Cancer Network Newsletter

2022: Issue 1

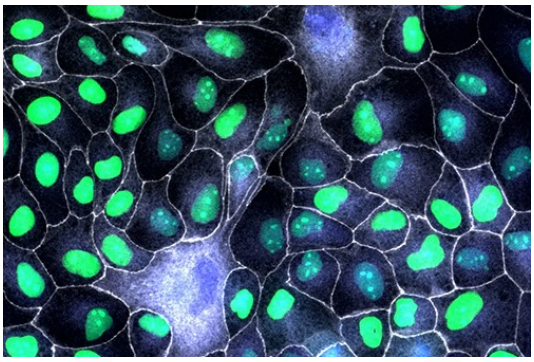
Bristol Cancer Research Network

Cell migration in epithelial repair

Epithelial tissues are the linings that protect the body's external skin and internal cavities. Wounded epithelia repair themselves thanks to the ability of the remaining cells to start migrating, collectively, to seal the breach. Specialised migratory cells (leader cells) arise from damaged epithelia, promoting epithelial migration. However, it's unclear what molecules and signals in epithelial cells make them become migratory leaders and how some wounded cells develop leader behaviour whilst some do not.

A study found that, when epithelial cells are damaged, the damage activates a molecular programme that turns cells into migratory leader cells so that the breach can be repaired. The same programme also makes sure that these highly migratory cells are removed when the breach is closed, so that the tissue restores its normal epithelial tissue structure.

Using a wound model the team identified the molecular signal that makes leader cells emerge. Following injury, cells at the border of the epithelial gap elevate p53 and p21, suggesting that the injury triggers the migratory programme. Once the breach was repaired, leader cells were eliminated from the population by their healthy epithelial neighbours. The cells damaged by the wound were able to cause wound closure, but are then sacrificed to maintain a functional tissue with normal epithelial morphology.



Collective migration is important in other areas, for example in cancer, where groups of cells move together from the primary tumour to create metastases. It would be important to know if the same proteins that we identified in the wound model are at play in this situation, so that current therapeutic treatments could be modified.

Dr Giulia Pilia

Kozyrska K *et al.* (2022). p53 directs leader cell behavior, migration, and clearance during epithelial repair. *Science*.

Image: *Once the collective migration of cells has closed the breach, the damaged leader cells need to be cleared from the tissue. When the leaders (blue nuclei) cannot be eliminated by their neighbours (green nuclei) their permanence in the epithelium compromises its regular architecture.*

Inside this issue:

@BristolCancer

cancer-research@bristol.ac.uk

bristol.ac.uk/cancer

+44 117 455 6360

University of BRISTOL

Elizabeth Blackwell Institute for Health Research

EVENTS

Let's Talk Digital Conference
18 March 2022, 9.00 - 17.00, University of Gloucestershire, Park Campus, The Park, Cheltenham, GL50 2RH and online

Basic statistics and data interpretation: Live Q&A session
22 March 2022, 11.00 - 12.00, online

Life Sciences Careers Beyond Academia
23 March 2022, 13.00 - 14.00, A Jones (Clinical Bioinformatician, NHS STP) & R Wilson / J Godwin (PolicyBristol Associates), Ada Lovelace Building SM2

What can genetic variants actually tell us about perturbing drug targets?
23 March 2022, 10.30 - 11.30, Dr Dipender Gill (Imperial College London), online

Prospective CDT supervisors workshop themed on 'Cancer'
23 March 2022, 14.00 - 16.00, Wills Memorial Building room 3.30

Cancer Research Network Early Career Researchers' symposium 2022
24 June 2022, 10.00 - 14.30, Life Sciences Building

This half-day event will comprise oral and poster presentations from ECRs as well as a **keynote** talk from **Prof Tim Frayling** (University of Exeter)

CALL FOR ABSTRACTS NOW OPEN
Priority for oral presentations will be given to abstracts under the general theme of "metabolism and cancer", which can include wet-lab discovery, clinical trials and epidemiology, amongst other areas. However, abstracts in all cancer research areas are welcome.

Register and download the abstract submission form

Advanced influencing policy: How to engage with policymakers and the policy-making process
24 March 2022, 14.00 - 15.00, online

Cracking the Cell Death Code
24 March 2022, 14.00 - 15.00, Prof Carla V. Rothlin (Dorys McConnell Duberg Professor of Immunobiology and Professor of Pharmacology, Yale University), online

Translating Population Health Research into Impact
24 March 2022, 15.00 - 16.00, Neil Pearce (LSHTM) and Debbie Lawlor (Bristol), online

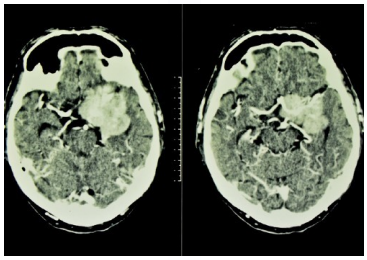
Presentation from Wellcome's Director on Wellcome vision and strategy
25 March 2022, 11.30 - 12.30, Sir Jeremy Farrar (Director, Wellcome), Powell lecture theatre, Physics Building and online

SEE ALL EVENTS ON THE CANCER RESEARCH NETWORK WEBSITE

NEWS

Hormone drug and brain tumours

Typically slow-growing, meningiomas are benign tumours, which are often revealed incidentally by imaging but can cause significant disability due to compressing or squeezing the adjacent brain, nerves and vessels and pressure effects within a fixed cranial vault. Recent studies have reported an association between the growth of meningiomas and hormonal treatments, particularly prolonged and high dose use of the drug, cyproterone acetate (CPA), widely used in the treatment of conditions such as excessive hair growth, early puberty, and prostate cancer.



