Published in final edited form as:
Cancer Causes Control. 2012 December ; 23(12): 1893–1898. doi:10.1007/s10552-012-0064-1.

Infectious mononucleosis and risk of breast cancer in a prospective study of women

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BACKGROUND

Breast cancer is the most common cancer in women with 207,000 estimated new cases in the United States in 2010.[1] Compared to other cancers, there have been advances over the past decade in the treatment of breast cancer as well as an increase in cure rate for early stage disease.[2] Despite this, estimated deaths due to breast cancer in 2010 are close to 40,000.[1] Viruses such as human papillomavirus and mouse mammary tumor virus have been studied with inconsistent results with respect to risk of breast cancer. [3, 4]. Another prime candidate virus for an etiological agent in breast cancer is the Epstein-Barr virus (EBV),[5] a ubiquitous herpesvirus that infects >90% of the human population and persists for life.[3] EBV is transmitted through mucous membranes; infection in early in life typically manifests as a subclinical (i.e., asymptomatic) illness. However when infection is delayed to early adulthood, some individuals, especially those in economically developed countries, will develop infectious mononucleosis (IM).[6–9] In general, most humans tolerate latent EBV infection without adverse effects. However, in certain individuals, EBV has been linked to the development of African Burkitt's lymphoma, Hodgkin lymphoma and nasopharyngeal carcinoma among other malignancies.[10]

Several histopathologic studies support a role for EBV directly effecting either the initiation or exacerbation of the clinical course of breast cancer. A recent meta-analysis that included 1535 breast cancer tumors found the overall prevalence of EBV DNA in tissue specimens to be 29%.[11] Another study reported a high frequency of EBV in triple-negative, high-grade breast tumors, and the absence of the virus in the adjacent normal tissue.[12] Additionally, a meta-analysis of nine case-control studies reported an increased prevalence of EBV DNA in breast tumor tissues of patients with breast carcinoma compared to controls.[6] Investigators have also reported that a response to EBV may alter the course of breast cancer by demonstrating that an EBV-infected subset of breast cancer cells appeared more resistant to treatments with paclitaxel (one of the standard chemotherapeutic agents used in treatment). [13] However, similar histopathologic studies with negative results have also been reported,

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CONFLICT OF INTEREST
The authors declare that they have no conflict of interest.

[14] leaving the association between the presence of EBV in breast cancer tissue and breast cancer initiation and course uncertain.

In addition to the possible direct effects of EBV, some have investigated whether an aberrant immune response to EBV may result in cell cycle derangement resulting in cancer.[15, 16] In particular, one investigation considered whether IM, a manifestation of EBV acquisition in adolescence or early adulthood, may be related to breast cancer. [17] Investigators in this study used international and United States cancer registries to estimate a correlation between breast cancer and IM incidence (international, 0.74; SEER, 0.88). This investigation also included a case-control study which found multivariate adjusted odds ratios of breast cancer increased monotonically with age (p-value 0.04), however the case/controls counts were small. These authors proposed that a delayed EBV infection could cause an immunologic response that may have an oncogenic effect on the breast epithelium.[7]

In order to further investigate the potential role of IM in the etiology of breast cancer we conducted an analysis in the Nurses' Health Study II. In this large, prospective cohort we investigated the association between self-reported history of and age at IM and invasive breast cancer. This association could be a critical one to determine because IM maybe a modifiable risk factor for the breast cancer through vaccines which could prevent primary EBV infection or modify it [18, 19].

SUBJECTS AND METHODS

Study population

The Nurses' Health Study II (NHS II) began in 1989, when greater than 116,000 female registered nurses completed a mailed questionnaire about lifestyle factors and medical history. Every two years participants in the NHS II are mailed follow-up questionnaires to update information on possible risk factors for disease, as well as to identify newly diagnosed illnesses. Response rates for the baseline questionnaire as well as each follow up questionnaire have exceeded 90%. The follow up for this analysis was 1989 through 2007. Participants were aged 24–44 years at the start of follow-up. The 2001 follow up questionnaire asked if a participant was ever infected with infectious mononucleosis and if so their age at onset.

We considered only those women who answered the 2001 questionnaire (n=101,118) and excluded women if they left the questionnaire about history of IM (ever/never) blank (n=17,830), had any diagnosis of cancer (excluding non-melanoma skin cancer) before 1989 (n=720), if their date of breast cancer diagnosis was before 1989 (n=73), or if their diagnosis was of in situ breast cancer (n=688). After these exclusions, there were 81,807 women were eligible for this analysis. Analyses which considered age at IM had 81,630 women, because 177 women did not provide this information on the 2001 questionnaire. These analyses were approved by the Institutional Review Boards of the Brigham and Women's Hospital and the Harvard School of Public Health.

