CORRESPONDENCE

Re: Detection of Epstein-Barr Virus in Invasive Breast Cancers

Bonnet and co-workers *(1)* presented evidence on the presence of Epstein-Barr virus (EBV) sequences in breast cancer cells. We wanted to examine whether epidemiologic evidence would support the role of EBV infection in breast cancer. The tumorigenicity of EBV appears best established for Hodgkin's disease in Europe and North America; some 40% of Hodgkin's disease cases are attributed to EBV infection *(2)*, and most show viral genomes in serum *(3)*. We reason that, if breast cancer were related to EBV, we should find an epidemiologic association between breast cancer and Hodgkin's disease. Saliva is the main route of EBV infection *(4)*, and family members of women with breast cancer should show an excess of Hodgkin's disease if EBV were the shared etiologic agent. To test these hypotheses, we used the nationwide Swedish Family-Cancer Database on 9.6 million people organized in families and containing cancer data from the Swedish Cancer Registry from years 1958 through 1996 *(5)*. Standardized incidence ratios (SIRs) were calculated based on age-standardized national rates available from the database; 95% confidence intervals (95% CI) were calculated assuming a Poisson distribution. We first analyzed Hodgkin's disease incidence as a second cancer in women diagnosed with breast cancer. There were 21 cases giving an SIR of 1.05 (95% CI = 0.65–1.55). Analyzing breast cancer incidence after Hodgkin's disease showed an SIR of 2.32 (n = 45; 95% CI = 1.69–3.04), but the excess was only observed greater than or equal to 5 years after Hodgkin's disease, a well-known effect of radiotherapy *(6)*; only two cases occurred 0–4 years after Hodgkin's disease diagnosis, while 7.44 cases were expected.

As a second hypothesis, we examined breast cancers and Hodgkin's disease incidence in daughters of mothers who had either disease, but there was no increase in any SIR (Table 1). We found 88 couples in whom the wife presented with breast cancer and the husband with Hodgkin's disease; the SIR for the wife with breast cancer was 0.94, and the SIR for the husband with Hodgkin's disease was 1.01. In one couple, both spouses presented with Hodgkin's disease compared with 1.6 couples expected. We thus failed to verify the hypotheses linking breast cancer and EBV, using Hodgkin's disease as a surrogate marker for EBV infection.

Table 1. Standardized incidence ratios (SIRs) for cancer in family members of breast cancer and Hodgkin's disease patients

Cancer in proband (relative, site or type)	Other cancer in family (relative, site or type)	Observed	Expected	SIR	95% CI*
Mother, Hodgkin's disease	Daughter, breast cancer	16	17.6	0.91	0.52–1.14
Mother, breast cancer	Daughter, Hodgkin's disease	40	39.7	1.01	0.72–1.34
Mother, Hodgkin's disease	Daughter, Hodgkin's disease	1	0.7	1.37	0.00–5.38
Husband, Hodgkin's disease	Wife, breast cancer	88	93.5	0.94	0.75–1.18
Wife, breast cancer	Husband, Hodgkin's disease	88	87.3	1.01	0.81–1.23

*CI = confidence interval.

Elsewhere, we have found epidemiologic evidence incriminating EBV. With the use of the above database, we studied second cancers after squamous cell carcinoma of the skin and found statistically significant increases for salivary gland and nasal cancers in men and women *(7)*. Nasopharyngeal cancer was also in excess, but the number of cases was small. Since salivary glands and nasopharynx are known target tissues for EBV-related carcinogenesis *(4)*, we attributed the findings to the presence of this virus among patients who may be immunocompromised. The finding of elevated risk of salivary gland cancer has been remarkably consistent, although unexplained, in at least six previous follow-up studies on skin cancer *(7)*. Recently, we were able to reproduce the findings for salivary gland and nasal cancers as second cancers in a follow-up study of patients with *in situ* squamous cell carcinoma of the skin. Although EBV-attributable cases of salivary gland and nasal cancers would be few in incidence, the results suggest that the virus may gain control once the immunologic surveillance falters, as it may locally in a tumor, such as breast cancer. This mechanism is consistent with the results of Bonnet et al. *(4)*.

