

FINAL REPORT OF N12 RESEARCH PROGRAMME REVIEW

30th November 2006

1. Executive summary

Colo-rectal cancer is the third most common cancer in the UK after breast and lung responsible for about 13% of all cancers. Every year in the UK, around 35,000 people are diagnosed with colo-rectal cancer and there are more than 16,000 deaths caused to colorectal cancer. The Government White Paper, Our Healthier Nation, has set targets to reduce death rates from cancer by at least a fifth by 2010.

The Agency aims to provide the best possible advice to consumers on a healthy balanced diet; the N12 research programme aims to provide evidence to develop dietary recommendations and help reduce diet-related disease, i.e. colo-rectal cancer.

Without reliable surrogate end-points for colo-rectal cancer, however, the exact relationship between dietary factors and colo-rectal cancer risk remains ill-defined. The N12 research programme's main focus is the development of reliable surrogate end-points for colo-rectal cancer relevant to dietary factors, which can be used in dietary intervention studies to provide evidence to develop dietary recommendations to reduce colo-rectal cancer risk.

The review concluded that the projects within the N12 research programme were appropriate to its remit. These projects investigate mechanisms and processes fundamental to carcinogenesis that are likely to be modified by dietary factors. The projects funded within the programme were also judged to be of a high scientific quality.

The aim of the programme, to develop surrogate end-points for colo-rectal cancer that are modified by dietary factors, was judged to be a research priority. It was noted, however, that achieving this aim would take considerable time and commitment. It was questioned whether this programme is still central to the Agency's policy needs. The Programme Manager working together with RCU will endeavour to interest other funders who remit it fits to work more in this area.

The panel recommended waiting until the current projects have reported before calling for new research, as this would enable an assessment of the approaches employed thus far.

2. Background to the review

3.1. The review panel

Professor John Baron	Dartmouth College, New Hampshire USA
Professor Timothy Key	University of Oxford
Professor Young-In Kim	University of Toronto, Canada
Professor Joseph Rafter	Karolinska University, Sweden
Professor David Shuker	The Open University, Milton Keynes

3.2. Rationale of the programme

The Agency aims to provide the best possible advice to consumers on a healthy balanced diet; this research programme aims to provide evidence to develop dietary recommendations and help reduce diet-related disease, i.e. colo-rectal cancer.

Colo-rectal cancer is the third most common cancer in the UK after breast and lung responsible for about 13% of all cancers. Every year in the UK, around 35,000 people are diagnosed with colo-rectal cancer and there are more than 16,000 deaths caused to colorectal cancer. The Government White Paper, Our Healthier Nation, has set targets to reduce death rates from cancer by at least a fifth by 2010.

It has been estimated that around two-thirds of cases of colo-rectal cancer may be preventable by changes in diet and lifestyle; however, the exact relationship between dietary factors and colo-rectal cancer risk remains ill-defined. Elucidating this relationship has been hampered by the lack of surrogate end-points for colo-rectal cancer that could be used in dietary intervention trials.

In most cases it would be impractical for dietary intervention studies to use incident cancer as an end point, e.g. study duration, compliance, cost. For this reason, the development of surrogate end points, biomarkers of preclinical carcinogenesis, is a priority. These offer the potential of smaller, shorter and less costly studies with achievable dietary interventions that could provide evidence to develop dietary recommendations to reduce colo-rectal cancer risk.

3.3. Origin of the programme

In 1996, during a review of nutrition research by Ministry of Agriculture Food and Fisheries (MAFF), colonic health was identified as an important area for future research – the nutrition research programmes were transferred from MAFF to the FSA when it was created in 2000.

It was agreed that a programme on Colonic Health should follow on from a previous MAFF-funded research programme, the Complex Carbohydrate research programme, and further understanding of the role of dietary fibre and other dietary components in preventing diseases of the colon and, with an

overall aim of defining optimal nutrition to protect against diseases of the colon.

FSA (previously by MAFF) also funds research on the effect of some dietary components on the development of colo-rectal cancer in the Risk Assessment Programme. The primary focus of this programme is on risk assessment for genotoxic carcinogens that occur unavoidably in food stuffs. It was subsequently proposed that the research programme on Colonic Health would be a natural progression of earlier research on complex carbohydrates and could complement the current research on risk assessment of dietary components.

