Breastfeeding and risk of rheumatoid arthritis

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Abstract

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We analyzed data previously collected as part of the Oral Contraceptives Rheumatoid Arthritis (OCRA) study to investigate whether breastfeeding among women is associated with risk of new onset RA. This is a population-based case-control study with 231 cases and 1,093 controls. We used odds ratios (OR) and corresponding 95% confidence intervals (CI) from logistic regression models to assess associations of history of breastfeeding and duration of breastfeeding with new onset of RA. We fitted three models: unadjusted model, partially adjusted model (adjusted for age, race, oral contraceptive use, parity, and length of time between RA onset or reference date and last pregnancy), and a fully adjusted model (adjusted for variables included in the partially adjusted model as well as education, income, and smoking). Among cases, 68% had a history of breastfeeding while among controls, 72% had a history of breastfeeding. Women with a history of breastfeeding had similar risk of new onset RA, compared with women who had no history of breastfeeding in all models: unadjusted (OR: 0.82, 95%CI: 0.60-1.11), partially adjusted (OR: 0.84, 95%CI: 0.61-1.16), and fully adjusted (OR: 0.89, 95%CI: 0.64-1.23). Duration of breastfeeding was inversely associated with new onset RA in the unadjusted model (p-value for trend = 0.031), although the association was attenuated in the partially adjusted (p-value for trend = 0.053) and fully adjusted (p-value for trend = 0.150) models. In this study population, we found suggestive evidence that duration of breastfeeding, but not history (yes/no) of breastfeeding, may be inversely associated with new onset of RA. Future larger studies in diverse populations are needed to better examine the relationship between breastfeeding and RA. Findings can contribute to better understanding of risk factors of RA and identifying populations who are at higher risk.

BACKGROUND

Rheumatoid arthritis (RA) is a systemic chronic inflammatory autoimmune disorder in which the immune system attacks its own body tissues, the hallmark feature of which is symmetrical inflammation of the joints. The typical prevalence of RA is between 0.5-1 percent (Jacobson, 1997; Silman, 2002). Females are at higher risk for developing RA compared to males (Oliver, 2006). The incidence rate among females between the ages 33 and 44 is 35.7 per 100,000, and 53.9 per 100,000 among females age 45-54 (Silman, 1994; Symmons, 1994). Disease activity may also differ in different racial and ethnic groups (Greenberg, 2013). Risk factors for RA include environmental, lifestyle, reproductive changes, and hormonal factors (Oliver, 2006).

Silman et al. reported that the incidence of RA is reduced during pregnancy (OR: 0.30, 95% CI: 0.04-2.6) and an increased risk of developing RA during the first 3 months post-partum, with an odds ratio of 5.6 (95% CI: 1.8-17.6) (Silman, 1992). The increase in the risk of RA during the postpartum period was notable and led to researchers to examine potential factors during the postpartum period that may contribute to risk of RA, including breastfeeding.

Breastfeeding is recommended for its multiple advantages to the mother and her newborn including the transfer of protective antibodies from the mother to infant. It has been hypothesized that prolactin plays an important role in the potential association of breastfeeding with RA onset (Brennan, 1994). During pregnancy, the pro-inflammatory hormone, prolactin, along with anti-inflammatory steroidal hormones levels increase; however, during the postpartum period, both of these hormone levels decrease, unless the mother breastfeeds (Brennan, 1994; Barrett, 2000). If the mother breastfeeds, the levels of prolactin remain high but the anti-inflammatory steroidal hormone levels decrease (Brennan, 1994; Barrett, 2000). Prolactin is a pro-inflammatory hormone; it could be linked to increased risk of RA – a chronic inflammatory disorder (Brennan,

1994). A limited number of studies have investigated breastfeeding and RA and reported inconsistent findings (Brennan, 1994; Barrett, 2000; Brun, 1995; Berglin, 2010; Karlson, 2004; Adab, 2014; Orellana, 2017).

In this project, we investigated association between breastfeeding and new onset of RA using data collected from a population-based case-control study. This research aims to contribute to the literature on the relationship between breastfeeding and the risk of RA among mothers. Findings of the study could help identify risk factors for RA and help elucidate mechanisms leading to RA.