Ascertainment of breast cancer cases

Breast cancer cases were identified on follow up questionnaires; the National Death Index was used to search for non-responders. Women who indicated a new diagnosis of breast cancer on a follow-up questionnaire were mailed a consent form to ask for medical records. Study investigators, who were blinded to the exposure status of the women, confirmed the diagnosis of breast cancer and collected information on invasiveness and histological type of the cancer. [20] During the follow-up, 2,349 cases of invasive breast cancer were documented.

Assessment of infectious mononucleosis

In the 2001 follow up questionnaire, women were asked if they ever had IM and if so, at what age (age groups: <5; 6–10; 11–15; 16–19; 20–24; 25–29; 30+). We collapsed the three youngest age groups into a ≤15 category because of small numbers of cases in this age range. We began follow up in 1989; women were assigned their IM status based on their responses to the 2001 questionnaire. We performed a secondary analysis in which follow-up started in 2001 to assess the possibility of recall bias. We also confirmed that no breast cancer cases occurred before onset of IM. Because some women may have developed IM between 1989 and 2001, we conducted an analysis where we excluded these women; results were unchanged and therefore not reported.

Statistical analysis

We analyzed whether history of IM (ever/never) or age at IM was associated with risk of invasive breast cancer. We also considered estrogen receptor (ER) and progesterone (PR) positive and negative tumors separately. Additionally, we stratified analyses by median age at onset of breast cancer and menopausal status.

Multivariable cox proportional hazards models stratified on age and questionnaire cycle were used to calculate relative risks (RRs) and 95% confidence intervals (CI). We controlled for potential confounding by established or suspected risk factors for breast cancer by including the following variables in multivariable models: height (inches: 50–62, 62–65, 65–68, 68+), age at first menarche (<12, 12, 13, 14+), family history of breast cancer, history of benign breast disease, body mass index (BMI) at age 18 (<18.5, 18.5–22.5, 22.5–30, 30+), parity and age at first birth (nulliparous; first birth, age <25, 1–2 children; first birth, age 25–29, 1–2 children; first birth, age 30+, 1–2 children; first birth age <25, 3+ children; first birth, age 25+, 3+ children), change in weight from age 18 (weight loss >5kg, weight gain or loss <5kg, weight gain 5–10kg, weight gain 10–20kg, weight gain 20kg), alcohol consumption (gm/day: 0, 0–5, 5–15, 15+), oral contraceptive use (current vs. not current user), and menopausal status.

We tested for trend in age at IM by excluding those who did not have IM and used ordinal values for categories of age at IM as a continuous variable in multivariable Cox proportional hazards models. All P values are two-sided. We conducted all analyses using SAS version 9 (SAS Institute, Inc., Cary, NC).

RESULTS

Table 1 shows the age-standardized baseline characteristics according to age at IM. There were no trends with age at IM and any of the characteristics considered. Of those that answered the question on ever vs. never having IM, 17.8% responded to having had IM. In this population of women at the start of follow up, 13.9% had a family history of breast cancer, mean BMI at age 18 was 21.2kg/m^2, and current oral contraceptive use was 12.6%. Responders and non-responders were similar on variables of interest including breast cancer, smoking history, and other variables.

History of IM was not associated with risk of invasive breast cancer; the multivariable adjusted RR was 1.00 (95% CI: 0.90–1.11)(Table 2). The relation between age at IM and breast cancer risk appeared to be non-linear: compared to women with no history of IM, breast cancer risk was lower among women who reported IM at ages ≤15 years (RR: 0.77; 95% CI: 0.60–0.97) and higher among women who reported IM between 25 and 29 years of age (RR: 1.45; 95% CI: 1.02–2.04) (Table 2). However, there was no association between IM and breast cancer for women diagnosed with IM at ages 16–19, 20–24, or 30+ (Table 2). Similar patterns were observed when we considered ER and PR+/− tumors separately (Table

