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REVIEW ARTICLE

Cow's milk consumption and risk of disease

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ABSTRACT

Milk and dairy products are important components of the human diet. This has been true since the beginning of domestication of lactating animals. However, milk of any species is geared towards the growth and development of its own offspring. Thus, the role of milk and dairy products in human nutrition has been increasingly discussed in recent years. To the best of our knowledge, problems such as lactose intolerance, protein allergies and an increased risk of cancer can occur when consuming cow's milk. Around 70% of the world's total population is lactose intolerant, while 20% of adults in Europe are lactose intolerant. In the small intestine, lactose is hydrolytically split into glucose and galactose by the enzyme lactase located in the mucous membrane cells. After infancy, lactase activity decreases as the ability to synthesize lactase is lost. As a result, adults can no longer tolerate large amounts of lactose, and many develop diarrhea and uncomfortable painful symptoms such as gas, cramps, and a bloated stomach. Since lactase activity is limited in the case of hereditary lactose intolerance, people can easily tolerate milk without lactose. Another aspect is that between 2-5% of children are allergic to cow's milk. The allergy is less common in adulthood. Most allergic reactions affect the skin, gastrointestinal tract, and respiratory system, and severe anaphylaxis can occur. A therapeutic approach related to the causes of this multi-organ disease does not yet exist. A possible approach to reducing protein allergens is to block IgE-binding epitopes in patients. The most effective treatment is an elimination diet and the use of appropriate substitution formulas. Camel milk may replace cow's milk in the event of intolerance. Furthermore, many studies have showed that people with a higher cow's milk intake had slightly increased cancer and all-cause mortality rates. In conclusion, it has not been clarified what exactly constitutes the harmful or health-promoting effects of cow's milk. Cow's milk is so rich in ingredients that both effects are conceivable. Due to the central importance of milk and dairy products for human nutrition, there is still great scientific interest in expanding knowledge concerning the ingredients and their nutritional and physiological effects.

Keywords: Lactose intolerance; Protein allergies; Cancer; Cow's milk; Children

INTRODUCTION

Milk occupies a special position among foods, as it is the only food that nature produces specifically for the nutrition of humans and animals. The introduction of cow's milk into the diet has a very long tradition. Humans have been drinking cow's milk for around 9000 (McGee H., 2004) or 7500 years (www.quarks.de, 2020). This makes man the only living being that continues to consume milk after weaning - although from a different species. Milk is still an important supplier of calcium (Michaelsen et al., 2011; www.utopia.de, 2015) and is known for its calming properties. In addition, cow's milk is consumed by large numbers of the population and used in the manufacture of a wide variety of foods. Therefore, a diet without milk and dairy products is hard to conceive. However, the role of milk and milk products in human nutrition has been increasingly discussed in recent years (Boye et al., 2010; Hochwallner et al., 2014; www.quarks.de, 2020), as they constitute a major allergen for infants and children (Santoro et al., 2019). Patients with cow's milk allergy must therefore be able to identify foods containing milk and avoid them in their diets (Santoro et al., 2019). The less precise diagnosis of cow's milk protein allergy or lactose intolerance summarizes some clinical symptoms in humans that appear after consumption of cow's milk and disappear again when the milk intake is stopped. The main reasons for this are disorders in the digestion of milk proteins and milk sugar. Around 70% of the world's total population are lactose intolerant (www.utopia.de, 2015; www.quarks.de, 2020), whereas in Europe about 10% (Krömker, 2007) or 30% (www.quarks.de, 2020) of adults suffer from lactose intolerance.

From an allergological point of view, cow's milk is the first food that is most likely to cause allergies in infants and young children (Host, 2002). The reported prevalence of cow's milk allergy varies dramatically between studies, possibly due to different diagnostic methods or differences

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in the age of the populations studied (Venter and Arshad, 2011). In general, the incidence of self-reported side effects of cow's milk is much higher than that of confirmed diagnoses (Lack, 2008), not only in children but also in adults (Fiocchi et al., 2010). Scientists assume that between 2-5% of children in Europe are affected by a cow's milk allergy (Host and Halken, 2014; Lifschitz and Szajewska, 2015). After the hen's egg, cow's milk is the second most important food allergen in children. The allergy is less common in adults.

