Breast cancer, cytomegalovirus and Epstein–Barr virus: a nested case–control study

B Cox*,1, A Richardson2, P Graham3, RE Gislefoss4, E Jellum5 and H Rollag6

1Department of Preventive and Social Medicine, Hugh Adam Cancer Epidemiology Unit, Dunedin School of Medicine, University of Otago, Dunedin, New Zealand; 2Community and Public Health, Canterbury District Health Board, Christchurch, New Zealand; 3Department of Public Health and General Practice, University of Otago, Christchurch, New Zealand; 4Cancer Registry of Norway, Institute of Population-based Cancer Research, Oslo, Norway; 5Institute of Clinical Biochemistry, Faculty of Medicine, University of Oslo, Rikshospitalet, Oslo, Norway; 6Institute of Microbiology, Faculty of Medicine, University of Oslo, Rikshospitalet, Oslo, Norway

BACKGROUND: We investigated whether elevation in serum cytomegalovirus (CMV) or Epstein–Barr virus (EBV) immunoglobulin G (IgG) antibody levels precedes the development of breast cancer.

METHODS: A nested case–control study was carried out within the Janus Serum Bank cohort. Two serum samples, one taken at least 4 years before diagnosis (sample 2) and an earlier sample (sample 1) from 399 women with invasive breast cancer and from 399 controls, matched for date of blood samples and age were tested for CMV and EBV IgG antibodies. Odds ratios (ORs) with 95% confidence intervals (CIs) for CMV and EBV seroconversion between the samples and unit changes in IgG optical density (OD) examined as a continuous variable were calculated using conditional logistic regression.

RESULTS: Eleven cases and three controls seroconverted for CMV IgG between the first and second blood samples, with an adjusted OR for CMV IgG seroconversion of 4.0 (95% CI = 1.1–14.4). The risk of breast cancer, adjusted for parity, increased per unit difference in CMV OD between samples (OR = 1.7, 95% CI = 1.1–2.5). In an analysis restricted to parous cases and age-matched parous controls, the OR for CMV seroconversion for IgG between the two samples, adjusted for parity and age at first birth, was 9.7 (95% CI = 1.2–77.3). The EBV seroconversion or change in EBV OD was not associated with risk of breast cancer.

CONCLUSION: Our hypothesis that elevation in serum CMV IgG antibody levels precedes the development of breast cancer in some women is supported by the results of this study. Changes in EBV IgG antibody are not associated with risk of breast cancer.

Keywords: breast cancer; cytomegalovirus; Epstein–Barr virus

There are major geographical differences in the age-standardised incidence of breast cancer (Ferlay et al, 2004) that cannot be entirely explained by variations in known risk factors between countries. Although differences in reproductive factors among populations are important, a similar geographical pattern for breast cancer in men has been found (Thomas, 1993).

Mouse mammary tumour-like viruses and Epstein–Barr virus (EBV) have been suggested to cause breast cancer, but the evidence that either is associated with breast cancer has been inconsistent (Xue et al, 2003; Glaser et al, 2004; Mant and Cason, 2004; Szabo et al, 2005). Recently, cytomegalovirus (CMV) has been linked to the development of inflammatory diseases and cancer (Söderberg-Naucler, 2006).

It has been hypothesised that breast cancer can be caused by late exposure to a common virus (Richards, 1997). Breast cancer incidence is frequently higher in countries where exposure to CMV may occur late than in countries where almost everyone is exposed in childhood. A strong negative inter-country correlation (Pearson’s correlation coefficient −0.79, P < 0.0001) was found between breast cancer incidence and the percentage of adults who are CMV seropositive (Richards, 1997). Delayed exposure to EBV (or CMV), measured by illness from infectious mononucleosis, has been suggested to increase risk of breast cancer (Yasui et al, 2001), but recall bias may have influenced the results.

