Cancer morbidity in alcohol abusers

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Summary Data on the association between alcohol abuse and cancer morbidity are scarce in large cohorts of non-hospitalised alcoholic men and women. Of 18,368 alcohol abusers who entered an outpatient clinic in Copenhagen during 1954-87, 18,307 were followed and their cancer incidence was compared with that of the total Danish population. On average the 15,214 men were observed for 12.9 years and the 3,093 women for 9.4 years. The overall morbidity of cancer was increased significantly. Of the men, 1,441 developed cancer [relative risk (RR) = 1.6; 95% confidence interval (CI) = 1.5–1.7], while 182 women did (RR = 1.5; 95% CI 1.3–1.8). Significantly increased incidences were found of cancer in the tongue, mouth, pharynx, oesophagus, liver, larynx, lung and pleura and secondary cancer. The women had significantly increased risk of cervical cancer (RR = 2.0; 95% CI 1.2–3.0). The men developed prostatic cancer significantly more frequently than expected (RR = 1.4; 95% CI 1.2–1.8). The risk of melanomas (RR = 0.5; 95% CI 0.2–0.8) was significantly lower than expected. The relative risks of cancer of the stomach, pancreas, kidney and endocrine system were only slightly increased. The study group did not develop more colonic (RR = 1.0; 95% CI 0.8–1.3) or rectal cancer (RR = 1.0; CI 0.7–1.3) than expected. The risk of breast cancer in women was slightly increased (RR = 1.3; 95% CI 0.9–1.7), but not statistically significant. Thus, the associations between alcohol and cancer of the upper digestive and respiratory tract and the liver are confirmed. In addition, this study indicates an increased occurrence of cancer of the prostate gland, pleura and uterine cervix in alcohol abusers.

Alcoholic beverages are carcinogenic to humans (IARC, 1988), and previous cohort studies of subjects with high consumption of alcoholic beverages have demonstrated increased risks of cancer of the upper parts of the digestive and respiratory organs, and of the liver (Sundby, 1967; Hakulinen et al., 1974; Nicholls et al., 1974; Monson & Lyon, 1975; Dean et al., 1979; Jensen, 1979; Robinette et al., 1979; Schmidt & Popham, 1981; Carstensen et al., 1990). Three cohort studies evaluated cancer morbidity (Hakulinen et al., 1974; Jensen, 1979; Carstensen et al., 1990), while most studies used cancer mortality as the outcome, and therefore had a reduced possibility of detecting an increased occurrence of cancers with low lethality. Some previous cohort studies have been of rather small size (Nicholls et al., 1974; Monson & Lyon, 1975; Robinette et al., 1979; Schmidt & Popham, 1981), the study from Finland had a short duration of follow-up (Hakulinen et al., 1974), and in several studies the diagnosis of alcoholism was not verified, though a high level of consumption was probable (Dean et al., 1979; Jensen, 1979; Carstensen et al., 1990). These methodological shortcomings are particularly relevant in the studies of women.

The aim of the present study was to describe the incidence of cancer in a large cohort of non-hospitalised severe alcoholics of both sexes.

Materials and methods

From 1954 to 1987, 18,368 alcoholics from Copenhagen entered a public outpatient clinic for free treatment (Figures 1 and 2).

On entry to the clinic a history of alcohol intake was obtained in a standardised fashion by an experienced social worker and a psychiatrist. A thorough medical examination was performed. The treatment included controlled disulphiram intake, 200 mg day^{-1}, which is a part of the Danish routine treatment of alcohol abusers. Virtually all the treated alcoholics relapsed; the period of abstinence from alcohol was 3–4 months on average (Jensen & Vang, 1983).
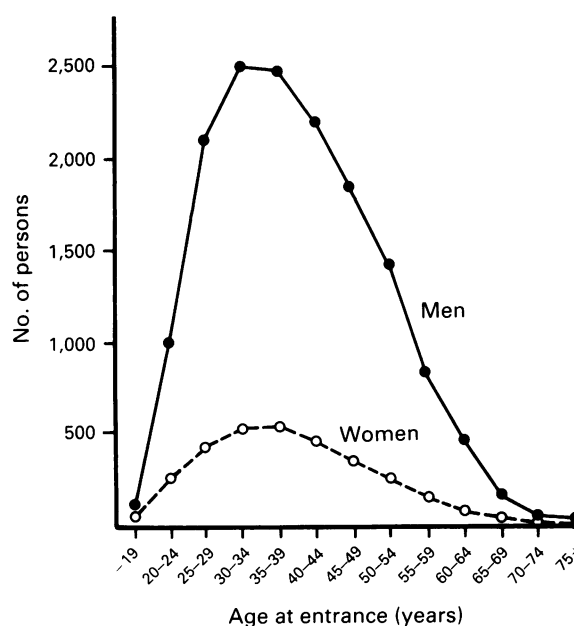
Figure 1 Age of the 18,307 alcohol abusers at entry to the outpatient clinic.

