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Asian Pacific Journal of Tropical Biomedicine
journal homepage: www.elsevier.com/locate/apjtb

Review article http://dx.doi.org/10.1016/j.apjtb.2015.12.021

Breastfeeding counsel against cancers

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ARTICLE INFO

Article history:
Received 3 Nov 2015
Received in revised form 30 Nov 2015
Accepted 20 Dec 2015
Available online 31 Mar 2016

Keywords:
Anticancer
Breastfeeding
Well being
Counselling
Nutrition

ABSTRACT

The anticancer potential by breastfeeding is not fully tapped in the light of the present knowledge of the subject. Literature indicates that breastmilk has anticancer action but may underestimate its full capacity. The protective spectrum within breastmilk hints on the need for a more comprehensive understanding of it as an anticancer tool. Exclusive breastfeeding could confer protection from carcinogenesis with a greater impact than realised. A literature review was conducted using four electronic databases. Selected areas were extracted after thorough perusal of the articles. The uninitiated would take exclusive breastfeeding seriously if actively counselled as an anticancer tool. Advice on details of the breastfeeding process and holistic information on breastfeeding may endow a greater impact among the skeptics. Counselling the breastfeeding mother on information sometimes not imparted, such as on maternal nutrition, details of the process of breastfeeding, benefits of direct breastfeeding versus milk expression and her psychosocial well being may make a difference in optimising anticancer action that exists in breastmilk. Additionally, its anticancer potential provides a platform to universally improve physical and psychosocial well being of women who breastfeed. Statistics of protection by breastfeeding in some maternal and childhood cancers are evident. "Bio-geno-immuno-nutrition" of breastmilk may shield the mother and infant from carcinogenesis in more ways than appreciated. The molecular basis of mother-to-infant signals and their "energies" need to be researched. Breastfeeding as a modifiable behaviour provides cost effective nutrition with potential for both cancer immunoprophylaxis and immunotherapy.

1. Introduction

The protective potentials within the lactating mammary gland against cancers are known [1–3]. Despite some statistical support, the actual numbers of children protected from cancers by breastfeeding may never be fully appreciated or appraised as many more children destined to enjoy such protection die of other causes; infections, being the commonest cause of childhood mortality [4]. This article reviews some statistics of breastfeeding protection from cancers for the breastfeeding mother and child, discusses the multifactorial causes of cancers and, based on these causes, reflects on the potentials within breastmilk that protect from the aetiopathogenesis of carcinogenesis.

2. Statistical relevance of breastfeeding and cancer protection in mother and child

Statistics indicate some level of protection by breastfeeding against cancers for the mother and infant [1–3]. For the mother, cohort studies suggest that each month of breastfeeding reduces the relative risk of ovarian cancers by 2% [relative risk = 0.98 per month, 95% confidence interval (*CI*) 0.97–1.00] [1]. Breastfeeding was found to have a significant role in reducing breast cancer, whereby activities to promote breastfeeding by information, education, and communication to inculcate awareness about breast cancer have been recommended [2]. In women who carried the *BRCA1* mutation, those who breastfed for at least one year had a 32% reduction

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Peer review under responsibility of Hainan Medical University. The journal implements double-blind peer review practiced by specially invited international editorial board members.

