**Name of journal: World Journal of Clinical Oncology**

**ESPS Manuscript NO: 9735**

**Columns: TOPIC HIGHLIGHT**

WJCO 5th Anniversary Special Issues (2): Breast cancer

Modification in the diet can induce beneficial effects against breast cancer

Aragón F *et al*. Diet and breast cancer

Felix Aragón, Gabriela Perdigón, Alejandra de Moreno de LeBlanc

**Felix Aragón, Gabriela Perdigón, Alejandra de Moreno de LeBlanc,** Centro de Referencia para Lactobacilos (CERELA-CONICET), T4000ILC San Miguel de Tucumán, Tucumán, Argentina

**Gabriela Perdigón,** Cátedra de Inmunología, Facultad de Bioquimíca, Química y Farmacia, Universidad Nacional de Tucumán, T4000ILC San Miguel de Tucumán, Tucumán, Argentina

**Author contributions:** All authors participated in the search of the data and writing the work.

**Supported by** Consejo Nacional de Investigaciones Científicas y Técnicas (CONICET); Argentina and Consejo de Investigación de la Universidad Nacional de Tucumán, Argentina, No. CIUNT-26/D442

**Correspondence to:** **Alejandra de Moreno de LeBlanc, PhD,** Centro de Referencia para Lactobacilos (CERELA-CONICET), Chacabuco 145, T4000ILC San Miguel de Tucumán, Tucumán, Argentina. [demoreno@cerela.org.ar](mailto:demoreno@cerela.org.ar)

**Telephone:** +54-381-4310465-129 **Fax:** +54-381-4005600

**Received:** February 25, 2014 **Revised:** May 15, 2014

**Accepted:** May 29, 2014

**Published online:**

**Abstract**

The population tends to consume foods that in addition to their nutritional values can offer some benefits to their health. There are many epidemiological evidences and research studies in animal models suggesting that diet plays an important role in breast cancer prevention or progression. This review summarized some of the relevant researches about nutrition and cancer during the last years, especially in breast cancer. The analysis of probiotics and fermented products containing lactic acid bacteria in cancer prevention and / or treatment was especially discussed. It was observed that a balance of fatty acids similar to those of traditional Mediterranean diet, the consumption of fruits and vegetables, dietary fiber intake, vitamin supplementation are, along with the intake of probiotic products, the most extensively studied by the negative association to breast cancer risk. The consumption of probiotics and fermented products containing lactic acid bacteria was associated to reduce breast cancer risk in some epidemiological studies. The use of animal models showed the modulation of the host’s immune response as one of the important effects associated to the benefices observed with most probiotics. However; future assays in human are very important before the medical community can accept the addition of probiotic or fermented milks containing lactic acid bacteria as supplements for cancer patients.

© 2014 Baishideng Publishing Group Inc. All rights reserved.

**Key words:** Breast cancer; Nutrition; Probiotic; Fermented products

**Core tip:** The population tends to consume foods that in addition to their nutritional values can offer some benefits to their health. In this sense, there are many epidemiological evidences and research studies suggesting that diet plays an important role in breast cancer prevention or progression. This review summarized some of the relevant researches about nutrition and cancer during the last years, especially in breast cancer. The analysis of probiotics and fermented products containing lactic acid bacteria in cancer prevention and / or treatment was especially discussed.

Aragón F, Perdigón G, de Moreno de LeBlanc A. Modification in the diet can induce beneficial effects against breast cancer. *World J Clin Oncol* 2014; In press

**INTRODUCTION**

The population tends to consume foods that in addition to their nutritional values can offer some benefits to their health.

The WHO reported that approximately 30% of cancer deaths are due to five behavioral risk factors and diet, such as high body mass index, low fruit and vegetable intake, lack of physical activity, tobacco use, alcohol use [1]

Breast cancer is a type of tumour in which there are many reports about the influence of nutrition[2,3].

Lactic acid bacteria (LAB) represent a heterogeneous group of microorganisms that are present in the normal diet of many people and also in the gastrointestinal and urogenital tract of animals, and some of these claimed to be probiotics. Probiotics are defined as live microorganisms which when administered in adequate amounts, confer a health benefit on the host[4]. These microorganisms and fermented foods containing LAB were growing in their popularity due to increasing numbers of studies proving that certain strains present health promoting properties, among them the prevention or treatment in the early stages of some types of cancers[5,6].

The use of experimental animal models has a number of advantages in that the environmental conditions and genetics can be either controlled or defined. The value of the models is the insight they can provide into the complex, multi-faceted processes and mechanisms that can result in cancer development. *In vitro* assays are also important to understand the mechanisms of action involved in the LAB or other dietary effects. However, the application of dietary modifications against cancer needs to be ultimately tested in human trials.

This review summarizes some of the relevant researches about nutrition and cancer during the last years, especially in breast cancer. The analysis of probiotics and fermented products containing LAB in cancer prevention and / or treatment will be discussed separately, with emphasis in the possible mechanisms involved.

**NUTRITION AND CANCER**

Several studies have been demonstrated a relationship (either beneficial or harmful) between diet and development of different types of cancer[7-9]. High fat diet, fiber consumption and vitamins are among dietary habits more reported by their association with cancer along with probiotic supplements, that will be discussed in a separately section.

Calorie restriction without malnutrition was associated to cancer prevention[10]. This effect was related to the reduction in the activity of pro-aging pathways, inflammation in the pre-cancerous cells, and to the increase in the apoptosis of damaged cells.

Several epidemiological studies have been shown the relationship between increase consumption of high fat diet and the risk to develop cancer, such as kidney, stomach, lung, esophagus, colon and breast cancer. Colorectal cancer (CRC) is a tumour for which there are many studies that associate obesity with increased risk, especially in men[11]. The exact mechanisms of this relationship are still unknown, but metabolic syndrome, insulin resistance[12], modifications in levels of adipocytokines[13] seem to be implicated. The role of the microbiota in the maintenance of intestinal homeostasis, and it relationship with intestinal inflammation and colon carcinogenesis was also extensively studied[14-16].

Dietary fat intake was also related to risk of ovarian cancer. It was suggested that higher intake of omega-3 may be protective, whereas high consumption of trans fat may increase risk of this cancer[17].

The fiber consumption is another important component of the diet that was associated inversely with cancer risk, such as CRC[18], nasopharyngeal carcinoma[18], oesophageal cancer[20].

The consumption of vitamins and mineral supplements are commonly used to prevent chronic diseases such as cancer. It was demonstrated that vitamin C (ascorbate) was selectively toxic to some types of tumor cells[21]. Recently, it was reported a case in which the consumption of this vitamin decreased chemotherapy associated side effects[22]. As regard to vitamin D, Bikle [23] revised its relationship with different cancers and described that animal and cellular studies supported a role for vitamin D in the prevention and treatment of cancer, but the same conclusion was not arrived from clinical studies.

Folate is essential for DNA synthesis and methylation and its role against cancer is controversial, even against one type of cacer, such as for prostate cancer[24]. Some studies implicated folates with tumour progression, such as the work reported by Dixon *et al*[25] showing evidences that folate intake affects ovarian cancer survival. On other hand, the chemopreventive effect of folic acid was evaluated *in vivo* using rat as model for liver carcinogenesis. This effect was observed in association with tributyrin and was related to the potential to inhibit tumour angiogenesis[26]. A recent review and meta-analysis showed that dietary folate intake was associated with a decreased risk of esophageal and pancreatic cancer, but not gastric cancer[27].

**NUTRTION AND BREAST CANCER**

There are many epidemiological evidences and research studies in human and animals suggesting that diet plays an important role in breast cancer prevention or progression[2,3]. Diet represents one of the most modifiable risk factors for breast cancer[28]. Changes in the dietary patterns are not only related to less risk but also patients diagnosed and treated for breast cancer who pursue healthier dietary habits can improve their health and survival.

