Short Communication

EBV-associated gastric carcinoma in high- and low-incidence areas for nasopharyngeal carcinoma

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BACKGROUND: Approximately 10% of gastric carcinomas are associated with Epstein–Barr virus (EBV). The Inuit in Greenland have a high incidence of EBV-associated nasopharyngeal carcinoma.

METHODS: We conducted a population-based case–control study comparing gastric carcinomas in Greenland and in Denmark.

RESULTS: The prevalence rate of EBV-associated gastric carcinomas was 8.5% in both populations.

CONCLUSION: The findings of this study argue against a general susceptibility to EBV-associated carcinomas among the Inuit.

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To determine whether the proportion of EBV-associated gastric carcinomas differs in the Inuit compared with that in the Danish population, we conducted a population-based comparative study of patients with gastric carcinoma in Greenland and Denmark.

MATERIALS AND METHODS

The proportion of EBV-associated gastric carcinomas in Greenland and Denmark was examined in a case–control design using the Danish Cancer Registry (DCR), the Danish Civil Registration System and the Danish Pathology Database. All individuals in Denmark and Greenland are registered in the Civil Registration System (CRS). The CRS was established in Denmark on 1 April 1968 and in Greenland on 1 June 1972, when all persons alive and resident were registered and assigned a unique personal identification number (the person number). Information on cancer was retrieved from the DCR. Reporting of cancer cases to the DCR is mandatory in both Greenland and Denmark, and the coverage of the Cancer Registry in Denmark has shown to be 95–98% (Storm et al., 1997). Since 1975, the main source of information in the registry in Greenland has been notifications from physicians diagnosing and treating cancer patients, supplemented by the information obtained from pathology reports and death certificates. Information in the registry related to cancer cases in Greenland before 1975 was obtained from a study based on review of patient records from all hospitals in Greenland (Nielsen, 1986; Storm et al., 1997). The proportion of cases based on histological verification during the period 1973–1997 was 93 and 85% in Denmark and Greenland, respectively (Friborg et al., 2003).

All gastric carcinomas diagnosed during the period 1973–2002 in individuals born in Greenland were identified in the Danish
Cancer Register. The 145 cases thus found were screened using the Danish Pathology Database, and tumour material was identified in 117 and frequency matched with gastric carcinomas in individuals born in Denmark. For every Greenlandic case, the Danish gastric carcinomas of equivalent gender, age (10-year interval) and year of diagnosis (5-year interval) were identified using the Danish Civil Registry System and the Danish Cancer Register. All these potential controls were listed on the basis of a random number, and the first number was selected as the control. To reduce logistic effort, Danish controls >40 years of age were recruited from Aarhus County (~650,000 inhabitants), whereas controls below 40 years were collected from all over Denmark (~5.2 million inhabitants). Paraffin-embedded tumour material was retrieved from pathology archives in 106 of 117 (90.6%) Greenlandic cases and in 106 of 117 Danish controls, thus collecting a total of 212 samples for analysis. Of the remaining 22 samples, 12 could not be traced (5 cases and 7 controls), were unsuitable for EBV analysis due to lack of tissue (3 cases and 1 control), were excluded due to a non-gastric carcinoma diagnosis (2 cases and 2 controls) and in 2 cases only tumour material from metastases was available (1 case and 1 control).

All cases were reclassified by expert histopathologists according to the WHO 2000 guideline for the diagnosis of gastric carcinomas (International Agency for Research on Cancer (IARC), 2000), sub-classified according to the Laurén classification and re-staged (pTNM). The pathologist was blinded to EBV status and country of origin. From the results of the original pathology report, the macroscopic location of the tumours was determined as proximal (proximal 2/3 of the stomach), distal (distal 1/3) or report, the macroscopic location of the tumours was determined and by the appropriate scientific ethical committees in both countries. 

The study was approved by the Danish data protection board and the appropriate scientific ethical committees in both countries.

**RESULTS**

We examined 212 gastric carcinomas, 106 from Greenland and 106 from Denmark, respectively, from 135 men (64%) and 77 women (36%). The average age at diagnosis was 55.1 (range: 26–78) years among the Inuit and 55.8 (range: 22–79) years among the matched Danes (Table 1). In both populations, the frequency of EBV-associated gastric carcinomas was 8.5% (9 of 106) (Table 2), representing an odds ratio (OR) of 1.0 (CI: 0.4–2.7). EBV-associated gastric carcinomas were more common among men (15 of 135 = 11.1%) compared with women (3 of 77 = 3.9%),

| Table 1 | The study population |
|---------|----------------------|
|         | Inuit N = 106        | Danes N = 106  |
| Age at diagnosis (range) | 55.1 (26–78) | 55.8 (22–79) |
| Males/females | 68/38 | 67/39 |
| EBV positive (%) | 8.5 | 8.5 |

