocellular carcinoma characterized by variant oestrogen receptors. Br J Cancer 2001

Phytoestrogens and liver disease. Mol Cell Endocrinol 2002

Estrogen receptor classification comparison with clinical staging JCO 2003

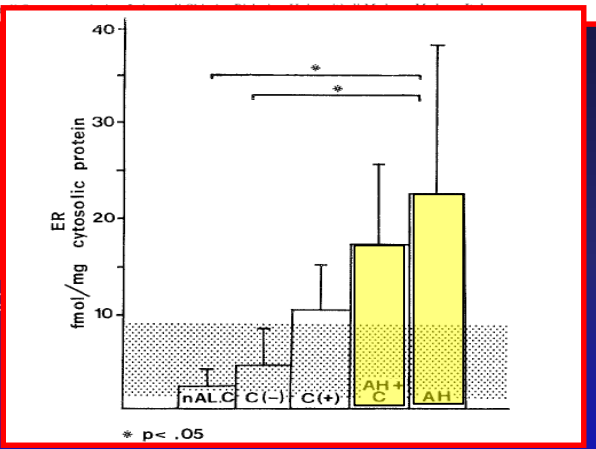
Characterization of Estrogen Receptor From Human Liver



Villa et al. Gastroenterolog

Ethanol-Induced Increase in Cytosolic Estrogen Receptors in Human Male Liver: A Possible Explanation for Biochemical Feminization in Chronic Liver Disease Due to Alcohol

Erica Villa, Grazia M. Baldini, Gian Paolo Rossini, Claudio Pasquinelli, Margherita Melegari, Elisabetta Cariani, Cristina Tata, Stefano Bellentani, Alberto Ferrari and Federico Manenti



- Eagon PK, Elm MS, Stafford EA, Porter LE. Androgen receptor in human liver:characterization and quantitation in normal and diseased liver. Hepatology. 1994 Jan;19(1):92-100
- Eagon PK, Francavilla A, DiLeo A, et al. . Quantitation of estrogen and androgen receptors in HCC and adjacent normal human liver. Dig Dis Sci. 1991Sep;36(9):1303-8.
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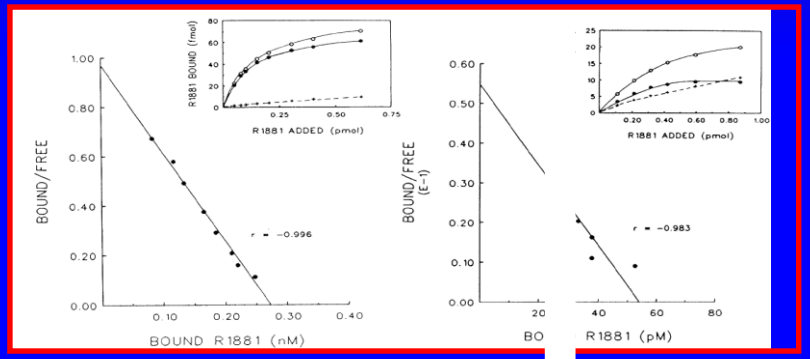
- Li Z, Tuteja G, Schug J, Kaestner KH. Foxa1 and Foxa2 are essential for sexual dimorphism in liver cancer. Cell. 2012 Jan 20;148(1-2):72-83.
- Zhu R, Zhang JS, Zhu YZ, Fan J, Mao Y, Chen Q, Zhu HG. HBx-induced androgen receptor expression in HBV-associated hepatocarcinoma is independent of the methylation status of its promoter. Histol Histopathol. 2011 Jan;26(1):23-35.

And many others……

Androgen Receptor in Human Liver: Characterization and Quantitation in Normal and Diseased Liver

Patricia K. Eagon,[1, 2, 3] Mary S. Elm,[2] Elizabeth A. Stafford[2]* and Lynne E. Porter[2]