Few of the alcoholic clients had been previously hospitalised in psychiatric departments or mental hospitals. Ninety per cent of the clients had developed several or all of the signs of alcohol dependence syndrome, while 10% used alcohol excessively, but were not addicted. Half of the clients consumed beer, a quarter drank beer and schnapps, while 10% drank strong alcoholic beverages exclusively. The intake of the remainder was mixed. The majority of the clients, both men and women, had a daily consumption of about 200 g of ethanol, while weekly or monthly drinking dominated in 15% (The Copenhagen Municipal Outpatient Clinic for Treatment of Alcoholism, 1960–88).

From 1954 to 1987 the average annual consumption of alcoholic beverages of Danes over 14 years of age increased from 4.7 to 12.0 litres of 100% ethanol per capita, i.e. 26 g of alcohol daily in 1987 (Statistical Yearbooks of Denmark, 1955, 1988).
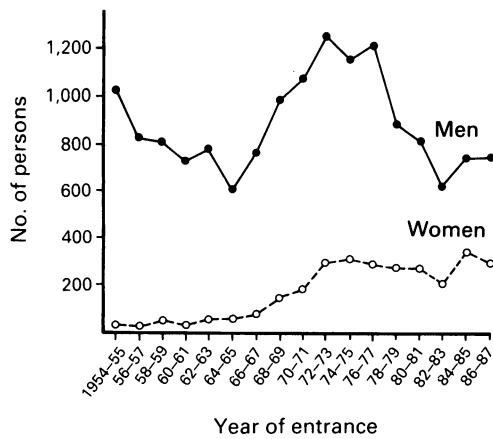
Figure 2 Year of entry to the outpatient clinic of 18,307 alcohol abusers.

The data recorded routinely at the outpatient clinic included date of birth, name and address. After 1968, personal identification numbers (PINs), unique ten-digit identifiers given to every Danish citizen, were recorded.

Follow-up for death

The 5,969 cohort members seen at the clinic before 1968 (i.e. without PINs) were sought by computer linkages in the municipal population registers, in the Central Danish Death Register, which is maintained at the Danish Institute of Clinical Epidemiology, and in the Danish Central Population Register, which since 1968 has maintained a computerised record of the Danish population. Cohort members with a PIN recorded were computer linked to the Central Population Register. Through these second linkages vital status and date of death or immigration were recorded for each individual. Fifty-nine persons could not be identified and were excluded.

Follow-up for cancer morbidity

Cancer cases diagnosed in members of the cohort were identified by record linkage with the Danish Cancer Registry, which since 1943 has recorded all cases of malignancies in the Danish Population (Storm *et al.*, 1990). The registry is considered to be more than 95% complete (Storm, 1984: Østerlind & Jensen, 1985). After record linkage with the Danish Cancer Registry, two cases of data inconsistencies occurred, probably reflecting erroneously recorded PINs. These two subjects were excluded from the study.

After these linkages and exclusions the cohort consisted of 15,214 men and 3,093 women.

Analyses

The period of risk of cancer was defined as being from the date of entering the outpatient clinic to emigration, death, or to 31 December 1987, whichever occurred first. The 15,214 men were observed for 12.9 years on average, and the 3,093 women for 9.4 years on average.

The number of person–years experienced by the cohort was calculated in 5-year intervals of age and calendar time (Coleman *et al.*, 1986). Expected numbers of cancer cases were obtained by multiplying the age-, sex- and calendar period-specific person–years by the corresponding incidence rates of cancer in the Danish population. The relative risk of cancer (RR) was estimated as the ratio of the observed number of cancer cases to the expected number. The RR 95% confidence interval (CI) was calculated assuming a Poisson distribution. When the CI did not include the value 1.0 the RR was considered to be significantly increased or decreased.