The aim of this overview study is to shed light on the risk factors after consuming cow's milk. Therefore, cow's milk protein allergy, lactose intolerance and cancer risk are described and discussed.

ALLERGY TRIGGERED BY CONSUMPTION OF COW'S MILK

Feeding babies with breast milk offers protection against allergic diseases. A foreign protein from cow's milk is partially absorbed in infants without being split, whereupon sensitization to the foreign protein can be triggered (Krömker, 2007). The first side effects of cow's milk were first described more than 2390 years ago by Hippocrates (Chabot, 1951; Host, 1997). About 500 years later a case of milk allergy was described by Galen (O'Keefe, 1953). At the beginning of the 20th century, observations of side effects of cow's milk were seen more frequently (Schlossmann and Moro, 1903; Finkelstein, 1905; Wernstedt, 1910). In 1938 allergic reaction due to inhalation of cow's milk protein was described in a Danish dairy worker (Hansen, 1938). Cow's milk allergy was considered an infrequent disease, but since the 1950s an increasing frequency has been noted (Hamburger, 1989; Hochwallner et al., 2014). Since the beginning of artificial infant feeding and its spread in almost the entire population, intolerance to cow's milk proteins has become a problem (Savilahti, 1981). It is estimated to affect around 1-5 % of babies under 1 year (Host, 2002; Venter et al., 2006; Eller et al., 2009). However, most children have outgrown it by the age of 3-5 years (Venter et al., 2008; Eller et al., 2009; www.nhs.uk, 2019). Fiocchi et al., (2010) reported that 0.6–2.5% of preschool children, 0.3% of older children and adolescents, and less than 0.5% of adults continued to suffer from cow's milk allergy. Another study found that the prognosis of cow's milk protein allergy is good with a remission rate of 45–50% after 1 year, 60–75% after 2 years and 85–90% after 3 years (Host and Halken, 2014). Although the majority of infants outgrow a cow's milk allergy (Host et al., 2002; Martorell-Aragones et al., 2015), Some affected children remain allergic much longer, which can persist into adulthood (Skripak et al., 2007).

BODY REACTION AFTER CONSUMPTION OF COW'S MILK IN ALLERGIC INFANTS AND CHILDREN

A cow's milk allergy can cause different kinds of reactions, depending on the chemicals released, and the allergy is categorised on the basis of these causes:

- **Immunoglobulin E (IgE)-mediated reactions against cow's milk allergy:** The immune system releases histamine and other chemicals in response to cow's milk protein. The immediate and IgE-associated mechanisms are responsible for approximately 60% to 70% of the side effects, starting within 15-30 min after exposure to cow's milk protein, even in low amounts (Franceschini et al., 2018; Santoro et al., 2019). The majority have two or more symptoms from two or more organ systems. That means, 50-70% have cutaneous symptoms, 50-60% gastrointestinal symptoms and 20-30% respiratory symptoms (Host and Halkan, 2014), in some cases skin reactions, respiratory diseases and gastrointestinal reactions, and in some extreme cases even systemic anaphylaxis can be induced (Monaci et al., 2006; Fiocchi et al, 2010; Kattan et al., 2011). Typical IgE-associated symptoms appear immediately or within 1–2 hours after ingestion of cow's milk. Especially in infancy and childhood, cow's milk triggers complaints in the digestive tract or on the skin, often in connection with an atopic dermatitis attack (Sampson et al., 1998; www.utopia.de, 2015).
- **Non-immunoglobulin E (IgE)-mediated reactions:** In addition to IgE-associated mechanisms, non-IgE-mediated mechanisms of hypersensitivity to cow's milk also occur, but these are difficult to diagnose (Sampson, 1999). Symptoms that are not associated with IgE are characterized by a delayed onset of about 2 hours to several days after consumption of cow's milk. Patients suffering from this form of hypersensitivity insufficiency circulate cow's milk protein-unspecific IgE and show negative results in skin samples (Burks et al., 1990; Pelto et al., 1999; Ewing and Allen., 2005; Shek et al., 2005; Kattan et al., 2011). It is estimated that around 0.5% of all infants have non-IgE-mediated cow's milk allergy, whereas it seems to be more common in adults (Katz et al., 2010). T- Cells are thought to be the trigger for the symptoms, which appear more gradually, from 48 hours up to a week after consuming cow's milk protein (Bischoff and Sellge 2003).
- **Mixed IgE and non-IgE reactions:** This is a combination of immunoglobulin E-mediated reactions and non-immunoglobulin E-mediated reactions. It is also possible for patients to experience mixed