In an Australian case–control study, cases and controls did not differ in seropositivity for CMV or EBV (Richardson et al, 2004). However, in seropositive women, mean immunoglobulin G (IgG) values were higher in cases than controls for CMV (1.20 vs 0.98 optical density (OD), P = 0.005), but not for EBV (2.65 vs 2.57 OD, P = 0.5). The adjusted odds ratios (ORs) per OD unit were 1.46 (95% confidence interval (CI) = 1.06–2.03) for CMV IgG and 1.11 (95% CI = 0.93–1.33) for EBV IgG. We hypothesised that the higher mean IgG levels found in women with breast cancer could be the result of more recent infection with CMV, and may indicate that late exposure to CMV (in adulthood rather than childhood) is a risk factor for breast cancer. Limitations of this work were that it was retrospective, with blood samples collected after the diagnosis of breast cancer, and only women aged <40 years were studied.
MATERIALS AND METHODS

To investigate whether CMV IgG levels were increased before the diagnosis of breast cancer, a case–control study conducted in the cohort of female donors to the Janus Serum Bank in Norway was undertaken. The Janus project was a study initiated in 1973 to collect and store blood samples from healthy women for later scientific use. Participants were recruited from several counties in Norway during routine health examinations or in conjunction with screening for risk factors of cardiovascular diseases. The participation rate was 85% during 1974 to 1978 and 75% during 1986 to 1991. Samples were also collected from blood donors from the Red Cross Blood Donor Centre in Oslo. The serum bank contains samples from approximately 333 000 people (151 000 women) and 10% are blood donors. The sera have been stored at $-25^\circ$C (Jellum et al., 1993, 1995).

The stored blood samples from cases and controls were tested for CMV and EBV IgG antibodies. The CMV and EBV antibody levels in stored blood remain stable despite prolonged storage (Jellum et al., 1993; Pappin et al., 1995; Levin et al., 2003). The study was approved by the Regional Ethics Committee of Southern Norway and Data Inspectorate, Norway.

Selection of cases and controls

Cases were randomly selected from women in the Janus Serum Bank cohort with invasive breast cancer who had been identified by linkage to the Norwegian Cancer Registry until 400 cases were attained. Women were eligible to be cases if they were aged 20 years and over at diagnosis, with a blood sample taken 4 or more years before the diagnosis of breast cancer (the index sample), and a blood sample at least 12 months earlier than the index sample. Eligible controls were women from the cohort who were alive and free of cancer (other than squamous or basal cell carcinoma of the skin) at the time that the case was diagnosed. They were frequency matched to the cases by 5-year age group and had a blood sample taken within ±2 months of the index sample of the case. From these eligible controls, women with at least one earlier sample were randomly selected. These controls were individually matched to cases by duration of sample storage (±2 months) of the earlier sample. Where it was not possible to find a control in which the earlier sample could be matched for duration of storage, an eligible control with the closest available early sample was randomly selected. The two samples for each case and individually matched control had to be separated in time by at least 12 months to allow adequate time for IgG levels to change between the samples, as CMV and EBV IgG titles rise initially after infection and then gradually decline, with residual antibody detectable for several years (IARC Working Group on the Evaluation of Carcinogenic Risks to Humans, 1997; Mendez et al., 1999). Table 1 shows the selection criteria for cases and controls.

| Cases                                      | Controls                                      |
|--------------------------------------------|-----------------------------------------------|
| Women aged 20 years and over               | Women alive without cancer (other than basal  |
| at diagnosis with invasive breast         | or squamous cell skin cancer) at              |
| cancer (identified by linkage to the       | the time the case was diagnosed, aged in the  |
| Norwegian Cancer Registry)                 | same 5-year age group as the case             |
| Available stored blood sample taken        | Available stored blood sample taken           |
| at least 4 years before the diagnosis of   | within ±2 months of the case's index sample.  |
| breast cancer (the 'index sample')         |                                               |
| Early available stored blood sample        | Available early sample (preferably taken      |
| (taken at least 1 year earlier than        | within ±2 months of the case's sample,       |
| the index sample described above)          | but otherwise the closest early               |
|                                            | sample taken at least 1 year earlier          |
|                                            | than the sample described above)              |