Results

The total cancer morbidity of both men and women was significantly increased with 1,441 and 182 observed versus 898.0 and 117.9 expected cases, yielding a relative risk of 1.6 (95% CI 1.5–1.7) for men and 1.5 (95% CI 1.3–1.8) for women (Table I).

The relative risks were increased for cancer of the buccal cavity and pharynx in alcoholic men (RR = 3.6; 95% CI 3.0–4.3) and women (RR = 17.2; 95% CI 10.8–26.0) as a result of the high incidence of cancer of the tongue, the salivary glands, the mouth and the pharynx. By contrast, the incidence of cancer of the lip was significantly lower than expected.

Among the digestive organs, statistically significant increased RRs were observed in men for cancer of the oesophagus and liver; increased but non-significant RRs were also seen in women. The incidence of gastric cancer and pancreatic cancer was slightly elevated and marginally significant. The observed numbers of cases of cancer of the colon and rectum were both very close to the expected.

The incidence of cancer of the respiratory organs was higher than expected (RR = 2.6; 95% CI 2.4–2.9), resulting from increased risks of laryngeal cancer, lung cancer and pleural cancer.

Breast cancer was not significantly increased among the alcoholic women. Further analysis by age revealed non-significantly increased risks in premenopausal and menopausal women (Table II).

The female alcohol abusers showed increased incidence of cervical cancer, but not of other female genital organs (Table I). The male alcoholics developed prostate cancer more often than expected. The RR of kidney cancer was increased with marginal significance. The women developed bladder cancer slightly more often than expected, but no excess was observed in men.

Melanoma of the skin occurred with significantly decreased frequency, while the observed number of non-melanoma skin cancers were close to the expected. Cancers of the endocrine system, predominantly of the suprarenal glands, occurred slightly more often than expected. Furthermore, RRs of the secondary and unspecified cancers were increased. The incidence of cancers of the lymphatic and haematopoietic tissues was not significantly different from expected (Table I).

In absolute terms, the excess cancer prevalence was 543 cases in men and 64 in women. In men, the excess incidence was attributable to increased incidence of lung cancer (51%), laryngeal cancer (9%), oesophageal cancer (8%), pharyngeal cancer (7%), oral cancer (5%) and prostatic cancer (5%). In women, lung cancer also dominated the excess morbidity (33%) followed by cervical cancer (17%), pharyngeal cancer (14%) and breast cancer (14%). Further analyses (Rothman & Boice, 1982) by age and by time since first visit to the clinic showed that the relative risk increased significantly with age for lung cancer in alcoholic women only (1–49 years, RR = 2.4; 50–59 years, RR = 2.9; 60–69 years, RR = 5.6; 70 + years, RR = 5.4; *P* < 0.05). The analyses of cancer morbidity by time from entry showed a trend in relative risk for cancer of the buccal cavity in men (0–4 years, RR = 2.2; 5–9 years, R = 3.7; 10 + years, RR = 4.1; *P* < 0.05). No other trends with age or with time from entry were found.

Discussion

In the present analysis, a large number of associations have been assessed. Table I includes 30 estimated RRs in men and 31 in women. It is to be expected that a number of these associations appear to be statistically significant by chance only. When statistical significance is judged from whether the 95% confidence interval includes the value 1.0 (corresponding to a two-tailed *P*-value of 0.05), around 5% of the 61 associations, i.e. three associations, are expected to appear as statistically significant by chance. Therefore, especially

Table I Observed (O) and expected (E) numbers and relative risk (RR) with 95% confidence interval (CI) of cancer among Copenhagen alcoholics after entering the outpatient clinic. Minor deviations in RR (= O/E) are due to abbreviations of the decimals of E in the table

