Reduced Risk of IDDM Among Breast-Fed Children

The Colorado IDDM Registry

ELIZABETH J. MAYER, RICHARD F. HAMMAN, ELIZABETH C. GAY, DENNIS C. LEZOTTE, DAVID A. SAVITZ, AND GEORGEANNA J. KLINGENSMITH

The hypothesis that breast-feeding can provide protection against the development of insulin-dependent diabetes mellitus (IDDM) and would, therefore, be less common among subjects with IDDM was tested with a retrospective design. Cases (*n* = 268) were selected from the Colorado IDDM Registry and the Barbara Davis Center for Childhood Diabetes (Denver, CO). Two control groups were recruited, one from physicians' practices throughout Colorado (*n* = 291) and the second through random-digit dialing from the Denver area (*n* = 188). Cases were less likely to have been breast-fed than controls after adjustment for birth year, maternal age, maternal education, family income, race, and sex [adjusted odds ratio (OR) = 0.70; 95% confidence interval (CI) = 0.50–0.97]. This finding was consistent for both control groups and by birth-year intervals. A greater decrease in risk of IDDM was seen among subjects who had been breast-fed to an older age (for breast-feeding duration of ≥12 mo, adjusted OR = 0.54, 95% CI = 0.27–1.08). The amount of IDDM that might be explained by breast-feeding habits (population percentage attributable risk) ranged from 2 to 26%, varying according to the breast-feeding prevalence reported in other studies. Replication of this work in different populations, controlled for the strong secular trends in breast-feeding habits, is critical before the hypothesis of protection is accepted.
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The etiology of insulin-dependent diabetes mellitus (IDDM) is complex and appears to involve interactions of genetic, immunologic (including autoimmune), and environmental factors (1–12). An international group of collaborating investigators has recently advocated efforts directed toward elucidating environmental etiologic agents because such agents may be amenable to efficacious preventive measures (13). Evidence for a causal role of infectious agents in the onset of some cases of IDDM has been suggested by animal experiments (1), human case reports (1,8,14), biochemical studies (1,5,8,10,14), and epidemiological observations (1,8,15–18). Human colostrum and breast milk contain specific and nonspecific components active against infectious agents, including T- and B-lymphocytes, various immunoglobulins, components of the complement system, lysozymes, and lactoferrin (19–24). Studies of diseases other than IDDM have linked protection from infectious diseases to infant-feeding practices. In developing countries, epidemiological studies that have examined breast-feeding and infant morbidity have consistently demonstrated decreased morbidity among infants who were breast-fed (20,21,25,26). Results from industrialized countries have been less consistent (27–30).

An inverse relationship between rates of IDDM and breast-feeding in a Scandinavian population was observed by Borch-Johnsen et al. (31). In a study designed to examine the hypothesis that breast-feeding and the incidence of IDDM were inversely related, they observed a significantly shorter duration of breast-feeding among diabetic than control children. A negative history of breast-feeding was more likely to be found in children with IDDM than in control children. Two subsequent studies conducted in different populations failed to confirm these results (32, 33). Most recently, a protective effect of breast-feeding against IDDM was observed in a study that compared children with IDDM in western Australia and classmate control children (34).

This retrospective study of breast-feeding history and IDDM was conducted to test the following hypotheses: *1*) a smaller proportion of children with IDDM will have been breast-fed as infants than healthy, nondiabetic children; and *2*) the duration of breast-feeding will have been shorter for those diagnosed with IDDM than for healthy, nondiabetic children.

From the Departments of Preventive Medicine and Biometrics and of Pediatrics, University of Colorado School of Medicine; and Children's Hospital, Denver, Colorado; and the Department of Epidemiology, School of Public Health, University of North Carolina, Chapel Hill, North Carolina.

Address correspondence and reprint requests to Dr. Richard Hamman, Department of Preventive Medicine and Biometrics, University of Colorado School of Medicine, Denver, CO 80262.

