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Forum

Specific nutritional infections early in life as risk factors for human colon and breast cancers several decades later

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Introduction

Red meat and dairy products are currently been considered as risk factors for colon, breast, lung and a few additional cancers (recent reviews Ref. 1,2). Our group postulated a specific relationship of these cancers to infections by meat and milk consumption obtained from Aurochs-derived Eurasian dairy cattle - the global epidemiological patterns of colon and breast cancer incidence points to a close relation to the consumption of products originating from these specific breeds of cattle.[3] The suggested species-specific risk triggered the hypothesis that infections derived from these types of cattle may represent the donors of, at that time, still undefined infections resulting from the nutritional uptake of infected meat and milk products.[2] This stimulated the initiation of an analysis of 120 sera obtained from individual dairy cows, from commercially available dairy products and several human sera from multiple sclerosis patients, chronic human diseases and healthy blood donors. Initially the isolation of 20 different genomes of single-stranded circular DNA was published.[4–8] After their classification into four groups, we designated them as bovine meat and milk factors (BMMF). The first two groups (BMMF1 and BMMF2) have been more intensively analyzed – specific types of group 1, presently 13 in number, and 95 distinguishable types in group 2 (de Villiers *et al.*, unpublished results). Since most of them show similarity in nucleotide sequences to specific bacterial plasmids, mainly of *Acinetobacter baumannii,*[2] we ruled out the possibility of a laboratory contamination with bacterial DNA by transfecting several of the isolated molecules into human cells. The transfected DNA was transcriptionally active and replicated autonomously in specific types of human cell lines.[9] Recently, evidence emerged linking specific types of BMMF1 and 2 to colon cancer development, acting as specific triggers for random mutations in target cells for malignant conversion (Bund *et al.*, unpublished results). This triggering results from chronic inflammatory foci in the *lamina propria* close to the Lieberkühn crypts of the colon. These foci produce reactive oxygen species (ROS) which induce mutations within the rapidly replicating adjacent Ki67 positive crypt cells, but seem to leave the nonreplicating cells within the foci (Ki67 negative) unaffected (Bund *et al.* unpublished results).

The present contribution attempts to link existing data on BMMF infections with reported protective effects related to prolonged breast-feeding periods. Many reports claim such effects for newborns, as well as for the nursing mothers. In addition, prolonged intake of nonsteroidal anti-inflammatory drugs (NSAID) protects against some of the same cancers. Here we present the view that blocking of receptors by sugars, selectively found in human milk, protect against specific infectious agents and cancers. In the chronic persistent inflammatory lesions caused by BMMFs, NSAIDs should act defensively by interfering with the mode of action of such inflammations.

Protection of Newborn Babies During Breast-Feeding Period

Long-time breast-feeding (> 6 months) has repeatedly been reported to prevent several types of infections, such as noro- and rotaviruses, specific parvoviruses, human polyomavirus type 9, human immunodeficiency viruses and *Candida albicans.*[2] Specific glycoconjugates, identified in human milk, block the binding of several infectious agents to cell membrane receptors. *Disialyl-lacto-N-tetraose,* in addition to *2′-fucosyllactose* and *3′-fucosyllactose*, emerge as most abundant oligosaccharides in human milk, yet, they are missing in milk of other species.[10] Bovine milk contains other *fucosylated glycans.* The bovine types, however, apparently protect calves from infections with potentially dangerous bovine pathogens.

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A number of reports also described a protective effect of long-time breast-feeding for specific cancers (e.g., acute lymphoblastic leukemia, Hodgkin's disease), multiple sclerosis, and childhood diabetes (reviewed in 2). It has been postulated that a specific sialic acid (*N-glycolylneuraminic acid [Neu5Gc]*), not synthesized in humans, but present in animal dairy products and meat, becomes integrated into human cellular glycoproteins and gangliosides during the weaning and post-weaning phase.[1] This changes the binding affinity of these receptors and permits several agents, which were blocked for infection during the breast-feeding period now to bind, penetrate and to exert potentially pathogenic functions (e.g., Ref. 11). Neu5Gc is not synthesized in chicken and either not found in fish or present there in a highly rearranged form.

Neu5Gc as an isolated molecule seems to be unable to induce an immune response, but acts as an antigen after incorporation into glycoprotein or ganglioside receptors (reviewed in Refs. 12–14). This "*xeno-immunization,*" induced by nutritional uptake of dairy products or red meat had been proposed as the mechanism by which red meat consumption contributes to the risk of colon cancer. It seems, however, to be difficult to reconcile this interpretation with the remarkably low colon and breast cancer risk in certain countries (e.g., Mongolia), in spite of a very high consumption even of bovine red meat, the latter differing from the one of the Eurasian type of dairy cattle (reviewed in Ref. 2).

Protection of the Breast-Feeding Mothers During This Period?

