Carcinoma Hepatocelular na Doença Hepática Gordurosa Alcoólica e Não- Alcoólica

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SÃO PAULO CLÍNICAS
LIVER CANCER GROUP

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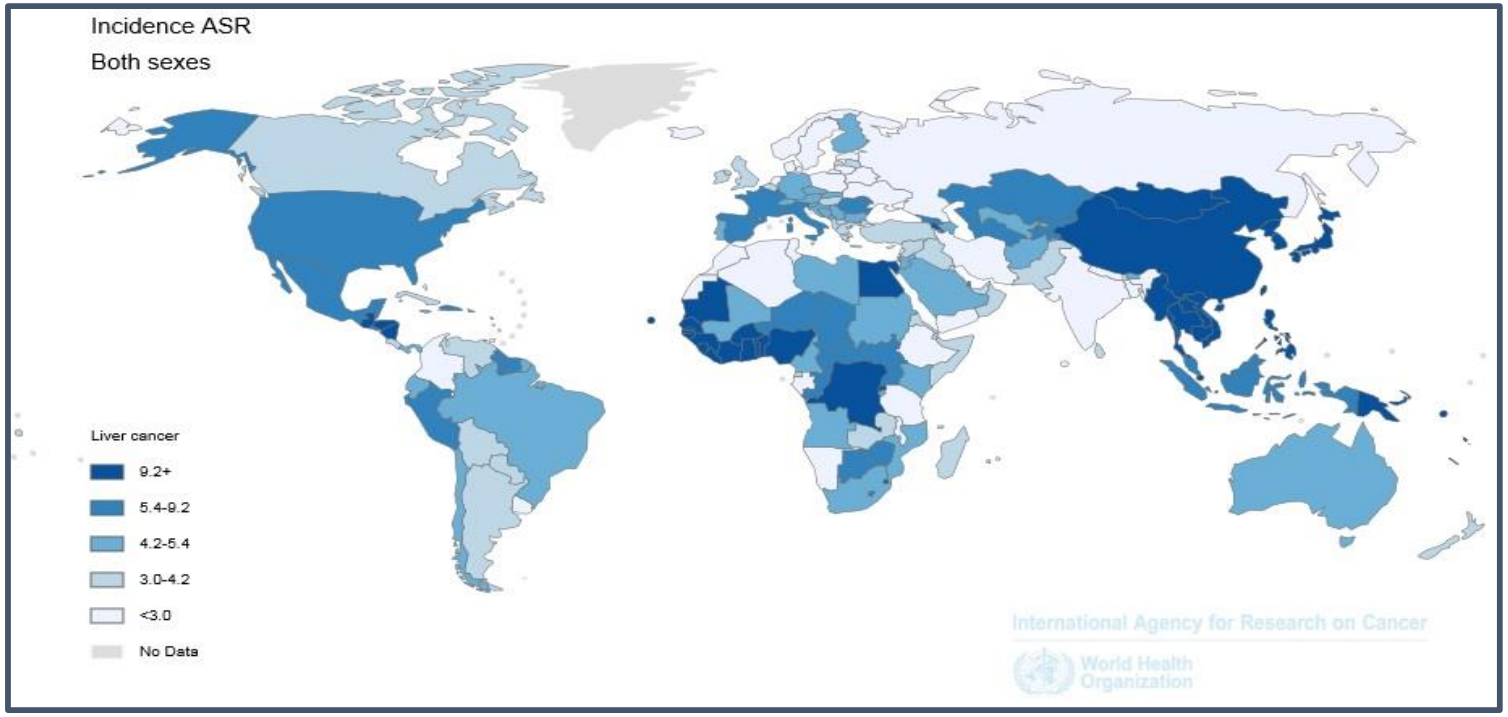
ORGANIZAÇÃO SOCIAL DE SAÚDE

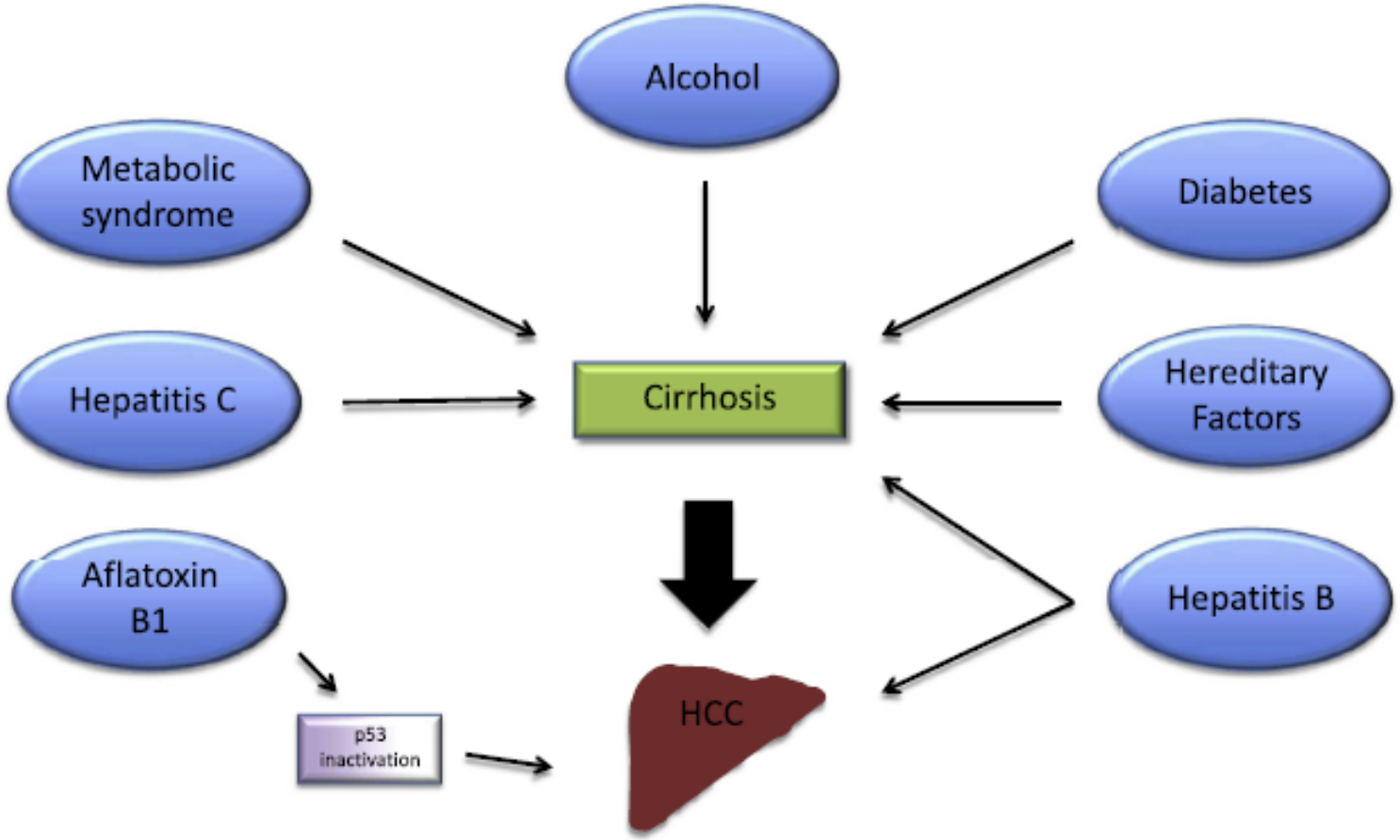
Epidemiologia do CHC

- O carcinoma hepatocelular (CHC) corresponde a 6ª causa de câncer e 3ª causa de morte por câncer no mundo
- > 700.000 mortes por ano.
- Principal causa de óbito em pacientes com cirrose compensada



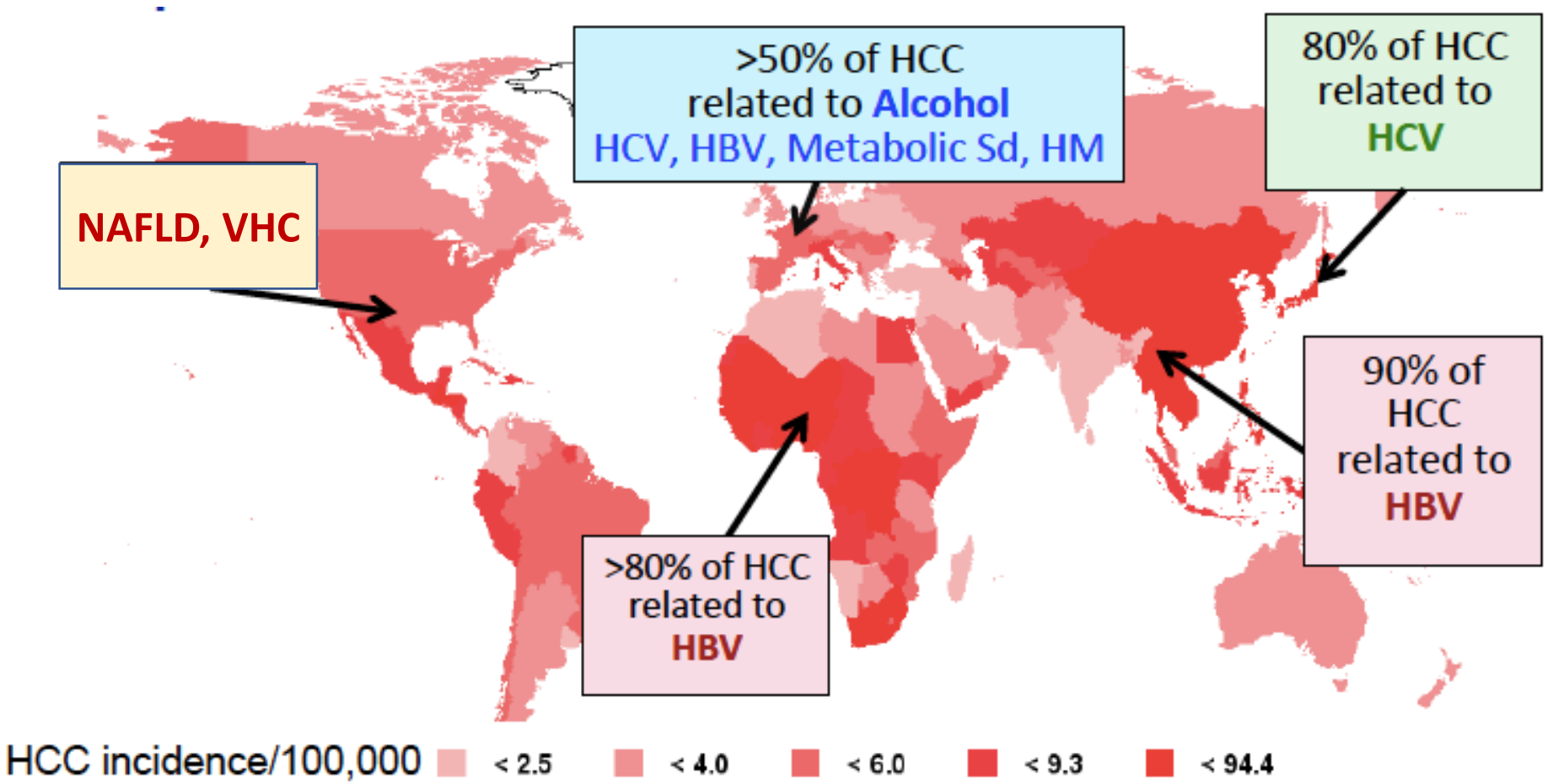
GLOBOCAN 2012. *Int J Cancer,* 2014; 136 (5):E359-E386
Sagiovanni et al . *Hepatology ,* 2006; 43(6):1303-10

Fatores de Risco de CHC



Lafaro KJ et al, Surg Oncol N Am, 2015 (24)

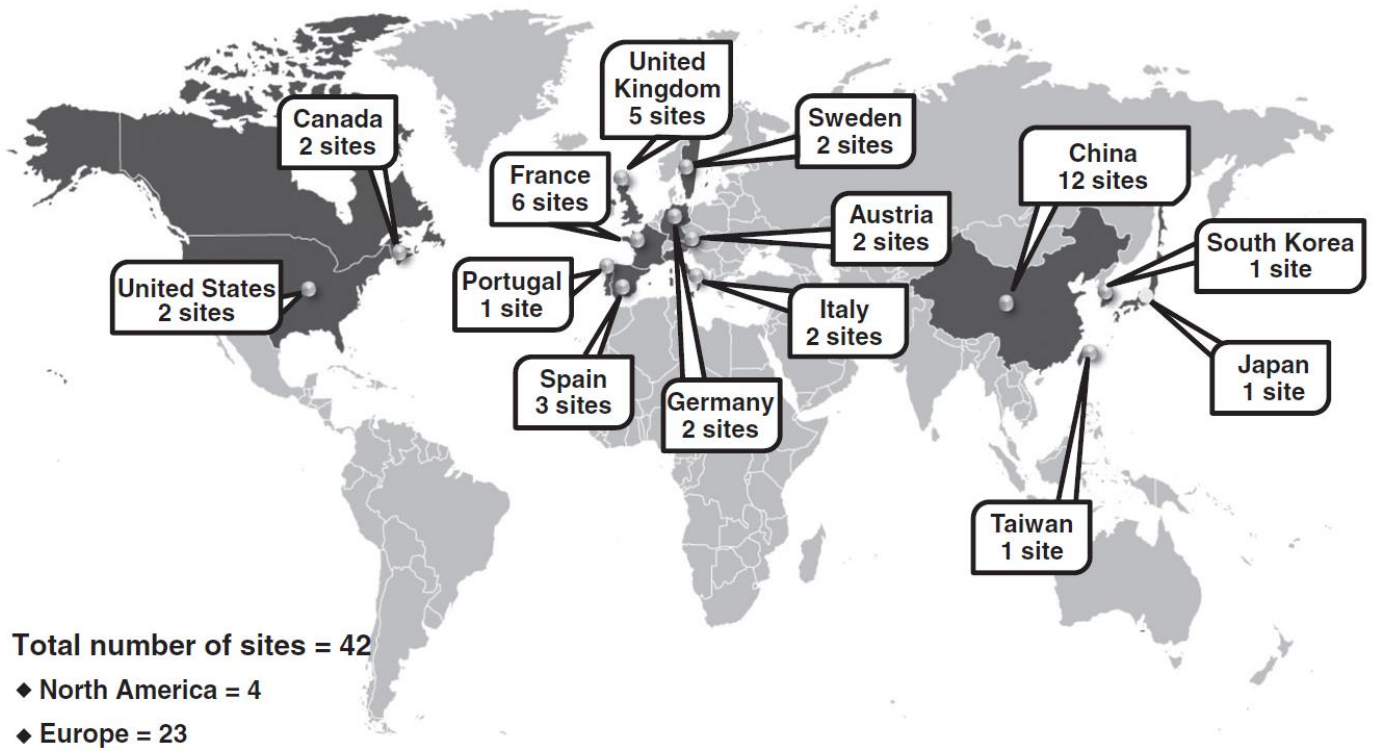
Epidemiologia do CHC



Globocan, 2012
Journal of Hepatology 2016 vol 56 908-943

Global patterns of hepatocellular carcinoma management from diagnosis to death: the BRIDGE Study

Joong-Won Park[1], Minshan Chen[2], Massimo Colombo[3], Lewis R. Roberts[4], Myron Schwartz[5], Pei-Jer Chen[6], Masatoshi Kudo[7], Philip Johnson[8], Samuel Wagner[9], Lucinda S. Orsini[10] and Morris Sherman[11]



Liver Int. 2015; 35: 2155–2166

Table 1. Patient demographics and clinical characteristics at diagnosis (N = 18 031)

