Special Report: Policy

A review of human carcinogens—Part E: tobacco, areca nut, alcohol, coal smoke, and salted fish

In October, 2009, 30 scientists from 10 countries met at the International Agency for Research on Cancer (IARC) to reassess the carcinogenicity of tobacco, areca nut, alcohol, coal smoke, and salt-preserved fish, and to identify additional tumour sites (table) and mechanisms of carcinogenesis. These assessments will be published as part E of Volume 100 of the IARC Monographs.[1]

Tobacco smoking is the single largest cause of cancer worldwide. More than 1 billion people around the world are current smokers. New evidence continues to add to the extensive list of tobacco-related cancers (table); there is now sufficient evidence that tobacco smoking causes cancer of the colon[3] and of the ovary.[4] More than 150 epidemiological studies of tobacco smoking and breast cancer were reviewed. Large cohort studies[5,6] published since 2002[2] consistently show a small positive association (relative risks 1·1–1·3). Many chemicals in tobacco smoke cause mammary-gland tumours in animals, and these carcinogens are stored in breast adipose tissue in women; therefore, the Working Group concluded that there is limited evidence that tobacco smoking causes breast cancer.

A causal link between parental smoking and childhood cancers has been established. Four recent studies showed that children born of parents who smoke (father, mother, or both, including the preconception period and pregnancy) are at significantly higher risk of hepatoblastoma, a rare embryonic cancer. The UK Childhood Cancer Study[7] reported a relative risk of 1·86 for paternal smoking only and 2·02 for maternal smoking only, increasing to 4·74 (95% CI 1·68–13·35) when both parents smoke. For childhood leukaemia, a meta-analysis reported an association with paternal smoking before pregnancy (summary relative risk 1·12, 1·04–1·21).[8]

Second-hand smoke causes lung cancer.[2] There is now limited evidence for an association with cancers of the larynx and the pharynx,[9] whereas evidence for female breast cancer remains inconclusive. Since second-hand smoke contains most of the constituents of mainstream smoke, it might also be associated with other cancer sites.

Many types of smokeless tobacco are marketed and all contain nicotine and nitrosamines. Hundreds of millions of people use smokeless tobacco, mainly in India and southeast Asia, but also in Sweden and the USA. Earlier findings showed a causal association between use of smokeless tobacco and cancers of the oral cavity and pancreas, and there is now sufficient evidence for cancer of the oesophagus.[10]

All of the forms of tobacco discussed above induce malignant tumours in laboratory animals. Among the many carcinogens present in tobacco are nitrosamines, including the tobacco-specific nitrosamines 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone

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	Tumour sites for which there is sufficient evidence	Tumour sites for which there is limited evidence	Tumour sites for which there is evidence suggesting lack of carcinogenicity
Tobacco smoking	Oral cavity, oropharynx, nasopharynx, and hypopharynx, oesophagus (adenocarcinoma and squamous-cell carcinoma), stomach, colorectum,* liver, pancreas, nasal cavity and paranasal sinuses, larynx, lung, uterine cervix, ovary (mucinous)*, urinary bladder, kidney (body and pelvis), ureter, bone marrow (myeloid leukaemia)	Female breast*	Endometrium (postmenopausal*), thyroid*
Parental smoking (cancer in the offspring)	Hepatoblastoma*	Childhood leukaemia (in particular acute lymphocytic leukaemia)*	
Second-hand smoke	Lung	Larynx,* pharynx*	
Smokeless tobacco	Oral cavity, oesophagus,* pancreas		
Areca nut			
Betel quid with added tobacco	Oral cavity, pharynx, oesophagus		
Betel quid without added tobacco	Oral cavity, oesophagus*	Liver*	
Alcohol consumption	Oral cavity, pharynx, larynx, oesophagus, liver, colorectum, female breast	Pancreas*	Kidney, non-Hodgkin lymphoma
Acetaldehyde associated with alcohol consumption	Oesophagus,* head and neck*		
Chinese-style salted fish	Nasopharynx	Stomach*	
Indoor emissions from household combustion of coal	Lung		

*New sites.

Table: **Evidence for carcinogenicity in humans of Group 1 agents assessed**

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Conflicts of interest
SSH has given expert testimony in a smokeless tobacco trial in the USA. The other Monograph Working Group Members declared no conflicts of interest.

Invited Specialists
None

(NNK) and N′-nitrosonornicotine (NNN).[10,11] Tobacco smoke also contains carcinogens as combustion products, such as arylamines, polycyclic aromatic hydrocarbons, and volatile organics.[11] Many studies have investigated possible associations between polymorphisms in carcinogen-metabolising genes and tobacco-related cancers; most results are ambiguous, with the possible exception of *NAT2* in bladder and breast cancers, and *GSTM1* alone or in combination with *CYP1A1* in lung cancer. Tobacco smoking, second-hand smoke, and smokeless tobacco were all reaffirmed as carcinogenic to humans (Group 1), along with NNK and NNN.

Around 600 million people are estimated to chew betel quid in India and southeast Asia (prevalence of up to 80% in parts of India). Betel quid generally consists of areca nut, betel leaf, catechu, slaked lime, and often tobacco. Carcinogenic nitrosamines derived from the areca nut, the primary ingredient in betel quid, are formed in the saliva of chewers. Areca nut induces oral preneoplastic disorders with a high propensity to progress to cancer.[12] The Group 1 classification of betel quid with or without added tobacco, and of areca nut, was reaffirmed. There is now sufficient evidence that betel quid without added tobacco causes oesophageal cancer,[13] and limited evidence for liver cancer.[14]

Nearly 2 billion adults consume alcoholic beverages regularly, with an average daily consumption of 13 g ethanol (about one drink). Alcohol consumption causes cancers of the oral cavity, pharynx, larynx, oesophagus, colorectum, liver, and female breast;[15] evidence for the pancreas is limited.[16] The relative risk of breast cancer increases with increasing alcohol intake by about 10% per 10 g per day. Alcohol drinking results in exposure to acetaldehyde, derived from the beverage itself and formed endogenously. Acetaldehyde is a genotoxic compound that is detoxified by aldehyde dehydrogenases (ALDH). The *ALDH2**2 variant allele, which encodes an inactive enzyme, is prevalent (up to 30%) in east-Asian populations. Heterozygous carriers, who have about 10% enzyme activity, accumulate acetaldehyde and have higher relative risks of alcohol-related oesophageal and head and neck cancers compared with individuals with the common alleles.[17] The Working Group concluded that acetaldehyde associated with alcoholic beverages is carcinogenic to humans (Group 1) and confirmed the Group 1 classification of alcohol consumption and of ethanol in alcoholic beverages.

Salt-preserved fish is consumed in several regions around the world. Chinese-style salted fish causes cancer of the nasopharynx and possibly of the stomach;[18] however, the mechanism of carcinogenesis is uncertain. Two hypotheses are nitrosamine formation and reactivation of Epstein–Barr virus.

About half the world's population, mostly in low-income and middle-income countries, uses solid fuels for cooking or heating, often in poorly ventilated spaces. Women and young children receive the highest exposure. The Working Group confirmed the carcinogenicity of indoor emissions from the combustion of coal as household fuel.[19]

Tobacco and alcoholic beverage consumption, and betel-quid chewing are highly prevalent addictive and harmful activities for which exposure is preventable at an individual level.

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