Alcohol and cancer

BY ALBERT J. TUYNS

International Agency for Research on Cancer, 150 cours Albert-Thomas, 69372 Lyon Cédex 08, France

Alcohol is one of the very few examples of a chemical which has never been shown to cause cancer in experimental animals but which is nevertheless clearly implicated in the causation of certain human cancers.

The experimental findings. Despite repeated attempts to produce cancer in mice, rats and hamsters by the administration of pure ethanol or of alcoholic beverages, it has never been possible to increase significantly the production of tumours in these animals. By using alcohol together with some known carcinogens such as 3-4-benzpyrene (Horie *et al.* 1965) or selected nitrosamines (Griciute *et al.* 1982, 1987) some experimentalists have observed an enhancement of the incidence of certain tumours, sometimes at sites comparable to those affected in man.

The evidence in man. This, by contrast, is so obvious that clinicians, particularly ENT surgeons, incriminated alcohol long before epidemiological investigations confirmed their observations and demonstrated the association. Over the last 30 years, evidence of the causal relationship between alcohol consumption and cancer of the mouth, larynx, hypopharynx and oesophagus has accumulated and a relationship is suspected for several other sites (International Agency for Research on Cancer, 1988). Both cohort studies and case–control surveys on selected cancer sites have confirmed an excess risk related to intake of alcoholic beverages, more convincingly than simpler observational studies on population groups.

When the distribution of oesophageal cancer mortality throughout the French 'départements' was compared to that of cirrhosis and alcoholism, a significant correlation was observed, suggesting a common causal agent: alcohol (Tuyns, 1970). Mortality from rectal cancer was also found to be correlated with per capita consumption of beer in the USA and in European countries (Breslow & Enstrom, 1974). In a correlation study on laryngeal cancer, mortality from this cancer was noted to correlate better with alcohol than with tobacco consumption (Tuyns, 1982).

More demonstrative was the observation of a reduced risk for certain cancers among religious groups known or reputed to abstain from alcohol such as Mormons (Enstrom, 1980) or Seventh-Day Adventists (Phillips *et al.* 1980).

COHORT STUDIES

Several authors have studied the mortality of groups of people who had been treated for alcohol-related diseases in various European countries (Sundby, 1967; Hakulinen *et al.* 1974; Nicholls *et al.* 1974), in the USA (Klatsky *et al.* 1981) and in Canada (Schmidt & Popham, 1981). All these studies have constantly shown an overall excess of cancer deaths due to greater numbers of cancers of the upper aerodigestive tract. When studies of a similar design were carried out on groups of people with presumably high exposure, such as brewery workers in Denmark, an excess of cancers of the same sites was again

Table 1. *Relative risks* for oral cavity and pharyngeal cancer according to level of exposure to smoking and alcohol (from Rothman, 1976)*

	Smoking (cigarette equivalents/d)			
Ethanol (g/d)	0	<20	20–39	>40
0	1·0	1·6	1·6	3·4
<9·5	1·7	1·9	3·3	3·4
9·5–35	1·9	4·9	4·8	8·2
>37	2·3	4·8	10·0	15·6
Cases/controls	26/85	66/97	248/197	143/68

* Risks are expressed relative to a risk of 1·0 for persons who neither smoked nor drank.

observed. With respect to cancers thus related to alcohol consumption, it is remarkable that so many cohort studies have consistently provided the same picture: an excess risk for cancer of the mouth, larynx, hypopharynx and oesophagus.

CASE-CONTROL STUDIES

These associations were eventually confirmed by *ad hoc* case–control studies which had the advantage of recording information not only on alcohol but also on other exposures such as smoking or diet, known or suspected to be additional risk factors. This was particularly rewarding in so far as tobacco certainly, as well as some dietary deficiencies, were found to combine their effects with that of alcohol.

Cancer of the mouth. This was investigated as early as 1957 by Wynder *et al.* (1957) who found that the risk was directly and proportionally related to the number of drinks/d, even after adjustment for smoking. Later studies in the USA (Graham *et al.* 1977) confirmed this finding. In another more recent study in British Columbia, Canada (Elwood *et al.* 1984), alcohol and smoking were again found to be the major risk factors, the association being the strongest for the former.