Variable/group*	North America n = 2326	Europe n = 3673	China n = 8683	Taiwan n = 1587	South Korea n = 1227	Japan n = 534
Age, mean (SD)	62 (11)	65 (11)	52 (12)	61 (12)	57 (10)	69 (9)
Gender (male), n (%)	1786 (77)	2860 (78)	7497 (86)	1143 (72)	1021 (83)	340 (64)
Comorbidities, n (%)						
Tobacco use†	1187 (61)	1759 (54)	3042 (36)	531 (34)	802 (69)	173 (39)
Alcohol abuse†	759 (40)	1459 (44)	2034 (24)	287 (18)	779 (67)	7 (2)
HCC risk factors, n (%)‡	n = 2243	n = 3466	n = 8538	n = 1580	n = 1172	n = 446
HBV	522 (23)	362 (10)	6575 (77)	987 (63)	884 (75)	64 (14)
HCV	876 (39)	1590 (46)	255 (3)	489 (31)	112 (10)	284 (64)
ALD	471 (21)	1290 (37)	416 (5)	66 (4)	110 (9)	59 (13)
NASH	275 (12)	334 (10)	53 (1)	84 (5)	68 (6)	9 (2)
AFP, ng/mL	n = 2023	n = 2922	n = 8048	n = 1572	n = 1169	n = 445
Median	24	17	219	25	101	18
Child-Pugh status, n (%)	n = 2051	n = 2513	n = 7859	n = 1559	n = 1164	n = 442
A	1458 (71)	1801 (72)	6819 (87)	1439 (92)	911 (78)	390 (88)
B	469 (23)	627 (25)	960 (12)	115 (7)	228 (20)	49 (11)
C	124 (6)	85 (3)	80 (1)	5 (<1)	25 (2)	3 (1)
BCLC stage, n (%)	n = 1588§	n = 2261§	n = 6501	n = 1461	n = 1152	n = 433
0	107 (7)	84 (4)	192 (3)	213 (15)	82 (7)	107 (25)
A	474 (30)	582 (26)	1973 (30)	810 (55)	290 (25)	206 (48)
B	157 (10)	253 (11)	591 (9)	176 (12)	149 (13)	62 (14)
C	673 (42)	1158 (51)	3606 (55)	250 (17)	605 (53)	53 (12)
D	177 (11)	184 (8)	139 (2)	12 (1)	26 (2)	5 (1)

Epidemiologia do CHC

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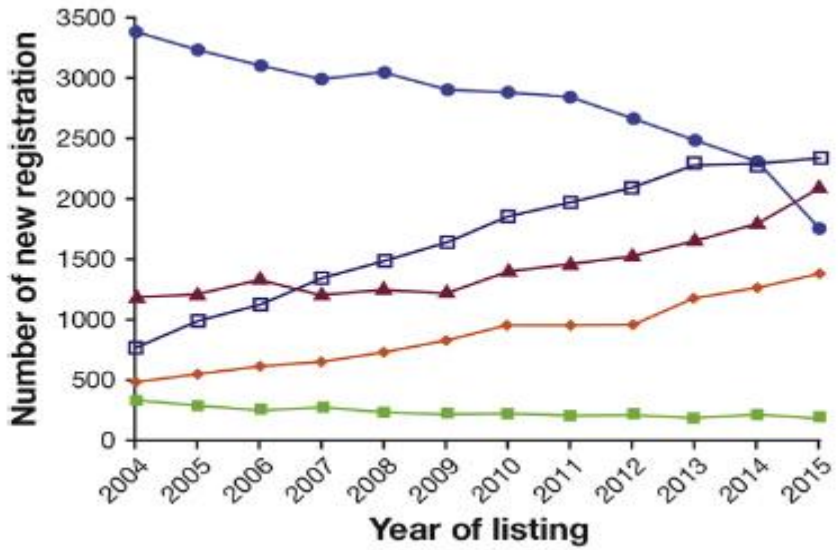
- Aumento da incidência nos países de baixo-risco (EUA, Reino Unido, Austrália);

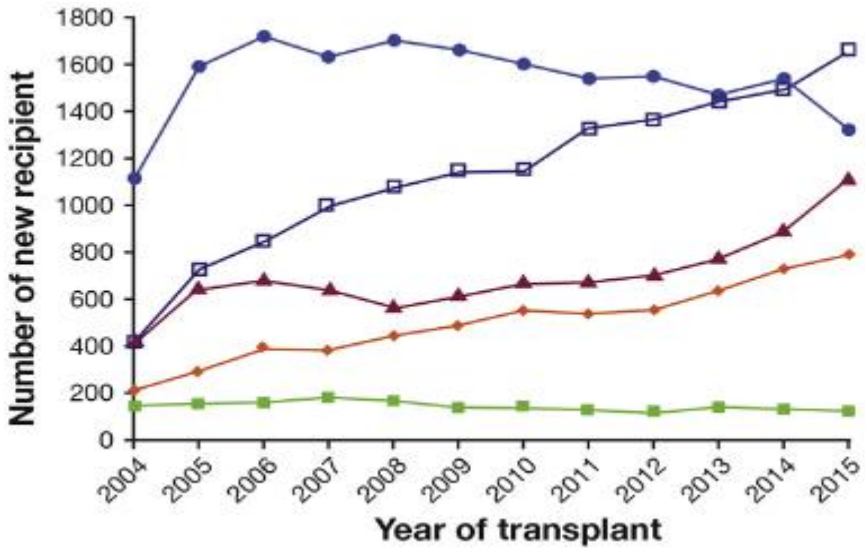
  Desde 2014 - Hepatite C – DAAs (cura);
  - NAFLD (principal causa de CHC nos USA)

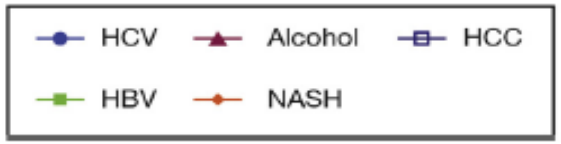
- Redução nas taxas de incidência em países de alto-risco para CHC (China/ Japão)
  - Vacinação para VHB
  - Diminuição da exposição à aflatoxina B1

Hepatocellular Carcinoma Is the Most Common Indication for Liver Transplantation and Placement on the Waitlist in the United States

Ju Dong Yang,* Joseph J. Larson,‡ Kymberly D. Watt,* Alina M. Allen,* Russell H. Wiesner,* Gregory J. Gores,* Lewis R. Roberts,* Julie A. Heimbach,§ and Michael D. Leise*







CANCER

WILEY Liver INTERNATIONAL

Hepatocellular carcinoma in South America: Evaluation of risk factors, demographics and therapy

- 1.336 pacientes com CHC acompanhados em 14 centros da América do Sul.
- Fatores de risco de CHC na América Latina:

- 48% Hepatite C
- 22% Álcool
- 14% Hepatite B
- 9% NAFLD

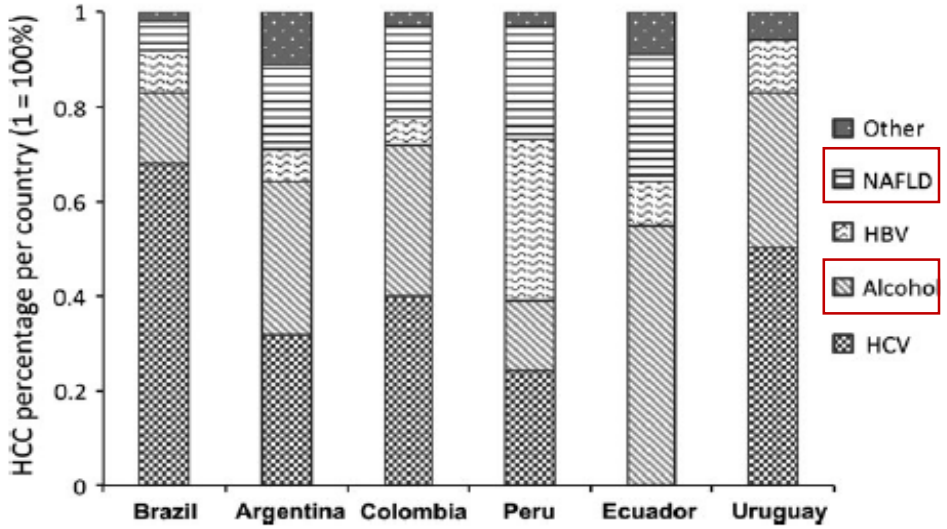
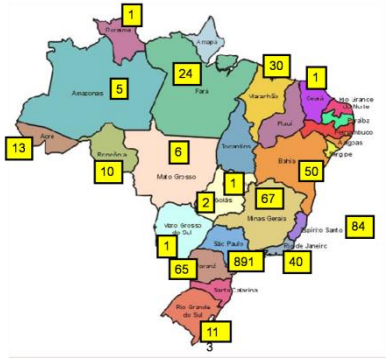


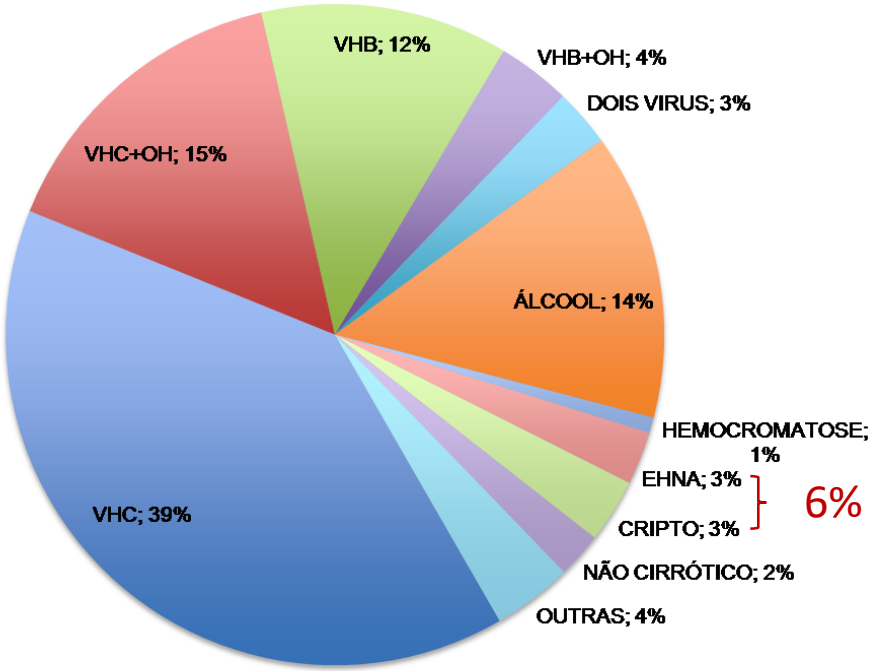
FIGURE 2 Distribution of risk factors for hepatocellular carcinoma within each country. *Y*-axis represents percentage of the cases per each country (1 represents 100%); *X*-axis represents each country. Filling of bar correlates with description of each risk factor, corresponding to percentage of risk factor within the total of each country. NAFLD, non-alcoholic liver disease; HBV, hepatitis B virus; HCV, hepatitis C virus

Debes et al, Liver Intern, 2018 Jan;38(1):136-143.

Inquérito Nacional do Carcinoma Hepatocelular



- 1405 pacientes
- Idade média: 59 anos
- Sexo
  - Masculino: 78%
  - Feminino: 22%
- Cirrose hepática em 98%
- Álcool: 14%
- DHGNA + Cripto: 6%



Carrilho F J, Clinics 2010; 65(12):1285-1290

Epidemiologia do CHC no Brasil

Ano	Autor	n	Período	Idade (média)	Homens (%)	Mulheres (%)	HBV (%)	HCV (%)	Alcool (%)	NASH (%)	Cirrose (%)
2010	JF Carrilho[2]	1405	2004 - 2009	59a	78	22	16	54	14	3	98
2011	RCP Alves[3]	32		60a	78,1	21,9	6,3	46,9	21,9	9,4	71,2
2014	D Paranagua-Vezozzo[4]	884	1998 - 2009	57a	56,9	43,1	16,4	65,3	15,3	3,2	56,9
2016	R. S. S. M. Alencar[5]	88	2010 - 2014	61a	73	27	9	68	11	9	95
2017	SR Almeida-Carvalho[6]	247	2000 - 2012	60a	74	26	8	55	12	11	92
2017	F Branco[7]	127	2010 - 2014	60.9a	76,3	23,6	8,6	70,8	9,4	11	94
2018	RCP Alves[8]	175	2007 - 2016	62	77	23	6	46	14	17	97

1. L. Kikuchi, C. P. Oliveira, M. R. Alvares-da-Silva, C. M. Tani, M. A. Diniz, J. T. Stefano, A. L. Chagas, R.M. Alencar, D. C.P. Vezozzo, G. R. Santos, P. B. Campos, V. AF. Alves, V. Ratziu, F. J. Carrilho; Am J Clin Oncol 2016;39:428–432 **2.** FJ Carrilho, L Kikuchi, F Branco, CS Gonc¸alves,, AA de Mattos e Brazilian HCC Study Group CLINICS 2010;65(12):1285-1290 **3.** Alves R, Alves D, Mattos C, Soares S, Harriz M, Vanini H et al. Safety of sorafenib tretament for intermediate/advanced HCC in patients with child´s A B or C (abstract no. 1722. hepatology 2009; 50(S4): 1101A **4.** D Paranaguá-Vezozzo, SK Ono, MV Alvarado-Mora, AQ Farias, M Cunha-Silva, JID França, VAF Alves, M Sherman, FJ Carrilho. Epidemiology of HCC in Brazil: incidence and risk factors in a tem-year cohort. Annals of Hepatology 2014: 386-393 **5.** RSSM. Alencar, L Kikuchi, CM. Tani, AL. Chagas, CC Camargo, TEF Pfiffer, PMG Hoff, FJ Carrilho. Better Management of Adverse Events Favors Sorafenib Treatment of HCC Patients and Impact on Survival Journal of Cancer Therapy, 2016, 7, 275-284 **6.** SR Almeida-Carvalho, ML Gomes-ferraz, CAL Matos, AEB Silva, RJ Carvalho Filho, RR Perz, AM Gonzalez, AAS Neto, D Szejnfeld, G D´Ippolito, VP Lanzoni, ISS Silva. Practical Considerations of Real Life HCC in a Tertiary Center of Brazil. Annals of Hepatology Vol 16 No 2, 2017: 255-262 **7.** F Branco, RSM Alencar, F Volt, G sartori, A Dode, L Kikuchi, CM Tani, AL Chagas, TEF Pfiffer, PMG Hoff, FJ Carrilho, AA Mattos. The Impact of Early dermatologic Events in the Survival of Patients with HCC Treated with Sorafenib. Annals of Hepatology Vol16 No2, 2017:263-268 **8.** RCP Alves. A single hepatologist's experience with sorafenib in a broad population of hepatocellular carcinoma patients. 2018 in press

