Cancer Network Newsletter
September-December 2020

University of BRISTOL
Elizabeth Blackwell Institute for Health Research

New Cancer Research Network Co-Leads

The Bristol Cancer Research Network has experienced a change in leadership.

Paul Martin, Professor of Cell Biology in the Schools of Biochemistry and Physiology, Pharmacology and Neuroscience, has stepped down as the basic science lead after more than five years in post. Thanks are extended to him for his indefatigable work, alongside clinical lead Dr Axel Walther, in creating the Network and bringing Bristol cancer research to the fore.

Prof Anne Ridley, Head of School of Cellular and Molecular Medicine, takes up the mantle as basic science co-lead. Her group studies how cell migration contributes to cancer progression. Cell migration underlies the invasion and metastasis of tumour cells, as well as immune response to tumours; the research focuses on Rho family GTPases, which coordinate cell migration by driving cytoskeletal and cell adhesion dynamics with the aim of identifying proteins that could be targeted therapeutically to treat cancer.

Dr Axel Walther will continue to act as clinical co-lead. He is a Consultant Medical Oncologist at the Bristol Cancer Institute (University Hospitals Bristol NHS Foundation Trust) and lead of the clinical trials unit there. He also holds an Honorary Senior Lectureship with the University of Bristol. Axel specialises in the use of chemotherapy, novel agents and immunotherapy to treat cancer patients, particularly those with gynaecological and bowel cancers.

Richard Martin, Professor of Clinical Epidemiology, is the new co-lead in epidemiology, which is playing an ever-increasing role in the prevention and early diagnosis of cancer. His research looks at prostate cancer aetiology (with a focus on metabolic factors), predicting its progression and secondary and tertiary prevention of the disease via population-based screening and low-toxicity nutritional and lifestyle interventions.

Welcome all!

Inside this issue:

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EVENTS

Bristol Research Forum on Ageing
15 September 2020, 14.00 - 15.30, online

Health Innovation Day 2020: Implementation of information driven care – from data driven insights to health care improvement
17 September 2020, 9.00 - 16.15, online

Prediction Methods for Health and Care should focus on Benefits, not Risks
17 September 2020, 12.00 - 14.00, Prof Niels Peek (University of Manchester), online

CRUK / Start Codon Entrepreneurial Training webinar: Bringing Your Product to Patients
17 September 2020, 12.00 - 13.00, Dr Michelle Griffin, online

startcodon | CANCER RESEARCH UK

RoB 2: Learning Live webinar series: Bias in measurement of the outcome
17 September 2020, 15.00 - 16.00, Asbjørn Hrobjartsson (Professor of evidence based medicine & clinical research methodology, Department of Clinical Research, University of Southern Denmark), Isabelle Boutron (Professor of epidemiology, Université de Paris), online

Cochrane Training

Elizabeth Blackwell Institute Focus Week: COVID-19
21 - 25 September 2020, online

University of BRISTOL
Elizabeth Blackwell Institute for Health Research

Cancer Research UK Online Project Launch and Networking Session
22 September 2020, 9.45 - 12.30, online

2020 Bristol Health Partners Health Integration Teams Virtual Conference: The Impact of COVID-19 - Leading positive change in a changing world
28 September 2020, 14.00 - 16.30, Sir Robert Lechler, Prof Adam Finn, Councillor Asher Craig, online

Bristol Health Partners

Crick Cancer Research Symposium
5 - 6 October 2020, Keynote: Fiona Watt, FRS FMedsci, Crick Institute and Zoom

THE FRANCIS CRICK INSTITUTE

Early Detection of Cancer Conference
6 - 8 October 2020, online

RoB 2: Learning Live webinar series: Bias in selection of the reported result
15 October 2020, 9.00 - 10.00, Matt Page (Research Fellow, School of Public Health and Preventive Medicine at Monash University) and Isabelle Boutron

SEE ALL EVENTS ON THE CANCER RESEARCH NETWORK WEBSITE

EVENTS CON'T

Cancer Research UK Online Project Launch and Networking Session

22 September 2020, 9:45 - 12:30, online

Register here

Around 60,000 patients in the UK are living with a brain tumour. Overall, only 20% of brain tumour patients are alive five years after diagnosis, in part because they present late with large inoperable tumours.

In the UK in 2013 38 percent of brain tumour patients visited their GP five times or more before referral to secondary care for diagnosis by imaging MRI/CT scan and neurosurgical biopsy, because symptoms, such as headache, are so non-specific.

University of Bristol Principal Investigators Dr Kathreena Kurian (Bristol Medical School: Population Health Sciences) and Dr Sabine Hauert (Department of Engineering Mathematics) have been awarded just under £500,000 from Cancer Research UK's Early Diagnosis Project Grant team to Develop a cheap sensitive blood test for early detection of new and proven biomarkers of glioblastoma using fluorescent carbon dots and nanophotonics which will start in October 2020.

The team includes a number of co-leads: Dr Neciah Dorh (FluoretiQ Limited), Prof Carmen Galan (Chemistry), Prof Richard Martin (Bristol Medical School: Population Health Sciences) and patient/charity lead Dr Helen Bulbeck (Brainstrust).

This research project will explore the use of nanoparticles to fluorescently label very low levels of biomarkers in blood samples and other fluids and thus develop a new, quick and affordable test to detect early stage brain tumours without the need for costly or invasive procedures.

Come and join members of the research team as they explain how the research idea was conceived, developed and turned into a funding application, and gain insight into how an interdisciplinary team comprising clinicians, academics, industrial partners and charity representatives worked together to successfully build a concept into a workable project.

CANCER RESEARCH UK | NHS North Bristol NHS Trust | University of BRISTOL

Cancer Research UK Online Project Launch and Networking Session

Development of a cheap sensitive blood test for early detection of new and proven biomarkers of glioblastoma using fluorescent carbon dots and nanophotonics

22 September 2020

PROGRAMME

Chair: *Kathreena Kurian*

09:45 - 09:50	Welcome: John Iredale	PVC (Health), Bristol
09:50 - 10:05	David Crosby	Head of Prevention and Early Detection Research, CRUK
10:05 - 10:20	Kathreena Kurian / Ping Chen	Brain Cancer
10:20 - 10:35	Sabine Hauert	Modelling
10:35 - 10:50	Neciah Dorh	FluoretiQ Ltd.
10:50 - 11:10	Break / Networking	
11:10 - 11:25	Carmen Galan	Nanotechnologies
11:25 - 11:40	Richard Martin	Cancer Epidemiology
11:40 - 11:55	Julie Stock	CRUK Entrepreneurs
11:55 - 12:10	Helen Bulbeck	Brainstrust
12:10 - 12:30	Networking	

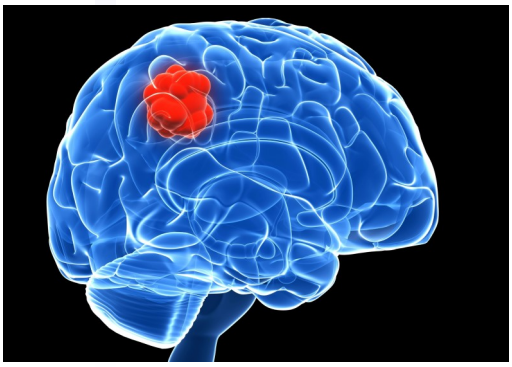
NEWS

Blood tests to diagnose brain tumours

A new simple blood test for brain tumours that could be used by GPs in primary care will be developed thanks to funding of nearly £500,000 by Cancer Research UK. Around 60,000 patients in the UK are living with a brain tumour, but only 20% of patients are still alive five years after diagnosis, partly because they present late with large inoperable tumours.

The University of Bristol-led research project to develop an affordable, point of care blood test to diagnose brain tumours earlier using fluorescent carbon dots and nanophotonics will be headed by Dr Kathreena Kurian (Bristol Medical School) and Dr Sabine Hauert (Engineering Mathematics) in collaboration with co-investigators: Profs Carmen Galan (Chemistry) and Richard Martin (Bristol Medical School) and Drs Necia Dorh (FluoretiQ Limited) and Helen Bulbeck (Brainstrust).

In the UK in 2013, 38% of brain tumour patients visited their GP five times or more before being referred for diagnosis by imaging MRI/CT scan and neurosurgical biopsy, because the symptoms such as headache are non-specific. There is an urgent need to develop new tests for brain tumours to help GPs diagnose brain tumours earlier, faster and at reduced cost. This project aims to discover new blood biomarkers for brain cancer and state-of-the-art technology that allows for its sensitive detection.



