

# Probiotic Bulletin

A Newsletter for Healthcare Professionals



## The gut microbiota and cancer risk: Could there be potential for probiotics?



**Professor Ian Rowland's** research has focussed on understanding the links between diet and the risk of chronic diseases such as cancer. We caught up with him at the University of Reading to chat about his career and research interests.

**Q** You are a Professor of Human Nutrition yet started as a microbiologist – what was your career path?

**A** Yes, I originally trained as a microbiologist at UCL then got a job at the British Industrial Biological Research Association (BIBRA) where I was asked to work on gut microbiota. This was back in the 1970s and very much the early days of gut bacteria research. I started working on production of N-nitroso compounds by gut bacteria. There were concerns at the time about nitrosamines in food as they are very potent carcinogens. This really started my interest in gut microbes and cancer – very few people were working on it in those days. I got interested in what the gut bacteria actually do, their role in health and any metabolites they produced that might be associated with cancer.

In 1997 I moved to the University of Ulster as Head of Nutrition where I started doing a lot more work on cancer biomarkers and non-invasive methods of estimating cancer risk. Then about seven years ago, I moved to the University of Reading.

### In this issue:

Gut microbiota and cancer risk	1-3	Gut Week 2013 Gut Health Award	4	Gut Health Round Table Community Nutrition HCP Awards	5	Biomarkers of Enteropathy	6
New research papers	7	FINA World Championships	7	NEW - Yakult study day 2014	8	Brighter breakfast recipes	8

# Q&A

## Interview with an expert (Prof Ian Rowland, continued)

**Q** Your interests include diet and risk of breast and prostate cancer – tell us more?

**A** I got interested because I started working on soy, first at BIBRA and later at Ulster. Soy contains isoflavones - phytoestrogens with weak oestrogenic effects, so there has been interest in their role in hormone-dependent cancers – breast and prostate being the obvious ones. Interestingly, both of the main isoflavones, daidzein and genistein, get extensively metabolised by gut bacteria - as do a lot of plant components. We know the microbiota is very important, as it alters the bioactivity of these compounds, for instance by converting daidzein to a compound called equol, which in fact is more oestrogenic than daidzein *in vitro*. Interestingly, in studies conducted in many different countries, only a third of people produce equol.

A lot of epidemiological evidence indicates that soy has protective effects against breast and prostate cancer and currently there is considerable interest in whether equol-producers may be more protected than non-producers. It is a very good example of a diet-gut microbiota interaction that could have significant consequences for human health.

**Q** A study has just been published by researchers from the University of Tokyo investigating *Lactobacillus casei* Shirota (LcS) and isoflavone consumption and reducing breast cancer risk (Toi et al). Have you read this?

**A** Yes – it is a fairly large case-control study that found a good protective effect for both soy and LcS individually. There was slightly better effect when the two were combined, although it wasn't statistically significant. Japan is a good place to carry out such research, for two reasons: they have high consumption of soy but, also, because they have a unique home delivery service for the probiotic, you can get very good quantitative data. So for epidemiological studies, this is such a good resource. Dietary data is always the weak point, as it is so difficult to measure accurately what people eat.

**Q** Could you possibly speculate on the mechanisms of activity?

**A** There are two possible mechanisms. One is immune function, and this probably underlies a lot of the effects of LcS, particularly in the cancer studies. The other possibility is, as we discussed, through metabolism and the conversion to equol.

Interestingly, the Japanese seem to have a slightly higher proportion of equol producers compared to western populations. This may be because they are being exposed to soy isoflavones early in life, when the microbiota is still developing, so the gut bacteria may adapt to having more of these isoflavones around.

**Q** Metchnikoff promoted the idea that modulating the colonic microbiota could reduce the risk of putrefactive substances and toxins in the gut. Do you think the gut microbiota can reduce and/or increase risk of cancer?

**A** Although somewhat circumstantial, there is pretty strong evidence that the gut microbiota is linked to cancer risk. The problem is that we don't know which bacteria are associated with increased or decreased risk, as the data are inconsistent.

A lot of studies have compared microbiotas of cancer patients and controls. The problem is you don't know whether the differences in microbiota are due to the cancer (which they could well

be) or whether they are responsible for the difference in cancer risk. Like all epidemiological studies they just show an association. Nevertheless, metagenomic studies are showing some differences. The bacteria which seem to be protective (i.e. there are fewer numbers in cancer patients) are those producing butyrate, such as *Faecalibacterium* and *Roseburia*. High intakes of dietary fibre and vegetables (which are associated with lower colon cancer risk) have been shown to increase numbers of butyrate producers, so there is some consistency there.