Experiência do ICESP

- 364 pacientes com diagnóstico de CHC de 2010 a 2012

- Idade média: 62 anos

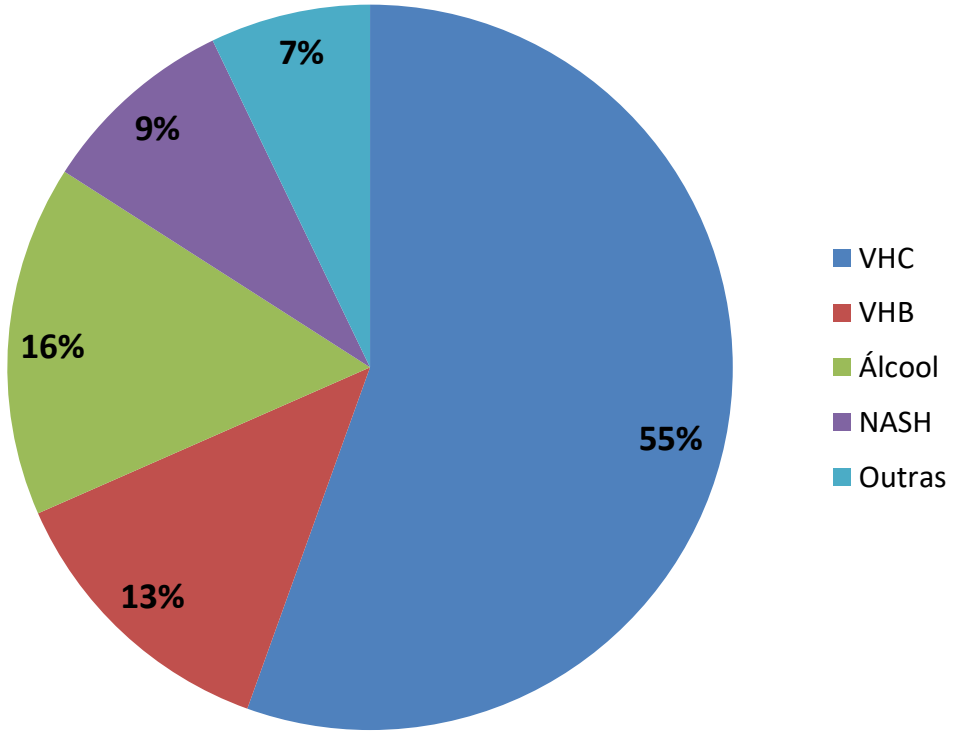
- Sexo
  - Masculino: 74%

- Cirrose em 95%
- 62% CHILD A

- 9% NASH

- 16% Álcool

- 65% em programa de rastreamento antes do diagnóstico

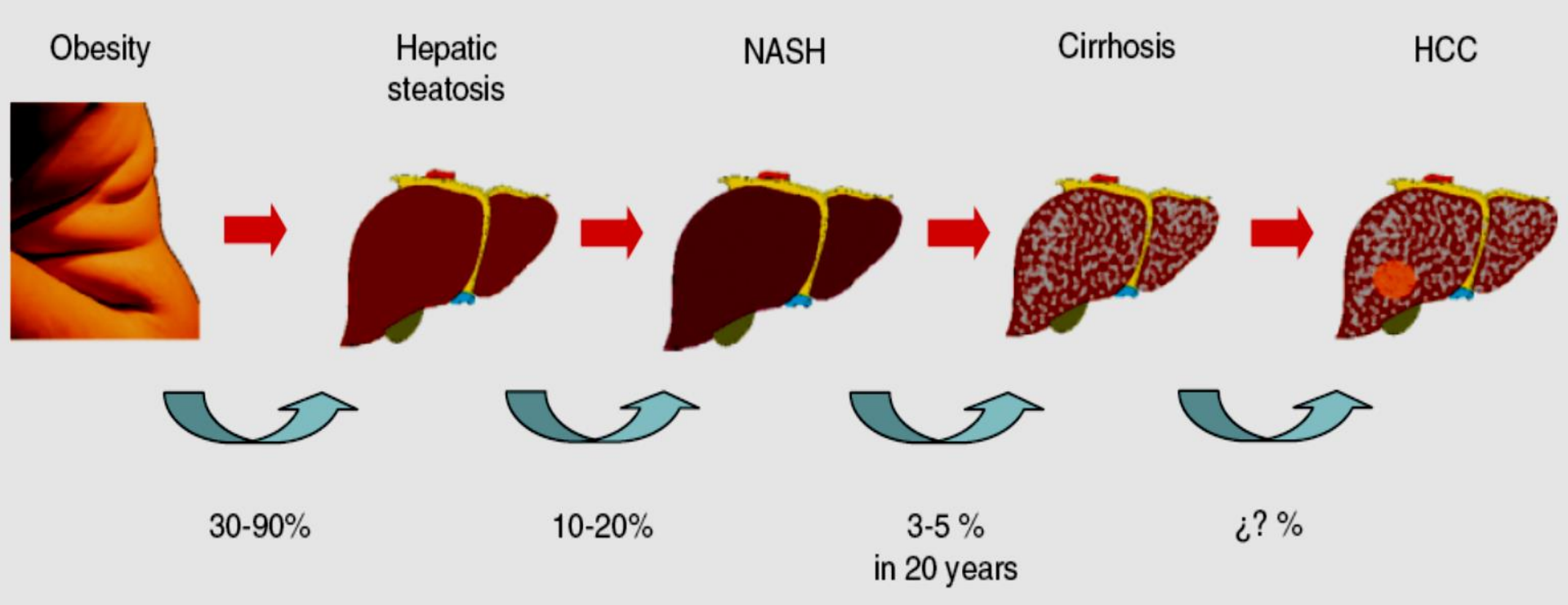


Kikuchi L, Defesa de Tese de Doutorado, 2015

Síndrome metabólica, DHGNA e CHC

HISTÓRIA NATURAL - DHGNA

- DHGNA → manifestação hepática da síndrome metabólica



Caldwel SH et al, Hepatology 1999
Bugianesi E et al, Gastroenterology 2002

NAFLD May Be a Common Underlying Liver Disease in Patients With Hepatocellular Carcinoma in the United States

Jorge A. Marrero, Robert J. Fontana, Grace L. Su, Hari S. Conjeevaram, Dawn M. Emick, and Anna S. Lok

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- 105 pacientes com CHC em 24m (90% com cirrose).
- VHC (51%) e CH criptogênica (29%)
- Criptogênica: 50% com NASH na histologia ou suspeita clínica de NAFLD.
- CH criptogênica: 13% dos CHC
- Estudo Italiano: NAFLD em 23/641 (4%) dos pacientes com CHC

Table 2. Comparison of HCC Patients With Cryptogenic Cirrhosis Versus Other Etiologies

	Cryptogenic (n = 30)	Other Etiologies (n = 75)	*P* Value
Female (%)	60	28	.001
Mean age ± SD (yr)	57 ± 16	62 ± 13	>.05
Non-Hispanic white (%)	90	72	>.05
BMI >30 (%)	58	25	.02
Diabetes (%)	47	8	.006
Hypertriglyceridemia (%)	16	2	.001
Hypercholesterolemia (%)	13	2	.07
Maximal tumor diameter mean ± SD (cm)	7.6 ± 6	4.4 ± 5	.03
AFP <20 ng/mL (%)	27	30	>.05
Detected by surveillance (%)	23	61	.01

Marrero e cols, Hepatology, 2002

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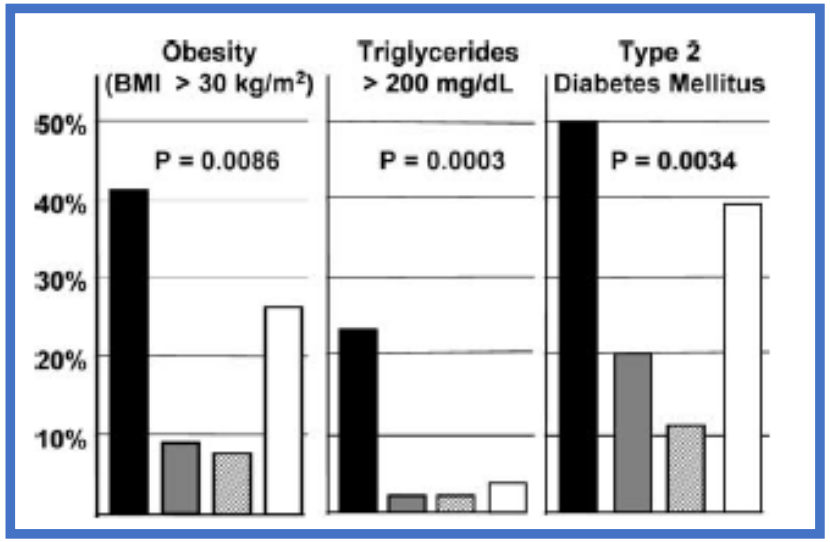
Expanding the Natural History of Nonalcoholic Steatohepatitis: From Cryptogenic Cirrhosis to Hepatocellular Carcinoma

- 641 pacientes com CH e CHC
- 44 CH criptogênica: 23 pacientes acompanhados (caso-controle)
- Prevalência aumentada de DM, obesidade e hipertrigliceridemia



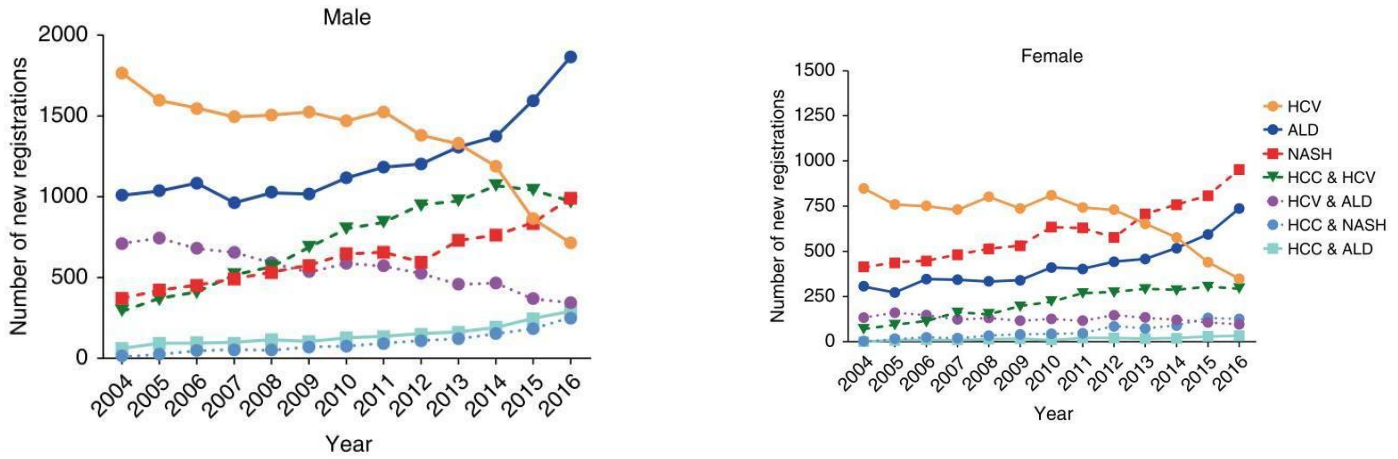
Bugianesi e cols, Gastroenterology 2002; 123:134-140

NASH é a principal causa de Transplante Hepático em mulheres: Análise atualizada de indicações de transplante hepático por variação de etnia e gênero

Table 1 Change in rates of liver transplant waitlist registration over time by gender

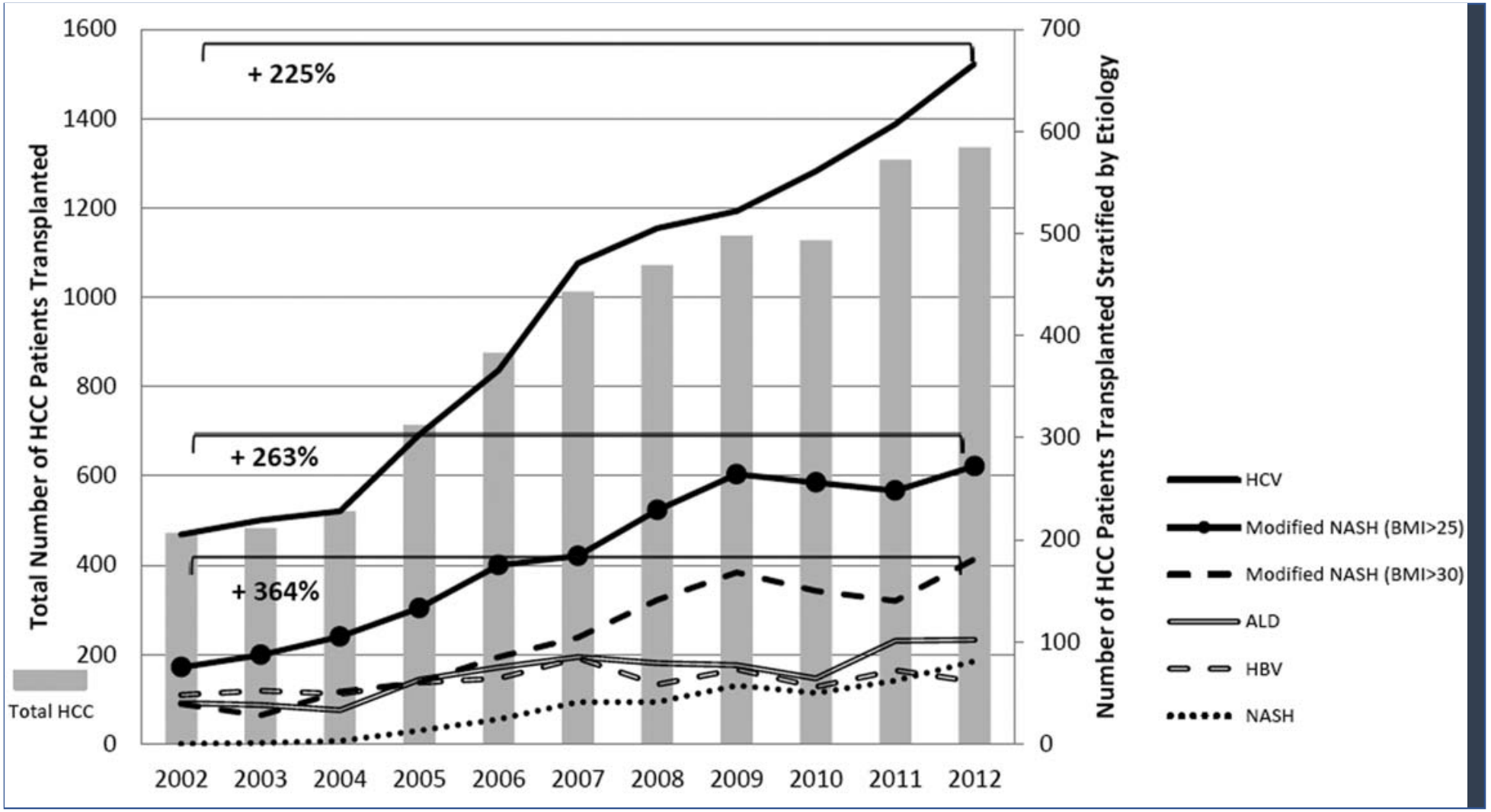
Etiology	Males 2016 v 2004		Males 2016 v 2015		Females 2016 v 2004		Females 2016 v 2015	
	Change	*p*-value	Change	*p*-value	Change	*p*-value	Change	*p*-value
HCV	−67%	<0.0001	−22%	<0.0001	−68%	<0.0001	−27%	<0.0001
ALD	49%	<0.0001	10%	0.0957	87%	<0.0001	15%	0.0564
NASH	114%	<0.0001	12%	0.0991	80%	<0.0001	9%	0.2061
HCC & HCV	171%	<0.0001	−12%	0.0139	233%	<0.0001	−11%	0.1576
HCV & ALD	−61%	<0.0001	−12%	0.0932	−43%	0.0103	−15%	0.2266
HCC & NASH	1172%	<0.0001	29%	0.0203	2383%	<0.0001	−11%	0.3322
HCC & ALD	273%	<0.0001	11%	0.3195	n/a	<0.0001	5%	0.8819

Percent change computed from observed counts over time and *p*-values computed from multinomial regression analysis within each sex; n/a indicates percent change not computed due to zero observations in divisor
HCV Hepatitis C virus, ALD Alcoholic liver disease, NASH Non-alcoholic steatohepatitis, HCC Hepatocellular carcinoma



Nicholas N Nissen et al; The American Journal of Gastroenterology; 2018; 1-11.

NASH está Impulsionando o Aumento à Necessidade de Transplantes Hepáticos por CHC



Wong et al, Hepatology, 2014

DHGNA e CHC

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- Aumento da incidência da DHGNA/EHNA → aumento da incidência do CHC relacionado a DHGNA.

- DHGNA afeta 80 milhões de americanos, sendo a causa mais comum de doença hepática nos EUA.

- Doença hepática corresponde a 3ª causa de morte nos pacientes com DHGNA/EHNA e o CHC é a principal causa nesses pacientes.

- DHGNA/EHNA provavelmente vai se tornar a causa mais comum de CHC nos países desenvolvidos no futuro.

