The Relationship of Breastfeeding to the Development of Atopic Disorders

Robert S. Zeiger, Noah J. Friedman

Department of Allergy, Kaiser Permanente Medical Center, and Department of Pediatrics, University of California, San Diego, Calif., USA

Introduction

Allergy prevention efforts must be instituted early in life since there appears to be a critical period for sensitization to food allergens shortly after birth. Some atopic risk factors susceptible to modulation include: (1) intact protein formula feeding; (2) early introduction of allergenic foods, and (3) environmental tobacco smoke. Since Grulee and Sanford [1] reported in 1939 a significant 7-fold reduction in eczema in infants who were breastfed, much uncertainty has surrounded this potential benefit of breastfeeding. Methodological differences and design limitations were observed among studies. However, the complex immunological characteristics of breast milk and maternal–infant interactions may also be at play. Do genetic differences in infant/mother pairs affect the composition of breast milk and influence the modulating effect of breast milk on emerging allergic disorders? Are the nanogram concentrations of food allergens found in breast milk sensitizing or protective?

What is not controversial is that breast milk is the preferred infant nutrition with rare exception (maternal HIV infection) owing to its nutritional, immunological, and psychological benefits. It is included as an important element in allergy prevention guidelines [2, 3]. Since breastfeeding is the recommended infant feeding method, it is more appropriate to examine breastfeeding in the light of ‘what may be lost by not breastfeeding?’ rather than in its allergy-preventive attributes. From the evidence that will be presented here and that we reported in more detail elsewhere [4], one can expect a higher incidence of eczema and wheezing illnesses in early childhood in high-risk infants fed intact formula to the exclusion of breast milk.
The complexity of the interaction between breast milk and an infant’s intestinal milieu and immune system has only recently received attention. Diverse immunological and nutritional factors in breast milk may have pro- or anti-inflammatory functions and as such may exert opposing effects on the development of allergy (table 1).

The increase in food antigen absorption which occurs early postnatally in animals is inhibited by breast milk. While colostrum and breast milk secretory-IgA is passed to the infant from the mother, it is unclear whether low levels of non- or specific secretory-IgA predispose to cow’s milk allergy (CMA) in infants as reported by some but not by other prospective studies. Immune factors in milk including IgE antibodies and cytokines involved in IgE synthesis (IL-4 and IL-13) and eosinophil induction (IL-5) are at higher levels in breast milk from atopic than non-atopic mothers, but do not seem to affect the development of allergy.

Breast milk may support Th1 responses that suppress a Th2 bias associated with atopy by supplying IL-1, TNF-α, nucleotides, oligosaccharides, CD14 for bacteria recognition and functional T cells that induce interferon-γ. Transforming growth factor-β (TGF-β) is the dominant cytokine in human

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**Table 1.** Factors in breast milk that are currently being evaluated as either inducing or protecting against food allergies

<table>
<thead>
<tr>
<th>Constituents</th>
<th>Inducing</th>
<th>Protective</th>
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<tbody>
<tr>
<td>Food allergens</td>
<td>Sensitizing</td>
<td>Tolerizing</td>
</tr>
<tr>
<td>Cytokines</td>
<td>IL-4</td>
<td>TGF-β</td>
</tr>
<tr>
<td></td>
<td>IL-5</td>
<td>s-CD14</td>
</tr>
<tr>
<td></td>
<td>IL-13</td>
<td>IL-10</td>
</tr>
<tr>
<td>Immunoglobulins</td>
<td>s-IgA</td>
<td></td>
</tr>
<tr>
<td>Polyunsaturated fatty acids (PUFA)</td>
<td>Arachidonic acid</td>
<td>Eicosapentaenoic acid</td>
</tr>
<tr>
<td></td>
<td>C22:4n-6</td>
<td>Docosapentaenoic acid</td>
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<tr>
<td></td>
<td>C22:5n-6</td>
<td>Docosatetraenoic acid</td>
</tr>
<tr>
<td>Chemokines</td>
<td>RANTES</td>
<td></td>
</tr>
<tr>
<td>Eosinophil-derived granular proteins</td>
<td>IL-8</td>
<td></td>
</tr>
<tr>
<td>Prebiotic oligosaccharides</td>
<td>Eosinophil cationic protein</td>
<td>Bifidobacteria, lactobacilli</td>
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Transforming growth factor-β (TGF-β), regulated on activation, normal T-cell expressed (RANTES).
Revised and reprinted with permission from Leung et al: Pediatric Allergy, Principles and Practice. St Louis, Mosby, 2003, p 496.

