Institution: University of Bristol

Unit of Assessment: 1 – Clinical Medicine

Title of case study: Use of aspirin and high dietary fibre to prevent and reduce deaths from bowel and other cancers, influencing global policy on cancer prevention and major public health campaigns ('five-a-day').

1. Summary of the impact (indicative maximum 100 words)

Thousands of people across the world with a genetic predisposition (HNPCC) to bowel cancer, together with the population at large, have benefited from research on aspirin and dietary fibre undertaken at the University of Bristol since 1993. Clinical trials involving the Bristol group show that the incidence of bowel cancer has fallen in HNPCC patients who take aspirin. Moreover, aspirin use after diagnosis of bowel cancer has reduced colorectal cancer mortality. Furthermore, a high fibre diet also lowers the risk of bowel cancer. These studies led to national public health initiatives (such as the 'five-a-day' campaign) that have been instrumental in increasing public awareness of the importance of aspirin and dietary fibre in reducing the risk of bowel cancer, and in establishing international guidelines on dietary advice.

2. Underpinning research (indicative maximum 500 words)

Background to the need for novel preventive and treatment strategies for bowel cancer

Bowel cancer is the second most common cause of cancer-related deaths in the UK, with 16,000 deaths a year. Worldwide, 600,000 such deaths occur annually. Hence there is an urgent need to develop novel preventive and therapeutic strategies. It is also vital to increase public awareness of the causes of bowel cancer, since 60-80% of cases are preventable by dietary intervention. The University of Bristol-based Cancer Research UK Colorectal Tumour Biology Research Group was set up in 1993 to focus on new prevention and treatment strategies for bowel cancer. The research has been funded by five consecutive Cancer Research UK programme grants, running until 2015.

In the 1980s and early 1990s, epidemiological studies suggested a possible role for aspirin and dietary fibre in the prevention of bowel cancer, but there was very little scientific evidence for a plausible mechanism. Research into cancer prevention, although extremely important, is inherently challenging when dealing with a healthy population. Mechanistic studies on how dietary factors and aspirin prevent cancer, together with proof-of-principle chemoprevention trials in patients at high risk of cancer, such as HNPCC (hereditary nonpolyposis colorectal cancer) patients, are important because they can be extrapolated to the general worldwide population as well as other high cancer risk patients involving other major cancers such as breast, lung and prostate.

Dietary fibre

Work undertaken between **1993** and **1995** at Bristol was the first to show that the candidate chemopreventive agent, butyrate (bacterial fermentation product of dietary fibre), and other short chain fatty acids, induced apoptosis (programmed cell death) in human colorectal adenoma and carcinoma cells. This was the first report that candidate dietary chemoprevention agents can induce apoptosis and one of the very first cell culture models developed to study apoptosis.[1] [2].

Aspirin and other NSAIDs induce apoptosis in colorectal adenoma and carcinoma cells

Further studies between **1993** and **1997** showed for the first time that aspirin, a non-selective anti-inflammatory drug,[3] and cyclooxygenase-2 (COX-2) selective NSAIDs,[4] induce apoptosis in human colorectal adenoma and cancer cells. The use of human adenomas as well as cancers was important, from a prevention point of view, in investigating how adenomas regress and how to prevent adenomas becoming cancer.[1-4] The human colorectal adenoma cell lines used in these studies were the first in the world and were developed in the laboratory of Professor Paraskeva. They have been used worldwide ever since (cited in [1] [3]).

Aspirin as an adjuvant for treatment as well as in prevention

The findings that aspirin and COX-2 selective agents induced apoptosis led to the important hypothesis that these might also be used as adjuvants for bowel cancer as well as for cancer prevention;[5],[6] (also see BBA Reviews in Cancer, 2006, 1766,104-19).

Summary

These Bristol based discoveries [1-4] showing for the *first* time that butyrate and aspirin induce apoptosis in colon tumour cells were used as scientific evidence to justify further laboratory-based chemopreventive studies and, importantly, clinical and epidemiological trials to investigate the role of dietary fibre and aspirin in the prevention of bowel cancer.[a,d,e,f,k] Furthermore, trials to investigate whether aspirin can be a novel treatment for bowel cancer were also recommend by

the Bristol scientists.[5,6] Since these studies, the Bristol group has published over 60 papers on chemoprevention. More recently in **2012/13** the Bristol group has linked aspirin to inhibiting the survival of adenoma and cancer stem cells (Gut, 61,1306-14, 2012; Carcinogenesis, 34, 1150-7, 2013) providing a possible mechanisms of how NSAIDS cause adenoma regression and are chemopreventive as well as of therapeutic interest.