manifestations caused by IgE and non-IgE mediated reactions. Both humoral and cell-mediated mechanisms can produce symptoms, including acute and chronic manifestations (Caffarelli et al., 2010; Hochwallner et al., 2014; Kansu et al., 2016).

SYMPTOMS OF A COW'S MILK ALLERGY

A cow's milk allergy can occasionally cause severe allergic symptoms that come on suddenly.

- **Skin reactions:** Itchiness, reddening of the skin, sudden itchy rash (urticarial - either in one spot or generally all over), or swelling, most often of the lips, face, and around the eyes. Sometimes the skin allergy turns into a topic eczema. Various studies have reported that between 33 and 81% of children with infantile eczema have IgE-mediated food allergy (Sampson, 1998; Eigenmann and Calza, 2000). Furthermore, a study of 2184 infants showed that the risk of egg, cow's milk, or peanut allergy was approximately twice as high if eczema was present in the first 6 months of life compared with the second 6 months of life (Hill et al., 2008).
- **Gastrointestinal reactions:** Swelling of the tongue or palate in the mouth, itching in the mouth, nausea, vomiting, colicky abdominal pain, blood in the stool, and failure to thrive or diarrhoea.
- **Respiratory reactions:** Itchy nose, sneezing, runny nose, congestion, cough, wheezing, or shortness of breath.

It is noteworthy that infants who have been fed cow's milk since birth can develop cow's milk protein intolerance within the first two to three months of life. Furthermore, various studies have reported that there is still no suitable therapy for cow's milk allergies other than avoidance. Therefore, research must focus on developing suitable and safe immunotherapies that do not cause serious side effects (Hochwallner et al., 2014).

CAUSE OF COW'S MILK ALLERGY AND EXAMINATION OF WHICH MILK COMPONENTS ARE RESPONSIBLE FOR THE ALLERGY

Since the factors that contribute to cow's milk allergy are not yet fully understood, it has been suggested that factors such as low levels of pepsin activity in the stomach at birth may be an immature mechanism for gastric acid production, and defective pancreatic and intestinal enzymes are responsible. Hence the gastric proteolysis could be limited and the risk of allergic reactions could be increase (Sakai et al., 2000).

Various mechanisms are discussed that lead to the initial sensitization to cow's milk proteins. One hypothesis is that sensitization can occur before birth: in this context, it has been shown that small amounts of dietary proteins consumed by pregnant women can reach the foetus via the placenta (Szepfalusi et al., 2000). In fact, it has been speculated that IgE is produced by foetuses in early pregnancy and can be detected in blood (Kamemura et al., 2012). The other possibility is sensitization soon after birth through intake of Cow's milk (Mastrorilli et al., 2020). However, it is still controversially discussed whether early contact with cow milk proteins leads to sensitization or to clinical tolerance to cow milk (Hochwallner et al., 2014). It is common knowledge that all infants should be breast-fed for the first six months, if possible (Saarinen et al. 1999; Host and Halken, 2004). It is noteworthy that sensitization to human milk has also been reported (Schulmeister et al., 2008). Clinical reactions usually begin very early in life after breastfeeding is stopped and cow's milk has been added to the diet, while symptoms rarely appear during breastfeeding (Schulmeister et al., 2008; Jarvinen and Suomalainen, 2001; Kattan et al., 2011).

In principle, several immunological mechanisms can be responsible for non-IgE-mediated reactions to cow's milk proteins (Bischoff and Sellge, 2003).