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**Immunologic Complexity of Breast Milk**

The complexity of the interaction between breast milk and an infant’s intestinal milieu and immune system has only recently received attention. Diverse immunological and nutritional factors in breast milk may have pro- or anti-inflammatory functions and as such may exert opposing effects on the development of allergy (table 1).

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Breast milk may support Th1 responses that suppress a Th2 bias associated with atopy by supplying IL-1, TNF-α, nucleotides, oligosaccharides, CD14 for bacteria recognition and functional T cells that induce interferon-γ. Transforming growth factor-β (TGF-β) is the dominant cytokine in human
breast milk. It may promote specific-IgA to foods and at high levels in breast milk was associated with a lower prevalence of infantile wheeze [5].

It is unclear whether a high arachidonic acid to eicosapentaenoic acid ratio in breast milk is associated with a higher risk of atopy. Spermine and spermidine in breast milk may act immunoprotectively by reducing intestinal permeability. Recently eosinophil cationic protein at higher levels in breast milk was associated with a higher incidence of CMA and atopic dermatitis in infants. It will require future study to determine the real effect of the complex interaction of these immunomodulatory factors in breast milk between the mother and infant in the development of allergic disease.

**Role of Infection**

Early childhood infection may have a dual effect on allergy and asthma development that is modulated by breast milk. Anti-viral antibodies and other factors supplied by breast milk may reduce respiratory syncytial virus and other viral infections that predispose susceptible infants in early childhood to wheezing episodes. Other infections by stimulating Th1 immunity may protect against allergy development. The ‘hygiene hypothesis’ proposes that in the high risk, exposure to the ‘right’ infections may preferentially induce a Th1-predominant immune system, thereby decreasing allergy risk. In support of this potential dual role, attendance at daycare or the presence of older siblings in the house was associated with lower rates of asthma after age 6 years, but higher incidences of early onset wheezing in infancy [6]. Intracellular organisms may play a role by inducing a polarized Th1 response causing long-term immunity. Breast milk may protect against allergy by a Th1 mechanism by promoting intestinal colonization of lactobacilli and bifidobacteria. The favorable effect of breastfeeding on respiratory and gastrointestinal infections in infancy and their sequelae, including wheezing illnesses, must be interpreted in the context of the complex immunomodulatory role of early infections on the development of allergic diseases.

**Allergens in Breast Milk**

Major food allergens from cow's milk, egg, wheat, and peanut can be detected immunochemically in nanogram concentrations in the breast milk of about 50% of the mothers. As reviewed recently, these allergens appear in 1–6 h after ingestion of 120 ml of milk, 1 raw egg, 1 slice of bread, 50 g of peanut [7]. It is unclear, however, whether food allergens in breast milk promote sensitization or tolerance to foods in non-sensitized infants. We do know that atopic infants already sensitized to these foods may experience disease exacerbation after ingesting breast milk containing these allergens and with maternal avoidance of these foods experience disease amelioration.
Studies Evaluating the Role of Breastfeeding in the Development of Atopy

In evaluating these studies, one needs to understand their design: are the cohorts unselected or at high risk, are the studies observation or intervention, are the groups self-selected or randomized. The only randomized prospective study evaluating the role of human milk in the development of atopic dermatitis was done on an unselected cohort of premature infants (n = 446) who were randomized to receive either preterm cow's milk formula or banked human breast milk [8]. In the cohort as a whole, no difference in the development of atopic dermatitis was observed. However, in subgroup analysis of only infants with a positive family history of allergy, preterm formula compared to banked breast milk use early in infancy was associated with an increased incidence of atopic dermatitis by 18 months (odds ratio 3.6; 95% CI 1.2–11, p < 0.05). These findings are of particular interest given the delayed gut maturity in premature infants. Unfortunately, immunological analyses were not performed.