The relationship between obesity and breast cancer was reviewed in many articles because the high incidence and prevalence of both diseases. Overweight and obesity at the time of diagnosis were associated with a worse prognosis in breast cancer patients[29]. A study in Italy showed that a diet high in glycemic load was associated with increased breast cancer risk[30].

A systematic review showed that there are some strategies to prevent weight gain that may decrease the risk of breast cancer or improve cancer outcomes in women with breast cancer[31].

de Lorgeril and Salen suggested that a high omega-3 to omega-6 ratio, such as the case of traditional Mediterranean diet, reduce the risk of cancer, especially breast cancer[32]. A cohort study of breast cancer survivors showed that intake of marine fatty acids EPA (eicosapentaenoic) plus DHA (Docosahexaenoic) was associated with improved prognosis[33]**.** Omega-3 fatty acid, in particular EPA and DHA found principally in oily fish have been demonstrated to exert anti-angiogenic effects inhibiting production of different angiogenic mediators[34]. The beneficial effect of EPA and DHA intakes was also associated by reducing inflammation through different mechanisms such as the suppression of NF-κB, and the alteration of the plasma membrane micro-organization (lipid rafts)[35]**.**

Canola oil has also been associated with a reduced risk of breast cancer. The inhibition of cancer cells *in vitro* and the reduction of tumour volume in rats with chemical induced mammary tumour that consumed canola oil was reported[36]. It was also suggested that canola oil can be used as prenatal nutritional strategies to reduce breast cancer risk in humans[37]. This suggestion was based in results obtained *in vivo* using a chemical induced mammary tumour in offspring rats of canola-fed dams. These animals showed significantly decreased tumor volume with increased survival rate comparing to the control group whose mothers received control diet with soybean oil during pregnancy and lactation.

Diets rich in fruits and vegetables are also implicated in breast cancer risk reduction. A meta-analysis including fifteen prospective studies that reported decreased risk of breast cancer associated with fruit and vegetable intake, showed that high intake of fruits, and fruits and vegetables combined can be associated with reduction in risk of breast cancer[38]. Similar results were obtained in a meta-analysis of prospective studies of blood concentrations of carotenoids and breast cancer risk[39]. Carotenoid concentrations in blood can be used as biomarkers of fruit and vegetable intake and in this sense; the authors showed that blood concentrations of carotenoids were strongly associated with reduced breast cancer risk. Recently, an inverse association between citrus fruits intake and the risk of breast cancer was suggested[40].

Dietary fiber intake was also inversely associated with breast cancer risk[41]. The ingestion of dietary phytoestrogens may increase risk of estrogen receptor alpha (ERα)-positive breast cancer and this effect was associated with their estrogenic effects observed *in vitro* and *in vivo*. The proliferative effect of soy isoflavones was mainly observed in animal models of tumours. However; paradoxically, consumption of phytoestrogens has also been associated with reduced risk of breast cancer[42-46]. This controversy with regard to the effect of soy isoflavones on breast cancer risk was analyzed and it was demonstrated that soy isoflavone phase II metabolism differs between humans and rodents, and this should be taken in count to understand the value of the use of these rodents for investigate the effects of isoflavones in humans[47]. Epidemiologic data indicate that soy intake is associated with a decreased breast cancer risk in Asia. A systematic review among women showed the possible protective effect of isoflavones on breast cancer risk[48]. It was also demonstrated that soy isoflavone intake was associated with lower risk of recurrence among post-menopausal patients with breast cancer and those who were receiving adjuvant endocrine therapy[49].

The understandings of the hormonal and non-hormonal mechanisms by which isoflavones can exert the beneficial effects were subject of many researches. The chemical structure of soy isoflavones is similar to that of estrogens. They are therefore considered to be possible selective estrogen receptor modulators (SERMs), which may bind to estrogen receptors and selectively stimulate or inhibit estrogen-like action in various tissues[50]. It was demonstrated that sera of adult mice consuming soy isoflavone genistein (GEN) or blueberry (BB) polyphenol-containing diet altered mammosphere formation *in vitro* using receptor-positive and estrogen receptor-negative human breast cancer cell lines[51]. Recently, this group demonstrated that breast cancer prevention by GEN was related to the regulation of mammary adiposity[52]. The cytotoxic action of GEN against breast cancer cells involved mobilization of endogenous copper ions and generation of reactive oxygen species[53].

Vitamin supplementation is another strategy, as was explained above, used to reduce cancer risk. With regard breast cancer, there was no found clear evidence of cancer prevention for vitamin supplements[54]. Folates and folic acid were evaluated in breast cancer patients and also *in vivo* using animal models, and as was explained, the role of folates is controversial. There are epidemiological studies suggesting an inverse association between folate status and the risk of breast cancer[55,56]. Some studies have also suggested that with alcohol consumption, folate supplementation reduces the risk of breast cancer[57,58]. The beneficial effect associated to folate intake in some populations was associated to genetic polymorphisms of folate-metabolizing enzyme, methylenetetrahydrofolate reductase (MTHFR)[59]. A population-based case-control study in Saudi Arabia showed that the MTHFR C677T polymorphism may modify the association between dietary folate intake and breast cancer risk[60]. Similar results were obtained from the Shanghai Breast Cancer Study[61] and in a case-control study in the Jiangsu Province of China[62]. A recent work suggested that intake of natural folates can be inversely associated with breast cancer risk, but this association may vary by race, menopausal status or estrogen receptor status[63]. The authors also observed an increased risk in European American women with the highest intake of synthetic folate from fortified foods. In this sense, a systematic review analyzed the effect of high folate intake post fortification, especially when folic acid was used, and demonstrated a higher risk of breast cancer in these populations[64]. The authors showed the need to be cautious with high intakes of folic acid, especially in countries with mandatory food fortification, as Chile.

Animal models were used to understand the mechanisms by which folates and folic acid exert their effects, especially in breast cancer patients. Mammary tumors were chemically induced in rats and then, the animals received a diet containing different levels of folic acid[65]. Folic acid supplementation was associated with significantly higher volume of mammary tumors and increased expression of BAX, PARP, and HER.

Riboflavin intake was also analyzed and an inverse association with breast cancer risk was documented[66].

Selenium (Se) is an essential micronutrient having high anticancer properties in different animal models[67,68]. As regard to breast cancer, it was demonstrated, using an animal model, that organic Se supplementation may reduce breast cancer metastasis, while selenite exacerbated it[69].

Another dietary component (even though is minor in our diet) that was reported as effective against cancer is the inorganic sulfur. It was showed that inorganic sulfur significantly decreased proliferation of MDA-MB-231 human breast[70]. This effect was due to reduction of ErbB2 and ErbB3 protein and mRNA expression, affecting the he ErbB-Akt pathway. Previously, it was reported that inorganic sulfur reduced cancer cell motility and invasion by inhibiting activity and mRNA expression of matrix metalloproteases (MMP-2 and MMP-9)[71].

**PROBIOTICS AND CANCER**

Probiotic microorganisms and fermented foods containing LAB have been growing in popularity due to increasing numbers of studies proving that certain strains present health promoting properties, among them the prevention or treatment in the early stages of some types of cancers[5,6,72].

The effects of probiotics and fermented products on intestinal disorders have been the most extensively studied considering that these microorganisms enter the organism orally and can positively modulate the intestinal microbiota involved in many of these disorders. The benefits of probiotics on the gut immune system in the prevention of cancer has also been previously described[73,74]. There are many different mechanisms by which probiotics and fermented products containing viable LAB may lower the risk of colon cancer; among them, the modulation of the intestinal microbiota[75-80], the inactivation of carcinogenic compound[81-83], anti-oxidant effects[84-86], and the modulations of the host’s immune response[87-89]. Recently, the administration of probiotic Dahi containing *Lactobacillus* (*L.*) *acidophilus* LaVK2 and *Bifidobacterium bifidum* BbVK3 alone or in combination of piroxicam showed anti-neoplastic and anti-proliferative activities in a model of DMH-induced CRC in rats[90].