Cholankeril et al, WJH 2017 9(11):533-543

DHGNA e CHC

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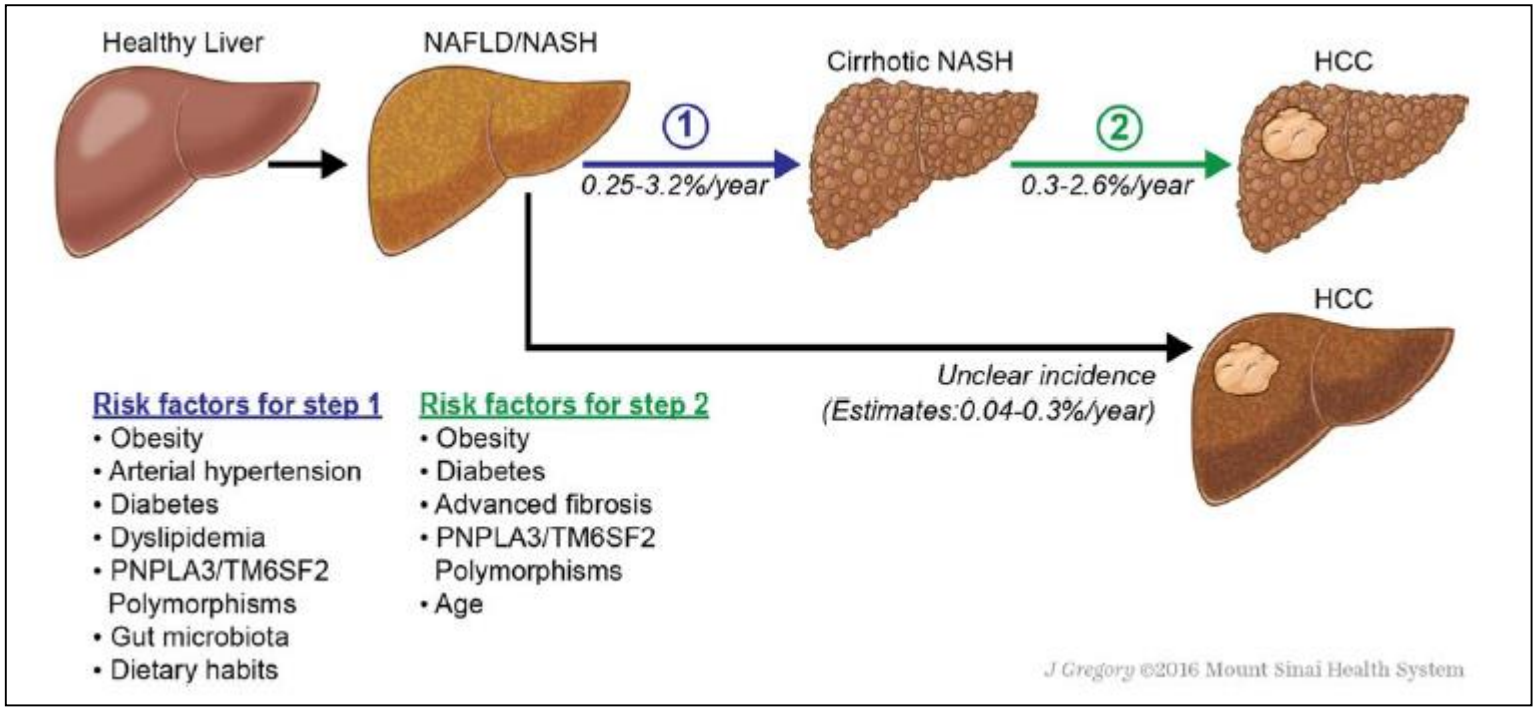
Author, Year, Publication	NASH/NAFLD Diagnostic Criteria	Study Population	Follow-up (years)	Annual HCC Incidence	Risk Factors for HCC Development
Sanyal, 2006, Hepatology[17]	Biopsy proven, alcohol intake <40 g/week, negative tests for other causes of cirrhosis	152 NASH-cirrhosis	10	0.2%	Not identified
Bhala, 2011, Hepatology[13]	Biopsy proven	247 NASH (cirrhosis 52%, advanced fibrosis 48%)	7.1	0.3%	Not identified
Kawamura, 2012, Am J Gastroenterol[15]	Fatty liver at ultrasound, alcohol intake <20 g/day, negative tests for other causes of cirrhosis	6508 NAFLD (not reported % of significant fibrosis/cirrhosis)	5.6	0.04%	Age Elevated alanine aminotransferase Low platelet count Diabetes
Adams, 2005, Gastroenterology[18]	Fatty liver at ultrasound or biopsy, alcohol intake <140 g/week, HCV/HBV-negative, or cryptogenic cirrhosis with criteria of metabolic syndrome	420 NAFLD (cirrhosis 2%)	7.6	0.06%	Not analyzed
Ascha, 2010, Hepatology[14]	Biopsy-proven or cryptogenic cirrhosis with metabolic syndrome without history of significant alcohol intake	195 NASH-cirrhosis	3.2	2.6%	Older age Any alcohol consumption

D' Avola et al, Clin Liv Disease 8 (4), 2016

História Natural do CHC na DHGNA



D' Avola et al, Clin Liv Disease 8 (4), 2016

DHGNA e CHC

- Incidência anual do CHC em pacientes com cirrose secundária a NASH de **2,4 %.**

- CHC pode acontecer nos pacientes com DHGNA/ EHNA na ausência de cirrose (40 – 50%).

- Em pacientes com CHC e EHNA sem cirrose o tumor em geral se apresenta com tumores grandes → ausência de screening.

- Uma das hipóteses → desenvolvimento do CHC no contexto do Adenoma em pacientes com DHGNA sem cirrose

Cholankeril et al, WJH 2017 9(11):533-543
Klein et al, Hepatol Oncol 2017; 4 (3): 83-98

Does hepatocellular carcinoma in non-alcoholic steatohepatitis exist in cirrhotic and non-cirrhotic patients?

A.L. Chagas, L.O.O. Kikuchi, C.P.M.S. Oliveira, D.C.P. Vezozzo, E.S. Mello, A.C. Oliveira, L.C. Cella, P. Herman, T. Bachella, S.H. Caldwell, V.A.F. Alves and F.J. Carrilho

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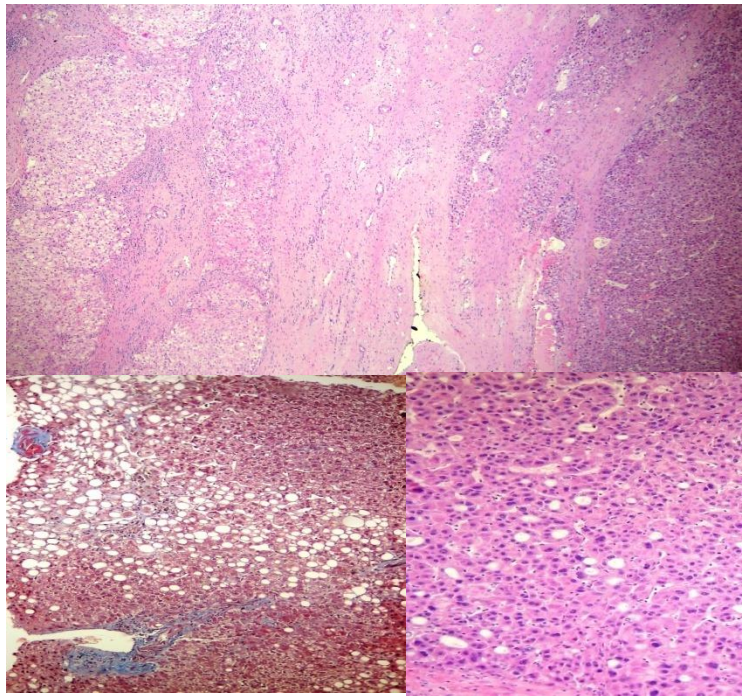
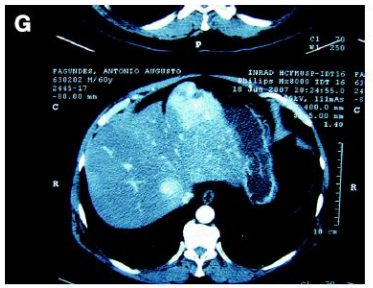
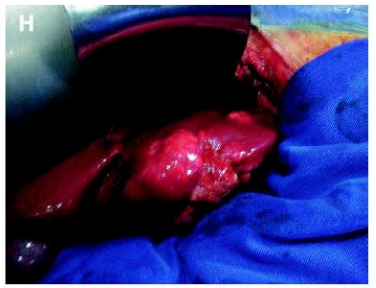


	1	2	3	4	5	6	7
Gender	F	M	M	M	F	M	F
Age (years)	59	71	61	77	35	65	73
Diabetes mellitus	Y	Y	N	N	Y	N	Y
Overweight	Y	Y	Y	Y	Y	Y	Y
Dyslipidemia	N	Y	N	N	N	Y	N
Cirrhosis	Y	Y	Y	Y	Y	N	Y
Child-Pugh	A6	A5	A5	A5	B9	-	A6
AFP (ng/mL)	6	10	21	10	3	7	17
HCC Rx	TACE	Resection	PEI + TX	Resection	TACE	TACE	PEI
HCC differentiation	NA	GII	GII	GIII	NA	GI	GI
Number of nodules	1	1	3	1	4	2	1
Echo pattern	High	High	High	NA	Low	Mixed	High
HCC size (mm)	33	34	30	43	28	52	33
Stage (BCLC)	Early	Early	Early	Early	Intermediate	Intermediate	Early





Braz J Med Biol Res, October 2009, Volume 42(10) 958-962

DHGNA não-cirrótico e CHC

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Study, authors, [Ref.]	Cases (n)	Gender	Tumor	Fibrosis (stage)
Bencheqroun *et al.*, (France, 2004) [104]	1	M (1)	Solitary	F2
Bullock *et al.*, (UK, 2004) [105]	2	M (2)	Solitary	F0
Gonzalez *et al.*, (France, 2004) [106]	1	M (1)	n.r.	F1
Regimbeau *et al.*, (France, 2004) [42]	10	M (10)	n.r.	F2-F3
Cuadrado *et al.*, (Spain, 2005) [107]	1	M (1)	Solitary	F2
Hai *et al.*, (Japan, 2006) [108]	1	M (1)	Solitary	F2
Ichikawa *et al.*, (Japan, 2006) [109]	2*	M (1), F (1)	Solitary	F2-F3
Hashizume *et al.*, (Japan, 2007) [110]	3	M (3)	Solitary (2), multifocal (1)	F1-F3
Guzman *et al.*, (USA, 2008) [51]	3	M (1), F (2)	Multifocal	F0
Paradis *et al.*, (France, 2009) [50]	16**	M (16)***	n.r.	F0-F2
Kawada *et al.*, (Japan, 2009) [90]	6	M (3), F (3)	Solitary	F2-F3
Hashimoto *et al.*, (Japan, 2009) [102]	4	n.r.	Solitary (70%)	F1-F2
Chagas *et al.*, (Brazil, 2009) [111]	1	M (1)	Multifocal	F1
Takuma *et al.*, (Japan, 2010) [33]	7	M (3), F (4)	Solitary (5), multifocal (2)	F1-F3
Ikura *et al.*, (Japan, 2011) [112]	1	M (1)	Solitary	F0
Ertle *et al.*, (Germany, 2011) [34]	10	M (83.3%)	n.r.	F0-F3
Yasui *et al.*, (Japan, 2011) [35]	43	M (76.7%)	Solitary (72%)	F1-F3

Baffy et al, J Hepatology 2012; 56:1384-1391

CHC secundário a DHGNA x outras etiologias

SÃO PAULO CLÍNICAS
LIVER CANCER GROUP

- A maioria dos pacientes com CHC e NASH apresenta comorbidades – HAS, DM, doenças cardiovasculares.

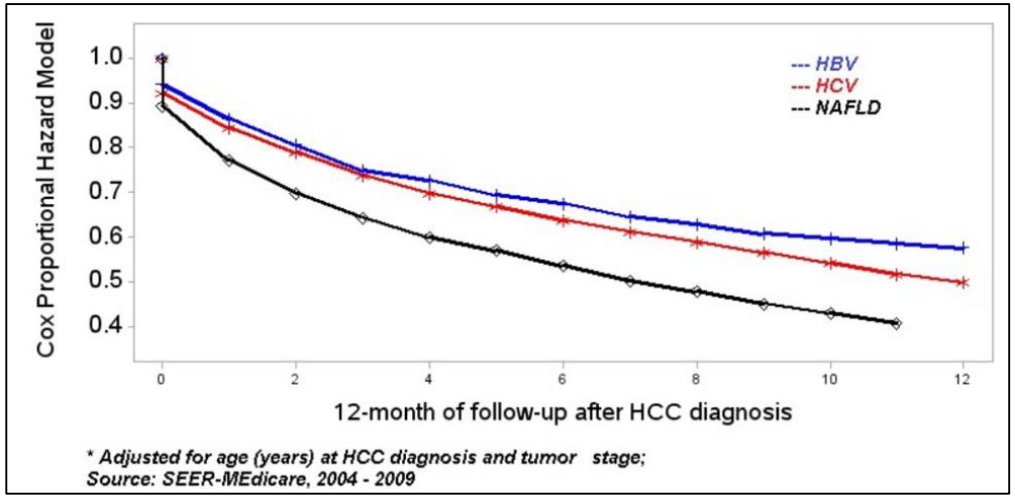
- Cerca de 40 – 50% dos casos de NASH acontece em pacientes sem cirrose.

- Pacientes com NAFLD: mais velhos, tumor maior ao diagnóstico, menos realização de screening.

Klein et al, Hepatol Oncol 2017; 4 (3): 83-98

Association of Nonalcoholic Fatty Liver Disease (NAFLD) with Hepatocellular Carcinoma (HCC) in the United States From 2004 to 2009

- 4.929 casos de CHC e 14.937 controles
- Etiologia do CHC:
- VHC: 54,9%
- Álcool: 16,4%
- NAFLD: 14,1%
- VHB:9,5%
- No período de 6 anos o número de casos de CHC-NAFLD apresentou um aumento anual de 9% na incidência.
- Pacientes com NAFLD: mais velhos, menor sobrevida, maior incidência de doença cardíaca e tiveram maior probabilidade de morrer do tumor primário de fígado.
- Apenas 5% dos casos de TX - CHC eram por NAFLD
- NAFLD aumento o risco de morte em 1 ano (OR:1.21; 95%IC: 1.01 -1.45)