**Q** So the gut microbiota is driven by diet?

**A** Yes. The types of bacteria, and particularly their metabolic activities, are very much driven by diet. We know lots of metabolites are potentially carcinogenic. A prime example is secondary bile acids. Primary bile acids, produced by the liver and secreted into the small intestine, are involved in absorption of fats. They move down into the colon and there get converted to secondary bile acids, such as deoxycholic and lithocholic acids, by various types of bacteria in the gut. These secondary bile acids are much more toxic to the intestinal tract lining than the primary bile acids. In particular, they appear to be able to disrupt the tight junctions between the cells lining the gut which are responsible for maintaining the gut barrier to infections and potentially inflammatory agents, and also for ensuring cell-cell communication. This has important implications for cancer since disruption of tight junctions is a characteristic of tumour promotion. In contrast to these detrimental effects of secondary bile acids, we have shown that other gut bacterial metabolites, notably short-chain fatty acids like acetate and butyrate produced by dietary fibre fermentation, actually tighten up the cell junctions. So there appears to be an interplay of bacterial metabolites in the colon.

**Q** Are there any good biomarkers for colorectal cancer risk?

**A** The trouble is there are very few validated biomarkers for cancer and it's very difficult to validate them. But it is possible to look at potential risk factors which might be associated with cancer.

We worked with Joseph Rafter at the Karolinska Institute in Sweden looking at faecal water and the bioactive soluble compounds in this fraction that might be involved with initiating or protecting against cancer. Aware that colon cancer develops through DNA damage to the colon mucosa, we looked at the ability of faecal samples to damage colon cells *in vitro* and found some people had very high levels of DNA-damaging activity while others had virtually none. So there are clearly factors in faecal samples that can cause DNA damage and hence potentially may be involved in colon cancer development. However, to validate this activity as a biomarker for cancer would be very complicated and expensive.

We also looked at the effect of faecal water samples on cell models of tumour promotion (by assessing disruption of the tight junctions as described earlier) and tumour invasion. Interestingly, faecal water from older people caused tight junction disruption more than that from younger people – and obviously older people get cancer more than younger people. So we've got the ability to look at the impact of faecal metabolites on various stages of cancer, from the early stages of DNA damage, to invasion.

**Q** There is a range of cancer-related research with LcS – for instance, the large colorectal cancer intervention trial published by Ishikawa et al in 2005. What is your opinion of this study?

**A** The advantages of this study were that it was long-term and had a long follow-

up (four years). The study also looked at recurrence of tumours, which is a pretty good indicator of cancer risk. They investigated people with previous cancer or benign tumours who had had the tumours removed. They followed them up regularly, so it was a good model for looking at cancer development. The results showed a decrease in recurrence of tumours for the people taking LcS, although this wasn't significant. However, there was a significant decrease after four years, in occurrence of tumours with atypia, which in fact are more likely to go on and develop into malignant tumours. This certainly indicated it would be worthwhile exploring this further.

**Q** Human intervention studies are difficult with cancer, as a large number of subjects are usually needed over a long period of assessment.

**A** Yes, it is really, really difficult – which is why we have to rely on epidemiological studies. The problem is cancer can take around 20 years or more to develop, so intervention studies with cancer as an endpoint are impractical. So this is why you have to rely on biomarkers. Cancer is probably one of the most difficult diseases to study as the development period is so long and the biomarkers are not all that great, but actually, I think the evidence for links between probiotics and cancer is very strong.

**Q** And have you any comment about the LcS studies investigating bladder cancer?

**A** Yes, there is quite a lot of research with LcS and bladder cancer in humans. Those studies were looking at recurrence of

tumours, so a strong endpoint. The most likely mechanism is immune modulation - there is evidence that certain probiotics can stimulate activity or numbers of a type of white blood cell called natural killer (NK) cells which target cancer cells in the body. In fact we published a paper earlier this year showing that NK cell activity was increased in elderly subjects given LcS. All probiotics are different and more research is needed.

**Q** There is a strong association between HPV and cervical cancer. What were your thoughts on the LcS pilot study published last year (Verhoeven et al)?

**A** That was an interesting study. It was a pilot study, so very small and it wasn't blinded, but it provided some positive results. It is clearly worth doing on a larger scale, as it had such a significant reduction, with so few numbers. Once again, there is probably an immune effect underlying this.