The first apoptosis studies [1] [2] published in Bristol were very timely, because they preceded the massive increase in apoptosis research which subsequently followed the realisation that defects in apoptosis regulation were important in carcinogenesis. In the mid-**1990s**, the publications and subsequent publicity obtained by Bristol through press releases about their research on dietary fibre/aspirin and apoptosis led Professor Paraskeva to be invited onto national clinical colorectal cancer committees (see section 4). While on these committees, he was involved in setting up subsequent clinical trials. Importantly, the mechanisms studies were used to support both aspirin and dietary fibre laboratory-based experimental studies as well as clinical/epidemiological trials (a,d,e,f,k, see section 5).

Those involved with the Bristol Research (Chemoprevention Grant Income to date >£7m)

Professor Chris Paraskeva is chemoprevention group leader (since 1993) and the research was all carried out at Bristol between 1993 and 2013. Other key individuals are: Ann Williams (CRC Fellow and now Professor (1990-date)); Hart was an intercalating medical student (1992-1993); Hicks was a university technician (1994-2012); and Hague (1993-2000), Elder (1993-1999), Qualtrough (2001-2006) and Smartt (2007-2012) were Cancer Research UK-funded scientists.

3. References to the research (indicative maximum of six references)

[1] Hague, A., Manning, A., Hanlon, K., Huschtscha, L.I., Hart, D., Paraskeva, C. (1993). Sodium Butyrate induces apoptosis in Human Colonic Tumour cell lines in a p53 independent pathway: Implications for the possible role of dietary fibre in the prevention of Large Bowel Cancer. Int. J. Cancer, 55, 498-505 (**cited >430**) (**All citations are Web of Science**) PMID: 8397167

[2] Hague, A., Elder, D.J.E., Hicks, D.J., Paraskeva, C. (1995). Apoptosis in colorectal tumour cells: induction by the short chain fatty acids butyrate, propionate and acetate and by the bile salt deoxycholate. Int. J. Cancer, 60, 400-406 (**cited >265**) PMID: 7829251

[3] Elder, D.J.E., Hague, A., Hicks, D.J., Paraskeva, C. (1996). Differential growth inhibition by the aspirin metabolite salicylate in human colorectal tumor cell lines: Enhanced apoptosis in carcinoma and in vitro-transformed adenoma relative to adenoma cell lines. Cancer Res., 56, 2273-2276. (**cited >160**) PMID: 8625297

[4] Elder, D.J.E., Halton, D.E., Hague, A., Paraskeva, C. (1997) Induction of apoptotic cell death in human colorectal carcinoma cell lines by a cyclooxygenase-2 selective non-steroidal anti-inflammatory drug: independence from cyclooxygenase-2 protein expression. Clin. Cancer Res., 3, 1679-1683. (c254) (**cited >290**) PMID: 9815550

[5] Elder, D.J.E., Paraskeva, C. (1998) COX-2 inhibitors for colorectal cancer. Nature Medicine, 4 (4), 392-393. PMID: 9546780

[6] Elder, D.J.E., Paraskeva, C. (1996). Are aspirin and other non-steroidal anti-inflammatory drugs effective in the prevention and treatment of colorectal cancer? Lancet, 348, 485 PMID: 8709821

Selected grants which have supported the work (Total of grants (non-selected) **>£7m)**

Cancer Research UK programme grant: Colorectal Tumour Cell Survival and Chemoprevention (2010-2015)
Total Grant £1,200,000
Grant Holders C. Paraskeva (Director) and A.C. Williams

Cancer Research UK programme grant: Regulation of apoptosis and prevention of colorectal cancer (2006-10)
Total Grant £1,025000
Grant Holders C. Paraskeva (Director) and A.C. Williams

Cancer Research UK Programme Grant: Apoptosis as a target for prevention and therapy in colorectal cancer (2001-06)
Total Grant £800,000
Grant Holders C. Paraskeva (Director) and A.C. Williams

Cancer Research Campaign Programme Grant: Cell and Molecular Biology of Colorectal Cancer (1996–2001)
Total Grant £650,000
Grant Holders C. Paraskeva (Director) and A.C. Williams

Cancer Research Campaign Programme Grant: Cell and Molecular Biology of Colorectal Cancer (1993-1996)
Total Grant £500,000
Grant Holders C. Paraskeva (Director) and A.C. Williams

