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New pathogens in beef and cow's milk products: More research required

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In February 2019, the German Cancer Research Centre (DKFZ) presented findings on new infectious agents referred to as “Bovine Milk and Meat Factors” (BMMFs). According to these findings, the previously unknown pathogens can cause inflammation. According to the DKFZ, they have been detected thus far in cow's milk, cow's milk products and the blood serum of healthy cattle. From the scientific findings made to date, it seems possible that an indirect connection could be interpreted between the consumption of various foods originating from cattle and the occurrence of several cancer types in humans. The DKFZ is assuming that infants whose immune system has not yet fully matured become infected with BMMF during their first year of life through supplementary feeding with cow's milk. They therefore conclude that infants should not be given cow's milk too early.

According to the DKFZ, BMMFs are new pathogens similar in type to both viruses and bacteria. Because they are related to plasmids, they are currently being called “plasmidomes”. As far as can be established by the DKFZ researchers, the BMMF do not occur as “naked” genetic material but rather together with proteins.

The German Federal Institute for Risk Assessment (BfR) and Max Rubner-Institut (MRI) jointly conclude that an assessment of the possible risks posed by so-called BMMFs as possible cancer risk factors has not yet been possible due to insufficient data. The presumed connection between the BMMFs and the incidence of cancer in humans should be examined further.

In line with the latest available information regarding nutrition, the BfR and MRI agree with the following recommendation: On the basis of currently published epidemiological studies on the connection between the consumption of red and processed meat and an increased risk of colon cancer and in concurrence with the German Nutrition Society (DGE), it is recommended that meat consumption be limited to a maximum of 600 grams per week. However, the consumption of cow's milk without any restriction is still recommended in compliance with the latest available knowledge and is still advocated in the first year of life in accordance with the recommendations of the *Gesund ins Leben* Network. Breastfeeding in order to prevent various diseases is also fundamentally advocated.

The German Federal Institute for Risk Assessment (BfR) and Max Rubner-Institut (MRI) have assessed a press release on an event held at the German Cancer Research Centre (DKFZ) in Heidelberg on “new infection pathogens from milk and meat as cancer risk factors” and state their joint position on this in the following paragraphs.

Background of the DKFZ press release

In the opinion of the DKFZ, a certain class of pathogens in beef and milk, the so-called “Bovine Meat and Milk Factors” (BMMFs), could be the cause of chronic inflammations which could form the basis for a malignant degeneration of cells in the breast and colon. According to the DKFZ (2019) and zur Hausen et al. (2017), the geographical distribution pattern of the incidence rates of colon and breast cancer indicates a close connection with the consumption of milk and meat products from European cattle (*Bos taurus*).

According to the documents provided at the DKFZ press conference (2019), BMMFs are single-stranded, ring-shaped DNA elements which bear a great similarity to the sequences of specific bacterial plasmids. All BMMFs known to date possess a gene for the “rep” protein (replication initiator protein) required for their own replication, irrespective of other genes which may exist. According to Eilebrecht et al. (2018), most BMMFs show a similarity to plasmids of the species *Acinetobacter baumannii*, although several BMMFs also have similarities with certain viruses having small, circular, single-strand genomes (DKFZ, 2019). Furthermore, they probably do not occur in nature as naked DNA but rather in association with proteins. BMMFs constitute, according to the DKFZ, a new class of pathogens whose characteristics lie between viruses and bacteria. Due to their relationship with plasmids, they are therefore currently being referred to as “plasmidomes”. The DKFZ points out that it has not yet been possible to clearly define the nature of these pathogens.

Over 120 different types of BMMF DNA have been isolated until now from commercially available cow’s milk, cow’s milk products and from serum samples from healthy cattle (Whitley et al., 2014; Falida et al., 2017; DKFZ, 2019). A replication of various BMMFs in human cells was proven (Eilebrecht et al., 2018), whereby the pathogens depend on cellular proteins which have not yet been determined. Furthermore, serum antibodies against BMMF were detected in a total of 350 individuals (healthy people and cancer patients), thus proving exposure to the pathogen. According to the DKFZ, BMMF proteins have been so far found in the colon, prostate gland and brain, whereas BMMF DNA was detected in the human colon.

Areas of tissue infected with BMMFs show increased levels of reactive oxygen compounds, which are a typical characteristic of inflammation and which favour the development of genetic changes. Due to these observations, particularly the epidemiological ones, the DKFZ is assuming that an infection with BMMFs can result from the consumption of dairy products and/or beef, especially among infants whose immune system has not yet fully developed. No indications of a possible time of infection are to be found in the literature. The immune system is not fully developed at birth, or rather works at a reduced level, according to the latest findings (Ulas et al., 2017), and develops itself further step by step through exposure to antigens during childhood (Simon et al., 2015). However, infection at a later stage of life with a fully developed immune system cannot be excluded at present.