Table 1. Eligibility of cases and controls

Sample size calculations

On the basis of our earlier results (Richardson et al., 2004), samples from 400 cases and 400 controls were predicted to provide, for the assessment of CMV and EBV IgG levels, at least 80% power to detect a difference of 0.15 units of OD in mean CMV IgG levels between cases and controls (a difference of 21.4% of the s.d.), with $\alpha = 0.05$. As we also wished to examine changes in CMV IgG and EBV IgG levels over time in cases and controls, two samples for each case and each control were tested. We had no estimates of the magnitude of changes in CMV or EBV IgG over time or the rate of seroconversion, so they were not used to estimate the sample size or statistical power of the study, however, the CIs indicate the precision of the ORs obtained. In total, 1600 samples were tested; 800 from the cases (two samples from each of the 400 cases) and 800 from the controls (two samples from each of the 400 controls).

Health care and diagnostic services in Norway are based on the health insurance principle. The health services are available to all residents of the country, and the costs of diagnosis and treatment of cancer are covered by the public insurance system. To determine the seroconversion incidence, we used a nested case–control study design. To study the association between seroconversion and breast cancer risk, the CMV IgG and EBV-VCA antibody internal control sera were placed in wells in the first row and last row of each test plate. If the CMV IgG and EBV-VCA antibody internal control sera were placed in wells in the first row and last row of each test plate. If the OD of these two wells on the test plate differed by >20%, the results were rejected and the sera reanalysed. In addition, an internal laboratory control was analysed on each plate to control inter-assay variations.

The CMV IgG antibodies were assessed by Enzygnost Anti-CMV/IgG test kit, Dade Behring, Marburg, Germany. The OD cutoff value was 0.200. A reference serum provided with the kit was used as a correction factor to standardise the OD value between test plates. The EBV-VCA IgG antibodies were assessed by Novitex EBV-VCA IgG test kit, His Diagnostics, Freiburg, Germany. The OD cutoff value for this test was also 0.200.

RESULTS

Cases of breast cancer were diagnosed between February 1982 and December 2003, with 53% of cases diagnosed from 1998 onwards.
The mean CMV IgG for cases for sample 1 was 1.09 OD (s.d. = 0.230) and the internal laboratory standard had a mean OD value of 0.900 ± 0.230. There was no difference in the overall distribution of CMV IgG and EBV IgG levels in cases compared with controls.

Table 3 shows the risk of breast cancer by parity, age at first birth, BMI and seroconversion for CMV and EBV. There were 343 cases and 344 controls with at least one birth. Among the 301 case–control pairs who were both parous, there was no statistically significant difference in age at first birth (χ² = 8.11, 4 df, P = 0.09).

Although a significantly increased risk of breast cancer was observed for parous women whose first birth occurred at age 28 years or older, no increased risk with increasing age at first birth with adjustment for parity was observed (OR = 1.02, 95% CI = 0.98 – 1.06). Nulliparity did not confer reduced risk (OR = 1.0, 95% CI = 0.9–1.1). The risk of breast cancer was significantly lower for women with five or more children compared with nulliparous women (OR = 0.3, 95% CI = 0.2–0.7), with or without adjustment for age at first birth or CMV IgG seroconversion, and was similar with additional adjustment for BMI for the 277 case–control pairs for whom it was possible. In parous women, with adjustment for age at first birth, the risk of breast cancer decreased with increasing parity with an OR of 0.8 (95% CI = 0.7–0.9) per additional child after the first and was not appreciably changed with additional adjustment for age at first birth.

