Short Communication

Epstein–Barr virus serology and gastric cancer incidence and survival

J Koshiol*,1,2, Y-L Qiao3, SD Mark4, SM Dawsey2, CC Abnet2, F Kamangar2, ET Lennette5, Z-W Dong3 and PR Taylor2

1Cancer Prevention Fellowship, Division of Cancer Prevention, National Cancer Institute, 6120 Executive Blvd., MSC 7236, Bethesda, MD, USA; 2Division of Cancer Epidemiology and Genetics, National Cancer Institute, Bethesda, MD, USA; 3Cancer Institute, Chinese Academy of Medical Sciences, Beijing, People’s Republic of China; 4Department of Preventive Medicine and Biometrics, University of Colorado Medical Center, Boulder, CO, USA; 5Nectandra Institute, San Ramon, Costa Rica

Among 185 cases of gastric cancer and 200 controls in Linxian, China, Epstein–Barr virus (EBV) seropositivity was not associated with increased risk of gastric cancer: High EBV nuclear antigen titres were associated with longer survival in cardia cancer cases, possibly due to chance.

British Journal of Cancer (2007) 97, 1567 – 1569. doi:10.1038/sj.bjc.6604063 www.bjcancer.com

Published online 6 November 2007
© 2007 Cancer Research UK

Keywords: EBV; gastric cancer; incidence; survival

MATERIALS AND METHODS

The NIT was a cancer chemoprevention trial in Linxian, China, conducted from March 1986 through May 1991, that enrolled 29,584 participants (Blot et al., 1993). Follow-up for additional survival is available through May 2001 (Tran et al., 2005). We analysed the relation of baseline EBV seropositivity to gastric cancer incidence in a nested case–control study of cardica cancer cases (N = 102, a random sample of the 435 cases that arose during the trial period), non-cardica cancer cases (N = 83), and randomly selected controls (N = 200). Case and control selection methods have been described elsewhere (Mark et al., 2000). We also analysed the association between EBV seropositivity and survival among gastric cancer cases.

*Correspondence: Dr J Koshiol; E-mail: koshiolj@mail.nih.gov
Received 13 August 2007; revised 3 October 2007; accepted 8 October 2007; published online 6 November 2007

RESULTS

Cases tended to be older than controls and were more likely to be males, smokers, and HP positive (Table 1). Among all subjects, EBV VCA IgA was detectable in 2%, EA-D IgA in 14%, and EA-R IgG in 9%. VCA IgG EBNA and antibody titre levels were above the median in the controls in 37% of all subjects.

Overall, prediagnostic EBV seropositivity was not positively associated with gastric cancer in this population (Table 2). In fact, the direction and magnitude of the associations suggested that EBV seropositivity was associated with decreased risk, especially tumours originating in the gastric cardia. A restricted analysis of...
cases diagnosed ≥2 years after serology strengthened the association for high VCA IgG but not EBNA.

There was no difference in survival by VCA IgG. Survival was longer among individuals with high vs low EBNA (hazard ratio (HR): 0.71, 95% CI: 0.51 –0.98). This difference was found in cardia (HR: 0.46, 95% CI: 0.29 –0.74) but not in non-cardia cancer cases (HR: 1.18, HR: 0.74 –1.88) (Figure 1). Using the likelihood ratio test for multiplicative interaction, the HR for baseline EBNA seropositivity and gastric cancer varied by tumour location (P-value = 0.03). It is relevant to note, however, that the data become sparse in the tails of the survival curves, so these findings may be due to chance.

**DISCUSSION**

We found that prediagnostic EBV seropositivity was not positively associated with gastric cancer in this population and rather may be associated with decreased risk, especially for gastric cardia cancer which, unusually, is more common than non-cardia gastric cancer in Linxian (Blot et al, 1993). High baseline EBNA titres were also associated with decreased risk of death after diagnosis among gastric cardia cancer cases. Since EBV seropositivity is established by both viral activity and immune response, these associations may reflect an increased immune response due to viral infection leading to reduced gastric cancer incidence and longer survival.

In contrast to our study, the only previous prospective study reported generally elevated ORs, suggesting an increased risk of gastric cancer with EBV seropositivity (Levine et al, 1995). The opposite patterns of risk found in these two studies may be due to (1) chance, with no true underlying association, (2) differences in study populations, or (3) different distributions of tumour location since the previous study included few gastric cardia cancers, while over half the cases in our study had cardia cancer.

Although previous studies of EBV DNA in gastric tumour tissue and survival have produced inconsistent results (Chang et al, 2001; Lee et al, 2004), some have found improved survival associated with EBV, at least in subgroups (Koriyama et al, 2002; Lee et al, 2004; van Beek et al, 2004). Our association between high EBNA titres and improved survival was also limited to a subgroup, cardia cancers, although this finding may be due to chance. Further, we did not have tumour tissue available to directly test for EBV DNA.

In conclusion, we did not find a positive association between prediagnostic EBV seropositivity and gastric cancer. In fact, there was some evidence that EBV seropositivity was associated with a reduced risk of cancer and a reduced risk of death after diagnosis of cardia cancer. These results support the hypothesis that cardia and non-cardia cancers may be aetiologically different and should be evaluated separately in future studies.

