| | | | | |
|---|---|---|---|---|
| 198 women | Non-drinker | 149 | 1.00 (reference) | |
| | Ex-drinker | 6 | 1.56 (0.68–3.60) | |
| | Current drinker | 43 | 1.03 (0.72–1.45) | |
| | 0.0–0.9 (go/day) | 22 | 1.06 (0.67–1.68) | |
| | ≥1.0 | 5 | 1.22 (0.49–3.03) | 0.96* |
| Rectum | | | | |
| 150 men | Non-drinker | 30 | 1.00 (reference) | |
| | Ex-drinker | 14 | 1.25 (0.66–2.38) | |
| | Current drinker | 106 | 1.01 (0.67–1.52) | |
| | 0.0–0.9 (go/day) | 16 | 0.61 (0.33–1.13) | |
| | 1.0–1.9 | 35 | 1.01 (0.62–1.65) | |
| | 2.0–2.9 | 29 | 1.21 (0.72–2.04) | |
| | ≥3.0 | 12 | 1.32 (0.67–2.63) | 0.027* |
| 61 women | Non-drinker | 50 | 1.00 (refereace) | |
| | Ex-drinker | 1 | 0.78 (0.11–5.78) | |
| | Current drinker | 10 | 0.71 (0.35–1.42) | |
| | 0.0–0.9 (go/day) | 5 | 0.69 (0.27–1.74) | |
| | ≥1.0 | 2 | 1.53 (0.36–6.47) | 0.36* |

NA, not available; NS, not significant.

**Table 2.** Alcohol drinking and colorectal cancer risk, case–control study among Japanese populations

| Reference | Study period | Study subjects | | | | Category | Odds ratio (95% confidence interval or *P*) | *P* for trend | Confounding variables considered | Comments |
|---|---|---|---|---|---|---|---|---|---|---|
| | | Type and source | Definition | No. of cases | No. of controls | | | | | |
| Kondo (17) | 1967–73 | Hospital-based (Three hospitals in Nagoya) | Cases: 91% were histologically confirmed; Controls: inpatients without history of cancer of the digestive organs, oral cavity, pharynx, lung or larynx, or other diseases of the colorectum | Colon | | | | | Matched (1 : 2) for age (±5 years) and sex | *Total no. of controls for colorectal cancer cases. No. for each site was not shown. |
| | | | | 93 men | 406 men* | Sake: less use | 1.00 | | | |
| | | | | | | Daily | 0.69 (NS) | | | |
| | | | | | | Beer: less use | 1.00 | | | |
| | | | | | | Daily | 0.49 (<0.05) | | | |
| | | | | | | Wine: less use | 1.00 | | | |
| | | | | | | ≥6/month | 1.81 (NS) | | | |
| | | | | | | Whisky: less use | 1.00 | | | |
| | | | | | | Daily | 0.58 (NS) | | | |
| | | | | 86 women | 174 women* | Sake: less use | 1.00 | | | |
| | | | | | | ≥6/month | 0.45 (NS) | | | |
| | | | | | | Beer: less use | 1.00 | | | |
| | | | | | | ≥6/month | 1.11 (NS) | | | |
| | | | | | | Wine: less use | 1.00 | | | |
| | | | | | | ≥6/month | 1.80 (NS) | | | |
| | | | | Rectum | | | | | | |
| | | | | 112 men | 406 men* | Sake: less use | 1.00 | | | |
| | | | | | | Daily | 0.71 (NS) | | | |
| | | | | | | Beer: less use | 1.00 | | | |
| | | | | | | Daily | 0.61 (NS) | | | |
| | | | | | | Wine: less use | 1.00 | | | |
| | | | | | | ≥6/month | 0.93 (NS) | | | |
| | | | | | | Whisky: less use | 1.00 | | | |
| | | | | | | Daily | 0.35 (<0.05) | | | |
| | | | | 99 women | 174 women* | Sake: less use | 1.00 | | | |
| | | | | | | ≥6/month | 0.42 (NS) | | | |
| | | | | | | Beer: less use | 1.00 | | | |
| | | | | | | ≥6/month | 0.67 (NS) | | | |
| | | | | | | Wine: less use | 1.00 | | | |
| | | | | | | ≥6/month | 0.96 (NS) | | | |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Watanabe et al. (18) | 1977–83 | Hospital - based (five hospitals in Kyoto, Shiga, Hyogo) | Cases: histologically confirmed cases; Controls: inpatients without history of cancer or any diseases of large bowel | Colon | | | | | Matched (1 : 1) for hospital, sex and age (±5 years) | |
| | | | | 138 men and women | 138 men and women | Non-drinker | 1.00 | | | |
| | | | | | | Drinker | 0.73 (0.43–1.23) | | | |
| | | | | Rectum | | | | | | |
| | | | | 65 men and women | 65 men and women | Non-drinker | 1.00 | | | |
| | | | | | | Drinker | 0.86 (0.40–1.85) | | | |
| Tajima and Tominaga (19) | 1981–83 | Hospital -based (Aichi Cancer Center) | Case: histologically confirmed cases; Controls: inpatients without history of cancer | Colon | | | | | Adjusted for age | *Common controls for cases of cancer of the stomach, colon or rectum. |
| | | | | 27 men | 111 men* | Non-drinker | 1.00 | | | |
| | | | | | | Drinker | 0.68 (NS) | | | |
| | | | | | | Non-drinker | 1.00 | | | |
| | | | | | | Sometimes | 0.40 (NS) | | | |
| | | | | | | Daily | 0.77 (NS) | NA | | |
| | | | | | | Non-drinker | 1.00 | | | |
| | | | | | | <360 ml/day | 0.41 (<0.05) | | | |
| | | | | | | ≥360 | 1.25 (NS) | NA | | |
| | | | | Rectum | | | | | | |
| | | | | 25 men | 111 men* | Non-drinker | 1.00 | | | |
| | | | | | | Drinker | 0.60 (NS) | | | |
| | | | | | | Non-drinker | 1.00 | | | |
| | | | | | | Sometimes | 0.85 (NS) | | | |
| | | | | | | Daily | 0.47 (NS) | NA | | |
| | | | | | | Non-drinker | 1.00 | | | |
| | | | | | | <360 ml/day | 0.58 (NS) | | | |
| | | | | | | ≥360 | 0.69 (NS) | NA | | |
| Kato et al. (20) | 1979–87 | Registry- based (Aichi Cancer Registry) | Cases: histologically confirmed (90%); Controls: patients with other sites of cancer excluding known alcohol-related cancers (mouth, pharynx, oesophagus, liver and unknown sites) | Colon | | | | | Adjusted for age | *Compared with non-drinker |
| | | | | 1716 men | 16 600 men | Non-drinker | 1.00 | NA | | |
| | | | | | | Occasional | 1.23 (1.05–1.44) | | | |
| | | | | | | Daily | 1.10 (0.97–1.25) | | | |
| | | | | | | Sake* | 1.00 (0.88–1.13) | | | |
| | | | | | | Beer* | 1.54 (1.32–1.79) | | | |
| | | | | | | Whisky* | 1.18 (0.85–1.66) | | | |
| | | | | Proximal colon | | | | | | |
| | | | | 445 men | 16 600 men | Non-drinker | 1.00 | | | |
| | | | | | | Occasional | 1.09 (0.83–1.45) | | | |
| | | | | | | Daily | 0.80 (0.63–1.02) | NA | | |
| | | | | | | Sake | 0.75 (0.59–0.96) | | | |
| | | | | | | Beer | 1.49 (1.13–1.95) | | | |
| | | | | | | Whisky | 1.09 (0.59–2.02) | | | |