Cancer of the hypopharynx. Most of the few studies on hypopharyngeal cancer also included either the mouth (Rothman & Keller, 1972) or larynx (Tuyns *et al.* 1988). When Rothman (1976) recalculated relative risks according to amount of alcohol and tobacco consumed daily (Table 1), he noted that risk increased with alcohol consumption within each tobacco consumption category and *vice versa* for smoking, the combination of the two factors suggesting a multiplicative effect, which was also found later in a study carried out in research centres in France, Italy, Spain and Switzerland (Tuyns *et al.* 1988).

Cancer of the larynx. Laryngeal tumours occur much more frequently in males than in females. Within Europe, male mortality rates are highest in Spain, Italy and France, in contrast to the distribution of lung cancer, which predominates in the UK and the Benelux countries (Tuyns, 1982).

When Wynder *et al.* (1976) investigated 200 cases of laryngeal cancer in the USA, they noted that consumption of alcohol considerably increased the risk of disease among smokers but not in non-smokers; they concluded that the main causal factor was tobacco, alcohol acting only in the presence of tobacco. Later studies in Canada (Burch *et al.*

Table 2. *Relative risks for cancer of the endolarynx according to level of exposure to smoking and alcohol (from Tuyns* et al. *1988)*

	Cigarettes (d)			
Ethanol (g/d)	0–8	8–15	16–25	>26
0–40	1·0	6·7	12·7	11·5
41–80	1·7	5·9	12·2	18·5
81–120	2·3	10·7	21·0	23·6
≥121	3·8	12·2	31·6	43·2
Total no. of cases	50	147	357	173

Table 3. *Combined effect of alcohol and tobacco on relative risks* for cancer of the oesophagus (from Tuyns* et al. *1977)*

	Tobacco consumption (g/d)		
Ethanol (g/d)	0–9	10–19	≥20
0–40	1·0	3·4	5·1
41–80	7·3	8·4	12·3
≥81	18·0	19·9	44·4
Total no. of cases	78	58	64

* Risks are expressed relative to a risk of 1·0 for persons smoking <10 g/d and drinking ≤40 g/d.

1981; Elwood *et al.* 1984), however, found increased risks among drinkers who were life-long non-smokers; a study in south-west Europe (Tuyns *et al.* 1988) came to the same conclusion. In the study, a multiplicative model provided an adequate description of the findings (Table 2).

Cancer of the oesophagus. This is probably the cancer site for which the widest range of incidence values has been reported (Day & Muñoz, 1982) under the most varied environmental conditions. In the Western world, the association with both alcohol and tobacco consumption was identified in the USA by Wynder & Bross (1961) and a few years later in Puerto Rico (Martinez, 1969); several studies later confirmed these associations.

In Europe, very high mortality rates in males have been found in France, in the provinces of Brittany and Normandy (Tuyns, 1970). Advantage was taken of the existence of a high average level of alcohol intake in these provinces to investigate the risk of developing oesophageal cancer in relation to alcohol consumption. The first study carried out in Ille-et-Vilaine (Brittany) showed a clear dose–response relationship with daily alcohol intake, adjusting for tobacco (Tuyns *et al.* 1977). The combination of alcohol and tobacco exposures resulted in risks described as multiplicative (Table 3).

A subsequent larger study in Calvados provided similar results. The number of cases was large enough to permit the calculation of risk of disease related to alcohol intake among life-long non-smokers (Tuyns, 1983). There was a similar dose–response relationship both in males and in females (Table 4). This observation was of particular

Table 4. *Relative risks (RR) for oesophageal cancer in relation to average daily alcohol consumption by non-smoking males and females in Normandy, France (from Tuyns, 1983)*

	Males		Females	
Ethanol (g/d)	No. of cases	RR	No. of cases	RR
0–40	7	1·0	25	1·0
41–80	15	3·8	8	5·6
81–120	9	10·2	3	11·0
⩾121	8	101·0	—	—

Table 5. *Relative risks of oesophageal cancer for combined levels of dietary score and alcohol consumption*

(Confidence limits in parentheses)