4. Details of the impact (indicative maximum 750 words)

Impact of CRUK publications on committee invitations and development of clinical trials

Publications [1-4] and press releases in the 1990s importantly led to Professor Paraskeva being invited onto several UK national research and trials committees and pharmaceutical scientific advisory committees (Merck), which organised clinical trials, including: Medical Research Council (MRC) Molecular and Cellular Medicine Board (1996-1998); MRC Advisory Board (1998-2003); National Translational Cancer Research Network (NTRAC) Clinical Study Group (2002-2005); UK Co-ordinating Committee on Cancer Research (UKCCCR) Sub-Committee on Colorectal Cancer (1996-2001); National Cancer Research Institute (NCRI) Colorectal Clinical Studies Group (2001-2005); the World Cancer Research Fund International Grant Panel (2010-date).
Membership of these committees led to Professor Paraskeva's direct involvement in clinical trials such as the CAPP2 study below.

Aspirin significantly reduces colorectal cancer incidence in HNPCC hereditary bowel cancer patients (CAPP2 trial) at very high risk of bowel cancer

Professor Paraskeva was a collaborator and on the Data Monitoring Committee of an international trial examining aspirin's ability to reduce bowel cancer incidence in high-risk HNPCC patients published in **2011.**[a] The study involved 861 people and showed that 600mg of aspirin a day for a mean of 25 months significantly reduced bowel cancer incidence in carriers of hereditary bowel cancer.[a] CAPP2 was the first randomised trial of aspirin as a chemopreventive agent with cancer as the primary endpoint. It is of particular importance since HNPCC is the most common form of hereditary bowel cancer, affecting thousands of people worldwide, and provides a basis for recommendation of aspirin chemoprevention in HNPCC patients as standard of care.[a] This Lancet publication received worldwide TV, radio and newspaper exposure.[b] [c] The Bristol work on apoptosis as a plausible mechanism for the chemopreventive action of aspirin,[3] justifying further trials, continues to be cited in journals such as the Lancet (reference [3]; cited in [d]).

Impact of high dietary fibre on reducing the risk of bowel cancer in the general population and increasing public awareness

Research from Bristol on dietary fibre and apoptosis [1] [2] has been cited as a plausible mechanism to support the chemopreventive properties of fibre and to justify further research (for example, cited in [e]) and there have been a number of high profile publications reporting that high dietary fibre is associated with a reduced risk of colorectal cancer ([f], and papers cited in [f]). Importantly, the research and subsequent publicity has also influenced global policy on cancer prevention and major public health campaigns (five-a-day) and increasing fibre may be influential in reducing other obesity-related cancers, such as breast cancer.[e-j]

Impact of aspirin as an adjuvant therapy for colorectal cancer

The finding that aspirin induced apoptosis in adenoma and cancer cells led to the proposal that aspirin be used as an adjuvant to treat bowel cancer and not just in prevention;[3-6] (also see BBA Reviews in Cancer, 2006, 1766,104-19).Two independent epidemiological studies in **2009** and **2012** involving over 2,000 patients have shown that regular aspirin use after diagnosis of colorectal cancer is associated with lower risk of colorectal cancer-specific and overall mortality. Thus aspirin, as originally hypothesized,[5] [6] shows promise as an adjuvant to cancer therapy [k] as well as in chemoprevention,[a] and has saved a large number of lives of patients with bowel cancer.[k]

Impact of aspirin on saving lives in several major cancers, not just colorectal cancer

Daily aspirin intake was reported in **2011** to reduce deaths in a number of other human cancers including brain, oesophageal, lung, prostate and stomach cancer, as well as colorectal cancer. The paper concerned (Lancet, 2011,377,31-41) cites the Elwood 2009 Lancet paper,[d] which in turn cites the Paraskeva 1996 Cancer Research paper.[3]

Impact of Bristol publications on national and international public awareness and public understanding of cancer prevention

The four original publications [1-4] not only led to invitations onto influential committees (see section 4) and involvement in clinical trials (as noted above) but also to the Bristol Beating Bowel Cancer (BBBC) Public Fund Raising Campaign in the late 1990s, run jointly between the University of Bristol and the Cancer Research Campaign (CRC). This led to posters of men's and women's

bottoms throughout Bristol and a public campaign to increase awareness of bowel cancer. BBBC raised £1.5m of new money for bowel cancer research, and their appeal was debated favourably in the Houses of Parliament: House of Commons Hansard Debates for 6 Jul 1999 (pt 4).
The importance of diet and dietary fibre in cancer prevention generally, as well as in bowel cancer, was a successful BBBC public awareness campaign. Professor Paraskeva has given 6-10 public talks per year on cancer awareness and cancer prevention for nearly 30 years. For example, in **2012-13** two public talks given at Bristol's M Shed and Watershed both attracted audiences of more than 100. Every year several dozen members of the public have tours and cancer prevention talks at the Bristol Cancer Research UK Laboratories.

