CC/2014/20

COMMITTEE ON THE CARCINOGENICITY OF CHEMICALS IN FOOD, CONSUMER PRODUCTS AND THE ENVIRONMENT

CONSUMPTION OF ALCOHOL AND RISK OF COLORECTAL CANCER

Background

1. As part of the strategy proposed to consider the role of alcohol consumption and cancer risk, it was suggested that the COC review the epidemiological data on alcohol consumption and cancer. In 2007 (IARC, 2010; http://monographs.iarc.fr/ENG/Monographs/vol96/mono96.pdf, page 542ff), IARC reviewed the epidemiological evidence on the possible association between alcoholic beverage consumption and cancer at 27 anatomical sites (cancers of the oral cavity and the pharynx, larynx, oesophagus, liver, breast stomach, colon and/or rectum, pancreas, lung, urinary bladder, endometrium, ovary, uterine cervix, prostate, kidney, lymphatic and haematopoietic system, testis, brain, thyroid, melanoma and other female cancers (vulva and vagina)). They re-affirmed their previous conclusion (IARC, 1988) that cancers of the upper digestive tract (oral cavity, pharynx, larynx, oesophagus) and the liver are causally related to the consumption of alcoholic beverages. In addition, IARC considered that there is sufficient evidence to conclude that cancer of the colorectum and female breast are causally related to the consumption of alcoholic beverages (IARC, 2007). Following another IARC review in 2009 (IARC 2012; http://monographs.iarc.fr/ENG/Monographs/vol100E/mono100E-11.pdf, pp 383-386), IARC reaffirmed their position on the aforementioned associations. It also confirmed that acetaldehyde associated with the consumption of alcoholic beverages is carcinogenic in humans (Group 1).

2. In view of the recent IARC evaluation, Members agreed that an update review of the epidemiological literature on alcohol consumption and all the cancer sites was not necessary at this time. However, Members agreed that a review of the epidemiological literature published since the IARC review in 2009 should be undertaken for those cancer sites where alcohol consumption was causally associated. This review considers epidemiological studies (pooled/meta-analysis, cohort and case-control studies) published since the last IARC review on alcohol consumption and risk of colorectal cancer.

Colorectal cancer statistics for the UK

3. Colorectal cancer (CRC) was the 4th most common cancer in males and females combined in the UK in 2011. In 2011, there were 41,600 new cases of CRC in the UK: 23,200 (56%) in males and 18,400 (44%) in females. The crude incidence rate shows that there are 58 new CRC cases for every 100,000 males in the UK, and 37.6 for every 100,000 females. CRC rates have increased by 6% over the last decade. Incidence is strongly related to age, 95% of cases occur in people aged 50 or over. CRC is the 2nd most common cause of cancer death in the UK (2011).

There were 15,659 deaths from CRC in the UK in 2011: 8,520 (54%) in men and 7,139 (46%) in women, giving a male:female ratio of around 1:0.8. Bowel cancer death rates have been falling since the 1970s. Over the last decade, deaths have dropped by around 14% (Cancer Research UK, 2014).

Colorectal cancer risk factors

4. Parkin et al (2011) estimated that, in the UK in 2010, 56.5% of CRCs in men and 51.9% in women were attributable to lifestyle factors. Meat consumption is a major risk factor, with Parkin *et al* (2011) estimating that 21.1% of CR cancer cases were caused by this. Other major risk factors were reported to be fibre consumption (12.2% of cases), being overweight or obese (13.0%), and alcohol (11.6% of cases). Haggar et al (2009) also attribute 12% of CRC deaths to smoking. Other non-lifestyle risk factors are age, a personal history of adenomatous polyps, personal history of inflammatory bowel disease, a family history of CRC or adenomatous polyps, and certain recognised hereditary conditions (Haggar et al, 2009).

Alcohol consumption

5. From the studies considered in its Monograph 96 (2010), IARC concluded that there was little evidence of a higher than expected risk for colon or rectal cancer in heavy alcoholic beverage drinkers, alcoholics or brewery workers but that a large body of evidence from prospective cohort studies reported a statistically significant positive association between alcoholic beverage intake and the risk of colon, rectal or colorectal cancer, and no study reported an inverse association. These findings were supported by other studies. The strength of association appeared to be modest with a relative risk of 1.4 for an intake of $\geq$ 45g alcohol per day compared with 0g per day. However, there was uncertainty about the dose relationship. In Monograph 100E (IARC 2012), IARC concluded that the more recent data reviewed supported the conclusion that consumption of alcoholic beverages is causally related to cancer of the colorectum. Most of the evidence suggested that it was positively associated with both cancer of the colon and of the rectum and was similar in men and women, although the data were not entirely consistent. There was some evidence that risk may only be increased at relatively high levels of intake (i.e. >30g/day). There was consistent evidence that risk does not differ by beverage type; whether the risk associated with consumption of alcohol differs by smoking status or intake of dietary folate was considered inconsistent.

Meta- and Pooled Analysis (Table 1)

6. 3 meta-analyses and 5 pooled analyses have been performed since the last IARC review.

7. Fedirko et al (2011) carried out a meta-analysis of studies presenting results for at least three categories of alcohol intake, identified from a PubMed search of articles published before May 2010. The summary relative risks were estimated by the random effects model. Second-order fractional polynomials and random effects meta-regression models were used for modelling the dose-risk relationship.

8. Of the original studies located in the search, 22 reported fully adjusted risk estimates and 36 reported risk estimates adjusted for tobacco smoking. These

comprised 35 case-control studies and 23 cohort studies. From these, the pooled random effects RRs and 95% CIs for comparison with non-drinkers were as follows: any drinkers 1.12 (1.06-1.19), light drinkers 1.00 (0.95-1.05), moderate drinkers 1.21 (1.13-1.28), and heavy drinkers 1.52 (1.27-1.81). The relative risks were higher for rectal than for colon cancer among any drinkers (p = 0.03) and light drinkers (p = 0.05), but about the same among moderate and heavy drinkers. Geographical region, type of study, study quality, adjustment for main confounders (age, sex, smoking, Body Mass Index (BMI), and physical activity), and year of publication were not significant sources of heterogeneity. For CRC, a potential heterogeneity by geographical location was observed only among heavy drinkers (p = 0.04), with the highest risk summary estimate of 1.81 (1.33-2.46) for studies conducted in Asia and the lowest risk summary of 1.16 (0.95-1.43) for studies conducted in Europe. RRs were systematically higher in hospital-based case-control studies than in population-based case-controls; however, the difference was not statistically significant. The authors concluded that the meta-analysis provides strong evidence for an association between alcohol drinking of >1 drink/day and CRC risk. This paper is attached at Annex 1.

9. Bagnardi et al (2013) carried out a meta-analysis of light alcohol drinking and cancer, including CRC. They included 222 unique papers published before December 2010, 54 of which reported estimates for CRC. Twenty-six studies where cohort studies and 28 were case-control. Since the included studies usually reported alcohol exposure in intervals, the authors considered as light every interval whose midpoint was $\leq$12.5 g/day (1 drink/d) of alcohol. Where studies reported two or more adjusted risk estimates for light drinking, they combined them into a single estimate.

10. The site-specific pooled estimates for light drinkers vs. non-drinkers indicated that alcohol significantly increased the risk of oesophageal cancer, oral cavity and pharynx cancer, and female breast cancer. No significant association was found for CRC (RR = 0.99, 95% CI 0.95-1.04), liver or larynx. No significant effect was found for CRC if calculated by geographical area (Europe, N America or Asia) or by sex.

11. According to Li et al (2011), consumption of alcohol has increased markedly in China in recent years; the overall heavy drinking rate of adults in China has also increased rapidly, from 4.7% in 2002 to 37.04% in 2007, and 65.39% of drinkers have poor health. The authors carried out a systematic review of the role of alcohol in the incidence of cancer, including CRC, in the Chinese population. The types of alcohol consumed included beer, yellow rice wine, red wine and spirits. Neither pooled results from cohort studies nor a meta-analysis of case-control studies showed any association between alcohol consumption and CRC. Combined results of case-control and cohort studies showed no association either, although they were positive associations with oesophageal and gastric cancers.

12. A pooled analysis by Nan *et al* (2013) investigated the risk of CR cancer before and after mandatory folic acid fortification of enriched grain-based foods in the US which began in 1998. They reported that, as a folate antagonist, alcohol inhibits folate-mediated methionine synthesis, causing abnormal neoplasia. High folate intake mitigates the adverse influence of high alcohol consumption on CR cancer. They examined whether folic acid fortification attenuates the influence of alcohol consumption on colorectal cancer in 2 prospective cohort studies, the Nurses' Health Study (NHS) and the Health Professionals Follow-up Study (HPFS).

13. The NHS enrolled 121,700 female registered nurses aged 30-55 years in 1976 and the HPFS included 51,529 male health professionals aged 40-75 years in 1986. Data has been updated biennially with >90% follow-up. In this study, only participants with alcohol intake level at baseline of 1980 in the NHS and 1986 in the HPFS, with plausible energy intakes and no diagnosis of cancer or ulcerative colitis, were included. Dietary information was obtained by means of food frequency questionnaires (FFQ). Information on the use of multivitamins and folic acid supplements was elicited from 1980 (NHS) and from 1986 (HPFS), and onwards every 2 years. Drinking pattern was assessed in 1988 in both cohorts.

14. Previous studies have found a significantly lower risk of CRC among participants with relatively high folate intake compared with those with low folate intake (Kim et al, 2010; Sanjoaquin MS et al, 2005). Nan *et al* (2013) conducted cohort-specific analyses for the association between alcohol intake and colorectal cancer risk among the whole population as well as individuals confined to the prefolic acid fortification period and post-fortification period. During the follow-up of 26 years among 87,856 women and 22 years among 46,874 men, they documented 2793 cases of invasive CR cancer (1628 women and 1165 men).