	Alcohol consumption (ethanol g/d)			
Dietary score	0–40†	40–80	80–120	>120
HHH, HHM, HMM	1	3·7 (1·1–12·6)	15·8 (4·3–58·1)	13·6 (8·3–136·6)
HHL, HML, MML	4·1 (1·1–15·4)	10·2 (2·9–35·6)	32·0 (0·1–111·9)	147·0 (39·1–557·2)
HLL, MLL, LLL	16·3 (4·5–58·4)	38·8 (11·2–135·1)	41·6 (11·8–147·1)	89·3 (25·0–320·5)

H, high; M, moderate; L, low consumption of fresh meat, citrus fruits, and oils respectively.
* Adjusted for age, area of residence, and tobacco smoking.
† 40 g equals approximately 1·4 oz; 1 ml alcohol weighs 0·8 g.

interest in view of the unusually high sex ratio (over 20) in the province, the lower female rate resulting from a considerably lower average consumption of alcohol and of tobacco. Additional investigations on the role of diet in the same study group indicated that, in addition to alcohol and tobacco, insufficient intake of meat, oils and citrus fruit was also a risk factor (Table 5), again with a combination of effects suggesting a multiplicative model (Tuyns *et al.* 1987).

Primary liver cancer. This cancer is often associated with liver cirrhosis, which may be induced by a variety of agents, of which alcohol is probably the most frequent in many European countries. The impact of alcohol on primary liver cancer is difficult to measure because of the existence of other agents, in particular hepatitis B, which has already been shown to be responsible for the very high incidence of primary liver cancer in Africa and Asia. In one large cohort of 8646 blood donors in Japan who were carriers of hepatitis B surface antigen (Oshima *et al.* 1984), the risk of developing primary liver cancer was considerably increased for alcohol consumers, and this was dose-dependent.

Other cancers. Since cancer of the rectum has been correlated with sales of beer

(Breslow & Enstrom, 1974), two retrospective cohort studies were undertaken on brewery workers, one in Dublin and one in Denmark. An excess of rectal cancer cases was observed in the former (Dean *et al.* 1979) but not in the latter (Jensen, 1979). The results of various case–control studies were equally divergent. No firm conclusion can be drawn as to the association (International Agency for Research on Cancer, 1988).

Cancer of the breast is widely distributed throughout the world, and its causation is still far from being understood. When several large, well-conducted cohort studies (Schatzkin *et al.* 1987; Willett *et al.* 1987) simultaneously described an increased risk among women drinkers, this caused some consternation. The increased risks observed, however, are modest (about 1·5). Even though the known confounding factors were taken into account, the possibility of confounding by some other as yet unknown factor cannot be ruled out. Again, no firm conclusion can be formulated on the basis of the facts at our disposal (International Agency for Research on Cancer, 1988).

For a few more sites an association with alcohol has occasionally been suspected, but never with the strength and consistency as for cancers of the upper aerodigestive tract. In some cases an excess risk was observed for a cancer related to another factor which was itself closely associated with alcohol, such as smoking. The clearest example is the excess of lung cancer noticed among drinkers (Jensen, 1979). However, whenever the risk could be adjusted for smoking the effect of alcohol disappeared.

THE CASE OF ALCOHOL AND THE MORE GENERAL PROBLEMS OF CANCER CAUSATION

The clearcut role in alcohol in the causation of certain cancers is instructive in many respects. It is often associated with other factors – smoking, dietary deficiencies – which may in themselves be important causal agents. The most illustrative example of this is the unusual geographic distribution of oesophageal cancer throughout the world. In the Western world it is obviously mainly caused by alcohol, but it is also highly prevalent in regions where drinking is not so widespread and where dietary deficiencies are probably the causative factor.

If the principle of such a multiplicity of interacting causal factors were more widely accepted, it might perhaps be easier to understand why our investigations on single dietary factors in relation to other digestive cancers sometimes produce divergent results. When we deal with diet, we are certainly playing with the most intricate combination of factors.

Summary. Although alcohol is not a chemical carcinogen which produces cancer in experimental animals, there is overwhelming evidence that consumption of alcohol increases the risk of cancer.