in risk of breast cancer [odds ratio (OR) = 0.68, 95% *CI* 0.52–0.91, *P* = 0.008]; breastfeeding for two or more years conferred a greater risk reduction (OR = 0.51, 95% *CI* 0.35–0.74) [5]. Among *BRCA2* mutation carriers, no noted link was found between at least a year's breastfeeding and breast cancer risk (OR = 0.83, 95% *CI* 0.53–1.31, *P* = 0.43) [5]. The effect of parity on a woman's long-term risk of breast cancer is modified by age at first full-term pregnancy and possibly by breastfeeding [6]. Protection against aggressive basal breast carcinomas as opposed to intraluminal tumours was seen in women who breastfed [7]. For children, ever having breastfed were associated with a 21% reduction in risk of childhood acute leukaemias (OR for all types combined = 0.79, 95% *CI* 0.70–0.91) [8]. In the commonest childhood tumours, breastfeeding and delayed introduction of artificial formula reduce the risk of acute lymphoblastic leukaemias but not childhood brain tumours [9]. According to a meta-analysis, compared with no or shorter breastfeeding, any breastfeeding for 6 months or longer had a 19% lower risk for childhood leukaemia (OR = 0.81, 95% *CI* 0.73–0.89) [3]. Two meta-analyses found a 1.3-fold higher risk of acute lymphoblastic leukaemias (95% *CI* 1.1–1.4) among formula-fed children compared with children who were breastfed for less than 6 months [10,11], and a 1.2-fold higher risk of acute myeloid leukaemia (95% *CI* 1.0–1.4) in formula-fed infants compared to infants breastfed for more than 6 months [10]. Another meta-analysis indicated that ever breastfed compared with never breastfed had a 11% lower risk for childhood leukaemia (OR = 0.89, 95% *CI* 0.84–0.94) [3].

3. Multifactorial causes of cancer

The multifactorial aetiologies and time sequence of carcinogenesis are not entirely known. Microbial homeostasis, immunocompetence, intact gut mucosae and regulated inflammation protect from carcinogenesis [12].

Over 20% of malignancies worldwide are attributed to infectious agents [13]. Viruses by direct expression of viral oncogenes, can cause cancer, or exert indirect effects by persistent inflammation [13].

Virchow postulated carcinogenesis as an infection related consequence of loss of epithelial integrity and proinflammatory processes [14]. Bacterial and parasitic causes of cancers are well recognised [15,16]. Immunosuppression in the absence of cancer surveillance contributes to carcinogenesis [13].

3.1. Influence of more than one agent in cancer causation

Additive or synergistic influence of two or more agents may lead to cancer and is known as co-carcinogenesis [17]. Human papilloma viruses, cervical tar exposures and fumes by coal or wood-burning stoves causing cervical cancer is an example of such synergy [18].

3.2. Suppression of cellular immunity and the link to cancers

Suppression of cell mediated immunity predisposes to infectious cancers [13], including Kaposi's sarcoma-associated herpesvirus-linked lymphomas, Kaposi's sarcoma-associated herpesvirus sarcomas, Ebstein-Barr virus, human papilloma viruses, head and neck and cervical carcinomas and Merkel cell carcinomas [13,19]. HIV is an indirect carcinogen and HIV-induced immunosuppression promotes the development of tumours [20].

3.3. Early exposures, nutritional influences and specific cancers

Early exposures could initiate carcinogenesis and subsequent infections can trigger cancers [21]. Micronutrient deficiencies contribute to squamous cell oesophageal cancer and the potential prevention, through dietary diversification and increased consumption of rich sources of selenium and zinc have been proposed in endemic areas [22]. Obesity predisposes to cancers of the urogenital tract, gastrointestinal tract, liver, endometrium and breast [23].

3.4. Some dietary genotoxins and their links to cancers

Dietary genotoxins are carcinogens in cooked food, some plants and mushrooms, fungal products, nitrites, polycyclic aromatic hydrocarbons and oxidative agents [24–26]. Heterocyclic amines are associated with breast, colonic and prostatic cancers [25,26].

3.5. The association of cancer to some drugs and hormones

Drugs and hormones may have a role too. Sex hormones, implicated in gene expression could lead to carcinogenesis of the head and neck [27].

3.6. Lifestyle factors and cumulative exposures in cancer causation

Lifestyle factors contribute to the global cancer incidence and estimates from the World Health Organization and the International Agency for Research on Cancer are that toxic environmental exposures contribute about 7%–19% to cancers [28]. The cumulative effects of non-carcinogenic chemicals could act via different mechanisms affecting organ systems, tissues and cells to produce cancers [28].