15. In the whole population, they found that alcohol consumption was associated with an increased risk of CRC. Compared with nondrinkers, the pooled multivariate RR for drinkers of >30g alcohol/d versus nondrinkers was 1.35 (95% CI, 1.14-1.59; p for trend, 0.0004). The association did not materially change when the analysis was confined to the prefolic acid fortification period. In contrast, alcohol consumption was not significantly associated with an increased risk of CRC in the postfortification period, although the test for heterogeneity by period was not statistically significant (p value = 0.45). An examination of drinking patterns in relation to CRC risk showed that neither frequency of drinking nor quantity of drinking was associated with the risk of CRC. A secondary analysis, which excluded users of multivitamins and/or folic acid supplements found that the effect of folic acid fortification on high alcohol intake and CRC was similar in the supplement non-user group to that in the whole population. The pooled multivariate RRs for greater than 30g alcohol/d drinkers versus nondrinkers were:

Whole period*:* 1.36 (95% CI 1.09-1.70; p for trend, 0.02)

Prefortification period: 1.31 (95% CI 1.00-1.71; p for trend, 0.10)

Fortification period: 1.07 (95% CI 0.69-1.65; p for trend, 0.67)

Nan *et al* also examined the association between intake and colorectal cancer among those taking multivitamins or folic acid supplement. Along with their main findings, they found more pronounced increase in CRC for $\geq$ 30g alcohol/d versus nondrinkers in the prefortification era [RR=1.4 (95% CI 1.03-1.91)] than postfortification era [RR=1.15; 95% CI 0.08-1.65)].

16. Cho et al (2012) used the same cohorts to investigate whether the association between alcohol consumption and colon cancer risk differed by family history of CRC. During the follow-up of 26 years among 87,856 women and 20 years among 47,290 men, 1801 cases of colon cancer were identified. Higher alcohol consumption was associated with an elevated risk of colon cancer, although the

association was only significant at the highest intake category of ≥ 30g/day, with no significant linear trend. The association between alcohol consumption and colon cancer risk differed by family history of CRC; in comparison with nondrinkers, the pooled multivariate RRs for alcohol consumption of ≥ 30g/day were 1.23 (95% CI 0.96 – 1.57) for those with no family history and 2.02 (1.30 – 3.13) for those with a family history of CRC (P value for difference = 0.05). In comparison with nondrinkers with no family history, the RR for colon cancer was 2.80 (2.00 – 3.91) for individuals who consumed ≥ 30g/day and who had a family history of CRC. It should be noted that the effect of family history was more marked in the HPFS than in the NHS.

17. Rosato et al (2013) investigated risk factors for colorectal cancer in early-onset cancers, by analysing data from 3 Italian and Swiss case-control studies conducted between 1985 and 2009. These included 329 CRC cases and 1,361 controls aged ≤ 45 years. Odds ratios were computed from unconditional logistic regression models, including terms for age, sex, centre, study, year of interview, education, family history, alcohol consumption and energy intake. The OR of young-onset CRC was 1.56 for ≥ 14 drinks/week of alcohol. No significant associations emerged for physical activity, being overweight, or diabetes.

18. Magalhâes et al (2012) conducted a systematic review and meta-analysis of studies addressing the association between dietary patterns and CRC. Studies quantifying the association between dietary patterns (defined *a posteriori*) and CRC were identified in PubMed and through backward and forward citation tracking. Summary relative risk estimates and 95% CIs were computed for highest versus lowest levels of exposure, for colon cancer and rectal cancer and for proximal and distal colon cancer, by random effects meta-analysis. Eight cohort studies and 8 case-control studies defining patterns through principal components and factor analyses were included in the systematic review. Meta-analyses were conducted for 3 patterns: (1) 'drinker', characterised by high alcohol consumption, (2) 'healthy', characterized by high fruit/vegetables consumption, for which a significantly lower incidence of colon cancer was found; and (3) 'western', characterised by high intake of red and processed meat, for which a significantly higher association of colon cancer was seen. No significant associations were observed for rectal cancer, nor with heavy alcohol consumption [RR = 0.98 (95% CI 0.77-1.26)].

19. Wang et al (2011) conducted a meta-analysis of 6 case-control studies on the association between the acetaldehyde dehydrogenase 2 (ALDH2) genotype and CR neoplasia, using the ALDH2 genotype as a marker of alcohol intake, to avoid distortion by confounding and errors in self-reporting of alcohol intakes. A polymorphism of ALDH2 (ALDH2 Lys/Lys) is mainly found in Asian populations such as the Japanese and Chinese. These individuals have a reduced ability to metabolise alcohol and suffer adverse effects in response to consumption of alcohol. Wang et al hypothesised that individuals homozygous for this variant are likely to avoid alcohol. In the meta-analysis, they used the ALDH2 genotype as an instrument for indexing alcohol intake at a group level, producing groups with relatively heavy drinking (Glu/Glu), moderate drinking (Glu/Lys) and nondrinkers (Lys/Lys). They found that the pooled OR for CRC was 1.31 (95% CI: 1.01-1.70) for the Glu/Glu vs the Lys/Lys genotype. The overall risk for Glu/Lys heterozygotes relative to Lys/Lys homozygotes was 1.13 (0.86-1.48).

20. S Park et al (2014) report that, in 2003-5, the average adult per capita consumption of pure alcohol in Korea was estimated to be 14.8 litres per year, 81% of which was in the form of spirits. They conducted a systematic analysis of attributable causes of cancer in Korea and reported estimates of the cancer burden caused by alcohol consumption. A number of cancer sites for which there is convincing evidence of a positive association with alcohol consumption were studied, including colon and rectum. Sex- and cancer-specific population attributable fractions (PAF) were calculated based on: 1) the prevalence of alcohol drinkers among adults ≥20 years of age in 1989; 2) the average daily alcohol consumption (g/day) among drinkers in 1998; 3) RR estimates for the association between alcohol consumption and site-specific cancer incidence obtained either for a large Korean cohort study or, when more than one Korean study was available for a specific cancer site, meta-analyses were performed and the resulting meta-RRs were used; 4) national cancer incidence and mortality data from 2009. The results showed that, among men, the PAF of CRC incidence for alcohol was 8.6%, with 1281 avoidable incident cancer cases. Among women, the PAF was 4.2%, with 414 avoidable cases. Sensitivity analysis showed that the PAF estimates were more sensitive due to higher uncertainty in RR estimates for CRC than some other cancers.

21. The authors comment that the lower overall PAF for alcohol consumption in Korea, compared to other countries, may be partly due to the fact that a large proportion of the Korean population are slow metabolisers of acetaldehyde and consequently suffer a flushing reaction due to accumulation of acetaldehyde after drinking alcohol. Therefore, a high proportion (about 30%) of East-Asian populations avoid drinking alcohol, or drink less than in other population groups such as Western countries. Alternatively, the lower PAF may be due to the fact that the number of cancers attributable to other factors such as smoking and infection is high.

Cohort studies (Table 2)

22. JY Park et al (2009) examined the effect of modest alcohol consumption of specific types of alcoholic beverages (beer, sherry, wine or spirits) in relation to overall or site-specific CRC risk in a UK-based prospective population study of 24,244 participants. There were 407 incident CRC cases after 11 years of follow-up. Total alcohol consumption was not associated with CRC risk before or after adjustment for age, sex, weight, height and smoking status (Hazard Ratio (HR) = 0.80, 95% CI 0.51-1.26, for alcohol consumption of ≥21 units/week compared with non-drinkers), and further adjustment for education, exercise, family history of CRC and dietary factors did not significantly alter the risk estimates. No significant associations were seen between consumption of beer, sherry or spirits and CRC risk when compared with non-drinkers after adjustment for lifestyle and dietary factors. Daily consumption of ≥ 1 unit of wine appeared inversely related to CRC risk (HR = 0.61, 0.40-0.94). No evidence was found for sex-specific relationships and further exclusion of cases incident within 3 years of baseline did not change the associations observed. The authors note that alcohol has been known to act as a synergistic carcinogen with tobacco smoking. In the study, increasing intake of alcohol within the range of low-to-moderate was associated with non-significant increased CRC risk in current smokers and a borderline significant interaction was observed ($p_{interaction}$ = 0.06).

23. Razzak et al (2011) made use of data from the IOWA Womens' Health Study to investigate CRC risk by molecularly defined subtypes. In brief, in this study, a 16-page questionnaire was mailed out at baseline (January 1986) to 99,826 randomly selected women, ages 55 to 69 years, who resided in Iowa and held a valid driver's licence. A total of 41,836 women (42%) returned the baseline questionnaire and comprised the IWHS cohort. The women were followed up for 22 years. Incident CRC cases were identified through annual linkage with the Iowa Cancer Registry (further details are given in table 2).

24. In the full analytic cohort, no statistically significant association was observed between incident CRC and alcohol intake levels of either 3.4 g/d or less, or more than 3.4 g/d, based on comparisons to alcohol nonconsumers in multivariate adjusted risk models (RR = 1.00; 95% CI 0.86-1.15 and RR = 1.06, 95% CI 0.91-1.24; p for trend = 0.50, respectively). No significant associations were seen, either, based on alcohol intake levels of 30 g/d or less, or more than 30 g/d, nor by quartile distribution. Null associations were also observed between each alcohol intake level and microsatellite instability-, CpG island methylator phenotype-, or BRAF mutation-defined CRC subtypes (p>0.05 for each comparison).