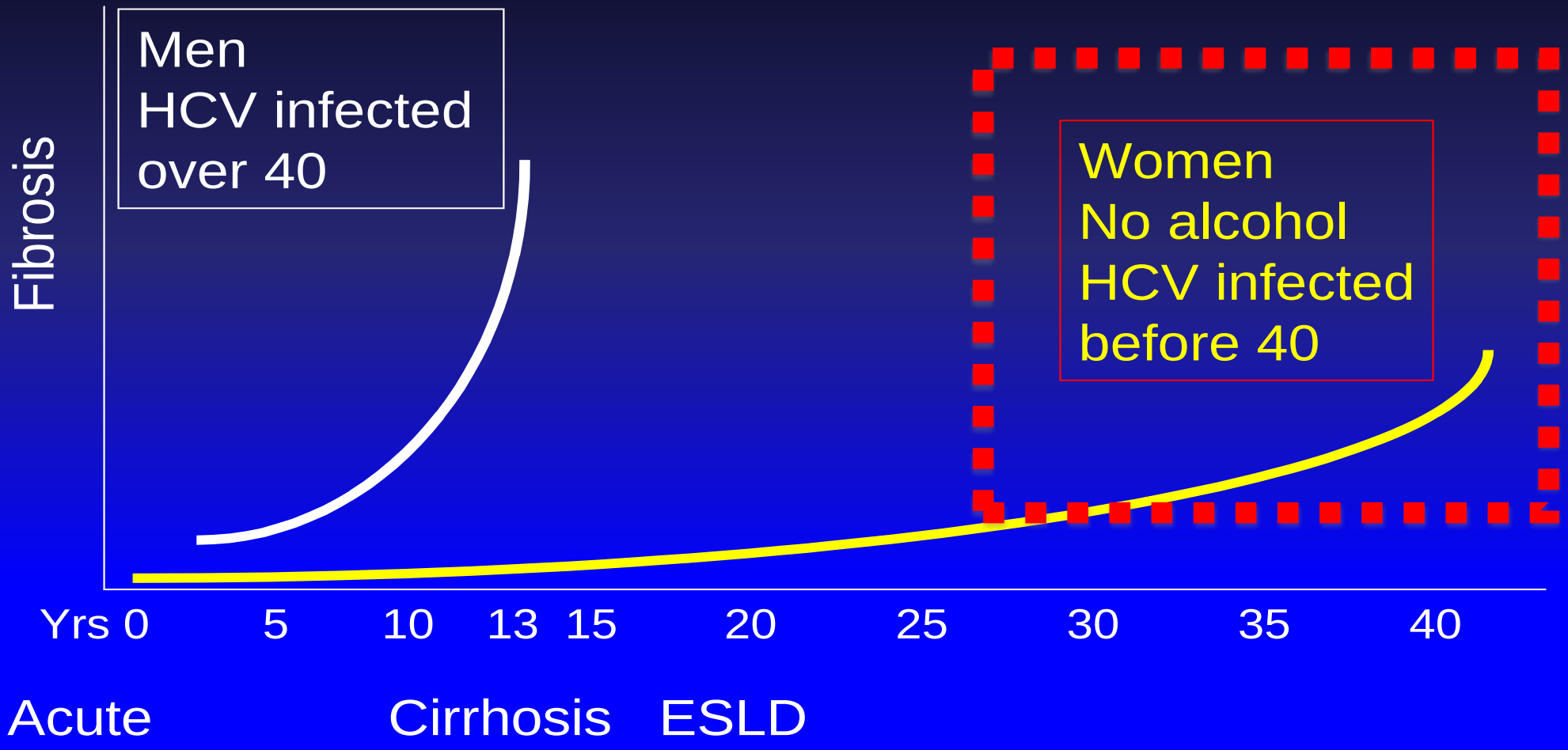


Hepatology 1994

Normal Testosterone and Estradiol levels throughout life (rough estimate)

The HCV model:
reproductive factors and fertility

The natural history of chronic hepatitis C from Fibrosis to Cirrhosis



Poynard et al., Lancet 1997

Four groups of women selected according to timing of reproductive phases

- Full reproductive (n. 123): i.e. women with regular menses and <45 years of age)
- Pre-menopausal (n. 38): women included in this group were those who entered menopause 3 to 5 years after enrolment in the study.
- Early menopausal (n. 50): included in this group were women menopausal from not more than 5 years from enrolment;
- Late menopausal (n. 144): women that were menopausal since at least 10 years.
- Four groups of males, pair-matched by age in a 1:1 proportion, were subsequently selected in order to have four perfectly comparable pairs

Villa et al., Gastro 2011

Baseline Demographic, Laboratory, Metabolic and Histological Features of 1000 Patients with Chronic Hepatitis C According to Gender

Variables	Men (n=558)	Women (n=442)	p
Mean Age at enrolment - years	**47.9±11.6**	51.9±11.3	<.001
Mean Body Mass Index – Kg/m^2	**26.3±3.6**	24.7±3.8	<.001
Platelets count X 10^3/mm^3	**179.0±56.5**	203.4±66.5	<.001
Alanine Aminotransferase – IU/L	**98.6±87.4**	73.4±67.4	<.001
GGT – IU/L	**57.1±52.4**	37.1±37.3	<.001
Insulin – µU/mL	6.1±3.5	10.0±6.4	.093
HOMA-score	1.5±0.7	2.6±2.2	.124
Length of HCV infection (years)	14,1 ±1.6	13,5 ±2.2	.073
Histology at Biopsy			
Steatosis:			
<5%	328 (63.1)	261 (63.5)	.95
≥5% to <20%	150 (28.8)	116 (28.2)	.99
≥20%	42 (8.0)	34 (8.2)	.99
Grade of Inflammation			
0-5	391 (71.89)	332 (80.2)	
6-11	128 (24.5)	74 (17.9)	.018
12-18	4 (0.8)	8 (1.9)	
Stage of Fibrosis			
0-3	**443 (84.4)**	372 (80.6)	
4-6	82 (15.6)	43 (10.4)	.020
Cirrhosis	**69 (12.3)**	30 (6.7)	.003

Villa et al., Gastro 2011

Univariate and multivariate analysis for fibrosis in pts with chronic hep C

Women

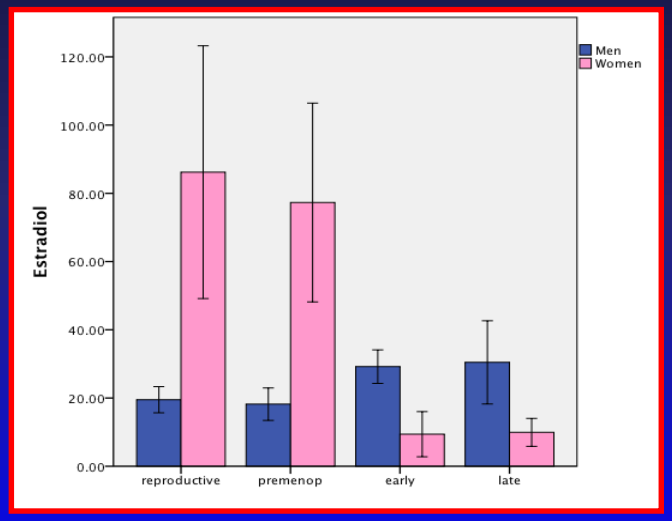
	Univariate		Multivariate	
	OR (95% CI)	*P*	OR (95% CI)	*P*
Age (years)	1.089 (1.040–1.140)	0.000	1.028 (0.939–1.126)	0.553
Duration of HCV infection (years)	1.118 (1.037–1.205)	0.004	1.015 (0.884–1.166)	0.833
HCV infection's Acquisition Age	1.036 (1.015–1.057)	0.001	1.000 (0.879–1.139)	0.996
Necro-inflammation	1.458 (1.277–1.665)	0.000	1.506 (1.181–1.1.922)	0.001
Steatosis (0 *vs.* >20%)	1.775 (1.018–3.095)	0.043	3.029 (1.154–7.951)	0.024
Circulating Estradiol (pgml)	0.977 (0.963–0.991)	0.001	0.973 (0.947–0.999)	0.041
Baseline HCV RNA (IU/mL)	1.000 (1.000–1.000)	0.024	1.000 (1.000–1.000)	0.578
ALT (IU/L)	1.009 (1.004–1.013)	0.000	1.011 (0.003–1.019)	0.009
GGT (IU/L)	1.028 (1.016–1039)	0.000	1.008 (0.992–1.025)	0.327
Platelet count ($\times 10^3/mm^3$)	0.970 (0.969–0.981)	0.000	0.988 (0.974–1.002)	0.099
Portal vein diameter (mm)	2.392 (1.804–3.171)	0.000	2.644 (1.657–4.220)	0.0001