Researchers conducted a systematic review and meta-analysis study to assess the evidence of the association between CPA and incidence of meningiomas. There is strong evidence to suggest a plausible role for sex hormones in the onset of meningioma. In light of these results, prescription of high-dose cyproterone acetate, especially for off label indications, should be considered carefully. Additionally, we suggest that routine screening and meningioma surveillance by brain MRI offered to patients prescribed with cyproterone acetate is likely a reasonable clinical consideration if given at high doses for long periods of time.

Lee KS *et al*. (2022). A systematic review and meta-analysis of the association between cyproterone acetate and intracranial meningiomas. *Scientific Reports*.

Funding successes and awards

Prof Ash Toye and Allison Blair (School of Cellular and Molecular Medicine [CMM]) were awarded £440,000 from the **Engineering and Physical Sciences Research Council** for *Engineering Inducible Anhydrides for Irreversible Red Blood Cell Decoration*, in collaboration with Mark Howarth at Oxford University.

Dr Jules Lavalou (CMM) was awarded a **European Molecular Biology Organization** (EMBO) postdoctoral fellowship to fund research on cell competition and cancer in Eugenia Piddini's lab.

Prof Eugenia Piddini (CMM) was awarded a Senior Research Fellowship renewal from **Wellcome** for her project *Ribosome mutant-induced cell competition: from mechanisms to identification of cancer vulnerabilities*. The grant is worth over £1.8 million for five years.

Dr Michael Baumgartner (Piddini lab, CMM) won the University of Bristol's Life Sciences **2021 Doctoral Prize** for his thesis *Building of an image analysis pipeline and its use to dissect the mechanisms of Cell Competition in* Drosophila. He studied one way in which the body gets rid of problem cells that have mutated (cell competition); when a mutant or loser cell is close to healthy or winner cells, the winners will eliminate the loser and replace it with a new, healthy cell. This could help keep tissues healthy, e.g. in defending against cancer. Michael is now studying medicine at the University of Pennsylvania with plans to become a physician-scientist. Six winners - one for each of the University's faculties - were picked from a pool of 510 submissions.

Read about all six awardees of the 2021 Doctoral Prize

Most influential women in Bristol

The Bristol Post named 137 influential women in Bristol in celebration of International Women's Day on 8 March 2022. Included among the listing were:

Kathreena Kurian: The Professor in Neuropathology wanted to be a consultant at medical school, but caught the investigative bug during her Experimental Pathology intercalated BSc. She kept doing research while being an NHS consultant and then got the opportunity to join the University of Bristol as an associate professor. She also runs the Brain Tumour Research Centre at Bristol Medical School, Southmead Hospital. Prof Kurian's research looks at finding new ways to treat brain tumours.

Caroline Relton: Caroline is a Professor of Epigenetic Epidemiology in Bristol Medical School, conducting research into how our genes and the environment work together to impact health and disease. Her work is very data driven, although she does generate data in the labs from biological samples.

She has a number of other roles and responsibilities in the University including being Director of Bristol Population Health Science Institute and co-Director of the Integrative Cancer Epidemiology Programme. Over the last two years, Prof Relton has led the University's COVID-19 Scientific Advisory Group.

Both Kathreena and Caroline are members of the Bristol Cancer Research Network steering group.

Read the full article

Cytokines and cancer risk

Epidemiological and experimental evidence has linked chronic inflammation to cancer aetiology. It is unclear whether associations for specific inflammatory biomarkers are causal or due to bias. In order to examine whether altered genetically predicted concentration of circulating cytokines are associated with cancer development, we performed a two-sample Mendelian randomisation (MR) analysis.

A genome-wide association study (GWAS) meta-analysis of 47 circulating cytokines was performed. Corresponding germline GWAS summary data for five cancer outcomes (breast, endometrial, lung, ovarian, and prostate), and their subtypes were selected from the largest cancer-specific GWASs available.

There was evidence of inverse associations of macrophage migration inhibitory factor with breast cancer, interleukin-1 receptor antagonist with endometrial cancer, interleukin-18 with lung cancer, and beta-chemokine-RANTES with ovarian cancer and positive associations of monokine induced by gamma interferon with endometrial cancer and cutaneous T-cell attracting chemokine with lung cancer. These associations were similar in sensitivity analyses and supported in colocalization analyses.

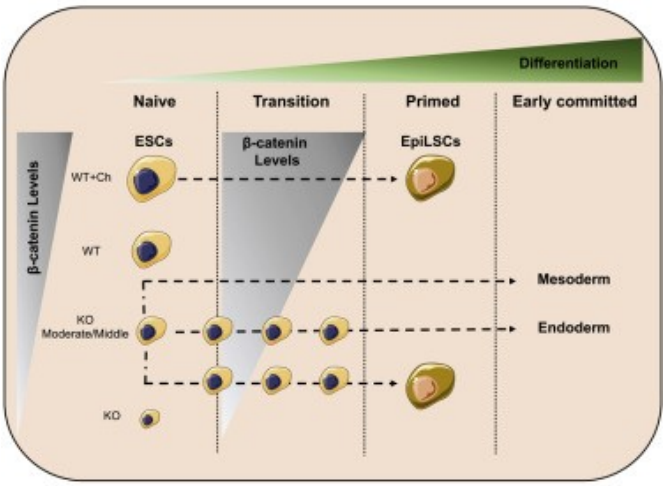
The study adds to current knowledge on the role of specific inflammatory biomarker pathways in the development of cancer. Further validation is needed to assess the potential of these cytokines as pharmacological or lifestyle targets for cancer prevention.