An allergy to cow's milk is due to different components (Wood et al., 2013; Martorell-Aragones et al., 2015). There are at least 40 individual protein components in cow's milk that can trigger antigenic reactions in humans (Table.1). As a rule, the cow's milk allergy does not consist of just one component, but most affected individuals have a sensitivity to both caseins and whey proteins (Bartuzi et al., 2017). Casein and β-lactoglobulin (β-Lg) have been classified as the main allergens, while bovine serum albumin (BSA), α-lactalbumin (α-La), immunoglobulin (Ig) and lactoferrin (LF) are known to be minor allergens (Monaci et al., 2006). However, the β-Lg in cow's milk is responsible for most intolerances in infancy. The properties of these proteins are detailed as follows:

β-Lg: This protein makes up 57% of the total protein in the whey fraction of milk (Kaskous, 2020). There are seven genetic variants of β-Lg (A, B, C, D, E, F, G) (Kaskous, 2020). β-Lg is relatively stable to denaturation and resistant to proteolytic hydrolysis by chymotrypsin and pepsin, but is susceptible to trypsin hydrolysis. (Maynard et al., 1998). Six IgG-binding regions and seven different IgE-binding epitopes have been identified that cause allergic reactions in humans (Selo et al., 1999; Jarvinen et al., 2001).

It is noteworthy that the bovine β-Lg, which is the main allergen in infancy and childhood, could not be detected

Table 1: Compositional protein quality in cow's milk (Kaskous, 2020)

Protein components	Protein subclasses	Concentrations (g/kg)
Caseins	α_{s1}-casein (A, B, C, D, E)	10.3
	α_{s2}-casein (A, B, C, D)	2.7
	β-casein (A1, A2, A3, B, C, D, E, F, G, H^1, H^2, I)	9.6
	k-casein (A, B)	3.5
	γ-casein	0.8
Whey Proteins	α-Lactalbumin (A, B, C)	1.2
	β-Lactoglobulin (A, B, C, D, E, F, G)	3.4
	Serum albumin	0.4
	Immunoglobulins (A, G1, G2, M, E)	0.7
	Lactoferrin	0.1
	Transferrin	0.1
	Other minor proteins	0.1
Enzymes	About 60 enzymes in five groups: oxidoreductases, transferases, hydrolases, lyases and isomerases	traces
Peptide Hormone	Prolactin, growth hormone, insulin growth factor (IGF)	traces
Non-protein-nitrogen	Urea, creatine, creatinine, peptide, uric acid, hippuric, orotic acid, free amino acids, nucleic acids.	1.1

in camel milk (El-Agamy et al., 2009; Smits et al., 2011; Kaskous and Pfaffl, 2017). This is why camel milk can replace cow's milk in the event of intolerance. In camel milk, whey protein α-La is the major whey milk component (Wernery, 2007; Al hag and Al Kanhal, 2010), whereas in cow's milk whey, β-Lg is the main component (57%) and α-La is the second (20%) (Frister, 2007).

Casein: Caseins constitute about 80% of the total proteins of cow's milk (Kaskous, 2020). The casein protein fractions are α_{s1}-casein (30.3%), α_{s2}-casein (7.9%), β-casein (28.2%), k-casein (10.3%) and γ-Casein (2.4%) (Jost, 1988; Wal, 1998a; Kaskous, 2020). It is believed that after consuming casein, most of the potentially antigenic or allergenic structures are modified under acidic gastric conditions by the action of digestive enzymes and absorption through the intestinal mucosa (Wal, 1998b). In milk allergic children with persistent symptoms, a significantly higher content of specific IgE antibodies against linear epitopes of α_{s1}-casein and β-casein was found than in children who had achieved tolerance (Vila et al., 2001).

It is also noted that if there is an allergy to casein, no other milk will be tolerated; even breast milk is not tolerated because it also contains casein. Since casein is not animal-specific, all types of milk must be avoided if there is a proven allergy to casein. However, in camel milk β-casein is the main fraction, followed by α_{s1}-casein, α_{s2}-casein and k-casein (El-Agamy, 2006; Hamed et al., 2012; Kaskous and Pfaffl, 2017). It is hypothesised that since β-casein is more sensitive to peptic hydrolysis than other fractions, the higher percentage of this casein fraction in camel milk as compared to bovine milk could reflect its higher rate of digestibility and lower the incidence of allergy in the infants nourished with camel milk (El-Agamy et al., 2009; Jadhav et al., 2019).