**Table 2.** *Continued*

| Reference | Study period | Study subjects | | | | Category | Odds ratio (95% confidence interval or *P*) | *P* for trend | Confounding variables considered | Comments |
|---|---|---|---|---|---|---|---|---|---|---|
| | | Type and source | Definition | No. of cases | No. of controls | | | | | |
| | | | | Distal colon | | | | | | |
| | | | | 756 men | 16 600 men | Non-drinker | 1.00 | | | |
| | | | | | | Occasional | 1.40 (1.12–1.74) | | | |
| | | | | | | Daily | 1.33 (1.11–1.58) | NA | | |
| | | | | | | Sake | 1.15 (0.97–1.37) | | | |
| | | | | | | Beer | 1.65 (1.34–2.04) | | | |
| | | | | | | Whisky | 1.33 (0.85–2.08) | | | |
| | | | | Rectum | | | | | | |
| | | | | 1611 men | 16 600 men | Non-drinker | 1.00 | | | |
| | | | | | | Occasional | 1.39 (1.19–1.63) | | | |
| | | | | | | Daily | 1.06 (0.93–1.22) | NA | | |
| | | | | | | Sake | 1.10 (0.97–1.85) | | | |
| | | | | | | Beer | 1.88 (1.62–2.18) | | | |
| | | | | | | Whisky | 1.35 (0.98–1.85) | | | |
| Kato et al. (21) | 1986–90 | Hospital -based (Aichi Cancer Center Hospital) | Cases: histologically confirmed cases among examinees of colonoscopy at the hospital; Controls: population controls selected through the telephone directories | Colon | | | | | | |
| | | | | 132 (M: 79, F: 53) | 578 (M: 377, F: 201)* | Never | 1.00 | | Matched for residence, sex and age (5-year age group) | *Common controls for cases of cancer of the colon and rectum |
| | | | | | | Past | 2.81 (1.33–5.97) | | | |
| | | | | | | Daily | 0.77 (0.44–1.33) | | | |
| | | | | | | Non-whisky drinker | 1.00 | | | |
| | | | | | | Whisky drinker | 0.93 (0.50–1.75) | | | |
| | | | | Rectum | | | | | | |
| | | | | 91 (M: 60, F: 31) | 578 (M: 377, F: 201)* | Never | 1.00 | | | |
| | | | | | | Past | 4.30 (1.76–10.52) | | | |
| | | | | | | Daily | 1.64 (0.84–3.18) | | | |
| | | | | | | Non-whisky drinker | 1.00 | | | |
| | | | | | | Whisky drinker | 1.16 (0.59–2.31) | | | |
| Yoshida et al. (22) | 1987–90 | Hospital -based (Sapporo medical college and affiliated hospitals) | Case: patients diagnosed at the First department of surgery of Sapporo Medical University or its affiliated hospitals; Control: selected from telephone books | Colorectum | | Alcohol intake (g/day)* | | | Matched (1 : 2) for sex and age (±3 yrs) | *Reference is other categories of consumption. For instance, >10 is compared with ≤10. **OR is not shown. |
| | | | | 330 (M: 171, F: 159) | 660 (M: 342, F: 318) | >10 | 1.46 (1.04–1.96) | | | |
| | | | | | | >35 | 1.52 (1.10–2.11) | | | |
| | | | | | | >50 | 1.60 (1.13–2.29) | | | |
| | | | | | | >80 | 1.76 (1.10–2.83) | | | |
| | | | | | | >100 | 2.05 (1.13–3.70) | | | |
| | | | | 171 men | 342 men | >35 | 1.48 (1.03–2.13) | | | |
| | | | | | | >50 | 1.55 (1.05–2.27) | | | |
| | | | | | | >80 | 1.79 (1.09–2.96) | | | |
| | | | | | | >100 | 2.26 (1.21–4.23) | | | |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | 159 women | 318 women | >5 | 1.79 (1.08–2.95) | | | |
| | | | | | | >10 | 2.13 (1.21–3.73) | | | |
| | | | | | | >35 | 1.73 (0.83–3.64) | | | |
| | | | | Colon | | | | | | |
| | | | | 177 (M: 81, F: 96) | 354 (M: 162, F: 192) | >10 | 1.75 (1.11–2.76) | | | |
| | | | | | | >35 | 1.98 (1.25–3.13) | | | |
| | | | | | | >50 | 1.97 (1.20–3.25) | | | |
| | | | | | | >80 | 2.17 (1.13–4.15) | | | |
| | | | | | | >100 | 2.46 (1.11–5.44) | | | |
| | | | | Rectum | | | | | | |
| | | | | 153 (M: 90, F: 63) | 306 (M: 180, F: 126) | | NS** | | | |
| Hoshiyama et al. (23) | 1984–90 | Hospital -based (Saitama Cancer Center Hospital) | Cases: histologically confirmed cases; Controls: population controls | Colon | | | | | Adjusted for sex and age | *Common controls for cases of cancer of the colon and rectum; **daily drinker versus never drinker |
| | | | | 79 (M: 37, F: 42) | 653 (M: 343, F: 310)* | Never | 1.0 | | | |
| | | | | | | Past | 0.4 (0.0–2.0) | | | |
| | | | | | | Occasional | 0.6 (0.3–1.1) | | | |
| | | | | | | Daily | NA | | | |
| | | | | | | <50 ml/day | 0.3 (0.1–0.8) | | | |
| | | | | | | ⩾50 | 0.3 (0.1–0.9) | NA | | |
| | | | | | Type of beverage | Sake** | 0.5 (0.1–1.4) | | | |
| | | | | | | Beer** | 0.5 (0.1–1.7) | | | |
| | | | | | | Spirits** | 0.6 (0.2–1.8) | | | |
| | | | | | Lifetime consumption | Never | 1.0 | | | |
| | | | | | | <500 l | 0.4 (0.1–1.0) | | | |
| | | | | | | ⩾500 | 0.7 (0.2–1.8) | 0.46 | | |
| | | | | Rectum | | | | | | |
| | | | | 102 (M: 61, F: 41) | 653 (M: 343, F: 310)* | Never | 1.0 | | | |
| | | | | | | Past | 0.3 (0.0–1.7) | | | |
| | | | | | | Occasional | 0.5 (0.2–1.0) | | | |
| | | | | | | Daily | NA | | | |
| | | | | | | <50 ml/day | 0.5 (0.2–1.1) | | | |
| | | | | | | ⩾50 | 0.6 (0.3–1.3) | NA | | |
| | | | | | Type of beverage | Sake** | 1.4 (0.6–3.3) | | | |
| | | | | | | Beer** | 1.1 (0.4–2.7) | | | |
| | | | | | | Spirits** | 0.8 (0.3–2.4) | | | |
| | | | | | Lifetime consumption | Never | 1.0 | | | |
| | | | | | | <500 l | 0.7 (0.3–1.6) | | | |
| | | | | | | ⩾500 | 0.9 (0.4–2.2) | 0.98 | | |