4. Breastmilk cancer protection

As an effective anticancer tool, breastmilk must incorporate overt or covert mechanisms as well as specific and nonspecific means to destroy cancer cells. Nonspecifically, it must promote an environment not conducive for the establishment of tumours by reducing or counteracting the multifactorial causes of cancers, remove early tumour nidus and provide a milieu that does not encourage tumour progression and metastases. A central antitumour mechanism is apoptosis or programmed cell death [29]. Directly, ideal antitumour action must promote apoptosis in tumours and spare normal cells. As an anticancer tool, breastmilk must also have the potential to overcome mechanisms deployed by tumours to evade the immune system. Additionally, anticancer action must include the capacity to decrease or eliminate tumour predisposition and improve innate immunity of surrounding tissue so that apoptotic cells are removed and normal cells continue to thrive.

4.1. Innate immunity within breastmilk and protection by "bio-geno-immuno-nutrition"

Innate immunity in breastmilk provides substrates for much effective anticancer functions. Lactoferrin and its peptide lactoferricin are breastmilk proteins with anti-infective, antioxidant, immunomodulatory, and anti-inflammatory activities [30,31], which in a broad sense, are anticancer actions.

From maternal plasma, innate immunity, via the milk fat globule contains multifunctional mucins [32,33]. Purified breastmilk mucin, MUC1 and MUC4, blocks infection by HIV [32], which is associated with immunosuppression. Both MUC1 and MUC4 block infection by *Salmonella enterica* serovar *typhimurium* [33], *Salmonella*, a bacterial species linked to cancers [15].

Dendritic cell-specific intercellular adhesion molecule-3-grabbing non-integrin (DC-SIGN), in the gastrointestinal tract of the infant binds to MUC1 in breastmilk and protects via Lewis x-type oligosaccharides, a response found only in breastfed infants [34]. In fact, it is postulated that the infant immune system is "shaped" by DC-SIGN [34]. Strengthened mucosal immunity, augmented intestinal barriers and proper immune maturation are anti-infective in the short term but also shield from chronic inflammation in the long term. Chronic inflammation promotes tumour growth, progression, and metastatic spread [35].

Innate and adaptive immunity cooperate to optimise anticancer function. Fatty acids regulate immunity linking intraluminal exposures, maternal nutrition and microbes [36], a triad, when nurture is cancer protective. For the mother, *in vitro* docosahexaenoic acid, a ligand of peroxisome proliferator-activated receptors, is able to modulate peroxisome proliferator-activated receptorβ mRNA expression inhibiting mammary tumour growth [37]. Substantial amounts of ω-3 and ω-6 long-chain polyunsaturated fatty acids in breastmilk suppress the production of tumour necrosis factor-α and may suppress autoimmune disease and suggestion is that it may also prevent DNA damage and remove emerging tumour cells [38]. Milk fat is the most highly variable macronutrient of milk with high contents of palmitic and oleic acids [31]. About 25% of the variation in lipid concentration between mothers' milk may be explained by maternal protein intake [31,39]. As alluded to earlier, obesity predisposes to some cancers. Leptin, an antiobesity hormone in breastmilk, was significantly increased at night possibly reflecting a 24 h pattern [40]. These observations emphasize the counsel of uninterrupted and continuous breastfeeding in enhancing its anticancer action.

4.2. Breastfeeding and protection from early infections

In utero infection may trigger carcinogenesis [22], but this can be modified by breastfeeding. Breastmilk has passive antibodies due to maternal exposure and modulates immunity to postnatal exposure [41]. Via unified immune communication between the mother and the nursing infant through the enteromammary axis, of which the lactating mammary gland is a part of, secretory immunoglobulin A (sIgA) is produced [41,42], protecting from early exposures to infections. Specific sIgA from B cells confer specific protection without inflammation [41,42]. A cytokine, interleukin 21 drives B cells to differentiate to IgA^+ cells and with transforming growth factor β1, augment IgA class switch recombination [43]. At the cellular level, micro RNAs (miRNAs) in breastmilk, play a role in innate immunity. miRNAs are involved in the development of B cells and B cell subsets differently express miRNA profiles [44]. miRNA has a pivotal role in B cell maturation and if this is disrupted, malignant transformation could occur [44]. Specific antibodies against *Shigella* and *Salmonella* lipopolysaccharides in colostrum and breastmilk are mainly IgA [41]. Exclusive breastfeeding decreases *Helicobacter pylori* (*H. pylori*) colonization, postpones infection and shortens duration of symptoms [45]. Inadequately resolved chronic inflammation due to *H. pylori* causing chronic gastritis may increase the risk of cancer [46]; hence, *H. pylori* protection by breastmilk may be recognised as an anticancer event.