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NOTES

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Recently, Bonnet et al. *(1)*, using the polymerase chain reaction, found evidence of the Epstein-Barr virus (EBV) genome in 51% of breast cancers. With the use of somewhat differing methodologies, previous studies have failed to find evidence for EBV in breast cancer specimens, whereas other studies have found evidence for EBV in 20%–40% of specimens [*(1)* and references therein]. I

would like to raise a potential issue with the link between EBV and breast cancer—the apparent extreme discordance in their antiquities. Although association does not mean causation, and a confluence in the historical antiquities of a disease and a possible cause is not sufficient to prove causality, it is necessary. Indeed, a restaurant cannot cause a food-poisoning outbreak if it has not yet opened.

The surgeon Leonides *(2,3)* from Alexandria recognized and treated (with incision and cautery) malignant breast lesions. Galen (A.D. 129–201) was also aware of breast cancer. As well, there have been possible reports of breast cancer in Celcius (42 B.C. to A.D. 37), Hippocrates, the library of King Ashurbaipal (699–62 B.C.), and the Edwin Smith papyrus (~2500 B.C.) [*(2)* and references therein]. Thus, breast cancer is at least 1800 years old, if not older. More germane to this discussion, breast cancer has been diagnosed in Europe and attempts at treatment made for at least 500 years *(4)*. For example, famed barber-surgeon Ambroise Paré (1510–1590) appreciated the metastatic spread of breast cancer to axillary lymph nodes *(4)*.

Recently, I have noted that the antiquity of EBV in Europe can be traced through infectious mononucleosis, of which, the vast majority of cases are now known to be caused by EBV *(5)*. The first report of infectious mononucleosis was in 1885 *(6)*. It is possible that infectious mononucleosis was observed, but that modern writers have failed to find the previous descriptions. However, extensive checking of 19th century sources by myself and others have failed to find any earlier mentions of a disease resembling infectious mononucleosis. Furthermore, I have noted that demographic differences between the past and present in Europe might have caused the incidence of infectious mononucleosis to have been increased in the past *(5)*.

EBV cannot be the cause of breast cancer if it did not arrive in Europe until hundreds of years after the descriptions of breast cancer. However, because Bonnet et al. find evidence for EBV in only approximately one half of the cases—most frequently in the more aggressive tumors—it is possible that, although breast cancer is not a new disease, EBV-associated breast cancer is a new disease. As women died of breast cancer even after local therapy (mastectomy) earlier than 1885, it cannot be ruled out *a priori* that aggressive breast cancer was not also present in Europe before 1885. I hope that this discordance in the antiquities of EBV and breast cancer stimulates more research into the antiquity of EBV and into a possible link between EBV and breast cancer link in general.

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RESPONSE

Epstein-Barr virus (EBV) infects more than 95% of the adult human population, with no serious consequences in the vast majority of the cases. In a few infected people, EBV-associated tumors develop. To the best of my knowledge, there is no record of the number of cases in which patients harbor two different EBV-associated diseases, such as Burkitt's lymphoma and nasopharyngeal carcinoma or nasopharyngeal carcinoma and Hodgkin's disease. Similarly, Drs. Hemminki and Dong did not observe an epidemiologic association between breast cancer and Hodgkin's disease. They also did not find an increased standardized incidence ratio of breast cancer or Hodgkin's disease in the families of women with either disease. Spouses are likely to be infected by EBV before they meet. Moreover, if a specific pattern of EBV-related tumors occurred within a couple, it would imply that both partners harbored a more aggressive EBV variant. Although attempts have been made to associate a specific variant with the development of tumors, no definitive proof has been obtained to support this hypothesis. Because the development of EBV-associated tumors is a multistep process that includes viral as well as genetic and environmental factors, it is likely that, even if EBV is a common cofactor, it may not, by itself, be enough to provoke the initiation or the development of several EBV-associated tumors. Moreover, as suggested by Drs. Hemminki and Dong, the virus–host relationship, which is influenced by the immune status of the patient, is likely to influence the development of the disease.

Dr. Altschuler observed that, while breast cancer as a disease has been described since antiquity, infectious mononucleosis, which is caused by the Epstein-Barr virus, was first reported in 1885. Mononucleosis is a disease that largely occurs in countries with a high standard of living, where primary EBV infection can occur in teenagers or in young adults. In developing countries, clinically silent EBV infection occurs in early childhood. It is likely that, even if mononucleosis is a new disease, whose incidence rate increases with standard of living, EBV might have infected humans for a longer period of time. As suggested by Dr. Altschuler, demographic differences between the past and the present in Europe might have resulted in higher rates of infection in the past.

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