Younossi et al, Hepatology 2015; 62: 1723-1730

Fatores de Risco de CHC no NASH

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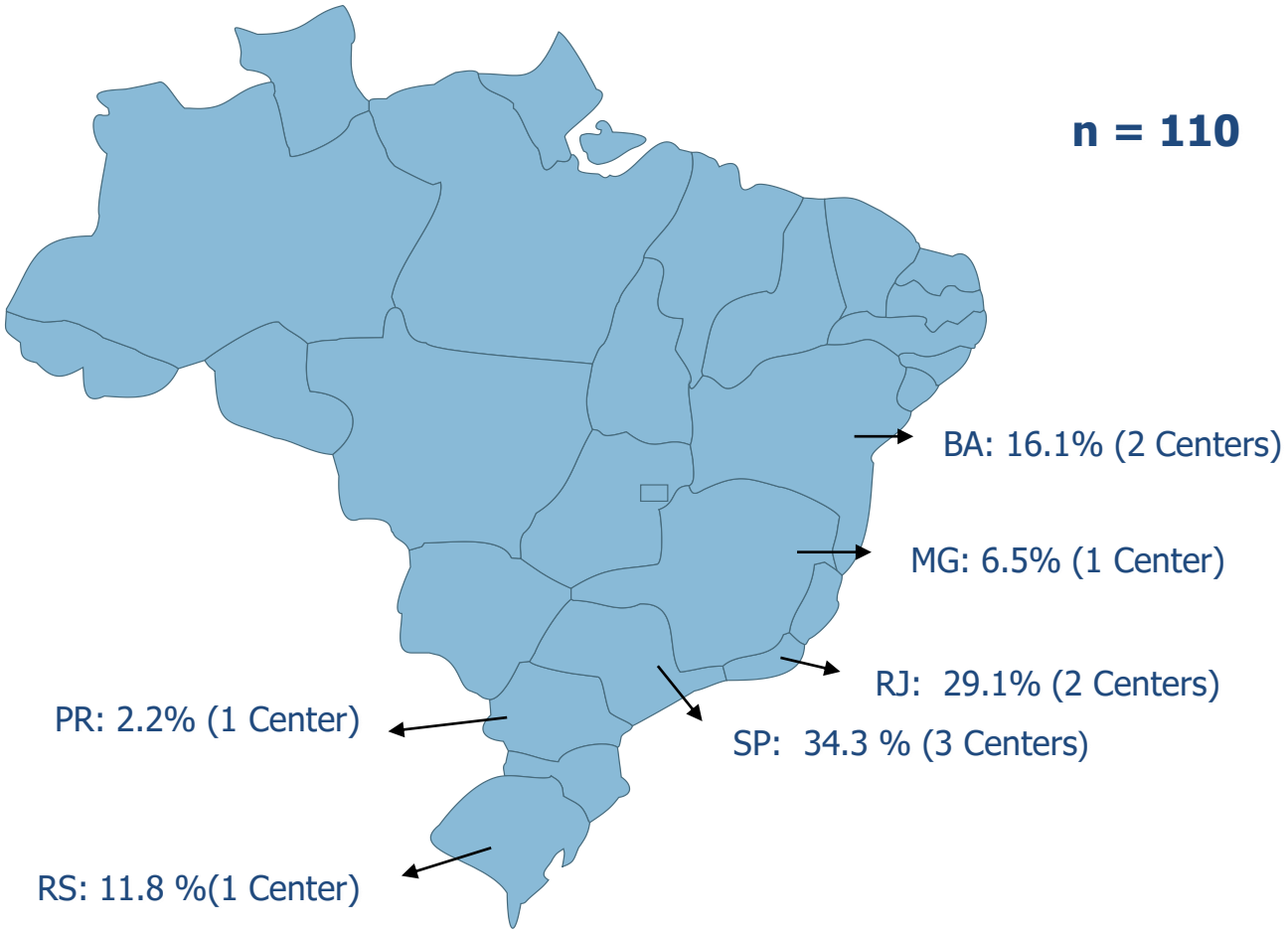
- Diabetes Mellitus
- Obesidade
- Resistência a insulina
- Síndrome metabólica
- Idade
- Fatores genéticos – PNPLA3 e TM6SF2
- Fibrose/cirrose
- Sobrecarga de ferro
- Consumo de álcool

Cholankeril et al, WJH 2017 9(11):533-543

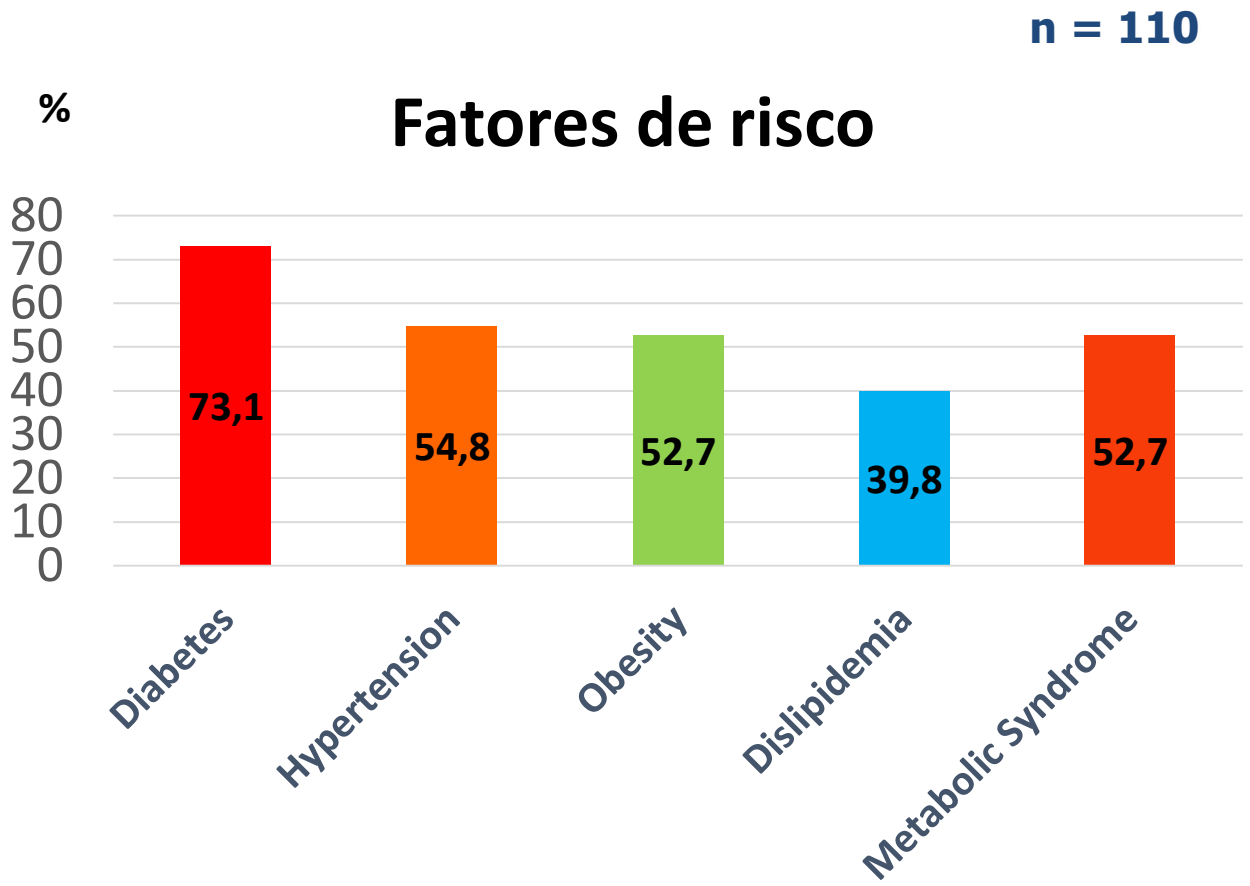
Argyrou et al, JBUON 2017 22(1):6-20

CHC ASSOCIADO COM NASH NO BRASIL: UM PROBLEMA CRESCENTE



COTRIM HP, OLIVEIRA CP, CARRILHO FJ & Brazilian Society of Hepatology Members. 2013

CHC ASSOCIADO COM NASH NO BRASIL: UM PROBLEMA CRESCENTE



COTRIM HP, OLIVEIRA CP, CARRILHO FJ & Brazilian Society of Hepatology Members. 2013

Diabetes e CHC

Diabetes e CHC

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- Aumento do risco de CHC em pacientes com cirrose sec VHB, VHC e OH
  El-Serag, AJG 2001

- Pacientes com DM tem um risco de CHC 2 -3x maior, independente da etiologia da doença hepática.

- Coorte de pacientes com DM (n = 650620) e sem DM (n = 173643): incidência de CHC 2 x maior em pacientes com DM

  El-Serag, Gastroenterol 2004

- Correlação entre o tempo de duração da DM e o risco de CHC.

Klein et al, Hepatol Oncol 2017; 4 (3): 83-98

Diabetes e CHC

SÃO PAULO CLÍNICAS
LIVER CANCER GROUP

- Há 20 anos *Adami et al* sugeriram uma correlação entre a diabetes e o desenvolvimento do CHC.
- Desde então uma série de trabalhos confirmaram esta correlação.
- 10 a 20% dos pacientes com cirrose → DM
- DM é um fator de risco independente para o desenvolvimento de CHC.

Klein et al, Hepatol Oncol 2017; 4 (3): 83-98

Diabetes e CHC

SÃO PAULO CLÍNICAS
LIVER CANCER GROUP

Table 1. Studies showing the elevated risk of hepatocellular carcinoma with diabetes mellitus.

Study (year)	Design	Population	Number of patients with HCC/diabetes	Key finding
Adami *et al.* (1996)	Population-based cohort	• n = 153,852 • Swedish in patient register • Hospital discharged diagnosis of diabetes in the period from 1965 through 1983 • until 1989	533/153,852	Risk of HCC SIRs: 4.1; 95% CI: 3.8–4.5 Men higher (SIR: 4.7; 95% CI: 4.2–5.2) Than in women (SIR: 3.4; 95% CI: 2.9–3.9)
Davila *et al.* (2005)	Case–control	• n = 8244 • Surveillance Epidemiology and En-Results program (SEER) Medicare-linked database • 1994–1999	2061/2090	Risk of HCC diabetes vs control OR_{adj}: 2.87; 95% CI: 2.49–3.3
El-Serag *et al.* (2004)	Retrospective, case–control	• n = 824,263 • Hospital discharge diagnosis of diabetes between 1985 and 1990 • Department of Veterans Affairs, Texas • Until 2000	832/173,643	Risk of HCC diabetes vs control HR: 2.16; 95% CI: 1.86–2.52 p < 0.0001
Hassan *et al.* (2010)	Case–control study	• n = 1524 • January 2000 through July 2008, at the University of Texas MD Anderson Cancer Center	420/255	Risk of HCC in diabetes OR: 4.2; 95% CI: 3.0–5.9 Duration of DM: 2–5 years compared with 6–10 years, OR: 1.8; 95% CI: 0.8–4.1 Duration of DM 2–5 years compared with >10 years, OR: 2.2; 95% CI: 1.2–4.8
Koh *et al.* (2013)	Prospective cohort	• n = 6,335,797 • Chinese health study • 1993–1998	499/5469	Risk of HCC diabetes vs nondiabetes HR: 2.14; 95% CI: 1.69–2.7
Li *et al.* (2017)	Case–control	• n = 817 • Patients hospitalized at The First Hospital of Jilin University in China • 2005–2016	300/112	Risk of HCC diabetes vs control OR_{adj}: 1.80; 95% CI: 1.17–2.75
Veldt *et al.* (2008)	Cohort	• n = 541 • Patient with DM and hepatitis C advanced fibroses or cirrhosis • Five large hepatology units in Europe and Canada • 1990–2003	38/85	Risk for HCC diabetes vs nondiabetes in patients with ISHAK score 6 HR: 3.28; 95% CI: 1.35–7.97 p = 0.009
Wang *et al.* (2012)	Systemic review and meta-analysis	• Medline from 1 January 1966 and EMBASE from 1 January 1974, through 31 July 2010 • 25 cohort studies	-/-	18 studies DM was associated with an increased incidence of HCC SRRs: 52.01; 95% CI: 1.61–2.51

DM: Diabetes mellitus; HCC: Hepatocellular carcinoma; HR: Hazard ratio, OR: Odds ratio; OR_{adj}: Adjusted odds ratio; SIR: Standardized incidence ratio; SRR: Summary relative risk; y: Year.

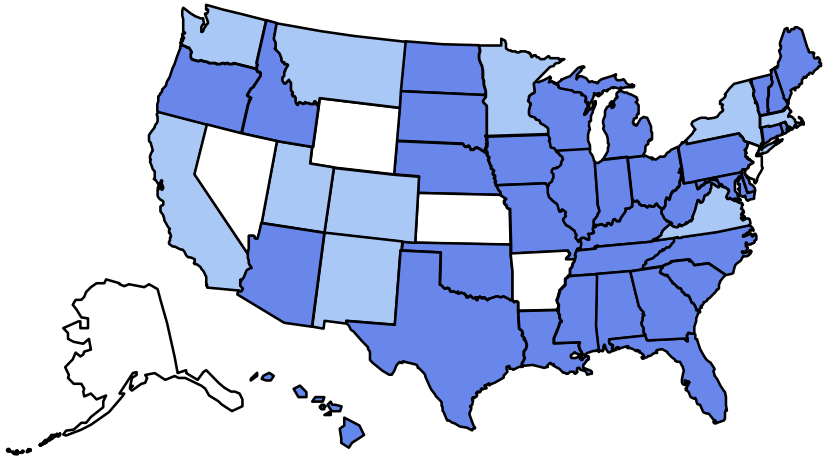
Klein et al, Hepatol Oncol 2017; 4 (3): 83-98

Obesidade e CHC

Tendência à Obesidade* entre Adultos nos USA

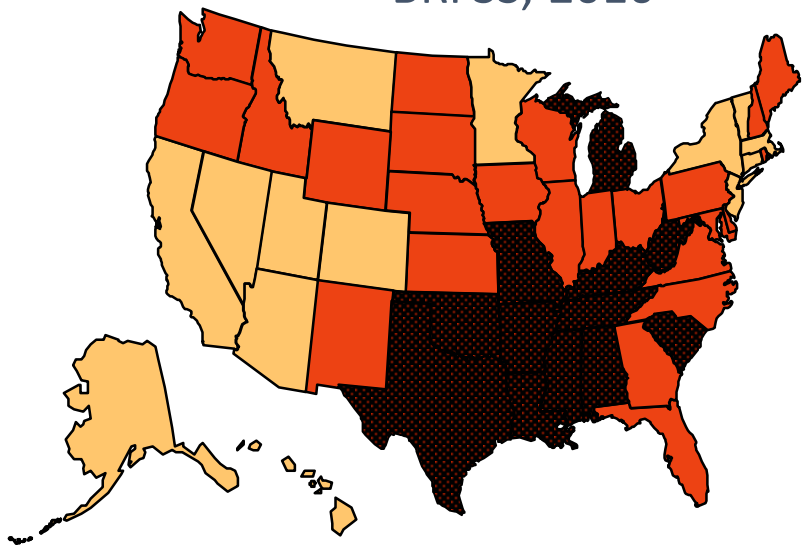
(*BMI ≥30, or ~ 30 lbs. overweight for 5’ 4” person)

BRFSS, 1990

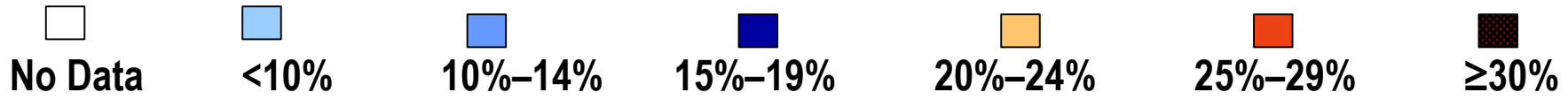


Source: Behavioral Risk Factor Surveillance System, CDC.

BRFSS, 2010



Source: Behavioral Risk Factor Surveillance System, CDC.



Obesidade e CHC

SÃO PAULO CLÍNICAS
LIVER CANCER GROUP

- Há 20 anos atrás *Moller et al* demonstraram uma correlação entre obesidade e um risco aumentado de câncer – risco particularmente alto para câncer de fígado e esôfago.

	Men			Women			Total		
Site	*n*	RR	95% CI	*n*	RR	95% CI	*n*	RR	95% CI
All cancers	694	1.16	1.07–1.25	1344	1.17	1.10–1.23	2038	1.16	1.11–1.21
Mouth and pharynx	22	1.4	0.9–2.1	15	1.1	0.6–1.7	37	1.2	0.9–1.7
Oesophagus	13	1.9	1.0–3.3	13	1.9	1.0–3.2	26	1.9	1.2–2.8
Stomach	30	1.1	0.7–1.5	43	1.1	0.8–1.5	73	1.1	0.9–1.4
Colon	59	1.3	1.0–1.7	136	1.2	1.0–1.4	195	1.2	1.0–1.4
Rectum	33	1.0	0.7–1.4	58	1.2	0.9–1.5	91	1.1	0.9–1.3
Liver	22	1.9	1.2–2.9	36	1.9	1.4–2.7	58	1.9	1.5–2.5
Gallbladder	2	0.5	0.1–1.8	26	1.4	0.9–2.1	28	1.3	0.8–1.8
Pancreas	34	1.8	1.2–2.5	67	1.7	1.3–2.2	101	1.7	1.4–2.1
Lung	99	0.9	0.7–1.0	69	0.8	0.6–1.0	168	0.8	0.7–1.0
Female breast				231	1.0	0.9–1.2	231	1.0	0.9–1.2
Cervix uteri				49	1.2	0.9–1.6	49	1.2	0.9–1.6
Corpus uteri				114	2.0	1.6–2.4	114	2.0	1.6–2.4
Ovary				58	1.1	0.8–1.4	58	1.1	0.8–1.4
Prostate	96	1.3	1.1–1.6				96	1.3	1.1–1.6
Kidney	21	1.2	0.7–1.8	58	2.0	1.5–2.6	79	1.7	1.3–2.1
Bladder	64	1.3	1.0–1.6	35	1.1	0.7–1.5	99	1.2	1.0–1.5
Melanoma	10	1.1	0.5–2.1	22	0.9	0.6–1.4	32	1.0	0.7–1.4
Non-melanoma skin cancer	80	1.0	0.8–1.2	110	0.8	0.6–0.9	190	0.9	0.7–1.0
Brain	8	0.7	0.3–1.4	35	1.5	1.0–2.1	43	1.2	0.9–1.7
Secondary and unspecified cancer	16	1.1	0.6–1.8	49	1.4	1.0–1.9	65	1.3	1.0–1.7
Non-Hodgkin's lymphoma	14	1.3	0.7–2.1	22	1.0	0.6–1.5	36	1.1	0.8–1.5
Leukaemia	23	1.5	0.9–2.2	28	1.2	0.8–1.7	51	1.3	1.0–1.7

European Journal of Cancer Vol. 30A, No. 3, pp. 344–350, 1994

Obesidade e CHC

- Desde então, numerosos estudos confirmaram a correlação da obesidade com o maior risco de câncer.
- Obesidade está associada com aumento de risco de morte por câncer. *Calle e cols, NEJM 2003*
- A obesidade está relacionada com um maior risco de morte por câncer – mortalidade 52% maior em homens obesos e 62 % maior em mulheres obesas comparados a pacientes com peso normal.
- Essa associação também foi observada nos países asiáticos.