An interesting question arose: do breast-feeding mothers also acquire specific protective effects during the breast-feeding period? It would be very difficult to find evidence for maternal protection against acute viral and other infections because most of them had been already acquired during childhood. Yet, in particular the analysis of multiparous women offers an opportunity for prospective analyses of the effect of prolonged breast-feeding periods on some chronic diseases. Indeed, here a number of observations reported evidence for maternal protection during the weaning and post-weaning phase after multiple deliveries and breast-feeding periods, specifically for breast cancer. Protective oligosaccharides in human milk occur in breast tissue during lactation (reviewed in Ref. 2). This leads to the question whether they are also entering the blood of nursing mothers. This is likely, since the same sugars are excreted in the urine of these mothers (see later). *Per se*, this does not permit the conclusion that infectious events may cause the reduction of breast cancer risks, but justifies a careful re-evaluation of these observations.

Here we analyze the protective effect of multiple breast-feeding episodes on three common human cancers: breast, colon and lung carcinoma incidence. In relation to the discussion of breast cancer, this analysis also partially includes ovarian and endometrial cancers.

Breast Cancer Risk of Multiparous Women

Risk reduction for breast cancers after several deliveries and breast-feeding periods has been described for several decades (reviewed in Refs. 15–23). Some of these studies reported that increased parity also reduced the risk for endometrial and ovarian cancers.[18,19,23] For women with five or more children a 50% reduction in breast cancer risk has been reported.[24] In a large study, this figure was later slightly reduced to 36%, summarizing 47 epidemiological cohort and case–control studies involving more than 122,000 women from 30 different countries[21] (Fig. 1).

The analysis of two US cohort studies concluded that each additional month of breast-feeding reduces the relative risk for subsequent breast cancer development by 2%.[25]

Several possible mechanisms have been proposed to explain the protective effect of multiple pregnancies and prolonged breast-feeding periods (reviewed in Ref. 23). A number of different factors were considered as being responsible: age at first full-term pregnancy and hormonal factors. In addition, mammary stem cells at young age recently found some interest (reviewed by Refs. 26, 27). Conclusive evidence, however, remains missing.

Certain genetic modifications, some of them inherited, are accepted risk factors for breast cancer (reviewed in Ref. 28). Most intensively investigated is the inherited susceptibility by mutations in the BRCA1/2 genes. It remains an interesting question whether specific sugars found in human milk could modify the risk of inherited genetic predispositions. For acquired genetic modifications, however, we can identify trigger(s) which, after prolonged exposure, initiate breast

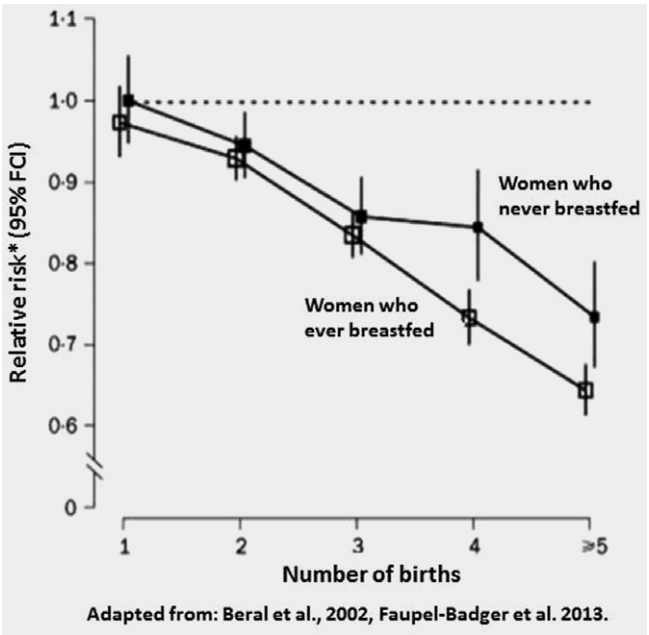

Figure 1. Breast cancer risk after multiple deliveries of women who ever or never breastfed.

cancers or which even synergize with predisposing genetic modifications.

In newborn babies, primary protection by human milk against various infections seems to result from modifying the structure and blocking the receptor function for such agents, thus, preventing these infections. For those reasons, the risk reduction for some cancers after multiple breast-feeding periods could point to one or more of such infectious factors in the etiology of these malignancies. During the past decades, a number of reports considered viral infections contributing to the etiology of human breast cancer. Genital papillomavirus types, Epstein–Barr virus, mouse mammary tumor virus, bovine leukemia virus, human endogenous retroviruses and a few others found some attention. Subsequent analyses, however, did not support these reports (reviewed in Ref. 29).

Yet, the preventive effect of specific sugars in human milk providing protection against several respiratory and intestinal infections in breastfed children[30,31] and also against breast cancer in nursing mothers (review in Ref. 23) could still be interpreted in favor of an engagement of infectious agents triggering these diseases. The same sugars are present in the breast tissue of the nursing mothers. Excretion of lactose-derivatives starts to increase in the urine at 22 weeks of pregnancy.[32,33] Figure 2 presents a schematic model of this mode of action.

Based on these epidemiological considerations,[2,3,34,35] we postulated a role of infectious bovine meat and milk factors (BMMF) as trigger of colorectal and breast cancers.