Bouras E *et al*. (2022). Circulating inflammatory cytokines and risk of five cancers: a Mendelian randomization analysis. *BMC Medicine*.

Wnt/β-catenin pathway

The Wnt/β-catenin pathway is involved in development, cancer and embryonic stem cell (ESC) maintenance; its dual role in stem cell self-renewal and differentiation is still controversial. Here, by applying an *in vitro* system enabling inducible gene expression control, we report that moderate induction of transcriptionally active exogenous β-catenin in β-catenin null mouse ESCs promotes epiblast-like cell (EpiLC) derivation *in vitro*.

Instead, in wild type cells moderate chemical pre-activation of the Wnt/β-catenin pathway promotes EpiLC *in vitro* derivation. Finally, we suggest that moderate β-catenin levels in



β-catenin null mouse ESCs favour early stem cell commitment towards mesoderm if the exogenous protein is induced only in the 'ground state' of pluripotency condition, or endoderm if the induction is maintained during the differentiation. Overall, our results confirm previous findings about the role of β-catenin in pluripotency and differentiation, while indicating a role for its doses in promoting specific differentiation programs.

Pedone E *et al*. (2022). β-catenin perturbations control differentiation programs in mouse embryonic stem cells. *iScience*.

Low iodine diet prior to thyroid cancer treatment

In the UK, many treatment centres use the UK Low Iodine Diet Working Group diet sheet and advise restricting fish, seafood, seaweed, dairy produce, eggs, iodised salt (although salt is not routinely iodised in the UK) and a wide variety of foods containing these ingredients, as well as nutritional supplements and cough mixture. However, different treatment centres give differing advice, particularly regarding length of dietary restriction, and when to restart usual diet. A survey of practice in 2018 found that around 75% of UK centres reported advising iodine restriction for two weeks prior to radioiodine remnant ablation (RRA) and the remainder for one week, or less, with two centres not advising a low iodine diet (LID) at all. However, in 2020 NHS Scotland updated guidance to advise a one-week only LID prior to RRA. This variation in practice arises because the effect of different LID advice on treatment success in the UK has not been examined or confirmed.

This paper describes a retrospective study of patients with differentiated thyroid cancer in three centres giving differing advice regarding the LID. The aim of the study was to collect routine clinical data and describe treatment practices and ablation success rates and examine whether LID advice is associated with success. We hypothesised that ablation success rates may differ according to the LID advice provided.

England C *et al*. (2021). Low iodine diet advice and differentiated thyroid cancer treatment: A historic exploration in three UK centres. *Clinical Nutrition ESPEN*.

BRAFV600 mutations within common brain tumours

Overall mortality rates in patients with brain tumours is very high, with less than 20% surviving beyond five years after diagnosis. Treating these tumours can be difficult. Standard surgery and general chemoradiotherapy tend to have a low success rate with frequent tumour regrowth after treatment. It's therefore urgent to develop new research and new personalised treatment options for patients. To develop better treatment approaches the team needed to first understand prevalence of BRAFV600E – a mutation in the BRAF gene that codes for cell replication. When this mutation occurs, it means cells replicate at much faster rates, causing cancerous tumours. Their systematic review established that the most common were a mixture of low and high-grade tumours which tend to be seen in younger patients. They were epithelioid glioblastoma, pleomorphic xanthoastrocytoma, anaplastic pleomorphic xanthoastrocytoma, ganglioglioma and anaplastic ganglioglioma.

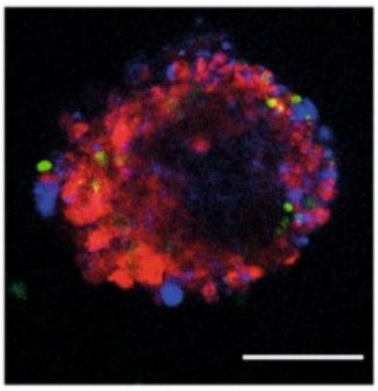
They then identified preliminary evidence that the use of BRAF and MEK (another gene used in cell replication) inhibitors, which have shown great success in treating skin cancers, should be trialled as a more effective treatment for brain tumours with the BRAF mutation.

Andrews L *et al*. (2021). Prevalence of BRAFV600 in glioma... *Neuro-Oncology*.

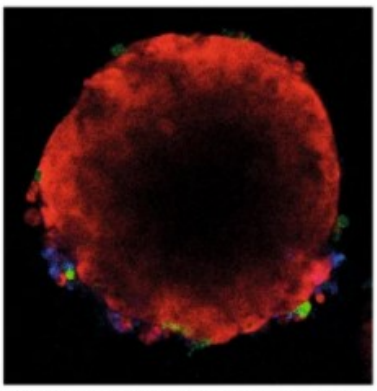
The tumour immune-suppressive environment

Tumours generate an immune-suppressive environment that prevents effective killing of tumour cells by CD8+ cytotoxic T cells (CTL). It remains largely unclear upon which cell type and at which stage of the anti-tumour response mediators of suppression act. We have combined an in vivo tumour model with a matching *in vitro* reconstruction of the tumour microenvironment based on tumour spheroids to identify suppressors of anti-tumour immunity that directly act on interaction between CTL and tumour cells and to determine mechanisms of action.

