Park, JY; Dahm, CC; Keogh, RH; Mitrou, PN; Cairns, BJ; Greenwood, DC; Spencer, EA; Fentiman, IS; Shipley, MJ; Brunner, EJ; Cade, JE; Burley, VJ; Mishra, GD; Kuh, D; Stephen, AM; White, IR; Luben, RN; Mulligan, AA; Khaw, KT; Rodwell, SA (2010) Alcohol intake and risk of colorectal cancer: results from the UK Dietary Cohort Consortium. British journal of cancer, 103 (5). pp. 747-56. ISSN 0007-0920 DOI: 10.1038/sj.bjc.6605802

Downloaded from: http://researchonline.lshtm.ac.uk/176010/

DOI: 10.1038/sj.bjc.6605802

Usage Guidelines
Please refer to usage guidelines at http://researchonline.lshtm.ac.uk/policies.html or alternatively contact researchonline@lshtm.ac.uk.

Available under license: http://creativecommons.org/licenses/by-nc-nd/2.5/
Alcohol intake and risk of colorectal cancer: Results from the UK Dietary Cohort Consortium

JY Park1, CC Dahm2, RH Keogh2–3, PN Mitrou3, BJ Cairns4, DC Greenwood5, EA Spencer4, IS Fentiman6, MJ Shipley7, EJ Brunner5, JE Cade5, VJ Burley6, GD Mishra8, D Kuh8, AM Stephen9, IR White3, RN Luben1, AA Mulligan2, K-T Khaw1,6 and SA Rodwell2,10

1Department of Public Health and Primary Care, University of Cambridge, Cambridge CB1 8RN, UK; 2Department of Public Health and Primary Care, Medical Research Council Centre for Nutritional Epidemiology in Cancer Prevention and Survival, University of Cambridge, Cambridge CB1 8RN, UK; 3Medical Research Council Biostatistics Unit, Institute of Public Health, University of Cambridge, Cambridge CB2 0SR, UK; 4Cancer Epidemiology Unit, University of Oxford, Oxford OX3 7LF, UK; 5Centre for Epidemiology and Biostatistics, Faculty of Medicine and Health, University of Leeds, Leeds LS2 9JT, UK; 6Academic Oncology Unit, Guy’s Hospital, London, SE1 9RT, UK; 7Department of Epidemiology and Public Health, University College London, London WC1E 6BT, UK; 8Department of Epidemiology and Public Health, Medical Research Council Unit for Lifelong Health and Ageing, University College London, 33 Bedford Place, London WC1B 3JU, UK; 9Medical Research Council Human Nutrition Research, Elsie Widdowson Laboratory, Cambridge CB1 9NL, UK

BACKGROUND: Epidemiological studies have suggested that excessive alcohol intake increases colorectal cancer (CRC) risk. However, findings regarding tumour subsites and sex differences have been inconsistent.

METHODS: We investigated the prospective associations between alcohol intake on overall and site- and sex-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 food frequency questionnaire (FFQ).

RESULTS: Compared with individuals in the lightest category of drinkers (>0–<5 g per day), the multivariable odds ratios of CRC were 1.16 (95% confidence interval (95% CI): 0.88, 1.53) for non-drinkers, 0.91 (95% CI: 0.67, 1.24) for drinkers with 5–<15 g per day, 0.90 (95% CI: 0.65, 1.25) for drinkers with 15–<30 g per day, 1.02 (95% CI: 0.66, 1.58) for drinkers with 30–<45 g per day and 1.19 (95% CI: 0.75, 1.91) for drinkers with ≥45 g per day. No clear associations were observed between site-specific CRC risk and alcohol intake in either sex. Analyses using FFQ showed similar results.

CONCLUSION: We found no significantly increased risk of CRC up to 30 g per day of alcohol intake within the UK Dietary Cohort Consortium.

British Journal of Cancer (2010) 103, 747–756. doi:10.1038/sj.bjc.6605802 www.bjcancer.com
Published online 20 July 2010
© 2010 Cancer Research UK

Keywords: colorectal cancer; alcohol intake; prospective cohort study; food diary; food frequency questionnaire

The descriptive epidemiology of colorectal cancer (CRC) shows significant geographical variation in incidence rates worldwide and provides strong circumstantial evidence that lifestyle has an important role in colorectal carcinogenesis (Stewart and Kleihues, 2003). Alcohol drinking is one such important lifestyle factor (Ferrari et al., 2003), and for a number of nutrients, food frequency questionnaires (FFQs) may have both large random and systematic measurement errors (Bingham et al., 2003; Prentice, 2003; Schatzkin et al., 2003), and for a number of nutrients, food

In the United Kingdom, 30 g of alcohol is equivalent to 3–4 units, 1 unit being ~8 g of alcohol (The National Health Service, 2010). Associations between alcohol intake and CRC risk according to anatomical subsites of the colorectum remain unclear (Chen et al., 2005; Akhter et al., 2007; Ferrari et al., 2007; Bongaerts et al., 2008; Lim and Park, 2008), although it is believed that colon and rectal cancers have different aetiologies (Li and Lai, 2009), and that within the colon, proximal and distal sites have biologically distinct functions (Bufill, 1990; Lindblom, 2001). Evidence has mostly been available for men with high alcohol intake (Allen et al., 2009), and risks of CRC with alcohol intake for men and women have not been consistent.

Many epidemiological studies which investigated an effect of alcohol on health have relied on self-reports of alcohol intakes. Owing to its simplicity in use and convenience in administration, food frequency questionnaires (FFQs) have been mostly used in alcohol intake assessment (Feunekes et al., 1999). However, as a nutritional instrument, FFQs may have both large random and systematic measurement errors (Bingham et al., 2003; Prentice, 2003; Schatzkin et al., 2003), and for a number of nutrients, food

Correspondence: Professor K-T Khaw; E-mail: kk101@medschl.cam.ac.uk

Professor Rodwell (professionally known as Bingham) read an initial draft of this manuscript, but sadly passed away in June 2009.

Received 13 April 2010; revised 9 June 2010; accepted 18 June 2010; published online 20 July 2010.
Alcohol intake and CRC risk
JY Park et al

Table 1 Description of studies participating in the UK Dietary Cohort Consortium and summary of alcohol intake among colorectal cancer cases and matched controls

| Study                  | Age range at baseline (years) | Size of the cohort at baseline | Assessment of alcohol intake | CRC cases | Mean alcohol intake for cases (s.d.) | CRC controls | Mean alcohol intake for controls (s.d.) |
|------------------------|------------------------------|--------------------------------|------------------------------|-----------|-------------------------------------|--------------|----------------------------------------|
| EPIC-Norfolk           | 40–77                         | 25 000                         | 7DD/FFQ                      | 179       | 15.2 (18.6)                         | 15.5 (21.1)  | 7.2 (10.8)                             |
| EPIC-Oxford            | 32–84                         | 65 429                         | 7DD/FFQ                      | 39        | 17.0 (17.5)                         | 21.0 (27.8)  | 8.1 (10.8)                             |
| Guernsey Study         | 39–78                         | 61 277                         | 4DD                          | 28        | 6.3 (7.3)                           | 9.8 (12.5)   | 9.1 (13.3)                             |
| Oxford Vegetarian Study| 26–79                         | 11 140                         | 4DD                          | 24        | 39.1 (66.1)                         | 28.9 (23.7)  | 13.6 (11.6)                           |
| MRC National Survey of Health and Development (NSHD) | 43                             | 53 627                         | 7DD                          | 16        | N/A                                 | N/A          | N/A                                    |
| UK Women’s Cohort Study (UKWCS) | 44–78                        | 35 792                         | 4DD/FFQ                      | 25        | N/A                                 | 8.1 (11.3)   |                                        |
| Whitehall II           | 41–62                         | 10 308                         | 7DD/FFQ                      | 12        | 25.8 (26.3)                         | 22.2 (20.4)  | 8.8 (10.4)                             |

Abbreviations: CRC = colorectal cancer; EPIC = European Prospective Investigation into Cancer and Nutrition; MRC = Medical Research Council; 7DD = 7-day food diary; 4DD = 4-day food diary; FFQ = food frequency questionnaire; N/A = not applicable. *A t-test indicated that there was no statistically significant difference in mean alcohol intake between cases and controls.