**Q** Hard to believe, but you are going to retire at the end of the year. What are you planning to do after this, and will you still be involved with probiotics at all?

**A** Yes, I am retiring from the University in December. I decided I wasn't going to haunt the corridors of Reading after I retire, but I will still be involved with some projects that are on-going. As for probiotics, I will continue my involvement with the Core and British Society of Gastroenterology initiative around gut microbiota, and I will participate in meetings of ISAPP (the International Scientific Association for Probiotics and Prebiotics). But first I'm going to take a long holiday...

### Did you know...

- Every year, 266.9 people out of 100,000 people develop cancer in the UK<sup>1</sup>
- Breast, lung, bowel and prostate cancer account for 54% of all new cases<sup>2</sup>
- Approximately a third of the most common cancers in the UK could be prevented through improved diet, physical activity and body weight<sup>1</sup>
- Epidemiological evidence suggests an association between increased risk of colorectal cancer and overweight/obesity (waist circumference), processed meat and alcohol<sup>1</sup>
- Decreased risk of colorectal cancer is associated with consumption of fibre, garlic, milk and calcium<sup>1</sup>

Reference list available at [www.yakult.co.uk/hcp](http://www.yakult.co.uk/hcp) or from [science@yakult.co.uk](mailto:science@yakult.co.uk)

**Toi et al (2013) Probiotic beverage with soy isoflavone consumption for breast cancer prevention: A case-control study** *Current Nutrition and Food Science* (2013) 9(4): 194-200

This Japanese study matched 306 women with breast cancer against 662 controls (aged 40 to 55) and investigated their diet, lifestyle and other breast cancer risk factors. Daily consumption of LcS drinks from the age of adolescence showed a significant inverse association with early breast cancer occurrence. A subgroup analysis according to menopausal status, also showed a significant inverse association in post-menopausal women for whom the odds ratio was 0.43 (CI 95%, 0.19-0.99, P=0.046).

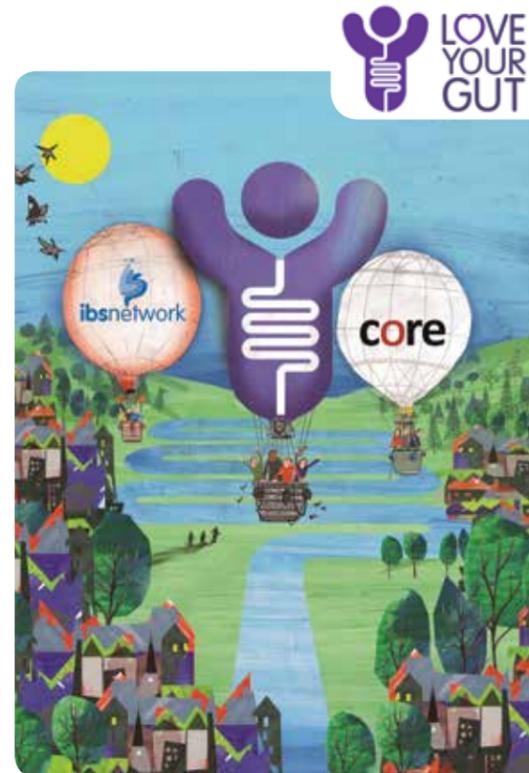
## Gut Week 2013 – thank you for making this a roaring success!

This national digestive health awareness campaign highlights the vital role of the digestive system and emphasises the importance of maintaining good gut health. Organised annually by the digestive health charities Core and the IBS Network in conjunction with Yakult UK Limited, Gut Week was also supported this year by Bowel Cancer UK and St. Mark's Hospital Foundation.

Gut Week celebrated its 15th anniversary in August and we were thrilled by the fantastic response from healthcare professionals wanting to take part. Over 150 different hospitals and practices requested Gut Week packs so they could set up their own stands and events.

On behalf of all the partners, we would like to thank everyone who helped make it such a successful year. We look forward to your continued support, in order to make Gut Week 2014 an even bigger success!

If you are interested in raising public health awareness of gut health in your area, contact [info@loveyourgut.com](mailto:info@loveyourgut.com) or visit the website [www.loveyourgut.com](http://www.loveyourgut.com).



## Gut Health Award: Winners

The winner of the Gut Health HCP Award 2013 is:

The **Garth Care Home**, Herefordshire, for their efforts to bring awareness about gut health to residents, their families and staff. This campaign, run and organised by Debbie Todd and colleagues was a great success for all involved – as the photos show. As well as carrying out various activities such as a quiz to increase people's knowledge of healthy foods, they also involved the kitchen staff, who made a selection of healthy snacks.