Seroconversion for CMV IgG between the first and second samples occurred for 11 cases and 3 controls, producing an unadjusted OR of 3.7 (95% CI = 1.0–13.1). When adjusted for parity, the OR for CMV IgG seroconversion was 4.0 (95% CI = 1.1–14.4). This was unaltered by adjustment for the length of time between tests, and was similar when restricted to case–control pairs for whom it was possible. In parous case–control pairs who were both parous, nulliparity did not confer reduced risk (OR = 1.0, 95% CI = 0.9–1.1). The risk of breast cancer decreased with increasing parity with an OR of 0.8 (95% CI = 0.7–0.9) per additional child after the first and was not appreciably changed with additional adjustment for age at first birth.

When the analysis was restricted to the subgroup for whom BMI was measured, the OR for the association between CMV IgG and breast cancer was significantly lower for women with five or more children compared with nulliparous women (OR = 0.3, 95% CI = 0.2–0.7), with or without adjustment for age at first birth or CMV IgG seroconversion, and was similar with additional adjustment for BMI for the 277 case–control pairs for whom it was possible. In parous women, with adjustment for age at first birth, the risk of breast cancer decreased with increasing parity with an OR of 0.8 (95% CI = 0.7–0.9) per additional child after the first and was not appreciably changed with additional adjustment for age at first birth.
Breast cancer, CMV and EBV: a nested case–control study

B Cox et al

Table 4 Unadjusted odds ratios for breast cancer by parity, age at first birth, CMV IgG and EBV IgG seroconversion

| Characteristic | Number of cases | Number of controls | Odds ratio for breast cancer (95% CI) |
|----------------|-----------------|--------------------|--------------------------------------|
| Nulliparity    |                 |                    |                                      |
| No             | 343             | 344                | 1.0                                  |
| Yes            | 56              | 55                 | 1.0 (0.6 – 1.5)                      |
| Number of children |        |                    |                                      |
| None           | 56              | 55                 | 1.0                                  |
| 1              | 55              | 45                 | 1.1 (0.7 – 2.0)                      |
| 2              | 122             | 124                | 1.1 (0.7 – 1.7)                      |
| 3              | 103             | 92                 | 1.0 (0.6 – 1.7)                      |
| 4              | 39              | 46                 | 0.8 (0.4 – 1.5)                      |
| 5+             | 14              | 37                 | 0.3 (0.2 – 0.7)                      |
| Age at first child (for parous women only) (years)* | | | |
| 0–20           | 63              | 72                 | 1.0                                  |
| 21–22          | 68              | 57                 | 1.4 (0.9 – 2.4)                      |
| 23–24          | 47              | 66                 | 0.9 (0.5 – 1.5)                      |
| 25–27          | 59              | 61                 | 1.2 (0.7 – 2.0)                      |
| ≥28            | 64              | 45                 | 1.8 (1.0 – 3.3)                      |
| BMI             |                 |                    |                                      |
| ≤22            | 83              | 81                 | 1.0                                  |
| 21.1–24        | 67              | 63                 | 1.1 (0.6 – 1.7)                      |
| 24.1–26        | 46              | 57                 | 0.8 (0.4 – 1.3)                      |
| >26            | 81              | 76                 | 1.0 (0.6 – 1.6)                      |
| Seroconversion for CMV IgG between samples | | | |
| No             | 388             | 396                | 1.0                                  |
| Yes            | 11              | 3                  | 3.7 (1.0 – 13.0)                     |
| Seroconversion for CMV IgG between samples in parous women* | | | |
| No             | 333             | 342                | 1.0                                  |
| Yes            | 10              | 2                  | 9.0 (1.1 – 71.0)                     |
| Seroconversion for EBV IgG between samples | | | |
| No             | 397             | 396                | 1.0                                  |
| Yes            | 2               | 3                  | 0.7 (0.1 – 4.0)                      |

Abbreviations: BMI = body mass index; CI = confidence interval; CMV = cytomegalovirus; EBV = Epstein–Barr virus; IgG = immunoglobulin G. *Restricted to 301 cases and 301-matched controls with at least one live birth. †Restricted to 277 cases and 277-matched controls with BMI available.