**Table 2.** *Continued*

| Reference | Study period | Study subjects | | | | Category | Odds ratio (95% confidence interval or *P*) | *P* for trend | Confounding variables considered | Comments |
|---|---|---|---|---|---|---|---|---|---|---|
| | | Type and source | Definition | No. of cases | No. of controls | | | | | |
| Kotake et al. (24) | 1992–94 | Hospital -based (10 hospitals in Kanto region) | Cases: histologically confirmed cases; Controls: screening controls and hospital controls, including cancer patients | Colon | | | | | Matched for sex, age (5-year age group) | |
| | | | | 187 (M: 111, F: 76) | 187 (M: 111, F: 76) | Non-drinker | 1.0 | | | |
| | | | | | | Daily | 0.8 (0.2–3.9) | | | |
| | | | | Rectum | | | | | | |
| | | | | 176 (M: 103, F: 73) | 176 (M: 103, F: 73) | Non-drinker | 1.0 | | | |
| | | | | | | Daily | 1.4 (0.4–5.9) | | | |
| Inoue et al. (25) | 1988–92 | Hospital -based (Aichi Cancer Center Hospital) | Cases: histologically confirmed cases; Controls: first-visit outpatients free from cancer | Colon: Proximal | | | | | Adjusted for age | *Common controls for cases of cancer of the colon and rectum |
| | | | | 51 men | 8 621 men* | Never | 1.0 | | | |
| | | | | | | Ever (habitual) | 1.3 (0.7–2.5) | | | |
| | | | | 43 women | 23 161 women* | Never | 1.0 | | | |
| | | | | | | Ever (habitual) | 0.8 (0.3–1.8) | | | |
| | | | | Colon: Distal | | | | | | |
| | | | | 75 men | 8 621 men* | Never | 1.0 | | | |
| | | | | | | Ever (habitual) | 1.1 (0.7–1.9) | | | |
| | | | | 62 women | 23 161 women* | Never | 1.0 | | | |
| | | | | | | Ever (habitual) | 0.8 (0.4–1.5) | | | |
| | | | | Rectum | | | | | | |
| | | | | 131 men | 8 621 men* | Never | 1.0 | | | |
| | | | | | | Ever (habitual) | 1.1 (0.7–1.6) | | | |
| | | | | 70 women | 23 161 women* | Never | 1.0 | | | |
| | | | | | | Ever (habitual) | 1.3 (0.7–2.2) | | | |
| Murata et al. (26) | 1984–93 | Nested case–control study (participants of stomach cancer screening by the Chiba Cancer Association) | Cases: confirmed by a record linkage to cancer registry data; Controls: screenees free from any cancer during the follow-up period | Colon | | | | | Matched (1 : 2) for sex, birth, age (±2 years) and residence | *One cup of sake (180 ml) includes 27 ml of ethanol. Intake of other beverages was converted to sake-equivalents; **compared with non-drinker |
| | | | | 61 men | 122 men | Non-drinker | 1.0 | | | |
| | | | | | | Drinker | NA | | | |
| | | | | | | ≤1.0 cups/day* | 3.5 (<0.01) | | | |
| | | | | | | 1.1–2.0 | 1.9 (NS) | | | |
| | | | | | | ≥2.1 | 3.2 (<0.05) | <0.05 | | |
| | | | | Colon | | | | | | |
| | | | | 61 men | 122 men | Non-drinker | 1.0 | | | |
| | | | | | | ≤1.0 cups/day* | 3.5 (<0.01) | | | |
| | | | | | | ≥1.1 | 2.3 (NS) | NA | | |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | Type of beverage | Sake** | 3.0 (<0.01) | | | |
| | | | | | | Others** | 2.8 (<0.05) | | | |
| | | | | Proximal colon | | | | | | |
| | | | | 24 men | 48 men | Non-drinker | 1.0 | | | |
| | | | | | | ≤1.0 cups/day* | 30.7 (<0.01) | | | |
| | | | | | | ≥1.1 | 12.4 (<0.05) | NA | | |
| | | | | | Type of beverage | Sake** | 20.6 (<0.01) | | | |
| | | | | | | Others** | 23.0 (<0.01) | | | |
| | | | | Sigmoid colon | | | | | | |
| | | | | 20 men | 40 men | Non-drinker | 1.0 | | | |
| | | | | | | ≤1.0 cups/day* | 1.4 (NS) | | | |
| | | | | | | ≥1.1 | 1.0 (NS) | NA | | |
| | | | | | Type of beverage | Sake** | 1.3 (NS) | | | |
| | | | | | | Others** | 1.1 (NS) | | | |
| | | | | Rectum | | | | | | |
| | | | | 43 men | 86 men | Non-drinker | 1.0 | | | |
| | | | | | | Drinker | NA | | | |
| | | | | | | ≤1.0 cups/day* | 0.8 (NS) | | | |
| | | | | | | 1.1–2.0 | 1.9 (NS) | | | |
| | | | | | | ≥2.1 | 1.4 (NS) | NS | | |
| Yamada et al. (27) | 1991–93 | Health check-up-based (PL Tokyo Health Care Center, multiphasic health check-up) | Cases: histologically confirmed cases; Controls: examinees without history of colorectal cancer and inflammatory bowel disease | Colorectum 66 (M: 55, F: 11) | 132 (M: 110, F: 22) | Non-drinker | 1.0 | | Matched (1 : 2) for sex, age and history of prior health check-up at the centre; adjusted for body mass index and smoking | Results for carcinoma *in situ* ($n$ = 129) were also presented. |
| | | | | | | Current | NA | | | |
| | | | | | | 1–2 times/month | 0.4 (0.1–2.1) | | | |
| | | | | | | 1–3 times/week | 1.1 (0.4–3.1) | | | |
| | | | | | | Almost daily | 1.2 (0.5–3.1) | 0.4 | | |
| | | | | | | Non-drinker | 1.0 | | | |
| | | | | | | 1–20 g/day | 1.1 (0.4–3.1) | | | |
| | | | | | | 21–40 | 0.7 (0.3–1.9) | | | |
| | | | | | | >41 | 2.0 (0.7–5.4) | 0.09 | | |
| | | | | | Index of cumulative consumption | Non-drinker | 1.0 | | | |
| | | | | | | 1–1000 g/year | 0.7 (0.3–1.8) | | | |
| | | | | | | 1001–2000 | 1.3 (0.5–3.7) | | | |
| | | | | | | ≥2001 | 3.2 (1.0–10.1) | 0.005 | | |

**Table 2.** *Continued*

| Reference | Study period | Study subjects | | | | Category | Odds ratio (95% confidence interval or *P*) | *P* for trend | Confounding variables considered | Comments |
|---|---|---|---|---|---|---|---|---|---|---|
| | | Type and source | Definition | No. of cases | No. of controls | | | | | |
| Ping et al. (28) | 1986–94 | Health check-up- based (Tokay University Hospital: health check-up examinees) | Cases: histologically confirmed cases; Controls: cancer-free examinees | Colorectum<br>100 (M: 77, F: 23) | 265 (NA) | Past*<br>Current* | 1.71 (1.07–2.74)<br>1.58 (0.98–2.57) | NA | Matched (1 : 3) for sex, age (±2 years), data of health checking (±3 months) and residence;35 controls were excluded owing to a lack of lifestyle data | *Large consumption of alcohol; definition of 'large consumption' is not described; reference comprises non-drinkers and other drinkers |
| Murata et al. (29) | 1989–97 | Hospital- based case–control study (Chiba Cancer Center Hospital) | Cases: those who underwent surgery Controls: outpatients free from cancer | Colorectum<br>267 men | 395 men | Non-drinker<br>Drinker<br><1.0 go<br>1.0–1.9<br>2.0–2.9<br>≥3.0 | 1.00<br>NA<br>0.51 (0.30–0.87)<br>0.85 (0.54–1.3)<br>1.81 (1.03–3.2)<br>2.19 (1.2–4.2) | <0.001 | Adjusted for age (10-year age group) | Women were also included in the study, but not analysed for the association with alcohol. |
| | | | | Colon<br>157 men | 395 men | Non-drinker<br>Drinker<br><1.0 go<br>1.0–1.9<br>2.0–2.9<br>≥3.0 | 1.00<br>NA<br>0.53 (0.29–0.99)<br>0.81 (0.48–1.4)<br>1.66 (0.88–3.1)<br>2.19 (1.1–4.5) | 0.003 | | |
| | | | | Rectum<br>110 men | 395 men | Non-drinker<br>Drinker<br><1.0 go<br>1.0–1.9<br>2.0–2.9<br>≥3.0 | 1.00<br>NA<br>0.48 (0.22–1.02)<br>0.84 (0.45–1.6)<br>2.04 (0.97–4.3)<br>2.10 (0.91–4.9) | 0.001 | | |

NA, not available; NS, not significant; M, men; F, women.

**Table 3.** Summary of the association between alcohol drinking and colorectal cancer risk, cohort study

| Reference | Study period | Study population | | | | | Magnitude of association* | | |
|---|---|---|---|---|---|---|---|---|---|
| | | Sex | No. of subjects | Age range (years) | Event | No. of incident cases or deaths | Colon | Rectum | Colorectum |
| Kono et al. (11) | 1965–83 | Men | 5130 | 27–89 | Death | 39 | NA | NA | — |
| Hirayama (12,13) | 1965–82 | Men | 122 261 | ⩾40 | Death | 256** | —*** | ↑ | NA |
| | | Women | 142 857 | ⩾40 | Death | 318** | —*** | — | NA |
| Shimizu et al. (14) | 1993–2000 | Men | 13 392 | ⩾35 | Incidence | 161 | ↑↑↑ | — | NA |
| | | Women | 15 659 | ⩾35 | Incidence | 134 | ↑↑ | ↑ | NA |
| Otani et al. (15) | 1990–99 | Men | 42 540 | 40–69 | Incidence | 457 | ↑↑ | ↑↑↑ | ↑↑↑ |
| | | Women | 47 464 | 40–69 | Incidence | 259 | NA | NA | — |
| Wakai et al. (16) | 1988–97 | Men | 23 708 | 40–79 | Incidence | 370 | ↑↑↑ | — | NA |
| | | Women | 34 028 | 40–79 | Incidence | 259 | — | ↑ | NA |

NA, not available.
*↑↑↑or ↓↓↓ strong; ↑↑or↓↓, moderate; ↑or↓, weak; —, no association (see text for more detailed definition).
**Colon only.
***Positive association was observed for sigmoid colon in men (↑↑↑) and in women (↑↑).