It was also demonstrated that oral administration of probiotic microorganisms can influence mucosal sites different to the intestine due to the existence of the common mucosal immune system. In this sense, after intestinal stimulation, both B and T cells can migrate from Peyer’s patches to mucosal membranes of the respiratory, gastrointestinal and genito-urinary tract, as well as to exocrine glands such as the lacrimal, salivary, mammary and prostatic glands[91]. The oral administration of *L. casei* CRL 431 to mice induced an immune stimulation not only at the intestinal level, but also in bronchus and mammary glands[92].

Beneficial effects of probiotic LAB administration were reported for non-intestinal tumors. The antitumor activity of *L. casei* CRL 431 was studied against a fibrosarcoma induced by methylcholantrene in mice. The administration of the probiotic strain inhibited tumor growth in a dose-dependent form[93,94], stimulated the immune system with high levels of macrophage activation (the main infiltrative cells in the tumor), high levels of TNFα and with a remarkable decrease in tumor volume.

The effect of LAB or fermented products containing these microorganisms in non-intestinal tumours reported during the last years (2011-2014) were obtained searching the words “probiotc and cancer” in PubMed database.

It was reported the beneficial effect against cervical cancer. A pilot study suggested that probiotic promotes the clearance of HPV-related cytological abnormalities[95].Common vaginal lactobacilli exerted cytotoxic effects on cervical tumour cells independently of pH and lactate[96].*L. casei* displaying E7 antigen at its surface protected mice against human papillomavirus type 16-induced tumours[97].

As regard hepatocarcinoma, the administration of probiotic fermented milk containing *L. rhamnosus* GG and, *L. casei* strain Shirota with chlorophyllin reduced liver pre-carcinogenic events in rat AFB1 induced liver carcinogenesis. This effect was attributed to an increased antioxidant status and decreased expression of oncogenes[98].

The beneficial effects of LAB were also reported in animal models of oral cancer[99], and skin carcinogenesis[100].

**PROBIOTICS AND BREAST CANCER**

Breast cancer is another tumour in which there are reports about the beneficial effects of probiotic administration. Many reports analyzed, as was explained above, the association of soy based products and especially soy isoflavones with breast cancer risk. In this context, soy isoflavone ingestion was studied accompanied with the co-administration of probiotic bacteria, and it was observed that high concentrations of probiotics may alter the metabolism of isoflavones[101]. Recently, the consumption of beverages containing *L. casei* Shirota and soy isoflavone was inversely associated with the incidence of breast cancer in Japanese women when they were consumed regularly since adolescence[102]. The cooperative prevention mechanism of soymilk and *L. casei* Shirota was evaluated using a rat carcinogenic model. It was observed that soymilk prevented the development of mammary tumors and that *L. casei* Shirota suppressed tumor growth[103].

In the West diet, fermented milks are more common as probiotic foods than soy based products. Milks fermented by different LAB and bifidobacteria strains (*B. infantis*, *B. bifidum*, *B. animalis*, *L. acidophilus* and *L. paracasei*) were evaluated *in vit*ro, and the inhibition of the growth of a breast cancer cell line was reported[104]. Other studies performed in humans, showed a negative association between yogurt consumption and breast cancer development[105]. van't Veer *et al*[106] showed similar results in The Netherlands, and suggested that these effects would be related to changes in the intestinal microbiota (which could alter the metabolism of estrogen) and to the modulation on the immune system.

In addition to containing LAB, fermented milks can possess non-bacterial components produced during fermentation that may contribute to their anti-tumor activities[107]. Thus, cultured dairy products can be proposed to inhibit the growth of many types of cancers, including breast tumors. In this context, milk fermented by *L. helveticus* R389 (a strain with high proteolytic activity) was studied comparatively with the milk fermented by a proteolytic deficient mutant, and both were able to delay tumour growth in an experimental breast cancer model using BALB/c mice[108,109]. This effect was related to the immunoregulatory capacity of the fermented milks that decreased IL-6 levels, modulating the relationship between immune and endocrine systems. The important increase of IL-10 in mice fed with milk fermented by *L. helveticus* R389 could explain the difference between both fermented milks, attributed principally to the components released into the milk after the fermentation with the proteolytic strain, where the regulation of the immune response was observed in serum, mammary gland and also in the tumour infiltrating immune cells.

Kefir was another fermented product also evaluated in a breast cancer model in mice. Kefir and its cell-free fraction (KF) possess several substances that can exert beneficial effects on the immune system and prevent certain types of cancer[110]. It was observed that mice receiving 2 d cyclical feeding with whole kefir diminished tumour growth, and the same cyclical feeding with KF showed the most significant delay of the tumour growth[111]. This effect was related principally to a decrease in IL-6. KF caused not only a decrease of this cytokine but also a regulatory response with increased levels of IL-10 in all the samples studied. The results also demonstrated that the most important effect in this tumour model was due to substances released during milk fermentation (and not the microorganisms themselves)[112].

Table 1 summarizes the effects reported for different LAB against breast cancer during the last years (2012-2014).

It was reported that *L. acidophilus* isolated from traditional home-made yogurt and also from neonatal stool induced a significant decrease in breast tumour growth pattern using a mouse model[113]. This effect was associated to the alteration of cytokine production into a Th1 protective pattern.

*L. casei spp. casei* ATCC 39392 was also analyzed in a model of invasive ductal carcinoma in mice, and its administration decreased the growth rate of tumor and prolonged the survival of the animals. This effect was associated to the improvement of the host immune response by inducing Th1 cytokine profile and natural killer cells[114].

The administration of selenium nanoparticle-enriched *L. plantarum* induced an efficient immune response in 4T1 breast cancer bearing mice. This effect was caused by the elevation of the pro-inflammatory cytokines IFN-γ, TNF-α and IL-2 levels and increased NK cell activity[115].

The importance of the stimulation of host immune cells by LAB and their beneficial effect against mammary carcinoma was analyzed using two mice models[116]. In one model, mice were fed a Westernized chow increasing risk for development of mammary tumors. The other model consisted of FVB strain erbB2 (HER2) mutant mice, genetically susceptible to mammary tumors. Animals received *L. reuteri* ATCC-PTA-6475 in drinking water. It was observed that LAB oral supplementation inhibited features of mammary neoplasia in both models. The protective mechanism was associated to triggered CD4+CD25+ lymphocytes because when they were isolated and transplanted into other subjects conferred anti-cancer protection in the cell recipient animals.

Recently, our research group evaluated the effect of milk fermented by the probiotic bacterium *L. casei* CRL 431 on a murine breast cancer model. It was observed that the administration of this probiotic fermented milk stimulated the immune response against this breast tumour, avoiding or delaying its growth when it was preventively administrated and also when the administration started after tumour cells injection[117].

**CONCLUSION**

There are many epidemiological evidences and research studies in animal models suggesting that diet plays an important role in breast cancer prevention or progression. A balance of fatty acids similar to those of traditional Mediterranean diet, the consumption of fruits and vegetables, dietary fiber intake, vitamin supplementation are, along with probiotic products, the most extensively studied. Although controversial data about isoflavones, epidemiological studies showed that the intake of soy based products in Asia was associated with decrease of breast cancer risk.

Probiotics and fermented products containing LAB have awakened the interest of many researches related to cancer and especially with breast cancer. Some epidemiological studies showed negative association between the consumption of these products and breast cancer development. Animal models were used to understand the possible mechanisms by which probiotic can exert the beneficial effects, and the modulation of the host’s immune response was associated to the effects observed with most probiotics.