Klein et al, Hepatol Oncol 2017; 4 (3): 83-98

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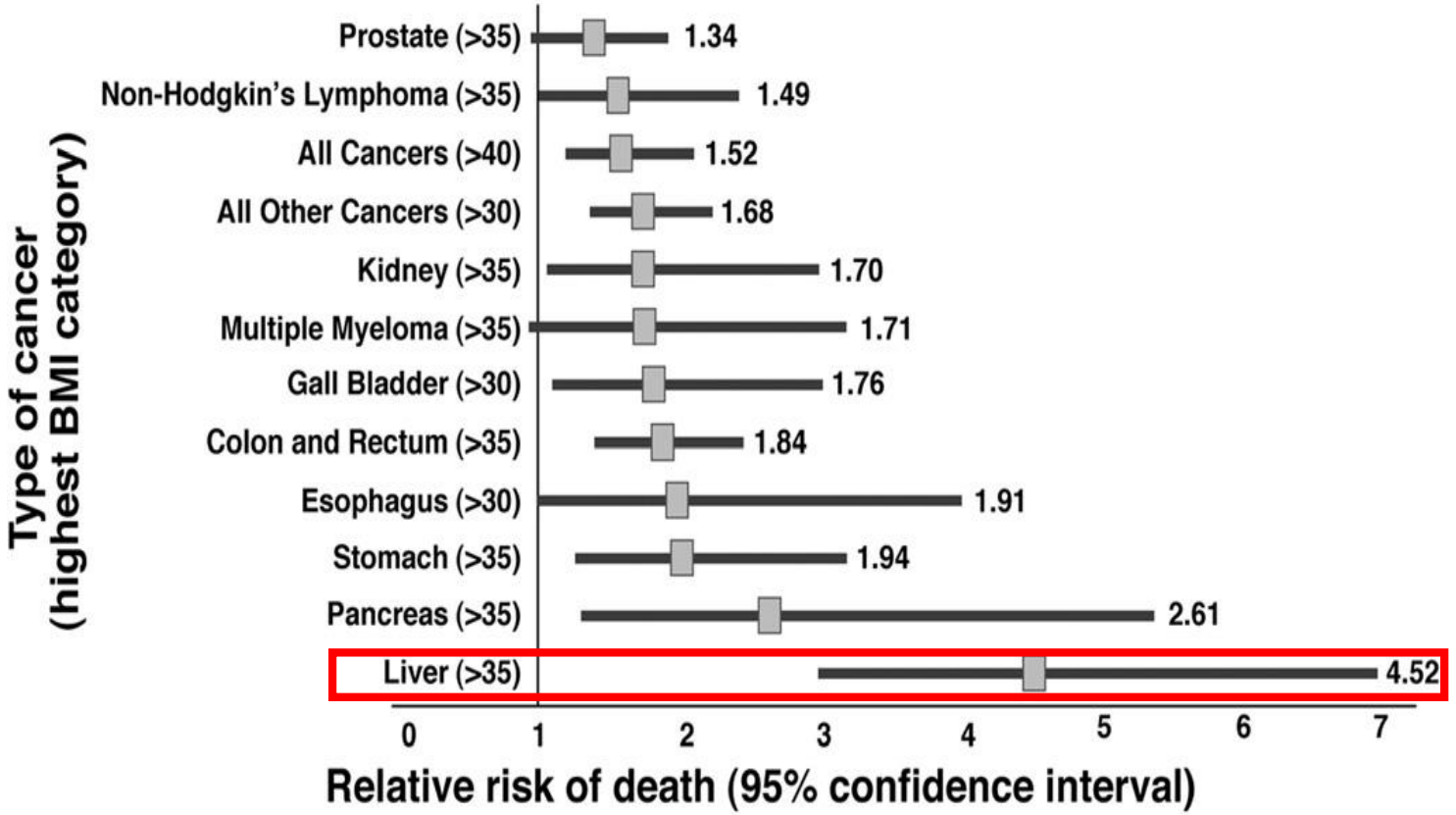
LIVER CANCER GROUP

Mortality Relative Risks from Cancer in *OBESE* men in U.S.A.



Calle EE, & et al, N Engl J Med 2003

Obesidade e CHC

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LIVER CANCER GROUP

- Obesidade é um fator de risco independente de CHC
- Aumento do risco de CHC de 1,5 a 4 vezes. *Samanic e cols, 2004; Moller e cols, 1994 ; Wolk e cols, 2001*
- O risco de CHC é significativamente maior em pacientes com obesidade e esteastohepatite alcoólica (RR: 3.2, 95% IC: 1.5 – 6.6) e cirrose criptogênica (RR: 11.1, 95% IC: 1.5 – 87.4).
- A obesidade aumenta em 4x o risco de CHC em pacientes com cirrose.
- Risco 2x maior de CHC em pacientes com IMC > 30 Kg/m^2 x IMC ≤ 30 Kg/m^2 (*Polese et al, 2008*)
- Obesidade visceral apresenta risco aumentado de CHC.
- Correlação entre o risco de CHC e a idade de desenvolvimento da obesidade - obesidade na infância e adolescência aumenta o risco de CHC.

Klein et al, Hepatol Oncol 2017; 4 (3): 83-98

Obesidade e CHC

SÃO PAULO CLÍNICAS
LIVER CANCER GROUP

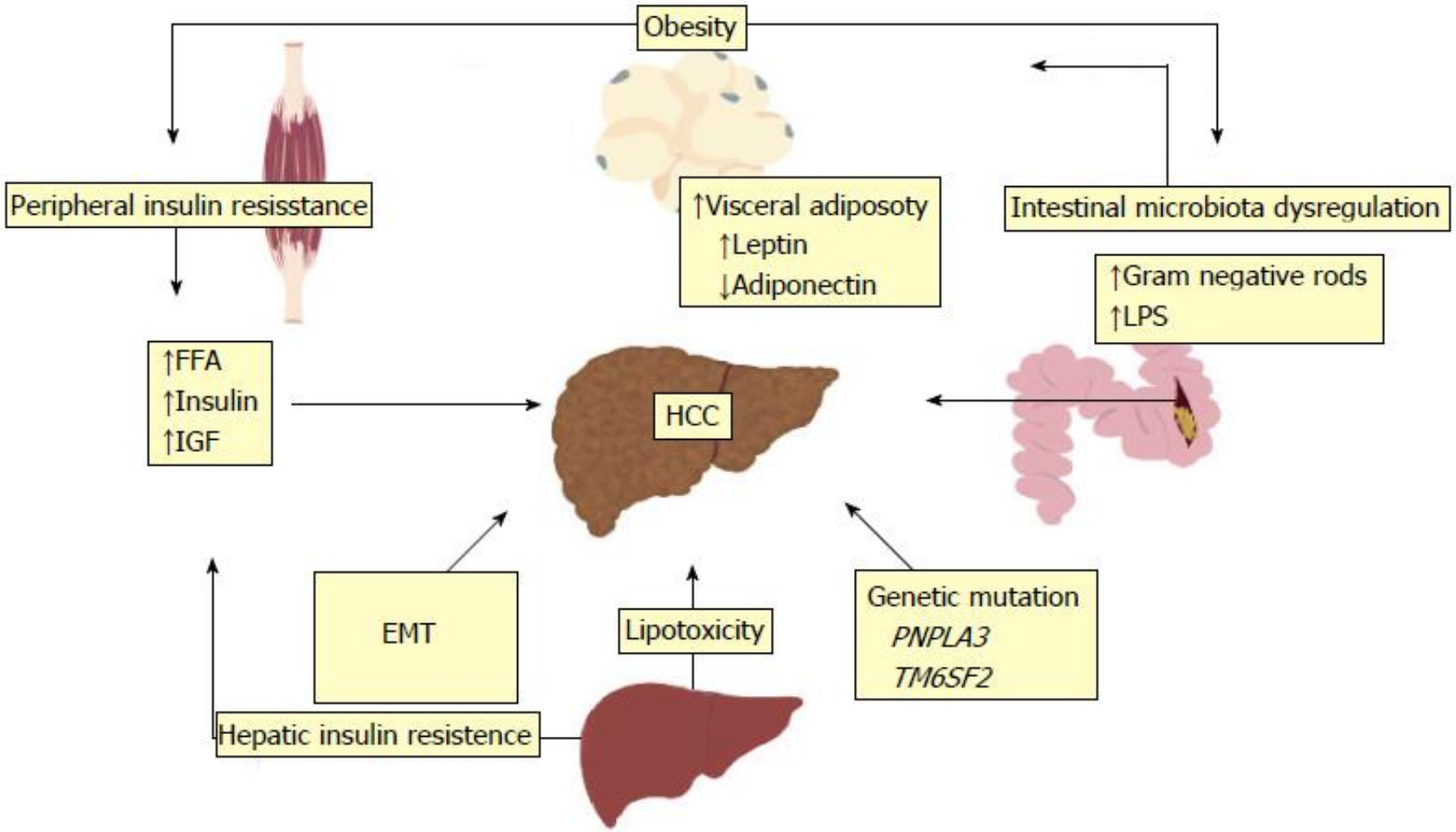
Table 2. Studies showing the elevated risk of hepatocellular carcinoma with obesity.

Study (year)	Design	Population	Number of patients with HCC/obesity	Key findings
Moller *et al.* (1994)	Cohort	• n = 43,965 • Discharge registrations from Danish hospitals	58/43,965	Elevated risk of cancer in obese people Overall incidence of cancer was increased by 16% Liver cancer RR = 1.9
Jee *et al.* (2008)	Prospective cohort	• n = 1,213,829 • Insured by the National Health Insurance Corporation • 1992–1995	8759/-	Elevated risk of cancer in obese men with BMI >30 kg/m^2 HR: 1.39 95%; CI: 1.00–1.94
Nair *et al.* (2002)	Cohort	• n = 19,271 • United Network of Organ Sharing examined explanted liver for HCC • 1991–2000	659/5358	Obesity as risk factor of HCC vs nonobesity Patients with alcoholic cirrhosis OR: 3.2; 95% CI: 1.5–6.6; p = 0.002 Patients with cryptogenic cirrhosis OR: 11.1; 95% CI: 1.5–87.4; p = 0.02
Marrero *et al.* (2005)	Prospective case–control	• n = 210 • Liver or General Medicine Clinics at hospital of University of Michigan • June 2002–August 2003	70/78	Risk of HCC in obese patients vs control OR: 4.3; 95% CI: 2.1–8.4
Polesel *et al.* (2008)	Case–control	• n = 589 • Province of Pordenone, Northeast Italy, and in the town of Naples, South Italy • 1999–2003	185/119	Risk of HCC obese vs control OR: 1.9; 95% CI: 0.9–3.9
Ohishi *et al.* (2008)	Nested case–control study	• n = 868 • Japan	224/163	Risk of HCC obese vs nonobese RR: 4.36; 96% CI:1.48–13.0

HCC: Hepatocellular carcinoma; HR: Hazard ratio; OR: Odds ratio; RR: Relative risk.

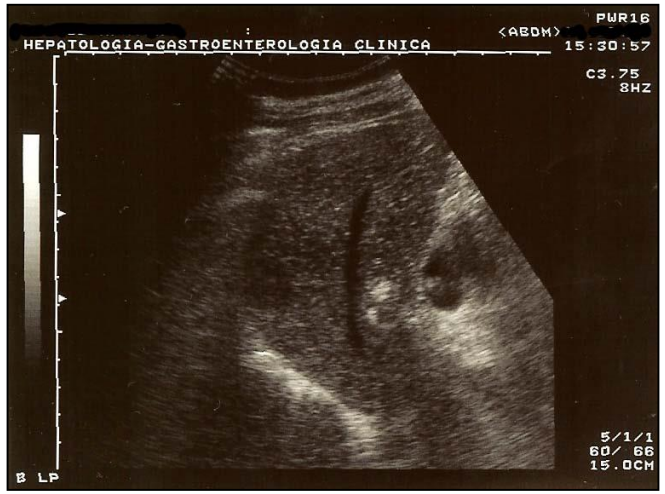
Klein et al, Hepatol Oncol 2017; 4 (3): 83-98

Hepatocarcinogênese na NAFLD



Cholankeril et al, WJH 2017 9(11):533-543

Rastreamento do CHC na DHGNA



Surveillance for Hepatocellular Carcinoma in Patients with NASH

Philippe Kolly [1,2] and Jean-François Dufour [1,2,*]

- Aumento da incidência de pacientes com NASH e CHC.
- CHC no contexto do NASH – cerca de 50% dos casos em pacientes não-cirroticos.
- CHC associado a NASH - diagnóstico com tumores maiores
- Realizam rastreamento com menor frequência antes do diagnóstico.
- Dificuldade na realização do rastreamento com USG

Diagnosis, 2016, 6 (22)

Screening para CHC em pacientes com NAFLD

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LIVER CANCER GROUP

- Dificuldade técnica para realização de rastreamento com NASH por conta da obesidade associada → associação de outros métodos de imagem?
- Quando rastrear o paciente com NASH não cirrótico? Em quem realizar o rastreamento?