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TABLE 1
Comparison of demographic characteristics for study cases from Registry and from Barbara Davis Center (BDC) to entire Colorado IDDM Registry

	Registry cases (%) (n = 204)	BDC cases (%) (n = 64)	Colorado IDDM Registry* (%) (n = 667)
Birth year			
1960–1972	44.6	65.6	61.6
1973–1985	55.4	34.4	38.4
Sex			
Male	48.5	62.5	50.5
Female	51.5	37.5	49.5
Race			
White	93.1	95.3	88.6
Other	6.9	4.7	11.4
Annual family income			
<$20,000	25.0	21.9	25.7
≥$20,000	75.0	78.1	66.9
Unknown	0.0	0.0	7.5
Maternal education			
≤12 yr	45.1	40.6	37.9
>12 yr	54.9	59.4	60.4
Unknown	0.0	0.0	1.6
Maternal age			
<30 yr	72.1	82.8	73.9
≥30 yr	27.9	17.2	21.7
Unknown			4.3

*Cases were identified from 1 January 1978 to 30 April 1986 and returned baseline questionnaire.

MATERIALS AND METHODS

Case selection. Patients with IDDM were identified from two sources: the Colorado IDDM Registry (n = 204), hereafter called *Registry cases*, and the Barbara Davis Center for Childhood Diabetes (Denver, CO), a referral treatment center at the University of Colorado Health Sciences Center (BDC cases, n = 64). The Registry case ascertainment was achieved by ongoing surveillance of physician practices throughout the state. Eligibility criteria for inclusion in the IDDM Registry were *1*) age <18 yr at the time of diagnosis, *2*) diagnosis on or after 1 January 1978, *3*) initiation of insulin therapy at diagnosis or within 2 wk of diagnosis, *4*) resident of Colorado at the time of diagnosis, and *5*) diabetes not secondary to other conditions (unpublished protocol manual, Colorado Insulin-Dependent Diabetes Mellitus Registry).

After case reports were received by the Registry, additional information about incident cases of IDDM was collected since 1978 by the Registry with self-administered questionnaires. In July 1984, questions about infant-feeding practices were added to the baseline questionnaire. During data collection for this study (July 1984 through October 1985), 204 of the 291 subjects who were contacted completed the questionnaire (70.1% response rate).

Eligibility criteria for inclusion of BDC cases in this study were *1*) ineligible for the Registry due to age, residence at diagnosis, or date of diagnosis; *2*) not a past recipient of the current Registry questionnaire; *3*) current Colorado address; and *4*) born on or after 1 January 1970.

Of the 118 eligible BDC cases, 64 returned a self-administered questionnaire (54.2% response rate). Attempts to contact BDC nonresponders by telephone were unsuccessful. The overall response rate for Registry and BDC cases was 65.5% (268/409).

Case ascertainment and validation efforts for the IDDM Registry cohort between January 1978 and April 1986 led to the identification of 667 eligible cases that returned a baseline questionnaire. The Registry response rate for return of questionnaires by eligible subjects at that time was 73% (667/914). It has been estimated that the Registry case ascertainment identifies >95% of all incident cases in the state (R.F.H., unpublished observations). To determine representativeness of the sample of Registry cases (n = 204, 30.3% of the total January 1978 to April 1986 Registry cohort with questionnaire data) and the BDC cases included in this study, comparisons of several sociodemographic variables were made (Table 1). Registry cases sampled for this study were younger than the complete Registry cohort, due to the data collection time frame for this study, and more often had mothers with higher education. Other characteristics (i.e., sex, race, income, and maternal age) were similar between these two groups. By design, BDC cases had earlier birth years than the Registry cohort. Maternal age and family income were also higher for BDC cases.

The data presented in Table 1 were also used to determine whether to pool the Registry and BDC cases. Registry cases were significantly more likely to have been born after 1972 by design) than BDC cases (P < .05). Because sociodemographic variables likely to be associated with breast-feeding (i.e., race, income, maternal age, and maternal education; 35, 36; M.R. Forman, K. Fetterly, B. Graubard, and K. Gaines, unpublished observations) did not differ significantly between the two groups, and because these variables could also be included in statistical adjustment procedures, the Registry and BDC case groups were pooled for the analyses reported herein.