An adenosine 2A receptor antagonist, as enhanced by blockade of TIM3, slowed tumor growth in vivo. Engagement of the adenosine 2A receptor and TIM3 reduced tumor cell killing in spheroids, impaired CTL cytoskeletal polarization ex vivo and in vitro and inhibited CTL infiltration into tumors and spheroids. With this role in CTL killing, blocking A2AR and TIM3 may complement therapies that enhance T cell priming, e.g. anti-PD-1 and anti-CTLA-4.



RencaHA tdTomato spheroid with F-tracin-GFP CL4 CTL



RencaHA tdTomato spheroid with F-tracin-GFP CL4 CTL + CGS-21680

Edmunds GL *et al*. (2022). Adenosine 2A receptor and TIM3 suppress cytolytic killing of tumor cells via cytoskeletal polarization. *Communications Biology*.

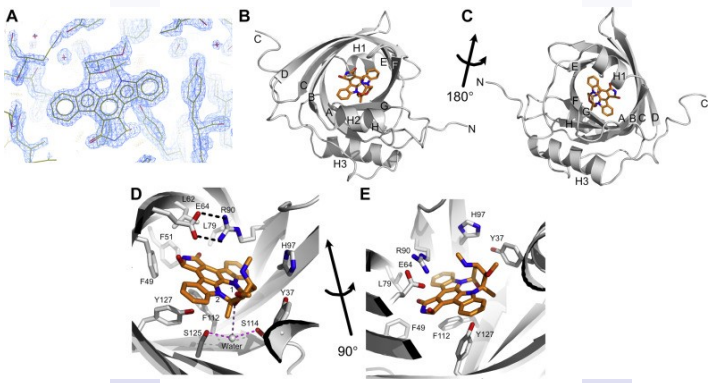
Triggering cell competition

Removal of damaged cells is important for maintaining tissue health and preventing disease. Cells that become damaged by mutation or due to ageing are actively eliminated from tissues by their fitter neighbouring cells through a process called cell competition. Cell competition was discovered in *Drosophila* through the study of Minute mutants, which are a class of mutations in ribosomal genes. Cells carrying a mutation in Minute genes are said to behave as losers, as over time, they are eliminated by competition with surrounding wild type cells. It is known that toxic protein aggregates in the cytoplasm contribute to the loser status of Minute cells. The factors Xrp1 and Irbp18 are also required for the elimination of Minute cells. Here we uncover the relationship between these factors and toxic protein aggregates in cell competition. We find that Xrp1 and Irbp18 promote protein aggregate formation and that, vice versa, protein aggregates induce Xrp1 and Irbp18 activity. This amplifies stress signalling and reduces the fitness of Minute cells, leading to their removal from tissues through cell competition. These findings shed light on an important mechanism by which cells carrying certain types of damage can be eliminated to preserve organism health.

Langton PF *et al*. (2021). Xrp1 and Irbp18 trigger a feed-forward loop of proteotoxic stress to induce the loser status. *PLOS Genetics*.

The structure of AGP2 and future therapeutics

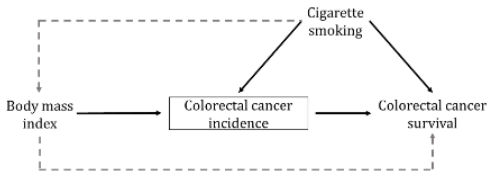
The α1-acid glycoprotein (AGP) is an abundant blood plasma protein with important immunomodulatory functions coupled to endogenous and exogenous ligand binding properties. Its affinity for many drug-like structures, however, means AGP can have a significant effect on the pharmokinetics and pharmacodynamics of numerous small molecule therapeutics. Staurosporine, and its hydroxylated forms UCN-01 and UCN-02, are kinase inhibitors that have been investigated at length as anti-tumour compounds. Despite their potency, these compounds display poor pharmokinetics due to binding to both AGP variants, AGP1 and AGP2. Recent renewed interest in UCN-01 as a cytostatic protective agent prompted us to solve the structure of the AGP2/UCN-01 complex by X-ray crystallography, revealing for the first time the precise binding mode of UCN-01. Solution NMR suggests AGP2 undergoes a significant conformational change upon ligand binding, but also that it uses a common set of sidechains with which it captures key groups of UCN-01 and other small molecule ligands. We anticipate that this structure and supporting NMR data will facilitate rational redesign of small molecules that could evade AGP and therefore improve tissue distribution.



Landin EJB *et al.* (2021). The structural basis for high affinity binding of α1-acid glycoprotein to the potent anti-tumour compound UCN-01. *Journal of Biological Chemistry*.

Nutrition and cancer

Dietary factors are assumed to play an important role in cancer risk, however evidence has been generated predominantly through observational studies. With major geographical differences and rapid changes in cancer incidence over time, it is crucial to establish which of the observational associations reflect causality and to identify novel risk factors as these may be modified to prevent the onset of cancer and reduce its progression. Here, we introduce the concept of Mendelian randomisation (MR) and discuss its current application in understanding the impact of nutritional factors (e.g.any measure of diet and nutritional intake, circulating biomarkers, patterns, preference or behaviour) on cancer aetiology and, thus, opportunities for MR to contribute to the development of nutritional recommendations and policies for cancer prevention. We provide applied examples of MR studies examining the role of nutritional factors in cancer to illustrate how this method can be used to help prioritise or deprioritise the evaluation of specific nutritional factors as intervention targets in randomised controlled trials.

