

Hypothesis

Breast Cancer Risk and “Delayed” Primary Epstein-Barr Virus Infection

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Abstract

Parallel to its established causal association with both infectious mononucleosis (IM) and young adulthood Hodgkin disease (YAHD), we propose a hypothesis that “delayed” primary EBV infection (*i.e.*, primary infection occurring during adolescence or adulthood) is associated with elevated breast cancer risk. We evaluated this hypothesis with two investigations, one descriptive and the other analytic. The descriptive study used international/United States cancer registry data to assess the association between incidence rates of breast cancer and those of YAHD. The incidence rates of the seemingly unrelated neoplasms were strongly correlated (correlation coefficients of 0.74 and 0.88 for international and United States data, respectively; these were higher than the correlation coefficients of YAHD with two other cancers that we considered). Populations with higher incidence rates corresponded to those with higher likelihood of delayed primary EBV infection. The analytical study was based on a population-based case-control study of breast cancer in middle-aged women. Age-adjusted odds ratios of breast cancer in women who reported a history of IM, relative to women who did not, increased monotonically from 0.55 [95% confidence interval (CI), 0.05–6.17] for women with 0–9 years of age at IM onset to 2.67 (CI, 1.04–6.89) for women with ≥ 25 years of age at IM onset ($P = 0.016$). An older age at tonsillectomy, another surrogate of delayed EBV exposure, was also associated with increased risk of breast cancer: odds ratios, 0.92 (CI, 0.57–1.48) and 1.76 (CI, 1.15–2.69) for women with tonsillectomy at 0–4 years of age and ≥ 15 years of age, respectively ($P = 0.018$). Adjusting for additional potential confounders did not modify the associations appreciably. The implications of the findings and a potential biological mechanism are presented.

Introduction

EBV, a ubiquitous human γ herpesvirus, infects and establishes a mostly asymptomatic life-long infection in B lymphocytes

(1, 2). During latency, an intact EBV genome resides in the cell as an extrachromosomal plasmid and evades surveillance and elimination by CTLs through down-regulation of many latent-cycle antigens that are the target of CTL attack (3, 4). Despite the nearly universal EBV seropositivity by late adulthood throughout the world, ages at which different populations experience primary EBV infection vary appreciably and appear to correlate with the level of economic development and housing density that generally determine the likelihood of viral transmission (1, 2, 5). In economically developing countries and in developed countries with a high population density such as Japan, over 90% of children develop antibodies to EBV in the first few years of life (1, 2, 5). Most of these primary infections are accompanied by no or mild clinical symptoms (1, 2, 5). In contrast, primary EBV infections are often delayed until adolescence or adulthood in many economically developed countries, particularly among affluent families (1, 2, 5). It is these “delayed” primary EBV infections that most often manifest clinically as IM (1, 2, 5).² Thus, EBV is similar to viral hepatitis, poliomyelitis, and some other common viruses in that the primary infection is more likely to cause clinical symptoms if delayed past early childhood (6, 7).

A recent comprehensive review of EBV-associated malignancies by the IARC concluded that HD is one of the malignancies for which EBV is a causal factor (8). In particular, HD incidence in young adulthood, most of which is of the nodular sclerosis subtype, closely resembles the epidemiological pattern of “delayed” primary EBV infection and IM (8, 9): (a) HD incidence rates are generally higher in economically developed countries than in economically developing countries and show a high peak in the former during young adulthood (9, 10); (b) HD risk in young adulthood (or HD of the nodular sclerosis subtype) has been shown to be positively associated with higher socioeconomic status, small family size, low-density housing in childhood, early birth order, and high maternal education, conditions that foster the delay of EBV infection (9–17); and (c) an approximately 3-fold excess risk of HD has been observed in six cohort studies of young adults with a history of IM (8, 9). In addition, serological studies have found a state of immunostimulation, identified by the pattern of EBV antibody titers, in HD patients before, as well as after, the diagnosis (8, 18).