International impact of Bristol publications and clinical trials on public understanding

International and national radio and newspaper coverage was given to the Bristol fibre and aspirin research publications.[1-4] The research has led to a considerable increase in public awareness of the role of diet and fibre in reducing the risk of bowel cancer and other cancers and has led to NHS Direct [g] and prestigious US agencies (Mayo Clinic [h] and NIH) to recommend a high-fibre diet. The famous 'five-a-day' slogan is also linked to dietary fibre. The World Cancer Research Fund, a major international cancer prevention charity, has stated from a recent report that they have found strong evidence that foods containing dietary fibre decrease the risk of bowel cancer and they recommend an increase in dietary fibre.[i] [j]

Impact of Bristol's Colon Cancer Group publications on clinical trials development

The original four research papers published by the Bristol Cancer Research UK Colorectal Cancer Group, showing that butyrate/fibre/aspirin induces apoptosis in human colorectal cancer and adenoma cells [1-4], have been cited over 1,000 times and led to more than 60 publications. They continue to be cited as evidence in discussions of the case for using aspirin for bowel cancer prevention (paper 3 cited in Lancet, 2009 [d]), and in the justification for clinical trials reported above and future such studies.

5. Sources to corroborate the impact (indicative maximum of 10 references)

[a] *Study corroborating Aspirin significantly reduced bowel cancer incidence in carriers of hereditary bowel cancer:* Long-term effect of aspirin on cancer risk in carriers of hereditary colorectal cancer: an analysis from the CAPP2 randomised controlled trial PMID: 22036019

[b] *National Cancer Institute website publicising above paper (a) showing aspirin reduces bowel cancer incidence:* http://www.cancer.gov/ncicancerbulletin/110111/page4

[c] *BBC news bulletin publicising above paper (a) showing aspirin reduces bowel cancer incidence:* http://www.bbc.co.uk/news/health-15475553

[d] *Lancet paper citing our research on aspirin preventing bowel cancer and apoptosis*: Aspirin, salicylates, and cancer Elwood et al (2009). The Lancet 373,1301-1309 PMID: 19328542

[e] *Major publication citing our research on fibre and bowel cancer prevention and apoptosis:* World Cancer Research Fund, 1997 publication. Food, Nutrition and the Prevention of Cancer: a global Perspective. ISBN: 1 899533 05 2. Can be supplied on request.

[f] *Publication corroborating that fibre reduces bowel cancer risk:* Dietary fibre, whole grains, and risk of colorectal cancer: systematic review and dose-response meta-analysis of prospective studies. *BMJ* 2011; 343 doi: 10.1136/bmj.d6617 (10 November 2011). Cite this as: BMJ 2011;343:d6617 PMID: 22074852

[g] *NHS choices and bulletins and public information on why Fibre and "5 A Day" is important:*
(i) http://www.nhs.uk/chq/pages/1141.aspx?categoryid=51&subcategoryid=167
(ii) http://www.nhs.uk/LiveWell/5ADAY/Pages/5ADAYhome.aspx

[h] *Mayo clinic bulletin: major USA clinic advising high fibre diets prevent bowl cancer:* http://www.mayoclinic.com/health/colon-polyps/DS00511/DSECTION=prevention

World Cancer Research Fund bulletins (i and j) that fibre reduces bowel cancer risk and recommending high fibre diets also for other cancers:

[i] http://www.wcrf-uk.org/cancer_prevention/recommendations/plant_foods_and_cancer.php

[j] http://www.wcrf-uk.org/cancer_prevention/types_of_cancer/bowel_cancer.php

[k] *Publications corroborating aspirin for the treatment as well as prevention of bowel cancer:*
(i) Aspirin Use and Survival after Diagnosis of Colorectal Cancer (2009). JAMA, 302, 649-658. PMID: 19671906
(ii) Aspirin use PI3CA mutation and Colorectal-Cancer Survival (2012). NEJM 2012, 367, 1596-1606. PMID: 23094721