In 1999 a scoping study to identify research priorities in the field of colonic health was commissioned. This was undertaken by British Nutrition Foundation. The research priorities were identified from discussions at a workshop of relevant experts and the research recommendations from the Committee on Medical Aspects of Food and Nutrition Policy's (COMA; superseded by the Scientific Advisory Committee on Nutrition) 1998 report on the Nutritional Aspects of the Development of Cancer. Findings from relevant MAFF funded research as well as other national and international research were also considered in identifying priorities for the proposed research programme on Colonic Health.

3.1. Objectives of the programme

Based on the suggestions for research made in both the scoping report and the COMA report, the objectives for the programme are:

- Develop techniques for the characterisation and validation of reliable diet-related intermediate bio-markers for colorectal cancer. Investigate the extent to which surrogate tissues (e.g. hair, skin, and blood) are appropriate for use with these markers.
- Using these techniques, investigate the impact of components of the diet; how these interact and whether dose response effects exist.
- Develop understanding of the interaction between diet, processes associated with colon health and genetic predisposition in determining susceptibility to cancer.

The first call for proposals under the Diet and Colonic Health research programme, in September 2000, addressed the first two suggestions listed above. This was based on the rationale that the development of techniques to identify valid and reliable biomarkers is crucial to underpin future research within this programme.

Since then, calls for proposals, within the programme, have focused on the first suggestion:

- To develop, characterize and/or validate reliable diet-related surrogate end points for colorectal cancer, with a view to developing, in the long term, dietary advice for the UK population
- To investigate the extent to which surrogate tissues are appropriate with regard to the above.

3.2. The review process

To determine:

- The appropriateness of the projects funded with regard to the programme objectives;
- Whether the research programme should solely focus on colorectal cancer or be broadened to include other nutrition relevant cancers;
- Priorities for future research.

3.3. Outputs of the programme

Workshop on emerging diet-related surrogate end points for CRC (2003)

In February 2003, the FSA convened a workshop on Emerging Diet-Related Surrogate End-Points for Colo-Rectal Cancer in which FSA-funded and relevant non FSA-funded projects were presented and discussed. The workshop was written-up and published in the British Journal of Nutrition (Sanderson et al 2004).

The workshop made the following recommendations: -

- The validation of current putative diet-related surrogate end points for CRC and the development of novel ones, particularly in the emerging fields of proteomics, genomics and epigenomics.
- To introduce into CRC-screening protocols measures of dietary exposure and collection and validation of putative diet-related surrogate end points.

In November 2006, the FSA convened a workshop on Foliates and Colo-Rectal Cancer Risk in which FSA-funded and relevant non FSA-funded projects were presented and discussed. The workshop is currently being written-up and will be published shortly in the British Journal of Nutrition.

Scientific publications from each project as listed in the workshop document (annex C).

3. Presentations made at the review

Professor Ian Johnson, Institute of Food Research, Norwich, presented the projects:

- Detection of CpG Island Methylation in Faecal DNA (N12001/5)
- Developing new biomarkers of colorectal neoplasia: Quantification of aberrant CpG island methylation in human faecal DNA (N12009/11)
- Applying Proteomic technology to identify biomarkers of colorectal cancer (N12004/8)

Professor John Mathers, Newcastle University, presented the projects:

- The impact of folate and its interaction with riboflavin on biomarkers of colorectal cancer risk (N12002/7)
- Validation of novel diet-related biomarkers of early colorectal neoplasia – use of proteomic technology and identification of mitochondrial DNA mutations (N12015)
- Markers of systemic and mucosal inflammation as biomarkers of vulnerability to colorectal cancer (N12016)

Dr Bernard Corfe, Sheffield University, presented the project:

- Protein acetylation as a diet-modifiable biomarker of colorectal cancer risk (N12017)

Dr Liz Lund, Institute of Food Research, Norwich, presented the projects:

- Gastro-intestinal health with special emphasis on reduction of risk of colon cancer and inflammatory bowel disease (FishGastro) (N12012)
- Further development of a non-invasive biomarker to monitor gastro-intestinal health with special emphasis on reduction of risk of colon cancer (BIOMICS) (N12013)
- Faecal methylation, gene expression and disease outcome in people consuming fish. (FishMet) (N12014)

Professor Stephen Downes, University of Ulster, presented the project:

- Novel DNA biomarkers for folate deficiency in surrogate tissues and colonic mucosa (N12003)

4.1. Summary of presentations

The abstracts for each project are given in Annex C (workshop booklet).