When a large group of experts met in Lyon, France, at the invitation of the International Agency for Research on Cancer, in order to review thoroughly the literature on the subject, they concluded that the 'occurrence of malignant tumours of the oral cavity, pharynx, larynx, oesophagus and liver is causally related to the consumption of alcoholic beverages'. Such groups of experts weigh their words and tend to be rather conservative in their written conclusions. Their last sentence was '*Alcoholic beverages are carcinogenic to humans*' (International Agency for Research on Cancer, 1988).

REFERENCES

Breslow, N. E. & Enstrom, J. E. (1974). Geographic correlations between cancer mortality rates and alcohol-tobacco consumption in the United States. *Journal of the National Cancer Institute* **53,** 631–639.

Burch, J. D., Howe, G. R., Miller, A. B. & Semenciw, R. (1981). Tobacco, alcohol, asbestos and nickel in the etiology of cancer of the larynx: a case-control study. *Journal of the National Cancer Institute* **67,** 1219–1224.

Day, N. E. & Muñoz, N. (1982). Esophagus. In *Cancer Epidemiology and Prevention*, pp. 596–623 [D. Schottenfeld and J. F. Fraumeni, editors]. Philadelphia: Saunders.

Dean, G., MacLennan, R., McLoughlin, H. & Shelley, E. (1979). Causes of death of blue-collar workers at a Dublin brewery, 1954–73. *British Journal of Cancer* **40,** 581–589.

Elwood, J. M., Pearson, J. C. G., Skippen, D. H. & Jackson, S. M. (1984). Alcohol, smoking and occupational factors in the aetiology of cancer of the oral cavity, pharynx and larynx. *International Journal of Cancer* **34,** 603–612.

Enstrom, J. E. (1980). Cancer mortality among Mormons in California during 1968–75. *Journal of the National Cancer Institute* **65,** 1073–1082.

Graham, S., Dayal, H., Rohrer, T., Swanson, M., Sultz, H., Shedd, D. & Fischman, S. (1977). Dentition, diet, tobacco and alcohol in the epidemiology of oral cancer. *Journal of the National Cancer Institute* **59,** 1611–1618.

Griciute, L., Castegnaro, M. & Béréziat, J.-C. (1982). Influence of ethyl alcohol on the carcinogenic activity of N-nitrosodi-n-propylamine. In *N-Nitroso Compounds: Occurrence and Biological Effects. IARC Scientific Publication* no. 41, pp. 643–648 [H. Bartsch, M. Castegnaro, I. K. O'Neill and M. Okada, editors]. Lyon: International Agency for Research on Cancer.

Griciute, L., Castegnaro, M. & Béréziat, J.-C. (1987). Influence of ethyl alcohol on carcinogenesis induced by volatile N-nitrosamines detected in alcoholic beverages. In *Relevance of N-Nitroso Compounds to Human Cancer: Exposures and Mechanisms. IARC Scientific Publication* no. 84, pp. 264–265 [H. Bartsch, I. K. O'Neill and R. Schulte-Hermann, editors]. Lyon: International Agency for Research on Cancer.

Hakulinen, T., Lehtimäki, L., Lehtonen, M. & Teppo, L. (1974). Cancer morbidity among two male cohorts with increased alcohol consumption in Finland. *Journal of the National Cancer Institute* **52,** 1711–1714.

Horie, A., Kohchi, S. & Kuratsune, M. (1965). Carcinogenesis in the oesophagus. II. Experimental production of oesophageal cancer by administration of ethanolic solutions of carcinogens. *Gann* **56,** 429–441.

International Agency for Research on Cancer (1988). *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans: Alcohol Drinking*, vol. 44. Lyon: International Agency for Research on Cancer.

Jensen, O. M. (1979). Cancer morbidity and causes of death among Danish brewery workers. *International Journal of Cancer* **23,** 454–463.

Klatsky, A. L., Friedman, G. D. & Siegelaub, A. B. (1981). Alcohol and mortality: a ten-year Kaiser-Permanente experience. *Annals of Internal Medicine* **95,** 139–145.

Martinez, I. (1969). Factors associated with cancer of the esophagus, mouth and pharynx in Puerto Rico. *Journal of the National Cancer Institute* **42,** 1069–1094.