All

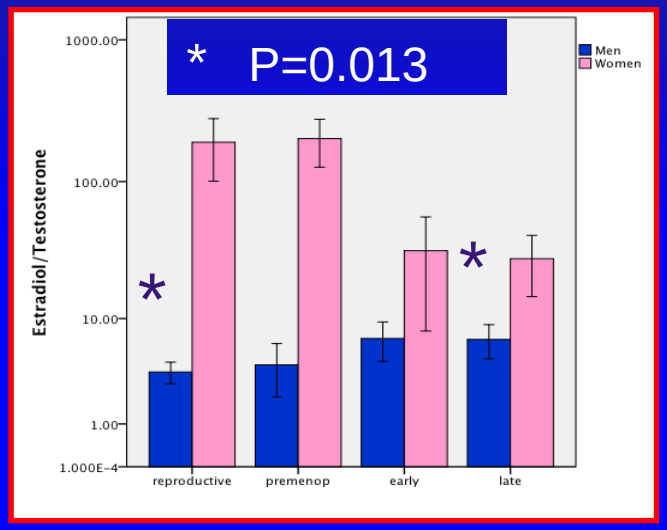
	Univariate		Multivariate	
	OR (95% CI)	*P*	OR (95% CI)	*P*
Sex*	0.406 (0.254–0.649)	0.000	0.460 (0.236–0.896)	0.023
Age (years)	1.049 (1.027–1.072)	0.000	1.031 (1.000–1.062)	0.050
Duration of HCV infection (years)	1.064 (1.023–1.107)	0.002	0.989 (0.941–1.039)	0.654
Necro-inflammation	1.427 (1.312–1.553)	0.000	1.401 (1.239–1.584)	0.0001
Circulating Estradiol (pg/ml)	0.982 (0.972–0.991)	0.000	0.980 (0.962–0.999)	0.040
Platelet count ($x10^3/mm^3$)	0.973 (0.967–0.979)	0.000	0.974 (0.967–0.981)	0.0001
Portal vein diameter (mm)	2.233 (1.901–2.622)	0.000	1.903 (0.539–2.354)	0.000

Villa et al, PlosOne 2012

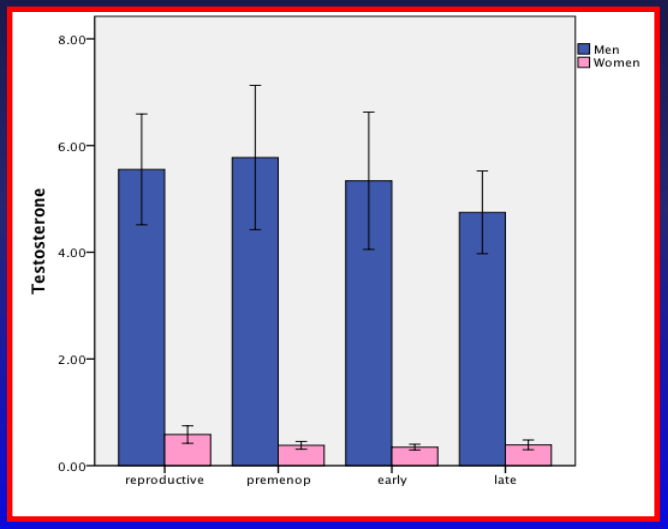
Estradiol and Testosterone serum levels and E2/T ratio in men and women divided according to women's reproductive phases