However, there are not enough human trials where the application of probiotics as biotherapeutics against breast cancer was tested. These assays are very important before the medical community can accept the addition of probiotic or fermented milks containing LAB as supplements for cancer patients.

**REFERENCES**

1 **WHO**. 2014. Cancer: Fact sheet N°297. Available from: http: //www.who.int/mediacentre/factsheets/fs297/en/

2 **Chajès V**, Romieu I. Nutrition and breast cancer. *Maturitas* 2014; **77**: 7-11 [PMID: 24215727 DOI: 10.1016/j.maturitas]

3 **Mohammadi S**, Sulaiman S, Koon PB, Amani R, Hosseini SM. Association of nutritional status with quality of life in breast cancer survivors. *Asian Pac J Cancer Prev* 2013; **14**: 7749-7755 [PMID: 24460363]

4 **FAO/WHO 2001**. Evaluation of health and nutritional properties of powder milk and live lactic acid bacteria. Food and Agriculture Organization of the United Nations and World Health Organization Expert Consultation Report Available from http: //www.fao.org/ag/agn/agns/micro\_probiotics\_en.asp.

5 **Shida K**, Nomoto K. Probiotics as efficient immunopotentiators: translational role in cancer prevention. *Indian J Med Res* 2013; **138**: 808-814 [PMID: 24434333]

6 **de Moreno de Leblanc A**, Perdigón G. The application of probiotic fermented milks in cancer and intestinal inflammation. *Proc Nutr Soc* 2010; **69**: 421-428 [PMID: 20550747 DOI: 10.1017/S002966511000159X]

7 **Baena Ruiz R**, Salinas Hernández P. Diet and cancer: risk factors and epidemiological evidence. *Maturitas* 2014; **77**: 202-208 [PMID: 24374225]

8 **Pericleous M**, Rossi RE, Mandair D, Whyand T, Caplin ME. Nutrition and pancreatic cancer. *Anticancer Res* 2014; **34**: 9-21 [PMID: 24403441]

9 **Pericleous M**, Mandair D, Caplin ME. Diet and supplements and their impact on colorectal cancer. *J Gastrointest Oncol* 2013; **4**: 409-423 [PMID: 24294513]

10 **Longo VD**, Fontana L. Calorie restriction and cancer prevention: metabolic and molecular mechanisms. *Trends Pharmacol Sci* 2010; **31**: 89-98 [PMID: 20097433 DOI: 10.1016/j.tips.2009.11.004]

11 **Bardou M**, Barkun AN, Martel M. Republished: obesity and colorectal cancer. *Postgrad Med J* 2013; **89**: 519-533 [PMID: 23955330 DOI: 10.1136/postgradmedj-2013-304701rep]

12 **Liu JJ**, Druta M, Shibata D, Coppola D, Boler I, Elahi A, Reich RR, Siegel E, Extermann M. Metabolic syndrome and colorectal cancer: is hyperinsulinemia/insulin receptor-mediated angiogenesis a critical process? *J Geriatr Oncol* 2014; **5**: 40-48 [PMID: 24484717 DOI: 10.1016/j.jgo.2013.11.004]

13 **Comstock SS**, Hortos K, Kovan B, McCaskey S, Pathak DR, Fenton JI. Adipokines and obesity are associated with colorectal polyps in adult males: a cross-sectional study. *PLoS One* 2014; **9**: e85939 [PMID: 24465801 DOI: 10.1371/journal.pone.0085939]

14 **Zackular JP**, Baxter NT, Iverson KD, Sadler WD, Petrosino JF, Chen GY, Schloss PD. The gut microbiome modulates colon tumorigenesis. *MBio* 2013; **4**: e00692-e00613 [PMID: 24194538 DOI: 10.1128/mBio.00692-13]

15 **Liu Z**, Cao AT, Cong Y. Microbiota regulation of inflammatory bowel disease and colorectal cancer. *Semin Cancer Biol* 2013; **23**: 543-552 [PMID: 24071482 DOI: 10.1016/j.semcancer.2013.09.002]

16 **Konstantinov SR**, Kuipers EJ, Peppelenbosch MP. Functional genomic analyses of the gut microbiota for CRC screening. *Nat Rev Gastroenterol Hepatol* 2013; **10**: 741-745 [PMID: 24042452 DOI: 10.1038/nrgastro.2013.178]

17 **Merritt MA**, Cramer DW, Missmer SA, Vitonis AF, Titus LJ, Terry KL. Dietary fat intake and risk of epithelial ovarian cancer by tumour histology. *Br J Cancer* 2014; **110**: 1392-1401 [PMID: 24473401 DOI: 10.1038/bjc.2014.16]

18 **Ben Q**, Sun Y, Chai R, Qian A, Xu B, Yuan Y. Dietary fiber intake reduces risk for colorectal adenoma: a meta-analysis. *Gastroenterology* 2014; **146**: 689-699.e6 [PMID: 24216326 DOI: 10.1053/j.gastro.2013.11.003]

19 **Bidoli E**, Pelucchi C, Polesel J, Negri E, Barzan L, Franchin G, Franceschi S, Serraino D, De Paoli P, La Vecchia C, Talamini R. Fiber intake and risk of nasopharyngeal carcinoma: a case-control study. *Nutr Cancer* 2013; **65**: 1157-1163 [PMID: 24098992 DOI: 10.1080/01635581.2013.828088]

20 **Tang L**, Xu F, Zhang T, Lei J, Binns CW, Lee AH. Dietary fibre intake associated with reduced risk of oesophageal cancer in Xinjiang, China. *Cancer Epidemiol* 2013; **37**: 893-896 [PMID: 24035237 DOI: 10.1016/j.canep.2013.08.012]

21 **Park S**. The effects of high concentrations of vitamin C on cancer cells. *Nutrients* 2013; **5**: 3496-3505 [PMID: 24022818 DOI: 10.3390/nu5093496]

22 **Carr AC**, Vissers MC, Cook J. Relief from cancer chemotherapy side effects with pharmacologic vitamin C. *N Z Med J* 2014; **127**: 66-70 [PMID: 24481389]

23 **Bikle DD**. Vitamin D and cancer: the promise not yet fulfilled. *Endocrine* 2014; **46**: 29-38 [PMID: 24402695 DOI: 10.1007/s12020-013-0146-1]

24 **Rycyna KJ**, Bacich DJ, O'Keefe DS. Opposing roles of folate in prostate cancer. *Urology* 2013; **82**: 1197-1203 [PMID: 23992971 DOI: 10.1016/j.urology.2013.07.012]

25 **Dixon SC**, Ibiebele TI, Protani MM, Beesley J, deFazio A, Crandon AJ, Gard GB, Rome RM, Webb PM, Nagle CM. Dietary folate and related micronutrients, folate-metabolising genes, and ovarian cancer survival. *Gynecol Oncol* 2014; **132**: 566-572 [PMID: 24368279 DOI: 10.1016/j.ygyno.2013.12.025]

26 **Guariento AH**, Furtado KS, de Conti A, Campos A, Purgatto E, Carrilho J, Shinohara EM, Tryndyak V, Han T, Fuscoe JC, Ross SA, Beland FA, Pogribny IP, Moreno FS. Transcriptomic responses provide a new mechanistic basis for the chemopreventive effects of folic acid and tributyrin in rat liver carcinogenesis. *Int J Cancer* 2014; **135**: 7-18 [PMID: 24302446 DOI: 10.1002/ijc.28642]

27 **Tio M**, Andrici J, Cox MR, Eslick GD. Folate intake and the risk of upper gastrointestinal cancers: a systematic review and meta-analysis. *J Gastroenterol Hepatol* 2014; **29**: 250-258 [PMID: 24224911 DOI: 10.1111/jgh.12446]

28 **Thomson CA**. Diet and breast cancer: understanding risks and benefits. *Nutr Clin Pract* 2012; **27**: 636-650 [PMID: 22948801 DOI: 10.1177/0884533612454302]