METHODS

Study Setting and Study Design:

The current study is an analysis of data that was collected as part of the Oral Contraceptive Rheumatoid Arthritis (OCRA) study that was designed to examine risk of new onset rheumatoid arthritis (RA) in relation Oral Contraceptive use. The OCRA study was a population based case-control study conducted among women residents of King County, WA and who were enrolled in Group Health Cooperative. The study design and methods have previously been reported (Nelson, 1993).

Study Population:

RA cases for the current analysis were defined as mothers with RA who had at least one live birth. Cases were identified between November 1986 and February 1991. Controls considered in the current analysis were mothers without RA with at least one live birth. Eligibility for study participation included King County, Washington residency (Nelson, 1993) or enrollment in Group Health Cooperative. Controls were identified using the Mitofsky-Waksberg method to select phone number digits for phone dialing or random selection of numbers from age-stratified list at Group Health Cooperative, an HMO serving a large population in King County (Nelson, 1993; Guthrie, 2010). Controls were frequency age-matched to cases. Pregnancies that resulted in multiple births were excluded from this analysis. Cases in which the onset RA occurred during pregnancy were also excluded. Length of breastfeeding that exceeded the length of time between end of pregnancy and onset RA was truncated to reflect the time between breastfeeding and onset RA to minimize issues of temporality. The final analytic population included 231 cases and 1,093 controls. All subjects provided consent. The OCRA study was approved by the Institutional Review Board of Fred Hutchinson Cancer Research.

Data Collection:

As a part of the parent study, a board-certified rheumatologist examined patients with suspected RA to identify potential cases. The Immunology Laboratory at the University of Washington performed a standardized rheumatoid factor test. The American College of Rheumatology (ACR) criteria were used to diagnose RA and all cases considered in this analysis met the 1987 ACR revised criteria for RA (Arnett, 1988). At the time of the study, testing for antibodies to citrullinated proteins (ACPA) was not part of clinical practice, but ACPA testing was conducted later on stored sera and results were added to the participant profiles. In-person interviews were conducted to collect data regarding participant characteristics and events prior to a reference date. The reference date for RA onset was defined as the date of first physician visit for symptoms that were diagnosed as RA (Guthrie, 2010). The reference date that was used for the controls was randomly selected among the distribution of RA reference dates of the cases (Guthrie, 2010). Collected data include socio-demographic factors (such as age, race, education, income, material status, and smoking history), and reproductive characteristics (such as oral contraceptive use, gravidity, parity, live birth history, and length of time between last full-term pregnancy and onset of RA.)

Statistical Analyses:

To describe the distribution of the cases and controls in terms of socio-demographic characteristics, we report means and standard deviation for continuous variables and the total number and percentage for categorical variables. We used the Fisher's Chi-square test for categorical variables and Student's t-test for continuous variables, to compare the distribution of characteristics between the two study groups. The exposures of interest were breastfeeding history and length of breastfeeding, and the outcome of interest was new onset RA.

Potential confounders were identified based on literature review, clinical relevance, or the p-value results from our chi-squared test or student's t-test. The following potential confounders were identified for the analyses: age, race, education, income, smoking, oral contraceptive use, number of full-term pregnancies, and time between RA and last full term pregnancy.

The total duration of breastfeeding accounting for all births was categorized in the following groups: 0.25 to 2 months, 2.25 months to 6.25 months, 7 to 14 months, or 15 months and longer, based on quartile distributions of duration of breast feeding among controls.

We fitted logistic regression models to assess the risk of RA in relation to postpartum breastfeeding (yes/no). We analyzed three models: unadjusted, partially adjusted (adjusted for age, race, oral contraceptive use, parity, and length of time between last full-term pregnancy to onset of RA or reference date for controls), and fully adjusted (adjusted for variables in the partially adjusted model as well as income, education, and smoking). In addition, we preformed an exploratory analysis to assess effect modification by race, fitting models that are stratified by race (white, black, Native American or Eskimo, Asian, or Hispanic).

Next, we examined associations between length of breastfeeding and new onset of RA. We fitted two models: one with the length of breastfeeding as a continuous variable and another with

length of breastfeeding grouped based on quartiles of duration of breastfeeding among controls (see above). We fitted unadjusted, partially adjusted, and fully adjusted models as described above. In addition, we compared women's risk of new onset RA with history (yes/no) of breastfeeding after first, second, and third pregnancy. In all of these analyses, women with no history of breastfeeding served as the reference group.

