Risk prediction and early detection of cancer and cardiovascular disease using the UKCTOCS Longitudinal Women's Cohort (UKLWC)

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Introduction

In 2016 the Chief Medical Officer highlighted in her report the importance of risk stratification to target screening/prevention strategies. This is especially relevant to cancer and cardiovascular disease (CVD) where there is a continuing need to reduce morbidity and mortality. Equally important to improving long-term survival of cancer patients is earlier diagnosis.

Risk stratification and early detection has been hampered by the lack of clinically useful biomarkers with those in use discovered at least 30 years ago. However, with advances in technologies to isolate and characterise genomic, proteomic and other biomarkers and increasing use of robust nested case-control study designs (PRoBE - Prospective Specimen Collection Retrospective Blinded Evaluation), the stage is set for discovery of markers, individually and in combination, to detect disease earlier.

The UKCTOCS Longitudinal Women's Cohort (UKLWC) with longitudinal samples and data preceding disease diagnosis provides a unique resource to move the field forward. Key features of the bioresource created in the course of the United Kingdom Collaborative Trial of Ovarian Cancer Screening (2001-date) are:

- ***Sample Size***: 202,280 women
- ***Representativeness***: Recruited through random invitation from NHS age sex registers in England, Wales and N. Ireland with a 16.3% acceptance rate
- ***Consent*** for use of samples in secondary ethically approved academic and industry studies
- ***Section 251 approval and established linkage to electronic health records*** (HES, ONS, cancer registry, NCIN and MINAP)
- ***Longitudinal follow up***: Currently median 14 years
- Large numbers of women diagnosed post recruitment with disease; for e.g. cancer (>24,000) and other common diseases (e.g. circulatory diseases >84,000)
- **High quality serum biorepository** (Figure 1)

Figure 1: Overview of UKLWC serum biorepository

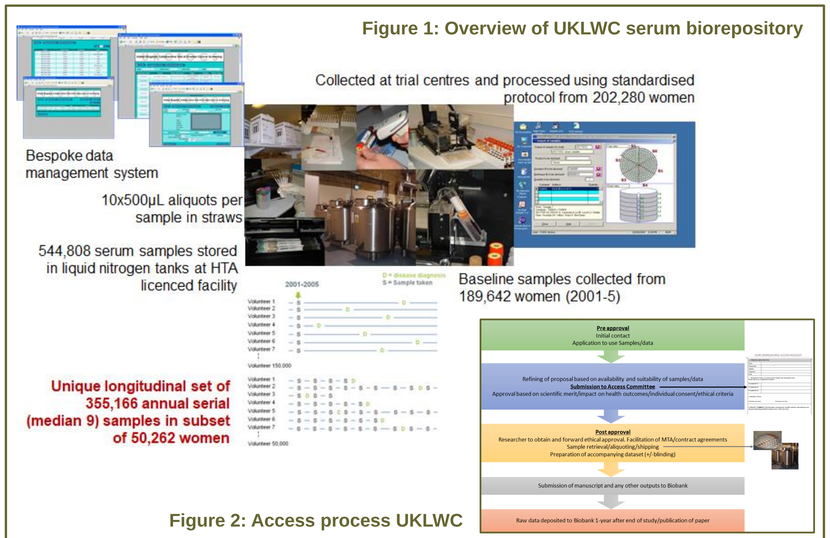

Figure 2: Access process UKLWC

Objectives

1. To undertake risk prediction and early detection biomarker studies in cancer/ cardiovascular disease
2. To evaluate the suitability of the serum samples for multi-omics analysis

Methods

Collaborations were set up using the Data Access process (Figure 2) to undertake nested case control studies in specific cancers and CVD using state-of-the-art technologies.