**Table 4.** Summary of the association between alcohol drinking and colorectal cancer risk, case–control study

| Reference | Study period | Study subjects | | | | Magnitude of association* | | |
|---|---|---|---|---|---|---|---|---|
| | | Sex | Age range | No. of cases | No. of controls | Colon | Rectum | Colorectum |
| Kondo (17) | 1967–73 | Men | Not specified | 205 | 408 | ↓↓↓ | ↓↓↓ | NA |
| | | Women | Not specified | 188 | 174 | — | — | NA |
| Watanabe et al. (18) | 1977–83 | Men and women | Not specified | 203 (M: 110, F: 93) | 203 (M: 110, F: 93) | — | — | NA |
| Tajima and Tominaga (19) | 1981–83 | Men | 40–79 years | 52 | 111 | — | — | NA |
| Kato et al. (20) | 1979–87 | Men | ⩾20 years | 3327 | 16 600 | —** | — | NA |
| Kato et al. (21) | 1986–90 | Men and women | Not specified | 223 | 578 | — | ↑ | NA |
| Yoshida et al. (22) | 1987–90 | Men and women | 25–79 years | 330 (M: 171, F: 159) | 660 (M: 342, F: 318) | ↑↑↑ | — | ↑↑↑ |
| Hoshiyama et al. (23) | 1984–90 | Men and women | 40–69 years | 181 (M: 98, F: 83) | 653 (M: 343, F: 310) | ↓↓↓ | ↓ | NA |
| Kotake et al. (24) | 1992–94 | Men and women | Not specified | 363 (M: 214, F: 149) | 363 (M: 214, F: 149) | — | — | NA |
| Inoue et al. (25) | 1988–92 | Men | 24–86 years | 257 | 8621 | — | — | NA |
| | | Women | 24–88 years | 175 | 23 161 | — | — | NA |
| Murata et al. (26) | 1984–93 | Men | Not specified | 104 | 208 | ↑↑↑ | — | NA |
| Yamada et al. (27) | 1991–93 | Men and women | 34–80 years | 66 (M: 55, F: 11) | 132 (M: 110, F: 22) | NA | NA | ↑↑↑ |
| Ping et al. 1998 (28) | 1986–94 | Men and women | 40–84 years | 100 (M: 77, F: 23) | 265 (NA) | NA | NA | ↑ |
| Murata et al. (29) | 1989–97 | Men | Not specified | 267 | 395 | ↑↑↑ | ↑↑ | ↑↑↑ |

NA, not available; M, men; F, women.
*↑↑↑or ↓↓↓, strong; ↑↑or↓↓, moderate;↑or↓, weak; —, no association (see text for more detailed definition).
**Weak positive association (↑) was observed for distal colon.

(22,26,27,29) showing a strong positive association also reported a significant dose–response relation.

We should mention methodological issues in general and specific to the Japanese studies reviewed here. Attention should be paid when interpreting the results of case–control studies. First, patient recall of lifestyles in the remote past may be influenced by recent lifestyles. Secondly, many diseases are potentially alcohol-related, and this may be a source of bias in case–control studies using patient group as the reference. Thirdly, colorectal cancer risk associated with ex-drinking may be overestimated because quitting drinking might be a result of cancer manifestation. Fourthly, since few case–control studies controlled for physical activity and obesity, identified factors predictive of colorectal cancer risk (6), confounding by these factors may account for the observed association between alcohol drinking and colorectal cancer. However, recent large-scale cohort studies (14–16) that controlled for known or suspected aetiologic factors of colorectal

cancer demonstrated a moderate or strong association, a finding arguing against confounding as an explanation for the association. Cohort studies have also their inherent limitations. Since only baseline information on lifestyles was used in analysis of the relation to colorectal cancer risk, the effect of bias related to changes in alcohol drinking habit during the time course cannot be ruled out. Moreover, we identified methodological differences among cohort studies reviewed; alcohol drinking habit was determined using simple, not-validated questionnaire, and death was the study outcome in earlier cohort studies, whereas in recent ones alcohol consumption was quantitatively estimated on the basis of a detailed, validated questionnaire and incidence was the study outcome. In this regard, more emphasis should be placed on the results of recent studies.

In experimental animals, there is sufficient evidence for the carcinogenicity of acetaldehyde (10), a metabolite of alcohol, whereas there is inadequate evidence for the carcinogenicity of ethanol and of alcoholic beverages (9). Although specific mechanisms whereby alcohol drinking influences colorectal carcinogenesis remains unclear, alcohol or acetaldehyde may induce DNA hypomethylation, an early step in colonic carcinogenesis, through its anti-folate effects (30). Moreover, acetaldehyde generated by intestinal bacteria may also increase the risk of colorectal cancer via folate deficiency (31).

The magnitude of association between alcohol drinking and colorectal cancer among Japanese studies appears to differ from that among Western populations. In a pooled analysis of Western cohort studies (32), relative risk of colon cancer for heavy alcohol drinkers consuming 45 g of alcohol or over per day versus non-drinkers was 1.2. In recent cohort studies in Japan, however, relative risks for colon cancer versus non-drinker category were 2.7 (14), 2.1 (15) and 2.4 (16) for the highest category of alcohol consumption, whose cut-off values were 37, 43 and 69 g of alcohol per day, respectively. Moreover, moderate drinking (<45 g/day) was materially unrelated to colon cancer risk in Western populations (32), whereas corresponding levels of alcohol consumption were associated with 1.4- to 1.8-fold increased risk of colon cancer among Japanese populations (14–16). These findings suggest that Japanese drinkers are more likely to develop colon cancer than Western counterparts. This may be explained in part by the relatively high prevalence of the slow-metabolizing ALDH variant among Japanese (7,29). Non-genetic factors may also contribute to the heterogeneity of risk among populations. For instance, a dietary pattern typical of Japanese drinkers—low consumption of fruits and vegetables and dairy foods (33)—may enhance the carcinogenic effects of alcohol or acetaldehyde. Furthermore, lean alcohol drinkers may be more likely to develop colorectal cancer than non-lean counterparts (32), presumably because of a differential effect of alcohol on insulin metabolism according to body composition. This may also account for the stronger alcohol–colon cancer association among the Japanese, who are on average leaner than Western people.

We found a consistent, moderate to strong positive association between alcohol drinking and colon cancer among major cohort studies, with some showing a dose–response relation, and among several case–control studies. For rectal cancer, most cohort studies showed a positive association with alcohol drinking, but the association was generally weaker than that for colon cancer. However, a pooled analysis of Western studies (32) did not exhibit significant variation in the magnitude of association according to site within the large bowel, and a Japanese study of alcohol and colorectal adenoma, a precursor of cancer, found a stronger association in the rectum compared with other sites of the colorectum (34). Thus, random variation may be a reason for the apparent inconsistent association for rectal cancer among Japanese studies. Moreover, the stronger and more consistent association in men than in women among Japanese studies may be attributable to a greater proportion of heavy drinkers in men, and not to a sex difference in disease susceptibility. Unfortunately, published data to date do not allow us to conduct a meta-analysis to confirm these, because results were presented according to alcohol consumption (in grams, millilitres or go) in most cohort studies but in less than half of the case–control studies among Japanese populations, whereas only drinking frequency was asked in other Japanese studies. A meta-analysis using original data set of recent cohort studies in Japan is now under way to clarify whether the magnitude of association differs according to site of the large bowel or sex and to quantify the impact of alcohol drinking on colorectal cancer risk among the Japanese population.