Odds ratios and corresponding 95% confidence intervals were used to estimate associations. Statistical significance was determined using the p-value <0.05 cutoff. Analyses were conducted using STATA 13.

RESULTS

RA cases and controls were similar in age, gravidity, parity, marital status and oral contraceptive use (Table 1). 68% of the cases and 72% of the controls had a history of breastfeeding. The mean total duration of breastfeeding for the RA cases was 6.2 (SD=10.1) months and 8.2 (SD=13.7) months for the control group (p-value=0.0376).

There was no statistically significant difference in the risk of new onset RA between women who had a history of breastfeeding and women who had no history of breastfeeding (partially adjusted OR: 0.84, 95% CI: 061-1.16, p-value 0.298 and fully adjusted OR: 0.89, 95% CI: 0.64-1.23, p-value 0.470) (Table 2). We also did not observe associations of history of breastfeeding after first, second, or third pregnancy with new onset RA (Table 3).

In the unadjusted model, the odds ratio comparing odds of RA for mothers who breastfed 0.25 to 2 months to mothers who did not breastfeed was 1.04 (95% CI: 0.71-1.55, p-value = 0.827). For those who breastfed 2.25 to 6.25 months compared to mothers who did not breastfeed, the odds ratio was 0.82 (95% CI: 0.53-1.27, p-value = 0.373). For mothers who breastfed for 7 to 14 months, the odds ratio was 0.71 (95% CI: 0.46-1.11, p-value = 0.132) compared to mothers who did not breastfeed. For mothers who breastfed for 15 months or longer, the odds ratio was 0.69 (95% CI: 0.44-1.08, p-value = 0.103). The trend test p-value for this unadjusted model was statistically significant (trend p-value=0.031) (Table 3).

In the partially adjusted model, the odds ratio comparing RA for mothers who breastfed for 0.25 to 2 months, 2.25 to 6.25 months, 7 to 14 months, and 15 to 109 months, to those who did not breastfed were 1.03 (95% CI: 0.69-1.53, p-value = 0.903), 0.86 (95% CI: 0.55, 1.35, p-value = 0.517), 0.72 (95% CI: 0.45-1.14, p-value = 0.156), and 0.68 (95% CI: 0.41-1.11, p-value = 0.125),

respectively. The trend test p-value for this partially adjusted model was marginally significant (trend p-value=0.053) (Table 3).

In the fully adjusted model, the odds ratio comparing odds of RA for mother that breastfed between 0.25 to 2 months, with odds of RA among women who did not breastfeed was 1.02 (95% CI: 0.68- 1.54, p-value = 0.910). For mothers who breastfed between 2.25 to 6.25 months compared to mothers who did not breastfeed, the odds ratio was 0.93 (95% CI: 0.59- 1.47, p-value = 0.760). For mothers who breastfed between 7 to 14 months the odds ratio was 0.75 (95% CI: 0.47-1.20, p-value = 0.235). And, for mothers who breastfed for 15 months or longer compared to mothers who did not breastfeed, the odds ratio was 0.75 (95% CI: 0.46- 1.25, p-value = 0.271). The trend test p-value for this fully adjusted model was not statistically significant (trend p-value=0.150).

We did not find significant differences in odds ratio estimates when associations were evaluated in strata defined by race (p-value for test of homogeneity = 0.8371) (data not shown).

DISCUSSION

In this study population, we found that duration of breastfeeding, but not history (yes/no) of breastfeeding, was inversely associated with new onset of RA. However, associations were attenuated after adjustment for potential confounders (age, race, education, income, smoking, oral contraceptive use, parity, and time between last full-term pregnancy and onset of RA). Associations were not modified by race.

The reduced risk of RA observed in our study, in relation to duration of breast feeding, is similar to some (Karlson, 2004; Pikwer, 2009; Adab, 2014; Brun, 1995; Orellana, 2017), but not other studies (Brennan, 1994; Berglin, 2010), that also observed that breastfeeding was associated with a lower risk of RA. Karlson et al. reported an inverse association between duration of breastfeeding and risk of RA among female nurses in the Nurses' Health Study; they reported that the adjusted risk of RA for women who breastfed for 24 months or longer was 0.5 (95% CI: 0.3-0.8) compared to females that did not breastfeed (Karlson, 2004). Similarly, in a Swedish study, Pikwer et al. concluded that the risk of developing RA may be reduced by a long history of breastfeeding; they reported that the ORs for the risk of RA associated with breastfeeding for 13 months or longer and for 1 to 12 months, compared to no history of breastfeeding, were 0.46 (95% CI: 0.24-0.91) and 0.74 (95% CI 0.45-1.20), respectively (Pikwer, 2009). Among Chinese women, Adab et al. reported that longer duration of breastfeeding may be associated with a decreased risk of RA; for those who breastfed for 36 months or longer, compared with women who never breastfed, the adjusted OR was 0.54 (95% CI 0.29-1.01) (Adab, 2014). Brun et al., in a population-based study, reported an association between decreased mortality from RA and the total time of lactation; they reported a mortality rate ratio of 0.49 (95% CI: 0.28-0.85) for those with total lactation of 30 months or greater compared to those who had zero months of lactation