Read more about the project

Cancer and Sleep (and other videos)

The Cancer Research UK-funded Integrative Cancer Epidemiology Programme (ICEP) has commissioned a series of videos, *ICEP Shorts*, in which researchers give a brief overview of their work.

On 8 July 2020 Dr Rebecca Richmond (Vice Chancellor's Fellow, Bristol Medical School) and Bryony Hayes (PhD student) summarised their findings showing that people with a morning preference have a lower risk of breast cancer. They outline plans for future research on sleep and health, including whether changing work patterns to accommodate natural sleep cycles could improve our health as a nation.

On 15 June 2020 Prof Richard Martin (Bristol Medical School) asked *Can exercise help prevent cancer?* by reviewing findings that show that regular exercise helps to prevent cancers of the bowel, breast and prostate.

The latest upload, *Can statins prevent ovarian cancer?*, comprises an animation providing an overview of research, led by Dr James Yarmolinsky (Bristol Medical School) suggesting that long-term use of statin medications could lower ovarian cancer risk.

Funding successes and external engagements

Dr Bethan Lloyd-Lewis (Vice Chancellor's Fellow, Cellular and Molecular Medicine) has won two years funding via the Springboard Award from the **Academy of Medical Sciences**.

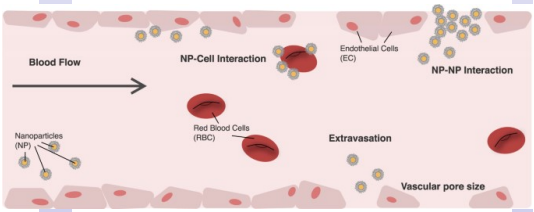
Dr Claire Perks and Kalina Biernacka (Bristol Medical School: Translational Health Sciences) participated in the UK Interdisciplinary Breast Cancer Symposium in January 2020. The meeting aimed to provide all those with an active interest in breast cancer research and treatment an opportunity to consider and discuss how the latest advances may impact upon their and others' areas of expertise. Treatment of breast cancer has for many years been dependent on the interaction of professionals from many disciplines, and research into improving our understanding of this complex disease—as well as prospects for improving its prevention and treatment— require interdisciplinary collaboration to make meaningful advances.

The latest lab tours for Cancer Research UK volunteers took place at Southmead in January 2020. Dr Claire Perks told an audience of CRUK supporters about the work of the Integrative Cancer Epidemiology Programme, and staff from CRUK spoke more broadly about the work of the organisation. This was followed by a series of lab challenges.

Congratulations to Dr Bethan Lloyd-Lewis for taking first place in the University of Bristol Art of Science 2020 exhibition with her submission entitled *Stemming the Flow*.

Nanoparticles in the treatment of cancer

Nanoparticles promise to improve the treatment of cancer through their increasingly sophisticated functionalisations and ability to accumulate in certain tumours. Yet recent work has shown that many nanomedicines fail during clinical trial. One issue is the lack of understanding of how nanoparticle designs impact their ability to overcome transport barriers in the body, including their circulation in the blood stream, extravasation into tumours, transport through tumour tissue, internalisation in the targeted cells, and release of their active cargo. Increased computational power, as well as improved multi-scale simulations of tumours, nanoparticles, and the biological transport barriers that affect them, now allow us to investigate the influence of a range of designs in biologically relevant scenarios. This presents a new opportunity for high-throughput, systematic, and integrated design pipelines powered by data and machine learning. With this paper, we review latest results in multi-scale simulations of nanoparticle transport barriers, as well as available software packages, with the aim of focussing the wider research community in building a common computational framework that can overcome some of the current obstacles facing efficient nanoparticle design.

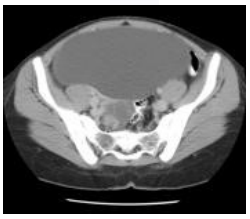


Stillman NR… Hauert S (2020). In silico modelling of cancer nanomedicine, across scales and transport barriers. *Nature npg Computational Materials.* 6: 92.

Could statins lower the risk of ovarian cancer?

In the UK, ovarian cancer is the sixth most common cancer in females. A new study has found evidence to suggest that statins could lower the risk of women developing ovarian cancer. Using Mendelian randomization, which can more reliably evaluate causal relationships between characteristics, such as drug targets, molecular traits, behaviours and health outcomes, researchers found evidence to suggest that statins may lower the risk of ovarian cancer. The findings were shown in both women who had no known family history of ovarian cancer and in those with mutations in BRCA1 or BRCA2 genes that put them at a higher lifetime risk of the disease.

If the findings were to be confirmed in a randomised controlled trial, statin use could be a viable non-surgical approach for reducing the risk of women developing ovarian cancer in the future, including women who are carriers of BRCA1/2 mutations and are thus at increased risk of developing ovarian cancer over their lifetime. The team's findings suggest that the use of statins, which are commonly prescribed, inexpensive, and safe, might be a new method for cancer prevention, as there are very few proven non-surgical approaches available to lower the risk of ovarian cancer.



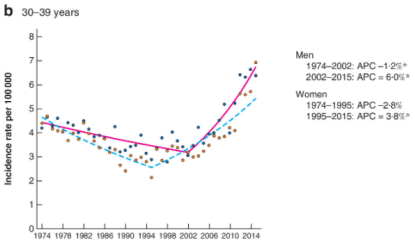
Yarmolinsky J *et al*. (2020). Association Between Genetically Proxied Inhibition of HMG-CoA Reductase and Epithelial Ovarian Cancer. *JAMA*.

Increase in bowel cancer in young adults

Using NHS patient data from the last 40 years, Mr Adam Chambers (Cellular and Molecular Medicine and Colorectal Registrar at University Hospitals NHS Foundation Trust) looked at more than 55,000 cases of colorectal cancer over 40 years in England.

Age has always been a major risk factor for bowel cancer, with the majority of cases being diagnosed in patients over 60 and therefore bowel cancer screening has focused on older age groups. However, this study shows that over the past 30 years, there has been an exponential increase in the incidence of bowel cancer among adults under 50.

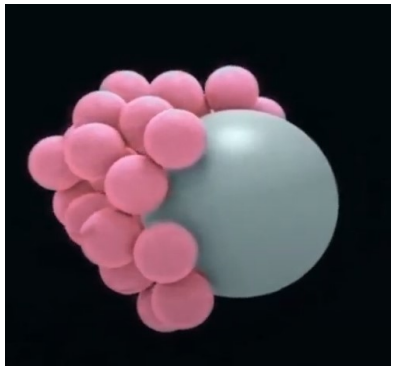
The study highlights the increase in bowel cancer incidence in young people is predominantly driven by an increase in tumours of the lowermost portion of the bowel, specifically the sigmoid colon and rectum. While this increase does not appear to be associated with gender or socioeconomic status, there are some marked geographical variations. The fastest increase in bowel cancer incidence was observed in southern regions, with an increase of more than ten per cent per year in the south west. The study supports the findings from recent European and American studies that also showed the incidence of bowel cancer to be increasing quickly in young adults and, importantly, provides far greater detail on how this relates to the characteristics of the young adult population.



Chambers AC *et al*. (2020). Demographic trends in the incidence of young-onset colorectal cancer: a population-based study. *BJS*.

Next generation cell therapies for cancer

University of Bristol spin-out company CytoSeek uses cell membrane augmentation technology to unlock the potential of next generation cell therapies, with a focus on treating solid tumours. In acknowledgment of World Cancer Day on 4 February 2020, the company created a video explaining how they are looking to revolutionise cancer therapies that target only cancer cells and leave healthy cells untouched.



World Cancer Day is an initiative of the Union for International Cancer Control (UICC), the largest and oldest international cancer organisation dedicated to taking the lead in convening, capacity building and advocacy initiatives that unite the cancer community to reduce the global cancer burden, promote greater equity, and integrate cancer control into the world health and development agenda.

Watch the video

Policy report: The Causes of Cancer

The Integrative Cancer Epidemiology Programme (ICEP) released a policy report in June 2020 which summarises key ICEP findings, and their policy implications, on:

- overweight and obesity
- physical activity
- sleep
- statins and ovarian and breast cancer
- diagnosing lung cancer
- screening for prostate cancer
- cancer and vitamin D

The knowledge outlined in the report can contribute to cancer prevention, its early detection and its treatment.