Data on breast cancer show some intriguing similarities to those on HD in young adulthood (or HD of the nodular sclerosis subtype). First, the incidence of both seemingly unrelated neoplasms is generally higher in economically developed countries and positively associated with social class within countries (9, 19). Second, parity and early age at first birth have been found to produce an appreciable reduction in the subsequent risk of both HD and breast cancer (12, 19, 20–24), although the evidence is less consistent for HD than for breast cancer (25–27). Third, consistent with the aforementioned prolonged im-

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² The abbreviations used are: IM, infectious mononucleosis; HD, Hodgkin disease; YAHD, young adulthood Hodgkin disease; SEER, Surveillance, Epidemiology, and End Results; OR, odds ratio; CI, confidence interval.

immunostimulation preceding the diagnosis of HD (18), immunosuppressive conditions appear to lower subsequent breast cancer risk (28, 29). In a large cohort of transplant patients, a negative dose-response relationship was observed between the use of post-transplant immunosuppressive drugs and breast cancer risk (30). Note that these results are also consistent with the immunosuppression associated with pregnancy (31) and with the effects of childbearing on the two neoplasms. Fourth, cells indistinguishable from Reed-Sternberg cells, a necessary but not sufficient diagnostic characteristic of HD, have been observed in an appreciable number of carcinomas of the breast (32). Finally, the EBV genome has been detected in a subset of tumor specimens of breast cancer as well as those of HD, although not consistently (8, 9, 33–39). See Magrath and Bhatia (40) for their comments on EBV detection methods that may explain the inconsistency. These similarities suggest a possible existence of a common etiology for breast cancer and HD.

In this paper, we propose a hypothesis that both IM and YAHD (or HD of the nodular sclerosis subtype) on one hand and breast cancer on the other are caused by a “delayed” primary EBV infection (*i.e.*, primary infection occurring during adolescence or adulthood). As a step toward testing the hypothesis, we conducted a pair of investigations, one descriptive and the other analytic, the results of which are reported here. The aim of the descriptive study was to assess the association between incidence rates of breast cancer and those of YAHD using international and United States cancer registry data. The analytic investigation was based on a population-based case-control study of breast cancer in middle-aged women in which questions were asked about previous history of several infectious diseases. Two surrogate indicators of “delayed” primary EBV infection were evaluated with respect to their associations with breast cancer risk. The method and results of the analytic investigation are presented after the descriptive study. “Discussion” explores possible implications of our results in view of previous findings and considers a potential biological mechanism consistent with the observed associations. The logical basis underlying our investigations is the established causal association between “delayed” primary EBV infection and both IM and YAHD.

The Descriptive Study

Methods. The goal of our descriptive investigation was to assess the population-level associations between breast cancer risk and HD risk in view of the hypothesized common risk factor, “delayed” primary EBV infection. As reviewed briefly in the “Introduction,” epidemiological evidence supporting the causal effect of EBV on HD is strongest for the nodular sclerosis subtype, which constitutes the great majority of YAHD cases. We, therefore, selected ages 15–34 as the most likely age group in which the effect of “delayed” primary EBV infection on HD risk would be evident. We calculated age-adjusted incidence rates of HD in females 15–34 years of age via a direct age adjustment using the world-standard population, based on age-specific incidence rates for 5-year groups for each reporting registry in Cancer Incidence in Five Continents VII (41). Some cancer registries reported the data stratified by race, in which case each registry-race combination was counted as a population. We used 135 populations with a female population size of at least one million to obtain stable estimates of incidence rates. We then generated a histogram to examine the distribution of the age-adjusted incidence rates of HD in females 15–34 years of age in the 135 populations (Fig. 1). As the smoothed distribution in Fig. 1 suggests, the 135 populations can be catego-

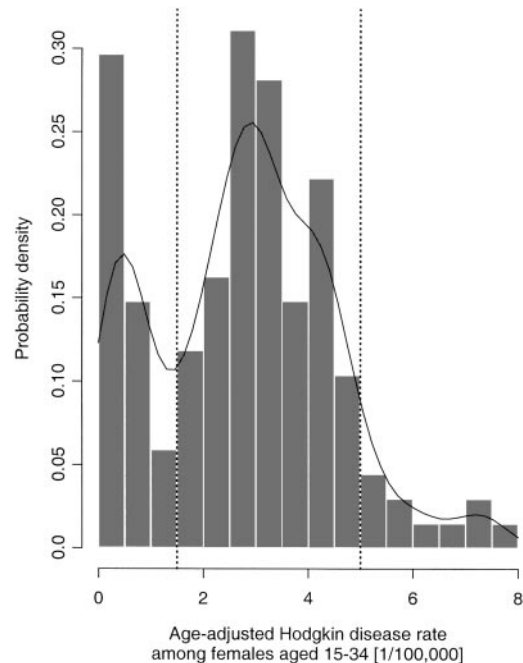


Fig. 1. Histogram and a smoothed probability distribution of age-adjusted HD rates in females 15–34 years of age in the 135 populations in the world.

rizied fairly naturally into three groups with the incidence rates of $<1.5/100,000$ (low), $1.5\text{--}5.0/100,000$ (moderate), and $\geq 5.0/100,000$ (high).