25. Poynter et al (2013) also used the IWHS to evaluate associations between anthropometric, lifestyle (including as alcohol consumption) and reproductive factors and the risk of several cancers, including colon and rectal cancers. Compared to non-drinkers, women who drank and were aged <75 had a Hazard Ratio for colon cancer of 1.04 (95% CI 0.88-1.24) and those aged $\geq$ 75 had a HR of 1.00 (0.85-1.17) for colon cancer. For rectal cancer, women aged <75 had a HR of 1.14 (0.84-1.55) and those aged $\geq$75 had a HR of 0.98 (0.68 – 1.41). Higher BMI and a reported diagnosis of diabetes were associated with reduced risk of colon cancer in both age bands whereas smoking was significantly associated with colon cancer in the younger age band, although the p value for interaction did not reach statistical significance.

26. Bamia et al (2013) investigated the association of adherence to Mediterranean diet with CR cancer risk in the European Prospective Investigation into Cancer (EPIC) and nutrition study. After 5,296,617 person-years of follow-up, 4,355 incident CRC cases were identified. However, the average follow-up was only 11.6 years. An association with ethanol intake was found only among men (HR = 1.20 (1.06-1.35) for the highest tertile compared with referent). No effect was seen in women or men and women combined. Adherence to a Mediterranean diet, measured by two scores, was associated with a borderline statistically significant 3 to 4% reduction in CR cancer risk. These associations were somewhat more evident among women, were mainly manifested for colon cancer risk and their magnitude was not altered when alcohol was excluded.

27. Everatt et al (2013) used data from two population-based cohorts in Kaunas, Lithuania to investigate total cancer incidence, and that of individual cancers such as CRC. The final number of participants was 7,150. All cohort members were interviewed at baseline using a structured questionnaire; frequency and amount of each type of drink were recorded. Study participants were followed from 1 January 1978 to 31 December 2008. Risk estimates were calculated for total cancers and types causally associated to alcohol consumption, including CRC. The data were adjusted for education, smoking, and BMI. There was a close relationship between

heavy smokers (≥20 cigarettes/day) and alcohol consumption frequency. The Hazard Ratio for total cancer was 1.36 (95% CI 1.11-1.65) amount men who consumed the highest amount (≥140.1 g/week) compared to those with the lowest consumption (0.0-10.0 g/week). For CR cancer, the risk was also raised but, after adjustment for confounders, was not statistically significant (1.67(95% CI 0.98-2.84)).

28. Hermann et al (2009) investigated the relationship between lifestyle factors, obesity and the risk of colorectal adenomas in the EPIC-Heidelberg prospective study. At recruitment, information on diet, anthropometry, lifestyle and medication was assessed in 25,540 participants of the EPIC-Heidelberg cohort. Until June 2007, 536 verified incident colorectal adenomas were identified. Participants with negative colonoscopy were included in the analytic cohort.

29. In multivariate logistic regression analyses, participants with the highest alcohol intake had an increased adenoma risk (OR 1.63; 95% CI 1.21 - 2.22) compared with the lowest intake group. Folate consumption modified the ethanol effect (p-interaction = 0.03). Current smokers had a significantly increased adenoma risk compared with never smokers (OR 1.40; 1.16 – 1.84). Regular NSAID use was associated with a lower risk in subjects who reported their use at least twice compared with nonusers (OR 0.70; 0.53-0.93). Physical activity, BMI and waist-to-hip ratio were not consistently associated with adenoma risk.

30. Dartois et al (2014) investigated the association between five lifestyle habits and cancer risk in 64,732 women from the French E3N prospective cohort aged 43 to 68 ears at baseline. During a 15 year follow-up period, 481 cases of CRC were diagnosed. They defined an index which aggregated 5 lifestyle characteristics: smoking, BMI, alcohol consumption, fruit and vegetable consumption, and physical activity. PAFs were used to estimate the proportion of cancer cases that could be prevented by healthier behaviours. The PAF for alcohol consumption and CRC when adhering to public health recommendations was 6.6 (-2.9 to 16.0). The PAF for adhering to all 5 combined characteristics was 12.8 (-2.4 to 27.4).

Case-Control Studies (Table 3)

31. JY Park et al (2010) investigated the prospective associations between alcohol intake on overall and site-specific CRC risk. Analyses were conducted on 579 CRC cases and 1996 matched controls nested within the UK Dietary Cohort Consortium using standardised data obtained from food diaries as a main nutritional method and repeated using data from FFQ. Compared with individuals in the lightest category of drinkers, no significant increase was seen in CRC incidence up to ≥45 g/day. No clear associations were observed between site-specific CRC risk and alcohol intake in either sex. Analyses using FFQs showed similar results.

32. Crockett et al (2011) investigated the relationship between alcohol consumption and distal CRC and rectal cancer specifically in the North Carolina Colon Cancer Study. This was a population-based case-control study of incident distal large bowel cancer (rectal, recto-sigmoid, or sigmoid cancer) in 33 counties in North Carolina, US. Rectal cancer accounts for approximately 30% of CRC cases.

33. The adjusted odds ratio for rectal cancer after comparing any vs. no alcohol intake was 0.73 (95% CI: 0.60-0.90). The OR for moderate alcohol intake (≤14

g/day) was 0.66 (0.53-0.82) while that for heavy alcohol (>14 g/day) was 0.93 (0.70-1.23). Moderate beer and wine intakes were also inversely associated with distal CRC.

34. Zhiotovskiy et al (2012) recruited 185 Russian colorectal cancer cases and 210 gender, age, and ethnicity-matched asymptomatic controls with no history of any malignant tumour, using a specially designed questionnaire to obtain relevant information. They found that alcohol drinking was statistically significantly associated with an increased risk of CR cancer (OR 8.73, 95% CI 5.49 – 13.87, P < 0.0001). Beer drinking and consumption of hard liquor were also each significantly associated with CR cancer, but wine-drinking was not.

35. The interaction between alcohol drinking and obesity (BMI) was investigated by Zhao et al (2012) using newly diagnosed CRC cases identified between 1999 and 2003 in Newfoundland and Labrador (NL). Cases were frequency-matched by age and sex with controls selected by random digit dialling. Cases (702) and controls (717) completed self-administered questionnaires assessing health and lifestyle variables. Odds ratios were estimated to investigate the associations both independently and when stratified by obesity status on the risk of CRC.

36. Overall, there was no significant association between alcohol intake and CRC. The adjusted OR for drinkers vs. non-drinkers was 1.0 (95% CI 0.7 - 1.3). Comparing by types of drinks, number of years drinking, or number of drinks per day also showed no significant association, nor did analysis of the results for males and females separately. However, among obese participants (BMI $\geq$ 30) (199 cases/161 controls), alcohol was associated with a higher risk of CRC (OR 2.2, 95% CI 1.2-4.0) relative to the non-alcohol category. Three or more different types of drink were associated with a 3.4-fold higher risk of CRC relative to non-drinkers. The risk of CRC also increased with drinking years and drinks daily among obese participants, reaching significance at 5+ drinks/day. However, no increased risk was observed in people without obesity (503 cases/556 controls).

Other studies

Studies investigating the relationship between smoking and alcohol consumption

37. In a case-control study, Austin et al (2008) investigated the relationship between different levels of alcohol consumption and colorectal adenomas, and whether smoking modified this relationship. The proportion of patients with adenomas was 29.6% in abstainers, 22.1% in moderate drinkers (0 - <7 drinks/week) and 36.1% in heavy drinkers ($\geq$ 7 drinks/week). There was significant modification of the relationship between alcohol consumption and CR adenomas by smoking. For individuals who had never smoked, heavy drinkers were at significantly increased odds of having an adenoma compared to moderate drinkers (OR 3.08; 95% CI 1.50-6.32), while no effect was seen for abstainers. Similarly, among individuals who had smoked from 1 to 14 years, heavy drinkers were at an increased odds of having an adenoma compared to moderate drinkers (OR 2.61; 1.04-6.51), and no difference was seen for abstainers (OR 1.02; 0.33-3.10). For individuals who had smoked for 15 years or more, heavy drinkers had a significantly lower risk of adenoma compared to abstainers (p = 0.04).

38. Acott et al (2008) queried the Central Arkansas Veterans Healthcare System tumour registry for all surgical patients with a diagnosis of colorectal lesion or CR carcinoma during the period 1/1/1997 to 1/1/2006. Relevant data were collected and alcohol and tobacco use were recorded as current use, past use greater than 1 year prior, or never users. Current users of both alcohol and tobacco were associated with a significantly younger age of CRC onset (60.14) compared with all patients (66.92). Patients who had never used alcohol or tobacco were associated with a significantly older age of onset (75.57 years) compared to all patients. The authors also compared the median age in the various groups exposed to tobacco and/or alcohol with the reference group that had used neither. In all cases, current alcohol consumption was associated with an increased likelihood of presenting with CRC at a younger age (OR 1.09; 95% CI 1.04-2.66).

Ecological study

39. An ecological study was conducted in Korea to determine the association between alcohol consumption and the risk of CRC, the incidence of which had increased sharply in recent years. Cho and Kim (2011) obtained CRC incidence rates for the years 1999-2007 from the Korean Central Cancer Registry and data on national alcohol consumption for the years 1998, 2001, 2005 and 2007 from the reports of the Korea National Health and Nutrition Examination Survey. Pearson's correlation coefficients were determined using data for alcohol intake and CRC incidence rate.