3). There were no apparent differences in associations between women who were diagnosed with breast cancer at an earlier age compared to a later age, or pre- vs. post-menopause (Table 4). Lastly, there is no significant association between IM history and breast cancer invasiveness (p-value 0.21). In secondary analyses, we included only breast cancer cases diagnosed after 2001, thus using a fully prospective design. Similar results were observed as compared to when follow up was started in 1989. The multivariable RR for ever vs. never IM was 0.96 (95% CI: 0.83–1.11). The multivariable-adjusted RRs for age at IM compared with women without history of IM were $RR_{\leq 15}$: 0.65, 95% CI: 0.46–0.92; $RR_{16–19}$: 1.02, 95% CI: 0.83–1.26; $RR_{20–24}$: 0.97, 95% CI: 0.72–1.31; $RR_{25–29}$: 1.81, 95% CI: 1.19–2.77; RR_{30+}: 0.90 95% CI: 0.55–1.47. Case numbers and person years for these age categories are as follows: RR no IM: 1,029/519,953; RR ≤15: 32/25,504; RR16–19: 100/48,224; RR20–24: 46/22,394; RR25–29: 22/6,285; RR30+: 16/8,773.

DISCUSSION

Our results do not support a clear association between history of IM and risk of invasive breast cancer. Although a significantly lower risk of breast cancer was associated with young age at IM (i.e., ≤ 15 years) vs. no IM and an increased risk was observed among women who had IM between 25 and 29 years of age, the lack of a consistent trend across age groups suggests that this may be a chance finding. Similar null results were obtained when ER and PR +/− tumors were considered separately. Further, neither age at diagnosis of breast cancer nor menopausal status significantly modified the results. Age and multivariable results are very similar, it is unlikely that there are many confounders for the association between IM and breast cancer. This association may be different in less affluent countries where IM is not as common.

Although our findings are likely due to chance, potential mechanisms for IM increasing risk of breast cancer have been detailed elsewhere [17], but briefly include a strong host response to IM which creates a prolonged immune-stimulation, resulting in elevated production of proinflammatory cytokines, in turn stimulating aromatase activity which has been postulated to increase risk of breast cancer.

Age at IM and breast cancer was found to be associated in one population based case control study, however case/control counts were very small in age categories at IM and therefore difficult to interpret (#cases/#controls: 1/2, 7/9, 9/6, 17/6). [17] The majority of the literature on breast cancer and EBV infection has been investigated mainly in histopathologic studies. A meta-analysis of nine case-control studies found an increase in EBV DNA in the breast tissue of women with breast cancer compared to those without (OR = 6.29, 95% CI = 2.13–18.59). [11] However, because of their retrospective design and differences in laboratory methods used to detect EBV DNA in tissue specimens, these studies cannot assess whether EBV infection is important in the etiology of the disease. Although our study does not support an association between late-age at EBV acquisition and breast cancer risk, this result does not contradict previous findings of an increased presence of EBV DNA in breast cancer tissue. [11]

There are a couple of potential limitations to our study. First, history of IM is self-reported. However, the fact that the association between history of IM and risk of multiple sclerosis in a nested case-control study among women in this cohort (RR=2.1, 95% CI=1.5–2.9)[21] is virtually identical to that found in studies based on laboratory confirmed IM (RR=2.27, 95% CI=1.87–2.75)[22], suggest that any misclassification is modest. There are no other breast cancer cohorts that have published data on IM prevalence- although in our cohort, rates of IM are what are typical of those in the US. We obtained similar results in secondary analyses using only prospective data, suggesting that differential recall of IM between

women with breast cancer and those without did not bias our results. Second, we may have had limited statistical power to detect modest associations for ER/PR-negative disease.

Despite some limitations, our study has several strengths, including the prospective study design, large sample size, and detailed exposure information about history of and age at clinical IM. Overall, the results of our analyses do not support a clear association between history of IM, a marker of age at EBV infection, and breast cancer risk. Given inconsistency of results in the published literature and limitations of prior histopathologic studies, further research is warranted to evaluate the possible role of EBV infection in breast cancer etiology.

Acknowledgments

This work was supported by research grant R01 CA50385 from the National Institutes of Health. K.A.B. was supported by the Nutritional Epidemiology of Cancer Education and Career Development Program (R25 CA098566).

In addition, we would like to thank the participants and staff of the Nurses' Health Study II, for their valuable contributions as well as the following state cancer registries for their help: AL, AZ, AR, CA, CO, CT, DE, FL, GA, ID, IL, IN, IA, KY, LA, ME, MD, MA, MI, NE, NH, NJ, NY, NC, ND, OH, OK, OR, PA, RI, SC, TN, TX, VA, WA, WY.