29 **Rodríguez San Felipe MJ**, Aguilar Martínez A, Manuel-y-Keenoy B. [Influence of body weight on the prognosis of breast cancer survivors; nutritional approach after diagnosis]. *Nutr Hosp* 2013; **28**: 1829-1841 [PMID: 24506358 DOI: 10.3305/nutr]

30 **Sieri S**, Pala V, Brighenti F, Agnoli C, Grioni S, Berrino F, Scazzina F, Palli D, Masala G, Vineis P, Sacerdote C, Tumino R, Giurdanella MC, Mattiello A, Panico S, Krogh V. High glycemic diet and breast cancer occurrence in the Italian EPIC cohort. *Nutr Metab Cardiovasc Dis* 2013; **23**: 628-634 [PMID: 22497978 DOI: 10.1016/j.numecd.2012.01.001]

31 Comparative effectiveness of strategies to prevent weight gain among women with and at risk for breast cancer: a systematic review. *Springerplus* 2013; **2**: 277 [PMID: 23853751]

32 **de Lorgeril M**, Salen P. New insights into the health effects of dietary saturated and omega-6 and omega-3 polyunsaturated fatty acids. *BMC Med* 2012; **10**: 50 [PMID: 22613931 DOI: 10.1186/1741-7015-10-50]

33 **Patterson RE**, Flatt SW, Newman VA, Natarajan L, Rock CL, Thomson CA, Caan BJ, Parker BA, Pierce JP. Marine fatty acid intake is associated with breast cancer prognosis. *J Nutr* 2011; **141**: 201-206 [PMID: 21178081 DOI: 10.3945/jn.110.128777]

34 **Spencer L**, Mann C, Metcalfe M, Webb M, Pollard C, Spencer D, Berry D, Steward W, Dennison A. The effect of omega-3 FAs on tumour angiogenesis and their therapeutic potential. *Eur J Cancer* 2009; **45**: 2077-2086 [PMID: 19493674 DOI: 10.1016/j.ejca.2009.04.026]

35 **Chapkin RS**, Kim W, Lupton JR, McMurray DN. Dietary docosahexaenoic and eicosapentaenoic acid: emerging mediators of inflammation. *Prostaglandins Leukot Essent Fatty Acids* 2009; **81**: 187-191 [PMID: 19502020 DOI: 10.1016/j.plefa.2009.05.010]

36 **Cho K**, Mabasa L, Fowler AW, Walsh DM, Park CS. Canola oil inhibits breast cancer cell growth in cultures and in vivo and acts synergistically with chemotherapeutic drugs. *Lipids* 2010; **45**: 777-784 [PMID: 20730604 DOI: 10.1007/s11745-010-3462-8]

37 **Mabasa L**, Cho K, Walters MW, Bae S, Park CS. Maternal dietary canola oil suppresses growth of mammary carcinogenesis in female rat offspring. *Nutr Cancer* 2013; **65**: 695-701 [PMID: 23859037 DOI: 10.1080/01635581.2013.789539]

38 **Aune D**, Chan DS, Vieira AR, Rosenblatt DA, Vieira R, Greenwood DC, Norat T. Fruits, vegetables and breast cancer risk: a systematic review and meta-analysis of prospective studies. *Breast Cancer Res Treat* 2012; **134**: 479-493 [PMID: 22706630 DOI: 10.1007/s10549-012-2118-1]

39 **Aune D**, Chan DS, Vieira AR, Navarro Rosenblatt DA, Vieira R, Greenwood DC, Norat T. Dietary compared with blood concentrations of carotenoids and breast cancer risk: a systematic review and meta-analysis of prospective studies. *Am J Clin Nutr* 2012; **96**: 356-373 [PMID: 22760559 DOI: 10.3945/ajcn.112.034165]

40 **Song JK**, Bae JM. Citrus fruit intake and breast cancer risk: a quantitative systematic review. *J Breast Cancer* 2013; **16**: 72-76 [PMID: 23593085 DOI: 10.4048/jbc.2013.16.1.72]

41 **Aune D**, Chan DS, Greenwood DC, Vieira AR, Rosenblatt DA, Vieira R, Norat T. Dietary fiber and breast cancer risk: a systematic review and meta-analysis of prospective studies. *Ann Oncol* 2012; **23**: 1394-1402 [PMID: 22234738 DOI: 10.1093/annonc/mdr589]

42 **Magee PJ**, Rowland I. Soy products in the management of breast cancer. *Curr Opin Clin Nutr Metab Care* 2012; **15**: 586-591 [PMID: 23075937 DOI: 10.1097/MCO.0b013e328359156f]

43 **Chi F**, Wu R, Zeng YC, Xing R, Liu Y, Xu ZG. Post-diagnosis soy food intake and breast cancer survival: a meta-analysis of cohort studies. *Asian Pac J Cancer Prev* 2013; **14**: 2407-2412 [PMID: 23725149]

44 **Nechuta SJ**, Caan BJ, Chen WY, Lu W, Chen Z, Kwan ML, Flatt SW, Zheng Y, Zheng W, Pierce JP, Shu XO. Soy food intake after diagnosis of breast cancer and survival: an in-depth analysis of combined evidence from cohort studies of US and Chinese women. *Am J Clin Nutr* 2012; **96**: 123-132 [PMID: 22648714 DOI: 10.3945/ajcn.112.035972]

45 **Kang HB**, Zhang YF, Yang JD, Lu KL. Study on soy isoflavone consumption and risk of breast cancer and survival. *Asian Pac J Cancer Prev* 2012; **13**: 995-998 [PMID: 22631686]

46 **Messina M**, Wu AH. Perspectives on the soy-breast cancer relation. *Am J Clin Nutr* 2009; **89**: 1673S-1679S [PMID: 19339397 DOI: 10.3945/ajcn.2009.26736V]

47 **Setchell KD**, Brown NM, Zhao X, Lindley SL, Heubi JE, King EC, Messina MJ. Soy isoflavone phase II metabolism differs between rodents and humans: implications for the effect on breast cancer risk. *Am J Clin Nutr* 2011; **94**: 1284-1294 [PMID: 21955647 DOI: 10.3945/ajcn.111.019638]

48 **Nagata C**, Mizoue T, Tanaka K, Tsuji I, Tamakoshi A, Matsuo K, Wakai K, Inoue M, Tsugane S, Sasazuki S. Soy intake and breast cancer risk: an evaluation based on a systematic review of epidemiologic evidence among the Japanese population. *Jpn J Clin Oncol* 2014; **44**: 282-295 [PMID: 24453272 DOI: 10.1093/jjco/hyt203]

49 **Kang X**, Zhang Q, Wang S, Huang X, Jin S. Effect of soy isoflavones on breast cancer recurrence and death for patients receiving adjuvant endocrine therapy. *CMAJ* 2010; **182**: 1857-1862 [PMID: 20956506 DOI: 10.1503/cmaj.091298]

50 **Setchell KD**. Soy isoflavones--benefits and risks from nature's selective estrogen receptor modulators (SERMs). *J Am Coll Nutr* 2001; **20**: 354S-362S; discussion 381S-383S [PMID: 11603644]

51 **Montales MT**, Rahal OM, Kang J, Rogers TJ, Prior RL, Wu X, Simmen RC. Repression of mammosphere formation of human breast cancer cells by soy isoflavone genistein and blueberry polyphenolic acids suggests diet-mediated targeting of cancer stem-like/progenitor cells. *Carcinogenesis* 2012; **33**: 652-660 [PMID: 22219179 DOI: 10.1093/carcin/bgr317]

52 **Montales MT**, Rahal OM, Nakatani H, Matsuda T, Simmen RC. Repression of mammary adipogenesis by genistein limits mammosphere formation of human MCF-7 cells. *J Endocrinol* 2013; **218**: 135-149 [PMID: 23645249 DOI: 10.1530/JOE-12-0520]