α-La: This protein represents 25% of whey proteins. Various studies have confirmed the presence in α-La of linear epitopes that are able to bind human IgE antibodies (Maynard et al., 1997; Jarvinen et al., 2001).

BSA: BSA makes up around 5% of total whey proteins. Antigenic epitopes on BSA that recognize human IgE antibodies and antibodies from mice have been identified (Beretta et al., 2001)

LF: LF is a milk-specific iron-binding protein representing less than 1% of total whey protein. However, to date, no studies have been conducted to identify LF IgE epitopes or T-cell epitopes.

IgG: The IgG fraction accounts for about 6% of whey proteins. Unfortunately, based on the available literature, there are no reports of B or T cell epitopes of bovine IgG.

INFLUENCE OF MILK PROCESSING ON THE ALLERGY-TRIGGER

The 15-minute heat treatment of milk at 90 °C reduced the immunoreactivity of α-La and β-Lg compared to raw milk to 12.72% and 18.74% respectively (Wroblewska and Jedrychowski, 1994). Duranti et al. (1991) in previous studies also showed that the immunoreactivity of α-La in sterilized milk decreased to 8% compared to raw milk. Severe heat treatment (60 minutes at 90 °C) did not remove all IgE binding activity (Ehn et al., 2004). Moreover, Kleber et al. (2004) reported that heat-induced denaturation (90 °C) increased the allergenicity of β-Lg by exposing previously hidden antigenic sites. It has been shown that up to 90% of β-Lg is aggregated in processed milk (Chen et al., 2005).

Furthermore, some researchers observed that with heat treatment of the milk at temperatures above 100 °C, α-La, BSA and immunoglobulins are inactivated. Intolerance to these proteins no longer occurs after consuming UHT milk. However, the products resulting from the heat treatment of the milk can also create the new active fractions. These new active fractions are called the Maillard reaction after the chemist Louis Camille Maillard (Ledl and Schleicher, 1990; Schleicher 1991). Here amino acids and sugars are converted into new compounds under the influence of heat. The melanoidins formed by heating from sugars and amino acids are responsible for the intolerance. Since these occur primarily in UHT milk or sterile milk, these must then be avoided.

Duranti et al. (1991) suggested that heating and lactic acid fermentation might be more effective in reducing the immunoreactivity of some milk proteins. Similarly, Jedrychowski and Wroblewska (1999) and Maier et al. (2006) reported that sterilization of milk followed by lactic acid fermentation reduced the immunoreactivity of cow's milk proteins.

TREATMENT OF COW'S MILK PROTEIN ALLERGY

Infants at risk of cow's milk protein allergy can be identified by a family history of atopic disease. Exclusive breastfeeding for 4-6 months (17-27 weeks) is recommended as the best method of infant allergy prevention (Kansu et al., 2016; Mastrorilli et al., 2017), particularly if the infant is at high risk of developing milk allergy. However, the rate of cow's milk allergy in nursing infants is lower than in infants fed with formula and has been reported to be around 0.5% (Host, 1994). It is noteworthy that there is no evidence that changing the mother's diet during pregnancy and/or breastfeeding, and delaying solid or even potentially allergenic foods in infants beyond 4 to 6 months can protect against allergies in vulnerable infants (Kansu et al., 2016). If the child has a cow's milk allergy, then the mother should eliminate all foods containing cow's milk protein, including cheese, yogurt, and butter from her diet (Kansu et al., 2016). When exclusive breastfeeding is not possible, infants at risk of developing CMPA may benefit from a partially hydrolyzed formula to prevent allergies until a health professional has assessed their risk (Host and Halken, 2014). For infants with CMPA consuming formula, the first therapeutic option is exclusively the hydrolyzed formula as per guidelines. Other options are an amino acid-based formula or a rice-based formula. A partially hydrolyzed formula should not be used in infants with CMPA (Majamaa et al., 1996). Substitutes such as sheep and goat milk are generally not acceptable due to high cross-reactivity with cow's milk protein. However, research shows that there were fewer cross-reactions with camel milk (Restani et al., 1999). That is why camel milk can replace cow's milk in the event of intolerance (Kaskous and Pfaffl, 2017).