## EVALUATION OF EVIDENCE ON ALCOHOL DRINKING AND COLORECTAL CANCER RISK IN JAPANESE

From these results and on the basis of assumed biological plausibility, we conclude that alcohol drinking probably increases the risk of colorectal cancer among the Japanese population. More specifically, the association for colon is probable, whereas that for rectum is possible.

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# Cigarette Smoking and Liver Cancer Risk: An Evaluation Based on a Systematic Review of Epidemiologic Evidence among Japanese

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**Background:** Emerging epidemiologic data suggest that cigarette smoking may increase the risk of primary liver cancer. We evaluated this association based on a systematic review of epidemiologic evidence among Japanese populations.
**Methods:** Original data were obtained from MEDLINE searches using PubMed, complemented with manual searches. The evaluation was performed in terms of the magnitude of association ('strong', 'moderate', 'weak' or 'no association') in each study and the strength of evidence ('convincing', 'probable', 'possible' or 'insufficient'), together with biological plausibility as previously done by the International Agency for Research on Cancer.
**Results:** A total of 12 cohort studies and 11 case–control studies were identified. Nine cohort studies (two with adjustment for hepatitis B and C virus infections and seven without it) reported weak to strong positive associations between smoking and liver cancer, with dose–response relationships shown in three studies. Five case–controls studies (three with the virus adjustment and two without it) demonstrated such positive associations, with a dose–response relationship shown in only one study, while in six case–control studies, the observed associations were judged to be of the lowest magnitude or inverse due to the lack of any dose–response relationship.
**Conclusion:** We conclude that cigarette smoking 'probably' increases the risk of primary liver cancer among the Japanese. Potential confounding by hepatitis virus infection and virus–smoking interactions need to be addressed in future studies.

*Key words: systematic review – epidemiology – smoking – liver cancer – Japanese*

## INTRODUCTION

Primary liver cancer is one of the most common cancers in Japan (1). Its primary prevention remains to be a major concern for both clinicians and epidemiologists, since patients with this tumor still present poor prognosis (1,2). More than 90% of primary liver cancers in Japan are known to be hepatocellular carcinomas (2), which are mostly attributable to chronic infection with hepatitis C virus (HCV) and hepatitis B virus (HBV) (2,3). However, emerging evidence suggests that hepatocarcinogenesis is a multistage process, in which environmental factors other than hepatitis viruses may play additional roles (4). One of such candidates is cigarette smoking, which has not yet attracted much attention of clinicians or the public. Recently, the International Agency for Research on Cancer listed liver cancer as a tobacco-related malignancy (5). In this context, the objective of the present study was to review and summarize epidemiological findings on cigarette smoking and liver cancer among Japanese populations. This work was

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conducted as part of a project of systematic evaluation of the epidemiological evidence regarding lifestyles and cancers in Japan (6).

## METHODS

The details of the evaluation method have been described elsewhere (6). In brief, original data for this review were identified by MEDLINE searches using PubMed, complemented by manual searches of references from relevant articles where necessary. All epidemiologic studies on the association between cigarette smoking and liver cancer incidence or mortality among the Japanese from 1963 to 2005, including papers in press if available, were identified using the search terms 'smoking', 'liver', 'hepatocellular', 'cohort', 'follow-up', 'case–control', 'Japan' and 'Japanese' as keywords. Papers written in either English or Japanese were reviewed, and only studies on Japanese populations living in Japan were included. The individual results were summarized in the tables separately by a study design as cohort or case–control studies.

The evaluation was made based on the magnitude of association and the strength of evidence. First, the former was assessed by classifying relative risk (RR) in each study into the following four categories, while considering statistical significance (SS) or no statistical significance (NS): (i) 'strong' (symbol ↓↓↓ or ↑↑↑) when RR < 0.5 (SS) or RR > 2.0 (SS); (ii) 'moderate' (symbol ↓↓ or ↑↑) when RR < 0.5 (NS), 0.5 ≤ RR < 0.67 (SS), 1.5 < RR ≤ 2.0 (SS) or RR > 2.0 (NS); (iii) 'weak' (symbol ↓ or ↑) when 0.5 ≤ RR < 0.67 (NS), 0.67 ≤ RR ≤ 1.5 (SS) or 1.5 < RR ≤ 2.0 (NS) and (iv) 'no association' (symbol −) when 0.67 ≤ RR ≤ 1.5 (NS). When RRs for three or more exposure levels were reported, that for the highest level was employed for this classification. In the case of multiple publications of analyses of the same or overlapping datasets, only data from the largest or most updated results were included. After this process, the strength of evidence was evaluated in a similar manner to that used in the WHO/FAO Expert Consultation Report (7), in which evidence was classified as 'convincing', 'probable', 'possible' and 'insufficient'. We assumed that biological plausibility corresponded to the judgment of the most recent evaluation from the International Agency for Research on Cancer (5). Notwithstanding the use of this quantitative assessment rule, an arbitrary assessment cannot be avoided when considerable variation exists in the magnitude of association between the results of each study. The final judgment, therefore, was made based on a consensus of the research group members, and it was therefore not necessarily objective. When we reach a conclusion that there is 'convincing' or 'probable' evidence of an association, we conduct a meta-analysis to obtain summary estimates for the overall magnitude of association.

## MAIN FEATURES AND COMMENTS

We identified a total of 12 cohort studies (8–19) (Table 1) and 11 case–control studies (20–30) (Table 2). Of the cohort studies, three presented results by sex (9,14,19), four for men only (8,10,11,18) and five only for men and women combined (12,13,15–17). The respective numbers for the case–control studies are one (29), five (20,24–27) and five (21–23,28,30). One cohort study showed results separately in two different areas (11), and two case–control studies reported results separately based on hospital controls and community controls (25,29).

Study populations in the cohort studies were classified as two different types: mostly healthy subjects ($n = 7$) such as local residents (9,11,17–19), physicians (8) and atomic bomb survivors (14) versus patients with chronic liver disease (10,12,13,15,16) ($n = 5$) (Table 1). Chronic infections with both HCV and HBV were taken into account in only three studies, all of which followed patients with chronic liver disease (13,15,16). In the case–control studies, a similar classification was possible based on the type of controls: hospital or community controls (21–25,27–30) ($n = 9$) versus HBV carriers (20) or patients with chronic liver disease without liver cancer (26) ($n = 2$) (Table 2). In only two case–control studies, both HCV and HBV infections were controlled for (26,28).

A summary of the magnitude of association for the cohort studies and case–control studies is shown in Tables 3 and 4, respectively. Among all 12 cohort studies, five (9,13–15,19) reported strong positive associations of cigarette smoking with liver cancer in either sex or for both sexes combined (Tables 1 and 3); of the five studies, three (9,13,15) demonstrated clear dose–response relationships. Moderate, but not strong, positive associations were found in three cohort studies (10,11,18), and a weak association in one cohort study (17), without any presentation of dose–response relation. In the remaining three (8,12,16), virtually no association was observed. Among the seven cohort studies in which mostly healthy subjects were followed, six (9,11,14,17–19) revealed at least weak positive associations, whereas three (10,13,15) out of the five follow-up studies of patients with chronic liver disease showed such positive associations.

Among all 11 case–control studies, five (20,26–29) reported weak to strong positive associations with cigarette smoking, with a dose–response relationship presented in only one study (20) (Tables 2 and 4). In the remaining six studies (21–25,30), the observed associations were judged to be null or inverse due to the lack of dose–response relationship, although around 2- to 4-fold risk excess in light to moderate exposure categories was observed in five of them (21–25). In the nine case–control studies employing hospital or community controls, three (27–29) demonstrated at least weak positive associations, whereas both case–control studies using controls of HBV carriers or patients with chronic liver disease (20,26) afforded such positive associations.