Colon Cancer Risk of Multiparous Women

A recent larger Nordic population based case–control study involving 22,185 cases of colorectal adenocarcinomas and 220,246 controls failed to find evidence between women's reproductive history and colorectal adenocarcinomas in parous women.[36] Two other prospective studies, however, reported different results: the study by Kuo *et al.*[37] from Taiwan analyzed the death rate risk for colon cancer among 1,292,462 women. They noted 670 colon cancer deaths during 34,980,246 person/years of follow-up. Their study claimed that parity and early age at first birth confer a protective effect on the risk of colon cancer. Another prospective study of 102,541 women (alive in 1974–2011) having had at least five deliveries, identified in the Finnish Population Register, also reported significantly fewer cases of colon and lung cancers, in addition to urinary bladder cancer.[38]

A larger number of case/control studies more uniformly reported a risk reduction of colorectal cancer in multiparous women.[39–48]

It is likely that the concentration of protective sugars produced during the breastfeeding period is high in the milk-producing breasts, but decreases with increasing physical distance from the producing organ. This may explain a somewhat lower rate of colon cancer reduction after multiple breastfeeding periods in comparison to breast cancer.

In the frame of these considerations, it may be relevant that in the vast majority of countries studied, females tended to have a lower incidence rate of colorectal cancers (by about

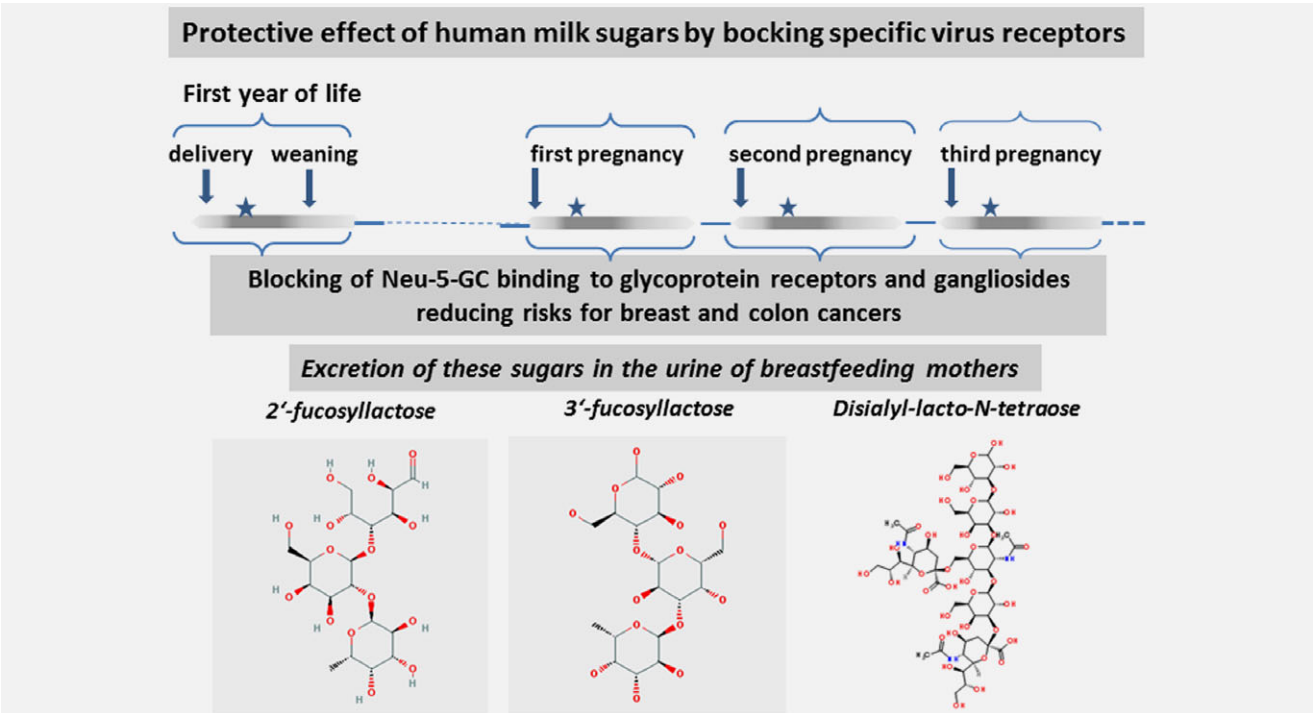

Figure 2. Synthesis of specific sugars in human milk during first and subsequent breastfeeding periods. * - Shaded areas symbolize the protective sugar production of mothers. [Color figure can be viewed at wileyonlinelibrary.com]

25%) than males,[49] except for 3 countries (Brazil, Colombia Costa Rica) where incidence rates have been reported to occur at same frequency in males and females. In 35 additional studies in Asia, Europe, Oceania (Australia and New Zealand) and North America, the incidence in males was substantially higher. Does this indicate an additional consequence of protective effects of breastfeeding periods? Higher alcohol and/or tobacco consumption of males, however, could be an alternative explanation.