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Table 1

Age-adjusted baseline characteristics according to age of infectious mononucleosis onset in NHS II, 1989

	Age at infectious mononucleosis					
	No IM	**≤15**	**16–19**	**20–24**	**25–29**	**30+**
N	67,245	3,290	6,241	2,898	819	1,137
Age (years)	34.6	33.3	34.2	34.9	34.2	35.0
Height (inches)	64.9	64.9	65.1	65.1	65.0	65.0
Age at first menarche	12.4	12.3	12.4	12.5	12.3	12.4
Family history of breast cancer (%)	13.7	14.8	15.0	15.5	12.9	13.7
History of benign breast disease (%)	7.8	8.0	8.3	8.6	8.1	9.5
BMI at age 18	21.3	21.0	21.0	21.4	21.8	21.4
Parity and age at first birth (%)[c]						
Nulliparous	30.1	31.3	27.7	36.2	41.1	29.5
first birth <25 children 1–2	18.1	19.2	17.2	10.8	17.7	19.3
first birth 25–29 children 1–2	24.0	23.6	26.3	25.2	17.3	21.8
first birth 30+ children 1–2	9.9	9.7	10.4	13.0	12.2	11.0
first birth <25 children 3+	10.6	10.5	10.4	6.7	7.4	12.3
first birth 25+ children 3+	7.4	5.6	8.1	8.1	4.3	6.1
Change in weight from age 18 (kg)	7.5	7.0	7.3	7.2	7.6	8.9
Alcohol consumption (gm/day)	3.1	3.6	3.4	2.9	2.6	2.5
Current oral contraceptive use (%)	12.6	14.1	12.9	12.5	13.6	11.2
Postmenopausal (%)	5.6	6.7	6.4	5.5	7.0	9.1

[a] Values are means unless otherwise indicated. All values (except age) are standardized to the age distribution of the study population.

[b] 8 breast cancer cases missing due to missing age at IM.

[c] Percentages may not equal 100 due to rounding.

Table 2

Relative risk of breast cancer according to infectious mononucleosis (ever/never and age at onset) in NHS II, 1989–2007

	RR and (95% CI) b					
IM (yes/no)						
Cases/ person year	(422/281,327) / (1,927/ 1,299,971)					
Age Adjusted RR †	1.03 (0.93–1.15)					
Multivariable RR§	1.00 (0.90–1.11)					
Age at IM	No IM	≤15	16–19	20–24	25–29	30+
Cases/ person year	1,927 / 1,299,971	69 / 63,811	186 /120,546	92/ 55,871	33/15,777	34/ 21,935
Age Adjusted RR †*	1.00	0.79(0.62–1.00)	1.06(0.91–1.24)	1.08(0.88–1.34)	1.45(1.02–2.04)	1.02(0.73–1.43)
Multivariable RR§	1.00	0.77(0.60–0.97)	1.03(0.88–1.19)	1.03(0.83–1.27)	1.45(1.02–2.04)	1.02(0.72–1.43)

† Relative Risk and 95% confidence interval from age (5 year categories) adjusted Cox proportional hazards model.

§ Relative Risk and 95% confidence interval from model above (†) additionally controlling for variables mentioned in Table 2.

* p for linear trend < 0.05, however, data suggest a non-linear relation and trend is driven by increased risk in 25–29 category.

Table 3

Relative risk of breast cancer according to age of infectious mononucleosis onset in NHS II by hormone receptor status, 1989–2007