Case ascertainment

Case patients were individuals who were free of cancer (except non-melanoma skin cancer) at the date of food diary commencement and who developed CRC at least 12 months after the date of diary commencement and before the end of the study period, defined for each study centre by the latest date of complete follow-up for both cancer incidence and vital status.

The last dates of follow-up varied between cohorts, from 31 December 2003 to 1 January 2007. Individuals with self-reported or registry-reported prevalent cancer (except non-melanoma skin cancer) were omitted from the study. Incident CRC cases (International Statistical Classification of Diseases and Related Health Problems (ICD) 10th Revision, C18–20) were ascertained by record linkage with local cancer registries and the United Kingdom Office for National Statistics, which provided notification of all cancer registrations and deaths by cause for the cohort. For this study, CRC cases were classified according to anatomical subsites: colon cancers were defined as tumours in the caecum, appendix, ascending colon and hepatic flexure, transverse colon, splenic flexure (proximal, C18.0–18.5; ICD 10th Revision), and descending and sigmoid colon (distal, C18.6–C18.7), as well as tumours that were overlapping or unspecified (C18.8 and C18.9). Cancer of the rectum included tumours occurring at the rectosigmoid junction (C19) and rectum (C20). Overall CRC was defined as a combination of all colon and rectal cancer cases.

Selection of matched controls

Cases were matched within their respective cohort to four controls each, with the exception of some cases from EPIC-Oxford, the Guernsey Study and the Oxford Vegetarian Study who were matched to two controls, and some from the UKWCS who were matched to five controls. Matched controls were selected at random from the appropriate stratum of the set of all cohort members who were free of CRC at the end of follow-up (due to death or censoring) and free of all cancer (except non-melanoma skin cancer) at the date of diary commencement. Matching criteria were sex, age at enrolment (±3 years) and month of diary completion (±3 months). Follow-up time for matched controls was also required to be at least as long as that for the case, with follow-up time defined as the time from the date of diary commencement to the date of CRC diagnosis for cases and the time from date of diary commencement until the end of follow-up.

Materials and methods

Study population

The UK Dietary Cohort Consortium comprises seven established UK cohorts (namely EPIC-Norfolk, EPIC-Oxford, Guernsey Study, Oxford Vegetarian Study, MRC National Survey of Health and Development (NSHD), the UK Women’s Cohort Study (UKWCS) and Whitehall II; Table 1) with a total cohort size of 153,000 individuals. The methods of recruitment, study design and ethical approval have been described for each of these cohorts in detail elsewhere (Appleby et al, 1999; Day et al, 1999; Davey et al, 2003; Cade et al, 2004; Allen et al, 2005; Marmot and Brunner, 2005; Wadsworth et al, 2006).

Diaries have been shown to provide measurements that are more strongly associated with biomarker data (Bingham et al, 1997, 2008; Day et al, 2001). Furthermore, it has been suggested that food diaries can capture a more complicated individual dietary intake more accurately (Bingham et al, 2003). However, less is known about whether food diaries provide a superior measure of food intake for infrequently or episodically consumed items, such as alcoholic drinks, compared with the FFQs. Therefore, it is important to compare the effects of alcohol intake on CRC risk using food diaries and FFQs.

In the United Kingdom, government recommendations on alcohol intake are for men to consume no more than 3–4 units per day (<32 g per day) and for women to consume no more than 2–3 units per day (<24 g per day) (The National Health Service, 2010); however, the average annual alcohol intake in the United Kingdom now exceeds the European Union average (Department of Health, 2009) and CRC is the second major cause of cancer death in the country (Westlake and Cooper, 2008). Worldwide, more than one million incident cases were recorded in 2002 (WCRF/AICR, 2007). Hence, even a moderate association between alcohol intake and CRC risk may have important public health implications.

The aim of this study was to examine the relationship between alcohol intake and overall and site-specific CRC risks, including differences in sex-specific risks, using a case-control study nested within the UK Dietary Cohort Consortium, from which nutritional data were ascertained by food diaries and FFQs at baseline.
for controls. A total of 579 CRC cases and 1996 matched controls were available for analysis.

**Diet and lifestyle assessment**

Each cohort collected dietary information using 4-day (Guernsey, Oxford Vegetarian Study, UKWCS) (Appleby et al, 1999; Cade et al, 2004) or 7-day food diaries (EPIC-Norfolk, NSHD, EPIC-Oxford, Whitehall II) (Bingham et al, 2001; Brunner et al, 2001; Davey et al, 2003; Wadsworth et al, 2006) completed on consecutive days at recruitment to the study or during a subsequent monitoring phase. Participants were asked to record in detail all the foods and beverages they consumed, prompted by time slots such as ‘Mid-morning – between breakfast time and lunchtime’ and also by photographs of standard plates with three different portion sizes of representative foods to help participants estimate the amounts they consumed (Bingham et al, 2001). Information on age, sex, height, weight, smoking status, educational level, social class, physical activity and family history of CRC, were collected either by trained researchers or in questionnaires administered before the completion of the food diary. In four of the seven studies (namely EPIC-Norfolk, EPIC-Oxford, UKWCS and Whitehall II), FFQs were also administered before this data collection, and were available for analysis from most participants in these cohorts. The FFQs were based on that used in the US Nurses’ Health Study, listed from 127 to 217 items, and have been validated for use in the United Kingdom (Bingham et al, 1997; Brunner et al, 2001; Cade et al, 2004).

The majority of data from the food diaries were coded to give nutrient intakes and food group information using data entry program Data Into Nutrients for Epidemiological Research (DINER) developed in the EPIC-Norfolk cohort (Welch et al, 2001). A total of 107 UKWCS food diaries were coded and processed using the Diet and Nutrition Tool for Evaluation (DANTE) program (Cade et al, 2006). We compared 100 food diaries coded under both systems and found good agreement between DANTE and DINER for most nutrients, although the geometric mean intake of alcohol from DANTE was 7% higher (95% confidence interval (95% CI): 3–11%) than from DINER. A total of 579 incident CRC cases and 1996 matched controls were available for analysis. The majority of data from the food diaries were coded to give nutrient intakes and food group information using data entry program Data Into Nutrients for Epidemiological Research (DINER) developed in the EPIC-Norfolk cohort (Welch et al, 2001). A total of 107 UKWCS food diaries were coded and processed using the Diet and Nutrition Tool for Evaluation (DANTE) program (Cade et al, 2006). We compared 100 food diaries coded under both systems and found good agreement between DANTE and DINER for most nutrients, although the geometric mean intake of alcohol from DANTE was 7% higher (95% confidence interval (95% CI): 3–11%) than from DINER.

**Alcohol intake assessment**

For the food diaries completed by all centres, beer (stout, bitter, lager; keg, draught, bottled, canned; low alcohol, strong, home-made; number of pints, bottles, cans), cider (sweet, dry, vintage, low alcohol; number of pints, bottles, cans), spirits (what sort: e.g., whisky, gin, vodka, rum; at home or in a pub; single measures as in pub), wine, sherry, port (white, red; sweet, medium, dry; low alcohol; glasses) were assessed for alcohol intake. The FFQs from EPIC-Norfolk, EPIC-Oxford, UKWCS and Whitehall II were designed to measure a participant’s usual food intake. The FFQs were also administered before this data collection, and were available for analysis from most participants in these cohorts. The FFQs were based on that used in the US Nurses’ Health Study, listed from 127 to 217 items, and have been validated for use in the United Kingdom (Bingham et al, 1997; Brunner et al, 2001; Cade et al, 2004).