In the cohort studies, cigarette smoking was almost consistently associated with elevated liver cancer risk. Information and selection biases may not be serious issues in those studies. However, potential confounding by chronic HBV and HCV

**Table 1.** Cohort studies on cigarette smoking and liver cancer among Japanese

| Reference | Study period | Study population | | | | Category | Number among cases | Relative risk (95% CI or *P*) | *P* for trend | Confounding variables considered | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Number of subjects for analysis | Source of subjects | Event followed | Number of incident cases or deaths | | | | | | |
| Kono et al. (8) | 1965–1983 | 5130 men | Male physicians in western Japan | Death | 51 men (primary 9, unspecified 42) | Never/past | | 1.00 | | Age, drinking | HBsAg and anti-HCV were not tested |
| | | | | | | 1–19 cigarettes/day | | 1.14 (0.59–2.20) | | | |
| | | | | | | ⩾20 cigarettes/day | | 1.04 (0.49–2.23) | | | |
| Akiba and Hirayama(9) | 1966–1981 | 265 118 (122 261 men and 142 857 women) | 95% of the census population in 29 health-center-covered areas in 6 prefectures | Death | 1050 (652 men and 398 women) | For men | | | | Age, prefecture, occupation, observation period | HBsAg and anti-HCV were not tested. Adjustment for alcohol consumption only slightly changed the relative risks |
| | | | | | | Never | 106 | 1.0 | 0.002 | | |
| | | | | | | Daily | 546 | 1.5 (1.2–1.9) | | | |
| | | | | | | 1–4/day | 8 | 1.1 (0.5–2.0) | | | |
| | | | | | | 5–14/day | 240 | 1.6 (1.3–2.0) | | | |
| | | | | | | 15–24/day | 254 | 1.4 (1.2–1.8) | | | |
| | | | | | | 25–34/day | 29 | 1.6 (1.1–2.4) | | | |
| | | | | | | ⩾35/day | 15 | 1.9 (1.1–3.2) | | | |
| | | | | | | For women | | | | | |
| | | | | | | Never | 334 | 1.0 | 0.001 | | |
| | | | | | | Daily | 64 | 1.6 (1.2–2.0) | | | |
| | | | | | | 1–4 /day | 9 | 1.4 (0.7–2.5) | | | |
| | | | | | | 5–14 /day | 42 | 1.4 (1.0–2.0) | | | |
| | | | | | | ⩾15 /day | 13 | 2.5 (1.3–4.1) | | | |
| Inaba et al. (10) | 1973–1988 | 270 men | Patients with liver cirrhosis at the Juntendo University Hospital | Death | 46 men | Never | | 1.00 | | Age, HBsAg, histories of transfusion, hepatitis and surgical operation, drinking | Anti-HCV was not tested |
| | | | | | | Current/past | | 2.57 (0.46–14.24) | | | |
| Shibata et al. (11) | 1958–1986 | 639 men in a farming area and 677 men in a fishing area | Residents in a farming or a fishing area in Kyushu | Death | 11 men (farming area) and 22 men (fishing area) | Farming area | | | | | |
| | | | | | | Non-smoker | 2 | 1.0 | >0.1 | Age | HBsAg and anti-HCV were not tested |
| | | | | | | Ex-smoker | 0 | – | | | |
| | | | | | | Current smoker | 8 | 1.1 (0.2–4.7) | | | |
| | | | | | | 1–9/day | 1 | 0.6 (0.1–3.7) | | | |
| | | | | | | 10–19/day | 7 | 1.2 (0.2–5.7) | | | |
| | | | | | | 20–29/day | 0 | – | | | |
| | | | | | | ⩾30/day | 0 | – | | | |
| | | | | | | Fishing area | | | | | |
| | | | | | | Non-smoker | 1 | 1.0 | >0.1 | Age | |
| | | | | | | Ex-smoker | 2 | 2.9 (0.3–29.0) | | | |

**Table 1.** *Continued*

| Reference | Study period | Study population | | | | Category | Number among cases | Relative risk (95% CI or *P*) | *P* for trend | Confounding variables considered | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Number of subjects for analysis | Source of subjects | Event followed | Number of incident cases or deaths | | | | | | |
| | | | | | | Current smoker | 19 | 3.6 (0.6–22.3) | | | |
| | | | | | | 1–9/day | 7 | 11.9 (1.5–96.8) | | | |
| | | | | | | 10–19/day | 3 | 1.1 (0.1–10.6) | | | |
| | | | | | | 20–29/day | 7 | 2.7 (0.4–19.2) | | | |
| | | | | | | ⩾30 /day | 2 | 3.2 (0.4–23.7) | | | |
| | | | | | | Fishing area | | | | | |
| | | | | | | Non/ex-smoker | 3 | 1.00 | | Age, drinking | |
| | | | | | | 1–19/day | 10 | 2.10 (0.44–9.95) | | | |
| | | | | | | ⩾20/day | 9 | 1.86 (0.37–9.40) | | | |
| Kato et al.(12) | 1987–1990 | 1784 | Patients with decompensated liver cirrhosis or post-transfusion hepatitis | Incidence | 122 | Never smoker | 39 | 1.00 | | Sex, age | HBsAg and anti-HCV status was unknown |
| | | | | | | Past smoker | 10 | 0.94 (0.44–2.02) | | | |
| | | | | | | Current smoker | 23 | 0.96 (0.53–1.75) | | | |
| | | | | | | Smoking index | | | | | |
| | | | | | | 0 | 39 | 1.00 | 0.82 | | |
| | | | | | | 1–599 | 11 | 0.83 (0.40–1.74) | | | |
| | | | | | | ⩾600 | 14 | 0.94 (0.47–1.89) | | | |
| Tsukuma et al. (13) | 1987–1991 | 917 (548 men and 369 women) | Patients with chronic hepatitis or compensated cirrhosis at the Center for Adult Diseases, Osaka | Incidence | 54 | Among all patients | | | | Age, sex, stage of disease, serum alpha-fetoprotein, HBsAg, anti-HBc, anti-HCV, drinking | HBsAg and anti-HCV status was adjusted for |
| | | | | | | Non-smoker | | 1.00 | 0.07 | | |
| | | | | | | Ex-smoker | | 1.68 (0.63–4.47) | | | |
| | | | | | | Current smoker | | 2.30 (0.90–5.86) | | | |
| | | | | | | Among patients with liver cirrhosis | | | | | |
| | | | | | | Non-smoker | | 1.00 | 0.003 | | |
| | | | | | | Ex-smoker | | 3.44 | | | |
| | | | | | | Current smoker | | 7.96 | | | |
| Goodman et al. (14) | 1980–1989 | 36 133 | Atomic bomb survivors | Incidence | 242 (156 men and 86 women) | For men | | | | Sex, city, age at the time of bombing, age, radiation dose to the liver | HBsAg and anti-HCV was not tested |
| | | | | | | Never-smoker | 6 | 1.00 | | | |
| | | | | | | Ever-smoker | 146 | 4.36 (1.93–9.86) | | | |
| | | | | | | Ex-smoker | 46 | 4.56 (1.95–10.7) | | | |
| | | | | | | Quit ⩾24 years ago | 14 | 4.04 (1.54–10.6) | | | |
| | | | | | | Quit 14–23 years ago | 14 | 4.11 (1.58–10.7) | | | |
| | | | | | | Quit <14 years ago | 14 | 5.60 (2.15–14.6) | | | |
| | | | | | | Present smoker | 100 | 4.26 (1.87–9.72) | | | |
| | | | | | | 1–22 pack-years | 38 | 6.47 (2.74–15.3) | | | |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | 23–40 pack-years | 39 | 4.43 (1.87–10.5) | | |
| | | | | | | ⩾41 pack-years | 41 | 3.09 (1.31–7.29) | | |
| | | | | | | For women | | | | |
| | | | | | | Never-smoker | 61 | 1.00 | | |
| | | | | | | Ever-smoker | 20 | 1.60 (0.97–2.66) | | |
| | | | | | | Ex-smoker | 7 | 1.66 (0.76–3.63) | | |
| | | | | | | Quit ⩾25 years ago | 3 | 2.31 (0.72–7.43) | | |
| | | | | | | Quit 10–24 years ago | 2 | 1.03 (0.25–4.24) | | |
| | | | | | | Quit <10 years ago | 2 | 10.4 (2.51–43.5) | | |
| | | | | | | Present smoker | 13 | 1.58 (0.86–2.88) | | |
| | | | | | | 1–15 pack-years | 8 | 1.81 (0.86–3.78) | | |
| | | | | | | ⩾16 pack-years | 8 | 1.51 (0.72–3.16) | | |
| Chiba et al.(15) | 1977–1993 | 412 (249 men and 163 women) | Patients with HCV-associated chronic hepatitis or compensated cirrhosis at the Tsukuba University Hospital | Incidence | 63 (54 men and 9 women) | Non-smoker | | 1.00 | | Sex, age, stage of disease, serum alpha-fetoprotein, anti-HBs, anti-HBc, histories of transfusion, surgical procedure and liver cancer in family, drinking | All subjects were anti-HCV-positive and HBsAg-negative |
| | | | | | | Smoking index <400 | | 1.67 (0.75–3.73) | | |
| | | | | | | Smoking index ⩾400 | | 2.46 (1.11–5.49) | | |
| Tanaka et al. (16) | 1985–1995 | 96 (62 men and 34 women) | Patients with liver cirrhosis at the Kyushu University Hospital | Incidence | 37 (27 men and 10 women) | Never smoker | 12 | 1.00 | | Sex, age, years since LC diagnosis, department, hospitalization status, serum albumin, AST, alpha-fetoprotein, HBsAg, anti-HCV, drinking | The relative risks were not described in the original paper, and were re-estimated by one of the authors (KT). HBsAg and anti-HCV status was adjusted for |
| | | | | | | Past smoker | 12 | 0.44 (0.11–1.79) | | |
| | | | | | | Current smoker | | | | |
| | | | | | | <20 cigarettes/day | 9 | 1.46 (0.29–7.37) | | |
| | | | | | | ⩾20 cigarettes/day | 4 | 1.00 (0.19–5.28) | | |
| Mori et al.(17) | 1992–1997 | 3052 (974 men and 2078 women) | Residents in a town in Saga prefecture | Incidence | 22 (14 men and 8 women) | History of cigarette smoking | | | | Sex, age | Anti-HCV and HBsAg status was available, but not adjusted for |
| | | | | | | No | 10 | 1.00 | | | |
| | | | | | | Yes | 22 | 2.10 (0.61–7.23) | | | |
| | | | | | | Never-smoker | 10 | 1.00 | 0.30 | | |
| | | | | | | Smoking index <200 | 1 | 3.26 (0.38–28.2) | | | |
| | | | | | | Smoking index ⩾200 | 11 | 1.97 (0.57–6.87) | | | |
| Mizoue et al. (18) | 1986–1996 | 4050 men | Residents in 4 municipalities in Fukuoka prefecture | Death | 59 men | Never smoker | 4 | 1.0 | | Age, study area, drinking | HBsAg and anti-HCV were not tested |
| | | | | | | Ex-smoker | 22 | 2.9 (1.0–8.4) | | | |
| | | | | | | Current smoker | 33 | 3.3 (1.2–9.5) | | | |
| | | | | | | 1–24 cigarettes/day | 25 | 3.5 (1.2–10.2) | | | |
| | | | | | | ⩾25 cigarettes/day | 8 | 2.8 (0.8–9.6) | | | |
| Ogimoto et al. (19) | 1988–1999 | 65 528 (28 287 men and 37 241 women) | Residents in 45 areas throughout Japan | Death | 186 (number by sex not described) | Men (40–59 years) | | | | Collaborating institutes | HBsAg and anti-HCV were not tested |
| | | | | | | Never smoker | | 1.00 | | | |
| | | | | | | Ex-smoker | | 2.37 (0.83–6.78) | | | |