Site of cancer	Men O	Men E	Men RR	Men (CI)	Women O	Women E	Women RR	Women (CI)	Total RR	Total (CI)
All cancers	1,441	898.0	1.6	(1.5–1.7)**	182	117.9	1.5	(1.3–1.8)**	1.6	(1.5–1.7)**
All sarcomas	10	11.1	0.9	(0.4–1.7)	1	1.5	0.7	(0.0–3.7)	0.9	(0.4–1.6)
Buccal cavity and pharynx										
Lip	3	13.8	0.2	(0.0–0.6)**	0	0.1	0.0	(0.0–27.3)	0.2	(0.0–0.6)**
Tongue	25	2.8	9.1	(5.9–13.4)**	6	0.2	32.9	(12.1–71.8)**	10.5	(7.2–15.0)**
Salivary glands	7	2.4	2.9	(1.2–6.0)**	0	0.2	0.0	(0.0–15.1)	2.6	(1.1–5.4)*
Mouth	33	5.2	6.4	(4.4–8.9)**	7	0.4	19.4	(7.8–40.0)**	7.2	(5.1–9.8)**
Pharynx	44	6.9	6.4	(4.6–8.5)**	9	0.4	25.0	(11.4–47.5)**	7.3	(5.4–9.5)**
Digestive organs										
Oesophagus	57	10.8	5.3	(4.0–6.9)**	2	0.4	4.9	(0.6–17.7)	5.3	(4.0–6.8)**
Stomach	60	47.0	1.3	(1.0–1.6)*	4	2.2	1.8	(0.5–4.6)	1.3	(1.0–1.7)*
Colon	61	57.3	1.1	(0.8–1.4)	4	7.0	0.6	(0.2–1.5)	1.0	(0.8–1.3)
Rectum	50	50.1	1.0	(0.7–1.3)	2	3.6	0.6	(0.1–2.0)	1.0	(0.7–1.3)
Liver	38	9.3	4.1	(2.9–5.6)**	1	0.6	1.6	(0.0–8.9)	3.9	(2.8–5.4)**
Gall bladder	7	6.0	1.2	(0.5–2.3)	3	1.0	3.0	(0.6–8.7)	1.4	(0.7–2.6)
Pancreas	39	28.6	1.4	(1.0–1.9)*	2	2.2	0.9	(0.1–3.3)	1.3	(1.0–1.8)*
Respiratory system										
Larynx	65	17.6	3.7	(2.8–4.7)**	1	0.5	2.2	(0.6–12.2)	3.7	(2.8–4.6)**
Lung	456	180.8	2.5	(2.3–2.7)**	29	7.7	3.7	(2.5–5.4)**	2.6	(2.3–2.8)**
Pleura	11	4.0	2.8	(1.4–5.0)**	1	0.2	6.5	(0.2–36.4)	2.9	(1.5–5.1)**
Breast	3	1.5	2.0	(0.4–6.0)	41	32.0	1.3	(0.9–1.7)	1.3	(1.0–1.8)*
Specific female organs										
Cervix uteri					22	11.1	2.0	(1.2–3.0)**		
Corpus uteri					3	6.8	0.4	(0.1–1.3)		
Ovary					6	7.1	0.9	(0.3–1.8)		
Specific male organs										
Prostate	91	63.2	1.4	(1.2–1.8)**						
Testis	15	19.7	0.8	(0.4–1.3)						
Urinary system										
Kidney	42	30.7	1.4	(1.0–1.9)*	4	2.3	1.7	(0.5–4.4)	1.4	(1.0–1.9)*
Bladder	76	71.6	1.1	(0.8–1.3)	6	2.2	2.7	(1.0–5.9)*	1.1	(0.9–1.4)
Skin										
Melanoma	10	19.3	0.5	(0.2–1.0)*	1	4.2	0.2	(0.0–1.3)	0.5	(0.2–0.8)*
Non-melanoma skin cancer	97	109.3	0.9	(0.7–1.1)	15	10.9	1.4	(0.8–2.3)	0.9	(0.8–1.1)
Brain and nervous system	21	29.0	0.7	(0.4–1.1)	1	3.6	0.3	(0.0–1.5)	0.7	(0.4–1.0)
Endocrine organs	4	1.5	2.7	(0.7–6.9)	1	0.2	6.5	(0.2–36.0)	3.1	(1.0–7.2)*
Secondary and unspecific cancer	41	19.3	2.1	(1.5–2.9)**	4	2.1	1.9	(0.5–4.9)	2.1	(1.5–2.8)**
Haematopoietic and lymphatic system										
Non-Hodgkin's disease	22	19.1	1.2	(0.7–1.7)	1	1.8	0.6	(0.0–3.1)	1.1	(0.7–1.7)
Multiple myelomatosis	10	9.5	1.1	(0.5–1.9)	0	0.7	0.0	(0.0–5.0)	1.0	(0.5–1.8)
Leukaemia	17	24.1	0.7	(0.4–1.1)	1	1.8	0.6	(0.0–3.1)	0.7	(0.4–1.1)
Other cancers	26				4					

*P ≤ 0.05, **P ≤ 0.01.

