IARC MONOGRAPHS

ASPARTAME, METHYLEUGENOL, AND ISOEUGENOL

VOLUME 134

This publication represents the views and expert opinions of an IARC Working Group on the Identification of Carcinogenic Hazards to Humans, which met in Lyon, France, 6–13 June 2023

LYON, FRANCE - 2024

IARC MONOGRAPHS ON THE IDENTIFICATION OF CARCINOGENIC HAZARDS TO HUMANS

Advance publication, 29 April 2024

International Agency for Research on Cancer

World Health Organization

ANNEX 3. SUPPLEMENTARY MATERIAL FOR SECTION 2, CANCER IN HUMANS

Fig. S2.1 illustrates a directed acyclic graph (DAG) created by the Working Group to identify potential confounders of the association between aspartame intake and liver cancer risk. The objective of this exercise was to infer the quality of control for confounding in the available studies. This DAG is a conceptual model of the most influential causal relations for which data are typically available in epidemiological studies and is not intended to be exhaustive. The Daggity web application was used to create the DAG (Textor et al., 2016)

Known risk factors for liver cancer (identified as those with *sufficient* evidence in humans according to the *IARC Monographs* classification; IARC, 2024) that are of relevance for aspartame exposure were added to the DAG. These include:

(i) Aflatoxins (IARC, 2012a)

No arrow was drawn connecting aflatoxins to aspartame exposure, because these two exposures seem unlikely to be associated. Hence, aflatoxin exposure is probably not a confounder.

(ii) Alcoholic beverages (IARC, 2012b)

Consumption of alcoholic beverages may be linked to aspartame exposure through socioeconomic status. Socioeconomic status is known to influence body mass index (BMI) status, which might be associated with aspartame exposure, through consumption of artificially sweetened beverages.

(iii) Estrogen–progestogen oral contraceptives (combined) (IARC, 2012c)

No arrow was drawn that connected contraceptive use and aspartame consumption, since these factors were deemed unlikely to be associated. Hence, exposure to estrogen–progestogen oral contraceptives (combined) is probably not a confounder.

(iv) Chronic infection with hepatitis B virus or hepatitis C virus (strong risk factors for liver cancer; IARC, 2012d) is captured in this DAG as "hepatitis infection".

The potential connection between hepatitis infection and aspartame consumption may be through socioeconomic status, which is connected to BMI status.

(v) Tobacco smoking (in smokers and in smokers' children) (IARC, 2012b)

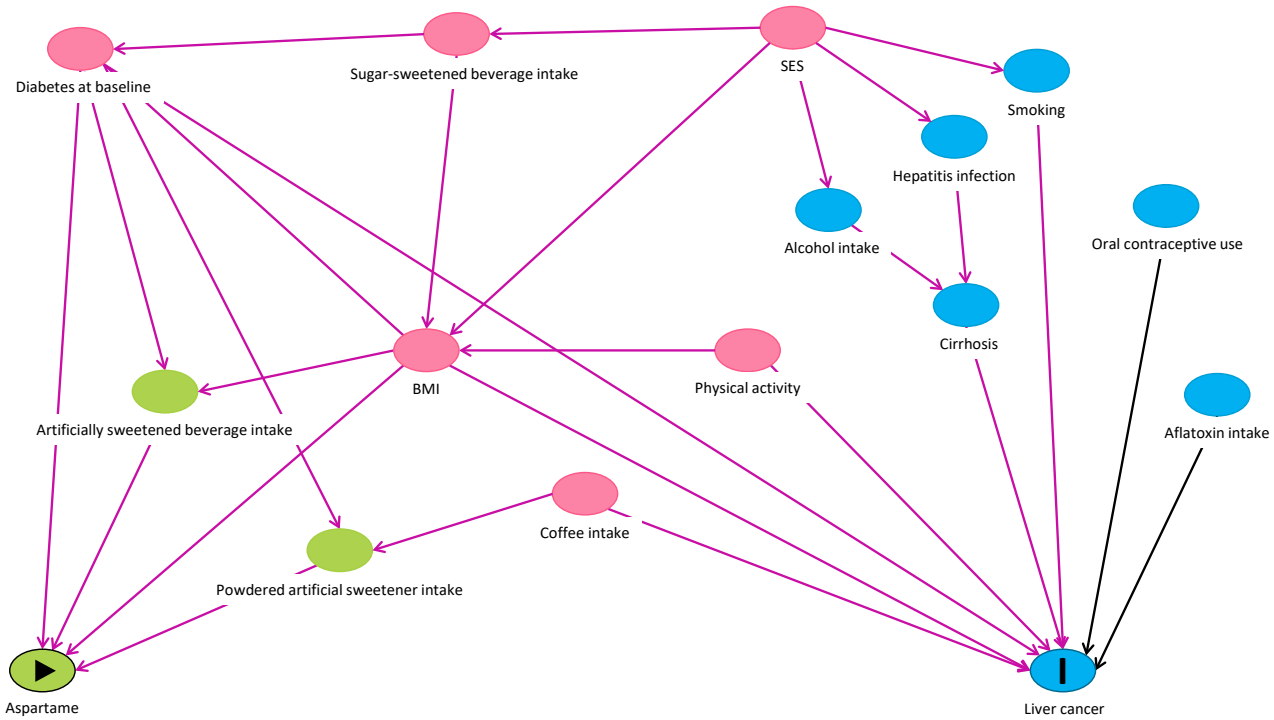
The potential connection between tobacco smoking and aspartame consumption may be through socioeconomic status, which is connected to BMI status.

The following potential risk factors for liver cancer were added:

(i) Higher BMI

This is a recognized risk factor for cancer, given the evidence for the protective effect

Fig. S2.1 Directed acyclic graph for the association between aspartame intake and liver cancer in studies of cancer in humans



BMI, body mass index; SES, socioeconomic status.

of absence of excess body fatness on risk of cancer (with *sufficient* evidence for liver cancer, evidence summarized in the IARC *Handbooks of Cancer Prevention*; Lauby-Secretan et al., 2016). BMI is connected to aspartame exposure via consumption of artificially sweetened beverages. Adjustment for BMI would control for this confounding and, because of the connection between BMI and socioeconomic status, would control for potential confounding by hepatitis, alcohol, and smoking behaviour.

(ii) Coffee intake

This was added because of the determination of *evidence suggesting lack of carcinogenicity* for liver cancer (with evidence of an inverse association) (IARC, 2018) and because of the potential link between coffee consumption and possible use of powdered artificial sweeteners. Because of the inverse association, lack of adjustment for coffee consumption would bias results towards the null.

(iii) Diabetes at baseline

This factor was added because of the emerging evidence that diabetes is a risk factor for liver cancer (Giovannucci et al., 2010).

Overall, the Working Group concluded that age, sex, BMI, socioeconomic status, diabetes, and consumption of sugar and/or sugar-sweetened beverages represented the minimal sufficient adjustment sets for estimating the effect of aspartame on the risk of certain cancers.

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