The majority of data from the food diaries were coded to give nutrient intakes and food group information using data entry program Data Into Nutrients for Epidemiological Research (DINER) developed in the EPIC-Norfolk cohort (Welch et al, 2001). A total of 107 UKWCS food diaries were coded and processed using the Diet and Nutrition Tool for Evaluation (DANTE) program (Cade et al, 2006). We compared 100 food diaries coded under both systems and found good agreement between DANTE and DINER for most nutrients, although the geometric mean intake of alcohol from DINER was 7% higher (95% confidence interval (95% CI): 3–11%) than from DANTE. A total of 579 incident CRC cases and 1996 matched controls were available for analysis. The majority of data from the food diaries were coded to give nutrient intakes and food group information using data entry program Data Into Nutrients for Epidemiological Research (DINER) developed in the EPIC-Norfolk cohort (Welch et al, 2001). A total of 107 UKWCS food diaries were coded and processed using the Diet and Nutrition Tool for Evaluation (DANTE) program (Cade et al, 2006). We compared 100 food diaries coded under both systems and found good agreement between DANTE and DINER for most nutrients, although the geometric mean intake of alcohol from DINER was 7% higher (95% confidence interval (95% CI): 3–11%) than from DANTE.

**Statistical analysis**

Conditional logistic regression models were used to estimate odds ratios (ORs) and 95% CIs for the CRC risk according to alcohol intake, with adjustment for potential confounding variables. The participants were categorised into six groups according to their baseline alcohol intake, with the lightest category of drinkers (>0–<5 g per day) as a reference group: 0 (non-drinkers), ≥5–<15, 15–<30, 30–<45, ≥45 g per day. An initial unadjusted model was first created to estimate ORs for CRC across categories of alcohol intake. As the matching of cases and controls by age was not exact, the conditional logistic regression models were adjusted for age in years to control for any residual confounding. Multivariable model 1 also included for alcohol intake (kcal per day), folate (µg per day), dietary fibre (g per day), red meat (g per day), and processed meat (g per day) in addition to height (m), weight (kg), smoking status (never, former, current) and social class (six categories). There were some missing data within studies, with ~1% of individuals missing weight, height and smoking status, and ~5% missing social class, all of which were recorded in all studies. The distribution of alcohol intake among individuals with and without these missing data was similar. For these variables, missing values were assumed to be missing at random and were imputed using multiple imputation. In all, 10 imputed data sets were created and multivariable models were fitted using the ‘ice’ (Royston, 2005) and ‘mim’ (Carlin, 2008) packages in STATA (StatCorp, College Station, TX, USA). Multivariable model 2 adjusted for physical activity (inactive, moderately inactive, moderately active and active) and educational level (none, GCSE (completed to age 15 years), A Level (completed to age 17 years) and degree level) in addition to the adjustments in multivariable model 1. Data on physical activity level were not available for NSHD and the Guernsey Study, and information on educational level was not available for the Oxford Vegetarian Study. The effects of adjustment for these variables were assessed by fitting multivariable models 1 and 2 using the subset of participants (458 cases and 1734 controls) with complete information on physical activity and educational level. Sex-specific and anatomical subsite-specific models were also fitted using multivariable models 1 (579 cases and 1996 controls) and 2 (458 cases and 1734 controls). Tumours that were overlapping or unspecified were not included in site-specific analyses of the proximal and the distal colon cancer (n = 60).

To investigate whether different nutritional instruments might alter our results, we repeated the analyses using FFQ data. Dietary data obtained from FFQs were available for participants in EPIC-Norfolk, EPIC-Oxford, the UKWCS and Whitehall II (496 cases and 1734 controls). Tumours that were overlapping or unspecified were not included in site-specific analyses of the proximal and the distal colon cancer (n = 60).

**RESULTS**

A total of 579 incident CRC cases and 1996 matched controls were available for analysis from the 7 participating UK cohorts. Of these cancer cases, 380 were located in the colon and 199 in the rectum. There were no statistically significant differences in the means of alcohol intake between cases and controls in each cohort (Table 1).

Table 2 presents participant characteristics according to categories of alcohol intake. Among drinkers, 82% consumed <30 g per day alcohol. The average alcohol intake was ~17 g per day.
### Distribution of participant characteristics by categories of alcohol intake as assessed by food diaries, shown separately for men and women

| Distribution of participant characteristics by categories of alcohol intake as assessed by food diaries, shown separately for men and women |
|---------------------------------------------------------------|
| **Baseline alcohol intake**                                    |
| Non-drinkers        | >0–<5 g per day | >5–<15 g per day | >15–<30 g per day | >30–<45 g per day | ≥45 g per day | **P-value** |
| All cases/controls (n) | 187/574 | 112/405 | 116/443 | 86/328 | 40/135 | 38/111 |
| **Men** cases/controls (n) | 68/200 | 39/175 | 55/224 | 45/188 | 28/96 | 31/97 |
| Alcohol at baseline (g per day) | 0.0 | 2.7 (1.4) | 9.5 (2.9) | 21.8 (4.2) | 36.6 (4.2) | 66.1 (24.4) |
| Age (years) | 64.2 (8.4) | 63.1 (8.3) | 61.7 (9.8) | 61.5 (9.1) | 60.0 (8.5) | 59.9 (9.2) |
| Height (m) | 1.73 (0.1) | 1.73 (0.1) | 1.75 (0.1) | 1.75 (0.1) | 1.75 (0.1) | 1.75 (0.1) |
| Weight (kg) | 77.9 (11.7) | 80.8 (13.2) | 78.1 (11.2) | 79.7 (10.3) | 80.7 (11.1) | 82.4 (11.6) |
| **BMI (kg m⁻²)** | 26.1 (3.4) | 26.9 (4.0) | 25.6 (3.2) | 26.1 (3.0) | 26.2 (2.9) | 26.8 (3.0) |
| Cigarette smoking status (%) | | | | | | |
| Never | 41.1 | 32.7 | 35.4 | 35.2 | 33.1 | 21.4 |
| Former | 49.1 | 60.7 | 57.4 | 55.4 | 53.2 | 60.3 |
| Current | 9.8 | 6.6 | 7.2 | 9.4 | 13.7 | 18.3 |
| Total energy (kcal) | 2077 (546) | 2117 (470) | 2218 (479) | 2225 (486) | 2345 (478) | 2478 (545) |
| Physical activity (%) | | | | | | |
| Low | 67.3 | 56.9 | 60.9 | 47.6 | 61.7 | 63.1 |
| High | 32.7 | 43.1 | 39.1 | 52.4 | 38.3 | 36.9 |
| Educational level (%) | | | | | | |
| Low | 58.0 | 43.1 | 41.3 | 42.3 | 37.9 | 33.9 |
| High | 42.0 | 56.9 | 58.7 | 57.7 | 62.1 | 66.1 |
| Social class | | | | | | |
| Non-manual | 50.2 | 59.6 | 64.3 | 76.3 | 80.0 | 77.0 |
| Manual | 49.8 | 40.4 | 35.7 | 23.7 | 20.0 | 23.0 |
| Family history of colorectal cancer (%) | | | | | | |
| No | 93.5 | 91.1 | 94.2 | 95.5 | 91.9 | 93.6 |
| Yes | 6.5 | 8.9 | 5.8 | 4.5 | 8.1 | 6.4 |
| Folate intake (µg per day) | 282 (90) | 274 (69) | 293 (82) | 294 (85) | 308 (86) | 314 (92) |
| Fibre intake (g per day) | 17 (7) | 17 (6) | 17 (6) | 16 (6) | 16 (5) | 14 (6) |
| Red meat intake (g per day) | 33 (30) | 34 (25) | 39 (30) | 40 (27) | 40 (30) | 46 (34) |
| Processed meat intake (g per day) | 24 (24) | 27 (22) | 25 (20) | 29 (24) | 27 (23) | 30 (22) |
| **Women** cases/controls (n) | 119/374 | 73/230 | 61/219 | 41/140 | 12/39 | 7/16 |
| Alcohol at baseline (g per day) | 0.0 (0.0) | 2.5 (1.4) | 9.4 (2.9) | 21.5 (4.5) | 35.3 (8.8) | 56.9 (11.3) |
| Age (years) | 63.1 (9.7) | 62.5 (9.0) | 60.2 (9.5) | 58.7 (10.6) | 57.8 (10.9) | 59.3 (11.5) |
| Height (m) | 1.60 (0.07) | 1.61 (0.06) | 1.62 (0.07) | 1.62 (0.06) | 1.64 (0.06) | 1.60 (0.05) |
| Weight (kg) | 66.8 (13.1) | 66.9 (11.7) | 66.5 (11.0) | 65.4 (10.9) | 66.7 (10.1) | 61.2 (9.4) |
| **BMI (kg m⁻²)** | 26.1 (4.8) | 25.9 (4.3) | 25.5 (4.0) | 24.9 (4.1) | 24.8 (3.3) | 23.9 (3.7) |
| Cigarette smoking status (%) | | | | | | |
| Never | 64.5 | 59.5 | 57.1 | 53.7 | 40.0 | 19.1 |
| Former | 27.8 | 33.1 | 33.2 | 37.3 | 38.0 | 61.9 |
| Current | 7.7 | 7.4 | 9.6 | 9.0 | 22.0 | 19.1 |
| Total energy (kcal) | 1639 (418) | 1653 (334) | 1747 (369) | 1803 (372) | 1909 (354) | 1916 (269) |
| Physical activity (%) | | | | | | |
| Low | 73.7 | 68.1 | 66.0 | 68.6 | 73.8 | 65.0 |
| High | 26.4 | 32.0 | 34.0 | 31.5 | 26.2 | 35.0 |
| Educational level (%) | | | | | | |
| Low | 71.6 | 69.0 | 58.2 | 60.9 | 47.9 | 27.8 |
| High | 28.4 | 31.0 | 41.8 | 39.1 | 52.1 | 72.2 |
| Social class | | | | | | |
| Non-manual | 69.0 | 72.1 | 79.6 | 85.6 | 83.3 | 95.2 |
| Manual | 31.0 | 27.9 | 20.4 | 14.4 | 16.7 | 4.8 |
| Family history of colorectal cancer (%) | | | | | | |
| No | 91.4 | 93.9 | 87.4 | 93.9 | 93.3 | 100.0 |
| Yes | 8.6 | 6.1 | 12.7 | 6.1 | 6.7 | 0.0 |
| Folate intake (g per day) | 246 (78) | 247 (70) | 252 (70) | 250 (73) | 251 (65) | 241 (72) |
| Fibre intake (g per day) | 15 (5) | 15 (5) | 15 (5) | 15 (5) | 14 (5) | 12 (5) |
| Red meat intake (g per day) | 25 (26) | 28 (26) | 29 (26) | 33 (32) | 41 (36) | 38 (25) |
| Processed meat intake (g per day) | 16 (18) | 15 (15) | 15 (15) | 17 (17) | 17 (16) | 16 (19) |