We then computed the age-adjusted incidence rates of breast cancer in females of all ages in the same 135 populations. Scatter plots were used to display the association between the rates of breast cancer and YAHD. Smoothed lines were drawn on the scatter plots by the robust locally weighted regression method (42). The Pearson correlation coefficient was computed. A formal assessment of the association between the two rates was conducted by Poisson regression analyses of disease rates (43, 44). Let D_{ij} and P_{ij} denote the number of female breast cancer cases and female population size of the j^{th} 5-year age group of the i^{th} population, where $i = 1, \dots, 135$ and $j = 1, \dots, 18$. The Poisson regression model had the log-linear mean:

$$\log(E[D_{ij}]/P_{ij}) = \alpha_j + \beta_{mod} \times HD_{mod} + \beta_{high} \times HD_{high}$$

where α_j s were the age-effect parameters and HD_{mod} and HD_{high} were indicator variables for the moderate ($1.5\text{--}5.0/100,000$) and high ($\geq 5.0/100,000$) groups, respectively, of age-adjusted HD incidence rates among females 15–34 years of age. The parameters of interest were β_{mod} and β_{high} representing the age-adjusted log rate ratios of breast cancer in the moderate ($1.5\text{--}5.0/100,000$) and high ($\geq 5.0/100,000$) HD risk groups, respectively, compared with the low risk group ($<1.5/100,000$). We used the Generalized Estimating Equation extension of Poisson regression (45) to account for the correlation between D_{ij} s across age groups within each population.

In addition to the analysis across countries described above, we conducted the same analysis within the United States using the SEER data from 1973 to 1996 (46). In this within-country analysis, we used nine SEER registries and three race groups (white, black, and other) to form 27 populations. Of the 27 populations, we used 18 populations with at least one mil-

Fig. 2. Age-adjusted breast cancer incidence rates in females by age-adjusted HD incidence rates in females 15–34 years of age in 135 populations in the world (Panel A) and in 18 United States SEER populations (Panel B) with a robust locally weighted regression line.

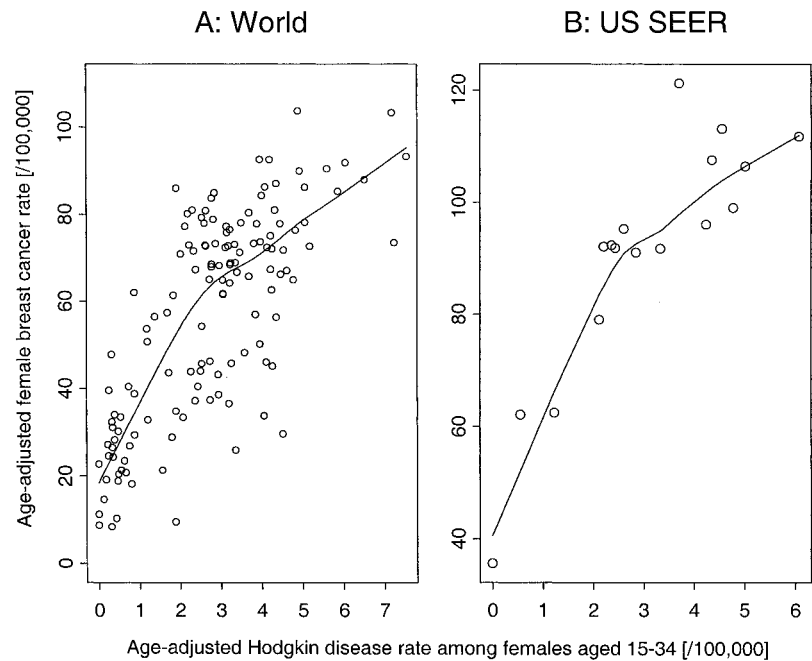


Table 1 Populations with age-adjusted HD incidence rates of 1.5/100,000 or lower among females 15–34 years of age

France, La Reunion (Africa)	Mali, Bamako
Uganda, Kyadondo	Zimbabwe, Harare: African
Brazil, Belem	Brazil, Goiania
Brazil, Porto Alegre	Colombia, Cali
Ecuador, Quito	Peru, Lima
United States, Central California: Hispanic	China, Qidong
China, Shanghai	China, Tianjin
Hong Kong	India, Bangalore
India, Barshi, Paranda, and Bhum	India, Bombay
India, Madras	India, Trivandrum
Israel: Jews born in Africa or Asia	Japan, Hiroshima
Japan, Miyagi	Japan, Nagasaki
Japan, Osaka	Japan, Saga
Japan, Yamagata	Kuwait: Kuwaitis
Philippines, Manila	Singapore: Chinese
Thailand, Chiang Mai	Thailand, Khon Kaen
Viet Nam, Hanoi	Spain, Tarragona