Estradiol



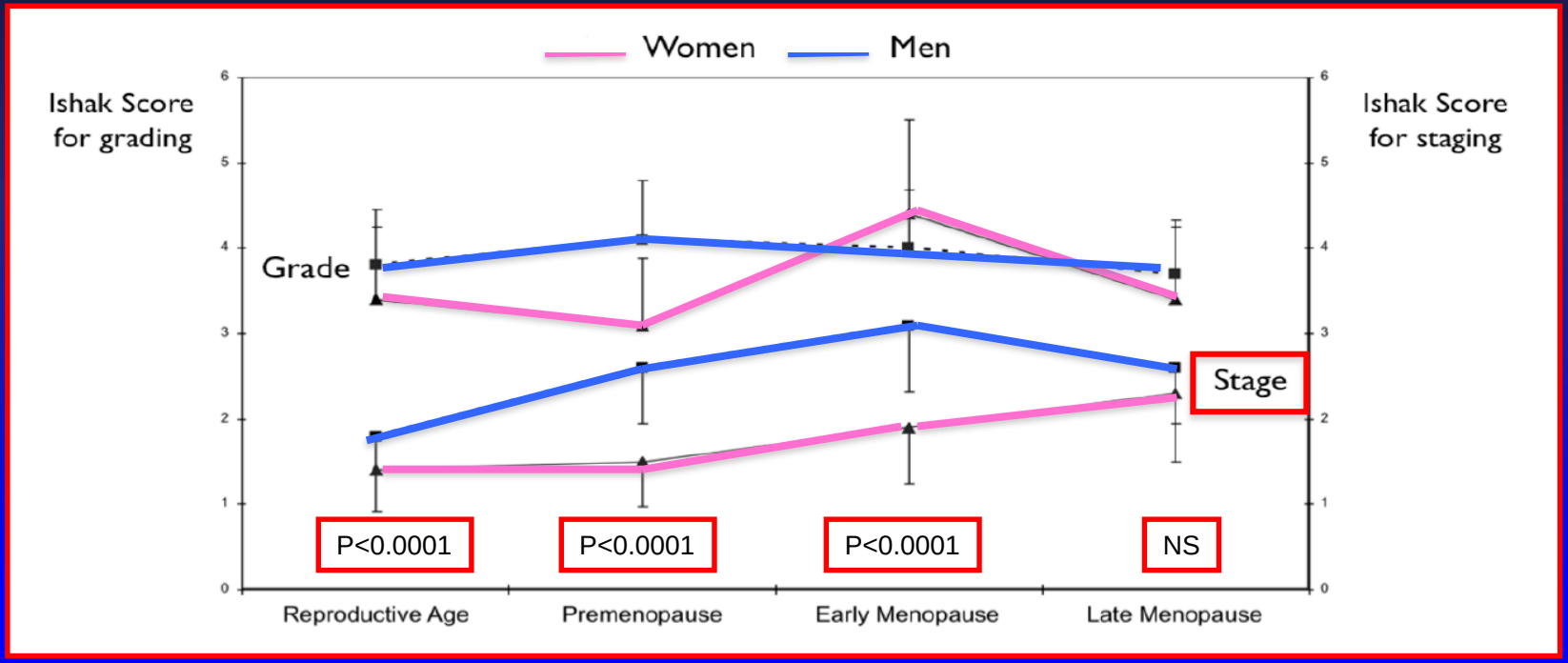
E2/T Ratio



Testosterone

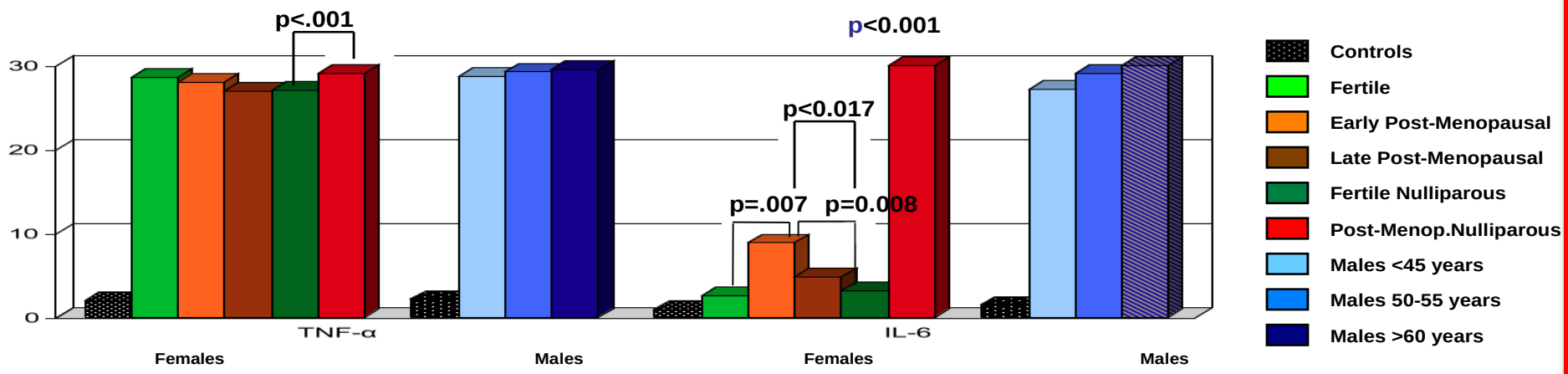
Villa et al, PlosOne 2012

Mean necro-inflammation and fibrosis scores in the 4 sub-groups of female and age-matched male patients with chronic hepatitis



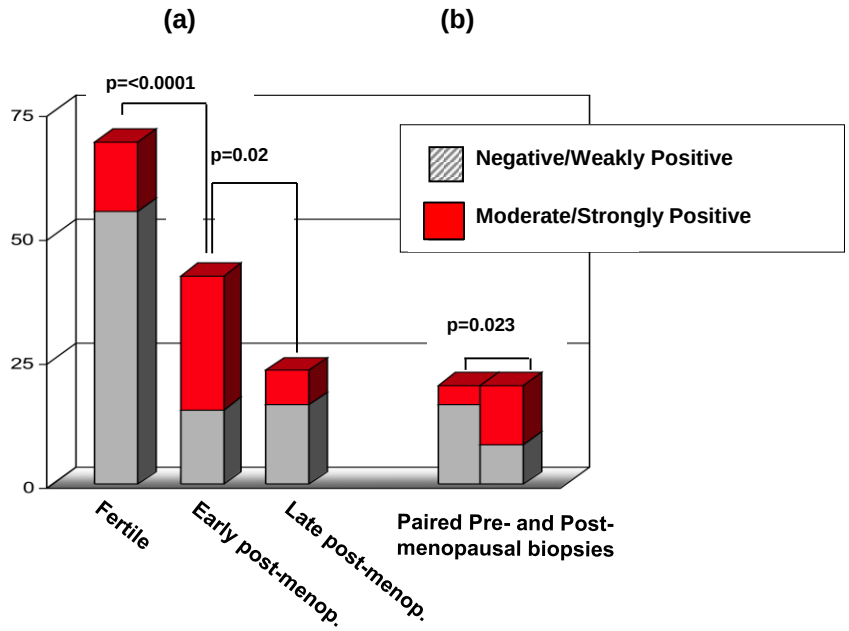
Villa et al, PlosOne 2012

TNF-alfa and IL-6 levels in fertile and post-menopausal HCV+ women compared with males stratified by age groups according to females reproductive status.

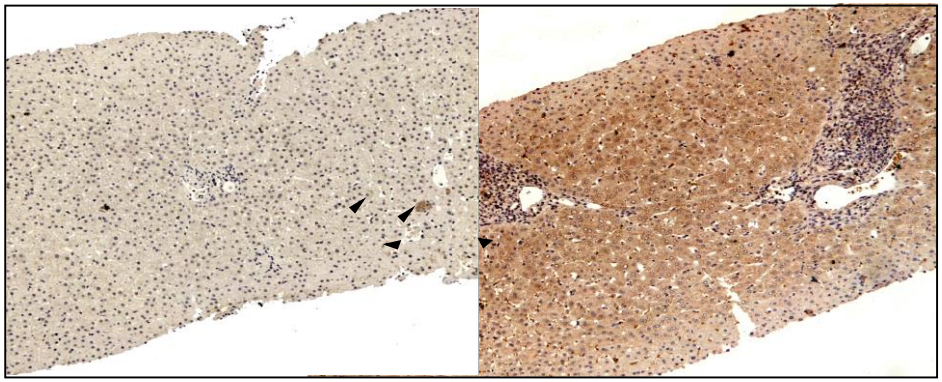


Villa et al. *Gastroenterology* 2011

TNF-α expression in the liver



Before menopause



After menopause

Villa et al., Gastro 2011

% of SVR in males and females of different age groups

Author	Patients n. (M/F ratio)	Type of IFN used	Menopausal status	Age	% SVR
Hayashi, 1998	311 (199/112)	Lymphoblastoid IFN	Not known	<40 years	Females: 75% Males 33%
				>40 years	Females : 15% Males 25%
Elefsiniotis, 2008	185 (74/44)	PEG 2b/Riba	Not known	<35 years 35-55 years > 55 years	Whole group 88.7% NR NR
Sezaki, 2009	490* (179/121)	PEG 2b/Riba	Not known	<50 years	Females: 52% Males 65%
				>50 years	Females : 22% Males: 53%
Reddy, 2009	569* (438/131)	PEG 2a/Riba	Not known	< 50years > 50years	Whole group 52% (29% females) 39% (40% females)