4.3. Chronic parasitosis, carcinogenesis and the benefits of breastfeeding

Chronic parasitosis is linked to carcinogenesis [16]; parasite-induced immunodeficiency and chronic inflammation contribute. Inflammation provides bioactive substances for a sustainable tumour microenvironment [46]. Epithelial mesenchymal transition, can initiate cancer progression and is enhanced by proangiogenic factors and metalloproteinases in chronic inflammation [46,47]. Inflammation also promotes genomic instability and immune evasion [46,47]. Breastmilk has the potential to counteract parasite pathogenicity as it has substances that reduce inflammation, and factors that are antiparasitic with nonspecific and specific function [31,48]. B and T cell maturation factors, antiprotozoal action of fatty acids and sIgA protect against protozoan parasites [31,48].

4.4. Viral factors, carcinogenesis and the recognised advantages of breastfeeding

Viral spread and pathogenesis can lead to carcinogenesis [13]. Viral spread is restricted by extracellular vesicles, exosomes in breastmilk [49]. Antiviral interferons and interferon-stimulated genes with inflammatory cytokines stimulate adaptive immunity to prevent virus induced pathogenesis [50,51]. It is now well recognised that the immunological powerhouse by exclusive breastfeeding through both innate and adaptive immunity have impressive broad-based and specific antiviral action [11,31,32,42,49].

4.5. Breastfeeding as an integrated system against oxygen free radicals (OFRs) and tumorigenicity

OFRs are tumorigenic, and affect the bases and the DNA backbone [52]. Inflammation is also linked to reactive oxygen and nitrogen species [53]. Enzymatic and non-enzymatic antioxidant components, vitamins E and C, retinol, β-carotene, lactoferrin, glutathione, catalase, superoxide dismutase and glutathione peroxidase are in breastmilk, hence it is evident that breastfeeding provides an integrated system against multifactorial causes of OFRs [54].

It is important to note that the antioxidant potential in breastmilk is more efficient than infant formula and bovine milk [55]. The total antioxidant capacity of breastmilk may be influenced by diet, ethnicity or race [56]. Refrigeration and freezing of breastmilk reduces individual antioxidants [56,57], practical points in counseling for working mothers.

4.6. More specific breastmilk protection

Some factors in breastmilk have more direct antineoplastic action [58,59]. Some have been used in the treatment of benign and malignant growths [58,59].

4.7. Human alpha-lactalbumin made lethal to tumor cells (HAMLET) in breastmilk

Partial digestion of its bionutrients has important anticancer action. The pH of the gastric acid in the infant stomach may trigger the change of the native whey protein to HAMLET [60]. Configurational changes of partial unfolding of alpha-lactalbumin and binding to oleic acid with calcium release bestows it selective anticancer action [60]. HAMLET therapy delays tumour progression without evidence of cell death in healthy brain tissue [61]; topically, it removes skin papillomas [58]. Local instillation in bladder cancer efficiently kills tumour cells without much toxicity [59].

HAMLET binds to sensitive cells and accumulates in the nucleus to initiate apoptosis whereas resistant cells do not show intracellular localization of the active complex [59,60]. HAMLET causes an ion channel-dependent response to kill cancer cells [62]. For tumour surveillance, it reduces possible tumour nidus [59,60] and initiates innate immune responses of normal cells, providing an immune environment for elimination of apoptotic cancer cells [59,60]. Through HAMLET-induced apoptosis, potentially malignant cells that may function as nuclei for the development of tumours are reduced explaining the decreased frequency of cancer in those who are breastfed [60].