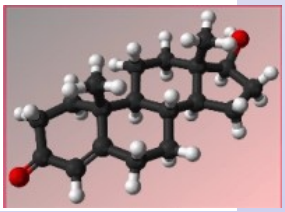


Wade K *et al*. (preprint). Applying Mendelian randomization to appraise causality in relationships between nutrition and cancer. *Cancer Causes and Control*.

Image: Directed acyclic graph illustrating selection bias in an MR analysis of cancer prognosis

Effect of sex hormones on breast and prostate cancers

Morning-preference chronotype has been found to be protective against breast and prostate cancer. Sex hormones have been implicated in relation to chronotype and the development of both cancers. This study aimed to assess whether sex hormones confound or mediate the effect of chronotype on breast and prostate cancer using a Mendelian Randomization (MR) framework. Genetic variants associated with chronotype and sex hormones (total testosterone, bioavailable testosterone, sex hormone binding globulin, and oestradiol) were obtained from published genome-wide association studies. These variants were used to investigate causal relationships with breast and prostate cancer using univariable, bidirectional and multivariable MR. In females, we found evidence for: i) Reduced risk of breast cancer per category increase in morning-preference; ii) Increased risk of breast cancer per SD increase in bioavailable testosterone and total testosterone; iii) Bidirectional effects between morning-preference and both bioavailable and total testosterone. In males, we found evidence for: i) Reduced risk of prostate cancer per category increase in morning-preference and ii) Increased risk of prostate cancer per SD increase in bioavailable testosterone. No bidirectional effects were found between morning-preference and testosterone in males. The protective effect of morning-preference on both breast and prostate cancer is clinically interesting, although it may be difficult to effectively modify chronotype.



Hayes BL *et al*. (2022). Do sex hormones confound or mediate the effect of chronotype on breast and prostate cancer? A Mendelian randomization study. *PLOS Genetics*.

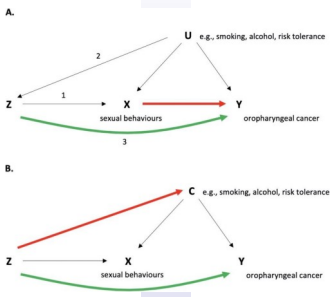
Ageing biomarkers as mortality predictors

Epigenetic clocks are biomarkers of ageing derived from DNA methylation levels at a subset of CpG sites. The difference between age predicted by these clocks and chronological age, termed "epigenetic age acceleration", has been shown to predict age-related disease and mortality. We aimed to assess the prognostic value of epigenetic age acceleration and a DNA methylation-based mortality risk score with all-cause mortality in a prospective clinical cohort of individuals with head and neck cancer: Head and Neck 5000. We investigated two markers of intrinsic epigenetic age acceleration (IEAAHorvath and IEAAHannum), one marker of extrinsic epigenetic age acceleration (EEAA), one optimised to predict physiological dysregulation (AgeAccelPheno), one optimised to predict lifespan (AgeAccelGrim) and a DNA methylation-based predictor of mortality (ZhangScore). In the setting of a large, clinical cohort of individuals with head and neck cancer, our study demonstrates the potential of epigenetic markers of ageing to enhance survival prediction in people with oropharyngeal cancer, beyond established prognostic factors. Our findings have potential uses in both clinical and non-clinical contexts: to aid treatment planning and improve patient stratification.

Benyon RA *et al*. (2022). Epigenetic biomarkers of ageing are predictive of mortality risk... *Clinical Epigenetics*.

Sexual behaviour and oropharyngeal cancer risk

Human papilloma virus infection is known to influence oropharyngeal cancer (OPC) risk, likely via sexual transmission. However, sexual behaviour has been correlated with other risk factors including smoking and alcohol, meaning independent effects are difficult to establish. We aimed to evaluate the causal effect of sexual behaviour on the risk of OPC using Mendelian randomization (MR).



Genetic variants robustly associated with age at first sex (AFS) and the number of sexual partners (NSP) were used to perform both univariable and multivariable MR analyses with data from genome-wide association studies (GWAS). In univariable MR, we found evidence supportive of an effect of both later AFS and increasing NSP on OPC risk. These effects were largely robust to sensitivity analyses accounting for horizontal pleiotropy. However, negative control analysis suggested potential violation of the core MR assumptions and subsequent CAUSE analysis implicated pleiotropy of the genetic instruments used to proxy sexual behaviours. Finally, there was some attenuation of the univariable MR results in the multivariable models.

Despite using genetic variants strongly related sexual behaviour traits in large-scale GWAS, we found evidence for correlated pleiotropy. This emphasizes a need for multivariable approaches and the triangulation of evidence when performing MR of complex behavioural traits.

Gormley M *et al*. (2022). Investigating the effect of sexual behaviour on oropharyngeal cancer risk: a methodological assessment of Mendelian randomization. *BMC Medicine*.