(Brun, 1995). Orellana et al. reported a potential inverse association between breastfeeding length and ACPA-Positive RA; women who breastfed for 7-12 months had an OR of 0.91 (95% CI: 0.72-1.15) and women who breastfed for 13 months or longer 0.74 (95%CI: 0.59-0.93) compared to those who breastfed for 6 months or less and adjusted for age and residential area, p-value trend = 0.0086 (Orellana, 2017). However, they reported that the association was not statistically significant when adjusted for age, residential area, smoking, and alcohol consumption (Orellana, 2017).

In contrast, several studies also suggested that breastfeeding increases the risk of RA. Brennan and Silman, in their case-control study of women in UK, reported that breastfeeding after first pregnancy may be associated with an increased risk of RA, with an adjusted OR of 5.4 (95% CI: 2.5-11.4) (Brennan, 1994). In a case-control study conducted in northern Sweden, Berglin et al. reported a potential positive association between duration of breastfeeding and risk of RA, OR of 5.7 (95% CI: 1.83- 17.95) comparing mothers who breastfed for 17 months or longer to mothers who breastfed for 1-3 months (Berglin, 2010).

The discrepancy seen between our results and some of these other studies could be due to difference in study design or characteristics of the study populations. While association estimates differed in direction in these studies, the confidence intervals for most studies were large, overlapped, and did not exclude one (i.e. estimates were not statistically significant). In addition, it is important to note that the studies were conducted over various time periods and breastfeeding recommendations and breastfeeding practices may be subject to changes over time and differ among different populations, contributing to observed differences in findings.

Strengths of the current study include the population-based study design and the well-characterized study population. The data were carefully documented with complete reproductive

history from in person interviews, including specific timing and duration of breastfeeding. Potential limitations of this study include misclassification, unmeasured and residual confounding, generalizability, and limited study power.

In summary, we examined the hypothesis that breastfeeding is associated with new onset of RA. We found evidence supporting inverse association of duration of breastfeeding with new onset RA. Future larger studies in diverse populations are needed to better examine the relationship between breastfeeding and RA. Findings can contribute to better understanding risk factors of RA and identifying populations who are at higher risk.

Table 1. Selected demographics and characteristics of study participants

Characteristics	**RA Cases** N=231 (%)	**Control** N=1093 (%)	**P-value**
Race			<0.000
White	198 (86)	1014 (93)	
Black	11 (5)	24(2)	
Native American or Eskimo	6(3)	5(0.5)	
Asian	9(4)	36(3)	
Hispanic	7(3)	5(0.5)	
Age (continuous)	Mean = 46.8 years SD= 10.8	Mean 46.3 years SD= 10.5	0.4966
Education			0.002
Grade school	9(4)	18(2)	
High school	107(46)	380(35)	
Technical school	9(4)	59(5)	
College	87(38)	530(48)	
Graduate school	19(8)	106(10)	
Income			0.015
Less than $15k	42(18)	129(12)	
$15k-30k	66(29)	296(27)	
$30k-45	57(25)	291(27)	
More than $45k	58(25)	357(33)	
Marital status			0.044
Single	5(2)	14(1)	
Married	165(71)	845(77)	
Separated	9(4)	17(2)	
Divorced	35(15)	162(15)	
Widowed	7(3)	33(3)	
Living as married (6+ months)	10(4)	22(2)	
Smoking			0.002
No	88(38)	539(49)	
Yes	143(62)	554(51)	
Oral contraceptive use			0.938
No	73(31)	345(32)	
Yes	160(69)	748(68)	
Gravidity	Mean = 3.3 pregnancies SD= 1.7	Mean = 3.3 pregnancies SD= 1.8	0.6782
Parity	Mean = 2.7 births SD= 1.4	Mean= 2.6 births SD= 1.3	0.6394
1 birth	49 (21)	196 (18)	0.058
2 births	68 (29)	423 (39)	
3 births	60 (26)	241 (22)	
4 births or more	54 (23)	233 (21)	