NR: non reported; * only genotype 1; ** median age

Univariate and Multivariate Logistic Regression Analysis of Risk Factors for SVR Failure in 442 Female Patients with Chronic Hepatitis C

Menopause	2.436 (1.620-3.662)	<.001	1.802 (1.154-2.813)	.01
Length of Estrogen deprivation -y				
<5 years	2.497 (1-010-8.172)	.047	8.055 (1.834-25.390)	.006
5-10 years	1.295 (0.497-3.375)	.597	1.683 (0.335-8.458)	.527
≥10 years	2.374 (1.137-4.354)	.021	4.277 (0.747-24.503)	.103
GGT - IU/L	1.017 (1.008-1.026)	<.0001	2.165 (1.364-3.436)	.001
Cholesterol – mg/dL	0.992 (0.983-1.001)	.074	0.967 (0.943-0.991)	.008
HCV Genotype				
1-4 vs 2-3	3.690 (2.427-5.617)	.000	3.861 (2.433-6.134)	.006
Histology at Biopsy				
Steatosis	1.402 (0.940-2.091)	.097	3.053 (0.925-10.076)	.067
Grade of Inflammation	1.131 (1.045-1.225)	.002	0.977 (0.748-1.276)	.863
Stage of Fibrosis	1.494 (1.246-1.793)	<.0001	0.614 (0.299-1.299)	.183
Cirrhosis	0.823 (0.206-3.292)	.783		

Villa E et al., Gastro 2011

Univariate and Multivariate Logistic Regression Analysis of Risk Factors for SVR Failure in 442 Female Patients with Chronic Hepatitis C with Genotype 1

Women with Genotype 1 HCV Infections (n=252)				
Menopause	3.625 (1.562-5.699)	.003	2.908 (1.544-5.478)	.001

Villa et al., Gastro 2011

Fertility in CLD

Fertility in women with chronic liver disease

- Sex hormone disturbances are common in women with CLD
- They are mainly due to the abnormality of the physiology of the hypothalamic-pituitary-gonadal axis and to the etiology of liver disease.
- In women with cirrhosis, chronic anovulation is a common problem, and it is manifested as secondary amenorrhea, oligomenorrhea, or irregular episodes of metrorrhagia.
- LT leads to partial improvements in both sex hormone levels and sexual function.
- Women achieve normal menstruation and fertility a few months after transplantation

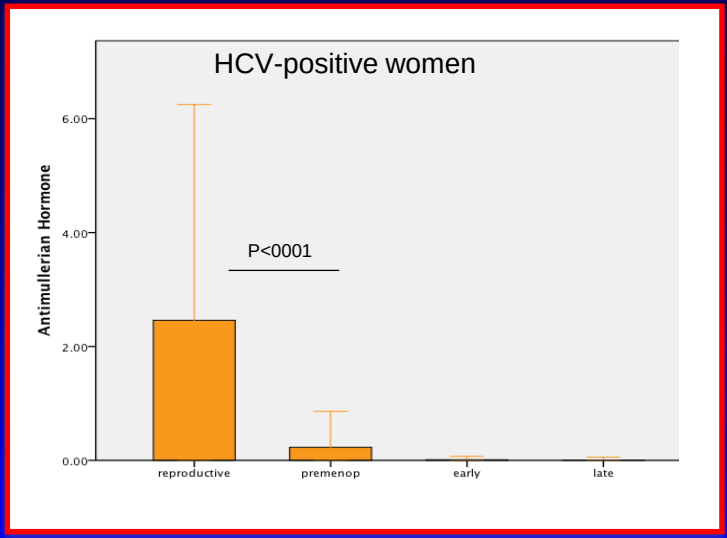
Gavaler JS.. Recent Dev Alcohol 1995;12:199–208.Mass K, et al. Transplantation 1996;62:476–479; Madersbacher S et al. Clin Endocrinol (Oxf) 1996;44:461–466; Parolin M et al Transpl Proc 2004;36:943–944.; Burra et al. Liver Ttanspl 2013; 19: 122-131; Burra P. Liver Transpl 2009;15:S50–S56.

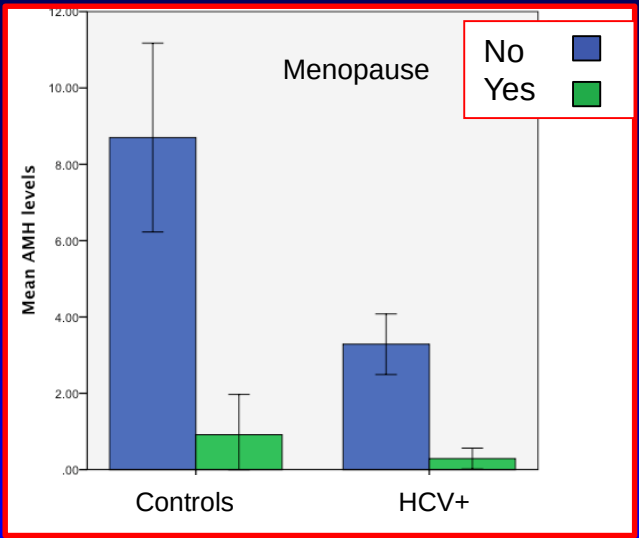
Reproductive factors and liver disease in HCV+ women