40. A significant correlation was observed in men between alcohol consumption and the CRC incidence rate ($r = 0.99$; $p = 0.001$) but not in women ($r = 0.82$; $p = 0.180$). It should be noted that both the alcohol intake and the increase in alcohol consumption for women were much lower than those for men (men: rising from 10.6 to 17.3 g/day; women: rising from 1.4 to 2.9 g/day). Similarly, the CRC rate rose from 27.0 to 44.5 cases per 10^5 in men and from 17.1 to 24.3 cases per 10^5 in women. In the <50-year age group, the age-specific incidence rate for men was comparable to that for women, but in the ≥50- year age group, it increased rapidly in men. They concluded that the increase in alcohol consumption appears to be attributable to an increase in the number of heavy drinkers among men aged 25-59 years, particularly among men aged 45-49 years.

Tumour phenotype

41. Poynter et al (2009) evaluated the relationships between smoking and alcohol consumption and CRC risk overall, by tumour location and microsatellite instability (MSI) status, using data from the CRC Family Registry (Colon CFR). They state that microsatellite unstable (MSI-H) tumours, which account for 10-20% of sporadic CRC, differ from microsatellite stable (MSS) tumours by clinical and patient characteristics. MSI-H tumours are associated with location in the right colon, female sex, older age at diagnosis, and more favourable diagnosis when compared with MSS tumours. Previous epidemiological studies had reported that the associations between CRC and both smoking and alcohol consumption differed by tumour MSI status, with both factors increasing the risk of MSI-H cancers in particular.

42. The study employed a population-based case-unaffected sibling design recruited to the Colon CFR. Associations were assessed using conditional logistic

regression, treating sibship as the matching factor. MSI was evaluated for all cases with available tumour tissue using a panel of 10 markers. Results were required for at least 4 markers to determine MSI status. Tumours were deemed MSI-H if instability was observed at ≥30% of markers, MSI-L if >0 and <30% of markers, and MSS if all markers were stable. Alcohol intake was associated with a modest increase in risk for CRC overall (OR 1.21, 95% CI 1.03 –1.44 for 12+ drinks per week vs. non-drinkers), with more marked increases in risk for MSI-L CRC (OR 1.85, 1.06 – 3.24) and rectal cancer (OR 1.48, 1.08 – 2.02). There was no positive association for MSI-H CRC cases (OR 0.63, 0.35 – 1.13).

Polymorphisms and genetic susceptibility

43. It has been hypothesised that alcohol itself is not carcinogenic, but its oxidation product, acetaldehyde, is the carcinogenic agent. In the liver, alcohol dehydrogenase (ADH) enzymes convert alcohol to acetaldehyde, which is then oxidized to acetate by aldehyde dehydrogenase (ALDH) enzymes (Bosron and Li, 1986). Single nucleotide polymorphisms (SNPs) have been described for ADH isoforms *ADH1B* and *ADH1C* and ALDH isoform *ALDH2*. In contrast to SNPs in *ADH1B* and *ALDH2*, one functional SNP in *ADH1C* is found frequently in Caucasian populations. Its two allelic variants are present in approximately equal frequency and homozygotes for the *ADH1C*1* allele metabolise alcohol 2.5 times faster than homozygotes for the *ADH1C*2* allele. Subjects with the various genotypes are classified thus:

*ADH1C*1/*1*	fast alcohol metaboliser
*ADH1C*1/*2*	intermediate alcohol metaboliser
*ADH1C*2/*2*	slow alcohol metaboliser.

44. Because of the different kinetic properties of the enzymes, the *ADH1C* polymorphism is speculated to underlie a genetic susceptibility to alcohol-associated cancers. According to Bongaerts et al (2011), overall, the fast-metabolizing *ADH1C*1/*1* genotype has been reported to be the high-risk genotype in alcohol-related diseases. However, three studies on CRC observed *ADH1C*2/*2* as the high risk genotype.

45. Therefore, Bongaerts et al (2011) (table 4) examined associations between alcohol consumption, the *ADH1C* genotype, and risk of CRC within the Netherlands Cohort Study on diet and cancer. In subjects who reported to have consumed equal amounts of total alcohol both 5 years before baseline and at baseline, drinkers of ≥ 30g/d with the *ADH1C*2/*2* genotype were associated with an increased risk of CRC relative to abstainers with the *ADH1C*1/*1* genotype, but the increase was not statistically significant (RR 1.91, 95% CI: 0.68-5.43). The risk estimate in this exposure group increased slightly when compared with light drinkers of ≥0.5 - <5 g/d with the *ADH1C*1/*1* genotype (RR 2.32, 0.80-6.72) but the interaction term was not statistically significant (P > 0.05). In subjects who reported to have consumed equal amounts of total alcohol both 5 years before baseline and at baseline, drinkers of ≥30 g of alcohol per day were non-statistically significantly associated with an increased risk of CRC relative to abstainers (RR 1.38; 0.80-2.38). This risk estimate for high level drinkers became stronger when compared with light drinkers (RR 1.74;

1.01-2.00). As the main effect of genotype, they observed that the *ADH1C*2/*2* genotype was associated with a 42% increase in risk of CRC when compared with the *ADH1C*1/*1* genotype. They concluded that both genotype and alcohol consumption were associated with an increased risk of CRC.

46. Ferrari et al (2012) carried out a nested case-control study (1269 cases matched to 2107 controls by age, sex, study centre and date of blood collection) within the EPIC study to evaluate the impact of rs1229984(A) *(ADH1B*), rs1573496 *(ADH7)* and rs441 *(ALDH2)* polymorphisms on CRC risk. These polymorphisms were chosen because investigations in Central European populations had indicated that they are associated with the risk of upper and aero-digestive tract cancer and that the association is potentially modifiable by the level of alcohol consumption. Using the wild-type variant of each polymorphism as reference category, CRC risk estimates were calculated using conditional logistic regression, with adjustment for matching factors.

47. Total alcohol and wine intakes were significantly higher in cases than controls but beer and spirit intakes were not. Individuals carrying one copy of the rs1229984(A) *(ADH1B)* allele (fast metabolisers) showed an average daily alcohol intake of 4.3g per day lower than subjects with two copies of the rs1229984(G) allele (slow metabolisers) (P_{diff}<0.01). None of the polymorphisms was associated with risk of CRC. Heavy alcohol intake was more strongly associated with CRC risk among carriers of the rs1573496(C) allele, with odds ratio equal to 2.13 (95% CI 1.26-3.59) compared with wild-type subjects with low alcohol consumption ($P_{interaction}$ =0.07).

48. Kim et al (2012) investigated the association between folate and alcohol intake, methylenetetrahydrofolate reductase (MTHFR) C677T polymorphism, and CRC risk in Koreans. 787 cases and 656 controls were recruited from 2 university hospitals. The controls had been hospitalized during the same period as the cases for a wide spectrum of non-neoplastic conditions. Cases had significantly lower BMI, number of patients with a positive family history for CRC, and were more likely to be current smokers and drinkers. *MTHFR* 677T homozygotes were at a lower risk of CRC (OR 0.60, 95% CI 0.46-0.78 for *TT* compared with *CC/CT*). High folate intake was associated with reduced CRC risk (OR: 0.64, 0.49-0.84 for high compared with low intake), and high alcohol consumption was associated with increased risk of CRC (OR 1.76, 1.26-2.46 for higher compared with low intake). When the effects of alcohol consumption on the association between MTHFR C677T genotype and CRC was studied, a positive association was found between alcohol and *CC/CT* genotype (OR 1.87, 1.29-2.71) for high vs low alcohol consumption, but not for alcohol and *TT* genotype (OR 0.89, 0.51-1.54). This association was stronger in patients with colon cancer than in patients with rectal cancer.

49. Tobacco use alone, without alcohol consumption, was not shown to influence the probability of CRC presenting at a younger age. In the whole population studied, there was no significant difference in the number of CRC cases presenting at stage 2A or greater. However, in younger patients (<70), the current use of both alcohol and tobacco significantly increased the probability of presenting with a higher stage CRC, when compared to those patients never using either variable.

Discussion

50. Epidemiological studies on alcohol and CRC published since the IARC review in 2009 have produced conflicting results, with the majority of studies reviewed here failing to show an association, or showing an association only for heavy drinkers. However, a good quality meta-analysis by Fedirko et al (2010) showed evidence for an association between alcohol drinking of >1 drink/day and increased CRC risk. A pooled analysis by Nan et al (2013) also found a significant association with consumption of >30g alcohol/d compared to non-drinkers but no significant association after introduction of food fortification with folate. However, the results of other pooled or meta-analyses and systematic reviews were conflicting. The majority of individual cohort and case-control studies produced negative results.

Questions for the Committee

51. a) What are the Committee's views on the recently published studies on alcohol consumption and colorectal cancer risk?

b) Do these studies add any weight to the statement by IARC (2007) that cancer of the colorectum is causally related to the consumption of alcoholic beverages?

c) Does the Committee consider that there is sufficient evidence to come to a conclusion about the amount of alcohol and frequency of drinking and colorectal cancer risk?

Secretariat
October 2014

References

Austin GL, Galanko JA, Martin CF and Sandler RS (2008). Moderate alcohol consumption is protective against colorectal adenomas in smokers. Dig Dis Sci 53(1): 116-122.

Bagnardi V, Rota M, Botteri E et al (2013). Light alcohol drinking and cancer: a meta-analysis. Annals of Oncology 24: 301-308.

Bamia C et al. (2013). Mediterranean diet and colorectal cancer risk: results from a European cohort. Eur J Epidemio. 28(4):317-28.

Cancer Research UK Statistical Team (2014). http://publications.cancerresearchuk.org/downloads/Product/CS_KF_BOWEL.pdf Accessed July 2014.

Cho YA, Kim J (2011). Association between alcohol consumption and colorectal carcinogenesis: an ecological study in Korea. Asian Pacific J Cancer Prev 12:761-764.

