Carcinogenicity of drinking coffee, mate, and very hot beverages

In May, 2016, a Working Group of 23 scientists from ten countries met at the International Agency for Research on Cancer (IARC) in Lyon, France, to evaluate the carcinogenicity of drinking coffee, mate, and very hot beverages. These assessments will be published in volume 116 of the IARC Monographs.[1]

Coffee is one of the world's most widely consumed beverages. It contains many different compounds and its composition varies depending on how it is produced and prepared for drinking. After consumption, caffeine, chlorogenic acids, and other compounds contained in coffee are absorbed and distributed throughout the body.

The carcinogenicity of coffee drinking was last assessed by IARC in 1991.[2] At that time coffee was classified as "possibly carcinogenic to humans" (Group 2B) based on limited evidence of an association with cancer of the urinary bladder from case-control studies, and inadequate evidence of carcinogenicity in experimental animals. However, there was also evidence suggesting a lack of carcinogenicity for cancers of the female breast and the large intestine.

For this re-evaluation, a much larger database of more than 1000 observational and experimental studies was available. In assessing the accumulated epidemiological evidence, the current Working Group gave the greatest weight to well-conducted prospective cohort and population-based case-control studies that controlled adequately for important potential confounders, including tobacco and alcohol consumption. For bladder cancer, there was no consistent evidence of an association with drinking coffee, or of an exposure–response gradient from ten cohort studies and several population-based case-control studies in Europe, the USA, and Japan.[3–5] In several studies, relative risks were increased in men but were null or decreased in women, consistent with residual confounding from smoking or occupational exposures among men. The Working Group concluded that positive associations reported in some studies could have been due to inadequate control for tobacco smoking, which can be strongly associated with heavy coffee drinking. By contrast, for endometrial cancer, the five largest cohort studies showed mostly inverse associations with coffee drinking. These results were supported by the findings of several case-control studies and a meta-analysis.[6] Inverse associations with coffee drinking were also observed in cohort and case-control studies of liver cancer in Asia, Europe, and North America. A meta-analysis of prospective cohort studies estimated that the risk of liver cancer decreases 15% for each 1 cup per day increment.[7] More than 40 cohort and case-control studies and a meta-analysis[8] including nearly 1 million women consistently indicated either no association or a modest inverse association for cancer of the female breast and coffee drinking. Similarly, numerous cohort and case-control studies of cancers of the pancreas and prostate consistently indicated no association between these cancers and coffee drinking. Data were also available for more than 20 other cancers, including lung, colorectal, stomach, oesophageal, oral cavity, ovarian, and brain cancers, and childhood leukaemia. Although the volume of data for some of these cancers was substantial, the Working Group judged the evidence to be inadequate for all of the other cancers reviewed for reasons including inconsistency of findings across studies, inadequate control for potential confounding, potential for measurement error, selection bias or recall bias, or insufficient numbers of studies.

The combination of evidence suggesting lack of carcinogenicity for cancers of the female breast, pancreas, prostate, uterine endometrium, and liver, with inverse associations for the latter two and inadequate evidence for all the other sites reviewed led to the conclusion that there is inadequate evidence in humans for the carcinogenicity of coffee drinking.

Coffee has been evaluated for carcinogenicity in several long-term studies in mice and rats, and has been tested for both tumour-promoting and cancer-preventing activity in a number of co-carcinogenicity studies in rats and hamsters. The Working Group concluded that these studies provided inadequate evidence in experimental animals for the carcinogenicity of coffee.

Coffee drinking exhibited strong antioxidant effects in studies in humans, including in randomised controlled trials.[9] Results for genotoxicity from studies in humans were inconsistent, and coffee did not induce chromosomal damage in rodents. Nonetheless, coffee gave positive results in bacterial mutagenesis assays, but only without metabolic activation. Coffee promoted apoptosis in human cancer cell lines.[10] Moderate evidence of an association of coffee drinking with reduced risk of colorectal adenoma was noted. Coffee has also been associated with beneficial effects on liver fibrosis and cirrhosis.

Overall coffee drinking was evaluated as unclassifiable as to its carcinogenicity to humans (Group 3).

Mate is an infusion made from dried leaves of *Ilex paraguariensis*. It is consumed mainly in South America and to a lesser extent in the Middle East, Europe, and North America. Mate is traditionally drunk very hot (>65°C), but it can also be consumed warm or cold. The carcinogenicity of mate was previously evaluated in 1991,[2] when

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hot mate drinking was classified as "probably carcinogenic to humans" (Group 2A).

Evidence on the carcinogenicity of mate comes mainly from hospital-based case-control studies on cancer of the oesophagus in South America. A pooled analysis[11] of most of the available studies showed the risk of oesophageal cancer increasing with the quantity of mate consumed. However, the trend was statistically significant only for mate consumed "hot" or "very hot", and a significant trend was observed with drinking temperature independent of the amount consumed. The single study that examined cold mate drinking showed no association with oesophageal cancer.

To further assess the effect of beverage temperature, the Working Group reviewed studies that reported on the association of oesophageal cancer with the drinking temperature of other beverages. Another pooled analysis[12] of South American case-control studies on oesophageal cancer showed significantly increased relative risks for drinking very hot tea and very hot beverages other than mate similar in magnitude to that for drinking very hot mate. A large cohort study and several case-control studies[13] showed an increased risk of oesophageal cancer when drinking tea very hot or hot, compared with lower temperatures. Similar results have been reported in other studies evaluating combinations of very hot drinks.

From these data, the Working Group concluded that there is limited evidence in humans for the carcinogenicity of drinking very hot beverages, and inadequate evidence in humans for the carcinogenicity of drinking mate that is not very hot.

In experimental animals, the carcinogenicity of mate and of beverage temperature has only been assessed in a few co-carcinogenicity studies. Locally instilled very hot water (at 65–70°C) increased the incidence of nitrosamine-induced oesophageal tumours in one study in mice[14] and one study in rats.[15] By contrast, cold mate administered as drinking fluid in rats reduced the incidence of oesophageal and liver tumours induced by nitrosamine and hot water combined. The Working Group concluded that there is limited evidence in experimental animals for the carcinogenicity of very hot water at 65°C or above, and inadequate evidence in experimental animals for the carcinogenicity of mate as a drinking fluid.

Pharmacokinetic and mechanistic data for mate drinking are sparse. Studies in humans and animals given orally administered mate did not report genotoxicity or other cancer related effects.

The Working Group noted that the epidemiological evidence for very hot beverages and human cancer has strengthened over time, with positive associations and trends in studies that considered qualitative gradations of temperature. Additionally, new studies in experimental animals show that hot water above 65°C can act as a tumour promoter. Although the mechanistic and other relevant evidence for very hot beverages is scant, biological plausibility exists for an association between very hot beverages and cell injury and the sequelae that might lead to cancer. On the basis of these considerations and on the totality of the evidence, drinking very hot beverages at above 65°C was classified as "probably carcinogenic to humans" (Group 2A). This evaluation of very hot beverages includes drinking of very hot mate. Drinking mate that is not very hot was evaluated as "not classifiable as to its carcinogenicity to humans" (Group 3).

We declare no competing interests.

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