Table 2 Populations with age-adjusted HD incidence rates of 5/100,000 or above among females 15–34 years of age

Canada, Ontario
United States, Central California: non-Hispanic white
United States, San Francisco: non-Hispanic white
United States, Connecticut: white
United States, Iowa
United States, Detroit: white
Israel: Jews born in Israel
Israel: Jews born in America or Europe
Italy, Varese
Italy, Veneto

lion females to obtain stable incidence rates. Note that the United States data contain a smaller number of populations but a longer period of observation than the international data. Scatter plots, the Pearson correlation coefficient, and Poisson regression analyses were used for the 18 SEER populations as described above for the international analysis.

To define the degree to which the breast cancer/YAHD association was specific, we also assessed the correlations of the international and SEER rates of YAHD with colon cancer rates in women and testicular cancer rates in men.

Results. Table 1 shows the list of 34 populations with the low (<1.5/100,000) age-adjusted HD incidence rates in females 15–34 years of age. These populations are found generally in economically developing countries, consistent with the seroepidemiological pattern of EBV infections in early childhood. Note, however, that populations with high per capita income but with high population densities (where early EBV infection

is also the norm) are also in the list, e.g., Hong Kong, Singapore, and Japanese registries (47). Table 2 shows the list of 10 populations with the high ($\geq 5.0/100,000$) age-adjusted HD incidence rates in females 15–34 years of age. These are white populations in North America, Jewish populations in Israel born in Europe, America, or Israel, and two northern Italian populations, also consistent with the seroepidemiological pattern of late EBV infections. Note that within the United States, the “United States, Central California, Hispanic” population shows a low rate, whereas the non-Hispanic white populations of the United States are mostly in the list of high rates. Similarly, Jewish populations in Israel born in Asia or Africa have a low rate, unlike those born in Europe, America, or Israel.

Fig. 2A and B show the scatter plots with smoothed lines of the age-adjusted incidence rates of breast cancer in females in relation to the age-adjusted incidence rates of HD in females 15–34 years of age for the 135 international populations and the 18 United States populations, respectively. Both figures display strong positive associations between the two rates, Pearson correlation coefficients of 0.74 for Fig. 2A and 0.88 for Fig. 2B. Note, in particular, the steady positive association throughout the incidence range. The gradient exists both across and within the three levels (low, moderate, and high) of the HD rates.

In contrast, the correlations between YAHD and colon

Table 3 Estimates and 95% CI of age-adjusted breast cancer rate ratios in females by age-adjusted HD incidence rates among females 15–34 years of age: 135 populations in the world in 1988–1992

Age-adjusted HD rate among females 15–34 years of age (1/100,000)	Rate ratio estimate	95% CI for rate ratio
<1.5	1.0	
1.5–5.0	2.6 ^a	(2.2, 3.0)
≥5.0	3.9 ^a	(3.3, 4.5)

^a $P < 0.001$.

cancer in women and testicular cancer in men were 0.57 and 0.58 (international) and 0.57 and 0.65 (SEER), respectively.

Table 3 shows the results of the Poisson regression analysis in the 135 international populations. Age-adjusted estimates of breast cancer rate ratios are presented by the three levels of age-adjusted HD rates in females 15–34 years of age. Compared to the 34 populations in Table 1 with the low rates of HD in females 15–34 years in age, the populations with the moderate-range rates had greater than a 2.5-fold increase in breast cancer rates. The 10 populations with the high HD rates had nearly a 4-fold increase in breast cancer rates.

Table 4 shows the results of the Poisson regression analysis in the 18 United States SEER populations in 1973–1996. Compared to the three populations with the low rates of HD in females 15–34 years of age, the populations with the moderate-range rates had a rate ratio of 1.6 for breast cancer. The three populations with the high HD rates had a rate ratio of approximately 2.0.

The Analytic Study

Our analytic investigation used a population-based case-control study of breast cancer and evaluated the association of two surrogate indicators of “delayed” primary EBV infection with breast cancer risk.

The Study Population and Data Collection. The study design and data-collection procedures were described in detail in a previous publication (48). Briefly, the study used a population-based case-control design in which cases were identified through the SEER population-based cancer registry of northwestern Washington State. Cases were white women 50–64 years of age residing in King County, Washington with a residential telephone who were diagnosed with histologically confirmed incident invasive or *in situ* breast cancer between January 1, 1988 and June 30, 1990. We interviewed 537 women (81.4%) of 660 eligible patients with *in situ* ($n = 87$) or invasive ($n = 450$) breast cancer. Controls were white women 50–64 years of age residing in King County, Washington, identified by random-digit telephone dialing, and were frequency matched to cases by age (same 5-year group). We identified 747 eligible control women and interviewed 545 (73.0%). Fifty-three women who were nonwhite or had a previous diagnosis of breast cancer were excluded, leaving 492 controls for analysis.