Diagnosis, 2016, 6 (22)

Klein et al, Hepatol Oncol 2017; 4 (3): 83-98

Indicações de Rastreamento do CHC

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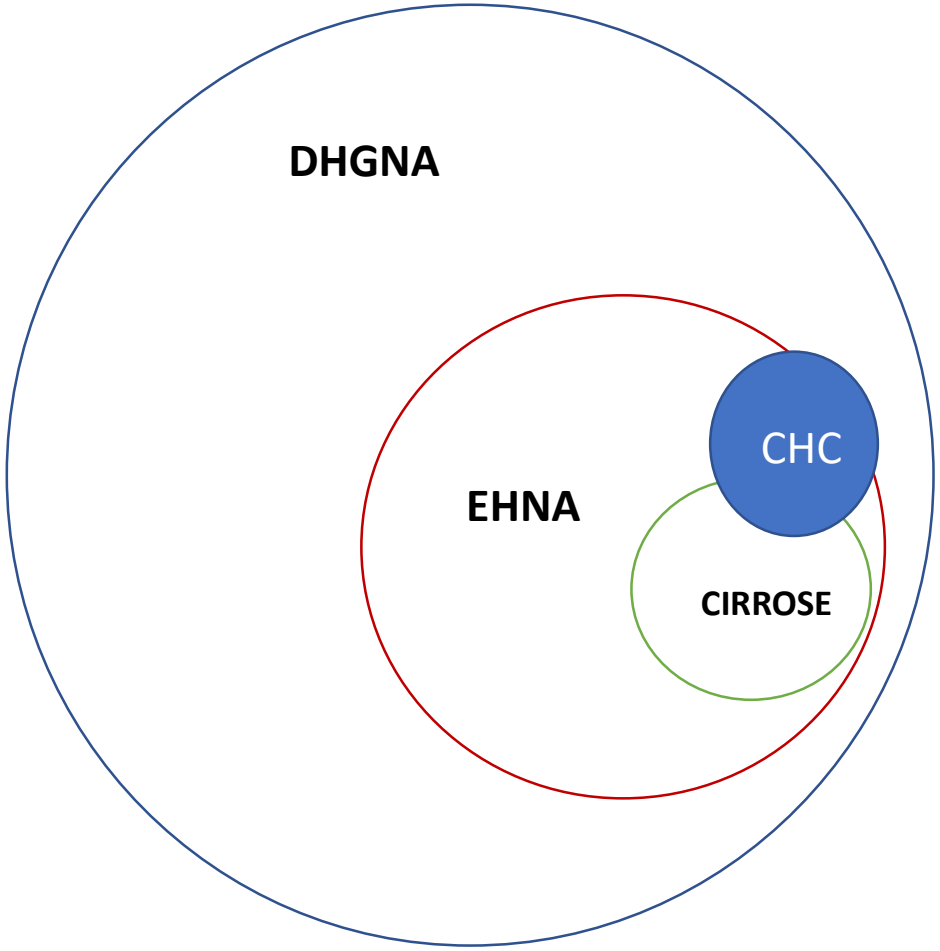
- Pacientes com Cirrose CHILD A e B
- Pacientes com Cirrose CHILD C em lista de transplante
- Hepatite B não-cirróticos com risco intermediário ou alto de CHC:
  - PAGE-B score 10 – 17 e ≥ 18
- Hepatite com fibrose avançada (F3) independente da etiologia devem ser considerados para rastreamento – baseado no risco individual → **NAFLD com F3 ou cirrose**
- Dados insuficientes para indicar screening em pacientes com NAFLD sem fibrose avançada

AASLD Pratice Guideline, Hepatology 2018; 67 (1)

EASL HCC Guideline, J hepatol 2018; 69 (1)

Em quem realizar o rastreamento?



- Pacientes com fatores de risco para presença de fibrose avançada:
- Diabetes
- Idade avançada
- Ingesta de álcool
- Obesidade
- Métodos não invasivos de avaliação da fibrose

- Elastografia, elastoRM, NALFD-escore, FIB4, APRI…

- Fatores genéticos – gene PNPLA3 e rs738409

Prevenção do CHC no NASH – Metformina

SÃO PAULO CLÍNICAS
LIVER CANCER GROUP

Table 3. Studies showing the reduced risk of hepatocellular carcinoma with metformin use.

Study (year)	Design	Population	Number of patients with HCC/diabetes/ metformin	Key finding
Donadon *et al.* (2009)	Retrospective, case–control	• n = 465 HCC, n = 618 cirrothic • n = 490 control • Caucasian • Attending the Liver Unit and Diabetic Clinic of 3rd Internal Medicine in the Pordenone General Hospital (Pordenone, Italy) • January 1994 to June 2006	465/351/87	Metformin in HCC vs metformin in control OR: 0.33; 95% CI: 0.1–0.7 p = 0.0006
Donadon *et al.* (2010)	Retrospective, case–control	• n = 610 HCC, n = 618, n = 1690 control • Three groups of Caucasian individuals • Attending the 3rd Internal Medicine of the Pordenone General Hospital (Pordenone, Italy) • January 1994 to December 2008.	610/594/129	Metformin in HCC vs metformin in control OR: 0.33; 95% CI: 0.1–0.61 p = 0.0005 Metformin in HCC vs metformin in liver cirrhosis OR: 0.15; 95% CI: 0.09–0.28; p < 0.0001
Hassan *et al.* (2010)	Case–control	• n = 420 HCC, n = 1104 control • Ongoing hospital-based case–control study • At the University of Texas M D Anderson Cancer Center	420/208/98	Use of Biguanide or thiazolidinediones in HCC vs control OR: 0.3; 95% CI: 0.2–0.6 p < 0.001
Nkontchou *et al.* (2011)	Prospective cohort-study	• n = 100 diabetic patients • Ongoing HCV cirrhosis • Screening program for HCC • 1988–2007	39/100/26	Metformin treatment vs no treatment Decrease in HCC occurrence HR: 0.19; 95% CI: 0.04–0.79 p = 0.023
Lai *et al.* (2012)	Retrospective cohort study	• n = 19,349 DM, n = 77,396 control • Taiwan National Health Insurance Research Database • 2000–2005	679/19.349/16.282	HCC risk reduction in metformin use vs nonuse HR: 0.49; 95% CI: 0.37–0.66
Chen *et al.* (2013)	Case–control	• n = 97,430 HCC, n = 194,860 control • Taiwan's National Health Insurance Research Database	97,430/47,820/-	Use of metformin vs nonuse Adjusted OR: 0.93; 95% CI: 0.91–0.94
Singh *et al.* (2013)	Systemic review	• n = 334,307 DM • Systematic search of Medline, EMBASE and Web of Science up to August 2012	22.650/334.307/-	Meta-analysis of observational studies showed a 50% reduction in HCC incidence with metformin use OR: 0.50; 95% CI : 0.34–0.73
Seo *et al.* (2016)	Retrospective cohort study	• n = 5494 HCC • National Health Insurance Service and Korea Center Cancer Registry	5494/751/533	Metformin use vs nonuse Risk of mortality with an HR: 0.38; 95% CI: 0.30–0.49 and retreatment events with an HR: 0.41; 95% CI: 0.33–0.52

DM: Diabetes mellitus; HCC: Hepatocellular carcinoma; HCV: Hepatitis C virus; HR: Hazard ratio; OR: Odds ratio.

Klein et al, Hepatol Oncol 2017; 4 (3): 83-98

Prevenção de CHC no NASH – Sinvastatina

SÃO PAULO CLÍNICAS
LIVER CANCER GROUP

- **Sinvastatina**

- Efeito protetor através das suas propriedades anti-inflamatórias por inibição da JAK.

- Redução no risco de CHC .

Table 4. Studies showing the reduced risk of hepatocellular carcinoma with statin use.

Study (year)	Design	Population	Number of patients with HCC/statin	Key finding
Friis *et al.* (2005)	Cohort study	• n = 334,754 • Patients with liver cancers • Prescription Database of North Jutland County and the Danish Cancer Registry • 1989–2002	171/12.251	Statin users vs nonusers Adjusted rate ration; 1.16; 95% CI: 0.46–2.90
El-Serag *et al.* (2009)	Case–control	• n = 6515 • Matched case–control study nested within a cohort of patients with diabetes	1303/3213	Statin vs nonuse Adjusted OR: 0.74; 95% CI: 0.64–0.87
Chiu *et al.* (2011)	Case–control	• n = 2332 • Data were retrospectively collected • Taiwan National Health Insurance Research Database • 2005–2008, age >50 years	1166/312	HCC vs control OR: 0.62; 95% CI: 0.45–0.83
Tsan *et al.* (2012)	Cohort study		1021/2785	Statin use vs nonuse Dose depending HR: 0.66; 95% CI: 0.44–0.99; 28– 90 cDDDs HR: 0.41; 95% CI: 0.27–0.61; 91–365 cDDDs HR: 0.34; 95% CI: 0.18–0.67; >365 cDDDs
Singh *et al.* (2013)	Meta-analysis	• n = 1,459,417 • Ten studies reporting • Systemic review on Medline	4298/-	Statin use vs nonuse OR: 0.63; 95% CI: 0.52–0.76
Tsan *et al.* (2013)	Cohort study	• n = 260,864 • Population-based cohort study • HCV-infected patients • Taiwan National Health Insurance Research Database • 1 January 1999–31 December 2010	27.883/35.023	A dose–response relationship statin use and nonuse HR: 0.66; 95% CI: 0.59–0.74; 28–89 cDDDs HR: 0.47; 95% CI: 0.40–0.56; 90–180 cDDDs HR: 0.33; 95% CI: 0.25–0.42; 180 cDDDs
McGlynn *et al.* (2014)	Case–control	• n = 562 • Members of the Health Alliance Plan HMO of the Henry Ford Health System • 1999–2010	94/258	Ever use of statins vs nonuse OR: 0.32; 95% CI: 0.15–0.67
McGlynn *et al.* (2015)	Case–control	• n = 5835 • United Kingdom's Clinical Practice Research Data link • Persons diagnosed with primary liver cancer • 1988–2011	1195/-	Statin use vs nonuse OR: 0.55; 95% CI: 0.45–0.69
Huang *et al.* (2016)	Cohort study	• n = 13,086 • Data from the Taiwanese National Health Insurance Research Database • 1997–2009 • CHB patients	314/6543	Statin use vs nonuse $p < 0.001$
Kim *et al.* (2017)	Case–control	• n = 2519 patients • Diabetes • Korea	229/405	Statin use vs nonuse OR: 0.36; 95% CI: 0.22–0.60

cDDD: Cumulative-defined daily dose; CHB: Chronic hepatitis B; HBV: Hepatitis B virus; HCC: Hepatocellular carcinoma; HMO: Health Maintenance Organization ; HR: Hazard ratio; OR: Odds ratio.

Klein et al, Hepatol Oncol 2017; 4 (3): 83-98

Prevenção do CHC no NASH – Aspirina

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Table 5. Studies showing the reduced risk of hepatocellular carcinoma, with aspirin use.

Study (year)	Design	Population	Number of patients using aspirin	Key finding aspirin vs nonuse
Sahasrabuddhe *et al.* (2012)	Prospective cohort study	• n = 300,504 • HCC patients aged 50–71 years • National Institute of Health AARP Diet and Health Study	219,291	HCC development: RR: 0.59; 95% CI: 0.45–0.77 Death due to chronic liver disease: RR: 0.55; 95% CI: 0.45–0.67
Petrick *et al.* (2015)	Meta-analysis	• n = 679 • Data from 10 US-based cohort studies in a total of 1,084,133 individuals	315	HCC development: HR: 0.68; 95% CI: 0.57–0.81
Li *et al.* (2016)	Retrospective matched-pair analysis	• n = 120 • Patients with HCC treated with TACE and aspirin	60	Mortality risk: HR: 0.498; 95% CI: 0.28–0.888

AARP: American Association of Retired Persons; HCC: Hepatocellular carcinoma; HR: Hazard ratio; RR: Relative risk; TACE: Trans arterial chemo embolization.

Klein et al, Hepatol Oncol 2017; 4 (3): 83-98

Doença Hepática Alcoólica e CHC

Epidemiologia da Hepatopatia sec Álcool

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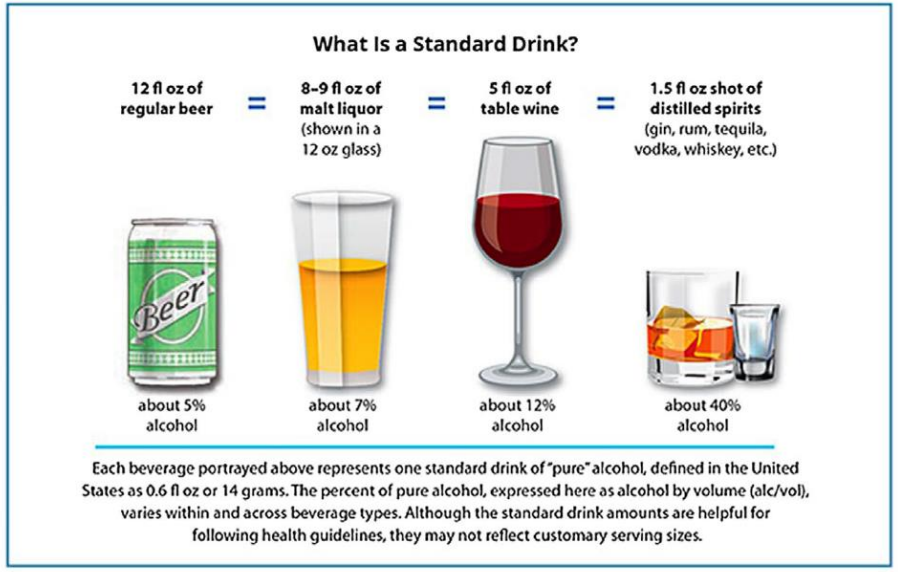
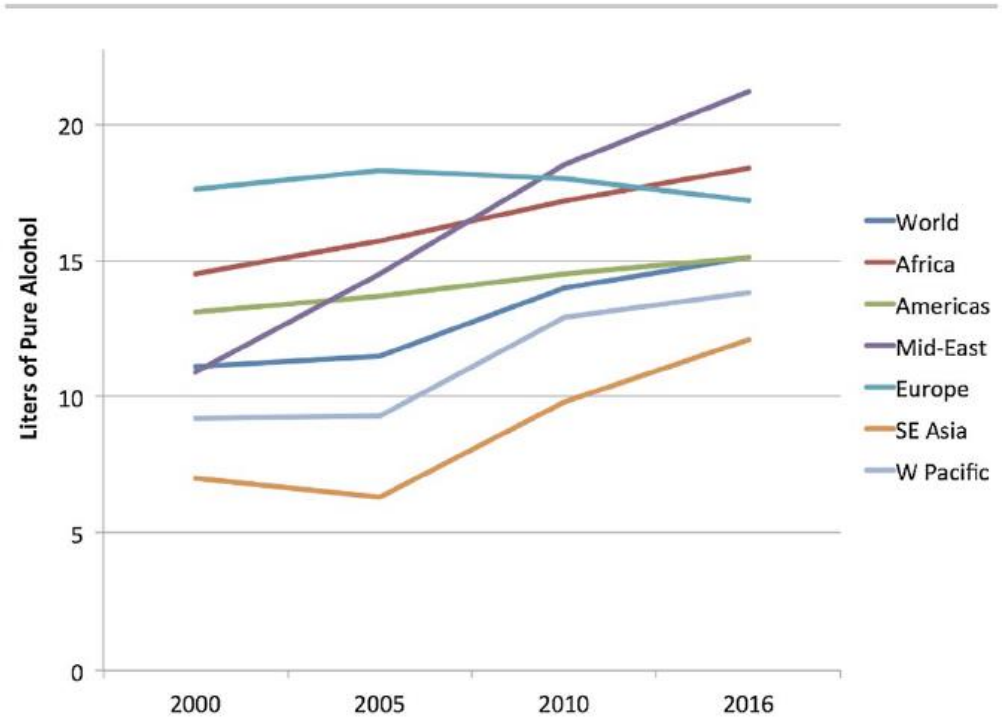
- Mortalidade e morbidade secundária ao álcool é elevada e está aumentando.
- Mortalidade atribuída ao álcool em 2016 → 38.8 /100.000 pessoas.
- A prevalência da cirrose por álcool aumentou em 43% nos EUA no setor privado.
- Aumento de 15% na mortalidade por doença hepática alcóolica entre 25-34 anos.
- Metade das mortes relacionadas a cirrose no mundo pode ser atribuída, pelo menos em parte, ao consumo de álcool.
- Risco de cirrose relacionado com a quantidade do consumo.
- Na mesma quantidade de ingesta as mulheres apresentam um risco maior de cirrose comparado com o homem – 48g/dia (4 drinks) – RR 10.1 x 5.6.

Mellinger et al, Clin Liv Dis 2019 (13)

Epidemiologia da Hepatopatia sec Álcool





- Consumo excessivo: 25 a 50g/d (mulher) e 60 a 80g/d (homem)
- Consumidores ativos: homem (54%) x mulher (32%)

Mellinger et al, Clin Liv Dis 2019 (13)

Álcool e CHC

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- Doença hepática alcoólica → esteatose → cirrose (20 a 25% dos pctes) → CHC

- Nos pacientes com outras doenças hepáticas crônicas, o consumo associado de álcool pode acelerar a progressão para cirrose, desenvolvimento de complicações e agir como um cofator aumentando o risco de CHC.

- Estudos tem demonstrado que fatores do hospedeiro, como gênero, etnia e fatores genéticos podem contribuir com a progressão da doença.