In addition, the extent of breastfeeding exposure (never versus ever or exclusive versus partial) and the duration of breastfeeding between different studies need to be known. A detailed description of the atopic outcome must be defined precisely including disorder (specific disorders such as atopic dermatitis (eczema), food allergy, recurrent wheezing versus asthma, allergic rhinitis or any of the above atopic manifestations) or sensitization (skin test or in vitro testing for specific IgE). Finally the period (infancy, early childhood, adolescence/adulthood) at which outcomes are determined must be considered as differential effects by age have been reported. The ideal intervention design will randomize study groups to enhance comparability and minimize bias. Randomization is nearly impossible in studies of breastfeeding versus formula feeding due to ethical considerations. As such, methodological differences are common between studies, as are limitations in study design, making it challenging to compare different studies. Many older studies were hampered by small sample size, brief duration of breastfeeding, lack of immunologic confirmation and insufficient blinding during evaluation [9]. Findings from these studies taken as a whole favored the protective effect of breast compared to intact formula feeding on some aspects of atopy; however, some studies also reported either no effect or a tendency for enhancing atopy.

Critical Evaluations and Meta-Analyses of Published Data

To better evaluate the scientific strength of the thousands of breastfeeding observation studies, Kramer [9] proposed criteria to assess their adequacy (table 2). Considering these criteria, a European expert panel critically analyzed the pertinent literature from 1966 to 2001 of over 4,000 publications
pertaining to breastfeeding and allergic disease [10]. Only 56 (1.3%) of the prospective and retrospective studies merited review by established criteria. The panel concluded that exclusive breastfeeding was associated with a reduced risk of asthma in childhood, and that any breastfeeding reduced recurrent wheeze for at least the first decade in all children, regardless of atopic risk. Benefit appeared to increase with increasing duration of breastfeeding up to 4 months. Atopic dermatitis in infancy, but not atopy in later life, was favorably affected by breastfeeding. Some evidence suggested a higher risk of CMA when intact cow’s milk formula in lieu of breast milk was fed in the first days of life, regardless of risk. The protective effect of breastfeeding on these outcomes was even greater in children at high risk of atopy [10].

The critical assessment of studies published between 1966 and 2000 was advanced by the strength of meta-analysis. The criteria presented in table 2 were defined further. Accepted studies met the following criteria: (1) blinded maternal feeding history recall of less than 12 months; (2) at least 3 months of any or exclusive breastfeeding; (3) strict diagnostic outcomes; (4) blinded assessments; (5) onset of disease recorded, and (6) controlled for confounding factors and high-risk children [11, 12]. Only prospective studies in developed countries were included in these meta-analyses. Eighteen studies with more than 4,000 subjects followed for 4.5 (range 1–5) years were accepted for the analysis of atopic dermatitis [11]. Twelve studies with more than 8,000 children followed for 4.1 (range 1–8.4) years were evaluated for the analysis of asthma [12]. A significant protective effect of exclusive breastfeeding for at least 3 months was reported for the development of atopic dermatitis in the cohort as a whole, particularly in children at high risk of atopy, but not in

Table 2. Kramer’s criteria for assessing adequacy of cohort observational studies examining the association of breastfeeding (BF) and development of allergic disorders [9]

<table>
<thead>
<tr>
<th>Exposure</th>
<th>Outcome</th>
<th>Statistics</th>
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<tbody>
<tr>
<td>1. No late mom recall</td>
<td>5. Strict diagnostic criteria</td>
<td>9. Control for confounding factors</td>
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children at low risk (fig. 1a) [11]. In addition, exclusive breastfeeding for 3 months protected against the development of early childhood asthma-like symptoms in those children at high risk of atopy, but not in those at low risk (fig. 1b) [12]. In contrast, a meta-analysis examining exclusive breastfeeding for at least 3 months did not note a significant protection on the development
of allergic rhinitis [13]. The latter finding was not unexpected given the imprecise diagnostic criteria used in these studies, the young age of the children (mean age of 2.4 years follow-up) and the usual onset of allergic rhinitis after age 3.