- Cases were identified using data from multiple sources - cancer registries (NHS Digital & Northern Ireland; National Cancer Intelligence Network - NCIN, Hospital Episode Statistics (England & Wales), death registry (NHS Digital & Northern Ireland) and MINAP (Myocardial Ischaemia National Audit Project), plus self reporting on follow up questionnaires
- Controls were matched to cases using minimum criteria
- Longitudinal sample sets were identified to assess biomarker change over time in the individual
- Where required, details of diagnosis and treatment were obtained through contacting GPs/treating clinicians (breast cancer) or retrieving hospital notes and independent review (ovarian cancer)
- Blinded assay of the biomarker was undertaken in randomly selected cases and controls divided into training and validation sets

Results

The initial study in 2007 was undertaken using the cutting edge proteomics strategy in an ovarian cancer sample set funded by an MRC grant. Since then, 44 collaborations (local, national and international) focussing on discovery/validation of risk and early detection biomarkers have been undertaken, supported by public, charity and industry funding (Tables 1a&b). The success of initial collaborations led to further exploration of the biomarker by other groups. For example, our longitudinal p53 autoantibody profiling of colorectal cancers with University of Copenhagen (2009-2013) led to evaluation of p53 autoantibody profile in ovarian cancer by the group at MD Anderson (2015-2017), with the same colorectal sample set currently being included in a collaboration "A Novel Microfluidic Platform for Ultrasensitive Autoantibody Detection" with Rutgers University, New Jersey, USA.

The initial BRC-funded work in genetics of cardiovascular disease and DNA methylation signatures in cancer (2008-2011) led to (1) further studies on metabolomics in the CVD case control set funded by the British Heart Foundation (BHF) and enabled AH to set up the UCLEB (UCL-LSHTM-Edinburgh-Bristol) Consortium and support an application under review for a BHF research excellence award, (2) EU FP7 funding to explore DNA methylation signatures as early detection markers.

Table 1a: Risk prediction/Early detection biomarker studies undertaken using a case-control design nested within UKLWC - academic collaborations

Department (Women's Cancer)	
Organisation (UCL)	
National (UK)	
International	

Disease	No	Nested case control early detection/risk stratification biomarker studies	Technologies investigated	Publication (Journal, Year)	Award/Funding agency
Academic collaborations					
Ovarian cancer	1	Proteomic markers	Mass Spectrometry	Cancer Genomics Proteomics (2011); Annals of Mathematics and Artificial Intelligence (2015); Progress in Artificial Intelligence (2012)	MRC
	2	Aberrant post translational modifications of O-glycoproteins	Autoantibodies to MUC1 (microararay platform)	Br J Cancer (2013)	£2,848,553; EU FP7
	3	Longitudinal profile of autoantibodies to key cancer antigens	p53 autoantibodies (MagPlex/xMAP technology - Luminex platform)	Clin Cancer Res (2017)	£68,506; CPRIT grant "Texas Cancer Diagnostics Pipeline Consortium"
	4	Longitudinal proteomic profiling	Mass Spectometry and SWATH-MS (Sequential Windowed Acquisition of All Theoretical Fragment Ion Mass Spectra)	Int J Cancer (2016); Oncotarget (2017); Br J Cancer (2017)	£1,620,000; CRUK / Eve Appeal
	5	Cancer antigen biomarker panel	ELISAs	Biomed Res Int (2015)	£1,000,000; Industry
	6	Serum free DNA methylation signature	DNA extraction and Illumina 27 k methylation array	Genome Med (2017)	€2,500,000; EU FP7 Grant
	7	Longitudinal profiling of CA125, Human Epididymis 4 (HE4), CA72.4 and p53 autoantibody	ELISAs (Roche platform)	Paper in draft	£1,640,000; CRUK/Eve Appeal
	8	Does HE4 add to CA125 and transvaginal ultrasound in differential diagnosis of adnexal masses in postmenopausal women	ELISAs (Roche platform)	Paper in draft	£1,000,037; NIHR
	9	Validation of the novel multimarker assay for early detection of ovarian cancer	Mulitple markers (Luminex platform)	Not published	£134,715; RO1, NIH, USA
Breast cancer	10	Serum free DNA methylation signature	Illumina 450k	Genome Med (2014)	CBRC, UCLH/UCL
	11	Risk factors in breast cancer (PhD)	Hormone assays (commercially available); Proteomics (Mass Spectrometry)	Endocr Relat Cancer (2012); Steroids (2016)	MRC
	12	Discovery and validation of early biomarkers of breast cancer	Proteomics (Mass Spectometry)	Br J Cancer (2017)	Eve Appeal
	13	EPI-FEM-CARE Breast Cancer epigenetics	DNA extraction and Illumina 27 k methylation array	Genome Med (2017)	EU FP7 Grant (shared funding with study 6)
	14	RANKL, OPG, Prolactin and CCL5 in breast cancer	ELISAs; Hormone assays	Oncotarget (2017)	Eve Appeal
Colorectal cancer	15	Investigation of a cancer specific serum response in relation to the development of colorectal cancer	Autoantibodies to p53, MUC1, MUC4 (using microarray platform)	Br J Cancer (2013); Int J Cancer (2014)	Danish Council for Independent Research
	16	Identifying biomarkers and risk factors for colorectal cancer	ELISAs	Br J Cancer (2015)	MRC
Pancreatic cancer	17	Interrogation of UKCTOCS serum bank for existing and novel markers of Pancreatic Ductal Adenocarcinoma (PDAC), Biliary Tract Cancer (BTC) and Liver Cancer (LC)	ELISAs; Proteomics (Mass Spectometry)	Clin Cancer Res (2015); J Proteomics (2015); Clin Cancer Res (2016); Int J Mol Sci (2017)	Pancreatic Cancer UK
CVD and stroke	18	An investigation of novel biomarkers for cardiac disease and stroke screening and diagnosis	Genomics	Circulation (2017); further papers in draft	CBRC, UCH/UCL
	19	Cardiometabolic disease prediction, causal analysis and drug development using high-resolution 1 H- nuclear magnetic resonance (NMR) metabolomics (The UCLEB consortium)	Nuclear magnetic resonance (NMR) spectroscopy platform	Circ Cardiovasc Genet (2017); further papers in draft	£795,445; BHF