4.2. Conclusions arising from discussions

The projects investigated mechanisms and processes fundamental to carcinogenesis and that were likely to be modified by dietary factors. The projects were, therefore, appropriate to the remit of the programme.

The projects were assessed to be of a high scientific standard. The panel recommended waiting until the current projects have reported before calling for new research, as this would enable an assessment of the approaches employed thus far.

The panel recommended the Agency endeavour to work with other relevant funders in pushing this priority forward.

General comments/Future work

- The panel noted that the FSA-funded projects had focused on the modification of 'field effects' and relate molecular mechanisms in the colon. The panel commended this approach, as changes in these were likely to play a central role in establishing the conditions under which carcinogenesis became more likely.
- The panel noted that there are no large cohort studies including biomarkers and highlighted the DH CRC Screening Programme as a potentially useful resource. It was suggested that potential participants be contacted between having a positive haemocol test text and the colonoscopy (this procedure would be paid for by the NHS).
- The panel noted that in order to validate biomarkers, it must be ensured that changes in the biomarker correlate with changes in disease occurrence.
- The panel warned that some contractors have tended to be over-optimistic in their predictions of effect size.
- The Agency should consider including (or 'piggy-backing') surrogate biomarkers in large-scale intervention trials investigating the impact of nutrition on cancer.
- The panel recommended that the programme should not be expanded to cover other cancers.

4. Review panel responses to discussion issues in the background paper

The panel agreed that all N12 projects are appropriate and relevant to the programme.

The panel agreed that the biomarker field has not progressed much since the initiation of the Programme five years ago; however, given the type of studies, one would not expect significant results in this time period.

They noted that biomarker studies do not have a big impact and therefore in isolation such studies are unlikely to influence policy. They stressed that biomarker intervention studies will help further the understanding of diet and colo-rectal cancer, leading to the development of dietary recommendations to help reduce colo-rectal cancer risk.

5. The scientific quality of the programme

The projects were assessed to be of a high scientific standard. The projects investigated mechanisms and processes fundamental to carcinogenesis and that were likely to be modified by dietary factors.

6. The programme's impact on Agency policy

The Agency aims to provide the best possible advice to consumers on a healthy balanced diet; this research programme aims to provide evidence to develop dietary recommendations and help reduce diet-related disease, i.e. colo-rectal cancer.

The biomarker studies, in themselves, do not have a big impact and in isolation such studies are unlikely to influence policy directly; however, achieving the objective of the programme would lead to the development of dietary recommendations to help reduce colo-rectal cancer risk.

7. Action plan

- To wait for the outcome of current projects/large scale trials before calling for further research in 2008/2009. The impact of this is that there will be no N12 call in 2007.
- To discuss the future of the N12 programme with the Research Co-ordination Unit and whether we should collaborate with MRC/BBSRC on this programme.
- To ascertain whether the N12 programme still fulfils an Agency's policy requirement.
- To work with the review panel and relevant experts to progress the programme

Annexes-See Workshop document for this information

A. RCU-B1 (ROAME A) statement

B. Table of projects in the programme, i.e. title, start and finish dates, contractor and total cost (£k)

C. Abstracts of presentations given at the review meeting

See Abstract booklet provided for review

D. Project summaries and outcomes of the research (including references to any published papers) and Reviewer's comments

See workshop booklet

E. List of delegates

Evaluation panel

Professor John Baron

Professor Timothy Key
Professor Young-In Kim
Professor Joseph Rafter
Professor David Shuker

Affiliation

Dartmouth College, New Hampshire
USA

University of Oxford
University of Toronto, Canada
Karolinska University, Sweden
The Open University, Milton Keynes

N12 project

contractors

Professor John Mathers

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