A detailed in-person interview was conducted to elicit information on menstrual, contraceptive, and reproductive histories; medical history; use of exogenous hormones (contraceptive and noncontraceptive); indices of body mass; diet and alcohol intake; smoking habits; family history of cancer; and social and demographic factors. History of IM was ascertained, and if a woman indicated a positive history, the age at the first

Table 4 Estimates and 95% CI of age-adjusted breast cancer rate ratios in females by age-adjusted HD incidence rates among females 15–34 years of age: 18 populations in the United States SEER data in 1973–1996

SEER registry	Race	HD ^a	Breast ^b	Rate ratio (95% CI)
New Mexico	Other	0.00	35.68	
Seattle (Puget Sound)	Other	0.55	62.07	1.0
San Francisco-Oakland	Other	1.22	62.48	
Hawaii	Other	2.11	79.00	
Connecticut	Black	2.20	92.10	
Detroit (Metropolitan)	Black	2.36	92.35	
Atlanta (Metropolitan)	Black	2.43	91.80	
San Francisco-Oakland	Black	2.60	95.26	
New Mexico	White	2.84	91.00	1.6 ^c (1.4, 1.9)
Utah	White	3.33	91.72	
Hawaii	White	3.70	121.21	
Seattle (Puget Sound)	Black	4.23	96.06	
Atlanta (Metropolitan)	White	4.35	107.56	
Seattle (Puget Sound)	White	4.55	113.13	
Iowa	White	4.77	98.99	
Detroit (Metropolitan)	White	5.01	106.43	
San Francisco-Oakland	White	5.14	119.31	1.9 ^c (1.6, 2.1)
Connecticut	White	6.07	111.80	

^a HD is the age-adjusted Hodgkin disease rate in females 15–34 years of age.

^b Breast is the age-adjusted breast cancer rate in females of all ages.

^c $P < 0.001$.

episode was recorded. Similarly, history of and age at tonsillectomy were recorded.

Data Analysis. As surrogate indicators of “delayed” primary EBV infection, we used age at (first) IM and age at tonsillectomy. The rationale behind this was that the likelihood of developing IM increases with age at the primary infection (7), and recurrent tonsillitis, a major reason for tonsillectomy, is often EBV associated (49–51). Later ages of these clinical events indicate the lack of humoral immunity to EBV in the preceding years. Age at (first) IM was grouped into “never,” “0–9,” “10–19,” “20–24,” and “25 or over.” Age at tonsillectomy was grouped into “never,” “0–4,” “5–9,” “10–14,” and “15 or over.” Our data analysis was focused on the association of these ages with breast cancer risk. We evaluated these associations by estimating ORs using logistic regression models (44, 52), controlling for relevant confounding factors. Initially, we fitted the models controlling for age (single-year categorical) only, and then controlling for additional established and suggested breast cancer risk factors: family history of breast cancer (none or unknown, first degree, or second degree); number of full-term pregnancies (nulliparous, 1, 2, 3, 4, or 5 or more full-term pregnancies); age at first full-term pregnancy (15–19 years, 20–29 years, or 30 years or over); body mass index (21.2 kg/m² or less, 21.2–23.7 kg/m², 23.7–27.2 kg/m², or 27.2 kg/m² or more); age at menarche (10 or under, 11, 12, 13, 14, or 15 or over); use of hormone replacement therapy (never, estrogen only, progestin only, estrogen and progestin, or unknown); cumulative duration of oral contraceptive use (0, less than 5 years, or 5 years or more); and average alcohol consumption/week (zero, less than one, one to four, four to seven, or seven drinks or more). Age at IM and age at tonsillectomy were evaluated simultaneously in the models to estimate the association with one controlling for the other. Linear trend tests (44, 52) were used to assess the statistical significance of a monotone trend in the association of breast cancer risk with age at IM onset and with age at tonsillectomy among women who experienced these events.