53 **Ullah MF**, Ahmad A, Zubair H, Khan HY, Wang Z, Sarkar FH, Hadi SM. Soy isoflavone genistein induces cell death in breast cancer cells through mobilization of endogenous copper ions and generation of reactive oxygen species. *Mol Nutr Food Res* 2011; **55**: 553-559 [PMID: 21462322 DOI: 10.1002/mnfr.201000329]

54 Vitamin supplement consumption and breast cancer risk: a review. *Ecancermedicalscience* 2013; **7**: 365 [PMID: 24171049 DOI: 10.3332/ecancer.2013.365]

55 **Shrubsole MJ**, Jin F, Dai Q, Shu XO, Potter JD, Hebert JR, Gao YT, Zheng W. Dietary folate intake and breast cancer risk: results from the Shanghai Breast Cancer Study. *Cancer Res* 2001; **61**: 7136-7141 [PMID: 11585746]

56 **Lajous M**, Lazcano-Ponce E, Hernandez-Avila M, Willett W, Romieu I. Folate, vitamin B(6), and vitamin B(12) intake and the risk of breast cancer among Mexican women. *Cancer Epidemiol Biomarkers Prev* 2006; **15**: 443-448 [PMID: 16537699 DOI: 10.1158/1055-9965.EPI-05-0532]

57 **Sellers TA**, Vierkant RA, Cerhan JR, Gapstur SM, Vachon CM, Olson JE, Pankratz VS, Kushi LH, Folsom AR. Interaction of dietary folate intake, alcohol, and risk of hormone receptor-defined breast cancer in a prospective study of postmenopausal women. *Cancer Epidemiol Biomarkers Prev* 2002; **11**: 1104-1107 [PMID: 12376515]

58 **Sellers TA**, Kushi LH, Cerhan JR, Vierkant RA, Gapstur SM, Vachon CM, Olson JE, Therneau TM, Folsom AR. Dietary folate intake, alcohol, and risk of breast cancer in a prospective study of postmenopausal women. *Epidemiology* 2001; **12**: 420-428 [PMID: 11416780]

59 **Beilby J**, Ingram D, Hähnel R, Rossi E. Reduced breast cancer risk with increasing serum folate in a case-control study of the C677T genotype of the methylenetetrahydrofolate reductase gene. *Eur J Cancer* 2004; **40**: 1250-1254 [PMID: 15110890 DOI: 10.1016/j.ejca.2004.01.026]

60 **Alshatwi AA**. Breast cancer risk, dietary intake, and methylenetetrahydrofolate reductase (MTHFR)single nucleotide polymorphisms. *Food Chem Toxicol* 2010; **48**: 1881-1885 [PMID: 20417243 DOI: 10.1016/j.fct.2010.04.028]

61 **Shrubsole MJ**, Gao YT, Cai Q, Shu XO, Dai Q, Hébert JR, Jin F, Zheng W. MTHFR polymorphisms, dietary folate intake, and breast cancer risk: results from the Shanghai Breast Cancer Study. *Cancer Epidemiol Biomarkers Prev* 2004; **13**: 190-196 [PMID: 14973091 DOI: 10.1158/1055-9965.EPI-03-0273]

62 **Gao CM**, Tang JH, Cao HX, Ding JH, Wu JZ, Wang J, Liu YT, Li SP, Su P, Matsuo K, Takezaki T, Tajima K. MTHFR polymorphisms, dietary folate intake and breast cancer risk in Chinese women. *J Hum Genet* 2009; **54**: 414-418 [PMID: 19557016 DOI: 10.1038/jhg.2009.57]

63 **Gong Z**, Ambrosone CB, McCann SE, Zirpoli G, Chandran U, Hong CC, Bovbjerg DH, Jandorf L, Ciupak G, Pawlish K, Lu Q, Hwang H, Khoury T, Wiam B, Bandera EV. Associations of dietary folate, Vitamins B6 and B12 and methionine intake with risk of breast cancer among African American and European American women. *Int J Cancer* 2014; **134**: 1422-1435 [PMID: 23996837 DOI: 10.1002/ijc.28466]

64 **Castillo-L C**, Tur JA, Uauy R. [Folate and breast cancer risk: a systematic review]. *Rev Med Chil* 2012; **140**: 251-260 [PMID: 22739957 DOI: 10.4067/S0034-98872012000200016]

65 **Deghan Manshadi S**, Ishiguro L, Sohn KJ, Medline A, Renlund R, Croxford R, Kim YI. Folic acid supplementation promotes mammary tumor progression in a rat model. *PLoS One* 2014; **9**: e84635 [PMID: 24465421 DOI: 10.1371/journal.pone.0084635]

66 **Bassett JK**, Baglietto L, Hodge AM, Severi G, Hopper JL, English DR, Giles GG. Dietary intake of B vitamins and methionine and breast cancer risk. *Cancer Causes Control* 2013; **24**: 1555-1563 [PMID: 23686442 DOI: 10.1007/s10552-013-0232-y]

67 **Yan L**, DeMars LC. Dietary supplementation with methylseleninic acid, but not selenomethionine, reduces spontaneous metastasis of Lewis lung carcinoma in mice. *Int J Cancer* 2012; **131**: 1260-1266 [PMID: 22095442 DOI: 10.1002/ijc.27355]

68 **Kim A**, Jung JY, Son M, Lee SH, Lim JS, Chung AS. Long exposure of non-cytotoxic concentrations of methylselenol suppresses the invasive potential of B16F10 melanoma. *Oncol Rep* 2008; **20**: 557-565 [PMID: 18695906 DOI: 10.3892/or\_00000042]

69 **Chen YC**, Prabhu KS, Das A, Mastro AM. Dietary selenium supplementation modifies breast tumor growth and metastasis. *Int J Cancer* 2013; **133**: 2054-2064 [PMID: 23613334 DOI: 10.1002/ijc.28224]

70 **Ha AW**, Hong KH, Kim HS, Kim WK. Inorganic sulfur reduces cell proliferation by inhibiting of ErbB2 and ErbB3 protein and mRNA expression in MDA-MB-231 human breast cancer cells. *Nutr Res Pract* 2013; **7**: 89-95 [PMID: 23610600 DOI: 10.4162/nrp.2013.7.2.89]

71 **Kim JJ**, Ha AW, Kim HS, Kim WK. Inorganic sulfur reduces the motility and invasion of MDA-MB-231 human breast cancer cells. *Nutr Res Pract* 2011; **5**: 375-380 [PMID: 22125673 DOI: 10.4162/nrp.2011.5.5.375]

72 **Kahouli I**, Tomaro-Duchesneau C, Prakash S. Probiotics in colorectal cancer (CRC) with emphasis on mechanisms of action and current perspectives. *J Med Microbiol* 2013; **62**: 1107-1123 [PMID: 23558140 DOI: 10.1099/jmm.0.048975-0]

73 **de Moreno de LeBlanc A**, Matar C, Perdigón G. The application of probiotics in cancer. *Br J Nutr* 2007; **98** Suppl 1: S105-S110 [PMID: 17922945 DOI: 10.1017/S0007114507839602]

74 **Frenkel M**, Abrams DI, Ladas EJ, Deng G, Hardy M, Capodice JL, Winegardner MF, Gubili JK, Yeung KS, Kussmann H, Block KI. Integrating dietary supplements into cancer care. *Integr Cancer Ther* 2013; **12**: 369-384 [PMID: 23439656 DOI: 10.1177/1534735412473642]

75 **Arthur JC**, Gharaibeh RZ, Uronis JM, Perez-Chanona E, Sha W, Tomkovich S, Mühlbauer M, Fodor AA, Jobin C. VSL#3 probiotic modifies mucosal microbial composition but does not reduce colitis-associated colorectal cancer. *Sci Rep* 2013; **3**: 2868 [PMID: 24100376 DOI: 10.1038/srep02868]