Soy proteins were the first recommended alternatives because of their hypoallergenicity, low cost, and convenience (Brady, 1986). However, the digestibility and nutritional quality of soy protein is affected by the presence of nutritional inhibiting factors such as trypsin inhibitors, phytic acid, and phenolic compounds (Boye et al., 2010). Researchers have reported that as many as 50% of children affected by cow's milk protein intolerance also develop soy protein intolerance if fed with soy-based formulas (Boyce et al., 2010; Koletzko et al., 2012). Reche et al. (2010) reported that the hydrolyzed rice protein formula was tolerated by more than 90% of children with cow's milk protein allergy and therefore could be a suitable and safe alternative to formulas hydrolyzed with cow's milk protein for these infants. New research has shown that treating cow's milk protein allergy with amino-acid formula appears to give better clinical results (high tolerance and less withdrawal due to taste or allergic reaction) (Berktas et al., 2020). In addition, recent evidence suggests that introducing complementary foods early (up to 6 months of age), including cow's milk, could prevent the development of food allergies. Several countries have included this new approach in their feeding guidelines (Mastrorilli et al., 2020). In the case of acute treatment, it must be mentioned that despite the best efforts of parents, medications like antihistamines can decrease the mild allergic reaction when a child accidentally consumes milk (Edwards and Younus, 2020). On the other hand, it was found that early barrier deficiency appears to promote the development of allergic sensitization, but does not appear to affect the acquisition of tolerance (Giannetti et al., 2019).

MILK ALLERGENS IN FOOD

Milk protein can be found in many foods that are not obviously related to milk - so consumers should pay attention to the labelling of the ingredients on food labels. According to the EU Consumer Information Regulation, milk and products made from it (including lactose) must be labelled and in the list of ingredients e.g., highlighted by font or background colour. This extended labelling requirement has been mandatory for packaged and unpackaged goods (open, loose goods) since December 2014.

LACTOSE INTOLERANCE

Lactose is the only dietary carbohydrate for babies in the first few months of life (Ingram et al., 2009) and its value as a carbohydrate and energy carrier appears to promote the absorption of Ca and other minerals such as phosphorus, magnesium, manganese and zinc (He, 2008; Michaelsen et al., 2011).

In the small intestine, lactose is hydrolytically split into glucose and galactose by the enzyme lactase located in the mucous membrane cells (Krömker, 2007). Only glucose and galactose can be absorbed into the blood through the intestinal mucosa. The activity of lactase is normally down-regulated after weaning (Krütli et al., 2014). This means, that most of human adults cannot digest lactose or can no longer digest it completely (lactose malabsorption) (Itan et al., 2010). This problem is found in around 65-70% of the adult population of Africa and Asia (Ingram et al., 2009; www.utopia.de, 2015; Bayless et al., 2017), while only around 15-20% of adult Caucasians have this syndrome (www.utopia.de, 2015). However, the continued production of lactase throughout adult life is a genetic trait and is found in Europe, especially Northern Europe (Leonardi et al., 2012), but also in regions of Central Africa, the Middle East and Asia (Krüttli et al., 2014) (Fig. 1).

A total of seven different genetic lactase polymorphisms have established themselves, which result in high lactase activity even in adulthood (lactase persistence) (Itan et al., 2010; Leonardi et al., 2012; Krüttli et al., 2014). Furthermore, various studies have reported that lactase persistence is the mutation, believed to be the result of strong positive selection that is only common in populations with a long history of pastoralism and milking. Scientists have determined the prevalence of lactose malabsorption or lactase non-persistence in many countries in the world, and the results have been presented below (Table 2).