To examine the possible implications of age of exposure

Table 5 OR estimates of breast cancer by time of first occurrence of infectious mononucleosis and tonsillectomy

Condition	Time of first occurrence (no. of cases/controls)	Age-adjusted		Multivariable-adjusted ^a	
		OR estimate	95% CI	OR estimate	95% CI
IM	Never had (503/469)	1.00	(Reference)	1.00	(Reference)
	Ages 0–9 (1/2)	0.55 ^b	0.05–6.17	0.41 ^c	0.03–5.09
	Ages 10–19 (7/9)	0.74 ^b	0.27–2.04	0.70 ^c	0.25–1.97
	Ages 20–24 (9/6)	1.58 ^b	0.55–4.54	1.29 ^c	0.44–3.79
	Ages ≥25 (17/6)	2.67 ^b	1.04–6.89	2.41 ^c	0.92–6.32
Tonsillectomy	Never had (175/178)	1.00	(Reference)	1.00	(Reference)
	Ages 0–4 (41/45)	0.92 ^d	0.57–1.48	0.82 ^e	0.50–1.35
	Ages 5–9 (170/159)	1.08 ^d	0.79–1.46	1.05 ^e	0.76–1.43
	Ages 10–14 (71/64)	1.13 ^d	0.76–1.69	1.08 ^e	0.72–1.64
	Ages ≥15 (80/46)	1.76 ^d	1.15–2.69	1.68 ^e	1.09–2.60
IM	Never had (503/469)	1.00	(Reference)	1.00	(Reference)
	Before menarche (2/2)	1.10	0.15–7.92	0.80	0.10–6.28
	After menarche (32/21)	1.45	0.82–2.58	1.30	0.72–2.34
	Never had (503/469)	1.00	(Reference)	1.00	(Reference)
	Before FFTP ^f (19/14)	1.35	0.67–2.76	1.12	0.54–2.33
	After FFTP ^f (12/7)	1.67	0.65–4.33	1.57	0.60–4.15
	Nulliparous (3/2)	1.19	0.19–7.57	1.13	0.17–7.50
	Never had (175/178)	1.00	(Reference)	1.00	(Reference)
Tonsillectomy	Never had (175/178)	1.00	(Reference)	1.00	(Reference)
	Before menarche (270/254)	1.07	0.82–1.41	1.03	0.78–1.37
	After menarche (92/60)	1.54	1.04–2.28	1.47	0.98–2.20
	Never had (175/178)	1.00	(Reference)	1.00	(Reference)
	Before FFTP ^f (299/274)	1.10	0.84–1.44	1.09	0.80–1.45
	After FFTP ^f (18/10)	1.80	0.80–4.03	1.96	0.85–4.50
	Nulliparous (45/30)	1.54	0.92–2.58	1.13	0.50–2.59

^a Adjusted for age, family history of breast cancer, number of full-term pregnancy, age at first full-term pregnancy, body mass index, age at menarche, use of hormone replacement therapy, cumulative duration of oral contraceptive use, and alcohol consumption.

^b *P* for trend = 0.016.

^c *P* for trend = 0.043.

^d *P* for trend = 0.018.

^e *P* for trend = 0.042.

^f FFTP, first full-term pregnancy.

versus time of exposure in relation to hormonally relevant events, we also calculated the ORs for breast cancer with IM and tonsillectomy before *versus* after menarche, and before *versus* after first full-term pregnancy.

To explore the specificity of the association between ages at IM and at tonsillectomy, we also examined the association between breast cancer risk and age at onset of acne and of allergies (the only other infective/immunological exposures on which we have relevant data).

Results. Characteristics of study subjects and differences between cases and controls have been described previously (48). Briefly, cases and controls were similar with respect to age at reference date (date of diagnosis for cases and a similar randomly assigned date for controls), age at menarche, menopausal status, age at menopause, income, history of benign breast disease, and prior use of oral contraceptives and hormone replacement therapy. Cases were somewhat more likely than controls to have higher educational levels, to be nulliparous, to have a later age at first full-term pregnancy, to have a higher body mass index, to have a family history of breast cancer, and to drink alcohol.

Thirty-four cases (6.4%) reported a history of IM, compared with twenty-three controls (4.6%; Table 5). The observed ratios of cases:controls increased monotonically with the age of IM onset. A history of tonsillectomy was common among the women in the study. About two-thirds of the cases and controls had undergone tonsillectomy (Table 5). The observed ratios of cases:controls increased monotonically with the age at tonsillectomy.

Age-adjusted ORs for developing breast cancer in women who reported IM, relative to women who did not, varied by age at the onset of IM (Table 5), monotonically increasing from 0.55 (95% CI, 0.05–6.17) for women with the age at onset of 0–9 to 2.67 (95% CI, 1.04–6.89) for women with the age at onset of 25 or over (*P* for trend = 0.016). Age-adjusted ORs for developing breast cancer in women who reported a tonsillectomy, relative to women who did not, also varied by age at tonsillectomy (Table 5), monotonically increasing from 0.92 (95% CI, 0.57–1.48) for women with the surgery at ages 0–4 to 1.76 (95% CI, 1.15–2.69) for women with the surgery at age 15 or over (*P* for trend = 0.018). Adjusting for additional potential confounders did not modify the results appreciably (Table 5). The estimated risk differences between before *versus* after menarche and before *versus* after first full-term pregnancy were generally consistent with, but not statistically significant and smaller in magnitude than, the sharp risk gradient observed with age at the onset of IM and tonsillectomy.