Between 2014 and 2019 ICEP produced over 120 peer reviewed scientific papers and nine database and analytical platforms that are openly accessible and widely used by the scientific and research community around the world. The programme has trained numerous scientists and doctors in population-based cancer sciences, including both at the University of Bristol and at overseas institutions. Several of the programme's investigators are amongst the most world's most highly cited researchers. We also have collaborations with the pharmaceutical industry in a programme of work to identify novel drug targets for cancer prevention.

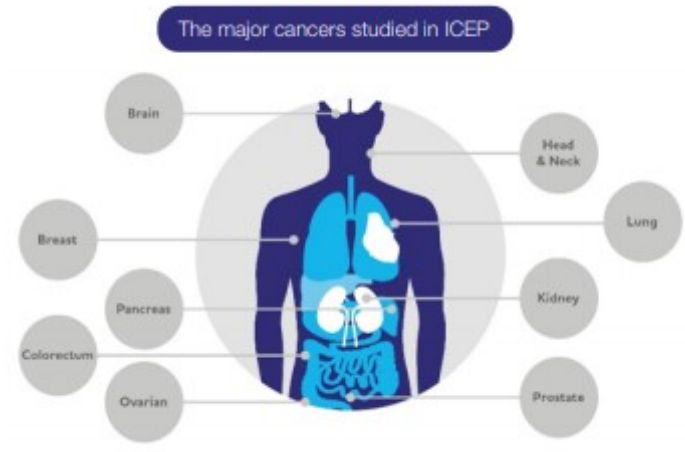
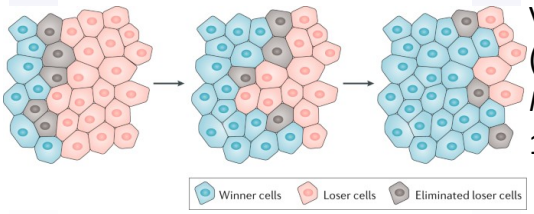


Image by Dirty Design Ltd

Read the report

Outcompeting cancer

The tumour microenvironment plays a critical role in determining tumour fate. Within that environment, and indeed throughout epithelial tissues, cells experience competition with their neighbours, with those less fit being eliminated by fitter adjacent cells. In this article, the authors discuss evidence suggesting that mutations in cancer cells may be selected for their ability to exploit cell competition to kill neighbouring host cells, thereby facilitating tumour expansion. In some instances, cell competition may help host tissues to defend against cancer, by removing neoplastic and aneuploid cells. Cancer risk factors, such as high-sugar or high-fat diet and inflammation, impact cell competition-based host defences, suggesting that their effect on tumour risk may in part be accounted for by their influence on cell competition. They propose that interventions aimed at modifying the strength and direction of cell competition could induce cancer cell killing and form the basis for novel anticancer therapies.



Vishwakarma M and Piddini E (2020). Outcompeting Cancer. *Nature Reviews Cancer*. 20: 187-198.

Looking for links between identified risk factors and glioma

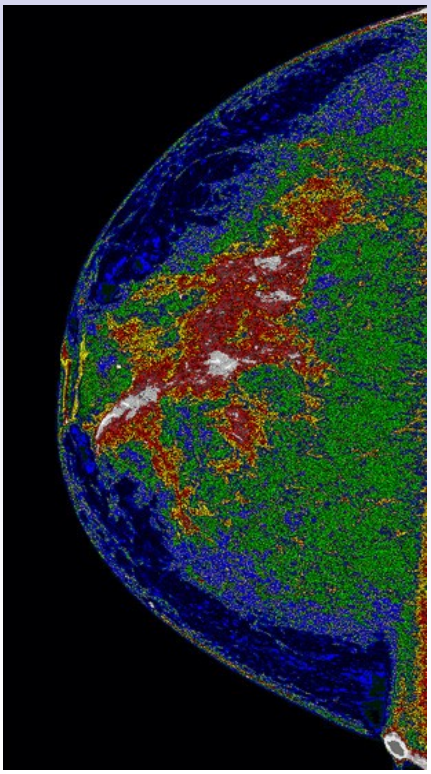
Whilst epidemiological studies have provided evidence of associations between certain risk factors and glioma onset, inferring causality has proven challenging. Using Mendelian randomization (MR), a team assessed whether associations of 36 reported glioma risk factors showed evidence of a causal relationship. The researchers performed a systematic search of MEDLINE from inception to October 2018 to identify candidate risk factors and conducted a meta-analysis of two glioma genome-wide association studies. MR analyses were performed using genetic variants to proxy for candidate risk factors. They investigated whether risk factors differed by subtype diagnosis (either glioblastoma or non-glioblastoma). Their search identified 36 risk factors that could be proxied using genetic variants. Using MR, the team found evidence that four genetically predicted traits increased risk of glioma, glioblastoma or non-glioblastoma: longer leukocyte telomere length, liability to allergic disease, increased alcohol consumption and liability to childhood extreme obesity. Two traits decreased risk of non-glioblastoma cancers: increased low-density lipoprotein cholesterol (LDLc) and triglyceride levels. The findings were similar across sensitivity analyses that made allowance for pleiotropy (genetic confounding). The investigation provides evidence of a causal link between both genetically predicted leukocyte telomere length, allergic disease, alcohol consumption, childhood extreme obesity, and LDLc and triglyceride levels, and glioma. The findings warrant further research to uncover mechanisms that implicate these traits in glioma onset.

Howell AE, Robinson JW, Wootton RE *et al*. (2020). Testing for causality between systematically identified risk factors and glioma: a Mendelian randomization study. *BMC Cancer*. 20:508.

The effect of lipids and breast cancer risk

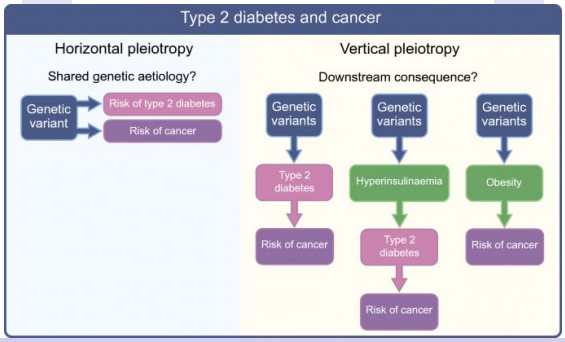
Circulating lipids have been associated with breast cancer (BCa). This association may, in part, be due to an effect of lipids on insulin-like growth factors (IGFs), which have been reliably associated with BCa. In two-sample Mendelian randomization (MR) analyses, a research team found that low density lipoprotein (LDL-C) was associated with IGFBP-3 and IGFBP-3 was associated with 40 postmenopausal BCa. They also found that triglycerides were associated with IGF-I and that IGF-I was associated with overall BCa. Taken together, these results suggest that IGFBP-3 may be a potential causal step between LDL-C and postmenopausal BCa and IGF-I a potential causal for triglycerides. These two-step MR results build on evidence linking circulating lipids and IGFs with BCa, however, multivariable MR analyses are currently unable to support this relationship due to weak instruments.

Tan V *et al*. (preprint). Estimating the effect of lipids on IGF axis and subsequent breast cancer risk. *medRxiv*.



Deciphering the link between type 2 diabetes and cancer

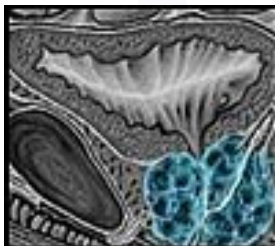
Recent developments in the field of genetics have accelerated our understanding of the aetiology of complex diseases. Type 2 diabetes mellitus and cancer are no exception, with large-scale genome-wide association studies (GWAS) facilitating exploration of the underlying pathology. Here, we discuss how genetics studies can be used to investigate the relationship between these complex diseases. Observational epidemiological studies consistently report that people with type 2 diabetes have a higher risk of several types of cancer. Indeed, type 2 diabetes and cancer share many common risk factors, such as obesity, ageing, poor diet and low levels of physical activity. However, questions remain regarding the biological mechanisms that link these two diseases. Large-scale GWAS of type 2 diabetes and cancer allow us to consider the evidence for shared genetic architecture. Several shared susceptibility genes have been identified, yet tissue specificity and direction of effect must be taken into account when considering common genetic aetiology. We also consider how GWAS, and associated techniques such as Mendelian randomisation, allow us to dissect the link between the two diseases and address questions such as 'Does type 2 diabetes cause cancer or is the increased risk observed driven by higher adiposity or another associated metabolic feature?'