Control selection. Physicians located throughout the state who had previously participated in the Registry and who were likely to see healthy nondiabetic children (i.e., practice not limited to diabetes or endocrine diseases) were contacted by telephone and asked to provide control subjects. The 25 participating practices agreed to provide a total of 560 patients, who were group matched by current age and sex to the Registry cases. To allow for inclusion of varied

TABLE 2
Demographic characteristics of pooled case and control groups

	Cases (n = 268)	Controls (n = 479)	P
Birth year			
Mean ± SD	1973.0 ± 4.4	1975.1 ± 5.7	<.0001
Range	1963–1984	1960–1985	
Sex (%)			
Male	51.9	55.7	.31
Female	48.1	44.3	
Race (%)			
White	93.7	90.2	.10
Other	6.3	9.8	
Annual family income (%)			
<$20,000	24.2	32.4	.02
≥$20,000	75.8	67.6	
Maternal education (%)			
≤12 yr	44.0	40.3	.32
>12 yr	56.0	59.7	
Maternal age (%)			
<30 yr	74.6	78.1	.28
≥30 yr	25.4	21.9	

TABLE 3
Breast-feeding history by case-control status

	Ever breast-fed		Never breast-fed		Total	
	n	%	*n*	%	*n*	%
Cases	134	50	134	50	268	100
Controls	299	62.4	180	37.6	479	100
Total	433	58	314	42	747	100

Odds ratio = 0.60; 95% confidence interval = 0.45–0.82.

socioeconomic backgrounds among controls, one health-maintenance organization participated, as did the Pediatric Clinic at the University of Colorado Health Sciences Center. At the close of data collection, 383 questionnaires had been received (68.4% of expected). Twenty-two subjects were excluded due to self-reported chronic illness other than diabetes (n = 19) or congenital anomalies (n = 3). Complete data were available for 291 of the remaining 361 eligible controls (80.6%). This control group is hereafter referred to as the *physician control group*.

A second control group (n = 188), referred to as *population controls*, was made available from a study of electromagnetic field exposure and childhood cancer (37). These subjects were selected by random-digit dialing within the metropolitan Denver area and were matched to cancer cases on age, sex, and telephone exchange as a proxy for geographic location. Seventy-nine percent of eligible contacts participated in a structured interview, which included questions designed to be consistent with infant-feeding questions used in the self-administered questionnaires for this study. Because childhood cancer is not strongly associated with socioeconomic status, these control subjects were likely to be representative of healthy children in the metropolitan Denver area within age and sex strata (38).

Analogous comparisons of the distribution of sociodemographic variables between the case groups were also made between the two control groups. The physician controls were significantly more likely than the population controls to have been born of younger mothers (82.5 vs. 71.3% with mothers <30 yr old; $P < .05$). A birth year before 1975 was more frequent among physician controls (39.5 vs. 54.3%; $P < .05$). Maternal education, family income, and race were similar between the control groups. Given the similarity between the groups and the ability to apply statistical adjustment procedures, the two control groups were pooled for subsequent analyses.

Odds ratios (OR) with 95% confidence intervals (CI) were used to estimate the association between IDDM and breast-feeding (39). Adjustment for variables that could confound results was achieved by logistic regression. The SAS statistical software package was used for these analyses and for descriptive statistics and t tests (40). Attributable risk was calculated according to the method described by MacMahon and Pugh (41).

RESULTS

Subject characteristics. A total sample size of 747 subjects, composed of 268 cases (204 from the Registry and 64 from BDC) and 479 controls (291 physician controls and 188 population controls), were included in the study. A summary of characteristics for the pooled cases (n = 268) and controls (n = 479) is shown in Table 2. As a group, cases were born ~2 yr before controls ($P < .0001$) and were more likely to come from higher-income families ($P = .02$). Sex, race, maternal education, and maternal age were distributed similarly between cases and controls.

Tests of breast-feeding and IDDM. It was postulated that cases would report a lower frequency of breast-feeding as infants than controls. The proportion of cases and controls who were ever breast-fed was 50.0 and 62.4%, respectively (Table 3). The crude OR for breast-feeding history (ever vs. never) between case and control groups was 0.60 (95% CI = 0.45–0.82). Therefore, cases were less likely to have been breast-fed than controls, as hypothesized.

There has been a strongly increasing trend of breast-feeding prevalence over the past two decades (35). Because there was a difference in birth-year distribution between cases and controls that could confound the crude OR, the percentage of cases and controls who were ever breast-fed was compared by four birth-year–specific intervals. A lower proportion of cases compared to controls who were ever breast-fed was observed consistently across all birth-year intervals.