We examined age at onset data on acne and on allergies. For neither of these two conditions did age at onset show an association with breast cancer risk (data not shown).

Discussion

On the basis of the relationship between the seroepidemiological data of cytomegalovirus and breast cancer incidence, Richardson (53) suggested that late exposure to a common virus might be associated with breast cancer risk. Our hypothesis, that “delayed” primary EBV infection is associated with breast

cancer risk, is similar to but more specific than Richardson's hypothesis, and it is supported by the results reported here. In our descriptive investigation, the population-level correlation between incidence rates of YAHD and those of breast cancer was remarkably high. The high correlation was observed both within and across countries. Because the incidence patterns of the two malignancies are closely related to the level of economic development, however, it is conceivable that distinct economic development-related causal factors are responsible for the two malignancies separately. This counter explanation presents some difficulty, however, because risk of both malignancies is low in some economically developed populations, such as Hong Kong, Singapore, and all of the six Japanese populations (Table 1). If distinct economic development-related causal factors are responsible for the two malignancies separately, then these factors must be simultaneously absent in Hong Kong, Singapore, and all of the six Japanese populations. An alternative explanation is that these populations have low risks for the two malignancies because of the high likelihood of EBV infection in early childhood. It remains possible, however, that factor(s) closely correlated with "delayed" EBV infection are responsible for one or both of the malignancies. For example, another virus with population patterns of infection, both worldwide and within the United States, similar to EBV could also be responsible for our results.

Our analytical investigation found a monotonic increase of breast cancer risk with both age at IM onset and age at tonsillectomy. Key to understanding this relationship with a ubiquitous infection is that it is not the history of IM or tonsillectomy itself but older age at the onset of these clinical events that was associated with the elevated risk of breast cancer. It is, therefore, unlikely that the pathological conditions of IM or tonsillectomy themselves cause breast cancer. Rather, factors associated with older age at IM onset and tonsillectomy, such as a strong host immune response to "delayed" primary EBV infection, are potential causative factors of breast cancer in middle-aged women. Because nearly every individual is seropositive for EBV antibodies by middle age (1, 2, 5), the study participants who reported no history of IM and tonsillectomy will have been infected with EBV at various ages without developing the clinical events. This is consistent with the results in Table 5, which show that the breast cancer risk estimate for women without a known history of IM or tonsillectomy is in the middle of the risk spectrum. One limitation of our analytic investigation is that the surrogate indicators of "delayed" primary EBV infection were available only from those who experienced either IM or tonsillectomy. If the age at primary EBV infection or its surrogate was measurable for each woman, we could investigate whether there is a risk gradient among women with no self-reported history of IM or tonsillectomy according to the age at primary EBV infection. At present, however, we are unaware of any functional indicators of "delayed" primary EBV infection, biological or self-reported, that can be used for every woman. Another related limitation of our analytic investigation is the accuracy of the surrogate measures we used for age at primary EBV infection. Specifically, because EBV is one of a few major causes of recurrent tonsillitis (49–51), age at tonsillectomy is by no means a perfect surrogate of age at primary EBV infection. This may explain the smaller gradient of breast cancer risk we observed with age at tonsillectomy than with age at the onset of IM.

Despite the strong epidemiological evidence linking delayed primary EBV infection to YAHD, molecular studies of tumor EBV status in HD have provided rather paradoxical observations. Glaser *et al.* (54) showed in their international

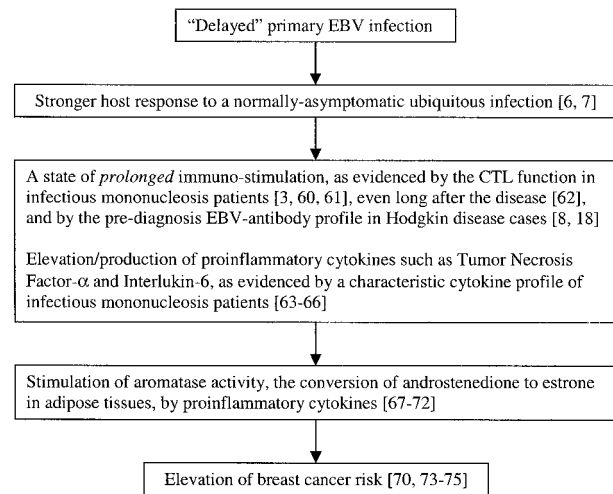


Fig. 3. A possible pathway under which "delayed" primary EBV infection elevates breast cancer risk.