**Abbreviation:** BMI = body mass index. *P* = number (%), and **P-values** for tests of association. **For continuous variables, analysis of variance or a Kruskal–Wallis test (for red meat and processed meat intake) was used to test whether the variables differed significantly across categories of alcohol intake. For categorical variables, **χ² tests were used to assess association with alcohol intake. Numbers do not sum to the total number of participants due to missing data. Total energy includes energy from alcohol. Low physical activity was defined as being inactive or moderately inactive, and high physical activity was defined as being moderately active or active. Educational levels were regrouped into low educational level (no qualification or General Certificate of Secondary Education (GCSE) level or equivalent) and high educational level (degree or equivalent, A-level or equivalent). Social class was classified according to the Registrar General’s occupation-based classification scheme and was dichotomised into non-manual (social class I, II and IIInm) and manual (IIIm, IV and V).**

© 2010 Cancer Research UK
Table 3  Odds ratios (95% confidence intervals) from multivariable models for colorectal cancer risk in categories of total alcohol intake as assessed by food diaries

| Alcohol intake (g per day) | Non-drinkers | >0–<5 g per day | 5–<15 g per day | 15–<30 g per day | ≥30–<45 g per day | ≥45 g per day | P for trend | P trend for drinkers |
|---------------------------|--------------|----------------|----------------|-----------------|------------------|-------------|------------|----------------------|
| Main modelsa              |              |                |                |                 |                  |             |            |                      |
| No. of all participants   | 761          | 517            | 559            | 414             | 175              | 149         |            |                      |
| Colorectal cancer cases   | 187          | 112            | 116            | 86              | 40               | 38          |            |                      |
| Age-adjusted modelb       | 1.15 (0.88–1.51) | 1.00          | 0.93 (0.69–1.26) | 0.93 (0.68–1.28) | 1.13 (0.74–1.72) | 1.29 (0.83–2.01) | 0.79 | 0.31                |
| Multivariable model 1c    | 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) | 0.82 | 0.44                |
| Male                      | 1.53 (0.98–2.41) | 1.00          | 1.06 (0.66–1.69) | 1.02 (0.63–1.66) | 1.20 (0.68–2.12) | 1.24 (0.69–2.22) | 0.78 | 0.21                |
| Female                    | 1.00 (0.70–1.42) | 1.00          | 0.84 (0.56–1.26) | 0.87 (0.55–1.37) | 0.90 (0.43–1.87) | 1.52 (0.56–4.10) | 0.72 | 0.97                |
| Sensitivity analysisd     |              |                |                |                 |                  |             |            |                      |
| Multivariable model 1c    | 1.48 (1.08–2.03) | 1.00          | 0.94 (0.66–1.33) | 1.00 (0.69–1.45) | 1.21 (0.75–1.96) | 1.41 (0.85–2.34) | 0.79 | 0.22                |
| Multivariable model 2e    | 1.49 (1.08–2.05) | 1.00          | 0.93 (0.65–1.33) | 0.98 (0.68–1.43) | 1.23 (0.76–1.99) | 1.39 (0.83–2.32) | 0.82 | 0.17                |

© 2010 Cancer Research UK
### Odds ratios (95% confidence intervals) by subsite of colorectal cancer according to alcohol intake