After infection, the pathogens are said to induce a chronic-inflammatory reaction in certain tissues (colon, breast) which can promote the development of cancer in the surrounding tissue (especially colon cancer, possibly also breast and prostate cancer). The outbreak of the disease is not expected to occur until decades after the actual infection (zur Hausen et al., 2019). BMMFs are thereby thought to have an indirect carcinogenic effect, meaning that they are not involved directly in the cancer-promoting molecular processes of the cells but create a – usually inflammatory – carcinogenic environment. For these reasons, the DKFZ concludes that there is no direct causality between an infection with BMMFs and colon cancer, for example, but that the BMMFs share a portion of the risk for colon cancer which cannot be exactly quantified (DKFZ, 2019).

The DKFZ mentions breastfeeding over a longer period (over 6 months) as a possible preventive measure against infection with BMMFs. Breast milk contains numerous substances with antipathogenic properties (Peterson et al., 2013). These often contain glycan structures, i.e. sugars, which occur either as free oligosaccharides (human milk oligosaccharides) or bound as macromolecules in the form of glycoconjugates (glycoproteins and glycolipids) (Peterson et al., 2013; Morozov et al., 2018). Human milk glycans are capable of mimicking the recognition points for some pathogens, binding themselves to them and hindering the pathogens from adhering to cell surfaces, thus preventing infections (Newburg et al., 2009; Peter-

son et al., 2013; Morozov et al., 2018). Breastfeeding goes hand in hand with a reduced risk of infection by various pathogens (e.g. rotaviruses), especially if infants are exclusively breastfed over the first 6 months (Krawczyk et al., 2016; Quigley et al., 2016). It cannot therefore be ruled out, and it is generally conceivable as a hypothesis, that human milk glycans could also protect against infections with BMMFs. This hypothesis cannot be substantiated at the moment, however, due to a lack of data.

The evidence of a connection between early feeding with breast milk and the risk of cancer of the progeny in adulthood is limited. The most extensive research has been conducted on the association with breast cancer, but the results are inconsistent (Ekbom et al., 1993; Freudenheim et al., 1994; Weiss et al., 1997; Titus-Ernsthoff et al., 1998; Martin et al., 2005; Wise et al., 2009).

Assessment

As explained above, it is currently not possible to determine or define the exact nature of BMMFs. The above-mentioned observations – especially the epidemiological ones – can be interpreted as preliminary indications of a possibly indirect connection between the consumption of various foods of bovine origin and the incidence of certain types of cancer in humans, but they do not as yet show a causal connection.

Valid, evidence-based examinations for estimating the potential risk are currently lacking. There is no data, for example, on the occurrence of BMMFs in other foods of non-bovine origin, on the occurrence of BMMFs in healthy people compared to cancer patients, on the mechanism of inflammation and cancer induction through BMMFs, and on the infectivity and inactivation of BMMFs in foods. The estimation of a connection between the consumption of bovine foods containing BMMFs and the incidence of tumour diseases seems hardly possible at the moment, since BMMFs are only supposed to act as indirect carcinogens and only after a very long latency period.

Moreover, the epidemiological studies published to date must be seen in a critical light. In the case of intestinal tumours, the studies published to date indicate that the consumption of red and processed meat correlates with the occurrence of colon cancer (WCRF, 2007; Huxley et al., 2009; Chan et al., 2011; Corpet, 2011), but that a high consumption of milk and dairy produce is accompanied by a reduced risk of colon cancer (WCRF, 2007). According to the WCRF (2018), neither the consumption of red meat nor of cow's milk results in increased incidence of breast cancer.

Conclusion

An assessment of the hazards posed by so-called “Bovine Meat and Milk Factors” (BMMFs) as possible cancer risk factors is currently not possible due to insufficient data.

On the basis of the epidemiological studies published to date with regard to the connection between the consumption of red and processed meat and increased risk of colon cancer, and in concurrence with the German Nutrition Society (DGE) it is recommended limiting meat consumption to a maximum of 600 g/week. However, the consumption of cow's milk without any restriction is still recommended in compliance with the latest available knowledge and, in accordance with the recommendations of the *Gesund ins Leben* Network is still advocated in the first year of life. The network *Gesund ins Leben* is headquartered at the Federal Centre

for Nutrition (BZfE), the competence and communication centre for nutrition issues in Germany.

Breastfeeding as a preventive measure against the occurrence of various diseases is fundamentally to be advocated. With regard to the prevention of an infection with BMMFs, however, the current lack of valid data precludes any conclusion.

More information on the topic of viruses in food at the BfR website

Viruses

https://www.bfr.bund.de/en/a-z_index/viruses-130212.html

Scientific publication on polyomaviruses in beef

https://www.bfr.bund.de/en/detection_and_genome_characterization_of_bovine_polyomaviruses_in_beef_muscle_and_ground_beef_samples_from_germany-240042.html



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About the BfR

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