study that the nodular sclerosis subtype was substantially less likely to be EBV-positive compared with the mixed cellularity subtype, especially in the age group of 15–49. ORs of EBV positivity were 0.14, 0.07, and 0.20 for ages 0–14, 15–49, and ≥ 50 , respectively. In addition, Sleckman *et al.* (55) found that 11 of 14 HD cases with a history of IM were EBV negative. Although the history of IM is associated with a 3-fold risk increase of HD, it did not seem to be associated with a higher rate of EBV presence in tumor cells in this small set of cases. Research data on breast cancer and EBV also imply the same paradoxical relationship; the proportion of EBV-positive cases of breast cancer was shown to be significantly higher in the hormone-receptor negative subtype than in the rest of breast cancer cases (33), the majority of which are presumably hormone-receptor positive (56–58). In populations with high breast cancer risk, the hormone-receptor positive subtype appears to be the dominant majority (59). Taken together, high-risk populations appear to have lower proportions of EBV-positive breast cancer cases, exactly analogous to the paradoxical observations for HD. A possible refinement of the hypothesis, suggested by the apparent paradoxical inverse correlation between molecular *versus* nonmolecular epidemiological evidence, is that the factor responsible for the two neoplasms is not the EBV genome itself, but an EBV-induced host response that inhibits EBV replication and controls the infection. We may infer that host defense mechanisms against EBV may have two consequences. Intended to inhibit EBV spread and control the infection, they also increase the likelihood of developing HD and breast cancer. Such dual effects of an EBV-induced host response may explain the absence of EBV genome in appreciable fractions of HD and breast cancer cases, in particular, in the subtypes that are linked to "delayed" primary EBV infection by nonmolecular epidemiological data. The refined hypothesis is also consistent with the tendency of stronger host response to "delayed" primary EBV infection, which most often manifests as clinical IM (7).

Some of the biological similarities between breast cancer and HD are shown in Fig. 3. Although our investigations were not directed at a specific pathway via which delayed primary EBV infection could lead to the elevation of breast cancer risk, we show some pertinent research results that broadly support

the idea in that figure. Delayed primary EBV infection appears to be associated with a prolonged state of immunostimulation characterized by the production of proinflammatory cytokines in IM patients (63–66) and by the elevated EBV-antibody titers in the prediagnosis serum of HD cases (8, 18). These proinflammatory cytokines, in particular, tumor necrosis factor- α and interleukin-6, stimulate aromatase function converting androstenedione to estrone in adipose tissues (67–72). Aromatase function is the major source of endogenous estrogens in the postmenopausal period (70), during which the international difference of breast cancer risk is clearest (41). Breast cancer risk, especially that of postmenopausal women, increases with the level of aromatase function (70, 73–75). Furthermore, immunosuppression may reduce aromatase function by inhibiting the production of the proinflammatory cytokines (71). The pathway presented in Fig. 3 is, therefore, one possible working hypothesis for future research.

Findings from both the descriptive and analytic studies would be seen to be much stronger if they could be shown to be specific. We examined the correlations between YAHD rates and colon cancer rates and testicular cancer rates in the descriptive study and estimated breast cancer risk by age of onset of acne and allergies in the analytic study. YAHD rates in females were positively correlated with the age-adjusted colon cancer rates in females and age-adjusted testicular cancer rates in males. The degree of correlations was, however, appreciably higher for breast cancer (international, 0.74; SEER, 0.88) than for colon cancer (international, 0.57; SEER, 0.57) and testicular cancer (international, 0.58; SEER, 0.65). We examined age at onset data on acne and on allergies. For neither of these two conditions did age at onset show an association with breast cancer risk. These additional analyses, although limited by the availability of data, strengthen the inference that the association between breast cancer risk and delayed primary EBV infection is specific.

The potential for developing EBV vaccines gains additional significance if it can eventually reduce the risk of breast cancer as our hypothesis suggests. Several strategies for vaccines have been considered (8), one of which has been tried in humans and shown to induce EBV-specific immune responses (76). Such vaccines can be prophylactic for preventing or modifying primary infection or can be used for postinfection, modifying the immune status of an infected individual (8). Even if primary infections cannot or even, perhaps, should not be prevented, the avoidance of an unusually strong host immune reaction associated with “delayed” primary EBV infections may reduce the incidence of breast cancer appreciably.

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