The runner-up prizes went to:



**The Complex Multiple Impairment Team at St. Mary's Hospital, Leeds.** This campaign, run by Sarah Waite and colleagues, combined Gut Week with Learning Disability Awareness Week. Sarah felt passionately that the education surrounding gut health should be made available to their service users with learning disabilities, which resulted in a highly successful and fun event.

**Derby Hospitals NHS Foundation Trust, Derby,** run by Tracy Selsby-Orlandi and colleagues. Stalls were run at their two main sites and literature made available in the public canteens. Their campaign was targeted at employees as part of their overarching health and wellbeing for work strategy, with the aim of supporting employees to make positive health choices and to share information with their patient groups.

**Congratulations to all winners and to all who took part in Gut Week 2013! Thank you!**

Love Your Gut (Gut Week) is a public health awareness campaign from Core and the IBS Network in association with Yakult UK Limited. Neither Core nor IBS Network endorses any specific commercial or pharmaceutical products.

## A Gut Health Round Table Meeting

Working together to help people manage their chronic gut symptoms: lessons from a multidisciplinary workshop

This event, held earlier this year, brought together healthcare professionals from six different disciplines to share their perspectives for the management of IBS. Each expert presented for discussion a case history of a patient with a gut health problem. As a result, the panel agreed several insights:

- Patients with IBS require a diversity of management
- IBS is an expression of the individual, their lifestyle and life situation
- It is more important to understand the patient than the disease
- Patients are often depressed. Motivational interviewing is a key skill
- Engagement is the most therapeutic principle, offering support rather than control



The panel members (left to right): Marianne Williams (dietitian), Gill Jenkins (GP: chairperson), John Smaldon (Core: observer), Nick Read (physician and psychotherapist), Nisha Desai (pharmacist), Lystra Rampersad-Smith (practice nurse), Linda Thomas (Yakult: rapporteur); John O'Malley (GP), Ayesha Akbar (gastroenterologist), Tom Smith (Core).

- It is vital to understand the context of the illness
- The right treatment is what is right for the patient
- The principle of effective management should be guided by self-care

For a short report of the meeting, visit <http://www.theibsnetwork.org/wp-content/uploads/2012/10/GR88.pdf> The full paper will be published soon in *Practice Nursing*.

## | HCP Awards

## Announcing the winners of the Yakult-sponsored Community Nutrition Professional of the Year award 2012/13 (Cue drum roll...)



Pictured from left to right are: Elaine Lambert-Knott\*, Sarah Boyle, Emma Harding, Carol Williams\*, Gail Bright, Tim Hoe, Jenny Marsh, Kate Kent, Anne Williamson. Unfortunately Sylke Bertram-Barclay was unable to join the Team for a photo. \* past members.

### Congratulations to the Community Nutrition Support Dietetic Team, East Sussex Healthcare NHS Trust!

Lesley Houston (Therapy Services Manager for Stroke and Community Dietetics) nominated them in recognition for their achievements over the last ten years. Having started with just one person in 2002, these seven dietitians and one dietetic assistant now provide a community nutrition support dietetic service (both oral and enteral nutrition support) across the whole of East Sussex.

One of their achievements has been the development of a 'Treating Adult Malnutrition Pack', a resource containing practical advice on screening, treating and monitoring those at risk of malnutrition in the community, as well as tools such as weight record charts, food charts and food preference charts. The team promote a 'Food First' approach to treating adult malnutrition and have developed treatment pathways and care plans, as well as training community care staff and other health professionals to identify, treat and manage those at risk of malnutrition or who are malnourished.

Recently they collaborated with their Medicines Management team on a project to provide an enhanced service in identified care homes in East Sussex, supporting a wider QIPP initiative. This was designed to help reduce inappropriate prescribing of nutritional supplements in the care homes. Looking forward, the team are working on standardising enteral feeding supplies, and will continue to promote appropriate treatments for adult malnutrition.

# Assessing biomarkers of environmental enteropathy: a pilot study in children in Africa.

A report from Steve Allen, Professor of Paediatrics & International Health at the College of Medicine, Swansea University

It has been known for many years that people living with poor sanitation have some degree of 'tropical' or 'environmental' enteropathy (EE). This is characterised by Th1-mediated inflammation and so is similar to the enteropathy of coeliac disease or Crohn's disease. It is associated with malabsorption and also increased leakiness of the gut mucosa, which may result in gut-derived sepsis.