#### Multivariable model

| Subsite                  | Overall colorectum | Colon | Proximal colon | Distal colon | Rectum |
|--------------------------|--------------------|-------|---------------|-------------|--------|
| **Cases**                | OR (95% CI)        | P trend | OR (95% CI) | P trend | OR (95% CI) | P trend | OR (95% CI) | P trend | OR (95% CI) | P trend | OR (95% CI) | P trend |
| Male participants        |                    |        |               |             |         |         |         |             |         |         |         |         |
| Non-drinkers             | 187                | 1.16 (0.88 – 1.53) | 0.72 0.69 | 122 | 1.18 (0.83 – 1.66) | 0.85 0.63 | 60 | 1.26 (0.81 – 1.97) | 0.54 0.59 | 46 | 0.97 (0.60 – 1.56) | 0.46 0.17 |
| 0–<5 g per day           | 112                | 1.00 (Reference) |        | 74 1.00 (Reference) |        | 58 | 0.88 (0.57 – 1.39) |        | 48 | 0.91 (0.58 – 1.45) |        |
| >5–<30 g per day         | 202                | 0.91 (0.69 – 1.19) |        | 132 | 0.88 (0.63 – 1.32) |        | 52 | 1.21 (0.77 – 1.90) |        | 23 | 1.03 (0.57 – 1.86) |        |
| ≥30 g per day            | 78                 | 1.09 (0.76 – 1.58) |        | 52 | 1.12 (0.77 – 1.62) |        | 23 | 1.04 (0.57 – 1.90) |        | 23 | 1.60 (0.85 – 3.01) |        |
| Male participants        |                    |        |               |             |         |         |         |             |         |         |         |         |
| Non-drinkers             | 68                 | 1.52 (0.97 – 2.39) | 0.23 0.17 | 46 | 1.82 (1.02 – 3.22) | 0.69 0.21 | 23 | 2.46 (1.10 – 5.51) | 0.40 0.28 | 20 | 1.22 (0.56 – 2.65) | 0.86 0.42 |
| 0–<5 g per day           | 39                 | 1.00 (Reference) |        | 26 | 1.00 (Reference) |        | 20 | 1.00 (Reference) |        | 19 | 1.00 (Reference) |        |
| >5–<30 g per day         | 100                | 1.04 (0.68 – 1.58) |        | 61 | 1.05 (0.62 – 1.77) |        | 28 | 1.41 (0.67 – 2.97) |        | 22 | 0.83 (0.42 – 1.66) |        |
| ≥30 g per day            | 59                 | 1.24 (0.76 – 2.03) |        | 39 | 1.49 (0.81 – 2.74) |        | 20 | 1.93 (0.83 – 4.50) |        | 16 | 1.16 (0.50 – 2.66) |        |
| Female participants      |                    |        |               |             |         |         |         |             |         |         |         |         |
| Non-drinkers             | 119                | 1.00 (0.70 – 1.43) | 0.54 0.32 | 76 | 0.93 (0.60 – 1.46) | 0.55 0.73 | 37 | 0.93 (0.53 – 1.63) | 0.16 0.14 | 26 | 0.88 (0.46 – 1.67) | 0.19 0.27 |
| >5–<30 g per day         | 102                | 0.85 (0.59 – 1.23) |        | 71 | 0.81 (0.51 – 1.27) |        | 30 | 0.73 (0.42 – 1.28) |        | 26 | 1.05 (0.55 – 2.00) |        |
| ≥30 g per day            | 19                 | 1.03 (0.54 – 1.96) |        | 13 | 1.09 (0.49 – 2.46) |        | 3 0.52 (0.17 – 1.61) |        | 7 | 3.34 (1.11 – 10.02) |        |
| Male participants        |                    |        |               |             |         |         |         |             |         |         |         |         |
| Non-drinkers             | 147                | 1.49 (1.08 – 2.05) | 0.93 0.32 | 99 | 1.63 (1.09 – 2.43) | 0.67 0.20 | 57 | 1.99 (1.18 – 3.34) | 0.76 0.77 | 34 | 1.31 (0.73 – 2.34) | 0.08 0.03 |
| 0–<5 g per day           | 84                 | 1.00 (Reference) |        | 55 | 1.00 (Reference) |        | 28 | 1.00 (Reference) |        | 23 | 1.00 (Reference) |        |
| >5–<30 g per day         | 156                | 0.95 (0.70 – 1.30) |        | 107 | 1.00 (0.68 – 1.47) |        | 49 | 0.97 (0.59 – 1.61) |        | 39 | 1.23 (0.71 – 2.12) |        |
| ≥30 g per day            | 71                 | 1.30 (0.86 – 2.05) |        | 47 | 1.47 (0.89 – 2.43) |        | 20 | 1.25 (0.63 – 2.47) |        | 23 | 2.36 (1.13 – 4.91) |        |
| Male participants        |                    |        |               |             |         |         |         |             |         |         |         |         |
| Non-drinkers             | 61                 | 1.64 (1.01 – 2.66) | 0.76 0.16 | 42 | 2.08 (1.14 – 3.82) | 0.53 0.14 | 23 | 2.80 (1.17 – 6.67) | 0.57 0.41 | 17 | 1.44 (0.63 – 3.29) | 0.63 0.21 |
| 0–<5 g per day           | 34                 | 1.00 (Reference) |        | 23 | 1.00 (Reference) |        | 9 | 1.00 (Reference) |        | 12 | 1.00 (Reference) |        |
| >5–<30 g per day         | 90                 | 1.05 (0.67 – 1.64) |        | 58 | 1.13 (0.65 – 1.95) |        | 27 | 1.43 (0.64 – 3.18) |        | 20 | 0.98 (0.47 – 2.06) |        |
| ≥30 g per day            | 56                 | 1.36 (0.80 – 2.20) |        | 37 | 1.65 (0.86 – 3.14) |        | 19 | 1.78 (0.71 – 4.66) |        | 16 | 1.64 (0.64 – 4.16) |        |
| Female participants      |                    |        |               |             |         |         |         |             |         |         |         |         |
| Non-drinkers             | 86                 | 1.34 (0.87 – 2.08) | 0.59 0.82 | 57 | 1.31 (0.76 – 2.28) | 0.75 0.92 | 34 | 1.65 (0.81 – 3.35) | 0.19 0.10 | 17 | 1.05 (0.43 – 2.57) | 0.09 0.26 |
| >5–<30 g per day         | 50                 | 1.00 (Reference) |        | 52 | 1.00 (Reference) |        | 19 | 1.00 (Reference) |        | 11 | 1.00 (Reference) |        |
| ≥30 g per day            | 66                 | 0.82 (0.52 – 1.30) |        | 49 | 0.88 (0.50 – 1.54) |        | 22 | 0.71 (0.34 – 1.49) |        | 19 | 1.56 (0.63 – 3.84) |        |
| Abbreviations: OR = odds ratio; CI = confidence interval. *Age, weight, height, smoking status, social class, intakes of energy, fibre, folate, red meat and processed meat, adjusted (579 cases and 1734 controls). **Age, weight, height, physical activity, educational level, smoking status, social class, intakes of energy, fibre, folate, red meat and processed meat, adjusted (458 cases and 1734 controls).
Table 5  Odds ratios (95% confidence intervals) from multivariable models for colorectal cancer risk in categories of alcohol intake as assessed by food diaries and FFQs among participants with both measures

| Alcohol intake (g per day) | Non-drinkers | >0–<5 g per day | 5–<15 g per day | 15–<30 g per day | 30–<45 g per day | ≥45 g per day | P for trend | P trend for drinkers |
|---------------------------|--------------|-----------------|-----------------|-----------------|-----------------|-------------|-----------|-------------------|
| Food diaries              |              |                 |                 |                 |                 |             |           |                   |
| No. of all participants   | 646          | 477             | 510             | 371             | 165             | 136         |           |                   |
| Colorectal cancer cases   | 149          | 100             | 100             | 75              | 38              | 34          |           |                   |
| Multivariable model 1*   | 1.18 (0.88–1.60) | 1.00 (0.66–1.26) | 0.92 (0.65–1.30) | 1.08 (0.68–1.70) | 1.24 (0.76–2.04) | 0.97        | 0.60      |                   |
| Multivariable model 2*   | 1.38 (1.00–1.91) | 1.00 (0.63–1.29) | 0.98 (0.67–1.42) | 1.20 (0.74–1.95) | 1.32 (0.79–2.22) | 0.84        | 0.25      |                   |
| FFQs                      |              |                 |                 |                 |                 |             |           |                   |
| No. of all participants   | 372          | 867             | 662             | 226             | 100             | 78          |           |                   |
| Colorectal cancer cases   | 84           | 171             | 150             | 46              | 26              | 19          |           |                   |
| Multivariable model 1*   | 1.43 (1.04–1.97) | 1.00 (0.94–1.58) | 1.16 (0.79–1.72) | 1.36 (0.81–2.28) | 1.40 (0.79–2.49) | 0.12        | 0.09      |                   |
| Multivariable model 2*   | 1.33 (0.96–1.86) | 1.00 (0.87–1.53) | 1.07 (0.71–1.61) | 1.18 (0.68–2.03) | 1.30 (0.72–2.38) | 0.36        | 0.07      |                   |

Abbreviation: FFQ = food frequency questionnaire. *Conditional logistic regression analyses were restricted to participants who completed both the FFQ and the food diary (496 cases and 1809 controls). Owing to missing information in FFQ data, models were not adjusted for intakes of energy, red meat and processed meat. Adjusting for these variables in models using diary information did not alter the results. P-values for trend were drawn from tests for trend by modelling alcohol intake as a continuous variable in a conditional logistic regression analysis, whereas P-values for trend for drinkers were drawn from tests for trend only from non-zero alcohol drinkers. Adjusted for age, weight, height, smoking status, social class, intakes of fibre and folate adjusted in the main model (496 cases and 1809 controls). Adjusted for age, weight, height, physical activity, educational level, smoking status, social class, intakes of fibre and folate in the sensitivity analyses restricted to individuals with complete covariate information (442 cases and 1701 controls).