Crohn's Disease and Ulcerative Colitis

Patients with inflammatory bowel disease have an increased risk for colorectal malignancies approximately 10 years after the first diagnosis.[50,51] Yet, data on protective effects of breastfeeding for inflammatory bowel disease for mothers are either scarce or not available. One report claims that parity is not associated with a lower risk for ulcerative colitis and Crohn's disease.[52] Difficulties in obtaining convincing results may result from an increased voluntary childlessness of women with inflammatory bowel disease.[53]

Lung Cancer Risk of Multiparous Women

The evaluation of a potential protective effect of parity and breastfeeding for lung cancer is more difficult in view of tobacco smoking being an identified risk factor for lung cancers.[54,55] Therefore, studies not differentiating between smoking and nonsmoking women are noninformative in this respect. Approximately 25% of female lung cancer patients had been nonsmokers throughout life[56] with substantial geographic variation. Four prospective studies, selectively analyzing this group, found a decreased risk in multiparous women, supporting a protective effect of multiparity.[56–59]

Since the 1980s several reports claim an increased risk for lung cancer, but also for oropharyngeal and laryngeal cancers in butchers, meat worker and animal farmers. Since the turn of this century, a few additional reports confirmed these observations.[60–62] Exposure to aerosols during slaughtering and meat cutting were the prime suspects for transmitting a putative virus infection. In the early phase specific types of human papillomaviruses were suspected to represent the culprits.[63] This has not found experimental support until today. Since in this occupational group of meat workers smoking habits seemed to be frequent, this could represent a confounding factor. Two additional studies, however, demonstrated that the increased risk persists even when smoking habits were considered.[64,65]

Although these observations in butchers and related professional groups do not prove the role of infectious components in lung cancer, they add to the previously outlined studies. Obviously, smoking contributes very significantly to lung cancers, but specific factors related to bovine milk and meat consumption may play an additional important role.[2,66–69]

Lactose Intolerance Reduces the Risks for Lung, Breast and Ovarian Cancers

Lactose intolerance, caused by genetic modifications resulting in lactase deficiency, affects individuals worldwide with great geographic variations.[70,71] Ji *et al.*[67] analyzed 22,788 individuals with lactose intolerance found in the Swedish Cancer registry and compared them to 69,922 of their first degree relatives (parents and siblings). A significant decrease for the risk of lung cancer (SIR = 0.55), for breast cancer (SIR = 0.79), and for ovarian cancer (SIR 0.61) was recorded. In their lactose tolerant family members, these decreased risks were not apparent. The authors argued that the protection against these cancers seems related to their specific dietary pattern. As a limitation of their study, the authors acknowledge the lack of information on smoking habits and alcohol consumption, as well as on psychosocial and sociocultural factors.

Inflammation and Cancer Risk

The role of inflammation in colon cancer has repeatedly been considered and postulated (reviewed in Refs. 72–76). All these authors come to an almost uniform conclusion that reactive oxygen and nitrogen radical systems (ROS and NOS), in part activate specific cytokines (e.g., interleukin-6, interleukin-8, prostaglandin E2, TNF-alpha) and promote pro-inflammatory conditions in colon cancer development, progression, invasion and metastasis. The role of ROS and NOS in carcinogenesis, frequently in relation to colon cancer, has been repeatedly discussed and reviewed (e.g., Refs. 77–79). It has also been reported to play a significant role as the molecular basis of alcohol-related gastric and colon cancers.[80] Specific microRNAs are upregulated in inflammation and cancers: these accounts for miR-21, miR-155 and miR-210.[81–84] MiRNAs have been identified in bovine milk.[85] Chronic inflammation in the affected colon target cells should result in increased mutational load.[86–88] Specific triggers for these inflammations, however, remained speculative.

As discussed elsewhere (Bund *et al.*, unpublished results), foci in the *lamina propria*, commonly surrounding the Lieberkühn's crypts, are stained with monoclonal antibodies directed against different epitopes of BMMF1 rep-proteins (Fig. 3). These foci contain CD68-positive inflammatory macrophages which in colon and breast cancers express the BMMF1 group-specific rep antigen. ROS activity is detectable by staining for 8-Hydroxydesoxyguanosin (8-Oxo-dG).[89,90] 8-Oxo-dG is considered as a marker of DNA damage induced by ROS.[74]

Nonsteroidal Anti-Inflammatory Drugs (NSAIDS) as Risk Reducers

In the context of the previous discussion, we emphasize here the preventive role of anti-inflammatory drugs in reducing the risks for colon, breast and several additional cancers. Our data provide mounting evidence that infections with BMMFs act as