Cho E, Lee JE, Rimm EB, Fuchs CS and Giovannucci EL (2012). Alcohol consumption and the risk of colon cancer by family history of colorectal cancer. Am J Clin Nutr 95:413-9.

Crockett SD, Long MD, Dellon ES, Martin FC, Galanko JA, and Sandler RS (2011). Inverse relationship between moderate alcohol intake and rectal cancer: Analysis of the North Carolina Colon Cancer Study. Dis Colon Rectum 54(7):887-894.

Everatt R, Tomosiunas A, Virviciute D, Kuzmickiene I and Reklaitiene R (2013). Consumption of alcohol and risk of cancer among men: a 30 year cohort study in Lithuania. Eur J Epidemiol 28(5):383-92.

Ferrari P, McKay JD et al. (2012). Alcohol dehydrogenase and aldehyde dehydrogenase gene polymorphisms, alchol intake and the risk of colorectal cancer in the European Prospective Investigation into Cancer and Nutrition study. Eur J Clin Nutr. 66(12):1303-8.

Fedirko V, Tramacere I, Bagnardi V et al (2011). Alcohol drinking and colorectal cancer risk: an overall and dose-response meta-analysis of published studies. Annals of Oncology 22:1958-1972.

Haggar FA and Boushey RP (2009). Colorectal cancer epidemiology: incidence, mortality, survival, and risk factors. Clin Colon Rectal Surg 22:191-197.

Hermann S, Rohrmann S and Linseisen J (2009). Lifestyle factors, obesity and the risk of colorectal adenomas in EPIC-Heidelberg. Cancer Causes Control 20:1397-1408.

Kim DH, Smith-Warner SA, Spiegelman D et al (2010). Pooled analyses of 13 prospective cohort studies on folated intake and colon cancer. Cancer Causes Control 21:1919-30.

Kim J, Cho YA, Kim D-H et al (2012). Dietary intake of folate and alcohol, *MTHFR* C677T polymorphism, and colorectal cancer risk in Korea. Am J Clin Nutr 95:405-12.

Li Y, Yang H and Cao J (2011). Association between alcohol consumption and cancers in the Chinese population – A systematic review and meta-analysis. PLSO One 6(4): e18776.

Magalhâes B, Peletelro B and Lunet N (2012). Dietary patterns and colorectal cancer : systematic review and meta-analysis. European Journal of Cancer Prevention 12:15-23.

Nan H, Lee JE, Rimm EB, Fuchs CS, Giovannucci EL and Cho E. (2013). Prospective study of alcohol consumption and the risk of colorectal cancer before and after folic acid fortification in the United States. Ann Epidemiol. 23(9):558-63.

Park JY, Mitrou PN, Dahm CC, Luben RN, Wareham NJ, Khaw KT and Rodwell SA (2009). Baseline alcohol consumption, type of alcoholic benverage and risk of colorectal cancer in the European Prospective Investigation into Cancer and Nutrition – Norfolk study. Cancer Epidemiology 33:347-354.

Park JY, Dahm CC, Keogh RH et al (2010). Alcohol intake and risk of colorectal cancer: Results from the UK Dietary Consortium. B J Cancer 103:747-756.

Park S, Shin HH-R, Lee B et al. Attributable fraction of alcohol consumption on cancer using population-based nationwide cancer incidence and mortality data in the Republic of Korea (2014). BMC Cancer 14:420-431.

Parkin DM, Boyd L, Walker LC (2011). The fraction of cancer atttributable to lifestyle and environmental factors in the UK in 2010. Summary and conclusions. Br J Cancer 105 (S2): S6-S13; doiL 10.1038/bjc.2011.475

Poynter JN, Haile RW, Siegmund KD et al (2009). Associations between smoking, alcohol consumption and colorectal cancer, overall and by tumor microsatellite instability status. Cancer Epidemiol Biomarkers Prev 18(10):2745-2750.

Poynter JN, Inoue-Choe M, Ross JA, Jacobs DR Jr and Robien K (2013). Reproductive, lifestyle, and anthropometric risk factors for cancer in elderly women. Cancer Epidemiol Biomarkers Prev. 22(4):681-7.

Razzak AA, Oxentenko AS, Vierkant RA et al (2011). Alcohol intake and colorectal cancer risk by molecularly defined subtypes in a prospective study of older women. Cancer Prev Res 4:2035-2043.

Rosato V, Bosetti C, Levi F, Polesel J, Zucchetto A, Negri E, and La Vecchia C (2013). Risk factors for young-onset colorectal cancer. Cancer Causes Control 24(2):335-41.

Sanjoaquin MA, Allen N , Couto E, Roddam AW and Key TJ (2005). Folate intake and colorectal cancer risk: a meta-analytical approach. Int J Cancer 113:825-8.

Wang J, Wang H, Chen H, Hao Y and Zhang P (2011). Alcohol ingestion and colorectal neoplasia: a meta-analysis based on a Mendelian randomization approach. Colrectal Disease 13: e71-e78.

Zhao J, Zhu Y et al. (2012). Interaction between alcohol drinking and obesity in relation to colorectal cancer risk: a case-control study in Newfoundland and Labrador, Canada. BMC Public Health 1:94.

Zhivotovskiy AS, Kutikhin AG, Azanov AZ, Yuzhalin AE, Magarill YA and Brusina EB (2012). Colorectal cancer risk factors among the population of South-East Siberia: a case-control study. Asian Pac J Cancer Prev 13(10):5183-8.

Table 1. Pooled and meta-analysis of consumption of alcoholic beverages and colorectal cancer

Reference, location, period	No. in analysis	No. of cases/ controls, n	Exposure assessment	Exposure categories	Pooled Relative Risk (RR) and confidence intervals (95% CI)	Adjustment factors	Comments
Fedirko V et al (2011) Meta-analysis Asia: 22 studies Australia: 2 studies W Europe: 13 studies N America: 24 studies 1974 - 2007	17770 cases in 23 cohort studies	22692/ 40975 in 35 case-control studies	Various	Light drinkers: ≤ 1 drink/day Moderate drinkers: 2-3 drinks/day Heavy drinkers: ≥ 4 drinks/day Reference category: non-drinkers or occasional drinkers. 1 drink = 12.5g alcohol	1.0 (0.95-1.05) 1.21 (1.13-1.28) 1.52 (1.27-1.81) Any drinker: 1.12 (1.06-1.19)	22 studies reported "fully adjusted" risk estimates i.e. age, sex, BMI, smoking, and physical activity 36 studies reported risk estimates adjusted for tobacco smoking	Sensitivity analyses carried out to assess whether summary estimates robust to inclusion of studies reporting estimates not adjusted for the main risk factors (age, sex, body fatnesss, smoking, and physical activity). Detailed evaluation of publication bias suggested that this unlikely.

Table 1. Pooled and meta-analysis of consumption of alcoholic beverages and colorectal cancer							
Reference, location, period	**No. in analysis**	**No. of cases/ Controls, n**	**Exposure assessment**	**Exposure categories**	**Pooled Odds Ratio (OR) and confidence intervals (95% CI)**	**Adjustment factors**	**Comments**
Li Y, Yang H and Cao J (2011) Chinese population	10 case-control studies and 1 cohort study investigated CRC.	3414/6948		Reference category ("non-drinkers") = participants described as drinking the smallest amount and those who said that they never drink. "Drinkers" = all other subjects.	From case-control studies: 1.58 (0.90-2.76) Test for overall effect: p = 0.04	Not discussed	Types of drinks consumed included beer, yellow rice wine, red wine and spirits. Pooled ORs for case-control studies and RRs for cohort studies calculated separately using RevMan 5.0 software. Studies on CRC had significant heterogeneity (p,0.10 and I^2>50%) so meta-analyses conducted using random effect model.

Table 1. Pooled and meta-analysis of consumption of alcoholic beverages and colorectal cancer							
Reference, location, period	**No. in analysis**	**No. of cases/ controls, n**	**Exposure assessment**	**Exposure categories**	**Pooled Relative Risk (RR) and confidence intervals (95% CI)**	**Adjustment factors**	**Comments**
Bagnardi et al, 2013 Meta-analysis Asia: 16 studies Europe: 13 studies N America: 23 studies Studies published before December 2010	Not given	Not given	Not given	Non-drinkers = reference category 12.5g/d alcohol (1 drink/day) exposed group	0.99 (0.95-1.04)	Only comment was that only a small no. of studies (all cancer sites) reported the effect of light drinking in different smoking strata.	Heterogeneity between the studies was moderate or low. Little evidence for publication bias was detected (p=0.059).

Table 1. Pooled and meta-analysis of consumption of alcoholic beverages and colorectal cancer							
Reference, location, period	**Cohort description (No. in analysis)**	**No. of cases/ controls, n**	**Exposure assessment**	**Exposure categories**	**Pooled Relative Risk (RR) and confidence intervals (95% CI)**	**Adjustment factors**	**Comments**
Magalhâes et al (2012). Various locations Studies published 1992 to 2010	No information	Not given	" 'Drinker' dietary patterns tended to have high loadings of alcoholic beverages". For this category, 20 RR estimates available from 6 studies.	Computed combined RR estimates for the highest vs lowest category of exposure to alcohol	RR for colon and rectal cancer combined = 0.98 (0.77-1.26, I^2 = 40.8%) Some evidence of publication bias for this category.	Not given	Heterogeneity quantified using the I^2 statistic. Publication bias assessed by visual inspection of funnel plot.