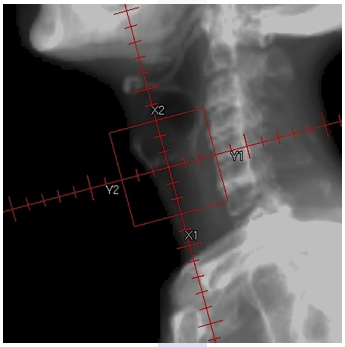
Physical activity and breast cancer

Epidemiologic research suggests that physical activity is associated with a reduced risk of breast cancer, but the causal nature of this link is not clear. Investigating mechanistic pathways can provide evidence of biological plausibility and improve causal inference. This project will examine three putative pathways (sex steroid hormones, insulin signaling, and inflammation) in a series of two-stage systematic reviews. Stage 1 used Text Mining for Mechanism Prioritisation (TeMMPo) to identify and prioritize relevant biological intermediates. Stage 2 will systematically review the findings from studies of (i) physical activity and intermediates and (ii) intermediates and breast cancer. Ovid MEDLINE, EMBASE, and SPORTDiscus will be searched using a combination of subject headings and free-text terms. Human intervention and prospective, observational studies will be eligible for inclusion. Meta-analysis will be performed where possible. Risk of bias will be assessed using the Cochrane Collaboration tool, or the ROBINS-I or ROBINS-E tool, depending on study type. Strength of evidence will be assessed using the GRADE system. In addition to synthesizing the mechanistic evidence that links physical activity with breast cancer risk, this project may also identify priority areas for future research and help inform the design and implementation of physical activity interventions.

Lynch BM *et al*. (2022). Linking Physical Activity to Breast Cancer: Text Mining Results and a Protocol for Systematically Reviewing Three Potential Mechanistic Pathways. *Cancer Epidemiology, Biomarkers & Prevention*.

Quality of life following treatment of glottic cancer

This prospective cohort study aims to assess generic- and disease-specific patient- reported quality of life (QoL) in patients treated with either surgery or RT for T1a glottic carcinoma. Participants were recruited as part of the multicentre, prospective Head and Neck 5000 cohort between 2011 and 2014.



Baseline demographic data were collected. All participants completed the EORTC QLQ C30 and EORTC QLQ H&N35 questionnaires at baseline, 4 months, 12 months and after 36 months. One hundred and twenty three participants received radiotherapy only or surgery only. Overall QoL scores were similar between both groups. The median (IQR) EORTC QLQ C30 summary scores at 12 months were 89.3 (79.1, 95.7) and 92.6 (74.4, 97.9) for the radiotherapy and surgery groups respectively. The equivalent summary scores for the EORTC QLQ H&N35 were 91.9 (83.8, 94.9) and 90.4 (85.5, 94.9). There was a modest difference in some QoL subscales between the groups, but no differences existed beyond 4 months.

The team concluded that patient- reported QoL is similar following either radiotherapy or surgery for T1a glottic carcinoma. These data support current guidance recommended TLM for this disease.

O'Hara J *et al*. (2021). Quality of life following treatment for T1a glottic cancer with surgery or radiotherapy: outcomes from the Head and Neck 5000 cohort. *Clinical Otolaryngology*.

Selenium and cancer risk

Evidence on the association between selenium and cancer risk is inconclusive. We conducted a Mendelian randomization study to examine the associations of selenium levels with 22 site-specific cancers and any cancer. Single nucleotide polymorphisms (SNPs) strongly associated with toenail and blood (TAB) and blood selenium levels in mild linkage disequilibrium (r2 < .3) were used as instrumental variables. Genetic associations of selenium-associated SNPs with cancer were obtained from the UK Biobank including a total of 59 647 cancer cases and 307 914 controls. Associations with P < .1 in UK Biobank were tested for replication in the FinnGen consortium comprising more than 180 000 individuals. The inverse-variance weighted method accounting for linkage disequilibrium was used to estimate the associations. Genetically predicted TAB selenium levels were not associated with the risk of the 22 site-specific cancers or any cancer (all 22 site-specific cancers). Similarly, we observed no strong association for genetically predicted blood selenium levels. However, genetically predicted blood selenium levels showed suggestive associations with risk of kidney cancer and multiple myeloma. Our study suggests that high selenium status may not prevent cancer development.

Yuan S *et al*. (2021). Selenium and cancer risk: Wide-angled Mendelian randomization analysis. *International Journal of Cancer*.

Estradiol and cancers in women

This Mendelian randomization study assessed the causal associations of endogenous 17β-estradiol (E2), the most potent oestrogen, with cancer risk in women. As primary genetic instrument, we used a genetic variant in the CYP19A1 gene that is strongly associated with serum E2 levels. Summary statistics genetic data for the association of the E2 variant with breast, endometrial, and ovarian cancer were obtained from large-scale consortia. We additionally estimated the associations of the E2 variant with any and 20 site-specific cancers in 198 825 women of European descent in UK Biobank. Odds ratios (OR) of cancer per 0.01 unit increase in log-transformed serum E2 levels in pmol/L were estimated using the Wald ratio.

Genetic predisposition to higher serum E2 levels was associated with increased risk of oestrogen receptor (ER)-positive breast cancer, endometrial cancer overall, and endometrial cancer of the endometrioid histology subtype.

There were suggestive associations with breast cancer overall, ovarian cancer of the endometrioid subtype, and stomach cancer, but no significant association with other cancers.

This study supports a role of E2 in the development of ER-positive breast cancer and endometrioid endometrial cancer but found no strong association with other cancers in women.

Larsson SC *et al*. (2021). Serum Estradiol and 20 Site-Specific Cancers in Women: Mendelian Randomization Study. *The Journal of Clinical Endocrinology & Metabolism*.

Wellcome GW4 PhD programme success

The GW4 Clinical Academic Training Programme for Health Professionals (GW4-CAT HP) will fund five annual intakes of five fellows, starting in autumn 2022. PhD fellows will have access to exceptional support, training and guidance from world-leading academics and research environments across the GW4 member universities of Bath, Bristol, Cardiff and Exeter. This will include supportive mentorship, assisting with the transition to a post-doctoral clinical academic role.

The award, worth £7 million, was announced in October 2021.