Number of live births 1 live birth 2 live births 3 live births 4 live births or more	Mean = 2.6 live births SD = 1.4 50 (22) 68 (29) 61 (26) 52 (23)	Mean = 2.6 live births SD = 1.3 200 (18) 428 (39) 240 (22) 225 (21)	0.6383 0.041
Length of time between last full-term pregnancy and onset of RA or Reference Date	Mean = 18.6 years SD= 10.7	Mean = 17.9years SD= 10.7	0.3376
Ever breastfed No Yes	 75 (32) 156 (68)	 309 (28) 784(72)	0.203
Total length of breastfeeding after all pregnancy (time after onset RA censored)	Mean = 6.2 months SD= 10.1	Mean= 8.2 months SD= 13.7	0.0376

Percentage may not add up to 100% because of missing data or not applicable subjects and due to rounding
% unless specified
RA: rheumatoid arthritis; SD = standard deviations
P-value for chi-squared test or Student's T-test

Table 2. Association of history of breastfeeding with new onset rheumatoid arthritis (RA)

	RA Cases	Controls	Unadjusted OR (95% CI)	Partially Adjusted* OR (95% CI)	Fully Adjusted** OR (95% CI)
Breast Fed					
Did not ever breastfeed	75	309	Referent	Referent	Referent
Yes	156	784	0.82 (0.60-1.11)	0.84 (0.61-1.16)	0.89 (0.64-1.23)
			P-value= 0.202	P-value = 0.298	P-value= 0.470
After First pregnancy					
No	84	358	Referent	Referent	Referent
Yes	111	541	0.87(0.64-1.20)	0.87 (0.63-1.21)	0.89 (0.64-1.25)
			P-value = 0.401	P-value= 0.415	P-value= 0.508
After Second pregnancy	80	372	Referent	Referent	Referent
No	84	453	0.86 (0.62-1.21)	0.92(0.64-1.30)	1.04(0.72-1.50)
Yes			P-value=0.387	P-value = 0.623	P-value = 0.828
After Third pregnancy					
No	66	252	Referent	Referent	Referent
Yes	51	257	0.76(0.51-1.14)	0.81 (0.53-1.25)	0.92 (0.59-1.44)
			P-value = 0.179	P-value = 0.337	P-value = 0.712

* Adjusted for age, race, oral contraceptive use, parity, and length of time between RA onset (or reference date) and last pregnancy

** Adjusted for age, race, education, income, smoking, contraceptive use, parity, and length of time between RA onset (or reference date) and last pregnancy

Table 3. Association of duration of breastfeeding with risk of new onset rheumatoid arthritis

Length of breastfeeding after all births

	RA Cases N=231	**Controls N=1093**	**Unadjusted OR (95% CI)**	**Partially Adjusted* OR (95% CI)**	**Fully Adjusted** OR (95% CI)**
Did not breastfeed	75	309	Referent	Referent	Referent
0.25 – 2 months	53	209	1.04(0.71-1.55) P-value = 0.827	1.03 (0.69-1.53) P-value = 0.903	1.02 (0.68-1.54) P-value = 0.910
2.25 – 6.25 months	36	181	0.82 (0.53-1.27) P-value = 0.373	0.86 (0.55-1.35) P-value = 0.517	0.93 (0.59-1.47) P-value = 0.760
7-14 months	35	202	0.71 (0.46-1.11) P-value = 0.132	0.72 (0.45-1.14) P-value = 0.156	0.75 (0.47-1.20) P-value = 0.235
≥15 months	32	192	0.69 (0.44-1.08) P-value = 0.103	0.68 (0.41-1.11) P-value = 0.125	0.75 (0.46-1.25) P-value = 0.271
Trend p-value			0.031	0.053	0.150

* Adjusted for age, race, oral contraceptive use, parity, and length of time between RA onset (or reference date) and last pregnancy

** Adjusted for age, race, education, income, smoking, contraceptive use, parity, and length of time between RA onset (or reference date) and last pregnancy

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