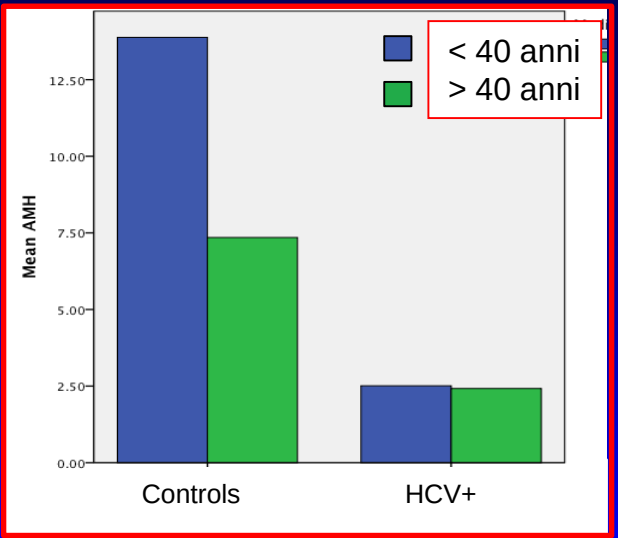
- Response to antiviral therapy with IFN-based therapies is much lower in menopausal women
- Progression of fibrosis in slower in women in fertile age
- Course of CLD is greatly accelerated by menopause
- HCC risk after menopause becomes equivalent to that found in males

Shimizu et al Liver 2001 ; Di Martino et al. Hepatology 2004; Codes et al. Gut 2007; Villa et al. Plos1 2012; Villa et al Gastroenterology 2011; Villa et al. JMV 2012

Mean serum levels of Anti-Mullerian Hormone levels in HCV-positive women divided according to reproductive phases

