CHIEF SCIENTIST OFFICE

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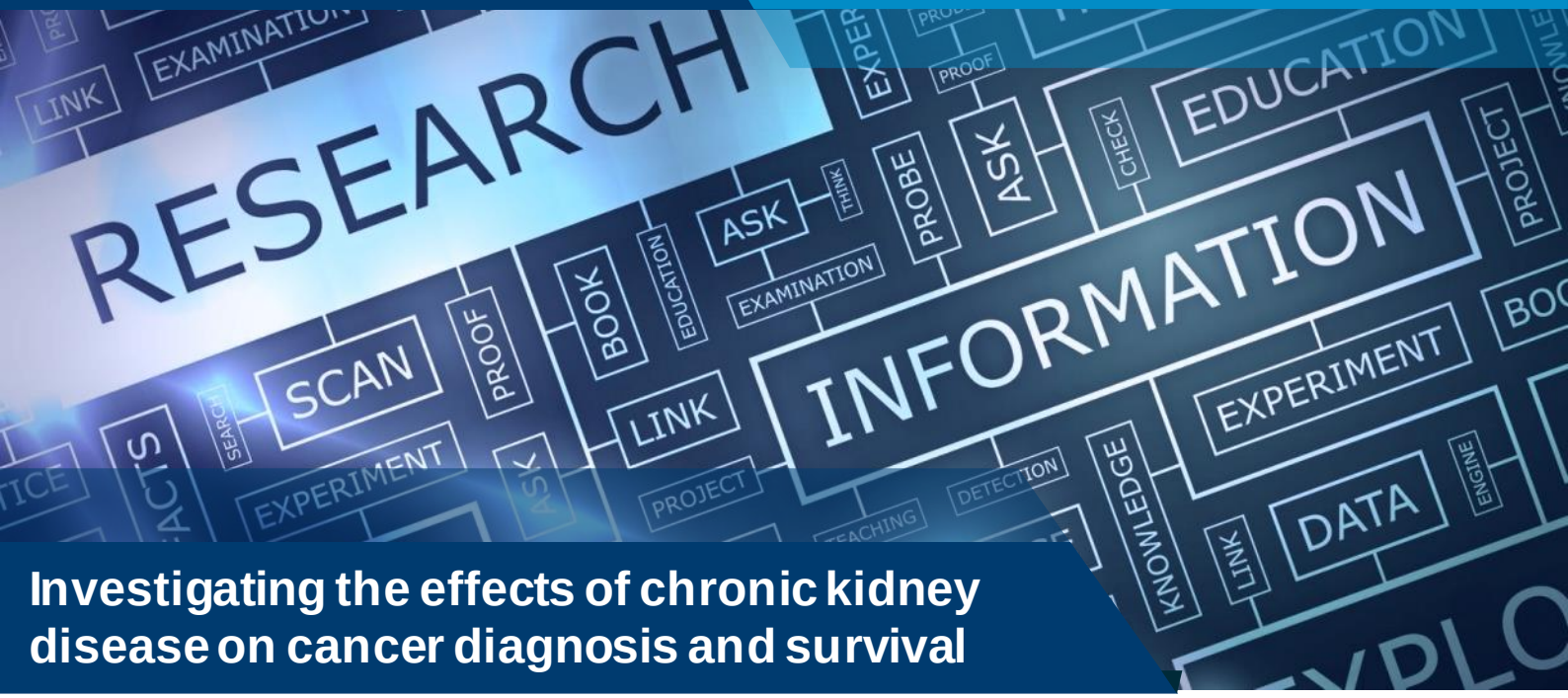
RESEARCH PROJECT BRIEFING



Investigating the effects of chronic kidney disease on cancer diagnosis and survival

AIMS

We aimed to research and report on:

- how pre-existing kidney disease affects the likelihood of developing cancer
- the survival prospects in kidney disease after a diagnosis of cancer has been made
- how treatments designed for use in cancer can affect future kidney and heart problems

KEY FINDINGS

- People with chronic kidney disease have a higher likelihood of developing cancer
- On average, people with chronic kidney disease are not more likely to present with advanced stage of cancer (i.e., when the cancer has spread to other areas of the body)
- Despite earlier presentation with cancer, chronic kidney disease is associated with a lower likelihood of survival after a diagnosis of cancer
- The association between chronic kidney disease, cancer incidence, cancer stage and cancer survival varies by the sex of the patient and by cancer site
- Medications that were originally developed for use in cancer, and are now also used to preserve eyesight in various eye diseases, may be associated with reduced survival, particularly in patients with diabetes. However, this effect is likely to be very small.

WHAT DID THE STUDY INVOLVE?

In this study, we analysed information that had previously been collected (and anonymised) from patients or research participants. We used statistical techniques to examine this patient information and to answer questions about how chronic kidney disease (CKD) affects cancer diagnosis and survival.