**Table 1.** *Continued*

| Reference | Study period | Study population | | | | Category | Number among cases | Relative risk (95% CI or *P*) | *P* for trend | Confounding variables considered | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Number of subjects for analysis | Source of subjects | Event followed | Number of incident cases or deaths | | | | | | |
| | | | | | | Current smoker | | 1.96 (0.75–5.14) | | | |
| | | | | | | Men (60–79 years) | | | | | |
| | | | | | | Never smoker | | 1.00 | | | |
| | | | | | | Ex-smoker | | 2.72 (1.21–6.11) | | | |
| | | | | | | Current smoker | | 2.62 (1.18–5.84) | | | |
| | | | | | | Women (40–59 years) | | | | | |
| | | | | | | Never smoker | | 1.00 | | | |
| | | | | | | Ex-smoker | | – | | | |
| | | | | | | Current smoker | | 2.82 (0.61—13.09) | | | |
| | | | | | | Women (60–79 years) | | | | | |
| | | | | | | Never smoker | | 1.00 | | | |
| | | | | | | Ex-smoker | | 1.18 (0.16–8.67) | | | |
| | | | | | | Current smoker | | 1.49 (0.46–4.87) | | | |

CI, confidence interval; HBsAg, hepatitis B surface antigen; anti-HCV, antibody to hepatitis C virus; anti-HBc, antibody to hepatitis B core antigen; anti-HBs, antibody to hepatitis B surface antigen; LC, liver cirrhosis; AST, aspartate aminotransferase.

**Table 2.** Case–control studies on cigarette smoking and liver cancer among Japanese

| Reference | Study period | Study subjects | | | | Category | Relative risk (95%CI or P) | P for trend | Confounding variables considered | Comments |
|---|---|---|---|---|---|---|---|---|---|---|
| | | Type and source | Definition | Number of cases | Number of controls | | | | | |
| Oshima et al. (20) | 1972–1980 | Nested case–control (HBsAg-positive blood donors at the Osaka Red Cross Blood Center) | Cases: confirmed by record linkage with the Osaka Cancer Registry; Controls: healthy HBV carriers | 19 men | 38 men | None or <10/day | 1.0 | >0.10 | Matched (1:2) for birth year Adjusted for drinking | All subjects were HBsAg-positive. Anti-HCV was not tested |
| | | | | | | 10–29/day | 1.2 | | | |
| | | | | | | ⩾30/day | 6.3 | | | |
| Tsukuma et al. (21) | 1983–1987 | Hospital-based (Center for Adult Diseases, Osaka) | Cases: histologically confirmed as HCC; Controls: inpatients with gastrointestinal disease, or examinees for health checkups or gastroendoscopy; no liver disease, cancer, or smoking/alcohol-related disease | 229 (192 men and 37 women) | 266 (192 men and 74 women) | Never | 1.0 | | Frequency matched for sex and age Adjusted for sex, age, HBsAg, history of blood transfusion, drinking, and family history of liver cancer | Anti-HCV was not tested |
| | | | | | | Ex-smoker | 0.7 (0.3–1.9) | | | |
| | | | | | | Current smoker | 2.5 (1.4–4.5) | | | |
| | | | | | | 1–19/day | 4.2 | | | |
| | | | | | | 20–39/day | 2.2 | | | |
| | | | | | | ⩾40/day | 1.1 | | | |
| | | | | | | Cigarette index | | | | |
| | | | | | | 0–399 | 1.0 | | | |
| | | | | | | 400–799 | 1.9 (1.1–3.3) | | | |
| | | | | | | 800–1199 | 2.0 (1.1–3.6) | | | |
| | | | | | | ⩾1200 | 1.0 (0.5–1.9) | | | |
| Tanaka et al. (22) | 1985–1989 | Hospital-based (Kyushu University Hospital) | Cases: 40% were histologically confirmed as HCC; Controls: health examinees at a public health center | 204 (168 men and 36 women) | 410 (291 men and 119 women) | Non-smoker | 1.0 | | Frequency matched for sex and age Adjusted for sex, age, HBsAg, history of transfusion, drinking, and family history of liver disease | Anti-HCV status was available for part of the subjects, but not adjusted for |
| | | | | | | Ex-smoker | 1.5 (0.8–2.8) | | | |
| | | | | | | Current smoker | 1.5 (0.8–2.7) | | | |
| | | | | | | Pack-years | | 0.41 | | |
| | | | | | | 0–10.9 | 1.0 | | | |
| | | | | | | 11.0–26.2 | 1.4 (0.8–2.4) | | | |
| | | | | | | 26.3–35.9 | 1.3 (0.7–2.5) | | | |
| | | | | | | ⩾36.0 | 1.3 (0.7–2.5) | | | |
| Fukuda et al. (23) | 1986–1992 | Hospital-based (Kurume University Hospital) | Cases: 77% were histologically confirmed as HCC; Controls: inpatients without chronic hepatitis or cirrhosis in two general hospitals in Kurume | 368 (287 men and 81 women) | 485 (287 men and 198 women) | Never | 1.0 | | Matched (1:1 for men and 1:4 for women) for sex, age (±5 years), residence, and time of hospitalization. Adjusted for sex | The odds ratios (and 95% CIs) and P value for trend were not described in the original paper, and were estimated by one of the authors (KT), based on the Mantel–Haenszel and Mantel Extension methods |
| | | | | | | Ex-smoker | 1.3 (0.8–2.2) | | | |
| | | | | | | Current smoker | 1.8 (1.1–3.1) | | | |
| | | | | | | Cigarette index | | | | |
| | | | | | | Non-smoker | 1.0 | 0.48 | | |
| | | | | | | 1–499 | 1.7 (1.0–2.8) | | | |
| | | | | | | 500–999 | 1.5 (0.9–2.5) | | | |
| | | | | | | ⩾1000 | 0.6 (0.3–1.4) | | | |

