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### Cigarette smoking as a risk factor for the development of and mortality from hepatocellular carcinoma; an updated systematic review of 81 epidemiological studies

O. Abdel-Rahman<sup>1</sup>, D. Helbling<sup>2</sup>, O. Schöb<sup>2</sup>, M. Eltobgy<sup>3</sup>, H. Mohamed<sup>3</sup>, J. Schmidt<sup>4</sup>, A. Giryes<sup>2</sup>, A. Mehrabi<sup>5</sup>, S. lype<sup>6</sup>, H. John<sup>7</sup>, A. Tekbas<sup>5</sup>, A. Zidan<sup>8</sup>, H. Oweira<sup>4</sup>

<sup>1</sup>Faculty of Medicine - Ain Shams University, Abasseya, Egypt

<sup>2</sup>Gastrointestinal Tumor Zentrum, Zurich, Switzerland

<sup>3</sup>Ain Shams University, Cairo, Egypt

<sup>4</sup>Hirslanden Hospital, Zurich, Switzerland

<sup>5</sup>University of Heidelberg, Heidelberg, Germany

<sup>6</sup>Cambridge University Hospital, Cambridge, United Kingdom

<sup>7</sup>Cambridge NHS Trust, Cambridge, United Kingdom

<sup>8</sup>Assiut University, Assiut, Egypt

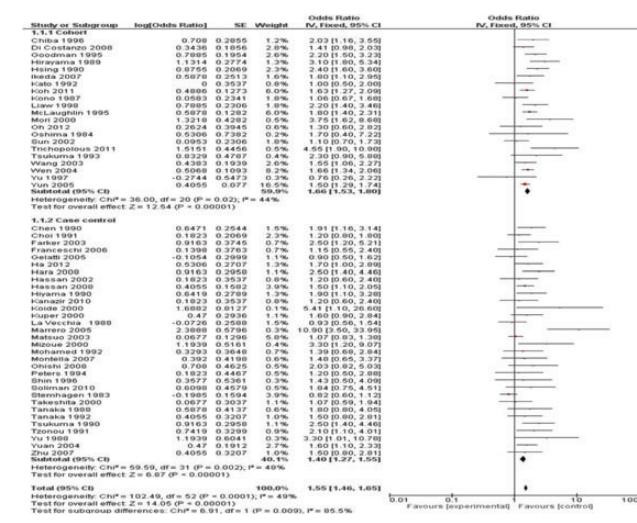
**Introduction:** Hepatocellular carcinoma (HCC) is the sixth most common cancer worldwide and its incidence has increased during the past decade. While hepatitis B and C virus infections and alcohol are established risk factors, the impact of smoking on the risk and mortality of HCC needs to be confirmed.

**Objectives:** We aimed to assess the correlation between cigarette smoking and HCC development and mortality.

**Methods:** Search methods: We reviewed cohort and case control studies evaluating the correlation between cigarette smoking and development risk and/or mortality risk of HCC from MEDLINE, and Google scholar. We also checked reference lists of original studies and review articles manually for cross-references up to February 2016. Data collection and analysis: We extracted the relevant information on participant characteristics and study outcomes, as well as information on the methodology of the studies. We also assessed the quality of the included trials using critical appraisal skills program checklists.

**Results:** After exclusion of non eligible studies, 81 studies were included in the systematic review. Pooled OR for the risk of HCC development with current smoking was 1.55 (95% CI: 1.46–1.65;  $P < 0.00001$ ) (see associated figure), pooled OR for the risk of HCC development with former smoking was 1.39 (95% CI: 1.26–1.52;  $P < 0.00001$ ) and pooled OR for the risk of HCC development with heavy smoking was 1.90 (95% CI: 1.68–2.14;  $P < 0.00001$ ). Pooled OR for the added mortality risk of current smokers with HCC was 1.29 (95% CI: 1.23–1.34;  $P < 0.00001$ ); and for former smokers with HCC, it was 1.20 (95% CI: 1.00–1.42;  $P = 0.04$ ).

**Conclusion:** Cigarette smoking increases the risk of development and mortality from HCC. Further studies are needed to evaluate possible impact of quitting smoking on decreasing this risk.



1.1.2 Case control

Chen 1990

Chen 1992

Farker 2003

Fujimoto 2006

Gelatti 2005

Han 2008

Han 2009

Hassan 2008

Hepatitis 2009

Kamazaki 2010

Konishi 2010

Kuper 2000

Lee et al. 1988

Martinez 2005

Mazouzi 2003

Mizouze 2000

Mizouze 2002

Mizouze 2007

Ohishi 2008

Ohishi 2014

Shim 1995

Souliman 2010

Stenhammar 1983

Tanaka 1992

Tanaka 2000

Tanaka 2002

Tsukuma 1990

Tsukuma 1991

Vu 1989

Yao 2004

Zhu 2007

**Subtotal (95% CI)**

**Heterogeneity: Chi<sup>2</sup> = 59.59, df = 31 ( $P = 0.02$ ),  $I^2 = 40\%$**

**Test for subgroup differences: Chi<sup>2</sup> = 8.87,  $P = 0.05001$**

Total (95% CI)

100.0%

1.55 [1.46, 1.65]

0.01

Favours [experimental]

Favours [control]