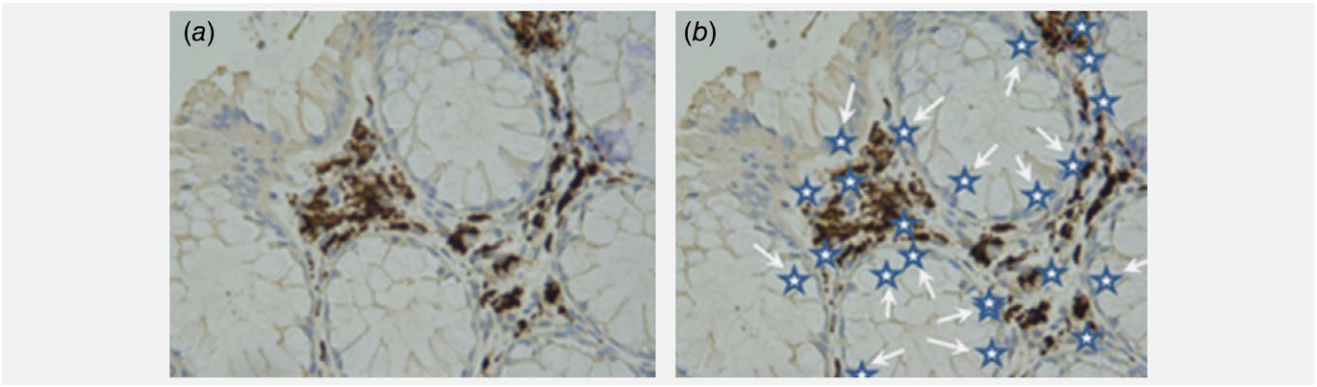

Figure 3. (*a*) BMMF1 anti-Rep monoclonal antibody staining of colon lamina propria cells surrounding Lieberkühn's crypts. Details of monoclonal antibody production and staining procedures are reported elsewhere (Bund *et al*., EP-16193119.1 and to be published). (*b*) Stars exemplify hits of suspected ROS activity. They should result in mutations in rapidly proliferating crypt cells representing targets for colon cancer development. The white arrows exemplify putative mutagenic hits in the epithelial cells of Lieberkühn's crypts, the cells at risk for malignant conversion. [Color figure can be viewed at wileyonlinelibrary.com]

specific triggers for chronic inflammatory foci in colon and breast tissue (Bund *et al*., unpublished results). Risk reductions for these cancers by nonsteroidal anti-inflammatory drugs (NSAIDs) seem to further support an indirect role of BMMFs in specific human cancers and possibly also in other chronic diseases.

In a meta-analysis, Harris *et al*.[91] reviewed 91 studies and analyzed the protective effect of aspirin, ibuprofen and other Cox-2 inhibitors for a number of cancers, including colon, breast, prostate and lung cancers (summarized in Fig. 4). According to this review, daily intake of aspirin was particularly effective in reducing the colon cancer risk, but also prevented about one third of three other cancers (breast, prostate, and lung). In addition, a remarkable effect was shown for cancers of the esophagus, stomach and ovary. It remains interesting to analyze the triggering factors for all these cancers. *Helicobacter pylori* has been identified as an initial trigger for inflammatory gastric ulcers and subsequently for stomach cancer. Yet, it remains an open question whether this infection causes this effect by itself or whether it depends on additional synergizing infections.

Besides aspirin and ibuprofen, several other compounds have been identified to interact as ROS-dependent anticancer agents for colon cancer (reviewed in Ref. 75). These include resveratrol, colchicine, statins, caffeine, curcumin and 1-alpha,25-dihydroxyvitamin D3 (reviewed in Ref. 73). The role of thioredoxin reductase as an effective antioxidant system may also deserve special attention (reviewed in Ref. 92).

The main aspect, common to all of these compounds, seems to be the inhibition of inflammatory processes. This is particularly well studied for aspirin and ibuprofen. The risk reduction for colon cancer by long-time low dose intake of these NSAIDs is obviously due to the diminished ROS and NOS radical induction in foci of the *lamina propria*. This results in a decrease of mutagenic events which affect the rapidly proliferating cells in the bottom and midsection of Lieberkühn's crypts. When analyzed with Ki67 antibodies, the foci in the *lamina propria*, stained by monoclonal antibodies against several epitopes of the BMMF1 rep-protein, only occasionally reveal a replicating cell. Ki67-positive cells are at least 100-fold less frequent in these locations than in the adjacent crypts.

The protective effect of NSAIDs in later phases of life either suggests a continuously (probably for decades) ongoing low grade inflammation, most likely combined with radical systems production. These infectious processes during these years may spread locally, resulting in enlarged areas of inflammatory reactions and increased ROS and NOS synthesis. Novel infections during the life span cannot be fully excluded. They could be initiated by additional BMMF types which differ in antigenic composition, but are also engaged in infections causing chronic inflammatory reactions.

Etiology and Pathogenesis

Our previous data emphasized risks for colon and breast cancers due to the consumption of red meat and dairy products from Aurochs-derived dairy cattle.[2,3,34,35] The apparent species-specificity of risk factors resulted in the hypothesis that infectious agents may trigger these types of cancer. The isolation of novel circular single-stranded DNA molecules from dairy cattle sera and milk, yogurt and crème fraiche, offered the opportunity to analyze their potential role directly. The development of monoclonal antibodies against the major protein (Rep, replication protein) of BMMF1 isolates permitted the direct analysis of colon cancer and adjacent tissue for the expression of this antigen (Fig. 3 and Bund *et al*., unpublished results). The identification of this antigen not within, but commonly around the crypts of Lieberkühn, accompanied by macrophage infiltration (CD68-positivity) and the demonstration of ROS reactivity permitted the development of a model of triggering mutations in the cells targeted for malignant conversion by an indirect mechanism (reviewed in Ref.