	RR and (95% CI)					
Age at IM	**No IM**	**≤15**	**16–19**	**20–24**	**25–29**	**30+**
ER +						
Cases/ person year	1,192 / 1,299,190	36/63,773	115/120,476	61/55,831	21/15,763	22/21,920
Age Adjusted RR[†*]	1.00	0.67(0.48–0.94)	1.07(0.88–1.29)	1.16(0.90–1.50)	1.49(0.97–2.29)	1.06(0.70–1.62)
Multivariable RR[§*]	1.00	0.65(0.46–0.90)	1.03(0.85–1.24)	1.10(0.85–1.42)	1.48(0.96–2.28)	1.06(0.70–1.62)
ER −						
Cases/ person year	337 / 1,298,240	13/63,747	33/120,387	15/55,778	4/15,748	4/21,906
Age Adjusted RR[†]	1.00	0.83(0.48–1.45)	1.07(0.75–1.53)	1.01(0.60–1.70)	0.99(0.37–2.66)	0.69(0.26–1.84)
Multivariable RR[§]	1.00	0.81(0.46–1.41)	1.04(0.73–1.49)	0.98(0.59–1.65)	0.99(0.37–2.65)	0.66(0.25–1.78)
PR+						
Cases/ person year	1,060 / 1,299,045	35/63,770	102/120,460	51/55,820	17/15,757	20/21,918
Age Adjusted RR[†*]	1.00	0.73(0.52–1.03)	1.06(0.87–1.30)	1.09(0.82–1.44)	1.36(0.84–2.19)	1.09(0.70–1.69)
Multivariable RR[§*]	1.00	0.71(0.50–0.99)	1.02(0.84–1.26)	1.03(0.78–1.37)	1.34(0.83–2.17)	1.08(0.70–1.69)
PR−						
Cases/ person year	452 / 1,298,366	14/63,750	44/120,402	23/55,786	8/15,754	6/21,908
Age Adjusted RR[†]	1.00	0.67(0.40–1.15)	1.07(0.78–1.45)	1.16(0.76–1.76)	1.48(0.74–2.98)	0.77(0.34–1.71)
Multivariable RR[§]	1.00	0.65(0.38–1.11)	1.03(0.76–1.41)	1.12(0.73–1.70)	1.49(0.74–2.99)	0.75(0.34–1.68)

[†]Relative Risk and 95% confidence interval from age (5 year categories) adjusted Cox proportional hazards model.

[§]Relative Risk and 95% confidence interval from model above (†) additionally controlling for variables mentioned in Table 2.

[*]p for linear trend < 0.05, however, data suggest a non-linear relation and trend is driven by increased risk in 25–29 category.

Table 4

Relative risk of breast cancer according to age of infectious mononucleosis onset in NHS II by median age at breast cancer diagnosis and menopausal status, 1989–2007

	RR and (95% CI)					
Age at IM	**No IM**	**≤15**	**16–19**	**20–24**	**25–29**	**30+**
Age at BC dx <48.9y*						
Cases/ person year	966 / 961,710	43/50,655	98/90,730	50/40,375	16/11,748	17/15,819
Age Adjusted RR†	1.00	0.88(0.65–1.20)	1.09(0.88–1.34)	1.21(0.91–1.61)	1.38(0.84–2.26)	1.05(0.65–1.70)
Multivariable RR§	1.00	0.85(0.63–1.15)	1.05(0.85–1.29)	1.15(0.86–1.52)	1.36(0.83–2.23)	1.06(0.66–1.71)
Age at BC dx =>48.9y						
Cases/ person year	961 / 346,999	26/13,791	88/30,483	42/15,811	17/3,990	17/6,285
Age Adjusted RR†	1.00	0.70(0.48–1.04)	1.05(0.85–1.31)	0.96(0.70–1.30)	1.53(0.95–2.47)	0.98(0.61–1.58)
Multivariable RR§	1.00	0.69(0.46–1.01)	1.02(0.82–1.26)	0.91(0.67–1.25)	1.58(0.98–2.56)	0.98(0.61–1.58)
Premenopausal						
Cases/ person year	1,246 / 951,341	44/47,982	113/89,459	58/40,256	20/11,463	21/14,903
Age Adjusted RR†*	1.00	0.75(0.56–1.02)	0.98(0.81–1.19)	1.07(0.83–1.40)	1.39(0.89–2.15)	1.08(0.70–1.67)
Multivariable RR§*	1.00	0.73(0.54–0.99)	0.95(0.78–1.15)	1.02(0.79–1.33)	1.36(0.87–2.11)	1.07(0.70–1.65)
Post menopausal						
Cases/ person year	505 / 257,088	18/11,418	51/22,738	27/11,964	12/3,170	10/5,176
Age Adjusted RR†	1.00	0.86(0.54–1.38)	1.17(0.87–1.55)	1.14(0.78–1.68)	1.98(1.12–3.51)	1.01(0.54–1.88)
Multivariable RR§	1.00	0.83(0.52–1.32)	1.12(0.84–1.50)	1.07(0.72–1.57)	1.99(1.12–3.52)	1.00(0.53–1.86)

† Relative Risk and 95% confidence interval from age (5 year categories) adjusted Cox proportional hazards model.

§ Relative Risk and 95% confidence interval from model above (†) additionally controlling for variables mentioned in Table 2.

* p for linear trend < 0.05, however, data suggest a non-linear relation and trend is driven by increased risk in 25–29 category.

* 48.9 median age at breast cancer diagnosis.

* p for linear trend < 0.05, however, data suggest a non-linear relation and trend is driven by increased risk in 25–29 category.