Applications opened on 1 November 2021. Further information on eligibility and details on how to apply will be available on the GW4-CAT website.

Tackling global malnutrition

The University of Bristol launched an ambitious research project which promises to address the common drivers of both obesity and under-nutrition in China and Southeast Asia on 15 December 2021.

Malnutrition is the leading cause of disease and mortality globally in Southeast Asia and carries substantial social and economic burdens. The multi-nation project: *Systems Actions to Malnutrition in All Its Forms in Chinese and Southeast Asian Cities – Developing Double Duty, Population-Level Interventions* (SYSTAM CHINA-SEACS) is funded by the Medical Research Council in the UK and will be led by Dr Bai Li (School for Policy Studies).

Through this world-first initiative, Dr Li plans to demonstrate that by developing systemic solutions to tackle under nutrition, governments and policy-makers can also prevent obesity and non-communicable diseases (NCDs) such as cancer, diabetes and stroke.

This approach is known as double-duty, and involves identifying interventions, programmes and policies that can simultaneously reduce the burden of both undernutrition (including wasting, stunting and micronutrient deficiency or insufficiency) and overweight, obesity or diet-related NCDs. The study will be piloted in the Chinese city of Fang Cheng Gang, which has been designated an international medical innovation city by President Xi Jinping and is the permanent host of the China-ASEAN Nutrition forum.

Read the full press release

ELIZABETH BLACKWELL FUNDING

Nurturing Research. Improving Health.

Discovery Research Support Funding call 2022
Funding is available to support early career biomedical researchers wishing to develop their research to explore and implement cutting edge methodologies to support our discovery science base.

Closing date: 21 March 2022

The Prudence Trust/Elizabeth Blackwell Institute Fellowship
With support from the Prudence Trust, funding is available for a for a researcher with substantial experience in the area of mental health in young people.

Closing date: 26 April 2022

Elizabeth Blackwell Institute support scheme for academic training 2022
This scheme is designed to provide support for attending or accessing externally-provided training courses, including training in research methods and techniques, in all areas of health research.

Closing date: 31 August 2022

Elizabeth Blackwell Institute academic bridging funding scheme 2022
We have funding available to provide bridging funding for salaries of academic staff in health-related research in all Faculties at the University of Bristol.

Closing date: 31 August 2022

Public Engagement seed funds
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.

Workshop support
We offer support for workshops in health and biomedical research to facilitate new interdisciplinary connections. Applications reviewed all year.

Returning Carers Scheme
The University of Bristol is running a Returning Carers Scheme (RCS) to support academic staff across all faculties in re-establishing their independent research careers. Applications reviewed all year.

FUNDING OPPORTUNITIES

Research Professional provides access to an extensive database of funding opportunities. You can set up individualised funding alerts based on keywords or areas of research . UoB staff and students have **FREE** online access to the database.

You can search for funding information by discipline, sponsor, database searches, by recent calls or by upcoming deadlines. 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 School Research Directors, and **are available on the Research Development website**.

Wellcome

Generation and utilisation of cancer organoid models course bursaries

Closing date: 13 April 2022 Award amount: 50% of course fee

These enable individuals to attend a course on generation and utilisation of cancer organoid models, to be held between 7 and 12 August 2022. The aim of the course is to provide participants with a broad overview of this new cell model generation technology with a specific focus on cancer models and to provide practical experience, knowledge and confidence for participants to begin using these models in their own institutes and research projects. The programme will include practical laboratory sessions, lectures and discussions.

Joseph Steiner Cancer Foundation

Cancer research award

Closing date: 15 April 2022 Award amount: CHF 1,050,000

This supports young investigators involved in projects related to the translation of new basic or theoretical insights into clinical applications, within basic or clinical cancer research.
Applicants should typically be 40 years or less, and able to provide the infrastructure needed to carry out the proposed project. Priority is given to applications from scientists based within European institutions.

National Cancer Institute

Advanced development and validation of emerging molecular and cellular analysis technologies for basic and clinical cancer research (R33 clinical trial not allowed)

Closing date: 22 April 2022 Award amount: USD 900,000

This supports exploratory research projects focused on further development and validation of emerging technologies offering novel capabilities for targeting, probing or assessing molecular and cellular features of cancer biology for basic or clinical cancer research.

Cancer Research UK
Drug development project

Closing date: 25 April 2022 Award amount: unspecified

This supports the development of new cancer treatments from preclinical development through to early phase patient trials. All technology areas are considered, including small molecule, biological and other therapeutics. Eligible projects include those requiring:

- preclinical development, including biomarkers, assays, and formulation development prior to a phase 1 trial
- phase 1 trials, including phase 1a and 1b, first-in-human and first-in-class
- combinations of unregistered and registered agents
- early phase 2 proof of principle trials
- studies on unlicensed agents in active commercial development that are off the company's critical path or repurposed novel agents

Applicants are also required to have a novel agent for cancer needing preclinical or clinical development, and have supporting *in vivo* efficacy data. Projects are supported for as long as necessary, usually between three and eight years. However, this is not a grant funding scheme, and projects will be run and managed by the Centre for Drug Development.

Horizon Europe
HORIZON-MISS-2021-CANCER-02 research and innovation actions supporting the implementation of the mission on cancer

Closing date: 26 April 2022 Award amount: €15 million

This supports research and innovation actions supporting the implementation of the mission on cancer. Funding is available under the following topics:

- HORIZON-MISS-2021-CANCER-02-01 develop new methods and technologies for cancer screening and early detection
- HORIZON-MISS-2021-CANCER-02-02 develop and validate a set of quality of life and patient preference measures for cancer patients and survivors
- HORIZON-MISS-2021-CANCER-02-03 better understanding of the impact of risk factors and health determinants on the development and progression of cancer

Proposals must take the form of research and innovation actions which require participation by at least three legal entities.