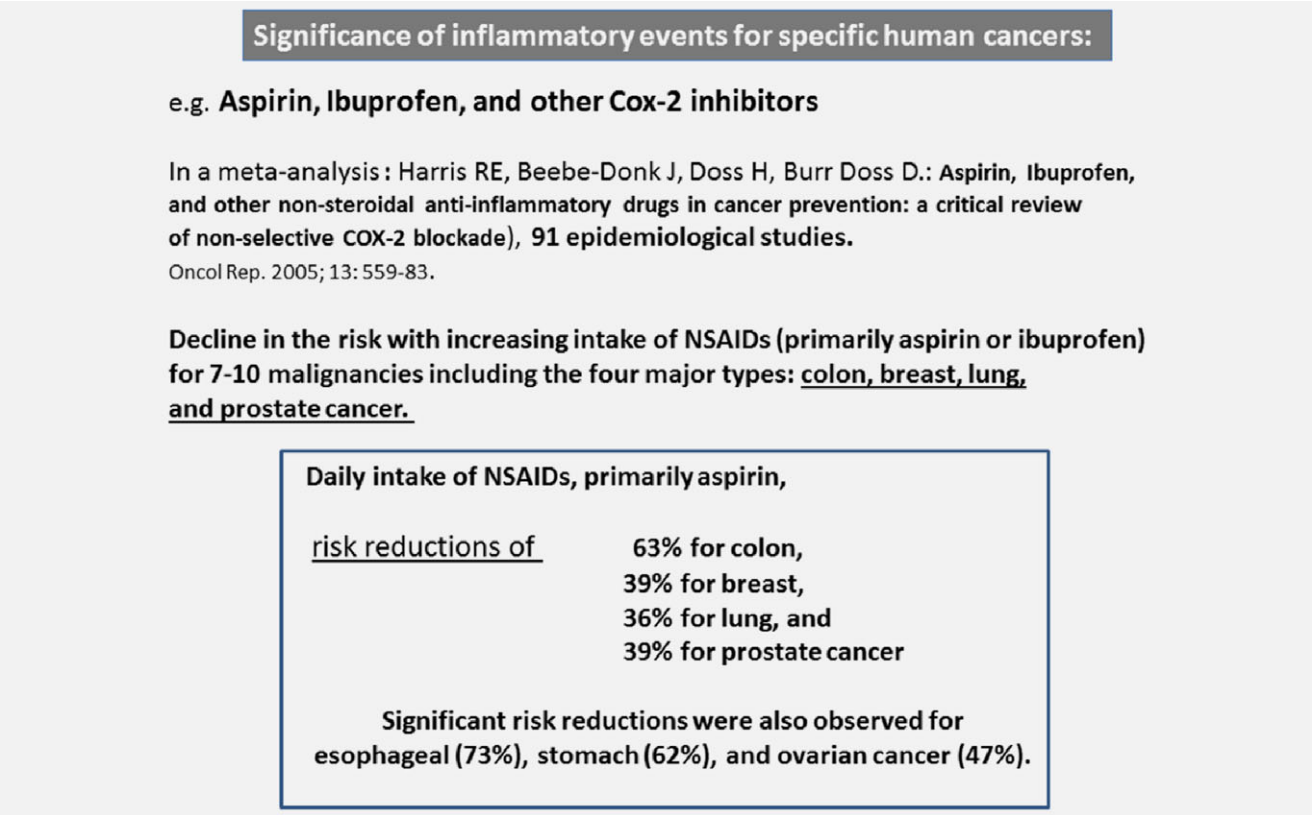

Figure 4. Reported protective effects by NSAIDs for various cancers. [Color figure can be viewed at wileyonlinelibrary.com]

93), predominantly affecting the proliferating cells in the Lieberkühn's crypts. As outlined previously, the bottom and the midsection of the crypts contain almost uniformly Ki67-positive proliferating cells. Indirect carcinogenesis by infectious agents does not require persistence of components of the cancer-inducing agents within the tumor cells.[93]

We have been unable to detect BMMF1 DNA or proteins in cell lines derived from colon or breast cancers (unpublished data). Similarly, sections of colon cancers only occasionally revealed a cell stained by the monoclonal antibodies against Rep. Related sets of data have been obtained from the analysis of breast cancer biopsies. The latter require, however, further confirmation. This is somewhat reminiscent of the carcinogenic function of hepatitis C virus in liver carcinogenesis (reviewed in Ref. 93). This virus also does not persist with its genome within the cancer cells. The emerging scheme of pathogenesis of colon cancer is shown in Figure 5. With minor modifications it should be also applicable to breast cancer.