**Alcohol intake and CRC risk**

JY Park et al

**DISCUSSION**

In this large nested case–control study of 579 CRC cases and 1996 matched controls, alcohol intake within the observed range was not associated with a significantly increased CRC risk after multivariable adjustment when compared with alcohol intake of >0–<5 g per day. In subgroup analyses of cancer sites including proximal/distal colon and rectum, no clear associations were observed with total alcohol intake. There was also no evidence of a difference between men and women in the association between alcohol intake and CRC risk. Analyses using a subset of participants who had completed both FFQs and food diaries showed similar shaped associations using each of the two instruments, although risk estimates were higher but still statistically non-significant when using FFQ data.

A meta-analysis of prospective cohort studies showed 19% of increased risk of CRC with an increase of 100 g per week in alcohol intake (Moskal et al, 2008). Recent cohort studies in which FFQs were the main nutritional instrument have shown no association (Chen et al, 2005), or a significant adverse effect of alcohol when intake is greater than ~16 g per day (Toriola et al, 2008), 30 g per day (Ferrari et al, 2007; Bongaerts et al, 2008; Mizoue et al, 2008) or ~45 g per day (Akhter et al, 2007) compared with study-specific reference groups of lower intakes. These individual studies have not found consistent results in sex- and subsite-specific analyses, with several studies finding greater risk of rectal than colon cancer for alcohol intake of ≥30 g per day (Ferrari et al, 2007; Bongaerts et al, 2008). The Million Women Study recently reported a positive association between moderate alcohol intake (>15 drinks per week) and rectal cancer risk but found no evidence of increased colon cancer risk among middle-aged women (Allen et al, 2009). Previous non-drinkers on the FFQ. Approximately 95% of individuals (n = 613) reporting zero alcohol intake on the food diary consumed <5 g per day of alcohol according to the FFQ. A total of 67 individuals (18%) reported zero alcohol intake on FFQ and >0 alcohol intake on the food diary.

**Figure 1** Comparison of odds ratios (ORs) in a log scale for categories of alcohol intake data (0, >0–<5 (reference), 5–<15, 15–<30, 30–<45 and ≥45 g per day) obtained by food diaries or FFQs. A total of 2305 study participants had complete alcohol intake information from both diaries and FFQs (n = 496 cases and 1809 controls). ORs for each category were plotted against the mean alcohol intake (g per day) for each category (0, 2.6, 9.4, 21.7, 36.4 and 64.2 g per day for food diaries and 0, 1.9, 9.1, 21.7, 35.6 and 61.3 g per day for FFQs, respectively) and were adjusted for age, weight, height, smoking status, social class, intakes of fibre and folate.
studies have, however, failed to reach clear consensus on the association between moderate alcohol drinking (≤30 g per day) and colon or rectal cancer risk, and there are still few studies which have investigated proximal and distal colon cancer separately.

It has been suggested that the aetiology of CRC varies by subsite (Stang and Kluttig, 2008; Li and Lai, 2009). The proximal and distal colons have different embryonic origins and their physiology and functions may vary (Stang and Kluttig, 2008). Studies have also shown that microsatellite instability is often linked to proximal colon cancer, whereas chromosomal instability is more common in distal colon cancer (Lindblom, 2001). Therefore, subsite-specific studies are required for a better understanding of the aetiology of CRC. Our study, exploring CRC subsites in men and women in detail, suggested elevated risks of distal colon cancer, whereas chromosomal instability is more common in proximal colon (Lindblom, 2001). Significant differences in association of subsite-specific colon cancer, whereas chromosomal instability is more common in proximal colon (Lindblom, 2001).

The mechanism by which alcohol may influence CRC risk is not well understood (Stewart and Kleihues, 2003). Hypotheses include a local solvent action which facilitates absorption of other carcinogens, for example, a synergistic effect with tobacco smoking and alcohol. Previous studies have shown that alcohol intake is associated with various CRC risk factors, such as obesity, physical inactivity, and dietary patterns (Stang and Kluttig, 2008). In our study, significant differences in association of CRC risk with alcohol intake were observed by subsite analysis. Therefore, future studies are warranted focusing on a possible role of alcohol use in the risk of colon cancer, especially proximal or distal colon cancer.

The analysis of alcohol intake and CRC risk in the WCRF/AICR Report confirmed no significantly increased risk of CRC with alcohol intake up to 30 g per day compared with the lightest category of drinkers (0–<5 g per day) and a possible dose–response relationship among drinkers when analysed for the subset of cohorts with complete covariate information. Thus, future studies are warranted focusing on a possible role of alcohol use in CRC risk.

Our results are consistent with the 2007 WCRF/AICR Report. We found no increased risk of CRC up to 30 g per day of alcohol intake, with no substantial differences detected in subsite-specific analyses. Although men and women have been shown to have different physiological responses to alcohol (Ely et al., 1999) and the effect of alcohol in our study seemed larger in men (OR: 1.24, 95% CI: 0.76–2.03 for drinkers with >30 g per day compared with the lightest category drinkers (0–<5 g per day)) than in women (OR: 1.03, 95% CI: 0.54–1.96 for drinkers with >30 g per day compared with the lightest category of drinkers (0–<5 g per day)), the associations were not statistically significant. We did not find differential associations with CRC risk by type of alcoholic beverage. This is consistent with the Report which judged that the causal factor is evidently alcohol itself, irrespective of the type of alcoholic drink. A limited number of studies were updated in the meta-analysis of alcohol intake and CRC risk in the WCRF/AICR Report. Therefore, our findings contribute to update the current evidence for future review, confirming no significantly increased risk of CRC with <30 g per day of alcohol intake.

The mechanism by which alcohol may influence CRC risk is not well understood (Stewart and Kleihues, 2003). Hypotheses include local solvent action which facilitates absorption of other carcinogens, for example, a synergistic effect with tobacco smoking (Boffetta and Hashibe, 2006), and an independent effect through association of deficiencies in nutrients, especially through changes in folate metabolism (Giovannucci et al., 1995). However, in our study, no significant interactions were observed between alcohol intake and folate intake or tobacco smoking with regard to CRC risk.

Our study has several strengths. Its prospective study design precluded bias attributable to differential recall of intake of alcohol by case status. We were able to examine the influence of alcohol intake on site- and sex-specific CRC risk. Furthermore, different types of alcoholic beverages from food diaries were assessed in association with CRC risk.

This study provided the measure of alcohol intake by using both food diaries and FFQs, whereas previous studies on alcohol and CRC risk have relied only on FFQs. The use of food diaries and FFQs for habitually consumed food items have been discussed (Bingham et al., 1997, 2003, 2008). However, there have been few direct attempts to compare those two different nutritional instruments prospectively for episodically consumed food items, including alcohol. Previous studies have shown that FFQs were not inferior in measuring alcohol intake relative to prospective food diaries (Feunekes et al., 1999), and FFQs showed a high level of reproducibility and validity compared with diet records as a reference method (Ferraroni et al., 1996). Our study, which has information both from food diaries and FFQs, found that although FFQs and food diaries cover different durations and measurements may differ between the two instruments, using well-constructed food diaries for measurement of infrequently consumed food items can provide results that do not differ substantially from those using FFQs.