**Table 1** Selected characteristics and univariate associations with gastric cancer for nested case–control subjects from the General Population Nutrition Intervention Trial cohort

| Characteristic                  | N Cases (%) | N Controls (%) |
|--------------------------------|-------------|----------------|
| **Age (years)**                |             |                |
| <50                            | 32 (17.7)   | 58 (29.0)      |
| 50–60                          | 79 (42.7)   | 68 (34.0)      |
| >60                            | 74 (40.0)   | 74 (37.0)      |
| **Gender**                     |             |                |
| Male                           | 113 (61.1)  | 98 (49.0)      |
| Female                         | 72 (38.9)   | 102 (51.0)     |
| **Smoking (regularly for ≥6 months)** |       |                |
| No                             | 102 (55.1)  | 139 (69.5)     |
| Yes                            | 83 (44.9)   | 61 (30.5)      |
| **Alcohol (in last 12 months)**|             |                |
| Never/rare                    | 143 (77.3)  | 160 (80.0)     |
| Sometimes/more often           | 42 (22.7)   | 40 (20.0)      |
| **Helicobacter pyloni**        |             |                |
| Negative                      | 48 (27.8)   | 73 (45.3)      |
| Positive                      | 125 (72.2)  | 88 (54.7)      |

*Numbers do not add up to totals because of missing values.

**Table 2** Association between prediagnostic EBV seropositivity and development of gastric cancer in the General Population Nutrition Intervention Trial cohort for all cases combined and stratified by tumour location

| EBV variable | All cases (n = 185) | Cardia (n = 102) | Non-cardia (n = 83) |
|--------------|---------------------|-----------------|---------------------|
|              | N positive cases    | OR (95% CI)     | N positive cases    | OR (95% CI)     | N positive cases    | OR (95% CI)     |
| VCA IgA positive | 3 (0.69 (0.15–3.21) | 1 (0.46 (0.05–4.20) | 2 (0.90 (0.15–5.40) |
| EA-D IgG positive | 26 (0.95 (0.53–1.70) | 13 (0.82 (0.41–1.67) | 13 (1.23 (0.58–2.60) |
| EA-R IgG positive | 11 (0.52 (0.24–1.11) | 6 (0.49 (0.19–1.23) | 5 (0.55 (0.19–1.57) |
| High VCA IgG* | 60 (0.72 (0.47–1.09) | 32 (0.63 (0.38–1.05) | 28 (0.83 (0.47–1.46) |
| Restricted* | 32 (0.60 (0.36–0.99) | 19 (0.54 (0.30–0.99) | 13 (0.70 (0.33–1.61) |
| Restricted* | 67 (0.91 (0.60–1.39) | 38 (0.97 (0.59–1.60) | 29 (0.79 (0.45–1.39) |

*Adjusted for age and gender. Odds ratios (ORs) for ordinal VCA IgG all cases, 0.89 (0.78 –1.02); cardia cases, 0.86 (0.74 –1.00); non-cardia cases, 0.96 (0.80 –1.14). *Restricted to cases diagnosed after 2 years of follow-up.
REFERENCES

Blot WJ, Li JY, Taylor PR, Guo W, Dawsey S, Wang GQ, Yang CS, Zheng SF, Gail M, Li GY, Yu Y, Liu B, Tangrea J, Sun Y, Liu F, Fraumeni JF, Zhang YH, Li B (1993) Nutrition intervention trials in Linxian, China: supplementation with specific vitamin/mineral combinations, cancer incidence, and disease-specific mortality in the general population. *J Natl Cancer Inst* 85: 1483 – 1492

Chang MS, Lee HS, Kim CW, Kim YI, Kim WH (2001) Clinicopathologic characteristics of Epstein–Barr virus-incorporated gastric cancers in Korea. *Pathol Res Pract* 197: 395 – 400

Koriyama C, Akiba S, Itoh T, Kijima Y, Sueyoshi K, Corvalan A, Herrera-Goepfer R, Eizuru Y (2002) Prognostic significance of Epstein–Barr virus involvement in gastric carcinoma in Japan. *Int J Mol Med* 10: 635 – 639

Lee HS, Chang MS, Yang HK, Lee BL, Kim WH (2004) Epstein–Barr virus-positive gastric carcinoma has a distinct protein expression profile in comparison with Epstein–Barr virus-negative carcinoma. *Clin Cancer Res* 10: 1698 – 1705

Levine PH, Stemmermann G, Lennette ET, Hildesheim A, Shibata D, Nomura A (1995) Elevated antibody titers to Epstein–Barr virus prior to the diagnosis of Epstein–Barr-virus-associated gastric adenocarcinoma. *Int J Cancer* 60: 642 – 644

Mark SD, Qiao YL, Dawsey SM, Wu YP, Katki H, Gunter EW, Fraumeni Jr JF, Blot WJ, Dong ZW, Taylor PR (2000) Prospective study of serum selenium levels and incident esophageal and gastric cancers. *J Natl Cancer Inst* 92: 1753 – 1763

Tran GD, Sun XD, Abnet CC, Fan JH, Dawsey SM, Dong ZW, Mark SD, Qiao YL, Taylor PR (2005) Prospective study of risk factors for esophageal and gastric cancers in the Linxian general population trial cohort in China. *Int J Cancer* 113: 456 – 463

van Beek J, zur Hausen A, Klein Kranenburg E, van de Velde CJ, Middeldorp JM, van den Brule AJ, Meijer CJ, Bloemena E (2004) EBV-positive gastric adenocarcinomas: a distinct clinicopathologic entity with a low frequency of lymph node involvement. *J Clin Oncol* 22: 664 – 670

Young LS, Rickinson AB (2004) Epstein–Barr virus: 40 years on. *Nat Rev* 4: 757 – 768

EBV and gastric cancer

J Koshiol et al

© 2007 Cancer Research UK

British Journal of Cancer (2007) 97(11), 1567 – 1569