Table 1b: Risk prediction/Early detection biomarker studies undertaken using a case-control design nested within UKLWC-industry collaborations

Disease	No	Nested case control early detection biomarker studies using technologies listed
Industry collaborations		
Lung cancer	20	CYFRA 21-1/CEA
	21	Exosomes
	22	DNA methylation
	23	Proteomics (Mass Spectometry)
	24	Autoantibodies
Breast cancer	25	Protein panel
	26	SIA assay
	27	mAb versus tumour MUC1
	28	microRNA, Proteomics, AutoAbs, Lipidomics, Exosomes, Glycans
Melanoma	29	Immunosignature
Pancreatic cancer	30	microRNA & autoAb
	31	microRNA
	32	BAG3 protein autoAbs
	33	CA199/Lewis antigen
	34	CA199/Lewis antigen
Colorectal cancer	35	Midkine protein marker
	36	CEA (Roche platform)
	37	DNA methylation
	38	Epigenetic markers
	39	microRNA, autoantibodies, proteomics, lipidomics
	40	Colorectal and Lung autoAbs markers
Ovarian cancer	41	Protein panel
Myeloma	42	Microvesicles
AML & MDS	43	Metabolomics, aptamers
CVD	44	Microfluidic technique- seeding protein aggregation

Published and unpublished nested case-control studies (Table 1) attest to (1) sample suitability for cutting edge technologies - array-based genotyping (n=4220 samples), proteomics (n=2458), ELISA (n>3000), NMR metabolomics (n=4841) and methylation (n=1097), miRNA (n=888) and lipidomic profiling (n=452) and that (2) longitudinal algorithms improve performance of individual biomarkers and panels.

In 2018, UKLWC was included in the newly formed International 100K Cohorts Consortium (IHCC) of large-scale (>100,000 participants) longitudinal cohorts, set up by the Heads of International Research Organizations (HIRO) group.

Conclusions

The resource has resulted in a number of successful collaborations which have explored a variety of risk/early detection markers/biomarker panels in cancers that contribute most to mortality (high grade serous ovarian cancer, pancreatic cancer, fatal breast cancer). For most, early detection biomarkers performance was improved by use of longitudinal algorithms.

https://www.ucl.ac.uk/womens-health/research/womens-cancer/gynaecological-cancer-research-centre/ukctocs-longitudinal-womens-cohort