This study used original data from seven UK mature cohorts with standardised diary data entry, which enabled us to create identical categories for alcohol intake across studies that were in line with previous studies (Cho et al., 2004), removing some potential sources of heterogeneity across studies. Furthermore, we were able to adjust for a range of known confounding factors. An important limitation of this study is that we were unable to differentiate life-long abstainers and former drinkers in the category of non-drinkers in either FFQs or diaries. As previously discussed, many non-drinkers may be former drinkers who had given up drinking because of incipient disease (Doll et al., 1994), although a sensitivity analysis excluding a further 111 cases incident within 3 years of diary completion did not materially change our results. Moreover, in the 4–7-day diaries, we were unable to differentiate non-drinkers from episodic drinkers who happened not to consume alcohol during the time period covered by the diary. Hence, it is likely that the ‘non-drinker’ category in our diary analyses contains participants who were actually drinkers at the time when diaries were administered. In light of this, we focused on analyses from non-zero alcohol drinkers and reported trend tests for drinkers separately (Allen et al., 2009). We found a moderate positive but non-significant CRC risk in those consuming >30 g per day of alcohol using data from both food diaries and FFQs. However, in our study, almost half of the participants reported drinking <5 g per day in both food diaries and FFQs and only 19% of men and 17% of women reported intake in excess of the recommended daily maxima of 3–4 units (≤32 g) daily for men and 2–3 units (≤24 g) daily for women. Insufficient participants in the heavier categories prevented us from estimating any potential effect of high alcohol intake with sufficient precision.

Another limitation was that alcohol intake was assessed only once by self-report. As heavy alcohol drinking is considered to be unhealthy, it is likely that individuals underreport their alcohol intake, particularly in the case of heavy intake (Rehm et al., 1999), resulting in overestimation of the actual carcinogenic effect of the habit. In addition, drinking habits are liable to change throughout the lifetime. However, we conducted a sensitivity analysis using data from the EPIC-Norfolk cohort in which information on alcohol intake from participants recalling their habits at ages 20 and 30 years is available, and we again did not find any evidence of an association with CRC risk, although participants tended to report higher alcohol intake at younger ages (data not shown). Nonetheless, more research with additional information on alcohol intake over a longer period of time and on specific drinking behaviour such as binge drinking is required to clarify any hazardous effect of excessive alcohol drinking on CRC risk.

In summary, we found no increased risk of CRC up to 30 g per day of alcohol intake within the UK Dietary Cohort Consortium. However, because of an insufficient number of participants in the heavier categories, a modest increased risk in those consuming ≥30 g per day cannot be excluded. Excessive alcohol intake has been causally related to numerous medical conditions (Rehm et al., 2003). Drinking-related morbidity and mortality constitute a large
burden of diseases in Europe and worldwide (Ezzati et al., 2004; Rehm et al., 2006). In the United Kingdom, there was a substantial increase in both hospital admissions and deaths specifically related to alcohol misuse between 1991 and 2007, costing over £2.7 billion to the National Health Service annually (Rachel et al., 2009). The risks of alcohol intake should therefore be carefully considered in any decisions about alcohol drinking.

ACKNOWLEDGEMENTS

The UK Dietary Cohort Consortium at the MRC Centre for Nutritional Epidemiology in Cancer Prevention and Survival is funded by the Medical Research Council. The cohort studies included in this consortium received funding from the British Heart Foundation; Cancer Research UK; the Department of Health, UK; the Food Standards Agency, UK; the Medical Research Council, UK; the Stroke Association, UK; and the World Cancer Research Fund.

Conflict of interest

The authors declare no conflict of interest.

Supplementary Information accompanies the paper on British Journal of Cancer website (http://www.nature.com/bjc)

REFERENCES

Akhter M, Kuriyama S, Nakaya N, Shimazu T, Ohmori K, Nishino Y, Tsunobo Y, Fukao A, Tsuji I (2007) Alcohol consumption is associated with an increased risk of distal colon and rectal cancer in Japanese men: the Miyagi Cohort Study. *Eur J Cancer* 43: 383 – 390

Allen NE, Beral V, Casabonne D, Kan SW, Reeves GK, Brown A, Green J, on behalf of the Million Women Study Collaborators (2009) Moderate alcohol intake and cancer incidence in women. *J Natl Cancer Inst* 101: 296 – 305

Allen NE, Roddam AW, Allen DS, Fentiman IS, dos Santos Silva I, Peto J, Holly JMP, Key TJ (2005) A prospective study of serum insulin-like growth factor-1 (IGF-I), IGF-II, IGF-binding protein-3 and breast cancer risk. *Br J Cancer* 92: 1283 – 1287

Appleby PN, Thouroude M, Mann JI, Key TJ (1999) The Oxford Vegetarian Study: an overview. *Am J Clin Nutr* 70: 525S – 553I

Baan R, Straif K, Grosse Y, Secretan B, El GF, Bouvard V, Alciati A, Cogliano V (2007) Carcinogenicity of alcoholic beverages. *Lancet Oncol* 8: 292 – 293

Bingham S, Luben R, Welch A, Low YL, Khaw KT, Wareham N, Day N (2008) Associations between dietary methods and biomarkers, and between fruits and vegetables and risk of ischaemic heart disease, in the EPIC Norfolk Cohort Study. *Int J Epidemiol* 37: 978 – 987

Bingham SA, Gill C, Welch A, Cassidy A, Runswick SA, Oakes S, Lubin R, Thornham DI, Key TJ, Roe L, Khaw KT, Day NE (1997) Validation of dietary assessment methods in the UK arm of EPIC using weighed records, and 24-h urinary nitrogen and potassium and serum vitamin C and carotenoids as biomarkers. *Int J Epidemiol* 26: S137 – S151

Bingham SA, Luben R, Welch A, Wareham N, Khaw KT, Day N (2003) Are imprecise methods obscuring a relation between fat and breast cancer? *Lancet* 362: 212 – 214

Bingham SA, Welch AA, McCaggart A, Mulligan AA, Runswick SA, Luben R, Oakes S, Khaw KT, Wareham N, Day NE (2001) Nutritional methods in the European Prospective Investigation of Cancer in Norfolk. *Public Health Nutr* 4: 847 – 858

Boffetta P, Hashibe M (2006) Alcohol and cancer. *Lancet Oncol* 7: 149 – 156

Bongaerts BW, van den Brandt PA, Goldbohm RA, de Goeij AF, Brunnhagen DJ, Key TJ, Roe L, Khaw KT, Day NE (1997) Validation of dietary assessment methods in the UK arm of EPIC using weighed records, and 24-h urinary nitrogen and potassium and serum vitamin C and carotenoids as biomarkers. *Int J Epidemiol* 26: S137 – S151

Bingham SA, Luben R, Welch A, Wareham N, Khaw KT, Day N (2003) Are imprecise methods obscuring a relation between fat and breast cancer? *Lancet* 362: 212 – 214

Bingham SA, Welch AA, McCaggart A, Mulligan AA, Runswick SA, Luben R, Oakes S, Khaw KT, Wareham N, Day NE (2001) Nutritional methods in the European Prospective Investigation of Cancer in Norfolk. *Public Health Nutr* 4: 847 – 858

Boffetta P, Hashibe M (2006) Alcohol and cancer. *Lancet Oncol* 7: 149 – 156

Bongaerts BW, van den Brandt PA, Goldbohm RA, de Goeij AF, Weijenberg MP (2008) Alcohol consumption, type of alcoholic beverage and risk of colorectal cancer at specific subtitles. *Int J Cancer* 125: 2411 – 2417

 Brunner E, Stallone D, Juneca M, Bingham S, Marmot M (2001) Dietary assessment in Whitehall II: comparison of 7 d diet diary and food-frequency questionnaire and validity against biomarkers. *Br J Nutr* 86: 405 – 414

Bufill JA (1990) Colorectal cancer: evidence for distinct genetic categories based on proximal or distal tumour location. *Ann Intern Med* 113: 779 – 788

Cade JE, Burley VJ, Greenwood DC (2004) The UK Women’s Cohort Study: comparison of vegetarians, fish-eaters and meat-eaters. *Public Health Nutr* 7: 871 – 878

Cade JE, Frear L, Greenwood DC (2006) Assessment of diet in young children with an emphasis on fruit and vegetable intake: using CADET-Child and Diet Evaluation Tool. *Public Health Nutr* 9: 501 – 508