**Recent Prospective Observational and Interventional Studies Supporting a Protective Role of Breastfeeding**

Several recent well-designed prospective intervention studies that fulfill Kramer’s criteria have confirmed the above meta-analyses and are summarized in table 3 [14–19]. In high-risk infants participating in an intervention study comparing hydrolyzed formulas to cow’s milk formula, exclusive...
breastfeeding compared to cow’s milk had a significant protective effect on the development of atopic dermatitis in the first 3 years of life [19]. Similar protective effects on the incidence of atopic dermatitis by age 1 [14, 18] and 2 years [15] were seen with exclusive breastfeeding for at least 3 or 4 months compared to lesser periods. Specifically a 46% reduction in the incidence of atopic dermatitis was seen in infants whose mothers participated in a program designed to facilitate breastfeeding compared to infants whose mothers were not provided such support [14]. A lower risk of asthma-like symptoms from 1 to 6 years of age was seen in infants breastfed exclusively for 4 months in observational studies from Sweden [16] and Australia [17, 20].

**Duration of Exclusive Breastfeeding**

Given that not breastfeeding may be associated with an increase in eczema and wheezing disorders in early childhood, how long should intact protein formulas be avoided?

A Swedish prospective, observational, birth cohort study demonstrated significant decreases with effect estimates from 20 to 34% in wheezing, asthma diagnosis, atopic dermatitis, and multiple allergic manifestations in

<table>
<thead>
<tr>
<th>Study</th>
<th>Birth cohorts</th>
<th>Comparison</th>
<th>Outcome, OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kramer et al. [14] (Belarus)</td>
<td>Unselected RC (n = 16,491)</td>
<td>BF support/promotion group vs. controls 43% of intervention group was exclusively BF at 3 months</td>
<td>1 year AD: 0.54 (0.31–0.95):</td>
</tr>
</tbody>
</table>
| Kull et al. [15, 16] (Sweden)               | Observational (n = 773 vs. 3,013) | Sole BF ≥4 vs. <4 months | (a) 2 years AD: 0.85 (0.7–1)  
(b) 2 years asthma, cumulative prevalence 0.7 (0.5–0.8)  
(c) 4 years asthma, period prevalence 0.72 (0.53–0.97) |
| Oddy et al. [28] (Australia)               | Observational (n = 2,602) | Predominant BF ≥4 vs. <4 months | 1 year wheeze and ≥2 acute visits: 0.6 (0.4–0.8) |
| Kerkoff et al. [18] (Netherlands)          | High-risk RC (n = 708) | Sole BF ≥3 vs. <3 months | 1 year AD: 0.4 (0.2–1.0) |
| Laubereau et al. [19] (Germany)            | High-risk RC (n = 2,030 vs. 522) | Sole BF ≥4 months vs. CMF | AD in 1st 3 years: 0.64 (0.45–0.90) |

OR = Odds ratio; RC = randomized controlled study; BF = breastfeeding; CMF = cow’s milk formula; AD = atopic dermatitis. Revised and reprinted with permission from Friedman and Zeiger [4, table 2] and Mosby, St Louis., Mo.
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infants breast-fed for ≥4 months [16]. An additive protective effect was observed in high-risk infants’ breastfed for 6 months. In agreement, an Australian birth cohort study of 2,187 children found that exclusive breastfeeding for at least 4 months was associated with a reduced risk of asthma and atopy at 6 years. Benefits reported included: (1) a longer time to first wheeze and physician-diagnosed asthma; (2) a lower incidence of recurrent wheezing after age 1 year; (3) less sleep disturbance from asthma within the past year, and (4) a lower incidence of at least 1 positive aeroallergen skin test [20]. Evidence was presented that supported the age of introduction of intact protein formula more than the duration of exclusive breastfeeding as responsible for the above effect, but the strong correlation between the two prevents rejection of the possible role of breastfeeding.