Table 5 Adjusted† odds ratios (95% confidence intervals) for CMV and EBV seroconversion and unit changes in IgG OD

|                          | All women | Parous women |
|--------------------------|-----------|--------------|
| CMV IgG seroconversion  | 4.0 (1.1 – 14.4) | 9.7 (1.2 – 77.3) |
| EBV IgG seroconversion  | 0.7 (0.1 – 4.0)  | 0.6 (0.1 – 6.8)  |
| Unit change in CMV OD    | 1.7 (1.1 – 2.5)  | 2.0 (1.2 – 3.4)  |
| Unit change in EBV OD    | 1.0 (0.7 – 1.3)  | 1.0 (0.7 – 1.4)  |

Abbreviations: CI = confidence interval; CMV = cytomegalovirus; EBV = Epstein–Barr virus; IgG = immunoglobulin G. Results for all women are adjusted for number of births; results for 301 parous cases and their 301-matched parous controls are adjusted for number of births and age at birth of first child.

Seroreversion and breast cancer with adjustment for parity was 3.7 (95% CI = 0.7 – 18.5) and 3.7 (95% CI = 0.7 – 18.4) when adjusted for parity and BMI. No trend in the ORs over the four categories of BMI, with adjustment for parity, was observed (OR = 0.99, 95% CI = 0.86 – 1.15). When restricted to parous women in this subgroup, the OR for CMV seroconversion was 7.6 (95% CI = 0.9 – 64) and was unchanged with additional adjustment for age at first birth.

Changes in CMV serology from positive to negative, or staying positive or staying negative, between samples were not associated with risk of breast cancer. Only 2 cases and 3 controls seroconverted for EBV IgG between the two samples. The crude OR per unit difference in CMV OD between samples was 1.6 (95% CI = 1.0 – 2.3), and the crude OR per unit difference in EBV OD between samples was 0.9 (95% CI = 0.7 – 1.3).

Table 5 gives ORs for seroconversion and unit changes in IgG values between samples, adjusted for parity and for parity and for women, with additional adjustment for age at first birth. The OR per unit difference in CMV OD between samples, adjusted for parity, was 1.7 (95% CI = 1.1 – 2.5), which was reduced to 1.6 (95% CI = 1.0 – 2.5) when those that seroconverted for CMV IgG were excluded. The OR per unit difference in EBV OD between samples, adjusted for parity, was 1.0 (95% CI = 0.7 – 1.3). In parous women, the ORs per unit difference in CMV OD and EBV OD, adjusted for parity and age at first child, were 2.0 (95% CI = 1.2 – 3.4) and 1.0 (95% CI = 0.7 – 1.4), respectively.

**DISCUSSION**

Our hypothesis that elevation in serum CMV or EBV IgG antibody levels precedes the development of breast cancer in some women is supported by the results of this study. Seroconversion of CMV IgG and increasing IgG levels between the samples were both associated with an increased risk of breast cancer among parous women.

The Janus serum bank cohort was ideal for this study because it meant that blood, which was collected years before the diagnosis of breast cancer, could be tested, so CMV and EBV IgG levels for cases are unlikely to have been affected by breast cancer and were not affected by treatment. Exposure to CMV and EBV was determined objectively using standard enzyme immunosassays for CMV IgG and EBV viral capsid antigen IgG, and laboratory staff were blinded to the case or control status of the samples, so these results are not vulnerable to recall bias or observer bias. The similar risk for case–control pairs before and after 1998, the year the Norwegian Breast Cancer Screening Programme began, suggests that the results were not affected by detection bias associated with screening.