Vincent E and Yaghootkar H (2020). Using genetics to decipher the link between type 2 diabetes and cancer: shared aetiology or downstream consequence? *Diabetologia*. 63: 1706-1717.

Cost-effective analysis of prostate cancer therapies

There is limited evidence relating to the cost-effectiveness of treatments for localised prostate cancer. The cost-effectiveness of active monitoring, surgery, and radiotherapy was evaluated within the Prostate Testing for Cancer and Treatment (ProtecT) randomised controlled trial from a UK NHS perspective at 10 years' median follow-up. Prostate cancer resource-use collected from hospital records and trial participants was valued using UK reference-costs. Adjusted mean costs, QALYs, and incremental cost-effectiveness ratios were calculated; cost-effectiveness acceptability curves and sensitivity analyses addressed uncertainty; subgroup analyses considered age and disease-risk. Active monitoring had lower adjusted mean costs (£5913) than radiotherapy (£7361) and surgery (£7519). Radiotherapy was the most likely (58% probability) cost-effective option at the UK NICE willingness-to-pay threshold (£20,000 per QALY). Subgroup analyses confirmed radiotherapy was cost-effective for older men and intermediate/high-risk disease groups; active monitoring was more likely to be the cost-effective option for younger men and low-risk groups. Longer follow-up and modelling are required to determine the most cost-effective treatment for localised prostate cancer over a man's lifetime.



Nobel SM *et al*. (2020). The ProtecT randomised trial cost-effectiveness analysis comparing active monitoring, surgery, or radiotherapy for prostate cancer. *British Journal of Cancer*.

Viral antibodies define nasopharyngeal carcinoma

Epstein-Barr virus (EBV) causes nasopharyngeal carcinoma (NPC) in endemic regions, where almost every tumour is EBV-positive. In Western populations, NPC is rare, and human papillomavirus infection (HPV) has been suggested as another viral cause. A team validated multiplex serology with molecular tumour markers, to define EBV-positive, HPV-positive and EBV-/HPV-negative NPCs in the United Kingdom, and analysed survival differences between those groups. Sera from NPC cases and age- and sex-matched controls from the Head and Neck 5000 clinical cohort study were analysed. IgA and IgG serum antibodies against 13 EBV antigens were measured and compared with EBER *in situ* hybridisation (EBER-ISH) data of 41 NPC tumours (29 EBER-ISH positive, 12 negative). IgG antibodies to EBV LF2 correctly diagnosed EBV-positive NPCs in 28 of 29 cases, while all EBER-ISH negative NPCs were seronegative to LF2 IgG. HPV early antigen serology was compared to HPV molecular markers available for 41 NPCs (13 positive, 28 negative). Serology matched molecular HPV markers in all but one case. EBV and HPV infections were mutually exclusive. Overall, 67% of the analysed NPCs were defined as EBV-positive, 18% as HPV-positive and 14% as EBV/HPV-negative. There was no statistical evidence of a difference in survival between the three groups. These data provide evidence that both, EBV-positive and HPV-positive NPCs are present in a low incidence country, and that EBV and HPV serum antibodies correlate with the viral status of the tumour.

Simon J *et al*. (2020). Epstein-Barr virus and human papillomavirus serum antibodies define the viral status of nasopharyngeal carcinoma in a low endemic country. *International Journal of Cancer*.

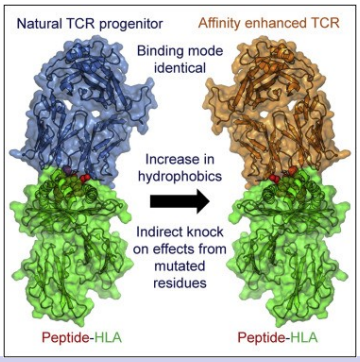
The management of malignant pleural effusions

Malignant pleural effusion (MPE) is a common problem for people with cancer. A number of treatment options are available to manage the uncontrolled accumulation of pleural fluid, including administration of a pleurodesis agent (via a chest tube or thoracoscopy) or placement of an indwelling pleural catheter (IPC). This study aimed to ascertain the optimal management strategy for adults with malignant pleural effusion in terms of pleurodesis success and to quantify differences in patient-reported outcomes and adverse effects between interventions. Two review authors independently extracted data on study design, characteristics, outcome measures, potential effect modifiers and risk of bias of randomised controlled trials of intrapleural interventions for adults with symptomatic MPE, comparing types of sclerosant, mode of administration and IPC use. They performed network meta-analyses of primary outcome data and secondary outcomes. Based on the available evidence, talc poudrage and talc slurry are effective methods for achieving a pleurodesis, with lower failure rates than a number of other commonly used interventions. IPCs provide an alternative approach.

Dipper A *et al*. (2020). Interventions for the management of malignant pleural effusions: a network meta-analysis. *Cochrane Systemic Review*.

Molecular rules for immunotherapy

Immuno-oncology approaches that utilise T cell receptors (TCRs) are becoming highly attractive because of their potential to target virtually all cellular proteins, including cancer specific epitopes, via the recognition of peptide-human leukocyte antigen complexes (pHLA) presented at the cell surface. However, because natural TCRs generally recognise cancer derived pHLAs with very weak affinities, efforts have been made to enhance their binding strength, in some cases by several million-fold. Here, we investigated the mechanisms underpinning human TCR affinity enhancement by comparing the crystal structures of engineered enhanced affinity TCRs with that of their wildtype progenitors. Additionally, we performed molecular dynamics simulations to better understand the energetic mechanisms driving the affinity enhancements. These data demonstrate that supra-physiological binding affinities can be achieved without altering native TCR-pHLA binding modes via relatively subtle modifications to the interface contacts, often driven through the addition of buried hydrophobic residues. Individual energetic components of the TCR-pHLA interaction governing affinity enhancements were distinct and highly variable for each TCR, often resulting from additive, or knock-on, effects beyond the mutated residues. This comprehensive analysis of affinity enhanced TCRs has important implications for the future rational design of engineered TCRs as efficacious and safe drugs for cancer treatment.



Crean RM *et al.* (2020). Molecular rules underpinning enhanced affinity binding of human T cell receptors engineered for immunotherapy. *Molecular Therapy: Oncolytics*.

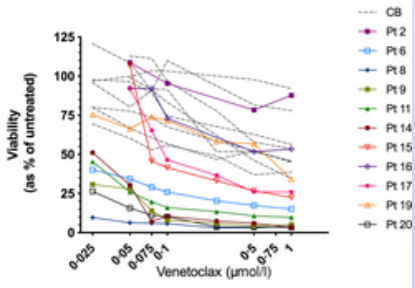
Exercise and risks of breast and colorectal cancer

Physical activity has been associated with lower risks of breast and colorectal cancer in epidemiological studies; however, it is unknown if these associations are causal or confounded. In two-sample Mendelian randomisation analyses, using summary genetic data from the UK Biobank and GWA consortia, a research team found that a one standard deviation increment in average acceleration was associated with lower risks of breast cancer and colorectal cancer. They found similar magnitude inverse associations for oestrogen positive (ER+ve) breast cancer and for colon cancer. The results support a potentially causal relationship between higher physical activity levels and lower risks of breast cancer and colorectal cancer. Based on these data, the promotion of physical activity is probably an effective strategy in the primary prevention of these commonly diagnosed cancers.

Papadimitriou N *et al*. (2020). Physical activity and risks of breast and colorectal cancer: A Mendelian randomization analysis. *Nature Communications*.