Nicholls, P., Edwards, G. & Kyle, E. (1974). Alcoholics admitted to four hospitals in England. II. General and cause-specific mortality. *Quarterly Journal of Studies on Alcohol* **35,** 841–855.

Oshima, A., Tsukuma, H., Hiyama, T., Fujimoto, L., Yamano, H. & Tanaka, M. (1984). Follow-up study of HBsAg-positive blood donors with special reference to effect of drinking and smoking on development of liver cancer. *International Journal of Cancer* **34,** 775–779.

Phillips, R. L., Garfinkel, L., Kuzma, J. W., Beeson, W. L., Lotz, T. & Brin, B. (1980). Mortality among California Seventh-Day Adventists for selected cancer sites. *Journal of the National Cancer Institute* **65,** 1097–1107.

Rothman, K. J. (1976). The estimation of synergy or antagonism. *American Journal of Epidemiology* **103,** 506–511.

Rothman, K. J. & Keller, A. (1972). The effect of joint exposure to alcohol and tobacco on risk of cancer of the mouth and pharynx. *Journal of Chronic Diseases* **25,** 711–716.

Schatzkin, A., Jones, D. Y., Hoover, R. N., Taylor, P. R., Brinton, L. A., Ziegler, R. G., Harvey, E. B., Carter, C. L., Licitra, L. M., Dufour, M. C. & Larson, D. B. (1987). Alcohol consumption and breast cancer in the epidemiologic follow-up study of the First National Health and Nutritional Examination Survey. *New England Journal of Medicine* **316,** 1169–1173.

Schmidt, W. & Popham, R. E. (1981). The role of drinking and smoking in mortality from cancer and other causes in male alcoholics. *Cancer* **47,** 1031–1041.

Sundby, P. (1967). *Alcoholism and Mortality*. Oslo: Universitetsforlaget.

Tuyns, A. J. (1970). Cancer of the oesophagus: Further evidence of the relationship to drinking habits in France. *International Journal of Cancer* **5,** 152–156.

Tuyns, A. J. (1982). Incidence trends of laryngeal cancer in relation to national alcohol and tobacco consumption. In *Trends in Cancer Incidence, Causes and Practical Implications*, pp. 199–214 [K. Magnus, editor]. Washington: Hemisphere.

Tuyns, A. J. (1983). Oesophageal cancer in non-smoking drinkers and in non-drinking smokers. *International Journal of Cancer* **32,** 443–444.

Tuyns, A. J., Estève, J., Raymond, L., Berrino, F., Benhamou, E., Blanchet, F., Boffetta, P., Crosignani, P., Del Moral, A., Lehmann, W., Merletti, F., Péquignot, G., Riboli, E., Sancho-Garnier, H., Terracini, B., Zubiri, A. & Zubiri, L. (1988). Cancer of the larynx/hypopharynx, tobacco and alcohol. *International Journal of Cancer* **41,** 483–491.

Tuyns, A. J., Péquignot, G. & Jensen, O. M. (1977). Le cancer de l'oesophage en Ille et Vilaine en fonction des niveaux de consommation d'alcool et de tabac: Des risques qui se multiplient. *Bulletin du Cancer* **64,** 45–60.

Tuyns, A. J., Riboli, E., Doornbos, G. & Péquignot, G. (1987). Diet and esophageal cancer in Calvados (France). *Nutrition and Cancer* **9,** 81–92.

Willett, W. C., Stampfer, M. J., Colditz, G. A., Rosner, B. A., Hennekens, C. H. & Speizer, F. E. (1987). Moderate alcohol consumption and the risk of breast cancer. *New England Journal of Medicine* **316,** 1174–1180.

Wynder, E. L. & Bross, I. J. (1961). A study of etiological factors in cancer of the esophagus. *Cancer* **14,** 389–414.

Wynder, E. L., Bross, I. J. & Feldman, R. L. (1957). A study of etiological factors in cancer of the mouth. *Cancer* **10,** 1300–1323.

Wynder, E. L., Covey, L. S., Mabuchi, K. & Mushinski, M. (1976). Environmental factors in cancer of the larynx: A second look. *Cancer* **38,** 1591–1601.

Printed in Great Britain