The absence of BMMF genomes in the cancer cells was an unexpected result, clearly supporting the indirect mode of carcinogenesis, as previously observed in Hepatitis C virus-induced liver cancers.[93] A second surprising aspect was relatively low antibody titers in colon and breast cancer patients in comparison to healthy controls and the virtual absence of B-, as well as T-cell infiltrates in the Rep-positive lesions, in spite of a strong macrophage invasion and CD68 reactivity. We interpret these observations as a partial immune tolerance resulting from an infection early in life. The exact mechanism requires further investigations.

A slow inflammation process resulting in random mutational events in the target cells for colon cancer (and the apparent requirement of more than one specific mutation for malignant conversion) is readily reconciled with the long latency periods elapsing between primary infection (most likely within the first year of life) and the development of the discussed cancers (on average commonly between 40 and 70 years later). Presently it is impossible, however, to exclude additional infections by antigenically different BMMF types later in life and other inflammatory events (e.g., resulting from the microbiome, high alcohol consumption, or linked to obesity).[77,80] They seem to play, at best, a very minor role in this process and would create substantial difficulties in explaining the previously discussed findings, correlated with colon and breast cancers.

HIV-Induced Immunosuppression and Risk for Breast and Colon Cancers

Obviously immune reactions play a significant role for the mutational events eventually leading to colon and breast