Table 1. Pooled and meta-analysis of consumption of alcoholic beverages and colorectal canc								
Reference, location, period	**Cohort description (No. in analysis)**	**No. of cases/ controls, n**	**Exposure assessment**	**Exposure categories**	**Pooled Odds Ratio (OR) and confidence intervals (95% CI)**	**Pooled Odds Ratios and confidence intervals (95% CI)[c]**	**Adjustment factors**	**Comments**
Nan et al (2013) US 1980-2008	Pooled analysis from the Nurses Health Study and the Health Professionals follow-up study of men.	a 717/ 134730 b 999/ 97878	NHS participants: FFQ administered in 1980, then expanded FFQ in 1984, 1986 and every 4 years thereafter. Similar expanded FFQ administered to HPFS in 1986 and every 4 years thereafter. Comprehensive diet records and plasma HDL concentrations from sub-samples used to validate questionnaire data.	Drinkers (≥ 30 g/day alcohol) vs nondrinkers Drinkers (≥ 30 g/day alcohol) vs nondrinkers. Pre-folic acid fortification period (1980 NHS/1986 HPFS) to 1998 compared to post- folic acid fortification period (1998-2008)	1.35 (1.14 - 1.59) P for trend 0.004 1.32 (1.06-1.63) P for trend 0.10[a] 1.13 (0.85-1.51) P for trend 0.17[b]	1.36 (1.09-1.70) P for trend, 0.02 1.31 (1.00-1.71) P for trend, 0.10 [a] 1.07 (0.69-1.65) P for trend, 0.67 [b]	a Pre-fortification period b Post-fortification period c Among nonusers of multivitamins and/or folic acid supplements	

Table 1. Pooled and meta-analysis of consumption of alcoholic beverages and colorectal canc							
Reference, location, period	**Cohort description (No. in analysis)**	**No. of cases/ controls, n**	**Exposure assessment**	**Exposure categories**	**Pooled odds Ratio (OR) and confidence intervals (95% CI)**	**Adjustment factors**	**Comments**
Rosato et al (2013) Italy and Switzerland 1985 - 2009		329/ 1361 All ≤ 45 years	Questionnaire administered by trained interviewers. Diet: food frequency questionnaire.		OR for ≥14 drinks/week 1.56 (1.12 – 2.15) P for trend = 0.009. The risk did not increase further for ≥ 21 drinks/week.	Model included terms for age, sex, centre, study, year of interview, education, family history, and alcohol consumption.	ORs and CIs estimated by unconditional multiple logistic regression models.

Table 1. Pooled and meta-analysis of consumption of alcoholic beverages and colorectal canc							
Reference, location, period	**Cohort description (No. in analysis)**	**No. of cases/ controls, n**	**Exposure assessment**	**Exposure categories**	**Multivariate Odds Ratio (OR) and confidence intervals (95% CI)**	**Adjustment factors**	**Comments**
Cho et al (2012)	Pooled analysis from the Nurses Health Study and the Health Professionals follow-up study of men.	339 678 233 195 201 155	NHS participants: FFQ administered in 1980, then expanded FFQ in 1984, 1986 and every 4 years thereafter. Similar expanded FFQ administered to HPFS in 1986 and every 4 years thereafter. Comprehensive diet records and plasma HDL concentrations from subsamples used to validate questionnaire data.	None, 0.1 - <5g/d, 5 - <10 g/d 10 - <15 g/d, 15 - <30 g/d. ≥ 30 g/d. None, 0.2 - <5g/d, 5 - <10 g/d 10 - <15 g/d, 15 - <30 g/d. ≥ 30 g/d.	1.00 1.16 (0.87 - 1.54)[a] 1.08 (0.91 - 1.28) [a] 1.26 (0.96 - 1.66) [a] 1.11 (0.92 – 1.33) [a] 1.36 (1.10 – 1.68) [a] p for trend = 0.14 1.00 1.41 (1.00 – 1.99)[b] 1.06 (0.72 – 1.55) [b] 1.19 (0.78 – 1.83) [b] 1.21 (0.81 – 1.82) [b] 2.02 (1.30 – 3.13) [b] p for trend = 0.15	Age, smoking, history of endoscopy, use of aspirin, energy intake, calcium, folate, red meat. In NHS, menopausal status and use of hormone replacement therapy also. In total cases, family history of CRC (yes/no) also.	In NHS, history of CRC in a father, mother or siblings elicited in 1982, updated in 1988, 1992, 1996 and 2000. In HPFS, CRC history in a father or mother elicited in 1986 and that in a father , mother or siblings in 1990, 1992 and 1996. a: Total cases, pooled b: Total cases, pooled, with family history

Table 1. Pooled and meta-analysis of consumption of alcoholic beverages and colorectal cancer							
Reference, location, period	**Cohort description (No. in analysis)**	**No. of cases/ controls, n**	**Exposure assessment**	**Exposure categories**	**Pooled Odds Ratio (OR) and confidence intervals (95% CI)**	**Adjustment factors**	**Comments**
Wang et al (2011) 5 studies in Japan, 1 in China	5123 participants in 6 studies	1960/3163	Genotype used as exposure measure.	<u>Glu/Glu vs Lys/Lys</u> Fixed-effect model Random-effect model <u>Glu-Lys vs Lys/Lys</u> Fixed-effect model Random-effect model	 1.31 (1.01-1.70) p=0.04 1.25 (0.85-1.83) p=0.26 1.13 (0.86-1.48) p=0.37 1.14 (0.87-1.49) p=0.36	N/A	7 studies eligible but one study in SW China found that individuals with the Lys-Lys variant continued drinking and so this was excluded. Note: 5 studies of CRC, one of CR adenoma. No evidence of interstudy heterogeneity (p = 0.12, I^2 = 42.7)

Table 1. Pooled and meta-analysis of consumption of alcoholic beverages and colorectal cancer							
Reference, location, period	**Cohort description (No. in analysis)**	**No. of cases/ controls, n**	**Exposure assessment**	**Exposure categories**	**Pooled relative risk (RR) and confidence intervals (95% CI) corresponding to average alcohol consumption**	**Adjustment factors**	**Comments**
Park et al (2014) Korea 1989 - 2009	Individuals ≥ 20 years	Not given for individual cancer types	Average alcohol consumption (g/day): frequency and amount	Average alcohol consumption in 1998: Men: 28.53 g/day Women: 6.38 g/day	Men: 1.12 (0.80-1.53) Women: 1.19 (0.88-1.60)	Unknown	PAF for men was 8.6%, with 1281 avoidable incident cancer cases. PAF for women was 4.2% with 414 avoidable cases. Higher uncertaintly in RR estimates for CRC than some other cancers.

Table 2. Cohort studies of consumption of alcoholic beverages and colorectal cancer								
Reference, location	**Cohort description (No. in analysis)**	**Exposure assessment**	**Exposure categories**	**No. of cases**	**Odds Ratio (OR) and confidence intervals (95% CI)**	**Relative Risk and confidence intervals (95% CI)**	**Adjustment factors**	**Comments and Star Rating**
Bamia et al (2013) Europe	EPIC cohort. 408,308 subjects from 10 European countries	Dietary intakes at enrolment assessed through validated centre-specific food-frequency questionnaires		4355 incident CRC cases	Ethanol intake (tertiles): T3 vs T1 (referrent) All 1.05 (0.96-1.14) P = 0.26 Men T3 vs T1 (referrent) 1.20 (1.06-1.35) P = 0.003 Women 0.98 (0.88-1.08) P = 0.65 All cohorts in relation to diet, per 2 unit increment: Mediterranean Diet Score (MDS) 0.96 (0.92-1.00) P trend = 0.02 Centre specific modified Mediterranean Diet Score (CCMMDS) 0.97 (0.93-1.01) P trend = 0.05		Age at enrolment, education, physical exercise, smoking, BMI	Cancer incidence ascertained through record linkage with cancer registries or active follow-up. Analysis used Cox proportional hazard models. P<0.05 considered statistically significant Average follow-up 11.6 years 6*

Table 2. Cohort studies of consumption of alcoholic beverages and colorectal cancer								
Reference, location, period	**Cohort description (No. in analysis)**	**Exposure assessment**	**Exposure categories**	**No. of cases**	**Odds Ratio (OR) and confidence intervals (95% CI)**	**Relative Risk and confidence intervals (95% CI)**	**Adjustment factors**	**Comments and Star Rating**
Everatt et al (2013) Lithuania 1978-2008	Cohort 1: 2447 Cohort 2: 5933 Total after exclusions: 7,150	Structured questionnaire administered at start of study	≥ 140.1 g/week vs. 0.1-10.0 g/week	1698	All cancers: 1.36 (1.11-1.65) Colorectal cancers: a: 1.78 (1.06-3.00) b: 1.67 (0.98-2.84)		a.Stratified by study b.Stratified by study, adjusted for smoking, education, BMI	No clear dose relationship for CR cancer Analysis using multivariate Cox proportional hazard regression models stratified by study 7*

Table 2. Cohort studies of consumption of alcoholic beverages and colorectal cancer							
Reference, location, period	**Cohort description (No. in analysis)**	**Exposure assessment**	**Exposure categories**	**No. of cases**	**Relative Risk and confidence intervals (95% CI)**	**Adjustment factors**	**Comments and Star Rating**
Razzak et al (2011) U.S. 1986- 2008	38,001 women from the IOWA Womens' Health Study, randomly selected, living in State of Iowa and holding a driver's licence and aged 77 to 91 at end of study.	Self-reported: questionnaire mailed out at baseline in 1986. Semi-quantitative FFQ. Subjects asked average alcohol use during past year for beer, red wine, white wine and spirits (glass, can, bottle, shot as appropriate)	Never or less than once per month; 1 to 3 per month, 1 per week, 2 to 4 per week, 5 to 6 per week, 1 per day, 2 to 3 per day, 4 to 5 per day, 6+ per day.	1255	Non consumers: 1.00 (ref) Median split: ≤3.4 g/d 1.00 (0.86-1.15) >3.4 g/d 1.06 (0.91-1.24) p for trend = 0.50 Threshold value: ≤30 g/d 1.03 (0.91-1.16) >30 g/d 1.00 (0.71-1.40) p for trend = 0.73	Age, BMI, WHR, smoking status, exogenous estrogen use, physical activity level, and daily intakes of total energy, total fat, sucrose, red meat, calcium, folate, methionine and vitamin E (mg/d)	Could be misclassification bias from using single, baseline exposure assessment to describe long-term alcohol consumption. 3*