Breastfeeding by Asthmatic Mothers

Recently, concern regarding the potential adverse consequences associated with breastfeeding by atopic or asthmatic mothers has been voiced due to the fear of transfer of higher levels of pro-Th2 cytokines or n-6/n-3 polyunsaturated fatty acids from their breast milk to their infants as discussed earlier.

Wright et al. [21] first raised this concern after reporting a higher rate of asthma in atopic children of asthmatic mothers starting at age 6 years in the Tucson Children’s Respiratory Study, a prospective longitudinal observational study of 1,246 newborns. This finding was in contrast to a significantly lower rate of wheezing, regardless of maternal asthma, up to age 3 years.

In contrast to the above study, an observational birth cohort study of 2,602 Australian children [17] found no interaction between maternal asthma and the lower rate of physician-diagnosed asthma and active wheeze at 6 years in infants exclusively breastfed for at least 4 months. Since both studies demonstrated an overall protective effect of breastfeeding on wheezing illness in early childhood, even the asthmatic mother should still be encouraged to breastfeed. Further studies are needed to determine which one of the above findings in school-age children is correct.

Recent Prospective Observational Studies not Supporting a Protective Role of Breastfeeding

A few recent studies not included in the above meta-analyses have reported an adverse association of breastfeeding on atopy development. Table 4 highlights these studies and comments upon their potential methodological limitations. A long-term observational birth cohort of more than 1,300 German children, the important Multicenter Atopy Study (MAS), examined
the role of breastfeeding in the development of allergic disease. After adjusting for potential confounding, MAS reported that breastfeeding was associated with an increased risk of atopic dermatitis from birth to age 7 years (p = 0.034). Breastfeeding for at least 1 month was associated with this adverse effect which could mean that an important maternal–infant interaction occurred early postnatally. It is possible that a confounding factor not addressed or inadequately adjusted for in the multivariate analysis might be responsible for these divergent findings. One such factor was the longer duration of breastfeeding by mothers who themselves or their spouses had atopic dermatitis. Adjustments were attempted but may have been inadequate to account for this important maternal behavior/practice. Supportive of the MAS study is an observational study from New Zealand [22]. This study enrolled patients at age 3 years from a cohort previously taking part in a separate earlier neonatal study. In all, 62.5% (n = 1,037) of the original birth cohort was enrolled in this latter study. Breastfeeding for 4 weeks or longer was associated with a significantly increased risk of asthma at ages 9–26 years (OR 1.8, 95% CI 1.4–2.5, p < 0.0001) and sensitization to aeroallergens at age 13 years (OR 1.9, 95% CI 1.4–2.6). Design limitations were raised [23]: (1) frequent intact cow’s milk ingestion in the nursery and therefore infrequent exclusive

<table>
<thead>
<tr>
<th>Study</th>
<th>Cohort</th>
<th>Finding</th>
<th>Comment</th>
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<tbody>
<tr>
<td>Kaplan and Mascie-Taylor [29]</td>
<td>14,000 British 7-year-olds</td>
<td>Any BF: increased asthma at 7 years BF ≥6 months: increased transient asthma; decreased late-onset asthma; no change in persistent asthma</td>
<td>Recall bias FH not controlled Recall bias No control FH atopy</td>
</tr>
<tr>
<td>Rusconi et al. [30]</td>
<td>16,333 Italian 6- to 7-year-olds</td>
<td></td>
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<tr>
<td>Wright et al. [21]</td>
<td>1,246 Tucson birth cohort: birth–13 years</td>
<td>BF ≥4 months: increased recurrent wheeze at age ≥6 years</td>
<td>BF recall at 2 years Questionnaires</td>
</tr>
<tr>
<td>Bergmann et al. [31]</td>
<td>1,314 German children: birth–7 years</td>
<td>&gt;BF &gt; AD to age 7 years: OR 1.03 (1.00–1.06)</td>
<td>Parent AD &gt;factor Nursery CM common</td>
</tr>
<tr>
<td>Sears et al. [22]</td>
<td>1,037 New Zealand; birth cohort: 3–26 years</td>
<td>BF 4 weeks or longer: increased current asthma 9–26 years; + skin tests at 13 years</td>
<td>Recall bias; lack of dose response</td>
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</table>