The breastfeeding child ingests around 2 g of α-lactalbumin abundant in breastmilk, which travels from the mammary gland through the gastrointestinal tract of the suckling child [60]. Through lactose, the water content of milk is controlled [60]. Milk from lactating mothers vary in the levels of medium-chain and *trans* fatty acid partly dependant on diet [63]. Oleic acid is a monounsaturated omega-9 fatty acid and the active part of HAMLET [59,60]; hence, attention to maternal diet or diet supplementation may potentially enhance the quality of breastmilk anticancer function.

4.8. TNF-related apoptosis inducing ligand (TRAIL) in breastmilk

Tumours evade apoptosis [29]. Direct anticancer action must deal effectively with it. TRAIL, is a cytokine abundant in colostrum [64]. TRAIL binds to surface receptors of the tumour necrosis factor receptor superfamily, TRAIL-R1 (DR4), TRAIL-R2 (DR5), TRAIL-R3 (DcR1), and TRAIL-R4 (DcR2) [65–67]. TRAIL-R1 and TRAIL-R2 contain the death domain and induce apoptosis [65]. TRAIL-R3 and TRAIL-R4 are capable of apoptotic signalling and have decoy function [65,66]. miRNAs in breastmilk regulate apoptosis through targeting oncogenes or tumour suppressor genes [67], via extrinsic and intrinsic pathways [67,68]. The extrinsic pathway involves the death receptor family with death domains as Fas, TRAIL-R1 (DR4), TRAIL-R2 (DR5) or TNF-R1 [69]. Multiple myeloma cells are sensitive to TRAIL-mediated apoptosis [69]. It is plausible that TRAIL in breastmilk is efficient in apoptosis via the extrinsic pathway. Decoy receptors for TRAIL could block TRAIL-mediated apoptosis [70]. *In vitro*, TRAIL is up-regulated during morphogenesis of MCF-10A mammary epithelial cells [71]. Milk osteoprotegerin, possibly from milk cells and the human mammary epithelial cell line, may contribute to TRAIL-induced inhibition of T cell proliferation [72], enhancing apoptosis by TRAIL.

The intrinsic apoptotic pathway leads to mitochondrial permeabilization of outer membranes and release of apoptogenic proteins into the cytosol [73]. This is controlled by the Bcl-2 family members [73,74]. Mammary gland tissue, expresses a number of different Bcl-2 relatives including bcl-x, bax, bak, bad, bcl-w, bfl-1, bcl-2 as well as the bcl-2 binding protein Bag-1 [74]. Lactaptin, from human milk kappa-casein, suppresses Bcl-2 mRNA expression and downregulates Bcl-2 protein expression [75]. Recombinant lactaptin penetrates cancers and suppresses growth of solid tumours [75]. There is suggestion that milk directly affects epigenetic changes [76]; hence given the role of milk kappa-casein on Bcl-2, could breastfeeding potentially influence genes of the Bcl-2 family proteins to modulate the intrinsic apoptotic pathway? If so, are there mother-to-infant signals for this in specific situations? This is not too far fetched as high levels of TRAIL are maintained in the milk of mothers who deliver prematurely [77]. Gene expression by miRNA is significant as a single miRNA can influence many genes [78]. Additionally, milk-derived exosomal miRNAs may control thymic T regulatory cell maturation [79]. The variable numbers of these micro-nucleotides in the mammary gland, in colostrum and mature milk [78], reflect vibrant gene expression during breastfeeding.

Breastmilk lactoferrin, a possible biomarker for illnesses [80], regulates apoptosis related genes and G1 cyclin-dependent kinases causing cell cycle arrest, targeting for anticancer therapy [81]. It is appreciated that within breastmilk lies cancer immunoprophylaxis and immunotherapy. Lactoferrin may be regulated by nutrition, growth and transcriptional factors and nuclear receptors [81]. At cellular levels, miR214 may influence lactoferrin expression and proapoptosis in mammary epithelial cells [82]. Psychological stresses can influence biological milieu [83]; this in turn can be postulated to possibly affect miRNA mediated processes at the cellular level contributing to anticancer action. If this were true, modifiable factors such as the well being of the mother are deemed essential to nurture for protection from cancers through breastfeeding.