76 **Sobhani I**, Tap J, Roudot-Thoraval F, Roperch JP, Letulle S, Langella P, Corthier G, Tran Van Nhieu J, Furet JP. Microbial dysbiosis in colorectal cancer (CRC) patients. *PLoS One* 2011; **6**: e16393 [PMID: 21297998 DOI: 10.1371/journal.pone.0016393]

77 **Marchesi JR**, Dutilh BE, Hall N, Peters WH, Roelofs R, Boleij A, Tjalsma H. Towards the human colorectal cancer microbiome. *PLoS One* 2011; **6**: e20447 [PMID: 21647227 DOI: 10.1371/journal.pone.0020447]

78 **Goldin BR**, Gorbach SL. The effect of milk and lactobacillus feeding on human intestinal bacterial enzyme activity. *Am J Clin Nutr* 1984; **39**: 756-761 [PMID: 6424430]

79 **Verma A**, Shukla G. Probiotics Lactobacillus rhamnosus GG, Lactobacillus acidophilus suppresses DMH-induced procarcinogenic fecal enzymes and preneoplastic aberrant crypt foci in early colon carcinogenesis in Sprague Dawley rats. *Nutr Cancer* 2013; **65**: 84-91 [PMID: 23368917 DOI: 10.1080/01635581.2013.741746]

80 **Le Leu RK**, Hu Y, Brown IL, Woodman RJ, Young GP. Synbiotic intervention of Bifidobacterium lactis and resistant starch protects against colorectal cancer development in rats. *Carcinogenesis* 2010; **31**: 246-251 [PMID: 19696163 DOI: 10.1093/carcin/bgp197]

81 **Sreekumar O**, Hosono A. The antimutagenic properties of a polysaccharide produced by Bifidobacterium longum and its cultured milk against some heterocyclic amines. *Can J Microbiol* 1998; **44**: 1029-1036 [PMID: 10029998]

82 **Sreekumar O**, Hosono A. The heterocyclic amine binding receptors of Lactobacillus gasseri cells. *Mutat Res* 1998; **421**: 65-72 [PMID: 9748508 DOI: 10.1016/S0027-5107(98)00155-9]

83 **Orrhage KM**, Annas A, Nord CE, Brittebo EB, Rafter JJ. Effects of lactic acid bacteria on the uptake and distribution of the food mutagen Trp-P-2 in mice. *Scand J Gastroenterol* 2002; **37**: 215-221 [PMID: 11843060]

84 **Rochat T**, Miyoshi A, Gratadoux JJ, Duwat P, Sourice S, Azevedo V, Langella P. High-level resistance to oxidative stress in Lactococcus lactis conferred by Bacillus subtilis catalase KatE. *Microbiology* 2005; **151**: 3011-3018 [PMID: 16151211 DOI: 10.1099/mic.0.27861-0]

85 **de Moreno de LeBlanc A**, LeBlanc JG, Perdigón G, Miyoshi A, Langella P, Azevedo V, Sesma F. Oral administration of a catalase-producing Lactococcus lactis can prevent a chemically induced colon cancer in mice. *J Med Microbiol* 2008; **57**: 100-105 [PMID: 18065674 DOI: 10.1099/jmm.0.47403-0]

86 **LeBlanc JG**, del Carmen S, Miyoshi A, Azevedo V, Sesma F, Langella P, Bermúdez-Humarán LG, Watterlot L, Perdigon G, de Moreno de LeBlanc A. Use of superoxide dismutase and catalase producing lactic acid bacteria in TNBS induced Crohn's disease in mice. *J Biotechnol* 2011; **151**: 287-293 [PMID: 21167883 DOI: 10.1016/j.jbiotec.2010.11.008]

87 **Matsuzaki T**, Takagi A, Ikemura H, Matsuguchi T, Yokokura T. Antitumor activity and action mechanisms of Lactobacillus casei through the regulation of immune responses. *Biofactors* 2004; **22**: 63-66 [PMID: 15630253]

88 **de Moreno de Leblanc A**, Perdigón G. Yogurt feeding inhibits promotion and progression of experimental colorectal cancer. *Med Sci Monit* 2004; **10**: BR96-B104 [PMID: 15039638]

89 **Appleyard CB**, Cruz ML, Isidro AA, Arthur JC, Jobin C, De Simone C. Pretreatment with the probiotic VSL#3 delays transition from inflammation to dysplasia in a rat model of colitis-associated cancer. *Am J Physiol Gastrointest Liver Physiol* 2011; **301**: G1004-G1013 [PMID: 21903764 DOI: 10.1152/ajpgi.00167.2011]

90 Probiotic Dahi containing Lactobacillus acidophilus and Bifidobacterium bifidum modulates the formation of aberrant crypt foci, mucin depleted foci and cell proliferation on 1, 2-dimethylhydrazine induced colorectal carcinogenesis in Wistar rats. *Rejuvenation Res* 2014; : [PMID: 24524423 DOI: 10.1089/rej.2013.1537]

91 **Brandtzaeg P**, Pabst R. Let's go mucosal: communication on slippery ground. *Trends Immunol* 2004; **25**: 570-577 [PMID: 15489184 DOI: 10.1016/j.it.2004.09.005]

92 **de Moreno de LeBlanc A**, Maldonado Galdeano C, Chaves S, Perdigón G. Oral administration of Lactobacillus casei CRL 431 increases immunity in bronchus and mammary glands. *Eur J Inflamm* 2005; **3:** 23-28

93 **Perdigón G**, de Jorrat M, Valdez J, de Budeguer M, Oliver G. Cytolytic effect of the serum of mice fed with Lactobacillus casei on tumor cell. *Microbiol-**Aliments-Nutr* 1995; **13**: 15-24

94 **Perdigón G**, de Jorrat M, de Petrino S, Rachid M. Antitumor activity of orally administered L. casei. Significance of its dose in the inhibition of a fibrosarcoma in mice. *Food Agric Immunol* 1993; **5**: 39-49.

95 **Verhoeven V**, Renard N, Makar A, Van Royen P, Bogers JP, Lardon F, Peeters M, Baay M. Probiotics enhance the clearance of human papillomavirus-related cervical lesions: a prospective controlled pilot study. *Eur J Cancer Prev* 2013; **22**: 46-51 [PMID: 22706167 DOI: 10.1097/CEJ.0b013e328355ed23]

96 **Motevaseli E**, Shirzad M, Akrami SM, Mousavi AS, Mirsalehian A, Modarressi MH. Normal and tumour cervical cells respond differently to vaginal lactobacilli, independent of pH and lactate. *J Med Microbiol* 2013; **62**: 1065-1072 [PMID: 23618799 DOI: 10.1099/jmm.0.057521-0]

97 **Ribelles P**, Benbouziane B, Langella P, Suárez JE, Bermúdez-Humarán LG. Protection against human papillomavirus type 16-induced tumors in mice using non-genetically modified lactic acid bacteria displaying E7 antigen at its surface. *Appl Microbiol Biotechnol* 2013; **97**: 1231-1239 [PMID: 23212671 DOI: 10.1007/s00253-012-4575-1]

98 **Kumar M**, Verma V, Nagpal R, Kumar A, Gautam SK, Behare PV, Grover CR, Aggarwal PK. Effect of probiotic fermented milk and chlorophyllin on gene expressions and genotoxicity during AFB₁-induced hepatocellular carcinoma. *Gene* 2011; **490**: 54-59 [PMID: 21963996 DOI: 10.1016/j.gene.2011.09.003]

