serious health consequences. Nearly 50% of Indian adults have different types of chronic energy deficiency, and have a BMI <18.5 kg/m². A similar study done in Lucknow, Uttar Pradesh has shown that there was a positive association between pack-years, BMI and socioeconomic class. In a study it was reported that there is a positive association between tobacco smoking and pulmonary (bacillary) TB. This association also shows a strong dose–response relationship. Since the magnitude of tobacco use and lower BMI is higher in India, clustering of these two effects in India is inevitable. This leads to a higher risk of deaths due to TB. The prevalence of tobacco use is also increasing. So, strategies for control of TB should be synergized with tobacco control efforts and should focus on the nutritional status of the patients to have a positive impact on reducing mortality due to TB.

REFERENCES


Heavy consumption of alcohol: A risk factor for cancer deaths?


SUMMARY

According to the International Agency for Research on Cancer, alcohol is a group 1 carcinogen, i.e. there is sufficient evidence of carcinogenicity in humans. However, results obtained from various epidemiological studies are inconsistent and demonstrate male–female differences. The exact dose–response relationship had not yet been reported by meta-analysis at the time of this study. Hence, this meta-analysis was done to elucidate the association of alcohol drinking with all cancer mortality, and the corresponding dose–response relationship.

A PubMed search was done to identify eligible studies published in English up to April 2012. Case–control, case–cohort and cohort studies which focused on the association of drinking alcohol with all cancer mortality, and which presented the odds ratio, risk ratio or hazard ratio estimates with the corresponding 95% confidence intervals (CI), were included. Other studies which provided sufficient data to calculate non-occasional drinking as the reference category, were also included. If multiple papers were published from the same population, the most informative one (often the most recent) was included. Studies reporting the estimates of only a specific kind of alcoholic beverage were excluded.

Finally, 18 eligible papers were included in the meta-analysis, 17 with an association for ≥3 categories of alcohol, and one with an association of drinking versus non-drinking. All of these were cohort studies. The duration of follow-up ranged from 4.6 to 19 years across studies. The number at risk ranged from 1620 to 490 000 persons in four studies, and 107 385 to 82 716 472 person-years in 14 studies. Two investigators independently extracted data with concealment of journals, authors, supporting funds and organizations. Two reviewers independently did quality assessment of the selected studies, using a set of questions modified from previous studies. On a scale of 0 to 10, the quality scores ranged from 3.5 to 8.5, with a median of 6.5 for methodological assessment. A total of 48 178 deaths from all cancers were observed among all these cohort studies.

Alcohol consumption reported across studies in various units were converted to grams of alcohol, and alcohol drinkers were grouped into three, viz. light, moderate and heavy drinkers defined as an ethanol intake of ≤12.5 g/day (<1 drink/day), 12.6–49.9 g/day (2–3 drinks/day) and ≥50 g/day (≥4 drinks/day), respectively. To evaluate heterogeneity, Cochrane Q test and I² statistics were calculated. Random effects model was used when a notable heterogeneity (p of Q test ≤0.1 and/or I² index ≥50%) was present. Subgroup analysis and cumulative meta-analysis were done. Publication bias was assessed by Egger linear regression and Begg rank correlation. Begg funnel plot was also drawn. Flexible restricted cubic splines method was used in the dose–response analysis.

As compared with non-/occasional drinkers, the pooled relative risks (RRs) were 1.05 (95% CI 1.00–1.10; p for heterogeneity=0.008) for any, 0.91 (95% CI 0.89–0.94; p for heterogeneity=0.449) for light, 1.02 (95% CI 0.99–1.06; p for heterogeneity=0.105) for moderate, and 1.31 (95% CI 1.23–1.39; p for heterogeneity=0.442).
for heavy drinkers. The dose–response relationship approximated a J-shaped curve for men and women together and for men alone. The study concluded that consumption of \( \leq 12.5 \) g/day of alcohol is protective and \( \geq 50 \) g/day is a risk factor for all cancer mortality.