EE occurring during early childhood in otherwise healthy children may contribute to poor growth. Some children with severe acute malnutrition (SAM) have severe and persistent enteropathy that no doubt impairs their response to nutritional management. Although vitamin A, zinc and other micronutrients are included in feeds for children with SAM, specific interventions to improve enteropathy, such as the immunomodulators used in Crohn's disease, are not part of current management regimens.

The gold standard way of detecting enteropathy is by duodenal endoscopy and biopsy but this is clearly inappropriate as a research tool and impracticable in the settings where malnourished children are common. The assessment of the frequency and severity of EE and also response to potential interventions would be greatly facilitated if one or more non-invasive biomarkers were available. Supported by Yakult UK Limited, I am working with Professor Segun Akinyinka and Dr. Adebola Orimadegun (Department of Paediatrics, University College Hospital, Ibadan, Nigeria) in a study of children with SAM and non-malnourished controls attending Gusau Hospital, Zamfara State in northwestern Nigeria.

To date, stool samples have been collected from 53 children with SAM and 17 controls. We plan to measure markers of intestinal inflammation such as calprotectin and also describe the gut microbiota in the two patient groups. In future studies, we plan to use the biomarker(s) and also clinical outcomes such as diarrhoea and weight gain to evaluate specific interventions targeted at improving enteropathy in children with SAM. The long-term aim, depending on progress, is to develop safe and acceptable interventions that could be used at the community level to prevent EE in infants and young children.

Dr Orimadegun assessing a patient



## Recent publications of studies with *Lactobacillus casei* Shirota (LcS)

### Reduction of antibiotic-associated diarrhoea (AAD) in spinal injury patients

In this randomised controlled trial, researchers at the National Spinal Injuries Centre (Stoke Mandeville), in conjunction with University College London, found that AAD developed in only 17.1% of patients given a daily LcS-fermented milk drink, compared to 54.9% for those not given the probiotic ( $P < 0.001$ ). Only one case of diarrhoea was caused by *Clostridium difficile*; this was in the control group. Poor appetite and associated undernutrition were identified as risk factors for AAD.

Wong S et al (2013) *British Journal of Nutrition* [Epub Sept 18]

### Elderly day care study: decreased duration of acute upper respiratory tract infections (URTIs)

This multicentre, double-blinded, randomised, placebo-controlled study involved 154 older women (average age: 83 years) attending day care facilities. Episodes of acute URTI were of shorter mean duration in the group drinking the LcS-fermented milk drink (3.71 d vs. 5.40 d,  $P = 0.037$ ); no difference in incidence rate was found.

Fujita R et al (2013) *American Journal of Infection Control* [Epub Jul 23]

### Case report: prevention of D-lactic acidosis in short bowel syndrome

The patient with short bowel syndrome had recurrent episodes of neurologic dysfunction due to D-lactic acidosis, and treatment with fasting and antibiotics to eliminate the bacteria producing the D-lactate had failed. The patient was then started on a synbiotic combination (*L. casei* Shirota, *Bifidobacterium breve* Yakult and a prebiotic galacto-oligosaccharide), which resulted in a decline in serum D-lactate levels, after which the problem did not recur.

Takahashi K et al (2013) *International Surgery* 98(2):110-113.

### Mechanistic study: impairment of pathogen motility

This French study found that LcS inhibited the motility of a *Helicobacter pylori* strain (irreversibly) and a *Salmonella Typhimurium* strain (reversibly) in vitro. The effect was linked to a small, heat-sensitive and partially trypsin-sensitive compound together with a secreted membrane-permeabilising lactic acid metabolite. This loss of motility affected the entry of the *Salmonella* strain into human cell lines.

Liévin-Le Moal V et al (2013) *Microbiology* [Epub Jul 19]

### Mechanistic study: effect on dendritic cells (DC) from ulcerative colitis (UC) patients

Blood DC from healthy people and UC patients were conditioned with heat-killed LcS, and used on stimulated T cells. Compared to the healthy samples, UC-DC had a reduced ability to stimulate T cells and enhanced expression of skin homing markers on stimulated T cells. Treatment with LcS partially restored these DC functions.

Mann ER V et al (2013) *Mediators of Inflammation* Article ID 573576. [Full paper available free]

### And finally... new German guidelines for constipation

For anyone who can read German, these guidelines recommend probiotics, and specifically mention LcS studies.