Carlin JB (2008) A new framework for managing and analyzing multiply imputed data in Stata. *Statia* 8: 49 – 67

Chen K, Jiang Q, Ma X, Li Q, Yao K, Yu W, Zheng S (2005) Alcohol drinking and colorectal cancer: a population-based prospective cohort study in China. *Eur J Epidemiol* 20: 149 – 154

Cho E, Smith-Warner SA, Ritz J, van den Brandt PA, Colditz GA, Folsom AR, Freudenhagen JL, Giovannucci E, Goldbohm RA, Graham S, Holmberg L, Kim DH, Malila N, Miller AB, Pietinen P, Rohan TE, Sellers TA, Speizer FE, Willett WC, Wolk A, Hunter DJ (2004) Alcohol intake and colorectal cancer: a pooled analysis of 8 cohort studies. *Ann Intern Med* 140: 603 – 613

Davey GK, Spencer EA, Appleby PN, Allen NE, Knox KH, Key TJ (2003) EPIC-Oxford: lifestyle characteristics and nutrient intakes in a cohort of 33 883 meat-eaters and 31 546 non meat-eaters in the UK. *Public Health Nutr* 6: 259 – 269

Day N, Oakes S, Luben R, Khaw KT, Bingham S, Welch A, Wareham N (1999) EPIC-Norfolk: study design and characteristics of the cohort. European Prospective Investigation of Cancer. *Br J Cancer* 80(Suppl 1): 95 – 103

Day NE, McKeown N, Wong MY, Welch A, Bingham S (2001) Epidemiological assessment of diet: a comparison of a 7-day diary with a food frequency questionnaire using urinary markers of nitrogen, potassium and sodium. *Int J Epidemiol* 30: 309 – 317

Department of Health (1999) Dietary Reference Values for Food Energy and Nutrients for the United Kingdom. HMSO Publications: London

Department of Health (2009) *Health Profile of England* 2008. Department of Health: London

Doll R, Peto R, Hall E, Wheatley K, Gray R (1994) Mortality in relation to consumption of alcohol: 13 years’ observations on male British doctors. *BMJ* 309: 911 – 918

Ely M, Hardy R, Longford NT, Wadsworth ME (1999) Gender differences in the relationship between alcohol consumption and drink problems are largely accounted for by body water. *Alcohol Alcohol* 34: 894 – 902

Ezzati M, Rodgers A, Lopez AD (2004) Mortality and burden of disease attributable to individual risk factors. In: *Comparative Quantification of Health Risks. Global and Regional Burden of Disease Attributable to Selected Major Risk Factors*. Volume 2 World Health Organization: Geneva

Ferrari P, Jenab M, Norat T, Moskal A, Slimani N, Olsen A, Tjonneland A, Overvad K, Jensen MK, Bouter-Ruault MC, Clavel-Chapelon F, Morois S, Rohrmann S, Linseisen J, Baroig H, Bergmann M, Koppotopoulou D, Trichopoulou A, Kassapa C, Masala G, Krog V, Vineis P, Panico S, Marino R, Vilsins D, Peeters C, Bueno-Mesquita H, Ocke MC, Skeie G, Lund E, Agudo A, Ardanaz E, Lopez DC, Sanchez MJ, Quirós JR, Amiano P, Berglund G, Manjer J, Palmqvist R, Van GB, Allen N, Key T, Bingham S, Mazzur M, Boffetta P, Kaaks R, Riboli E (2007) Lifetime and baseline alcohol intake and risk of colon and rectal cancers in the European prospective investigation into cancer and nutrition (EPIC). *Int J Cancer* 121: 2065 – 2072

Ferraroni M, Decarli A, Franceschi S, Vecchia CL, Enard L, Grig E, Arpinel M, Alvini S (1996) Validity and reproducibility of alcohol consumption in Italy. *Int J Epidemiol* 25: 775 – 782

Feunekes GIJ, van’t Veer P, van Staveren WA, Kok FJ (1999) Alcohol intake assessment: the sober facts. *Br J Nutr* 81: 105 – 112

Giovannucci E, Rimm EB, Ascherio A, Stampfer MJ, Colditz GA, Willett WC (1995) Alcohol, low-methionine-low-folate diets, and risk of colon cancer in men. *J Natl Cancer Inst* 87: 265 – 273

Li FY, Lau MD (2009) Colorectal cancer, one entity or three. *J Zhejiang Univ Sci B* 10: 219 – 229

Lim HJ, Park BJ (2008) Cohort study on the association between alcohol consumption and the risk of colorectal cancer in the Korean elderly. *J Prev Med Public Health* 41: 23 – 29
Lindblom A (2001) Different mechanisms in the tumorigenesis of proximal and distal colon cancers. *Curr Opin Oncol* 13: 63–69

Marmot M, Brunner E (2005) Cohort profile: The Whitehall II study. *Int J Epidemiol* 34: 251–256

Mizoue T, Inoue M, Wakai K, Nagata C, Shimazu T, Tsuji I, Otani T, Tanaka K, Matsuo K, Tamakoshi A, Sasazuki S, Tsugane S, for the Research Group for the Development and Evaluation of Cancer Prevention Strategies in Japan (2008) Alcohol drinking and colorectal cancer in Japanese: a pooled analysis of results from five cohort studies. *Am J Epidemiol* 167: 1397–1406

Moskal A, Norat T, Ferrari P, Riboli E (2006) Alcohol intake and colorectal cancer risk: a dose-response meta-analysis of published cohort studies. *Int J Cancer* 120: 664–671

Prentice RL (2003) Dietary assessment and the reliability of nutritional epidemiology reports. *Lancet* 362: 182–183

Rachel C, Jennifer M, Vasant H (eds) (2009) *Health Survey for England 2008: Physical Activity and Fitness*. Department of Health: London

Rehm J, Greenfield TK, Walsh G, Xie X, Robson L, Single E (1999) Assessment methods for alcohol consumption, prevalence of high risk drinking and harm: a sensitivity analysis. *Int J Epidemiol* 28: 219–224

Rehm J, Room R, Graham K, Monteiro M, Gmel G, Sempos CT (2003) The relationship of average volume of alcohol consumption and patterns of drinking to burden of disease: an overview. *Addiction* 98: 1209–1228

Rehm J, Taylor B, Patra J (2006) Volume of alcohol consumption, patterns of drinking and burden of disease in the European region 2002. *Addiction* 101: 1086–1095

Royston P (2005) Multiple imputation of missing values: update. *Statia J* 5: 188–201

Schatzkin A, Kipnis V, Carroll RJ, Midhune D, Subar AF, Bingham S, Schoeller DA, Troiano RP, Freedman LS (2003) A comparison of a food frequency questionnaire with a 24-h recall for use in an epidemiological cohort study: results from the biomarker-based Observing Protein and Energy Nutrition (OPEN) study. *Int J Epidemiol* 32: 1054–1062

Stang A, Kluttig A (2008) Etiologic insights from surface adjustment of colorectal carcinoma incidences: an analysis of the U.S. SEER data 2000–2004. *Am J Gastroenterol* 103: 2853–2861

Wadsworth M, Kuh D, Richards M, Hardy R (2006) Cohort profile: the 1946 National birth cohort (MRC National Survey of Health and Development). *Int J Epidemiol* 35: 49–54

WCRF/AICR (2007) *Food, Nutrition, Physical Activity, and the Prevention of Cancer: a Global Perspective*. AICR: Washington, DC

Welch AA, Taggart A, Mulligan AA, Luben R, Walker N, Khaw KT, Day NE, Bingham SA (2001) DINES (Data Into Nutrients for Epidemiological Research) – a new data-entry program for nutritional analysis in the EPIC-Norfolk cohort and the 7-day diary method. *Public Health Nutr* 4: 1253–1265

Westlake S, Cooper N (2008) Cancer incidence and mortality: trends in the United Kingdom and constituent countries, 1993 to 2004. *Health Stat Quart* 38: 33–46