If undigested lactose gets into the large intestine due to insufficient cleavage in the small intestine, it is used by the bacteria there and gaseous metabolic products such as hydrogen or methane are created (Report, 2014). Together with the osmotically induced water influx, these can cause flatulence, diarrhea and abdominal pain (lactose intolerance). Around 80% of colon bacteria have lactase activity, so they can break down lactose. Whether the fermentation of the lactose that entered the colon is causing symptoms is likely to depend on a number of factors. These include: (1) the composition of the intestinal microbiota and their metabolic activity; (2) the capacity of the intestine to absorb the fermentation products through the intestinal wall and thus remove them from the intestine; (3) the intestinal sensitivity (Leonardi et al., 2012; Venema, 2012). Bayless et al. (2017) reported that the symptoms of lactose malabsorption are influenced by many factors.

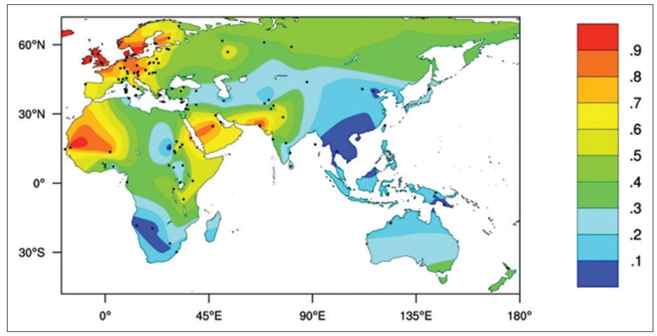

Fig 1. Map of old-world Lactase Persistence phenotype frequencies. Colors and color key show the frequencies of the lactase persistence phenotype estimated from surfaces. Number 9 is the highest frequency of lactase persistence and number 1 is the lowest frequency of lactase persistence according to Itan et al., (2010).

Table 2: Prevalence of lactase non-persistence (LNP) or lactose malabsorption (LM)

The Countries	%	The Countries	%
China (LNP)	100	Egypt (LM)	73
Vietnam (LM)	100	Germany (LM)	70
Japan (LM)	100	Hungary (LM)	56
Uganda, Bantu (LM)	100	Mexico (LM)	53
Peru, non-Caucasian (LM)	94	Northern Italy (LM)	52
Iraqi Jews (LNP)	93	Fulani (LNP)	50
Australian Aborigine (LM)	84	Greece (LM)	45
Nigerian Yorba (LM)	83	UK White (LNP)	22
Ashkenazi Jews (LNP)	83	Finland (LM)	17
Moroccan Jews (LNP)	82	USA White (LM)	15
USA Native American (LM)	81	Central Italy (LM)	15
Brazil (LM)	80	Ireland (LNP)	14
Chile (LM)	80	Denmark (LNP)	12
American African (LM)	75	Sweden (LNP)	10

(Swallow, 2003; Ingram et al., 2009; Raz et al., 2013; Paige, 2013; Bayless et al., 2017)

In order to avoid symptoms of lactose intolerance without giving up milk and/or dairy products, there are a number of options that are detailed in various publications (Vesa et al., 2000; Venema, 2012; Brown-Esters et al., 2012). It is also noted that some lactose intolerant people who do not have irritable bowel syndrome at the same time can have a glass of milk with a meal with no or minor symptoms (Bayless et al., 2017). Therefore, people can easily tolerate up to 300 ml of milk per meal, in which the lactase activity is limited in the case of hereditary lactose intolerance. Furthermore, lactase non-persistence and lactose intolerance are considered factors in global milk drinking habits (Szilagyi, 2015). Therefore, it was found that inhabitants of countries with a high prevalence of LNP consume less dairy products and conversely, in countries that have no problems digesting lactose, consume a lot of milk (Fig.1) (Shrier et al., 2008).