Table II Observed (O) and expected (E) numbers of cases and relative risk (RR) with 95% confidence interval (CI) of female breast cancer by age at diagnosis

	O	E	RR (CI)
Age at diagnosis			
1–44 years	12	8.2	1.5 (0.8–2.6)
45–54 years	17	12.1	1.4 (0.8–2.3)
55 + years	12	11.8	1.0 (0.5–1.8)
Total	41	32.0	1.3 (0.9–1.7)

associations that are only marginally significant, or which have a wide confidence interval or are based on only a few observed cases, should be interpreted with caution.

The present study corroborates the associations between alcohol consumption and cancer risk of the upper digestive tract, the liver and the respiratory organs previously found in cohort studies (Sundby, 1967; Hakulinen *et al.*, 1974; Nicholls *et al.*, 1974; Monson & Lyon, 1975; Dean *et al.*, 1979; Hirayama, 1979; Jensen, 1979; Robinette *et al.*, 1979;

Klatsky *et al.*, 1981; Schmidt & Popham, 1981; Gordon & Kannel, 1984; Pollack *et al.*, 1984; Kono *et al.*, 1986; Carstensen *et al.*, 1990). However, the relationship between alcoholism and cancers of the following sites in in disagreement with the literature.

Salivary glands and the lip

In contrast to previous investigations, the present study showed increased morbidity due to cancer of the salivary glands in men: two developed cancer of the parotic gland, one cancer of the submandibular glands and four developed unspecified cancers of the salivary glands. This may reflect a direct action of the alcoholic beverage on the mucosa/glands. The decreased morbidity of lip cancer is probably because the cohort members were less likely to work outdoors and to be exposed to ultraviolet light than the Danish population as a whole. The lack of previous similar findings may be because of the smaller numbers of subjects studied. Also, the kind of alcohol ingested, together with other factors such as smoking, may be of relevance.

Colon and rectum

The relative risk of cancer of the colon or rectum was not increased. This is in line with the findings of several earlier investigations (Sundby, 1967; Hakulinen et al., 1974; Nicholls et al., 1974; Monson & Lyon, 1975; Graham et al., 1978; Hirayama, 1979; Jensen, 1979, 1980; Robinette et al., 1979; Klatsky et al., 1981, 1988; Schmidt & Popham, 1981; Manousos et al., 1983; Kono et al., 1986; Potter & McMichael, 1986; Tuyns, 1988). Our study thus does not support the alleged association between alcoholic beverages (Wynder & Shigematsu, 1967; Pickle et al., 1984; Hirayama, 1989; Carstensen et al., 1990; Freudenheim et al., 1990; Longnecker, 1990) including beer (Wynder & Shigematsu, 1967; Miller et al., 1983; Pollack et al., 1984; Kabat et al., 1986; Kune et al., 1987; Carstensen et al., 1990; Freudenheim et al., 1990) and the development of rectal cancer in particular. Owing to the size of the present study the relative risk estimate of 1.0 is quite precise, and it is unlikely that these heavy alcoholics have a more than 30% increased risk. Furthermore, a meta-analysis of 27 studies revealed no conclusive relationship (Longnecker et al., 1990). The conflicting results may, in part, be explained by the differences in drinking habits of the study groups, and thus variations in displacement of cancer inhibitors from the diet by alcohol (Stemmermann et al., 1990).

Pancreas

Our results suggested a marginally increased risk of pancreatic cancer. The association between pancreas cancer and smoking may be regarded as causal (IARC, 1986; Hiatt et al., 1988), and smoking may be the confounder responsible for the increased risks found in our study and some other studies (Durbec et al., 1983; Heuch et al., 1983; Raymond et al., 1987; Cuzick & Babiker, 1989; Carstensen et al., 1990).

Pleura

Cancer of the pleura developed more often in the alcoholic men than expected (RR = 2.8; 95% CI 1.4–5.0). All but one of the 12 cases were histologically verified mesotheliomas. Associations between alcohol intake and mesothelioma have not been previously described.