**EBV =** Epstein–Barr virus.

| Table 2 | Tumour characteristics of gastric carcinomas according to ethnicity |
|---------|---------------------------------------------------------------|
|         | Inuit n = 106 | Danes n = 106 |
| EBV status | N | % | N | % | P-value |
| --- | --- | --- | --- | --- | --- |
| EBV-positive gastric carcinoma | 9 | 8.5 | 9 | 8.5 | 0.99 |
| EBV-negative gastric carcinoma | 97 | 91.5 | 97 | 91.5 | 0.48 |
| Material | | | | | |
| Biopsy | 42 | 39.6 | 38 | 35.8 | 0.07c |
| Gastrectomy specimens | 64 | 60.4 | 68 | 64.2 | 0.10b |
| Location | | | | | |
| Proximal | 25 | 23.6 | 40 | 37.7 | 0.005a |
| Distal | 55 | 51.9 | 37 | 34.9 | 0.07d |
| Diffuse | 5 | 4.7 | 11 | 10.4 | 0.65e |
| Unknown | 21 | 19.8 | 18 | 17.0 | 0.99f |
| Histology (WHO) | | | | | |
| Papillary | 3 | 2.8 | 3 | 2.8 | 0.24g |
| Tubular | 71 | 67.0 | 63 | 59.4 | 0.011 |
| Mucinous | 4 | 3.8 | 1 | 0.9 | 0.65e |
| Signet-ring cell | 20 | 18.9 | 25 | 23.6 | 0.40d |
| Undifferentiated | 7 | 6.6 | 13 | 12.3 | 0.40d |
| Adenosquamous | 1 | 0.9 | 1 | 0.9 | 0.40d |
| Histology (Laurèn) | | | | | |
| Intestinal | 72 | 67.9 | 67 | 63.2 | 0.40d |
| Diffuse | 31 | 29.2 | 39 | 36.8 | 0.40d |
| Mixed | 3 | 2.8 | 0 | 0 | 0.40d |
| Differentiation of tubular type carcinomas | | | | | |
| Good | 11 | 15.5 | 6 | 9.5 | 0.25h |
| Moderate | 37 | 52.1 | 31 | 49.2 | 0.40d |
| Poor | 23 | 32.4 | 26 | 41.2 | 0.40d |
| Degree of lymphocyte infiltration | | | | | |
| Low | 54 | 50.9 | 65 | 61.3 | 0.07h |
| Moderate | 46 | 43.4 | 38 | 35.8 | 0.07h |
| Abundant | 6 | 5.7 | 3 | 2.8 | 0.07h |
| Pattern of lymphocytic infiltration | | | | | |
| Lymphoepithelioma-like | 0 | 0 | 0 | 0 | 0.99i |
| Nodular | 22 | 20.7 | 22 | 20.7 | 0.99i |
| Diffuse | 80 | 75.5 | 84 | 79.2 | 0.99i |
| Follicular infiltration | 4 | 3.8 | 0 | 0 | 0.99i |

EBV = Epstein–Barr virus; WHO = World Health Organisation. Tubular adenocarcinomas were categorised as well differentiated (well-formed glands), moderately differentiated (intermediate between well differentiated and poorly differentiated) and poorly differentiated (highly irregular glands that are recognised with difficulty or single cells that remain isolated or are arranged in small clusters) according to WHO 2000. The pattern and degree of lymphocytic infiltration was assessed semi-quantitatively as either absent, mild, moderate or abundant infiltration by examining 10 medium power fields (×200 magnification). The pattern of lymphocytic infiltration was determined as lymphoepithelioma-like, nodular, diffuse or follicular. "Non-distal vs distal location, samples with 'unknown' location not included. Tubular histology vs other types. Samples with mixed histology not included. P-value represents trend test. *Nodular infiltration vs other types. **
DISCUSSION

We found an equal proportion of EBV-associated gastric carcinomas in the Inuit and Danes, suggesting that the factors responsible for the high incidence of EBV-positive NPC and salivary gland carcinoma in Greenland do not influence the risk of EBV-associated gastric carcinomas.

The risk of NPC and salivary gland carcinoma are strikingly higher among the Inuit in Greenland compared with the Danes in Denmark, with standardised incidence ratios of ~35 and 6, respectively (Friborg et al, 2003). There is also a clear increased familial risk of NPC and salivary gland carcinoma among the Inuit, with an eight-fold increased risk in first-degree relatives, which is among the highest reported for any cancer (Goldgar et al, 1994; Friborg et al, 2005). These high risks imply the existence of strong genetic or environmental risk factors for EBV-associated NPC and salivary gland carcinoma in the Inuit population. However, the similar proportion of EBV-associated gastric carcinomas in Greenland and Denmark argues against a general susceptibility to EBV-associated carcinomas among the Inuit.

EBV-associated carcinomas of the nasopharynx and salivary glands in the Inuit are mainly of the lymphoepithelial type (Nielsen, 1986). It must be noted that, we did not identify an increased incidence of gastric carcinomas of this histopathological type in Greenland.

The proportion of EBV-associated gastric carcinomas in Greenland and Denmark (8.5%) is comparable with frequencies found worldwide (IARC working group, 1997; Burgess et al, 2002; Hjalgrim et al, 2008). Studies of EBV positivity in gastric carcinomas have produced varied results, with prevalence ranging from 2 to 15%. Some of this variation may be attributed to differences in sample collection and EBV detection. The advantages of our study include a population-based case collection, and optimal, uniform methods for EBV detection.

We did not find an increased proportion of EBV-associated gastric carcinomas in Greenland, a high-incidence region for other EBV-associated carcinomas, arguing against a general susceptibility to EBV-associated carcinomas among the Inuit.

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