99 **Zhang M**, Wang F, Jiang L, Liu R, Zhang L, Lei X, Li J, Jiang J, Guo H, Fang B, Zhao L, Ren F. Lactobacillus salivarius REN inhibits rat oral cancer induced by 4-nitroquioline 1-oxide. *Cancer Prev Res (Phila)* 2013; **6**: 686-694 [PMID: 23658366 DOI: 10.1158/1940-6207]

100 **Lee JA**, Ko JH, Jung BG, Kim TH, Hong JI, Park YS, Lee BJ. Fermented Prunus mume with probiotics inhibits 7,12-dimethylbenz[a]anthracene and 12-o-tetradecanoyl phorbol-13-acetate induced skin carcinogenesis through alleviation of oxidative stress. *Asian Pac J Cancer Prev* 2013; **14**: 2973-2978 [PMID: 23803064]

101 **Cohen LA**, Crespin JS, Wolper C, Zang EA, Pittman B, Zhao Z, Holt PR. Soy isoflavone intake and estrogen excretion patterns in young women: effect of probiotic administration. *In Vivo* 2007; **21**: 507-512 [PMID: 17591361]

102 Probiotic Beverage with Soy Isoflavone Consumption for Breast Cancer Prevention: A Case-control Study. *Curr Nutr Food Sci* 2013; **9**: 194-200 [PMID: 23966890 DOI: 10.2174/15734013113099990001]

103 **Kaga C**, Takagi A, Kano M, Kado S, Kato I, Sakai M, Miyazaki K, Nanno M, Ishikawa F, Ohashi Y, Toi M. Lactobacillus casei Shirota enhances the preventive efficacy of soymilk in chemically induced breast cancer. *Cancer Sci* 2013; **104**: 1508-1514 [PMID: 23992486 DOI: 10.1111/cas.12268]

104 **Biffi A**, Coradini D, Larsen R, Riva L, Di Fronzo G. Antiproliferative effect of fermented milk on the growth of a human breast cancer cell line. *Nutr Cancer* 1997; **28**: 93-99 [PMID: 9200156 DOI: 10.1080/01635589709514558]

105 **Lê MG**, Moulton LH, Hill C, Kramar A. Consumption of dairy produce and alcohol in a case-control study of breast cancer. *J Natl Cancer Inst* 1986; **77**: 633-636 [PMID: 3091896]

106 **van't Veer P**, Dekker JM, Lamers JW, Kok FJ, Schouten EG, Brants HA, Sturmans F, Hermus RJ. Consumption of fermented milk products and breast cancer: a case-control study in The Netherlands. *Cancer Res* 1989; **49**: 4020-4023 [PMID: 2736542]

107 **LeBlanc JG**, Matar C, Valdéz JC, LeBlanc J, Perdigon G. Immunomodulating effects of peptidic fractions issued from milk fermented with Lactobacillus helveticus. *J Dairy Sci* 2002; **85**: 2733-2742 [PMID: 12487440 DOI: 0.3168/jds.S0022-0302(02)74360-9]

108 **de Moreno de LeBlanc A**, Matar C, Thériault C, Perdigón G. Effects of milk fermented by Lactobacillus helveticus R389 on immune cells associated to mammary glands in normal and a breast cancer model. *Immunobiology* 2005; **210**: 349-358 [PMID: 16164041 DOI: 10.1016/j.imbio.2005.05.024]

109 **de Moreno de LeBlanc A**, Matar C, LeBlanc N, Perdigón G. Effects of milk fermented by Lactobacillus helveticus R389 on a murine breast cancer model. *Breast Cancer Res* 2005; **7**: R477-R486 [PMID: 15987453 DOI: 10.1186/bcr1032]

110 **Vinderola CG**, Duarte J, Thangavel D, Perdigón G, Farnworth E, Matar C. Immunomodulating capacity of kefir. *J Dairy Res* 2005; **72**: 195-202 [PMID: 15909685]

111 **de Moreno de Leblanc A**, Matar C, Farnworth E, Perdigón G. Study of immune cells involved in the antitumor effect of kefir in a murine breast cancer model. *J Dairy Sci* 2007; **90**: 1920-1928 [PMID: 17369232 DOI: 10.3168/jds.2006-079]

112 **de Moreno de LeBlanc A**, Matar C, Farnworth E, Perdigon G. Study of cytokines involved in the prevention of a murine experimental breast cancer by kefir. *Cytokine* 2006; **34**: 1-8 [PMID: 16697655 DOI: 10.1016/j.cyto.2006.03.008]

113 **Maroof H**, Hassan ZM, Mobarez AM, Mohamadabadi MA. Lactobacillus acidophilus could modulate the immune response against breast cancer in murine model. *J Clin Immunol* 2012; **32**: 1353-1359 [PMID: 22711009 DOI: 10.1007/s10875-012-9708-x]

114 **Soltan Dallal MM**, Yazdi MH, Holakuyee M, Hassan ZM, Abolhassani M, Mahdavi M. Lactobacillus casei ssp.casei induced Th1 cytokine profile and natural killer cells activity in invasive ductal carcinoma bearing mice. *Iran J Allergy Asthma Immunol* 2012; **11**: 183-189 [PMID: 22761192 DOI: 011.02/ijaai.183189]

115 **Yazdi MH**, Mahdavi M, Kheradmand E, Shahverdi AR. The preventive oral supplementation of a selenium nanoparticle-enriched probiotic increases the immune response and lifespan of 4T1 breast cancer bearing mice. *Arzneimittelforschung* 2012; **62**: 525-531 [PMID: 22945771 DOI: 10.1055/s-0032-1323700]

116 **Lakritz JR**, Poutahidis T, Levkovich T, Varian BJ, Ibrahim YM, Chatzigiagkos A, Mirabal S, Alm EJ, Erdman SE. Beneficial bacteria stimulate host immune cells to counteract dietary and genetic predisposition to mammary cancer in mice. *Int J Cancer* 2014; **135**: 529-540 [PMID: 24382758 DOI: 10.1002/ijc.28702]

117 **Aragón F**, Carino S, Perdigón G, de Moreno de Leblanc A. The administration of milk fermented by the probiotic Lactobacillus casei CRL 431 exerts an immunomodulatory effect against a breast tumour in a mouse model. *Immunobiology* 2014; **219**: 457-464 [PMID: 24646876 DOI: 10.1016/j.imbio.2014.02.005]

**P-Reviewer:** De Siervi A **S-Editor:** Wen LL  **L-Editor: E-Editor:**

**Table 1 Examples of breast cancer animal models that have demonstrated the beneficial effects of lactic acid bacteria**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Model** | **Results** | **Mechanisms** | **LAB** | **Ref.** |
| 4T1 tumour bearing mice | Significant decrease of tumour growth | Modulation of the host’s immune response | *L. acidophilus* isolated from traditional home-made yogurt and from neonatal stool | 113 |
| Mice bearing invasive ductal carcinoma | Decrease of tumour growth rate and prolongation of mice survival | Modulation of the host’s immune response | *L. casei spp. casei* ATCC 39392 | 114 |
| 4T1 breast cancer bearing mice | Tumor volumes of mice treated with Se nanoparticle-enriched probiotic were decreased and their survival rate increased compared to mice that received probiotic alone or control mice. | Modulation of the host’s immune response | *L. plantarum* strain enriched with selenium nanoparticles | 115 |
| Swiss mice fed a Westernized chow and FVB strain erbB2 (HER2) mutant mice | Inhibition of mammary neoplasia in both models. | LAB triggered CD4+CD25+ lymphocytes that convey transplantable anti-cancer protection. | *L. reuteri*  ATCC-PTA-6475 | 116 |
| 4T1 breast cancer bearing mice | Decrease of tumour growth in mice fed preventively with LAB and also in mice fed probiotic after tumour detection | Modulation of the host’s immune response and decrease of tumour angiogenesis | *L. casei* CRL 431 | 117 |

LAB: Lactic acid bacteria.