**Table 2.** *Continued*

| Reference | Study period | Study subjects | | | | Category | Relative risk (95%CI or P) | P for trend | Confounding variables considered | Comments |
|---|---|---|---|---|---|---|---|---|---|---|
| | | Type and source | Definition | Number of cases | Number of controls | | | | | |
| Murata et al. (24) | 1984–1993 | Nested case–controls (male participants in a gastric mass screening by the Chiba Cancer Association) | Cases: confirmed by record linkage with the Chiba Cancer Registry; Controls: participants in the screening without liver cancer | 66 men | 132 men | Cigarettes/day | | | Matched (1:2) for sex, birth year (±2 years), and the first digit of the address code. No adjustment | Anti-HCV and HBsAg were not tested |
| | | | | | | None | 1.0 | 0.75 | | |
| | | | | | | 1–10 | 1.4 | | | |
| | | | | | | 11–20 | 2.0 ($P < 0.05$) | | | |
| | | | | | | ⩾21 | 0.4 | | | |
| Shibata et al. (25) | 1992–1995 | Hospital-based (Kurume University Hospital) | Cases: confirmed as HCC by histological, angiographical, and/or other findings; Hospital controls (HCs): inpatients without chronic hepatitis or cirrhosis in 2 general hospitals in Kurume; Community controls (CCs): randomly sampled citizens of Kurume | 115 men | 115 male HCs and 115 male CCs | Cigarette index, based on HCs | | | Matched (1:1) for sex, age (±5 years for HCs and ±3 years for CCs), residence (for HCs) and time of hospitalization (for HCs). Adjusted for matching factors | Anti-HCV and HBsAg status was available, but not adjusted for |
| | | | | | | Non-smoker | 1.0 | | | |
| | | | | | | 1-499 | 1.6 (0.6–4.0) | | | |
| | | | | | | 500-999 | 1.2 (0.5–2.9) | | | |
| | | | | | | ⩾1000 | 0.7 (0.2–2.0) | | | |
| | | | | | | Cigarette index, based on CCs | | | | |
| | | | | | | Non-smoker | 1.0 | | | |
| | | | | | | 1-499 | 2.1 (0.9–4.7) | | | |
| | | | | | | 500-999 | 1.9 (0.8–4.6) | | | |
| | | | | | | ⩾1000 | 1.2 (0.4–3.5) | | | |
| Mukaiya et al. (26) | 1991–1993 | Hospital-based (Sapporo Medical University Hospital) | Cases: histologically and/or clinically confirmed as HCC; Controls: chronic liver disease (hepatitis or cirrhosis) without HCC | 104 men | 104 men | Non-smoker | 1.00 | | Matched (1:1) for age (±3 years). Adjusted for age | Additional adjustment for drinking and HBV and HCV infections did not materially alter the results |
| | | | | | | Ever-smoker | 3.50 (1.41–8.70) | | | |
| | | | | | | Period < 5years | 1.00 | | | |
| | | | | | | Period ⩾ 5years | 3.33 (1.34–8.30) | | | |
| | | | | | | Cigarette index | | | | |
| | | | | | | <200 | 1.00 | | | |
| | | | | | | ⩾200 | 3.33 (1.34–8.30) | | | |
| Takeshita et al. (27) | 1993–1996 | Hospital-based (20 major hospitals in the southern part of Hyogo prefecture) | Cases: 64% were histologically confirmed as HCC; Controls: outpatients or inpatients with various diseases, but without liver disease positive for HBsAg and/or anti-HCV | 102 (85 men and 17 women) | 125 (101 men and 24 women) | Men | | | Frequency matched for hospital, sex, age, and living area Adjusted for age and drinking | All the controls were HBsAg-negative and anti-HCV-negative by definition |
| | | | | | | Non-smoker | 1.0 | | | |
| | | | | | | Ex-smoker | 0.7 (0.3–1.5) | | | |
| | | | | | | Current smoker | 1.6 (0.7–3.5) | | | |
| | | | | | | Women | | | | |
| | | | | | | Not described | | | | |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Koide et al. (28) | 1994 | Hospital-based (Nagoya City University Hospital) | Cases: clinically and/or histologically confirmed as HCC; community controls: selected from the same resident community as cases, with no signs of hepatic diseases or HCC | 84 (64 men and 20 women) | 84 (64 men and 20 women) | Never<br>Current + former | 1.00<br>5.41 (1.10–26.70) | Matched (1:1) for sex and age (±2 years)<br>Adjusted for sex, age, history of blood transfusion, anti-HBc, anti-HCV, and CYP2E1 | |
| Matsuo et al. (29) | 1995–2000 | Hospital-based (Kurume University Hospital) | Cases: confirmed as HCC by histological, angiographical, and/or other findings; hospital controls (HCs): inpatients without chronic hepatitis or cirrhosis in 2 general hospitals in Kurume; Community controls (CCs): randomly sampled citizens of Kurume | 222 (177 men and 45 women) | 326 HCs (177 men and 149 women) and 222 CCs (177 men and 45 women) | Men based on HCs<br>Non-smoker<br>1–24 pack-years<br>25-49 pack-years<br>≥50 pack-years<br>Men based on CCs<br>Non-smoker<br>1–24 pack-years<br>25–49 pack-years<br>≥50 pack-years<br>Women based on HCs<br>Non-smoker<br>1–24 pack-years<br>≥25 pack-years<br>Women based on CCs<br>Non-smoker<br>1–24 pack-years<br>≥25 pack-years | <br>1.00<br>2.95 ($P < 0.05$)<br>2.15 ($P < 0.05$)<br>1.13<br><br>1.00<br>4.39 ($P < 0.05$)<br>2.75 ($P < 0.05$)<br>2.90 ($P < 0.05$)<br><br>1.00<br>1.69<br>0.68<br><br>1.00<br>2.00<br>∞ | Matched for sex (1:4 for female HCs and 1:1 for other controls), age (±5 years for HCs and ±3 years for CCs), residence (for HCs), and time of hospitalization (for HCs)<br>Adjusted for matching factors | Anti-HCV and HBsAg status was available except for CCs, but not adjusted for |
| Munaka et al. (30) | 1997–1998 | Hospital-based (University of Occupational and Environmental Health Hospital) | Cases: no detailed description; controls: no evidence of cancer in any organ | 78 (61 men and 17 women) | 139 (94 men and 44 women) | Cigarette index<br>Never<br>1 ≤ 400<br>400 ≤ 800<br>≥800 | <br>1.00<br>1.14 (0.58–2.25)<br>1.09 (0.56–2.14)<br>1.09 (0.56–2.15) | Unmatched. Adjusted for sex and age | Anti-HCV and HBsAg status was available, but not adjusted for |

CI, confidence interval; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; anti-HCV, antibody to hepatitis C virus; HCC, hepatocellular carcinoma; HCs, hospital controls; CCs, community controls; HCV, hepatitis C virus; anti-HBc, antibody to hepatitis B core antigen; CYP2E1, cytochrome P450 2E1.