Breast

Female breast cancer was slightly and non-significantly increased in our study, owing to an increased risk among the premenopausal (9–44 years) and menopausal (45–54 years) women. In the last decade three cohort studies (Hiatt & Bawol, 1984; Schatzkin et al., 1987; Willet et al., 1987) and several case–control studies have shown a similar tendency for an increased risk of breast cancer in women with even a very light alcohol intake, i.e. a drink or so daily, compared with abstainers (Lê et al., 1984; Talamini et al., 1984; La Vecchia et al., 1985; Harvey et al., 1987; O'Connell et al., 1987; Rohan & McMichael, 1988). This association has not been consistent (Byers & Funch, 1982; Begg et al., 1983; Paganini-Hill & Ross, 1983; Webster et al., 1983; Meara et al., 1989; Rosenberg et al., 1990). However, meta-analysis of 16 studies revealed a significant trend in breast cancer risk with increase in light alcohol intake (Longnecker et al., 1988).

Some of the case–control studies adjusted for several confounding factors such as social status, reproduction, obesity, family history, tobacco and dietary parameters. The presumably lower socioeconomic status among the alcoholic women of the present cohort may cause some negative confounding (Talamini et al., 1984; O'Connell et al., 1987). Our results suggest that the association must be more complex than a direct effect of alcohol alone.

Female genital organs

We found an increased risk of cervical cancer morbidity. In previous cohort studies of alcoholics the numbers of women included were too small to draw any conclusions about a relationship between alcoholism and cervical cancer mortality. A case–control study from Lesotho, South Africa, found increased risk associated with alcohol use after adjustment for tobacco (Martin & Hill, 1984). This may indicate the effect of confounding factors such as sexual practices or social (Brinton et al., 1987) and nutritional factors (La Vecchia et al., 1984; Harris et al., 1986; Brock et al., 1988).

Male genital organs

Cancer of the prostatic gland was increased among the male alcoholics. This association has not been described previously. The lack of consistence with results of previous cohort studies of cancer incidence may be due to a higher alcohol intake (Hakulinen et al., 1974; Jensen, 1979; Carstensen et al., 1990) in the present study, and to the low mortality of prostate cancer. The aetiology of prostatic cancer is uncertain. Several factors have been suggested, such as fat intake (Graham et al., 1983; Ross et al., 1987; Kolonel et al., 1988; Mettlin et al., 1989), increased body mass index (Talamini et al., 1986) and overweight (Snowdon et al., 1984). None of these studies have reported information about alcohol consumption. Two studies of prostatic cancer have dealt with alcohol intake. One Japanese follow-up study found no association between mortality and alcohol intake (Hirayama, 1979). The other study was not designed to draw conclusions about alcohol, because half of the control group consisted of persons with alcohol-related cancers (Newell et al., 1989).

Urinary tract

The incidence of bladder cancer in women was higher than expected. The explanatory factor is probably smoking, since several case–control studies have found an increased risk of bladder cancer in alcohol drinkers that is reduced after adjustment for smoking (Morgan & Jain, 1974; Mommsen et al., 1982; Thomas et al., 1983). Surprisingly, the risk was not increased in men, although the increased RR of lung cancer suggests that smoking is more frequent than in the reference population.

The incidence of kidney cancer was slightly increased. Previous studies have not found this association (Hirayama, 1979; Jensen, 1979; Robinette et al., 1979); this finding also demands further investigation of possible confounding factors.

Skin

We found a significantly decreased incidence of melanomas of the skin. Skin melanoma is causally related to intermittent sun exposure of untanned skin, and it is likely that the lower RR is explained by lower exposure compared with the reference population. Like previous studies of melanoma in Denmark (Jensen, 1979; Østerlind, 1990) the present investigation provides no support for the hypothesis of an association between alcohol intake and melanoma mediated through an influence on the melanocyte-stimulating hormone (Williams, 1976).

Endocrine system

Cancer of the endocrine system occurred more frequently than expected in the cohort. All the cases, except one thymoma, were histologically verified suprarenal cancers. No cases of thyroid cancer were found, although an association with alcohol consumption has been suggested (Williams, 1976). We would expect to observe an increased risk of thyroid cancer because of the large numbers of subjects studied, and must doubt the existence of an association.

Conclusion

The present study of alcoholics corroborates the associations between alcoholism and cancer of the upper digestive tract and the liver.

The study also suggests that there may be an association between alcoholism and prostatic cancer, but no association was found for colorectal cancer. Female breast cancer was only slightly increased in this first study of a sizeable number of alcoholic women.

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