Andresen V et al (2013) *Zeitschrift für Gastroenterol* 51: 651-672 [Paper can be accessed with registration]

## | FINA Sponsorship



## FINA World Championships

The FINA World Championships were held this summer in Barcelona and as one of the official sponsors, Yakult was there! We (and our guests) were fortunate enough to not only see some of the events but also to attend a short symposium focussed on nutrition in sport.

Professor Mike Gleeson (Loughborough University) presented his research on the effects of probiotics and reduction of infection incidence in athletes, then Dr Claudia Osterkamp-Baerens (nutritionist at Olympic Training Centre Bavaria, Munich) discussed the importance of specifically designed nutrition programmes (that include probiotics) for top athletes in different endurance sports. Finally, Dr. Rik van der Kolk (Dutch male water polo coach) discussed his sport, and explained how Yakult is enjoyed by his team.

# SAVE THE DATE!

## 1st October 2014 – Yakult's study day for Healthcare Professionals

Yakult UK Limited will be organising a healthcare professionals study day on 1st October 2014 at Royal College of Physicians, London

The day will provide an update about and explanation of current knowledge about the gut, its microbiota and probiotics, in healthcare areas such as IBS, IBD, care of the elderly, and infection prevention.

We're always open to suggestions, so please do let us know if there is any particular topic you would like covered.

The event will be valuable CPD for nutritionists, dietitians, nurses and doctors from primary/secondary healthcare, microbiologists and pharmacists.

As always, the speakers will be internationally renowned experts from the UK and Ireland.

**Places are limited and on a first-come, first-served basis.**

To reserve a place please contact us at [science@yakult.co.uk](mailto:science@yakult.co.uk)  
Further details will follow in the next newsletter and at [www.yakult.co.uk/hcp](http://www.yakult.co.uk/hcp)



## New Breakfast Selector!

THE  
**Yakult**  
brighter  breakfast

Visit the website to view our NEW Brighter Breakfast Selector. There are lots of breakfast selections to choose from, with options for nutrient type, occasion and ingredient. Check out the breakfast library to view a selection of tasty morning recipes.

Take part in our British Breakfast Poll!  
We're building up a bite-sized view of Britain's breakfast habits.

To get involved visit [www.yakult.co.uk](http://www.yakult.co.uk)



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- ✓ A free educational talk for your department or surgery
- ✓ Advice on probiotics
- ✓ Copies of our newsletter, reprints and other material
- ✓ Free trial period of product (subject to discussion)

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### **PP1-3: The gut microbiota and cancer risk**

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- Ishikawa *et al* (2005) Randomized trial of dietary fiber and *Lactobacillus casei* administration for prevention of colorectal tumors *International Journal of Cancer* **116**:762-767
- Verhoeven *et al* (2012) Probiotics enhance the clearance of human papillomavirus-related cervical lesions: a prospective controlled pilot study *European Journal of Cancer Prevention* **22(1)**: 46-51

References to other bladder cancer studies using *Lactobacillus casei* Shirota can be found using the search tool ['cancer'] at [www.yakult.co.uk/hcp](http://www.yakult.co.uk/hcp)

### **P3 Did you know...?**

1. [http://www.wcrf-uk.org/research/cancer\\_statistics/world\\_cancer\\_statistics.php?gclid=COL8nsHiwLkCFc6d3godj1AAA](http://www.wcrf-uk.org/research/cancer_statistics/world_cancer_statistics.php?gclid=COL8nsHiwLkCFc6d3godj1AAA)
2. <http://www.cancerresearchuk.org/cancer-info/cancerstats/incidence/commoncancers/#Twenty>

### **P5 Working together to help people manage their chronic gut symptoms: lessons from a multidisciplinary workshop**

For a short report of the meeting, visit <http://www.theibsnetwork.org/wp-content/uploads/2012/10/GR88.pdf>

### **P7 Research roundup**

- Wong S *et al* (2013) Do probiotics prevent antibiotic-associated diarrhoea in patients with spinal cord injuries? : A randomized controlled trial. *British Journal of Nutrition* doi:10.1017/S0007114513002973
- Fujita R *et al* (2013) Decreased duration of acute upper respiratory tract infections with daily intake of fermented milk: A multicenter, double-blinded, randomized comparative study in users of day care facilities for the elderly population. *Journal of Infection Control* doi:10.1016/j.ajic.2013.04.005
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