BF = Breastfeeding; AD = atopic dermatitis; CM = cow’s milk; FM = family history. Revised and reprinted with permission from Friedman and Zeiger [4, table 3] and Mosby, Inc. St Louis., Mo.
breast-feeding; (2) no effect of atopic family history; (3) no dose response,
and (4) biased early recall of feeding patterns in infancy since the cohort was
enrolled at age 3 years. Evaluating only 60% of the original cohort may also be
a factor. Though Sears et al. [24] did not refute the first 3 criticisms, they
noted that maternal recall was corroborated with nurse home-visit records
obtained in the earlier neonatal study about 98% of the time. Notwithstanding
these criticisms, the study raises potentially important issues that can only be
resolved with long-term follow-up of the studies listed table 3.

Maternal Food Allergen Avoidance Diets during Lactation

One of the factors raised to help explain the differences in study outcomes
may relate to the variability of food allergens in breast milk that is dependent
on maternal eating habits. In addition, breast milk food allergens have been
blamed for the development of atopic disease and sensitization in approxi-
mately 6% of exclusively breastfed infants. As noted above, exposure to food
allergens through breast milk might either sensitize or tolerize.

A Cochrane meta-analysis evaluated the maternal lactation diet issue and
reported a small positive effect of maternal elimination diets on the develop-
ment of atopic dermatitis during the first 12–18 months of life [25]. However,
the report noted that the number of studies was limited, most of the effect
was due to 1 study [26], and the number of patients was small. As such, they
concluded that more studies are necessary to generalize these findings.

It is possible that a route other than breast milk, such as dermal food expo-
sure, may be responsible for the sensitization of exclusively breastfed infants.
A murine food allergy model provided proof of principle of primary IgE food
sensitization through dermal food exposure. Evidence that a similar mecha-
nism may be functional in humans is supported by the findings of the Avon
longitudinal study of nearly 16,000 children. In this study peanut allergy was
independently associated with the presence of eczematous skin and use of
skin care products containing peanut oil, but not with maternal ingestion of
peanut products during lactation [27]. These findings raise the real possibility
that sensitization may more readily occur through skin absorption than
through direct ingestion of peanut protein through breast milk.

Conclusions

We have examined the possible atopic consequences of not breastfeeding.
Meta-analyses of older studies and recent well-designed birth cohort studies
both provide reasonable evidence that exclusive breastfeeding for at least 4
months is associated with a reduction in atopic dermatitis and wheezing ill-
nesses up to age 6 years. There is weaker evidence to suggest that CMA and
atopic sensitization may also be reduced. A few observational studies question these conclusions, particularly in older children, but there is sufficient definitive evidence to discount these findings at least in early childhood. The effect of exclusive breastfeeding on atopy and asthma beyond age 6 years lacks sufficient study to make any reasonable conclusions. In addition, allergen avoidance diets during lactation should remain investigational. Finally, exclusive breastfeeding for at least 4 months should be a keystone of allergy-prevention efforts for both high- and low-risk infants as recommended by the AAP [2] and ESPACI/ESPGHAN [3] and supported by the evidence presented here and elsewhere [4]. Such recommendations are consistent with the principles of not interfering with Mother Nature or prematurely instituting unproven or burdensome interventions (lactation diets). Furthermore, the presence of maternal asthma should not deter from following these recommendations.