Cancer Research UK
Early detection and diagnosis project award

Closing date: 26 April 2022 Award amount: €15 million

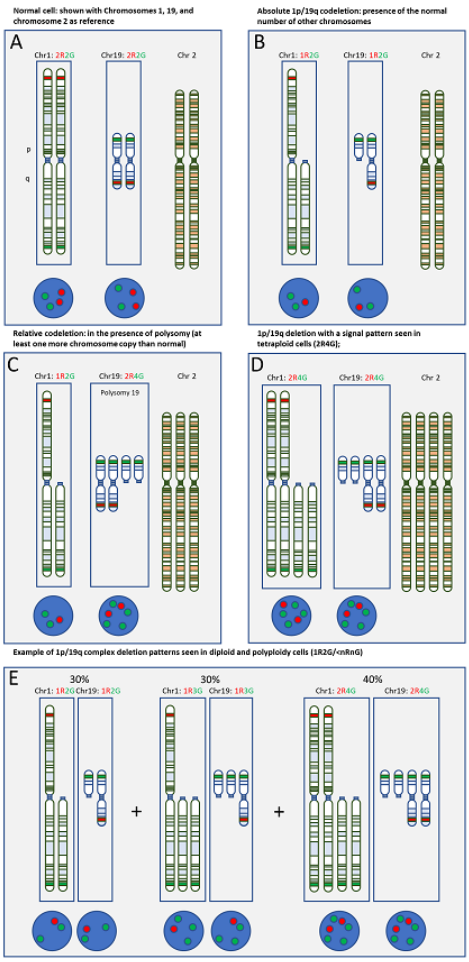
Projects should aim to detect and diagnose consequential precancerous changes and cancer at the earliest possible point at which an intervention might be made, reducing the burden of late-stage disease.

FEATURED PUBLICATION

Diagnostic test accuracy and cost-effectiveness of tests for codeletion of chromosomal arms 1p and 19q in people with glioma

McAleenan A *et al*. (2022). *Cochrane Database of Systemic Reviews*.

There are different types of glioma, with different changes in their genetic material. One of the possible genetic changes is the loss of parts of two of our 23 chromosomes. When both a specific part of chromosome 1 and a specific part of chromosome 19 are missing, it is known as '1p/19q codeletion'. 1p/19q codeletion is used to diagnose a glioma known as an oligodendroglioma. Presence of 1p/19q codeletion can also tell us how long a patient with a glioma may survive and which is the best medicine to treat that patient.



With this review we wanted to find out which is the most accurate and cost-effective way to identify 1p/19q codeletion in gliomas. The review examined and compared all methods to detect 1p/19q codeletion that are based on the DNA of the tumour. These include tests known as FISH and CISH, which are performed directly on tumour tissue and a number of other tests that are based on DNA extracted from the tumour including: PCR-based LOH, real-time PCR, MLPA, SNP array, CGH array and NGS. None of these tests is perfect, so there is no 'gold standard' against which to compare them. The two most commonly used tests (FISH and PCR-based LOH) were used as the best available reference tests against which to examine the others.

Using 53 studies, we found that most tests were good at identifying instances of 1p/19q codeletion that had been identified by either of the two common tests. However, there were some differences in how well the tests were able to rule out 1p/19q codeletion when it did not seem to be present. NGS and SNP arrays were better at this (i.e. having fewer 'false-positives' results) when considered against FISH as the reference test. The cost per correct diagnosis was lowest for MLPA, although this was not a firm finding because the amount of evidence was small.

Our certainty in the evidence was low or very low, because there were few studies for most of the tests and there were limitations to almost all the studies. Similarly, the economic analysis must be interpreted with caution due to the relatively small number of studies.

Image: Combinations of chromosomal deletions in oligodendrogliomas and the corresponding signals in fluorescent in situ hybridisation (FISH) in a schematic representation.

.

Cancer Network

CONTACTS

The Cancer Research Network is led by a Steering Group:

@BristolCancer

cancer-research@bristol.ac.uk

bristol.ac.uk /cancer

00 44 117 455 6360

Network Co-Leads:

- Anne Ridley, *Head of School of Cellular and Molecular Medicine*
- Axel Walther, *Senior Lecturer and Research Lead, Bristol Haematology & Oncology Centre*
- Richard Martin, *Professor of Clinical Epidemiology*

Steering Group members:

- Joseph Butler, *Research Development Associate* 
- Adam Chambers, *Clinical Lecturer* 
- Grace Edmunds, *Clinical Research Fellow* 
- Sabine Hauert, *Assistant Professor in Robotics* 
- Kathreena Kurian, *Professor of Neuropathology and Consultant Clinical Neuropathologist* 
- Paul Martin, *Professor of Cell Biology* 
- Caroline Relton, *Professor of Epigenetic Epidemiology* 
- Timothy Robinson, *Academic Clinical Lecturer in Medical Oncology* 
- Ann Williams, *Professor of Experimental Oncology* 
- Emma Vincent, *Research Fellow and Early Career representative* 
- Helen Winter, *Medical Oncologist* 
- Catherine Brown, *Network Administrator* 

University of BRISTOL
Elizabeth Blackwell Institute for Health Research

Bristol Cancer Research Network