Low prevalence of Epstein–Barr virus in incident gastric adenocarcinomas from the United Kingdom

An early report that the Epstein–Barr virus (EBV) was present in the majority of lymphoepithelial-like carcinomas (LELCs) of the stomach, a rare form of gastric neoplasia (Shibata et al, 1991), was followed by the detection of EBV in 16% of typical gastric adenocarcinomas (Shibata and Weiss, 1992). The subsequent finding of monoclonal EBV episomes (Imai et al, 1994; Ott et al, 1994) and transforming proteins (zur Hausen et al, 1994; Ott et al, 1994) not only suggested an aetiological role for this virus in these tumours, but also the possibility that immunotherapy, for example CTL-based anti-EBV therapies (Rooney et al, 1998) might prolong survival for patients with virus-positive tumours. Before investing in such a strategy it is necessary to determine the numbers of patients who are likely to benefit. Here we report the largest survey of the prevalence of EBV in gastric adenocarcinomas undertaken outside Asia.

MATERIALS AND METHODS

The base population comprised 497 consecutive patients who were first diagnosed with gastric adenocarcinoma between 1993–1999 and who had their tumours resected in one of three hospitals from the West Midlands, UK. This series was supplemented by an additional 69 patients with unresected disease in whom the diagnosis was made on gastric biopsy. Eight cases were excluded when histopathological review could not confirm the original diagnosis and 24 because there was insufficient material for the preparation of tissue arrays. EBV status was determined on the remaining 534 patients. All exclusions were from resected cases.

A 4 mm-diameter needle was used to sample representative tumour areas from paraffin blocks using a modification of the method described by Kononen et al (1998). Twenty cylindrical tumour cores were positioned in 5 mm holes cut from a 2.5 × 3 cm piece of paraffin-embedded liver tissue. Four micron thick sections cut from the array were adhered to Vectabond® coated slides and in situ hybridisation for the detection of the EBV-encoded RNAs (EBERs) performed according to standard methods (Wu et al, 1990). Positive controls which included cores from known EBV-positive gastric cancers were seeded into arrays. Seventy-five which tested negative for EBERs in tissue arrays, were re-evaluated by in situ hybridisation of the originating tissue blocks. U6 and sense control probes were included in all runs and assays were performed in duplicate.

RESULTS

The mean age of patients in this series was 65.4 years (range 34 – 87 years). The male to female ratio was 2.2:1. Among 465 patients with resected disease 214 (46%) were classified as intestinal type according to the criteria of Lauren (1965), 112 (24%) were diffuse, 108 (23%) mixed and 31 (7%) were unclassifiable. One hundred and sixty-two (35%) of resected tumours involved the cardia, 289 (62%) the corpus/antrum, two (0.4%) the gastric stump and in 12 (2.6%) subsite was unknown. EBERs were detected in 9 out of 534 (1.7%) tumours in eight patients with resected disease and in one of those diagnosed on gastric biopsy. Both gastric stump cancers were EBV-positive.

DISCUSSION

The prevalence of EBV-positive cancers in this series of gastric adenocarcinomas is substantially less than that reported elsewhere (Table 1). We believe this is not the result of sampling error in the preparation of the tissue arrays because re-evaluation of EBER-negative tumours using the originating tissue blocks revealed no false-negatives and our findings are similar to those reported in two smaller studies also undertaken in the UK which used tissue blocks when testing for the presence of EBERs (Rowlands et al, 1993; Shousha and Luqmani, 1994).

Keywords: Epstein – Barr virus; gastric adenocarcinoma; EBERs
and both gastric LELC and LELCs at other sites are more common to have a LELC. These tumours are strongly associated with EBV total testing positive for EBV. No patient in our series was found comparatively small numbers of cancers with only 10 tumours in been reported in other European series, estimates are based on

Although a higher detection rate of EBV-positive tumours has reported in other European series, estimates are based on comparatively small numbers of cancers with only 10 tumours in total testing positive for EBV. No patient in our series was found to have a LELC. These tumours are strongly associated with EBV and both gastric LELC and LELCs at other sites are more common in Asia (Gaffey and Weiss, 1990). The higher rate of detection of EBV in gastric adenocarcinomas observed in large Asiatic series suggests that gastric tumours are another site of cancer where the strength of the association with EBV varies with the population studied.

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Table 1 Prevalence of EBV in gastric adenocarcinomas

| Reference                   | Country                     | Number of gastric adenocarcinomas | Number of EBV+ gastric adenocarcinomas (%) |
|-----------------------------|-----------------------------|----------------------------------|------------------------------------------|
| Tokunaga et al (1993b)      | Japan                       | 1175                             | 102 (5.7)                                |
| Imai et al (1994)           | Japan                       | 991                              | 62 (6.2)                                 |
| Tokunaga et al (1993a)      | Japan                       | 990                              | 59 (5.9)                                 |
| Burgess et al (present study) | UK                          | 534                              | 9 (1.7)                                  |
| Chang et al (2000)          | Korea                       | 292                              | 10 (3.4)                                 |
| Galetsky et al (1997)       | Russia                      | 206                              | 18 (8.7)                                 |
| Rowlands et al (1993)       | UK                          | 117 UK                           | 2 (1.7)                                  |
| Qiu et al (1997)            | Japan                       | 51 Japan                         | 1 (2)                                    |
| Shibata and Weiss (1992)    | USA                         | 138                              | 22 (16)                                  |
| Wu et al (2000)             | Taiwan                      | 139                              | 19 (13.7)                                |
| Herrera-Goeppert et al (1999) | Mexico                      | 130                              | 6 (4.6)                                  |
| Montani et al (1996)        | Japan                       | 120                              | 5 (4.2)                                  |
| Yanai et al (1997)          | Japan                       | 109                              | 7 (6.4)                                  |
| Yuen et al (1994)           | Hong Kong                   | 71                               | 6 (8.4)                                  |
| Leoncini et al (1993)       | Italy                       | 65                               | 3 (4.6)                                  |
| Ham et al (1995)            | Taiwan                      | 54                               | 5 (9.3)                                  |
| Chapel et al (2000)         | France                      | 52                               | 4 (7.7)                                  |
| Nakamura et al (1994)       | Japan                       | 42                               | 4 (9.5)                                  |
| Ott et al (1994)            | Germany                     | 35                               | 3 (8.5)                                  |
| Ohfuji et al (1996)         | Japan                       | 23                               | 0                                        |
| Shousha and Luqmani (1994)  | UK                          | 11                               | 0                                        |

†LELC excluded, as were series in which LELC could not separately be distinguished from adenocarcinomas, includes only series with >10 cases.
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