4.9. Mother-to-infant communication

Biocommunication from mother-to-infant through milk microvesicles transfer genetic signals during breastfeeding [84]. Maternal genomic information incorporated into cells of the suckling infant may explain tolerance to maternal allografts in breastfed children [84]. Speculation is that RNA from a healthy wet-nurse through milk microvesicles and incorporation into the genome could even cure clinical manifestations in genetic diseases [84]. Integrated responses of maternal RNA with turnover of intestinal cells and intestinal microbiome to dietary substrates in the neonatal period, indicate that even donor milk, where pasteurization kills its bacterial inoculum from maternal gut, would be imperfect, such milk devoid of dynamic integration [84]. Furthermore, differences in expressed genes among breastfed and bottle fed infants stress the key role of dynamic bioactive breastmilk components with “more intense bimolecular cross talk” and a “co-expression of more genes” in the breast-fed [42]. What else activates “biosignaling”? Perhaps

initiated within the mammary epithelial cell, what is the impact of their function in protection? Much in-depth study needs to be done to throw more light on these events.

5. Discussion

Anticancer potential in breastmilk must be both understood and realised. The many probable causes of cancers necessitate unique, multipronged protection that preempts danger dynamically to "warning signals" for cancer causation, selectively clears cancer nidus and improves immunity of tissues that are nearby. As suggested in this review, such conviction is reasonably present in exclusive breastfeeding. Impossible to entirely emulate by cancer therapy or by specific incorporation into artificial formula, its cost effectiveness, absence of side effects and prized investment simply in maternal health and education are important to reiterate.

The anticancer protection by breastfeeding is possibly contributed to by maternal factors, factors affecting the breastfeeding process and "bio-geno-immuno-nutrition" alluded in this article that are within breastmilk (Figure 1).

It is hypothesised that nutrition and psychosocial issues may influence its potential. Cumulative duration of breastfeeding and the length of an individual feed may also be pivotal. Mothers of term infants are advised to exclusively breastfeed and to empty an entire breast prior to feeding from the other breast as hindmilk is more energy dense due to its higher lipid content [31,56]. It is useful to remember that the interactive interdependence of multinutrients *in vivo* [31,56], and its possible contribution to anticancer action, providing a window of opportunity to eradicate macro and micronutrient malnutrition globally.

Empowered with this knowledge of breastmilk protection, global rates of exclusive breastfeeding would improve significantly because every mother would want to protect her child from cancers. Specifically, in communities where carcinogenic toxins are known to be present at high levels or amongst individuals who are predisposed to higher cancer risks, extensive community and meticulous individual counsel of exclusive and prolonged breastfeeding may well be deemed essential for survival.

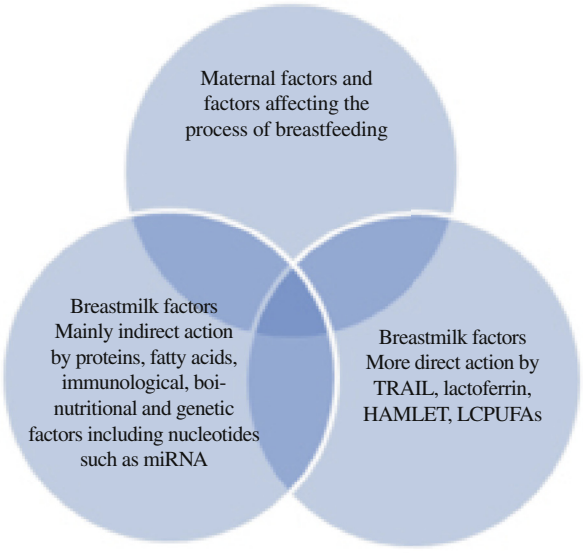

Figure 1. Hypothesis on anticancer protection of breastfeeding. LCPUFAs: Long-chain polyunsaturated fatty acids.

Conflict of interest statement

I declare that I have no conflict of interest.

Acknowledgments

I thank MAHSA University for its support during the writing of this review paper. I also thank the Dean of the Faculty of Medicine of MAHSA University for his support during the writing of this paper.

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