The response of paediatric leukaemia to inhibitors

Relapse of paediatric acute lymphoblastic leukaemia (ALL) may occur due to persistence of resistant cells with leukaemia-propagating ability (LPC). In leukaemia, the balance of B-cell lymphoma-2 (BCL-2) family proteins is disrupted, promoting survival of malignant cells and possibly LPC. A direct comparison of BCL-2 inhibitors, navitoclax and venetoclax, was undertaken on LPC subpopulations from B-cell precursor (BCP) and T-cell ALL (T-ALL) cases *in vitro* and *in vivo*. Responses were compared to BCL-2 levels detected by microarray analyses and Western blotting. *In vitro*, both drugs were effective against most BCP-ALL LPC, except CD34−/CD19− cells. In contrast, only navitoclax was effective in T-ALL and CD34−/CD7− LPC were resistant to both drugs. *In vivo*, navitoclax was more effective than venetoclax, significantly improving survival of mice engrafted with BCP- and T-ALL samples. Venetoclax was not particularly effective against T-ALL cases *in vivo*. The proportions of CD34+/CD19−, CD34−/CD19− BCP-ALL cells and CD34−/CD7− T-ALL cells increased significantly following *in vivo* treatment. Expression of pro-apoptotic BCL-2 genes was lower in these subpopulations, which may explain the lack of sensitivity. These data demonstrate that some LPC were resistant to BCL-2 inhibitors and sustained remission will require their use in combination with other therapeutics.



Diamanti P *et al*. (2020). Investigating the response of paediatric leukaemia-propagating cells to BCL-2 inhibitors. *British Journal of Haematology*.

Women in Science Day

Strathclyde Institute of Pharmacy and Biomedical Sciences (SIPBS) at Strathclyde University invited Dr Emma Vincent (Cellular and Molecular Medicine and Bristol Medical School: Population Health Sciences) to present on metabolic reprogramming in cancer for International Day of Women and Girls in Science 2020.

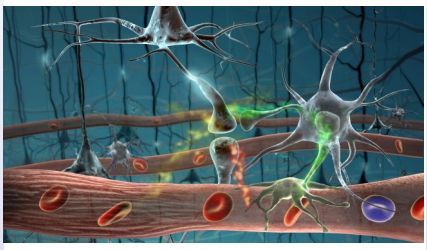
Science and gender equality are both vital for the achievement of the internationally agreed development goals.

Despite many efforts, women and girls continue to be excluded from participating fully in science; at present, fewer than 30% of researchers worldwide are women. Long-standing biases and gender stereotypes are steering girls and women away from science related fields. In order to achieve full and equal access to and participation in science for women and girls, and further achieve gender equality and the empowerment of women and girls, the United Nations General Assembly adopted a resolution declaring 11 February as the International Day of Women and Girls in Science.

Profiling for central nervous system tumour diagnosis

Marked variation exists in the use of genomic data in tumour diagnosis, and optimal integration with conventional diagnostic technology remains uncertain despite several studies reporting improved diagnostic accuracy, selection for targeted treatments, and stratification for trials. The aim of this study was to assess the added value of molecular profiling in routine clinical practice and the impact on conventional and experimental treatments.

This population-based study assessed the diagnostic and clinical use of DNA methylation-based profiling in childhood central nervous system (CNS) tumours using two large national cohorts in the UK. In the diagnostic cohort they assessed how the methylation profile altered or refined diagnosis in routine clinical practice and estimated how this would affect standard patient management. For the archival cohort of diagnostically difficult cases, the team established how many cases could be solved using modern standard pathology, how many could only be solved using the methylation profile, and how many remained unsolvable. Of 484 patients younger than 20 years with CNS tumours, 306 had DNA methylation arrays requested by the neuropathologist and were included in the diagnostic cohort. The data provide estimates of the impact that could be expected from routine implementation of genomic profiling into clinical practice, and indicate limitations where additional techniques will be required. The team concluded that DNA methylation arrays are a useful diagnostic adjunct for childhood CNS tumours.



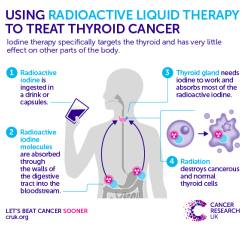
Pickles JC *et al*. (2019). DNA methylation-based profiling for paediatric CNS tumour diagnosis and treatment: a population-based study. *The Lancet Child and Adolescent Health*.

Low iodine diets in thyroid cancer treatment

International guidelines on the treatment of differentiated thyroid cancers (DTC) promote the use of low iodine diets (LID) prior to radioactive iodine remnant ablation (RIA), as high iodine status may interfere with radioiodine uptake. Most UK treatment centres adhere to these guidelines and advise people to consume a LID. There is limited research as to how people cope with the LID or its impact on daily life and well-being, and no studies have been conducted in the UK.

This study explored peoples' views and experiences in relation to consuming a LID during treatment for DTC with RIA.

Individuals advised to consume a LID believed that adhering to the diet would help their treatment. Most restricted their diets beyond what was recommended and there was confusion surrounding what they could eat as part of the diet. Food selection and preparation were important which included substitution of foods and ingredient checking. Being on the diet was considered to have both a physical and psychological impact. The results have relevance for professionals providing dietary guidance at oncology centres treating patients with RIA therapy in the UK.



Herbert G *et al*. (2020). Experiences of low iodine diets in the treatment of differentiated thyroid cancer with radioactive iodine ablation therapy. *Clinical Nutrition*.

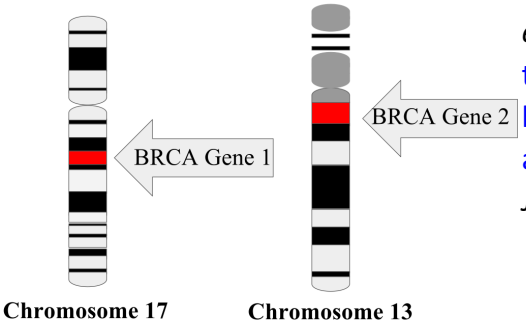
Signalling in colorectal cancer

First discovered as an oncogene in leukaemia, recent reports highlight an emerging role for the proto-oncogene BCL-3 in solid tumours. BCL-3 expression is upregulated in >30% of colorectal cancer cases and is reported to be associated with a poor prognosis. However, the mechanism by which BCL-3 regulates tumorigenesis in the large intestine is yet to be fully elucidated. In this study it was shown for the first time that knocking down BCL-3 expression suppressed cyclooxygenase-2 (COX-2)/prostaglandin E2 (PGE2) signalling in colorectal cancer cells, a pathway known to drive several of the hallmarks of cancer. RNAi-mediated suppression of BCL-3 expression decreased COX-2 expression in colorectal cancer cells both at the mRNA and protein level. This reduction in COX-2 expression resulted in a significant and functional reduction in the quantity of pro-tumorigenic PGE2 produced by the cancer cells, as shown by enzyme linked immunoassays and medium exchange experiments. In addition, inhibition of BCL-3 expression also significantly suppressed cytokine-induced COX-2 expression. Taken together, the results identified a novel role for BCL-3 in colorectal cancer and suggested that expression of BCL-3 may be a key determinant in the COX-2-meditated response to inflammatory cytokines in colorectal tumour cells. They suggest that targeting BCL-3 to suppress PGE2 synthesis may represent an alternative or complementary approach to using non-steroidal anti-inflammatory drugs [(NSAIDs), which inhibit cyclooxygenase activity and suppress the conversion of arachidonic acid to prostaglandin], for prevention and/or recurrence in PGE2-driven tumorigenesis.

Collared TJ *et al*. (2020). BCL-3 promotes cyclooxygenase-/prostaglandin E2 signalling in colorectal cancer. *Journal of Oncology*.

The genetics of epithelial ovarian cancer

Is there an association between genetically proxied inhibition of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase and epithelial ovarian cancer in the general population and among BRCA1/2 mutation carriers? In this case-control study that included 63 347 participants, genetically proxied HMG-CoA reductase inhibition equivalent to a 1-mmol/L (38.7-mg/dL) reduction in low-density lipoprotein cholesterol was significantly associated with lower odds of epithelial ovarian cancer in the general population (odds ratio, 0.60) and among BRCA1/2 mutation carriers (hazard ratio, 0.69). There was a significant association between genetically proxied inhibition of HMG-CoA reductase and epithelial ovarian cancer, but further research is needed to understand whether there is a similar association with medications that inhibit HMG-CoA reductase.



Yarmolinsky J, Bull C, Vincent E *et al.* (2020). Association between genetically-proxied inhibition of HMG-CoA reductase and epithelial ovarian cancer. *JAMA*.