References

Discussion

Dr. Lucas: Just to clarify our trial here. There was no effect of breastfeeding; there was only an effect when a subgroup analysis was done, and then it was found that the group with the positive family history had an effect but the group with the negative family history was, if anything, the other way around giving advantage to the cow's milk group. It was not quite significant but in fact in another trial comparing a high-protein with a low-protein formula, in the negative family history group the high-protein formula was associated with low atopic disease, suggesting that it was good if you had a negative family history to have cow's milk protein. So my point here is that you obviously recognize that there are many other reasons for maintaining breastfeeding but, based on atopy alone, this would not be the case even from the data that you presented showing that there is not a case for recommending breastfeeding if there is a negative family history of atopy, and that is the majority of infants.

Dr. Zeiger: I would agree. With an effect size of up to 30% reported by mainly observational studies for breastfeeding on the reduction of atopic disorders in early childhood in high-risk newborns, one should recommend breastfeeding in non-high-risk infants for...
its nutritional, physiological, immunological, and psychological benefits and not for its potential properties to reduce wheezing and atopic dermatitis in early childhood.

**Dr. Björkstén:** The bulk of the evidence is that breastfed babies are less prone to wheezing, and I would suggest that this is because breastfeeding clearly protects against infections. In addition, you do have at most a modest effect on dermatitis. But if you go into allergy prevention, I am less convinced. The Finnish study was started in the early 1970s and breastfeeding was not compared with modern infant formula. The recent Kramer study as I see it is irrelevant to Western Europe as it was done in the Republic of Belarus where the gut microbiota are different. So in summary, what you should say is that breastfeeding protects against infant wheezing of infectious origin, but you may not have an allergy protection.

**Dr. Zeiger:** I would agree. We probably should not be looking upon breastfeeding as allergy-preventive in the sense of preventing IgE-mediated disease. There are only one or two studies to suggest that specific IgE sensitization can be affected by breastfeeding and no study to show such an effect on allergic asthma. However, meta-analyses of multiple studies conclude that breastfeeding is associated with a significant reduction in episodes of wheezing within the first 2 years of life. We should recommend breastfeeding for its proven nutritional, immunological and physiological benefits. Breastfeeding may in addition reduce some aspects of wheezing and eczema early in childhood in high-risk children. As you suggest we should not promote breastfeeding in a way that would engender guilt in a mother who does not breastfeed for whatever reason.

**Dr. Sampson:** I have two questions that are a little bit unrelated. The first related to the study by Oddy et al. [1] and looking at whether or not it mattered if the mother was atopic. I can’t remember the exact article, but there was a study from Finland that suggested there was a difference if the mother had active disease at the time of breastfeeding as opposed to just having a history of atopic disease. I wonder if you would comment on that. The second question is related to maternal avoidance diets while breastfeeding. One of the things we struggle with, and I am sure you do as well, is when mothers come with one child in the family having peanut allergy and then wondering should they be avoiding peanuts while breastfeeding. I guess the thing I struggle with is whether or not peanut is really different from the other food allergens because when we look at a registry of over 5,000 peanut-allergic patients almost 90% of those children were breastfed and 80% of those children reacted on the first known exposure to peanut, suggesting that somewhere they had been sensitized. We know that the peanut protein is present in breast milk, we also know that dry roasting a peanut makes a more allergenic and much harder protein. When AraH1 has been dry-roasted, it forms a very robust trimer that it is very difficult to break down. So do you think that peanuts may be different?