Logistic regression was used to adjust for potential confounding by birth year and other variables (Table 4). Because preliminary analyses revealed that birth year was linearly related to breast-feeding prevalence and acted as a strong

TABLE 4
Association of breast-feeding history and selected variables with risk of IDDM

Variable	Regression equation codes		β*	Standard error	Odds ratio	95% Confidence interval	*P*
	0	1					
Intercept			−3.213	1.250			.01
Breast-fed	Yes	No	−0.036	0.167	0.70	0.50–0.97	.03
Birth year	†	†	0.065	0.016	1.07	1.04–1.10	<.01
Race	Other	White	−0.424	0.317	0.65	0.35–1.22	.18
Annual family income	<$20,000	≥$20,000	−0.317	0.188	0.73	0.50–1.05	.09
Maternal education	>12 yr	≤12 yr	−0.160	0.168	0.85	0.61–1.19	.34
Maternal age	<30 yr	≥30 yr	−0.277	0.186	0.76	0.53–1.09	.14
Sex	Male	Female	−0.196	0.158	0.82	0.60–1.12	.21

n = 747.
*Regression coefficient from logistic mode 1.
†Continuous, 1960–1985.

TABLE 5
Adjusted odds ratios for 6 levels of breast-feeding duration

Months of breast-feeding	*n*	Odds ratio	95% Confidence interval
0	314	1.00	
≤0.99	43	0.92	(0.47–1.82)
1.00–2.99	78	0.68	(0.39–1.18)
3.00–5.99	102	0.74	(0.46–1.20)
6.00–11.99	158	0.67	(0.43–1.04)
≥12.00	52	0.54	(0.27–1.08)

Adjusted by logistic regression for birth year, race, income, maternal education, maternal age, and sex.

confounder, it was included in the regression model as a continuous variable. Other potentially confounding variables (i.e., race, income, maternal education, maternal age, and sex) were dichotomized and coded as shown. The OR for breast-feeding after adjustment for these variables was 0.70 (95% CI = 0.50–0.97). Other than breast-feeding, only birth year contributed significantly to the model. Nonetheless, all other variables were left in the model for this presentation of results because other studies have shown them to be associated with breast-feeding (35,36), and their inclusion may give a better estimate of the true OR (39).

To explore the possibility that residual confounding by birth year remained an explanation for the observed association, the data were analyzed with birth year restricted to 1970–1979, where the greatest numbers of cases and controls were available for statistical adjustment for birth year. Again, breast-feeding was associated with reduced risk of diabetes (adjusted OR = 0.67; 95% CI = 0.45–0.99). An interaction term was also included in the logistic regression model, although there did not appear to be a biological reason to be concerned about an interaction between birth year and breast-feeding. The interaction term was not statistically significant (P = .20). An interaction term between sex and breast-feeding also did not contribute significantly to the model.

Because different potential biases existed in the two control groups that we pooled for this study, cases were compared with each control group separately. A protective effect of breast-feeding was seen with each control group. With only population controls, crude and adjusted ORs were identical (0.61; 95% CI for adjusted OR = 0.40–0.91). For the physician controls, this effect was somewhat weaker after adjustment (crude OR = 0.60; adjusted OR = 0.81; 95% CI = 0.55–1.18).

For the pooled case and control groups, duration of breast-feeding in months was considered the independent variable of interest rather than breast-feeding ever versus never. Among subjects who were ever breast-fed, the average number of months of breast-feeding for cases was 6.39 (range 0.01–23.97) and was 7.06 for controls (range 0.20–30.33; Student's t statistic = −1.23; one-tailed P value = 0.11). The duration of breast-feeding in months was included in the logistic regression model as a series of categorical variables (Table 5). For subjects who had never been breast-fed, duration was set to 0, and for subjects who had been breast-fed but who did not report duration (11 cases and 13 controls), duration was set to the mean duration for breast-fed cases and controls, respectively. Compared with the reference group of subjects who were never breast-fed (OR = 1.00 by definition), the risk of having IDDM decreased as duration of breast-feeding increased. The adjusted OR for the breast-feeding group of duration up to 1 mo was 0.92 (95% CI = 0.47–1.82) compared with an adjusted OR of 0.54 (95% CI = 0.27–1.08) for the group of subjects breast-fed for ≥12 mo. None of the ORs for duration groups was significantly different than 1, although this was likely due to reduced sample size for the individual breast-feeding by duration groups. However, the point estimates of the ORs were consistent with the hypothesis of increased protection by increased duration of breast-feeding.