Symptom management following gastrointestinal surgery

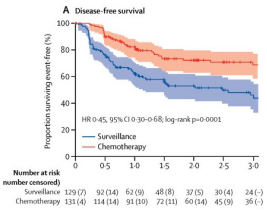
Complications following upper gastrointestinal (UGI) surgery are common. Symptom-monitoring following discharge is not standardised. An electronic patient-reported outcome (ePRO) system providing feedback to patients and clinicians could support patients and improve outcomes. Little is known about patients' experiences of using such systems. This qualitative sub-study explored patients' perspectives of the benefits of using a novel ePRO system, developed as part of the mixed methods eRAPID pilot study, to support recovery following discharge after UGI surgery.

Patients completed the online ePRO symptom-report system post-discharge. Weekly interviews explored patients' experiences of using ePRO, the acceptability of feedback generated and its value for supporting their recovery. Interviews were audio-recorded and targeted transcriptions were thematically analysed. Thirty-five interviews with 16 participants were analysed. Two main themes were identified: (1) reassurance and (2) empowerment. Feelings of isolation were common; many patients felt uninformed regarding their expectations of recovery and whether their symptoms warranted clinical investigation. Participants were reassured by tailored feedback advising them to contact their care team, alleviating their anxiety. Patients reported feeling empowered by the ePRO system and in control of their symptoms and recovery. Patients recovering at home following major cancer surgery regarded electronic symptom-monitoring and feedback as acceptable and beneficial; they felt the system enhanced information provision and provided a direct link to their care team.

Richards HS *et al*. (2020). Patient experiences of an electronic PRO tailored feedback system for symptom management following upper gastrointestinal cancer surgery. *Quality of Life Research*.

The POUT trial: upper tract urothelial carcinoma

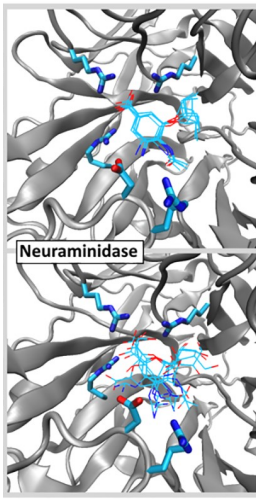
Urothelial carcinomas of the upper urinary tract (UTUCs) are rare, with poorer stage-for-stage prognosis than urothelial carcinomas of the urinary bladder. No international consensus exists on the benefit of adjuvant chemotherapy for patients with UTUCs after nephroureterectomy with curative intent. The POUT (Peri-Operative chemotherapy versus sUrveillance in upper Tract urothelial cancer) trial aimed to assess the efficacy of systemic platinum-based chemotherapy in patients with UTUCs. The team did a phase 3, open-label, randomised controlled trial at 71 hospitals in the UK. Adjuvant chemotherapy significantly improved disease-free survival at a median follow-up of 30·3 months. Three-year event-free estimates were 71% and 46% for chemotherapy and surveillance, respectively. Adjuvant platinum-based chemotherapy should be considered a new standard of care after nephroureterectomy for this patient population.



Birtle A *et al*. (2020). Adjuvant chemotherapy in upper tract urothelial carcinoma (the POUT trial): a phase 3, open-label, randomised controlled trial. *The Lancet*.

Virtual reality for designing new drugs

Many drugs are small molecules, and discovering new drugs involves finding molecules that bind to biological targets like proteins. In the study, users were able to use VR to 'step inside' proteins and manipulate them, and the drugs binding to them, in atomic detail, using interactive molecular dynamics simulations in VR (iMD-VR). Using this iMD-VR approach, researchers 'docked' drug molecules into proteins and were able to predict accurately how the drugs bind. Among the systems studied were drugs for flu and HIV.



To design new therapies, researchers need to understand how drug molecules fit into their biological targets. To do this, we use VR to represent them as fully three-dimensional objects. Users can then fit a drug within the 'keyhole' of a protein binding site to discover how they fit together.

Prof Adrian Mulholland (Chemistry), co-lead

Tests showed that users were able to predict correctly how the drugs bind to their protein targets. By pulling the drug into the protein, they could build structures that are very similar to the structures of the drug complexes found from experiments. Even non-experts were able to dock drugs into the proteins effectively. This shows that interactive VR can be used to predict accurately how new potential drugs bind to their targets.

Deeks HM *et al*. (2020). Interactive molecular dynamics in virtual reality for accurate flexible protein-ligand docking. *Plos One*.

New Academic Health Science Centre

Following a highly competitive process, Bristol Health Partners (BHP) is now one of only eight designated Academic Health Science Centres (AHSCs) in England. The AHSC will drive service change, leading to world-class health, clinical and economic outcomes for the regional population across Bristol, North Somerset and South Gloucestershire (BNSSG). The AHSC designation by the National Institute for Health Research (NIHR), NHS England and NHS Improvement builds upon BHP's current successes in research, innovation, education and training and recognises the outstanding local collaborations between academia, public health, the NHS, social care and the voluntary and community sector that the Partnership has created across BNSSG.

Over the next five years, Bristol Health Partners AHSC will be focusing on six key areas including public health and prevention; mental health and neuroscience; cardiovascular science; surgical innovation; perinatal, reproductive and children's health and delivering integrated, optimal and equitable care across BNSSG. Involving members of the public is a key priority for the Partnership, to empower people who use health and social care services, provide a route to influencing change and improvement in issues which concern people most.

Read more

Better Care South West Partnership

A new partnership led by the University of Bristol that will join up data and improve patient care in the South West has been announced by Health Data Research UK (HDR UK) today [29 April]. The HDR UK Better Care South West Partnership is being awarded £1.2 million over three years to drive forward data-led research projects and join up the region's considerable health data expertise.

The partnership is a collaboration of health and social care providers with the Universities of Bristol, Exeter and Bath. Key healthcare partners include Bristol, North Somerset and South Gloucestershire Clinical Commissioning Group, South Central and West Commissioning Support Unit, North Bristol NHS Trust and University Hospitals Bristol and Weston NHS Foundation Trust.

HDRUK
Health Data Research UK

It aims to address real-world health problems using the Bristol, North Somerset and South Gloucestershire (BNSSG) system-wide health and social care dataset, which is one of the largest linked health data sets in the UK. Enabling this joined-up approach is especially vital during the COVID-19 pandemic.

This new initiative represents a step forward in using advanced analytics to benefit patients and partner organisations. The partnership will lead on five data-driven projects, including personalised scores to reduce rates of unplanned admissions to intensive care, and optimised choice of antibiotics based on patients' individual history.
The newly-established HDR UK Better Care Northern and South-West Partnerships aim to boost the depth and breadth of expertise in health data research and innovation and complement the existing network of Health Data Research UK sites and hubs.

Read more

Disease trajectories of head and neck cancer

Few large studies describe initial disease trajectories and subsequent mortality in people with head and neck cancer. This study analysed data from the Head and Neck 5000 study to present mortality, place and mode of death within 12 months of diagnosis. 3% and 97% of participants were treated with 'non-curative' and 'curative' intent, respectively. Within a year 68% non-curative died compared with 9% curative. Catastrophic bleed was the terminal event for 10.4% and 9.8% in non-curative and curative respectively; terminal airway obstruction was recorded for 7.5% and 6.3% in the same groups. Similar proportions of people in both groups died in a hospice (~23%) and 45.7% of the curative group died in hospital. In addition to those with incurable head and neck cancer, there is a small but significant curative subgroup of people who may have palliative needs shortly following diagnosis. Given the high mortality, risk of acute catastrophic event and frequent hospital death, clarifying the level and timing of palliative care services engagement would help provide assurance as to whether palliative care needs are being met.

Mayland C *et al*. (2020). Disease trajectories, place and mode of death in people with head and neck cancer… . *Palliative Medicine*.

Adiposity, metabolites, and colorectal cancer risk

Evidence on adiposity altering colorectal cancer (CRC) risk differently among men and women, and on metabolic alterations mediating effects of adiposity on CRC, is unclear. This study aimed to examine sex− and site−specific associations of adiposity with CRC risk, and whether adiposity−associated metabolites explain associations of adiposity with CRC. Genetic variants from expanded genome-wide association studies of body mass index (BMI) and waist−to−hip ratio (WHR), and 123 metabolites (mostly lipoprotein subclass−specific lipids) from targeted nuclear magnetic resonance metabolomics were used as instruments. Sex-combined and sex−specific Mendelian randomization (MR) was conducted for BMI and WHR with CRC risk; sex−combined MR was conducted for BMI and WHR with metabolites, for metabolites with CRC, and for BMI and WHR with CRC adjusted for metabolite classes.