First, we examined anonymised information from over 500,000 people who participated in the UK Biobank: a voluntary study, in which patients were thoroughly assessed at a research visit (between 2006 and 2010) and then monitored for several years. We used this information to explore whether different markers or kidney function could be used to assess the likelihood of developing cancer and of surviving after a cancer diagnosis.

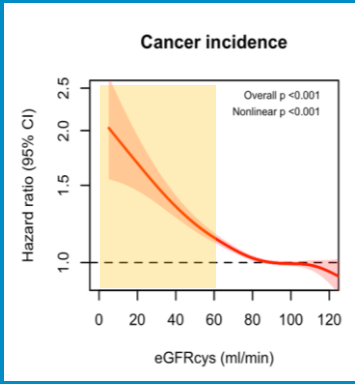
Second, we used anonymous patient information from Secure Anonymised Information Linkage (SAIL). SAIL is resource containing information about people who live in Wales and who are registered with a GP. We were able to link anonymous patient information collected by the GP (such as medical diagnoses, blood pressure and kidney function) and link this to the Welsh Cancer Registry (an accurate record of cancer diagnoses made in Wales). By linking this information while preserving patient anonymity, we could use statistical techniques to explore whether people with kidney disease were more or less likely to present with cancer at an advanced stage and how this affected their likelihood of survival.

Third, we reviewed clinical trials of medicines called “VEGF inhibitors” that were originally designed for use as cancer treatments. In the treatment of cancer, VEGF inhibitors have been shown to increase the risk of future kidney and heart disease. VEGF inhibitors are now also used to treat many eye diseases – including diabetic eye disease, macular degeneration and glaucoma – in order to preserve eyesight. We collected the summary information about the use of these VEGF inhibitors for eye disease from published scientific papers. We summarised the results of these clinical trials in order to assess whether use of these medications for eye disease was linked to higher risk of developing kidney or heart disease.

WHAT WERE THE RESULTS AND WHAT DO THEY MEAN?

How does pre-existing kidney disease affect the likelihood of developing cancer?

Kidney function is estimated from blood tests using a measure called “eGFR”. Usually, we use a cheap, widely available blood marker of muscle breakdown (creatinine) to calculate eGFRcr. We have shown that people with kidney disease are more likely to develop cancer. We then showed that using a different blood marker (cystatin C, which is used to calculate eGFRcys) is a better marker than eGFRcr to identify people who are at risk of developing cancer (see graphic overleaf). We have shown that this is particularly relevant for specific types of cancer: kidney and renal tract cancers, lung cancers, haematological (blood) cancers and cancers of the major organs in the abdomen. If we can use markers like eGFRcys to identify people who are at higher risk of cancer, this may allow us to target screening or treatment programmes specifically to people who are at higher risk.



This graph shows that as eGFRcys falls (i.e. kidney function gets worse), there is a higher chance of being diagnosed with cancer.

The yellow box indicates people who would be considered to have chronic kidney disease (CKD): these people are 15-50% more likely to be diagnosed with cancer than people with normal kidney function.

What are the survival prospects in people with CKD after a diagnosis of cancer has been made?

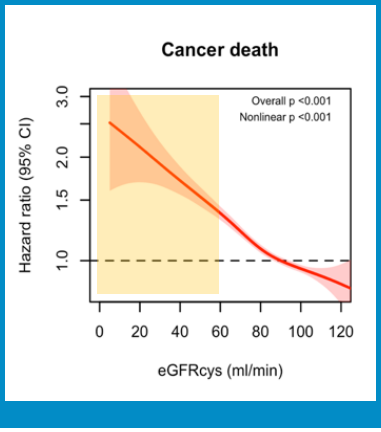
We have shown that people with CKD are less likely to survive after a diagnosis of cancer than people with normal kidney function. Again, eGFRcys is a better marker than the current marker (eGFRcr) to identify people who are less likely to survive after a diagnosis of cancer (see graphic below).

After we confirmed that people with CKD were less likely to survive after a diagnosis with cancer, we considered whether people with CKD were presenting at a more advanced stage of cancer (where the cancer had spread to other areas of the body by the time it was diagnosed). We found that men were more likely than women to present with an advanced stage of cancer. On average, people with CKD were not more likely to present at an advanced stage of most cancers. We think this is probably because people with CKD attend their GP or see hospital doctors more frequently and the cancer may be picked up earlier as a result.

Despite not presenting with a more advanced stage of cancer, people with CKD were less likely to survive for 1 year after a diagnosis of cancer. These patterns were very similar across many common cancers, including kidney, colorectal, prostate, breast and some haematological (blood) cancers such as lymphoma and leukaemia. On average, women were more likely than men to survive for 1 year after a diagnosis of cancer. However, CKD had a greater effect on reduced survival in women compared with men.

This graph shows that as eGFRcys falls (i.e. kidney function gets worse), there is a lower chance of survival after a diagnosis of cancer.