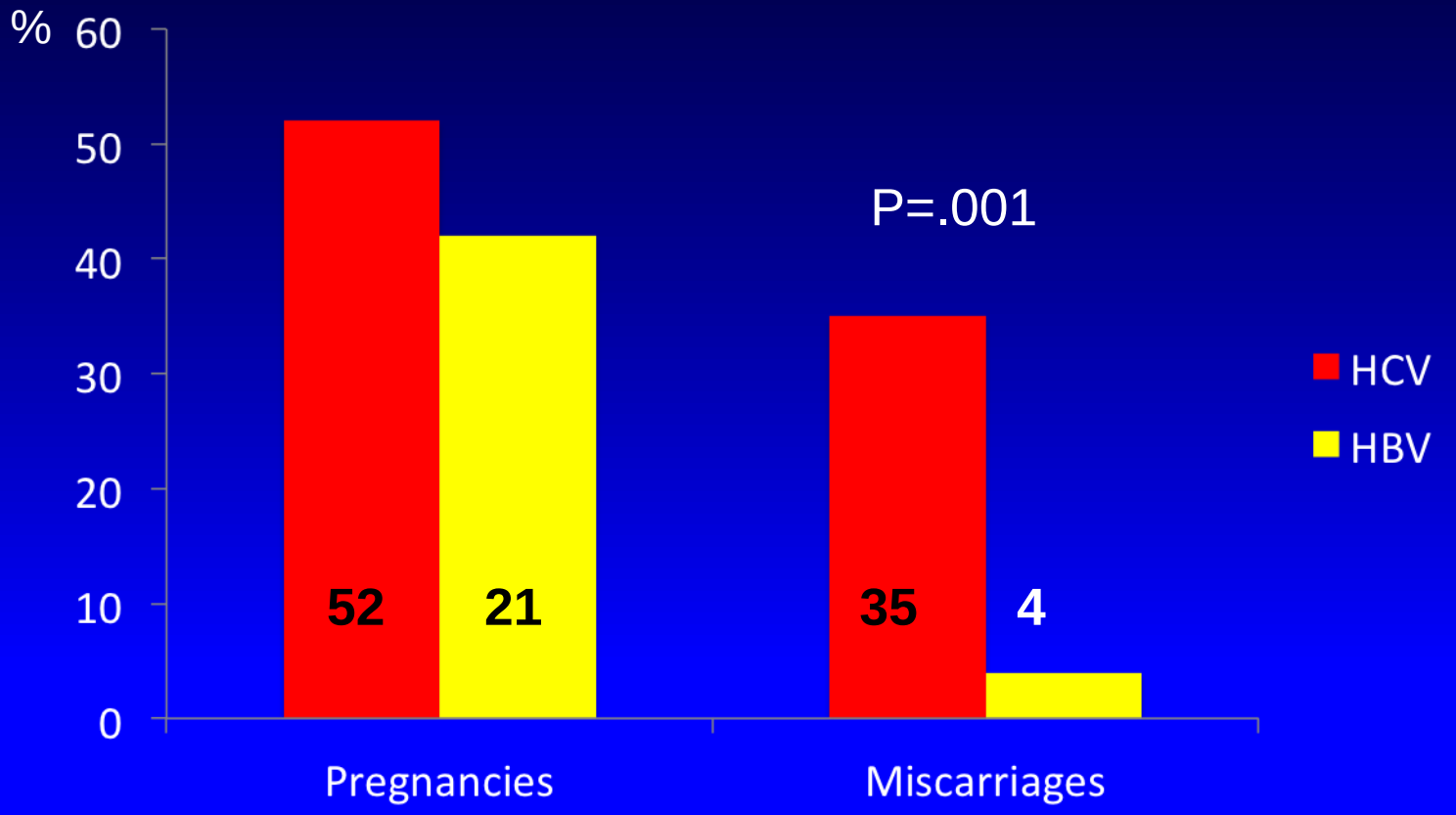






Plos1 2012, Karampatou et al. J Hep 2017

Relative proportion of pregnancies and miscarriage in HCV+ and HBV+ women



Karampatou et al J Hep 2017

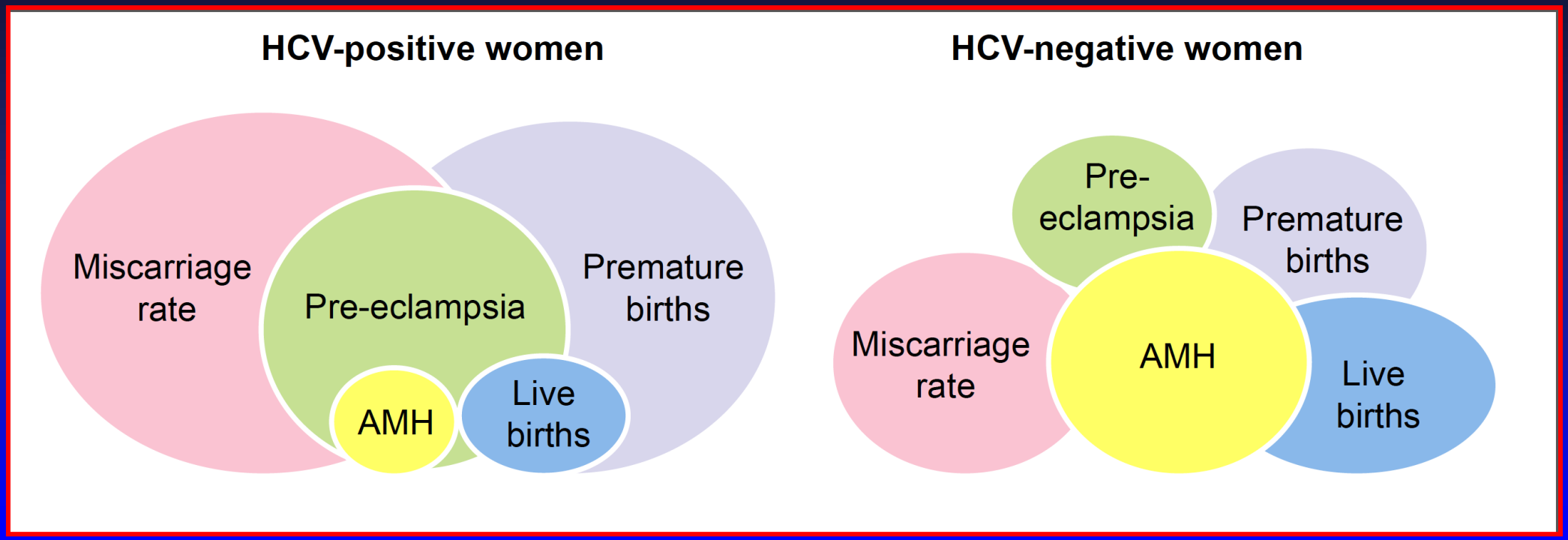
Data from the PITER HCV Cohort Study

590 HCV+ women
between 15 and 49 years of age

Total fertility rate

HCV+ women	0.7
Whole Italian population of the same age range	1.37

Karampatou et al J Hep 2017

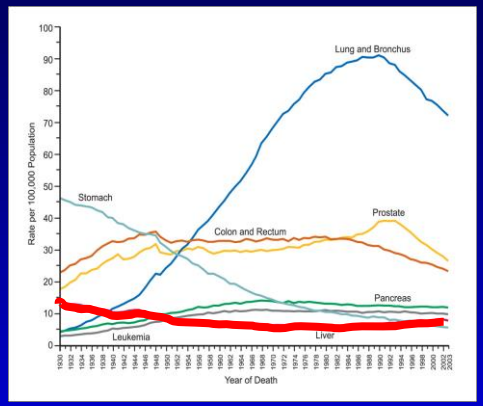


Karampatou et al J Hep 2017

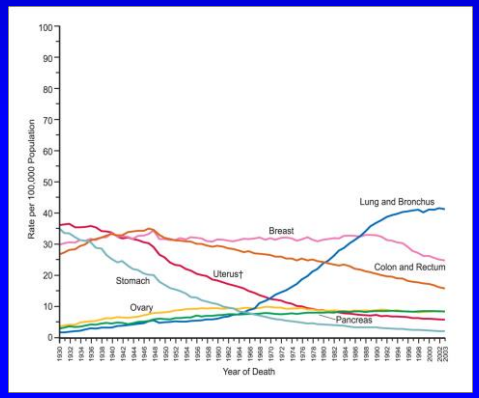
HCC

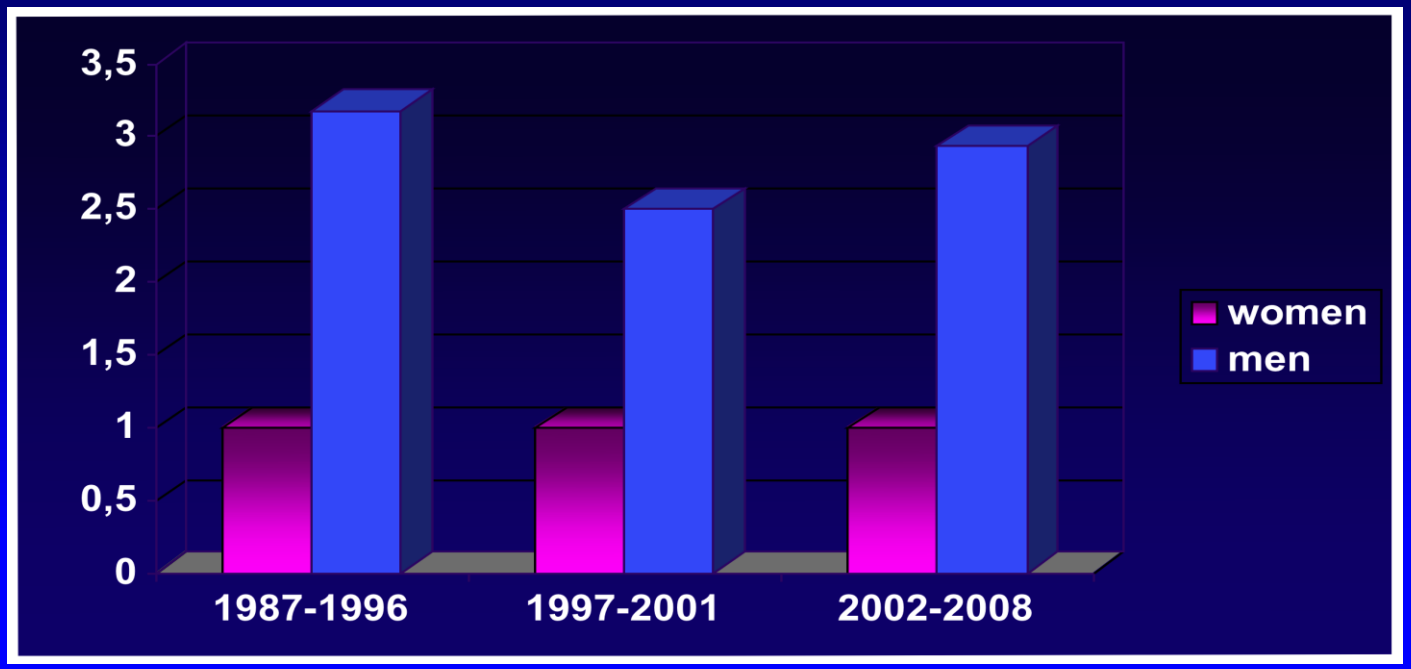
Risk Factors for HCC - Sex

Males



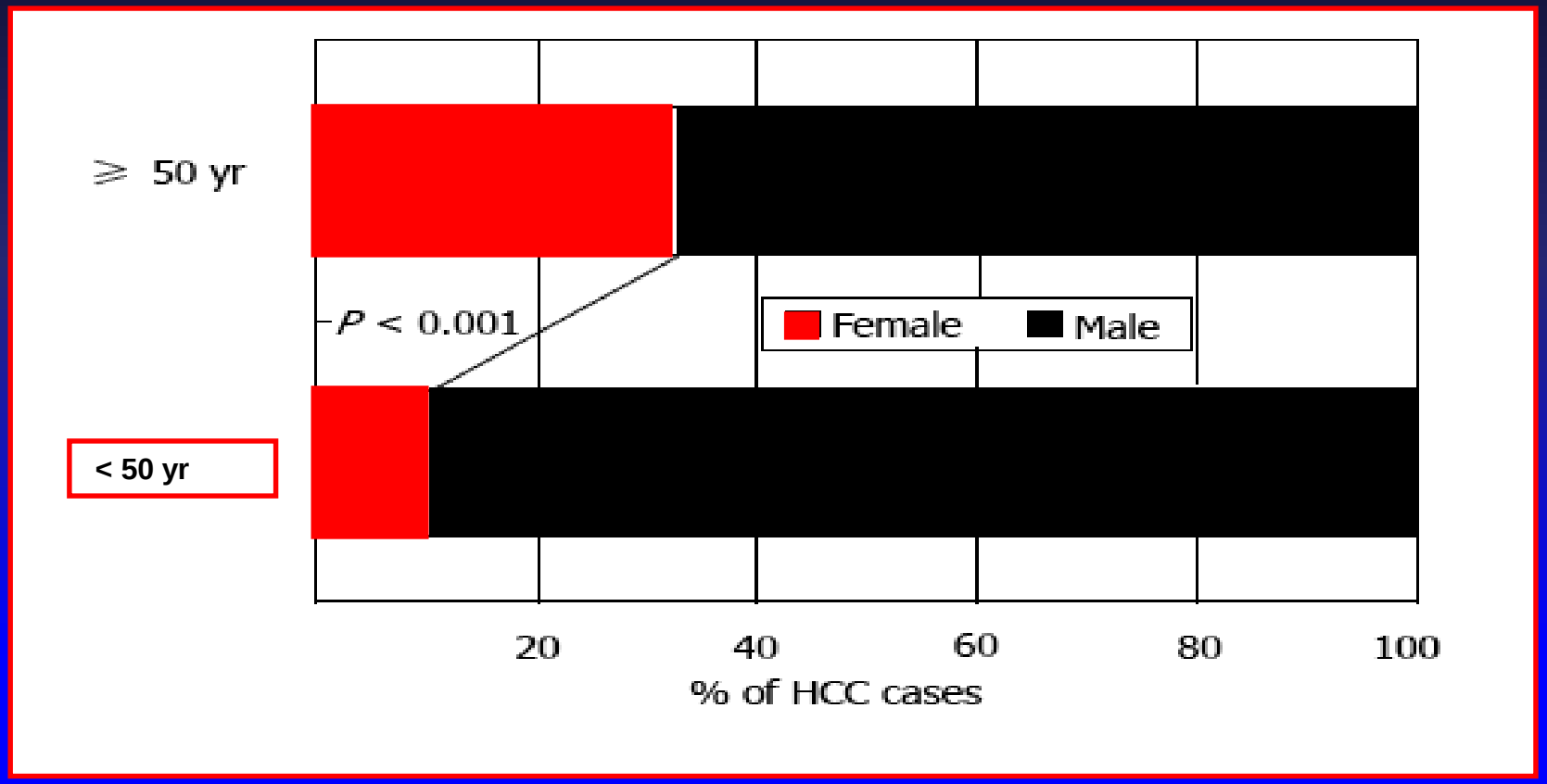
Females





Database ITA.LI.CA, 2008

Comparison of male-to-female ratio between two age groups of HBV-related HCC patients without HCV infection.



Shimizu, 2007

Gastroenterology, Modena
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WomenInHepatology

GENDER-C Project

Malattie Infettive, Università La Sapienza Gloria Taliani

Istituto Superiore di Sanità
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Special Article Digestive and Liver Disease 48 (2016) 120–137

AISF position paper on liver disease and pregnancy

The Italian Association for the Study of the Liver (AISF) ★

The two meetings were held in Modena during the Women in Hepatology Meeting in May 2014 and in Naples during the AISF Monothematic Conference in October 2014.

The Position Paper was generated by the Gender Committee of the Italian Association for the Study of the Liver (AISF) to provide an official position paper in a setting characterized by uncertain clinical behavior and lack of uniform approach.

★ Filomena Morisco, Raffaele Bruno, Elisabetta Bugianesi, Patrizia Burra,Vincenza Calvaruso, Alice Cannoni, Nicola Caporaso, Gian Paolo Caviglia,Alessia Ciancio, Silvia Fargion, Alessandro Federico, Annarosa Floreani,Giovanni Battista Gaeta, Maria Guarino, Pietro Invernizzi, Anna Licata,Carmela Loguercio, Giuseppe Mazzella, Felice Petraglia, Massimo Primignani,Kryssia Rodriguez-Castro, Antonina Smedile, Luca Valenti, Ester Vanni, SilviaVannuccini, Chiara Voltolini,