DISCUSSION

The analyses of these data support the hypothesis that breast-feeding confers some protection against the development of IDDM. Subjects with IDDM were 30% less likely to have ever been breast-fed as infants than healthy controls (adjusted OR = 0.70; 95% CI = 0.50–0.97). Although not statistically significant, the lowest point estimate of the OR was observed among subjects who were breast-fed for ≥12 mo (adjusted OR = 0.54; 95% CI = 0.27–1.08).

These results agree with those reported by Borch-Johnsen et al. (31), who observed significantly shorter duration of breast-feeding for diabetic children than for population or sibling control groups and slightly lower breast-feeding prevalence among diabetic children than healthy siblings. Similarly, in a study of the descriptive epidemiology of IDDM in western Australia, children with IDDM were less likely to report a history of established breast-feeding than classmate control children (34).

Two negative studies have also been published. Nigro et

TABLE 6
Summary of 5 studies of breast-feeding and IDDM

Ever breast-fed							
Cases		Controls					
%	*n*	%	*n*	Crude odds ratio	95% Confidence interval	Control source	Ref.
91	266	94	230	0.58	0.27–1.25	Siblings	31
71	396	67	6702	1.37	1.08–1.73	Population	32
18	95	18	194	0.99	0.82–1.20	Siblings	33
		18	95	1.00		Friends	33
65	194	71	753	0.74	0.52–1.05	Classmates	34
50	268	62	479	0.60	0.44–0.82	Physician's office, random-digit dialing	This study

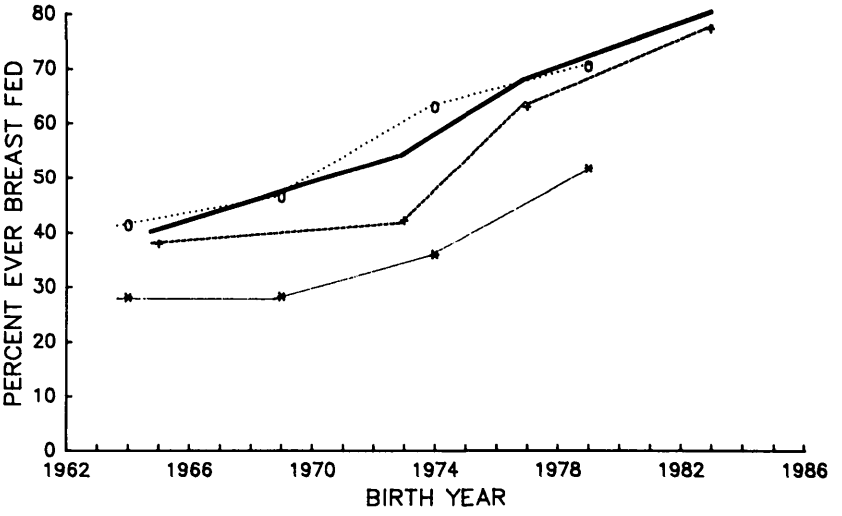

FIG. 1. Prevalence of breast-feeding: comparative data across birth years. The National Center for Health Statistics provided data from the National Survey of Family Growth, Cycle 3, for United States and for western United States, including Colorado (46). O, Family Growth Survey for western United States; *solid line*, Colorado controls; +, Colorado cases; *, Family Growth Survey for total United States.

al. (32) reported data from Italy in which population control group children were less likely to have been breast-fed and were weaned earlier than diabetic children. A report of breast-feeding among individuals with IDDM who had been followed in a New York hospital-based diabetes clinic, their nondiabetic siblings, and friend controls also failed to demonstrate a protective effect (33). These studies are summarized in Table 6.

Comparison studies show inconsistencies in findings between cases and controls and very large differences in the rates of reported breast-feeding. Breast-feeding rates have been shown to vary by geography in the United States and over time (35,36,42; National Center for Health Statistics, unpublished data; Ross Laboratories, Mothers Survey, unpublished data), so that differences in breast-feeding prevalence reported between these studies may be expected (Fig. 1). The prevalence of 18% found in the Fort et al. (33) study, however, was notably low compared with national and regional data. It is possible that the inconsistent findings from these studies may be due in part to control group selection. Use of incompletely specified population controls (31,32) is less than optimal because it is not possible to adjust for potential confounding factors. At the opposite extreme, sibling controls may be so nearly identical to the case group that overmatching occurs such that real differences in the exposure of interest may not be found (39). The well-documented genetic associations in the etiology of IDDM may make use of sibling controls less appropriate for the study of other etiological questions (1–5). We chose to select controls from physician offices and by random-digit dialing to reduce problems of overmatching and to enable collection of information about potentially confounding factors.