COW'S MILK AND CANCER RISK

In recent years there has been intense discussion about whether the consumption of cow's milk could increase the risk of cancer (www.utopia.de, 2015). The answer is that, it depends on the type of cancer. Milk has a certain growth factor "Insulin-like Growth Factor-1". (IGF-1) that makes people grow taller. However, more cells and more frequent cell division mean a higher risk of cancer (Friebe, 2019). An epidemiological study has shown that taller people (growth promoted by milk) have an increased risk of bone fractures-but only in women (www.quarks.de, 2020). In the case of prostate cancer, there seems to be a stronger connection, so that frequent and heavy consumption of milk (over 1.25 litters/day) increases the risk of prostate cancer significantly (Friebe, 2019; www.quarks.de, 2020). Various mechanisms have been proposed by which the consumption of milk and/or dairy products can influence the development of prostate cancer. These include: 1) calcium suppresses the production of calcitriol (1,25-dihydroxy-Vitamin D_3), which increases cell proliferation in the prostate; 2) consuming milk increases IGF-1 blood levels, which can lead to cell proliferation; 3) fat and saturated fatty acids (SFA) can be risk factors for prostate cancer (Stanton et al., 2013); 4) Branched-chain fatty acid metabolites can be carcinogenic (Ran-Ressler et al., 2014); and 5) the presence of oestrogens, which can be carcinogenic. These and the possible roles of fat and SFA have been studied in depth by Parodi (2009). The most important factor of the mentioned causes of prostate cancer seems to be an increased calcium intake from milk. Therefore, men do not have to get increased calcium from milk, as the risk of prostate cancer increases the more milk they consume (Song et al., 2013; www.quarks.de, 2020). Regarding the relationship between cow's milk intake and gastrointestinal cancer, it has been reported that the consumption of dairy products reduces the risk of gastrointestinal cancer (Park et al., 2009). Several meta-analyses of dairy products have shown protective effects against colon cancer (Cho et al., 2004; Aune et al., 2012). It is believed that the main protective factor is calcium (Muehlhoff et al., 2013), which inhibits the proliferation of aberrant crypt foci in the colon (Szilagyi, 2015). Studies with calcium intake have shown that high-dose calcium is necessary to protect against colon cancer and polyps (Weingarten et al., 2008). It is known that milk and dairy products contain high amounts of calcium. However, in western countries it is believed that adding vitamin D to milk also protects against colon cancer (Chandler et al., 2015; Bostick, 2015), but vitamin D is generally less likely to be added in Africa, Asia and the Middle East due to the abundance of sunshine there. Furthermore, a meta-analysis has shown that the consumption of dairy products reduces the risk of gastric cancer, as milk has a neutral effect (Guo et al., 2015). Hence, both women and men are advised that regular consumption of milk and dairy products can help prevent colon cancer. Conversely, it has been shown that dairy products may increase risk of breast cancer, through the following aspects; 1) high intake of dairy products that are high in saturated fatty acids; 2) dairy products can contain pesticides that can be carcinogenic; and 3) milk can contain growth factors, including IGF-1, that can promote the growth of breast cancer cells (Moorman and Terry, 2004). However, some ingredients in milk and dairy products such as calcium, vitamin D, unsaturated fatty acids, and whey protein can protect against breast cancer (Moorman and Terry, 2004; Parodi, 2005). In general, a reduced consumption of animal foods is recommended for adults.

CONCLUSION

- A milk allergy is an abnormal reaction by the body's immune system to milk and dairy products. It is one of the most common food allergies in children. Cow's milk is the most common cause of milk allergies, but milk from sheep, goats and buffalo can also cause a reaction. Camel milk is an exception as it contains different protein components. This is why camel milk can be used to treat food allergies.
- It is known that about 70% of the world's adult population suffer from hypolactasia after childhood. Milk consumption is lower in countries with a high prevalence of lactase non-persistence than in countries with lactase persistence. The three phenotypes lactase persistence, lactase non-persistence and heterozygotes are under genetic control. Our recommendation for people with non-persistent lactase is to consume adequate amounts of calcium and vitamin D, either from dairy products with reduced lactose content or as a supplement of calcium and vitamin D.
- Research on cow's milk and cancer risk suggests dairy products should be consumed for development and bone health. As described, dairy products can be beneficial for certain diseases (e.g., colon cancer). High intake of dairy products in older men is not recommended. However, for other diseases, more studies are needed to better define the risks.

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