

ASPECTS OF THE EPIDEMIOLOGY OF NASOPHARYNGEAL CARCINOMA AND EPSTEIN-BARR VIRUS INFECTION IN GREENLAND

Objectives. The Inuit traditionally exhibit a distinctive cancer pattern characterised by high frequencies of nasopharyngeal (NPC) and salivary gland carcinomas, and low frequencies of tumours common in Western populations. Both NPC and salivary gland carcinomas are closely associated with Epstein-Barr virus (EBV), a nearly ubiquitous infection in all populations, and infection among Inuit is characterised by a particular pattern with early primary infection and high antibody titres. NPC is believed to be the result of environmental factors, especially EBV, acting on genetically susceptible individuals. However, knowledge is sparse on the extent and importance of the individual susceptibility and the interaction with EBV. During the second half of the twentieth century considerable changes in living conditions and lifestyle have occurred in the Inuit population of Greenland, and the effects on the patterns of malignant disease and EBV acquisition are unknown.

The present thesis explores different aspects of the EBV-associated carcinomas among Inuit, with emphasis on the individual susceptibility of NPC and the epidemiology of EBV infection.

Design and methods. We examined the incidence of cancer in the Greenlandic population by creating a cohort consisting of all individuals born in Greenland, using the Danish Civil Registration System. The cohort was followed over the period 1973-1997 and cancer occurrence was determined using the Danish Cancer Registry.

To investigate the extent of the individual susceptibility for NPC among Inuit, we identified family members of all NPC cases diagnosed between 1973 and 1997 in the cohort. This was done using population-based registries, manual sources (church books and census papers) and interviews with relatives. The risk of cancer in NPC relatives and non-relatives in the cohort was compared by relative risks.

To explore the EBV immune response in NPC-relatives, we performed a case-control study in the towns of Sisimiut and Ilulissat. Using the family data collected, we selected NPC-unaffected first-degree rela-



Jeppe Friborg

tives in families with prior cases of NPC (n=19), and controls in families without prior cases of NPC (n = 90). Peripheral blood mononuclear cells (PBMCs), plasma, saliva and questionnaire information were collected, and EBV viral load and serological response were determined.

The response to EBV infection in Inuit was characterised using samples collected in 1997-1998 (n = 384), and in 2004 (n = 285) in Sisimiut children aged 0-11 years. 168 children participated in both surveys. Plasma samples were available from the survey in 1997-1998, and in 2004 we collected whole blood, plasma and saliva, together with information on sociodemographic factors, lifestyle factors and health conditions. EBV serological response was determined in the plasma samples and EBV viral load in whole blood and saliva.

Results. Total cancer incidence in Greenland increased by 4% and 6% per 5 years for men and women, respectively, in the period 1973-1997. Especially the incidences of cancers of the stomach (24% per 5 years), lung (23%), breast (14%) and colon (12%) increased significantly, while cancer of the uterine cervix decreased (-10%). The incidence of NPC showed a non-significant decrease. Compared to the Caucasian population in Denmark, high standardized incidence ratios (SIRs) were found for cancer of the nasopharynx, the salivary glands and the oesophagus, and low SIRs were found for cancers of the testis, prostate and breast.

Among 766 first-degree NPC relatives in the cohort of individuals born in Greenland, the relative risk of NPC following the family index case was 8.0 (95% CI: 4.1-14.0). Sex and age of the relative, or the index case, had no modifying effect on the familial risk of NPC. The relative risks of the like-wise virally-associated carcinomas of the salivary glands 8.4 (2.7-19.5) and uterine cervix 2.2 (1.1-3.9) were also significantly increased.

However, we found no difference in the EBV-specific immune responses between first-degree relatives to NPC patients and controls. The EBV viral load in PBMCs, plasma and saliva was equal, just as the serological EBV response was found to be comparable. We found a high anti-EBV (VCA) IgA sero-prevalence in both relatives (47%) and non-relatives (53%), making sero-positivity to this NPC marker common in the Inuit population.

The study of EBV infection in Greenlandic children confirmed earlier findings of primary infection occurring at an early age, as 96% of the children were EBV sero-positive at the age of 4 years. In the subset of children where multiple samples were available, we found the presentation of a high VCA-IgG level at an early age to be significantly associated with a high VCA-IgG level at a later age. However, we did not identify any factors significantly affecting the EBV immune response, as both early infection and a wide number of environmental determinants were found not to be associated with the EBV serological response, or levels of EBV-DNA in whole blood and saliva.

Conclusions. We confirmed the existence of a distinct cancer pattern among Inuit, but found the overall cancer incidence to be increasing due to increases in cancers common in Western populations. The increase was particularly high for cancers of the lung, breast and colon, indicating that changes in lifestyle and living conditions have had a significant impact on the cancer pattern. In addition, we observed a marked and unexplained increase in the incidence of stomach cancer, contrasting with global trends for this cancer.

The eight-fold increased risk of NPC among first-degree relatives of NPC patients is comparable to findings in Chinese NPC endemic populations. The increased risk among relatives was not limited to NPC, but also included increased risks of cancers of the salivary glands and uterine cervix. Given the high risk of the like-wise EBV-associated salivary gland carcinoma among first-degree relatives, the mechanisms leading to EBV infection and transformation of the epithelium in the nasopharynx and salivary glands are likely to be identical. However, the increased risk of NPC among relatives was not reflected in the EBV immune response, as this was found to be very similar in relatives and controls.

Early infection and a wide number of environmental determinants were not associated with the investigated EBV measures. This indicates that the particularly response to EBV infection observed in the Inuit population appears to be largely resistant to environmental factors, which in turn suggests that it could be genetically controlled. Further support for this was given by the finding that all Inuit children in our survey were infected with EBV very early (before the age of four years), equivalent to observations twenty years ago, reflecting that the age at which primary infection occurs has not been influenced by the considerable changes in living conditions during the recent decades.

Keywords: Inuit, Arctic, cancer, nasopharyngeal carcinoma, Epstein - Barr virus

Contact information:

Jeppe Friborg, MD
Department of Epidemiology Research
Statens Serum Institut
Artillerivej 5, 2300 Copenhagen S
Denmark
E-mail: jfr@ssi.dk