The control groups were pooled for two reasons other than the improved statistical power. First, control subjects recruited from physician's offices without chronic diseases may have been more attentive to positive health behaviors, including breast-feeding, leading to a possible selection bias. That is, controls would have reported more breast-feeding than cases, unrelated to their disease-free status. Inclusion of controls selected directly from the population minimized the impact of this potential bias. In a similar fashion, differential response bias might have been a source of error in our results if controls who participated were breast-fed more often than the general population or if responding cases were breast-fed less often than all cases. The latter seems unlikely, and the data in Fig. 1 show that the breast-feeding rate among the pooled controls in this study was similar to that reported by the National Center for Health Statistics, National Survey of Family Growth, Cycle 3, for the western U.S. (unpublished data). Similar breast-feeding prevalence was found in survey data from Ross Laboratories for the Mountain Region of the United States, which also supports the representativeness of our control group.

Second, the population controls more closely resembled the cases in birth-year distribution than did the physician controls, so their inclusion enabled more complete adjustment for potential confounding by birth year. The consistent pattern of lower breast-feeding prevalence among cases compared with controls across birth years (Fig. 1) and the results of the birth-year–restricted analysis provide assurance that the protective effect of breast-feeding demonstrated by these data cannot be explained by birth-year confounding.

A potential source of bias in retrospective studies of this type is differential maternal recall of breast-feeding. Although we did not require any particular individual to complete the questionnaires, >90% of respondents in this study were mothers of the subjects. Accurate maternal recall of breast-feeding has been demonstrated (43; B. Calkins, M. Monk, unpublished observations); however, duration may be somewhat less reliable than prevalence of breast-feeding. To examine the potential impact of maternal recall of up to 25 yr in our data, analysis was restricted to subjects with recall up to a maximum of 5 yr (34 cases and 100 controls), and a weakly protective effect was seen (adjusted OR = 0.91, 95% CI = 0.29–2.87). Other potential sources of bias in studies of infant-feeding practices have been reviewed elsewhere (44,45).

This retrospective study of breast-feeding history and IDDM supports the hypothesis that breast-feeding confers some protection against IDDM to the breast-fed infant. With the average annual incidence rate for IDDM from Colorado (15.1/100,000 people; R.F.H., unpublished observations) and data from this study, the population percentage attributable risk for not breast-feeding was 14%. This means that 14% of IDDM occurring in the Colorado population could be