Adjustment for the length of time between samples did not alter the results obtained and suggests that recent seroconversion rather than the duration of seropositivity may be the more important determinant of risk of breast cancer. Whether CMV remains in breast tissue after infection in human beings is not known. Increased CMV IgG levels may occur from recrudescence of latent infection or re-exposure to CMV without clinical infection. Increasing risk of breast cancer with increasing CMV OD might also occur if a significant risk factor for breast cancer was closely associated with screening. Day care workers and mothers are at increased risk of acquiring CMV from children they care for (Bright and Calabro, 1999; Joseph et al, 2005; Noyola et al, 2005), and this combined with the recognised increased risk of breast cancer within 10 years of a full-term birth (Lambe et al, 1994) might explain an association in parous women. However, when we restricted our analysis to women who were 50 or more years of age at diagnosis or reference date in the controls, the strong effect of recent adult CMV infection remained. The specificity of the association (for CMV, but not for EBV) supports a causal association between adult CMV infection and breast cancer in some parous women because if the results were due to bias or confounding an association between breast cancer and both CMV and EBV infection would be more likely than either by itself. Although the results for the women with
measurements of BMI suggest that BMI is not likely to be a confounder of the associations found between changes in CMV IgG and breast cancer, other potential confounders, such as the use of hormone replacement therapy or alcohol consumption, were not able to be included in the analysis. Further investigation of a possible function of CMV infection in the presentation of breast cancer is needed.

The risk of adult CMV infection might be expected to increase with increasing parity, but increasing parity is associated with a reducing risk of breast cancer. However, if the prevalence of pre-invasive disease increased with age and exposure to CMV only promoted the progression of pre-invasive disease, then infection from young children after an early age of first full-term birth or increasing parity would provide some immunity against infection at an older age, after the onset of pre-invasive disease, and thus reduce the risk of breast cancer. Then both early age of first birth and increasing parity would, as has been observed, reduce the lifetime risk of breast cancer. Moreover, the increased risk of breast cancer observed within 10 years of first full-term birth (Lambe et al, 1994) could be mediated through an increased chance of exposure to CMV after first full-term birth. However, this hypothesis does not explain the lack of an increased risk of breast cancer in the 10-year period after first full-term birth for women whose first full-term birth occurs when 35 or more years of age (Lambe et al, 1994). The observed increase in risk of breast cancer in parous women with CMV IgG seroconversion between samples was present for women diagnosed at 50 or more years of age, suggesting that CMV infection after 35 years of age may also increase risk of breast cancer. The increased risk observed was present for few women in this study, suggesting that CMV infection may only be involved in the development of a minority of breast cancers.

Studies involving the long-term follow-up of women who have been, and not been, infected with CMV are required to verify the findings of this study. A greater time period between blood samples would be expected to increase the proportion of women for whom CMV IgG seroconversion occurs and provide more definitive examination of the association with breast cancer and whether risk increases with increasing age of adult CMV infection. Assessment of whether the increased risk of breast cancer in the 10-year period after first full-term birth varies by occurrence of CMV infection during the period is also needed.

ACKNOWLEDGEMENTS

The Janus Serum Bank owned by the Cancer Registry of Norway provided the serum samples. Tone Berge, Institute of Microbiology, Rikshospitalet, Oslo, Norway, tested the samples. The Canterbury Medical Research Foundation, New Zealand, provided funding for the extraction and testing of the serum samples. Associate Professor Cox is supported by funds from the Director’s Cancer Research Trust.