**COMMENT**

This meta-analysis found that light alcohol drinking was protective and heavy drinking increased chances of all cancer deaths. Similar results have been reported elsewhere.\(^3\) This article also establishes a dose–response relationship between alcohol consumption and all cancer mortality. The authors did a literature search only in PubMed. However, details of the search strategy such as keywords used, limits activated were not reported, which precludes its repeatability; the dates of coverage and date last searched should have been indicated. Although cross-referencing was done, there was no mention of search for unpublished studies and those not in PubMed. In case of multiple studies from the same population, the most informative (often the most recent) was selected. This could have resulted in selection bias. The meta-analysis included 18 prospective studies and 48 178 deaths due to cancer. Slightly more than half the deaths were from the USA. There was no significant publication bias as evidenced by Begg test, Egger test and Begg funnel plots. The assessment of exposure, i.e. alcohol consumption was self-reported in most studies, which could have been a source of information bias. Also, no details about biases in an individual study are mentioned. Despite these limitations, the study does throw light on the dose–response relationship of alcohol and cancer mortality.

India is one of the largest producers of alcohol in the world. In the South Asian region, it contributes to 65% of production and nearly 7% of imports.\(^4\) However, alcohol consumption is quite low. According to the National Family Health Survey 2005–06, just under one-third of men and 2% of women drink alcohol.\(^4\) The total (recorded and unrecorded) adult per capita consumption in 2005 among adults over 15 years of age in litres of pure alcohol was estimated to be 2.59. The total per capita consumption among adult drinkers was 22.3 L, while that for men and women drinkers was 23.9 L and 10.4 L, respectively.\(^5\)

A study done in Bengaluru among 28 507 individuals revealed that 13% of them were alcohol users; 23.7% of men and 1.5% of women. Among them nearly three-fourths (72.1%) of users had been consuming alcohol for more than 5 years.\(^6\)

According to a study done in Mumbai, among 50 220 men aged \( \geq 45 \) years from the lower and lower-middle section of the general population, 18.8% of men were consuming alcohol at the time of the study; and the most popular product was country liquor. More than one-third of consumers of country liquor would consume over 53 g of ethanol on a day when they drank.\(^7\)

Another study done in rural Haryana among 1359 men and 1469 women 15–64 years of age, using the WHO STEPS tool revealed that current alcohol consumption was 24.6% among men and nil among women.\(^8\) The alcohol consumption according to a study done among 228 men aged >15 years in an urban area in Kolkata was 65.8%. Among them 14% were alcohol-dependent and 8% were hazardous or harmful consumers. However, only 16% of the consumers expressed concern over their drinking pattern. The mean age of initiation of the habit was 20 years, though the legal age for consuming alcohol in West Bengal is 21 years.\(^9\) It is indeed worrisome that alcohol use is often commenced before the legal age of drinking.\(^10\) The legal age of drinking in India varies from 18 to 25 years, across states.

The estimated cancer deaths in 2010 was 556 400 and 71% of deaths occurred in the 30–69 age group. The three major cancers causing mortality among men were those of the digestive and respiratory tract with age-standardized mortality rates (per 100 000) of 22.1, 12.5 and 11.6 for cancers of the lip, oral cavity and pharynx, stomach and respiratory tract (larynx, trachea and lungs), respectively. Among women, the major cancers causing mortality were those of the cervix, stomach, breast and upper digestive tract with age-standardized mortality rates of 16, 13.5 and 9.4, respectively.\(^11\)

Alcohol consumption has been identified as a carcinogenic for the following cancers: colon and rectum, female breast, larynx, liver, oesophagus, oral cavity and pharynx.\(^12\) The association between alcohol and cancers has been studied in India. A study by Ganesh et al. in Mumbai showed that drinking alcohol is associated with lung cancer with an odds ratio of 1.8 (95% CI 1.1–3.1).\(^13\) A similar effect has also been shown in southern India.\(^14\) The odds ratio for alcohol intake and oral, laryngeal and oesophageal cancers obtained in a case–control study in Chandigarh was 7.8 (95% CI 4.9–11.4).\(^15\) Other studies have also shown an association between alcohol consumption and cancer of the buccal and labial mucosa\(^16\) and prostate.\(^17\) According to a prospective community-based cohort study done in Thiruvananthapuram, the adjusted mortality risk associated with drinking alcohol was 1.13 (1.06–1.20) for all-cause and 1.32 (1.11–1.57) for cancer.\(^18\)

Thus, though there is information from India on alcohol consumption and cancer mortality, there is no information on the fraction of cancer deaths attributable to drinking alcohol. Also, there are insufficient data to establish a dose–response relationship. Studies similar to the current one need to be conducted in India, to further strengthen the evidence base for implementing measures to control alcohol consumption.