- A incidência do CHC relacionado ao álcool parece ser menor do que a observada nas outra causas de hepatopatia, como causas virais ou hemocromatose.

Joshi et al, Clin Liv Disease 2016; 563-580
Mellinger et al, Clin Liv Dis 2019 (13)

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Álcool e CHC

Área	N. estudos	N. pts	Seguimento (anos)	Incidência CHC
Europa	3	178.915	8.1	0.01
Europa	3	15.020	7.4	0.2
Europa	3	584	5	1.7
Japão	2	174	4.5	1.8

Fattovich. Gastroenterology, 2004

Epidemiologia do CHC na Hepatopatia sec Álcool

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Table 1
Summary of key studies investigating hepatocellular carcinoma risk for patients with compensated alcoholic cirrhosis (without concomitant viral hepatitis)

Study	Country	Total Patients (n)	Follow-up (y)	Age (y)	Male/ Female	Hepatocellular Carcinoma Cumulative Incidence
Toshikuni et al,[6] 2009	Japan	227	3.5[b]	59[b]	67/8	Annual: 0.6% 3-y: 1.3% 5-y: 6.8% 7-y: 6.8% 10-y: 6.8%
Jepsen et al,[7] 2012	Demark	8482	4.1[b]	54.4[b]	5655/2827	5-y: 1.0%
Ioannou et al,[11] 2007	USA	2126	3.6[a]	NA	2062/64	0.6/100 Patient-years
Uetake et al,[8] 2003	Japan	91	5.9[b]	50.1[b]	91/0	3-y: 2.4% 5-y: 6.4% 7-y: 18.9% 10-y: 28.7%
N'Kontchou et al,[9] 2006	France	771	4.1[a]	59.7[a]	336/142	5-y: 16%
Mancebo et al,[10] 2013	Spain	450	3.5[b]	53.9[a]	369/81	Annual: 2.6% 5-y: 13.2% 10-y: 23.2%
Lin et al,[12] 2013	Taiwan	966	5.2[a]	49.3[b]	165/37	Annual: 1.9% 3-y: 4.8% 5-y: 8.9% 10-y: 21.4%

- Incidência cumulativa em 10 anos variou de 6,8 – 28,7%
- Incidência baixa x moderada de CHC

Joshi et al, Clin Liv Disease 2016; 563-580

Álcool e CHC – Fatores de risco

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- **Idade >= 55 anos**

- < 50 anos risco de CHC em 5 anos de 0,3% x 1,9% em > 70 anos

- **Obesidade**

- IMC > = 30 (RR de 2.9 IC 95% 1.7 – 4.9)

- **Sexo masculino** (risco de CHC em 5 anos de 1,5% x 0,2% nas mulheres) – *Jepsen et al, 2012*

- Mulheres: maior risco de progressão para cirrose e uma progressão mais rápida

- **Diabetes Mellitus** (RR 1,6 IC 95% 1.1- 2.3)

- Em pacientes com DM: aumento do risco de CHC em 4.2x se consumo de álcool > 4 drinks/dia

- **Associação com outras hepatopatias**

– efeito sinérgico com o álcool

Mellinger et al, Clin Liv Dis 2019 (13)

Joshi et al, Clin Liv Disease 2016; 563-580

Clinical and epidemiological aspects of hepatocellular carcinoma in Brazil

Flair Jose Carrilho,[I] Luciana Kikuchi,[II] Fernanda Branco,[III] Carlos Sandoval Gonçalves,[IV] Angelo Aves de Mattos,[V] Brazilian HCC Study Group[IV]

CLINICS 2010;65(12):1285-1290

Table 1 - Clinical and epidemiological data from 1,405 HCC patients.

Variable	N	%
Gender (n, %)		
Male	1,066	78
Female	297	22
Age (median, SD)		
Male	59	11
Female	62	12
Etiology (n, %)		
HCV	516	39
HCV + alcohol	200	15
HBV	159	12
HBV + alcohol	47	4
HCV + HBV	30	2
HBV + hepatitis Delta virus	17	1
Alcohol	184	14
Nonalcoholic steatohepatitis	34	3
Hemochromatosis	10	1
Cryptogenic	41	3
Others	51	4
Noncirrhotic	29	2

Carrilho F J, Clinics 2010; 65(12):1285-1290

Álcool e CHC – Fatores de risco

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- **Tempo de consumo do álcool** – dose cumulativa.
- **Plaquetopenia**
- **Cirrose**
- **Vírus B oculto**

– Anti-HBCT pos AgHBs neg

- **Polimorfismo genético**

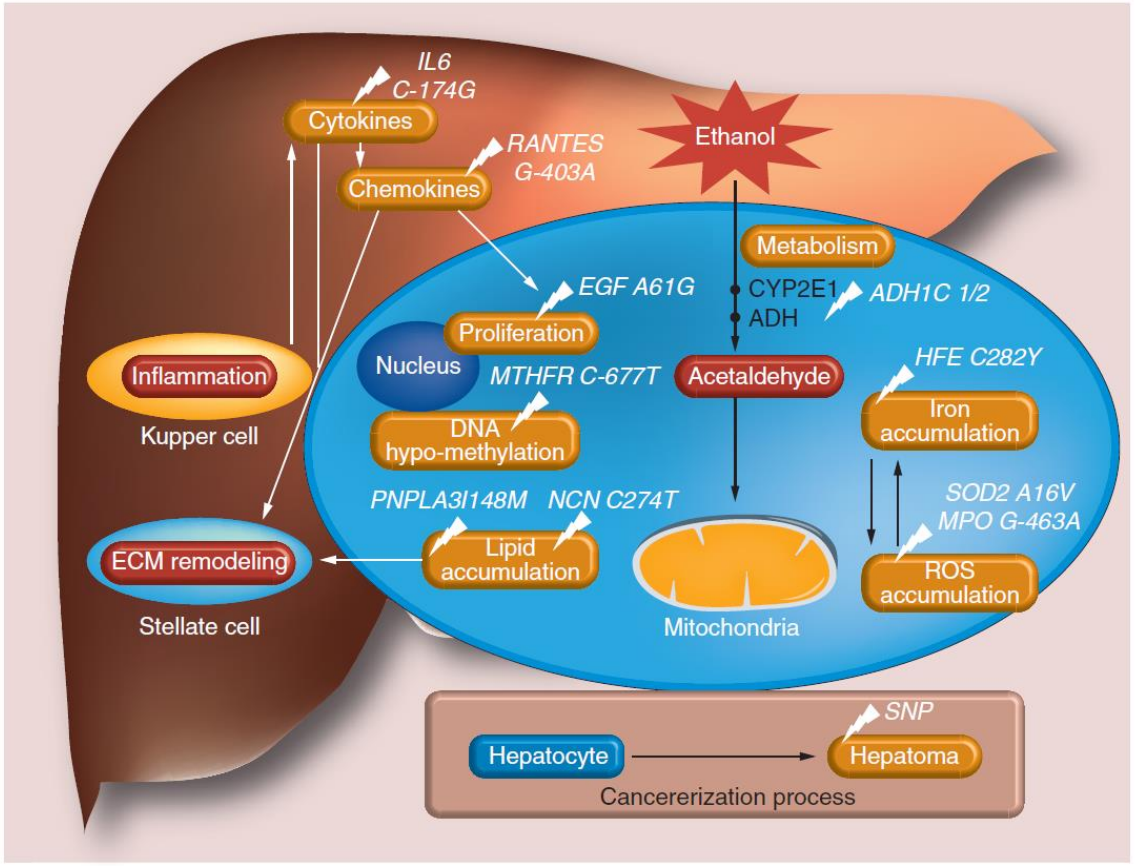
- Gene PNLPA3 (genótipo GC e GG)
- rs738409 C>G polimorfismo

Joshi et al, Clin Liv Disease 2016; 563-580

Álcool e CHC – Hepatocarcinogênese

- Efeito carcinógeno direto:
- Dano mitocondrial e de proteínas
- Stress oxidativo (↑ ROS)
- Hipometilação do DNA

- Expressão de oncogenes e genes supressores tumorais.



Nahon, et al Hepatol Oncol 2015 2 (1): 63-78

Álcool e CHC – Prevenção

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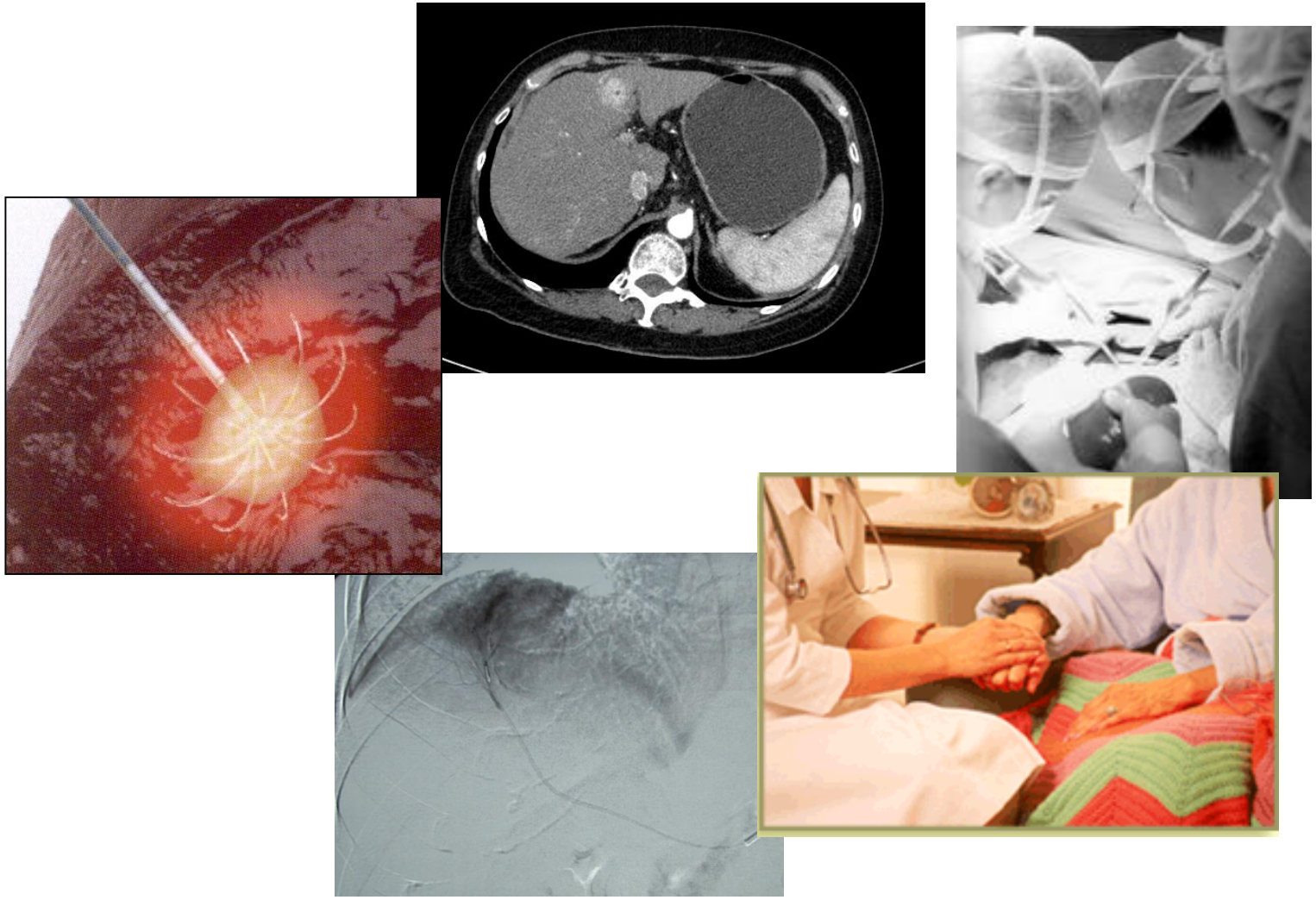
- **Abstinência!!!**

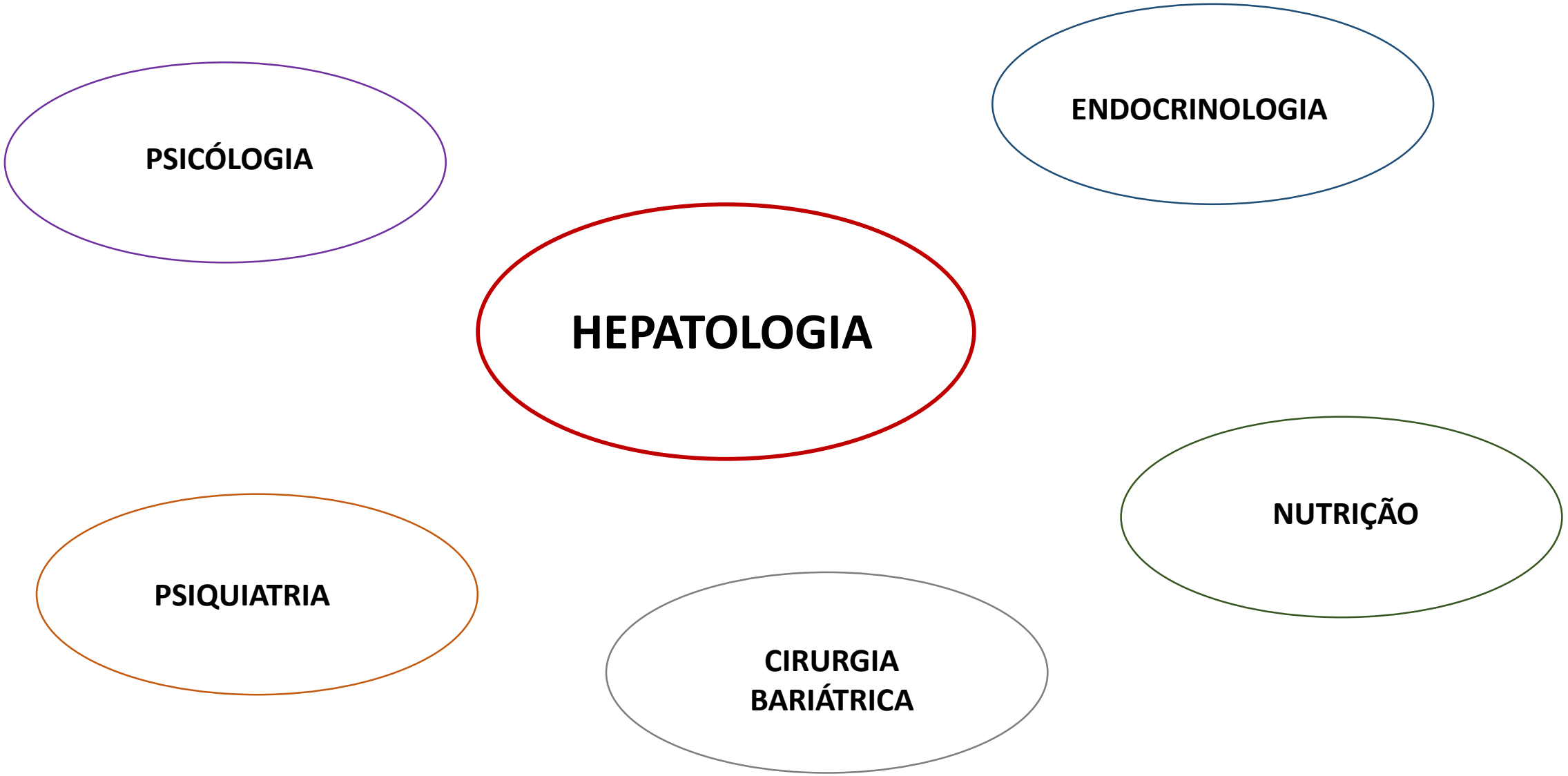
- **Risco de CHC permanece mesmo após a abstinência → manter rastreamento de CHC em pacientes cirróticos**
- **Controle de demais fatores de risco associados**

Joshi et al, Clin Liv Disease 2016; 563-580

CHC na DHGNA e Doença Alcoólica: abordagem multidisciplinar



CHC na DHGNA e Doença Alcoólica: abordagem multidisciplinar



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