Table 2. Cohort studies of consumption of alcoholic beverages and colorectal cancer								
Reference, location, period	**Cohort description (No. in analysis)**	**Exposure assessment**	**Exposure categories**	**No. of cases**	**Odds Ratio (OR) and confidence intervals (95% CI)**	**Relative Risk and confidence intervals (95% CI)**	**Adjustment factors**	**Comments and Star Rating**
Poynter et al (2014) U.S. 1986- 2008	Elderly, postmenopausal women with no history of cancer from Iowa Women's Health Study: Random sample of women ages 55 to 69 years at start. n = 37,432 women aged < 75 and 30,814 aged ≥75	Women asked about whether they drank alcohol or not at baseline.	Yes or no	604 in women aged < 75 707 in women aged ≥ 75	Compared to non-drinkers: Colon cancer: Aged <75 1.04 (0.88-1.24) p = 0.62 Aged ≥ 75 1.00 (0.85-1.17) p = 0.96 Rectal cancer: Aged <75 1.14 (0.84-1.55) p= 0.40 Aged ≥ 75 0.98 (0.68 – 1.41) p= 0.82		Age at baseline, BMI physical activity level, smoking and estrogen use.	5*

Table 2. Cohort studies of consumption of alcoholic beverages and colorectal cancer							
Reference, location, period	**Cohort description (No. in analysis)**	**Exposure assessment**	**Exposure categories**	**No. of cases**	**Odds Ratio (OR) and confidence intervals (95% CI)**	**Adjustment factors**	**Comments and Star Rating**
Hermann S et al (2009) Heidelberg Recruitment 1994-8. Assessment 2007.	25,540 participants in the EPIC-Heidelberg cohort	Validated food frequency questionnaire for alcohol intake. Face-to-face interviews and questionnaires for other variables.	Average lifetime ethanol intake (g/day): < 5 <15 <30 ≥30	Until June 2007, 536 verified incident CR adenomas.	1.00 (Ref) 1.24 (0.95 – 1.62) 1.57 (1.20 – 2.07) 1.63 (1.21 – 2.22) p for trend +0.002	Age at baseline, sex, energy intake without alcohol, total red and processed meat products, intake of milk and milk products, fibre intake, folate intake, family history of CRC, and education. Additionally, for pack-years of smoking, smoking status, intake of NSAIDs, BMI, and physical activity as appropriate.	8*

Table 2. Cohort studies of consumption of alcoholic beverages and colorectal cancer							
Reference, location, period	**Cohort description (No. in analysis)**	**Exposure assessment**	**Exposure categories (units/week)**	**No. of cases**	**Hazard Ratio (HR) and confidence intervals (95% CI)**	**Adjustment factors**	**Comments and Star Rating**
Park et al (2009). Norfolk, UK. Cohort recruited 1993-1997.	Recruited from age-sex registers of general practices as part of EPIC study. Individuals with history of cancer excluded, leaving 11,166 men and 13,078	Health and lifestyle questionnaire at baseline asked about no. of drinks per week of different beverages. Also FFQ and 7-day food diaries.	Non-drinkers >0 to <7 7 to <14 14 to <21 ≥21 Beer None >0 to <7 ≥ 7 Wine None >0 to <7 ≥ 7 Sherry None >0 to <7 ≥ 7 Spirits None >0 to <7 ≥ 7	407	1.0 (ref) 0.91 (0.69-1.21) 0.74 (0.52-1.07) 0.92 (0.60-1.42) 0.70 (0.44-1.13) 1.00 0.89 (0.71-1.13) 1.24 (0.87-1.78) 1.00 0.90 (0.72-1.12) 0.61 (0.40-0.94) 1.00 0.92 (0.74-1.13) 0.88 (0.45-1.72) 1.00 0.94 (0.76-1.16) 1.02 (0.68-1.51)	Age, sex, BMI, smoking, family history of CRC, physical activity, educational status, intakes of energy, folate, fibre, fat, calcium, total meat and processed meat.	HRs and 95% Cis estimated using Cox proportional hazards models. 8*

Table 2. Cohort studies of consumption of alcoholic beverages and colorectal cancer							
Reference, location, name of study	Cohort description (No. in analysis)	Exposure assessment	Exposure categories	No. of cases	Population Attributable Factor (PAF)for alcohol intake and colorectal cancer alone	Adjustment factors	Comments and Star Rating
Dartois et al (2014)	Set up in 1990 to investigate cancer risk factors. For the study of 5 lifestyle habits and cancer risk, population for analysis was 64,732 women aged 432 to 68 at baseline	Self-administered questionnaires sent every 2-3 years to ask about health status and lifestyle. "Validation studies, conducted to determine the accuracy of the reported anthropometric measurements and dietary data, demonstrated the reliability of the reported data."	Health index construction based on alcohol intake alone: Full (1 point) <1 Partial (0.5 points): 1or 2 Poor (0 point): ≥2 drinks/day I unit of alcohol = 10g	481	6.6 (-2.9 to 16.0)	Smoking status, BMI, fruit and vegtable consumption, recreational physical activity.	The PAF for all five characteristics was 12.8 (-2.4 to 27.4)

Table 3. Case-control studies of consumption of alcoholic beverages and colorectal cancer							
Reference, location, period	**Characteristics of cases**	**Characteristics of controls**	**Exposure assessment**	**Exposure categories**	**Odds Ratio and confidence intervals (95% CI)**	**Adjustment factors**	**Comments and star rating**
Crockett et al (2011) North Carolina	From urban, suburban and rural areas in 33 counties in NC, aged between 40 and 80, held NC driver's licence or identification card, could complete an interview in English and were capable of being interviewed. n=1033	As for cases. n=1011	Study data collected by trained nurse inverviewers during in-person interviews using a validated questionnaire. Participants asked whether they drank beer, wine or spirits, and frequency and amount of consumption 1 year prior to diagnosis (cases) or at time of interview (controls)	**All alcohol** None Moderate (>0 - ≤14 g/day) Heavy (>14 g/day) **Beer intake** None Moderate Heavy **Wine intake** None Moderate Heavy **Spirit intake** None Moderate Heavy	Distal CRC: 1.00 0.66 (0.53-0.82) 0.93 (0.70-1.23) 1.00 0.76 (0.60-0.96) 1.16 (0.79-1.70) 1.00 0.69 (0.56-0.86) 0.83 (0.50-1.36) 1.00 0.83 (0.66-1.05) 1.46 (0.92-2.36)	Age, sex, race, smoking status, BMI, education, red meat intake, use of NSAIDs and family history of CRC.	Diagnosis of cancer in cases confirmed by obtaining reports for review by study pathologist. Logistic regression used to estimate ORs. Cases and controls differered significantly in several factors. Cases also had higher proportion of non-drinkers and lower proportion of moderate drinkers. Retrospective study – residual confounding possible 8*

Table 3. Case-control studies of consumption of alcoholic beverages and colorectal cancer							
Reference, location, period	**Characteristics of cases**	**Characteristics of controls**	**Exposure assessment**	**Exposure categories**	**Relative Risk and confidence intervals (95% CI)**	**Adjustment factors**	**Comments and star rating**
Zhivotovskiy et al (2012) South-East Siberia	n = 210 From database of blood donor records, with distribution of ABO and Rh blood groups to reflect the general opulation of Kemerovo Region and Southern Siberia	n = 185 From medical records from 2,063 cancer patients living in Kermerovo and neighbouring settlements for ten year perod. All cases histopatholog-ically confirmed	By means of questionnaire gathered at interview	Alcohol: Non-drinkers vs drinkers Beer, wine, liquor: Non-drinkers vs drinkers and 3 levels between	Alcohol consumption: 8.73 (5.49-13.87) Beer: 9.24 (5.14-16.61) Wine: 1.51 (0.84-2.72) Liquor: 9.37 (5.92-14.82)	Not clear whether adjustment made.	Statistical analysis using Med Calc v.9.6.4.0 All differences between continuous variables evaluated by Mann-Witney test and for categorical variables, by χ^2 test Multiple comparisons so only P value <0.0005 considered statistically significant. 5*

Table 3. Case-control studies of consumption of alcoholic beverages and colorectal cancer							
Reference, location, period	**Characteristics of cases**	**Characteristics of controls**	**Exposure assessment**	**Exposure categories**	**Odds ratios and confidence intervals (95% CI)**	**Adjustment factors**	**Comments and star rating**
Zhao et al, 2012. Newfoundland and Labrador, Canada. 1999 – 2003	702 newly diagnosed with CRC in 1999-2003 identified from Newfoundland cancer registry. Pathology reports used to verify diagnosis.	Selected using random digit dialling, frequecy matched with cases by sex and age (5-year strata), aged 20 to 74. 717 in total, participation rate 44.8%.	Food frequency questionnaire filled in by participants.Specific questions asked about beer, wine, fortified wine or spirits consumed per day or per week. Alcohol drinkers regarded as those if they ever consumed any alcohol once a week for ≥ 6 months. BMI estimated from height and weight questions.	Non-drinker: non-drinkers or < one drink per day Drinker: (drinkers who ever consumed any alcoholic beverage once a week for 6 months or longer)	1.0 0.9 (0.7-1.2)[a] 1.0 (0.7-1.3)[b] 2.2 (1.2-4.0)[b c] 0.8 (0.6-1.1)[b d]	Age, sex, rural/urban, education, marriage, family history of CRC, diabetes, cholesterol, aspirin, fruits, BMI, laxatives, calcium and random effect of census area	a: unadjusted b: adjusted c: obese (BMI ≥ 30) d: non-obese 6*