REFERENCES

Bright KA, Calabro K (1999) Child care workers and workplace hazards in the United States: overview of research and implications for occupational health professionals. Occup Med 49: 427 – 437
Fetel J, Bray F, Pisani P, Parkin DM (2004) GLOBOCAN 2002: cancer incidence, mortality and prevalence worldwide. IARC CancerBase No. 5. IARC Press: Lyon
Glaser SL, Hsu JL, Gulley ML (2004) Epstein-Barr virus and breast cancer: state of the evidence for viral carcinogenesis. Cancer Epidemiol Biomarkers Prev 13: 688 – 697
IARC Working Group on the Evaluation of Carcinogenic Risks to Humans (1997) Epstein-Barr Virus and Kaposi’s Sarcoma Herpesvirus/Human Herpesvirus 8. International Agency for Research on Cancer: Lyon
Jellum E, Andersen A, Lund-Larsen P, Theodorsen L, Orjasaeter H (1993) The JANUS serum bank. Sci Total Environ 139: 527 – 535
Jellum E, Andersen A, Lund-Larsen P, Theodorsen L, Orjasaeter H (1995) Experiences of the Janus Serum Bank in Norway. Environ Health Perspect 103(Suppl 3): 85 – 88
Joseph SA, Beliveau C, Muecke CJ, Rahme E, Soto JC, Flowerdew G, Johnston L, Langille D, Gyorkos TW (2005) Risk factors for cytomegalovirus seropositivity in a population of day care educators in Montreal, Canada. Occup Med 55: 564 – 567
Lambe M, Hsieh C-C, Trichopoulos D, Ekborn A, Pavia M, Adami H-O (1994) Transient increase in the risk of breast cancer after giving birth. N Engl J Med 331: 5 – 9
Levin LI, Munger KL, Rubertone MV, Peck CA, Lennette ET, Spiegelman D, Asherio A (2003) Multiple sclerosis and Epstein-Barr virus. JAMA 289: 1533 – 1536
Mant C, Cason J (2004) A human murine mammary tumour virus-like agent is an unconvincing aetiological agent for human breast cancer. Rev Med Virol 14: 169 – 177
Mendez JC, Sia IG, Paya CV (1999) Human cytomegalovirus. In Laboratory Diagnosis of Viral Infections, Third Edition: Lennette EH, Smith TF (eds), Chapter 17, pp 361 – 372. Marcel Dekker, Inc.: New York
Noyola DE, Valdez-Lopez BH, Hernandez-Salinas AE, Santos-Diaz MA, Noyola-Frias MA, Reyes-Macias JF, Martinez-Martinez LG (2005) Cytomegalovirus excretion in children attending day-care centers. Arch Med Res 36: 590 – 593
Pappin A, Grissom M, Mackay W, Huang Y, Yomtovanov R (1995) Stability of cytomegalovirus antibodies in plasma during prolonged storage of blood components. Clin Diag Lab Immunol 2: 25 – 29
Richardson A (1997) Is breast cancer caused by late exposure to a common virus? Med Hypoth 48: 491 – 497
Richardson AK, Cox B, McCredie MR, Dite GS, Chang J-H, Gertig DM, Southey MC, Giles GG, Hopper JL (2004) Cytomegalovirus, Epstein-Barr virus and risk of breast cancer before age 40 years: a case-control study. Br J Cancer 90: 2149 – 2152
Söderberg-Naucler C (2006) Does cytomegalovirus play a causative role in the development of various inflammatory diseases and cancer? J Int Med 259: 219 – 246
SPSS Inc. (2007) SPSS 16.0.1 for Mac. SPSS: Chicago, IL
Szabo S, Haislip AM, Garry RF (2005) Of mice, cats, and men: is human breast cancer a zoonosis? Microscopy Res Tech 68: 197 – 208
Thomas DB (1993) Breast cancer in men. Epidemiol Rev 15: 220 – 231
Xue SA, Lampert IA, Haldane JS, Bridger JE, Griffin BE (2003) Epstein-Barr virus gene expression in human breast cancer: protagonist or passenger? Br J Cancer 89: 113 – 119
Yasui Y, Potter JD, Stanford JL, Rosing MA, Winget MD, Bronner M, Daling J (2001) Breast cancer risk and 'delayed' primary Epstein-Barr virus infection. Cancer Epidemiol Biomarkers Prev 10: 9 – 16