Among men, higher BMI was associated with 1.23 times higher CRC odds inverse−variance−weighted (IVW) model); among women, higher BMI was associated with 1.09 times higher CRC odds. Higher WHR was more strongly associated with CRC risk among women than men. BMI or WHR was associated with 104 metabolites including low-density lipoprotein (LDL) cholesterol, but these metabolites were generally unassociated with CRC in directions consistent with mediation of adiposity−CRC relations.

Results suggest that higher BMI more greatly raises CRC risk among men, whereas higher WHR more greatly raises CRC risk among women. Adiposity was associated with numerous metabolic alterations, but none of these alterations explained associations between adiposity and CRC. More detailed metabolomic measures are likely needed to clarify mechanistic pathways.

Bull CJ, Bell JA, Murphy N *et al*. (preprint). Adiposity, metabolites, and colorectal cancer risk: Mendelian randomization study. *medRxiv*.

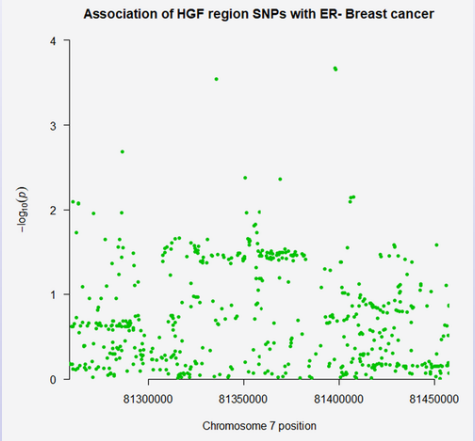
IGF-1 effect on localised prostate cancer

Localized prostate cancer (PCa) is a manageable disease but for most men with metastatic disease, it is often fatal. A western diet has been linked with PCa progression and hyperglycaemia has been associated with the risk of lethal and fatal prostate cancer. Using PCa cell lines, a team examined the impact of IGF-I and glucose on markers of epithelial-to-mesenchymal transition (EMT), migration and invasion. They examined the underlying mechanisms using cell lines and tumour tissue samples. A positive correlation existed between levels of IGFBP-2 and FOXA1 in benign and cancerous prostate tissue samples and *in vitro* and *in vivo* data indicated that FOXA1 strongly interacted with the IGFBP-2 gene in normal prostate epithelial cells that was associated with a negative regulation of IGFBP-2, whereas in cancer cells the level of FOXA1 associating with the IGFBP-2 gene was minimal, suggesting loss of this negative regulation. IGF-I and hyperglycaemia-induced FOXA1/IGFBP-2 play important roles in EMT.

Mansor R *et al*. (2020). IGF-1 and hyperglycaemia-induced FOXA1 and IGFBP-2 affect epithelial to mesenchymal transition in prostate epithelial cells. *Oncotarget*.

Adipokines and C-reactive protein on breast cancer risk

Circulating adipokines and C-reactive protein (CRP) have been linked to breast cancer risk in observational epidemiological studies. The causal nature of these associations is unclear because of the susceptibility of conventional observational designs to residual confounding, reverse causation and other forms of bias. Mendelian randomisation (MR) uses genetic variants as proxies for risk factors to strengthen causal inference in observational settings. We performed a MR analysis to evaluate the causal relevance of six previously reported circulating adipokines [adiponectin, hepatocyte growth factor (HGF), interleukin-6, leptin receptor, plasminogen activator inhibitor-1 and resistin] and CRP in risk of overall and oestrogen receptor-stratified breast cancer in up to 122,977 cases and 105,974 controls of European ancestry. Co-localisation was performed as a sensitivity analysis to examine whether findings reflected shared causal variants or genomic confounding. In MR analyses, there was evidence for an association of HGF with oestrogen receptor-negative cancer but little evidence for associations of other adipokines or CRP with overall or oestrogen receptor-stratified breast cancer. Co-localisation analysis suggested that the association of HGF with oestrogen receptor-negative breast cancer was unlikely to reflect a causal association. Collectively, these findings do not support an important aetiological role of various adipokines or CRP in overall or oestrogen receptor-specific breast cancer risk.



Robinson T, Martin RM and Yarmolinsky J (2020). Mendelian randomisation analysis of circulating adipokines and C-reactive protein on breast cancer risk. *International Journal of Cancer*.

Understanding the impact of disease on healthcare

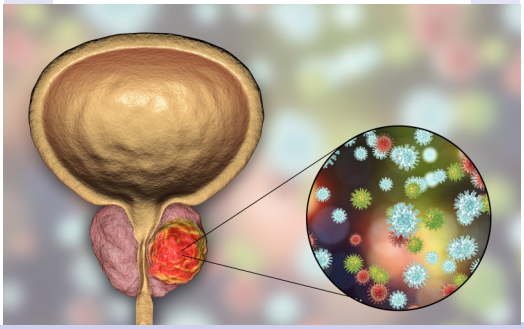
Much available research cannot meaningfully identify the long-term consequences of health conditions for healthcare cost and quality of life. This is because observational studies are prone to bias due particularly to reverse causality and omitted variable. Thanks to an Medical Research Council (MRC)-funded fellowship, Dr Padraig Dixon (Bristol Medical School: Population Health Sciences) has been using quasi-random variation in genetic liability to disease and other phenotypes to avoid this kind of bias. Using information of genetic variation as instrumental variables, he and his team have demonstrated that conventional methods may substantially underestimate the cost of obesity on the health system. Ongoing work demonstrates a similar relationship with rates of hospital admission. Other work-in-progress demonstrates that this kind of evidence can be used to inform robust causal inference for long-term policy decisions and interventions in relation to both costs and quality of life, particularly in cases where randomized controlled trials may not be feasible.

Dixon P *et al*. (2020). Mendelian Randomization analysis of the causal effect of adiposity on hospital costs. *Journal of Health Economics*.

Personalising prostate cancer screening

A polygenic hazard score (PHS), the weighted sum of 54 single nucleotide polymorphism (SNP) genotypes, was previously validated for association with clinically significant prostate cancer and for improved prostate cancer screening accuracy. Here, a research team assessed the potential impact of PHS-informed screening. United Kingdom population incidence data (Cancer Research UK) and data from the Cluster Randomized Trial of PSA Testing for Prostate Cancer were combined to estimate age-specific clinically significant prostate cancer incidence. Using hazard ratios (HRs) estimated from the ProtecT prostate cancer trial, age-specific incidence rates were calculated for various PHS risk percentiles. Risk-equivalent age, when someone with a given PHS percentile has prostate cancer risk equivalent to an average 50-year-old man, was derived from PHS and incidence data. Positive predictive value (PPV) of PSA testing for clinically significant prostate cancer was calculated using PHS-adjusted age groups.

The expected age at diagnosis of clinically significant prostate cancer differs by 19 years between the 1st and 99th PHS percentiles: men with PHS in the 1st and 99th percentiles reach the 50-year-standard risk level at ages 60 and 41, respectively. PPV of PSA was higher for men with higher PHS-adjusted age. PHS provides individualized estimates of risk-equivalent age for clinically significant prostate cancer. Screening initiation could be adjusted by a man's PHS.



Huynh-Le P-H, Fan CC, Karunamuni R *et al*. (2020). A Genetic Risk Score to Personalize Prostate Cancer Screening, Applied to Population Data. *Cancer Epidemiology, Biomarkers & Prevention*.

ELIZABETH BLACKWELL FUNDING

Nurturing Research. Improving Health.

EBI Seed Fund: Public Engagement with Health Research

Seed funding is available for health researchers who would like to deliver public engagement events and activities. Applications will be considered on a rolling basis.

EBI Identifying Candidates for Wellcome Trust Investigator Awards

This scheme is designed to support a small number of permanent academic staff at UoB within the first five years of their appointment, who are planning to apply for an Investigator Award from the Wellcome Trust. Applications will be accepted on a rolling basis.

Heads of Schools are asked to nominate members of staff who can be eligible for this scheme by emailing ebi-health@bristol.ac.uk

EBI Workshop support

Support interdisciplinary workshops in health research at new or emerging interface between two or more disciplines. Applications reviewed all year.

Returning Carers Scheme

To support academic staff across all faculties in re-establishing their independent research careers on return from extended leave (16 weeks or more) for reasons connected to caring (e.g. maternity leave, adoption leave, additional paternity leave, leave to care for a dependant.).

The deadline for applications is 30 April and 31 October each year.