Table 3. Case-control studies of consumption of alcoholic beverages and colorectal cancer							
Reference, location, period	**Characteristics of cases**	**Characteristics of controls**	**Exposure assessment**	**Exposure categories**	**Odds ratios and confidence intervals (95% CI)**	**Adjustment factors**	**Comments and star rating**
Kim et al (2012) S. Korea Patients admitted to hospital between 1998 and 2004	Patients at 2 university hospitals with confirmed diagnosis of CRC. Reconfirmed by path reports and chart review. Aged 30-79 yrs.	Hospitalised during same period as cases for wide spectrum of nonneoplastic conditions. Aged 30-79.	Structured questionnaire on diet and lifestyle characteristics administered by trained nurse interviewer.	<5, 5-30, ≥30 g/day	1.0 1.22 (0.88-1.69) 1.76 (1.26-2.46) p trend<0.001	Age, sex, family history, multivitamin use, BMI, smoking status, total energy intake, folate intake.	MTHFR genotype on dNA from venous blood collected at time of interview. 6*

Table 3. Case-control studies of consumption of alcoholic beverages and colorectal cancer							
Reference, location, period	**Characteristics of cases**	**Characteristics of controls**	**Exposure assessment**	**Exposure categories**	**Odds Ratio and confidence intervals (95% CI)**	**Adjustment factors**	**Comments**
Austin et al (2008) N. Carolina Nov 2001-Dec 2002	Outpatients who underwent colonoscopy at the University of N Carolina hospitals and found to have one or more adenomatous polyps. No history of colon cancer (or adenoma), inflammatory bowel dissease or previous colon resection. Excluded if had a polyposis.	As cases, except had no adenomatous polyps on colonoscopy.	FFQ and lifestyle questionnaire administered over phone by trained interviewer.	Abstainers (0 drinks/wk) n =199 Moderate drinkers (0 - <7 drinks/wk) n = 299 Heavy drinkers (≥ 7 drinks/wk) n = 147	Interaction variable for smoking and alcohol was significant (p=0.023). Never smoked: Heavy drinkers vs. abstainers 3.08 (1.50-6.32) Heavy drinkers vs. moderate drinkers 3.11 (1.40-6.92). Smoked 1-14 years: Heavy drinkers vs. abstainers 2.56 (0.81-8.11) Heavy drinkers vs. moderate drinkers 2.61 (1.04-6.51) Smoked at least 15 years: Abstainers vs. moderate drinkers 2.04 (0.91-4.59) Heavy drinkers vs. moderate drinkers 0.73 (0.27-1.97)	Sex, age, BMI, NSAID use, smoking. Never smoked, n = 332 Smoked 1-14 years, n = 141 Smoked ≥ 15 years, n= 172	Men 59% cases/ 39% controls. 5*

Table 3. Case-control studies of consumption of alcoholic beverages and colorectal cancer							
Reference, location, period	**Characteristics of cases**	**Characteristics of controls**	**Exposure assessment**	**Exposure categories**	**Relative Risk and confidence intervals (95% CI)**	**Adjustment factors**	**Comments**
Acott et al (2008) Arkansas, U.S. Diagnosis Jan 1997-Dec 2006	Veterans, did not have premalignant lesions, genetic CRC syndromes, a prior history of inflammatory bowel disease, any other concurrent malignancy.	As for cases but previous or current users of tobacco and/or alcohol.	Self-assessment in nursing admission records, preoperative surgical screening reports or from PCP reports within 30 days of admission for surgical intervention.	Never users of tobacco or alcohol (reference group). Past use greater than 1 year prior. Current use.	Compared to reference group: Current alc and tob: 1.09 (1.0-1.9) Current alc, prev tob: 1.04 (1.0-1.8) Current alc, never tob: 2.66 (1.3-3.4) Prev alc, current tob: 1.15 (1.0-2.0) Prev alc, prev tob: 0.89 (0.5-1.5) Prev alc, never tob: 0.95 (1.0-2.0) Never alc, current tob: 0.82 (0.4-1.4) Never alc, prev tobacco 0.63 (0.4-1.0)	Age, sex, BMI, ?other	Editorial errors in paper. Total patient population = 335 (332 male and 3 female). Only 47 had no history of either alcohol or tobacco use. 83% Caucasian. 3*

Table 3. Case-control studies of consumption of alcoholic beverages and colorectal cancer

Reference, location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	Odds Ratio and confidence intervals (95% CI)	Adjustment factors	Comments
Poynter et al (2009). US, Canada, Australia. Cases diagnosed from July 1998 – July 2005.	2253 cases recruited from 6 centres of CRC Family Register using population-based cancer registers. Some centres recruited all cases and others oversampled cases with family history of CRC or early age at onset. All interviewed within 3 yrs of diagnosis.	4,486 unaffected siblings with data abstracted from the Colon CFR central data repository.	Questionnaire administered at recruitment. Alcohol data reported for ages 20-30, 30-50 and >50 years. Evaluated alcohol consumption during time period corresponding to age at completion of questionnaire.	Drinks/week None (ref) 1-4 5-11 12+	 1.00 1.10 (0.93-1.30) 1.17 (0.99-1.38) 1.21 (1.03-1.44) p for trend = 0.02	Age, sex, income, education, BMI, ethnicity, physical activity and regular NSAID use	In males who consumed alcohol, 28% beer, 9% wine, 9% spirits,, 54% more than one type. In women, 10% beer, 38% wine, 13% spirits and 39% more than one type.

Table 3. Case-control studies of consumption of alcoholic beverages and colorectal cancer							
Reference, location, period	**Characteristics of cases**	**Characteristics of controls**	**Exposure assessment**	**Exposure categories**	**Relative Risk and confidence intervals (95% CI)**	**Adjustment factors**	**Comments**
Park et al (2010) UK To 2003-2007.	Members of UK Dietary Cohort Consortium: 7 established UK cohorts. Free of cancer at date of food diary commencement and developed CRC ≤ 12 months after this. Cases ascertained by record linkage with local cancer registries and ONS. 579 cases in total	Members of UK Dietary Cohort Consortium: 7 UK cohorts, n = 153,000. 4 matched controls per case. Matched by sex, age at enrolment (± 3 yrs) and month of diary completion (± 3 mnths). 1996 controls	4-day or 7-day food diaries completed at recruitment or during subsequent monitoring phase. In 4/7 studies, FFQs administered first.	Non-drinkers >0 - <5 g/day 5 - <15 g/day 15 - <30 g/day 30 - <45 g/day ≥45 g/day	1.16 (0.88-1.53) 1.00 0.91 (0.67-1.24) 0.90 (0.65-1.25) 1.02 (0.66-1.58) 1.19 (0.75-1.91) P for trend = 0.82	Age, weight, height, smoking status, social class, intakes of energy, fibre, folate, red meat and processed meat.	6*

Table 3. Case-control studies of consumption of alcoholic beverages and colorectal cancer							
Reference, location, period	**Characteristics of cases**	**Characteristics of controls**	**Exposure assessment**	**Exposure categories**	**p value for difference between cases and controls**	**Adjustment factors**	**Comments**
Ferrari et al, 2012 Europe	1269 subjects from 10 European countries who developed CRC in average 7.2 year period	2107 randomly selected controls by incidence density sampling among same cohort members alive and free of cancer at the time of case diagnosis, matched by sex, age, centre and date of blood sample collection	Alcohol consumption over last 12 months collected at recruitment by validated country-specific questionnaires	Mean alcohol consumption of total alcohol, wine, beer, spirits	Total alcohol (g/day): Cases: 20.2 (0.8-52.4) Controls: 17.4 (0.8-45.5) p = 0.16 Wine: p = 0.94 Beer p = 0.02 Spirits p = 0.20	Matching as given left.	Study designed to investigate effects of polymorphisms on alcohol consumption and CRC risk

Table 4. Cohort studies of consumption of alcoholic beverages and colorectal cancer							
Reference, location, name of study	**Cohort description (No. in analysis)**	**Exposure assessment**	**Exposure categories**	**No. of cases**	**Relative Risk and confidence intervals (95% CI)**	**Adjustment factors**	**Comments and Star Rating**
Bongaerts et al.(2011) Netherlands. 1986-1993.	58,279 men and 62,573 women aged 55-69 years at baseline. Case-cohort approach used following up all cases but only subcohort of 4774 cases used to estimate person years at risk	Self-administered semi-quantitative food frequency questionnaire	Abstainers < 30 g/day ≥ 30 g/day	594	Total study population 1.00 0.83 (0.63-1.08) 0.91 (0.59-1.41) *ADH1C*1/*1* 1.00 (ref) 0.77 (0.49-1.20) 0.98 (0.51-1.88) *ADH1C*1/*2* 1.06 (0.65-1.73) 0.87 (0.57-1.33) 0.98 (0.53-1.83) *ADH1C*2/*2* 1.29 (0.68-2.43) 1.20 (0.75-1.91) 0.98(0.42-2.32)	Age, sex, family history of CRC, BMI, non-occupational physical activity, total energy intake and energy-adjusted intakes of fat, fibre, and calcium.	No differences in mean daily alcohol consumption and confounding variables between cases and subcohort members.