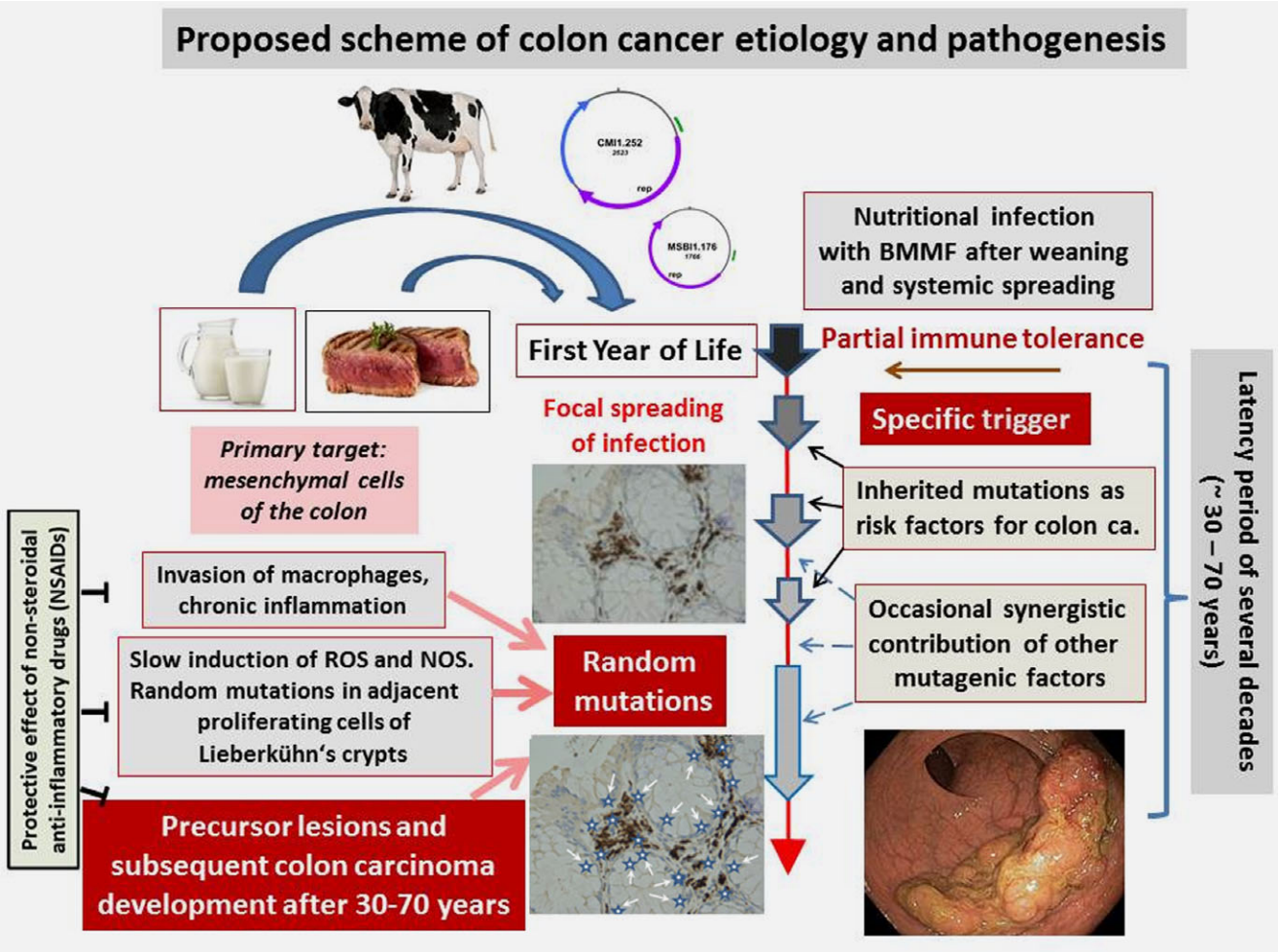

Figure 5. The initial consumption of dairy products commonly starts at the weaning period. This has almost simultaneously two consequences: the previously discussed uptake of Neu5Gc and the incorporation of the latter into glycoprotein and ganglioside receptors of cell membranes.[94,95] Since Eurasian cow milk products do contain BMMF1 and BMMF2 agents, these are now permitted to bind to those receptors and infect susceptible cells. In the colon, cells of the *lamina propria* emerge as a primary target of these infections with local spreading, expression of rep-protein, invasion of macrophages, resulting in a chronic inflammation, as evidenced by CD68 reactivity and demonstration of ROS activity. The infected foci reveal at least 100-fold less replicating cells in comparison to the lower and midsection parts of the Lieberkühn crypts. The high replicative activity of the latter should be prone to ROS-induced mutational events, resulting in an effective fixation of mutations and in specific events for selection of those modifications which provide growth advantage. Although it is anticipated that the mutations are random, the triggers (BMMF-type infections) should be specific. The progression to malignant growth requires a selection for cells which acquired specific mutations, or which contained inherited risk factors (e.g., BRCA 1/2 and a few others). In the latter case, less additional mutations will be required for malignant conversion, thus, enabling tumor development earlier and at younger age.

cancers. Does the risk for these cancers increase under immunosuppression? Immunosuppression, in particular when induced by human immunodeficiency virus (HIV) infections, provided an answer: prior to the introduction of the highly active anti-retroviral therapy (HAART) follow-up studies claimed a reduced risk for breast cancer in HIV-infected women (reviewed in Refs. 96,97). After successful HIV-therapy, the risk for these cancers, as well as for prostate cancer[98] remained comparable to the non-HIV-infected population. This contrasts the risk for patients with cancers induced by more "conventional" tumorviruses (reviewed in Ref. 99). Commonly, the latter cancers occur at much higher frequency under immunosuppression.

In the indirect carcinogenesis model described here, specific triggers induce inflammatory reactions outside of the potential target cells for malignant conversion. Yet, the latter are effectively replicating and affected due to ROS and NOS radicals from adjacent CD68-positive cells. Random mutations in the target cells accumulate over time. It is highly probable that chronic immunosuppression interferes with the inflammatory response, reduces oxygen and nitrogen radicals, and thus does not significantly increase the risks for those cancers.

Conclusions

Our previous studies permitted the identification of a novel class of multiple small circular single-stranded DNA genotypes, at least in part as human pathogens. They are related to specific bacterial plasmids and tentatively labeled as "*Infectious Plasmidom.*" The majority of them were isolated, sequenced and characterized from Eurasian dairy cattle sera or milk products (*Bovine Milk and Meat Factors – BMMF).* A number of them were isolated directly from human colon cancer biopsies and from a lesion of a multiple sclerosis brain autopsy. Others, labeled as Sphinx1.76 and Sphinx2.36 have been isolated from animal and human transmissible spongiform encephalopathies[100] Their close relationship to some of our isolates may also hint to their bovine origin.

Evidence is summarized pointing to human infections by nutrition in the early period of life, resulting in persistent chronic infections for lifetime. Foci of infected cells can be detected by specific monoclonal antibodies, directed against a replication-linked protein (Rep), commonly in close proximity to the actively replicating cells of Lieberkühn's crypts in the colon. Specific genomes have been directly isolated from these foci (de Villiers *et al*., unpublished results, Bund *et al*., unpublished results).

These data were the background for a model of indirect carcinogenesis[92] by BMMF for the development of colon and very likely of breast and possibly also of some other cancers (e.g., prostate and lung). This model includes infection early in life, during and after the weaning period and long-time persistence of infected foci in *lamina propria* cells of the colon. Induction of chronic inflammation with the formation of oxygen and nitrogen radicals is regarded as specific triggers for random mutational events over a period, commonly of 40 to 70 years.

A number of correlative observations published in the past for colon and breast cancer incidence find an explanation: the absence of Neu5Gc-containing receptors during the breast-feeding period has been shown to prevent several infections, very likely also those with BMMFs. A protective effect has also been noted for mothers with repeated breast-feeding periods for breast and colon cancers. Neu5Gc is not present in chicken and only in rearranged form in fish, explaining the absence of increased risk for colon and breast cancers after predominant chicken or fish consumption.[2] The preventive function of long-time intake of low doses of nonsteroidal anti-inflammatory drugs has been noted for a number of cancers, including those of colon, breast and prostate. By reducing inflammatory reactions, they should reduce radical formation, mutagenesis and specific cancer risks.

Finally, geographic differences in both, colon and breast cancer incidence seem to find an explanation in the apparent link of those cancers to Eurasian Aurochs-derived beef and dairy product consumption.

Other interesting candidates, potentially linked to similar infections are neurodegenerative diseases, autoimmune diseases (e.g., rheumatoid fever) and vascular inflammations in arteriosclerosis.[2]

The identification of BMMFs as risk factors for very common human diseases should have important consequences for their prevention, diagnosis, and hopefully also for novel therapeutic approaches.

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