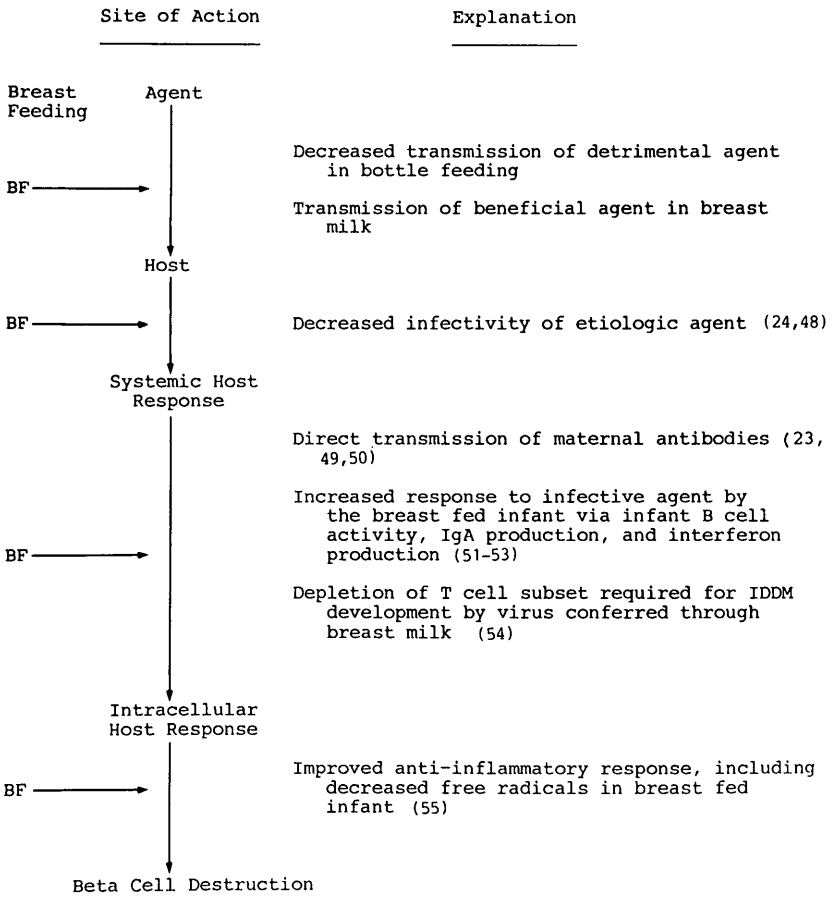

FIG. 2. Possible sites of biological action for protective effect of breast-feeding against development of IDDM.

attributed to lack of breast-feeding if the association were causal, which equals ~2 cases/100,000 people annually. When the figures for prevalence of breast-feeding from other studies were used (Table 6), the amount of disease in the population attributable to not breast-feeding could range from 2 to 26%.

The exact biologic mechanism or mechanisms that could lead to the protective effect suggested here are not understood. However, there are several plausible, although speculative, mechanisms. Conceptualized in terms of agent and host interactions, breast-feeding could intervene at one or more points to protect against the development of IDDM (Fig. 2). Avoidance of alternative nutrient sources by breast-fed infants (i.e., formula, cow's milk, or other foods) could diminish exposure to an unidentified diabetogenic agent, which may or may not be a virus (46,47). In the breast-fed infant, the infectivity of an environmental etiologic agent may be lessened (48). Hanson et al. (24) have described "microbial epithelial receptor analogues," which prevent or decrease adhesion of microbes to epithelial surfaces such as the oropharyngeal lining in breast-fed infants.

Alternatively or in addition, breast milk could be the vehicle for transmission of a specific agent that ultimately prevents pancreatic β-cell destruction. This agent could operate in systemic or intracellular host response functions. At the level of systemic host response, at least three protective mechanisms are plausible. First, specific maternal IgA antibodies conferred to the infant may prevent or decrease the severity of an infection that would otherwise contribute to β-cell damage (23,49,50). Second, infections in breast-fed infants may be less severe due to enhancement of the infant's own immune response. Juto (51) has reported increased β-cell proliferation and antibody secretion among breast-fed infants compared to formula-fed infants. Evidence of increased production of IgA (52) and increased interferon response to respiratory syncytial virus in breast-fed infants has also been reported (53). Third, it has recently been demonstrated in a susceptible animal strain that depletion of a particular T-lymphocyte subset by a virus prevents the development of diabetes (54). Extrapolated to humans, such a virus could be transmitted via breast milk as other viruses have been shown to be transmitted (49).

Breast-feeding may also protect against IDDM by beneficially altering intracellular host response. Goldman et al. (55) have reviewed the many anti-inflammatory agents that are present in human breast milk. Included are free radical scavengers, which could be potentially important if a recent hypothesis of free radical destruction of pancreatic β-cells is confirmed (56,57).

Because of the wide differences in breast-feeding prevalence over time and between geographic areas, replication of this work in different populations is critical before the hypothesis of a protective effect of breast-feeding against IDDM is accepted. Such studies would be particularly revealing if more quantitative data about breast milk intake were available so that a more rigorous examination of dose-response relationships would be possible. The use of an international IDDM registry consortium would facilitate the rapid testing of this hypothesis in various populations (13). Studies of breast-feeding prevalence and IDDM risk in the

general population, without individual data (so-called ecologic studies), are not useful, due to the need for careful control for potential confounding. Replication of these observations in animal models susceptible to IDDM could help define the physiological and immunological mechanisms by which breast-feeding might provide protection or bottle-feeding might prove harmful. Observations in epidemiological studies such as this provide exciting clues to the etiology of IDDM that must be vigorously pursued.

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