The yellow box indicates people with chronic kidney disease (CKD): these people are at least 30-50% less likely to survive after a diagnosis of cancer than people with normal kidney function.



How do VEGF inhibitor treatments – originally designed for use in cancer – affect future kidney and heart problems?

VEGF inhibitors were originally designed to reduce blood vessel growth and therefore to slow the growth of some cancers. However, VEGF inhibitors are now used to reduce blood vessel growth in the eye, and are extremely effective at preserving eyesight in people with certain types of eye disease, including diabetic eye disease, macular degeneration and glaucoma.

When VEGF inhibitors are given into the bloodstream to treat cancer, they commonly cause high blood pressure, protein in the urine and heart failure. When VEGF inhibitors are given into the eye to treat eye disease, they may be absorbed into the bloodstream and may cause similar problems to the blood vessels, heart and kidneys. We looked for any evidence that VEGF inhibitors cause heart or kidney problems in clinical trials of VEGF inhibitors for eye disease.

We found 78 published trials of VEGF inhibitors used for eye disease. Around one third of these trials looked for evidence of high blood pressure after treatment with VEGF inhibitors, but fewer than 10 trials recorded whether patients developed problems like heart failure, kidney failure or protein in the urine. In these very few trials, it was not possible to confirm whether use of VEGF inhibitors for eye disease caused kidney and heart problems or not. In patients treated with VEGF inhibitors for diabetic eye disease, there was a 62% increased risk of reduced survival after these treatments. We think it is important to point out that though the percentage change is quite large (increased relative risk), this is likely to translate into very small numbers of people in the real world who are at less likely to survive (low absolute risk). We have illustrated this concept in the graphic below.

This graphic is designed to illustrate the concept of relative and absolute risk. The green circle represents all people with diabetic eye disease (100%); the orange triangle represents people who are at risk of reduced survival (for example, 1%). If this 1% of people increased by 62% (red triangle) due to VEGF inhibitors, there would still be a small absolute number of people who would be at risk of reduced survival (<2%).

In practice, we think it is likely that VEGF inhibitors used for eye disease can cause some heart and kidney problems. We think we will be able to identify if there are problems more effectively by analysing information from people who are treated for eye disease in the real world, rather than in the small, select group of people who are treated in clinical trials. We are working on a new project to answer this question. After further discussion with our PPIE group, we also intend to quantify the absolute risk of loss of eyesight, kidney failure, heart disease and reduced survival for people treated with these medicines, which may allow patients to make a more informed choice about their treatment.

WHAT IMPACT COULD THE FINDINGS HAVE?

The results from this work are not likely to cause any immediate change to clinical practice; however, we have identified two broad hypotheses for further research:

- Is cancer biology different (more aggressive) in people with CKD?
- Are cancer treatments less effective, or used less effectively, in people with CKD?

Guided by our PPIE group, this research has been used to inform a larger package of work, exploring how cancer treatments are selected in CKD, how effective are these treatment strategies (and why), and whether there are strategies we can use to improve the evidence-base and the effectiveness of cancer treatments in people with CKD. This may make a substantial difference to improving survival after a cancer diagnosis in people with CKD.

HOW WILL THE OUTCOMES BE DISSEMINATED?

- Presentation at national (UK Kidney Association) and international (European Renal Association) scientific meetings
- Publication in scientific journals. Most of this work is already in print:
  - ❖ Lees JS et al, Nephrol Dial Transplant (2022): https://doi.org/10.1093/ndt/gfac305
  - ❖ Lees JS et al, Nephrol Dial Transplant (2022): https://doi.org/10.1093/ndt/gfac011
  - ❖ Lees JS et al, EClinicalMedicine (2021): https://doi.org/10.1016/j.eclinm.2021.101030

For the work related to cystatin C, we issued press releases through the University of Glasgow, which were picked up by national and international news outlets and blogs (including The Herald, The Times, The Daily Mail and The Metro). The Sunday Post wrote a special edition article which was released on 19th August 2021. We have used social media (Facebook and Twitter) to disseminate findings to scientific communities, patient groups and the public. We continue to liaise with our West of Scotland Kidney PPIE group to inform future dissemination plans, particularly in generating factsheets, infographics and video summaries for patients and the public. Dr Lees has also been asked to review fact sheets about cancer and CKD for a national patient organisation (Kidney Care UK).

CONCLUSION

People with CKD are more likely to develop cancer but less likely to survive after a cancer diagnosis. An alternative marker of kidney function (eGFRcys) may identify cancer risk earlier, potentially allowing targeted screening/treatment. Though cancer survival varies according to the age and sex of the patient and the cancer type, the differences in survival in patients with CKD raise fundamental questions about how we treat cancer in people with CKD and questions the effectiveness of these strategies. This is an important area for future research.

RESEARCH TEAM & CONTACT

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Additional Information

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