The Elizabeth Blackwell Institute for Health Research is officially a member of **Equality, Diversity and Inclusion in Science and Health**, or EDIS, an initiative set up by the Wellcome Trust, the Crick Institute and GSK.

FUNDING OPPORTUNITIES

Would you like to receive timely, tailored funding opps information?
Do you want to know what funding opportunities come up in your research area?

Research Professional provides access to an extensive database of funding opportunities, and can send out tailored alerts based on keywords that you input, ensuring that the funding alerts you receive are the ones you want to hear about. UoB staff and students have **FREE** online access to the database from any device – once you've registered then you can view upcoming funding opportunities from home or away, not just while on the University network.

You can search for funding information by discipline, sponsor, database searches, by recent calls or by upcoming deadlines. If you register for the site and log in, you'll be able to:

- **Set up automated funding opportunity email alerts** - **tailored according to your discipline and research interests**, an easy process that will take just a few minutes to set up through the use of keywords
- **Save searches and bookmarks** - store items of interest for future reference, download and email to colleagues
- **Sign up for higher education news bulletins** – want to hear about what is going on in the broader HE environment? Latest news on the REF, setting up of UKRI etc? Sign up for the 8am playbook or the Research Fortnight news publications and stay up to date with the latest news.

Find out more about **Research Professional** on the RED website. Note that some calls may have an internal process; do always remember to check the major bids webpage here to see if there is an internal process.

The following listings represent a *brief selection* of available funding for the Cancer Research community. **Full listings of opportunities** are sent out via Faculty Research Directors and/or School Research Directors, and **are available on the Research Development website**.

Cancer Research UK
Predoctoral research bursary

Closing date: 17-Sep-20 Award amount: £25,000

This allows clinicians and other health professionals to get involved in research projects early in their career. The bursary gives the applicant a greater understanding of research before deciding whether to undertake a PhD or MD, or gives the applicant the time and resources to obtain preliminary data before applying for a PhD or MD.

Cancer Research UK
Postdoctoral research bursary for clinical trainees

Closing date: 17-Sep-20 Award amount: £35,000

This supports clinical trainees undertaking a research project after completion of a PhD. Applications from any area of CRUK's funding remit, with the exception of clinical trials and drug discovery, are considered.

Cancer Research UK
Early detection primer award

Closing date: 17-Sep-20 Award amount: £100,000

This enables researchers at all stages to develop early, novel and outside-the-box ideas and collaborations to build and make progress in the early detection field. The award provides seed funding to develop new relationships, ideas and lines of research, and the generation of pilot data, and encourages scientists at all career stages to engage with the early detection of cancer field.

European School of Oncology
Paediatric fellowship programme

Closing date: 18-Sep-20 Award amount: not specified

This enables young paediatric haematologists and oncologists to gain clinical experience at centres in Europe. The aim is to familiarise the trainee with all diseases in this field, instruct them in diagnostics and therapy and give them experience in a multidisciplinary clinical setting designed for them and their needs. Trainees may be enrolled at a host institution with visiting observer status for three to six months or with visiting residency status for six months.

National Cancer Institute (USA)
Metastasis research network

Closing date: 28-Sep-20 Award amount: USD$6m

This supports several specialised centres to develop a comprehensive and cohesive understanding of cancer metastasis and create a metastasis research network. Each centre should propose an overarching scientific theme that will be pursued through two or three scientific inter- and multidisciplinary basic research projects.

National Cancer Institute (USA)
Early-life factors and cancer development later in life

Closing date: 05-Oct-20 Award amount: not specified

This aims to stimulates research focused on the role of early-life factors in cancer development in later life. A better understanding is sought in the following areas:

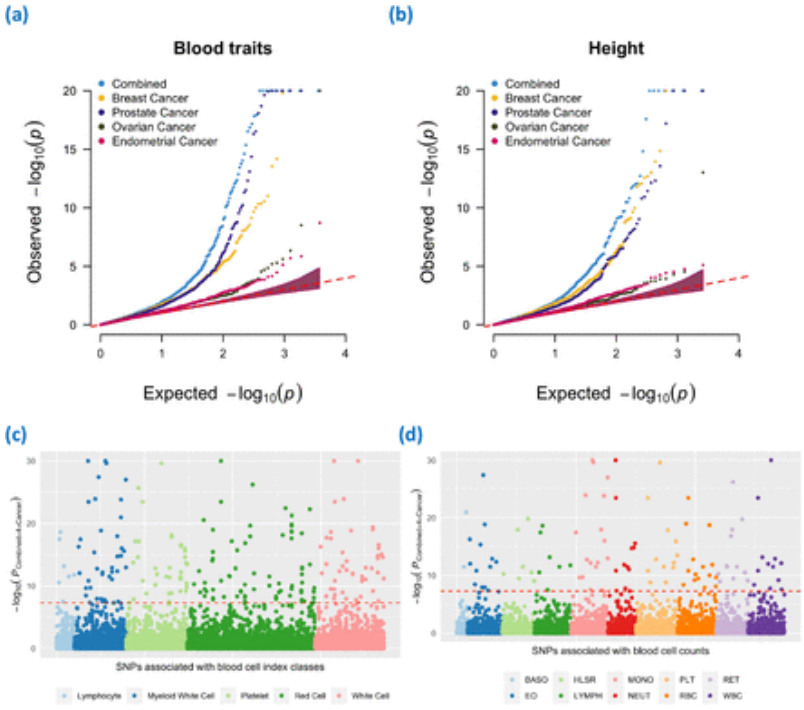
- early-life factors that are associated with later cancer development, including maternal-paternal, in utero, birth and infancy, puberty and adolescence, and teenage and adult years;
- how early-life factors mediate biological processes relevant to carcinogenesis;
- whether predictive markers for cancer risk based on what happens biologically at early-life can be measured and developed for use in cancer prevention strategies.

FEATURED PUBLICATION

Combining genome-wide studies of breast, prostate, ovarian and endometrial cancers maps cross-cancer susceptibility loci and identifies new genetic associations

Kar SP, Lindström S, Hung RJ et al. (preprint). bioRxiv.

We report a meta-analysis of breast, prostate, ovarian, and endometrial cancer genome-wide association data (effective sample size: 237,483 cases/317,006 controls). This identified 465 independent lead variants (P<5×10−8) across 192 genomic regions. Four lead variants were >1Mb from previously identified risk loci for the four cancers and an additional 23 lead variant-cancer associations were novel for one of the cancers. Bayesian models supported pleiotropic effects involving at least two cancers at 222/465 lead variants in 118/192 regions. Gene-level association analysis identified 13 shared susceptibility genes (P<2.6×10−6) in 13 regions not previously implicated in any of the four cancers and not uncovered by our variant-level meta-analysis. Several lead variants had opposite effects across cancers, including a cluster of such variants in the TP53 pathway. Fifty-four lead variants were associated with blood cell traits and suggested genetic overlaps with clonal hematopoiesis. Our study highlights the remarkable pervasiveness of pleiotropy across hormone-related cancers, further illuminating their shared genetic and mechanistic origins at variant- and gene-level resolution.



Quantile-quantile (Q-Q) plots of negative logarithm (base 10) P-values from the main meta-analysis ("Combined") and the single-cancer data (breast, prostate, ovarian, and endometrial cancer) at independent variants (r2 < 0.05) associated at genome-wide significance with (a) blood cell traits in Vuckovic et al.19 and (b) height in Yengo et al20. Manhattan plot of negative logarithm (base 10) P-values from the main meta-analysis at variants associated at genome-wide significance in Vuckovic et al. with (c) blood cell index classes and (d) blood cell type-specific counts. Classes and counts are described in detail in Vuckovic et al. (for example, the Red Cell class includes red blood cell counts and other indices such as hemoglobin and hematocrit while the RBC count includes the red blood cell counts only). The red dashed line in the Manhattan plots indicates genome-wide significance (P < 5 x 10−8). Negative log10(P-values) > 20 were set to 20 in the Q-Q plots and > 30 were set to 30 in the Manhattan plots to enable improved visualization of data points with less extreme values. Abbreviations: BASO, basophil; HLSR, high light scatter reticulocyte; MONO, monocyte; PLT, platelet; RET, reticulocyte; EO, eosinophil; LYMPH, lymphocyte; NEUT, neutrophil; RBC, red blood cell; WBC, *white blood cell.*

Cancer Network

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