**REFERENCES**

Glutamine in critically ill patients

Heyland D, Muscedere J, Wischmeyer PE, Cook D, Jones G, Albert M, Elke G, Berger MM, Day AG for the Canadian Critical Care Trials Group. (Kingston General Hospital, Kingston, Ontario; St Joseph’s Healthcare, Hamilton, Ontario; Ottawa Hospital, General Campus, Ottawa and Hôpital du Sacré-Coeur de Montréal, Montreal, Canada; University of Colorado School of Medicine, Aurora; University Medical Center Schleswig-Holstein, Campus Kiel, Kiel, Germany; Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland.) A randomized trial of glutamine and antioxidants in critically ill patients. N Engl J Med 2013;368:1489–97.

SUMMARY
This multinational, blinded, randomized, controlled trial aimed to prove that glutamine supplementation would reduce mortality in critically ill patients. In a 2-by-2 factorial design, 1223 mechanically ventilated patients with multiorgan failure in 40 intensive care units (ICUs) were enrolled and randomized to receive either intravenous glutamine (0.35 g/kg of ideal body weight) and enteral glutamine (30 g) supplementation, a supplement of anti-oxidants, both or placebo within the first 24 hours of admission to the ICU. The primary outcome was 28-day mortality. Secondary outcomes included in-hospital and 6-month mortality, time to discharge alive from the ICU and hospital. Glutamine supplementation had no significant effect on the outcomes of organ failure or infections. Plasma glutamine levels were normal at baseline among the groups but were significantly higher among patients who received glutamine, as was also the median time to discharge alive from the ICU and hospital. Glutamine supplementation had no significant effect on the outcomes of organ failure or infections. Plasma glutamine levels were normal at baseline among the groups but were significantly higher in the supplemented group on days 4 and 7 (p<0.01). The number of serious adverse events was not different among the groups, and the results were not different in several pre-specified subgroups.

COMMENT
Glutamine, an amino acid synthesized in large amounts by the human body, is capable of generating both glucose and glycogen and is the non-toxic transport form of nitrogen and ammonia. It is considered to be ‘conditionally essential’ in serious catabolic states. Release of glutamine in large amounts from muscles during serious illness is hypothesized to serve as a ‘stress signal’ leading to gene activation to promote cellular protection and immune regulation. In animal experiments, Wischmeyer et al. showed that parenteral glutamine is protective against pro-inflammatory induced injury via induction of heat shock proteins (HSP). Proliferating lymphocytes, monocytes and macrophages need glutamine for synthesis of nucleotides and expression of cell surface activation markers (CD25, CD45RO). Glutamine is preferred over glucose as a source of fuel for enterocytes, in settings of gut ischaemia. Human studies show that glutamine supplementation improves insulin sensitivity, leads to preservation of skeletal muscle, improves nitrogen balance, enhances immune cell function and is not pro-inflammatory. Further, it has antioxidant properties via metabolism to glutathione.

Glutamine deficiency, defined as low plasma concentration (<420 mmol/L), at ICU admission was found to be an independent predictor of mortality. Parenteral glutamine supplementation results in uniform uptake of glutamine across splanchnic areas whereas enteral glutamine absorption occurs principally through the proximal jejunum; the rest of the gut is unsupported by enteral glutamine. After uptake by enterocytes and immune cells only a fraction of enteral glutamine is detected in the portal blood. A further first pass elimination of 40%–90% of enteral glutamine occurs in the liver, resulting in low plasma concentration after enteral supplementation. Intravenous glutamine supplementation of 0.3–0.5 g/kg/day normalizes the plasma concentration in most critically ill patients.

Several studies on glutamine supplementation were available at the beginning of this century and Novak et al. did a systematic review of 14 randomized trials (including 751 patients) from 1993 to 2001. Overall, this review supported the view that glutamine supplementation was associated with a strong trend towards a reduction in mortality (RR 0.78, 95% CI 0.58–1.04), lower rates of infectious complications (RR 0.8, 95% CI 0.64–1.00, p=0.003) and shorter hospital stay (~2.6 days; 95% CI −4.5 to 0.7). As there was statistical heterogeneity in the studies, and to better understand the findings, the authors further looked at outcomes in pre-