**Dr. Zeiger:** The relationship of active atopic disease in a mother and the development of wheezing illnesses in her child has been examined in only a few studies. The Australian studies of Oddy et al. [1] specifically looked upon active asthma in mothers and the development of asthma in their children. There was no interaction between the mother’s active asthma and the protective effect of breastfeeding on wheezing illnesses. The Tucson Children’s Respiratory Study analyzed the effect of a mother’s history of wheezing, not active disease, on the development of wheezing in their probands [2]. This study reported an increased risk for recurrent wheeze starting at about 6 years in allergic sensitized children whose mothers had a history of asthma. I am not familiar with the Finnish study. There are enough disparate data on this issue to suggest that we do not alter our recommendations regarding breastfeeding based on these data. With respect to lactation diets and avoidance of peanut, my take on this issue is the following: I think there is more evidence perhaps for the food allergens in breast milk to be tolerizing than sensitizing. The concentration of milk allergen within
When breast milk is compared to the concentration of milk protein in Nutramigen, these milk protein levels are from a hundred thousand to a million lower than in cow's milk. There is no evidence to suggest that peanut protein concentrations in breast milk would be too different from cow's milk protein levels. Relative to exposure of an infant to peanut, excluding infant ingestion, one would expect a greater burden imposed by direct contact of the infant with peanut protein on the body or clothing of caregivers or home surfaces than from lactation. Peanut sensitization through abraded skin has been proposed as a potential non-ingestion mechanism for peanut sensitization as suggested by Lack et al. [3]. In addition, proof of principle for food sensitization by the dermal group was recently reported in a murine model of food allergy [4]. As such, one may need to be more concerned with reducing peanut contact than interfering with lactation diets.

Dr. Lake: Would you comment on whether or not peanut restriction plays a role in utero, in other words changing the maternal diet before the child is born?

Dr. Zeiger: The epidemiologic studies have not been convincing. Prospective randomized clinical control trials that were done by Dr. Björkstén's group were not able to demonstrate any benefit from the avoidance of milk and egg during the last trimester of pregnancy in the development of atopic disease from birth to 5 years of life. They did not study peanut avoidance. We should not be modifying pregnancy diets until there is evidence to show benefit from such modifications.

Dr. Björkstén: It is not only that the study was negative, all 5 of the 200 children who, by the age of 6 years, kept egg allergy were in the maternal avoidance group. As I mentioned yesterday when in Sweden we delayed the introduction of gluten until after the age of 6 months, we got an increase in celiac disease, and going back to gradually introducing gluten while breastfeeding we immediately went back to the normal incidence. So I am suggesting a word of caution.

Dr. Zeiger: I think a good deal of caution. We should not begin to interfere with Mother Nature unless we know definitively that it will be beneficial.

Dr. Chad: Do you think we should be looking at studies giving mothers who are pregnant and/or lactating more allergen to see if we can induce tolerance in the babies? I know that it is fooling with Mother Nature again, but it is going to the other extreme. We looked at avoiding and found no improvement.

Dr. Zeiger: We don’t know enough about it. There are very few animal studies to begin with and I think we need to do more animal studies to see whether there is a dose response that occurs with increasing tolerance.

Dr. Hamburger: I would certainly agree with your last statement, and I wonder about this whole business of obstetricians and gynecologists recommending that the mother drink a liter or two of milk a day in order to protect her teeth and bones as being bad advice as well.

Dr. Zeiger: Yes, that amount of milk daily might be considered excessive.

Dr. Roma: During the last years we have noticed an increase in allergic colitis in exclusively breastfed infants. Have you had the same experience and if so, have you got an explanation for that?

Dr. Zeiger: In my health plan membership of about 4,500 births yearly, as allergists, we have not been aware of an increase in allergic colitis in exclusively breastfed infants. Perhaps Dr. Lake might be able to give some overview related to colitis.

Dr. Lake: As gastroenterologists, we are recognizing more breastfed babies with eosinophilic proctitis in the first 2–6 months of life. More than 90% are non-IgE-mediated, so we are avoiding the term ‘allergic colitis’ [5]. A more dramatic increase in eosinophilic esophagitis and gastritis has been noted in infants presenting as eosinophilic reflux, poorly responsive to acid reduction and featuring food refusal as a prominent symptom. Confirming a specific dietary protein-induced etiology has been difficult [6].
**Dr. Laron:** What is known about the genes involved in atopy? We have a Jewish population coming from Iraq. Their children have a high incidence of asthma and a high incidence of G6PD deficiency.

**Dr. Zeiger:** There have been several hundred genes identified that relate to the causation of atopic disease, including asthma and atopic dermatitis. It is reasonable to expect that gene polymorphisms will be found that identify children at high risk for specific atopic disorders and even responsiveness to specific therapies. The practical use of these findings will be one of the major future challenges of allergy prevention.

**References**