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Identifying patients with undetected renal tract cancer in primary care: An independent and external validation of QCancer® (Renal) prediction model

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ABSTRACT

Introduction: To evaluate the performance of QCancer® (Renal) for predicting the absolute risk of renal tract cancer in a large independent UK cohort of patients from general practice records. *Materials and methods*: Open cohort study to validate QCancer® (Renal) prediction model. Record from 365 practices from United Kingdom contributing to The Health Improvement Network (THIN) database. 2.1 million patients registered with a general practice surgery between 01 January 2000 and 30 June 2008, aged 30–84 years (3.7 million person years) with 2283 renal tract cancer cases. Renal tract cancer was defined as incident diagnosis of renal tract cancer during the 2 years after study entry. Model discrimination was measured using the receiver operating characteristics derived area under the curve. Calibration plots examined the relationship between predicted and observed probabilities of undetected renal tract cancer. *Results*: The results from this independent and external validation of QCancer® (Renal) demonstrated good performance data on a large cohort of general practice patients. QCancer® (Renal) had very good discrimination with areas under the ROC curve of 0.92 and 0.95 for women and men respectively. QCancer® (Renal) was well calibrated across all tenths of risk and over all age ranges with predicted risks closely matching observed risks. QCancer® (Renal) explained 74.4% and 74.2% of the variation in men and women respectively. A limitation of our study is the recording of symptoms might be less complete, as patients with mild symptoms may not visit their general practitioner or not report mild symptoms. *Conclusions*: QCancer® (Renal) are useful tools to help in identifying undetected cases of undiagnosed renal tract cancer in primary care in the UK.

1. Introduction

Renal tract cancer, comprising cancer of the bladder, kidney, ureter or urethra, is a major health burden with over 450,000 new cases of bladder and kidney cancer diagnosed worldwide in 2008 (http://www.globocan.iarc.fr/). It is a major cause of death with 180,000 deaths worldwide attributed to bladder or kidney cancer. In the United Kingdom nearly 19,000 new cases of bladder or kidney cancer were diagnosed in 2008 (http://www.info.cancerresearchuk.org/) with 8800 attributed deaths.

With few symptoms, the most common being haematuria, the early identification of individuals with renal tract cancer is problematic. Finding new approaches for identifying individuals in primary care who have suspected renal tract cancer is an unresolved challenge. QCancer® (Renal) are a pair of multivariable prediction models (one for men; one for women) that have recently been developed to predict the risk of having undiagnosed renal tract cancer.

QCancer® (Renal) was developed and internally validated on a large cohort of 3.6 million patients from the QRESEARCH (http://www.qresearch.org/) database [1]. The QRESEARCH database is a large database comprising over 12 million anonymised health records from 602 general practices throughout the United Kingdom using the EMIS computer system (http://www.emis-online.com). QCancer® (Renal) was developed on 2.4 million patients aged between 30 and 84 years, contributing 2878 incident cases of renal tract cancer from 4.1 million person-years of observation between 01 January 2000 and 30 September 2010. The final prediction models based on a Cox proportional hazards model included 8 risk factors for women and 6 risk factors for men (Table 1). Open source code to calculate the QCancer® (Renal) scores are available from http://www.qcancer.org/renal released under the GNU Lesser General Public Licence, version 3. The performance of the QCancer® (Renal) was assessed on a separate sample of 1.2 million patients from the same QRESEARCH database with good discriminative ability and calibration [1].

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Table 1
Risk factors in QCancer® (Renal).

Risk factor	Women	Men
Age (years)	√	√
Currently consulting a GP with first onset of haematuria (yes/no)	√	√
Anaemia, defined as recorded haemoglobin <11 g/dl in past 12 months (yes/no)	√	√
Currently consulting a GP with first onset of abdominal pain (yes/no)	√	√
Smoking status (non-smoker; ex-smoker; light smoker [<10 cigarettes/day]; moderate smoker [10–19 cigarettes/day]; heavy smoker [≥20 cigarettes/day])	√	√
Currently consulting a GP with first onset of weight loss (yes/no)	√	√
Currently consulting a GP with first onset of appetite loss (yes/no)	√	
History of prior cancer other than renal tract cancer (yes/no)	√	

QCancer® (Renal) is part of a suite of prediction models that form the QCancer Scores (http://www.qcancer.org/) that have been developed to predict the risk of having undiagnosed lung [2], ovarian [3], colorectal [4], gastro-oesophageal [5], renal [1] and pancreatic cancer [6]. We are currently, using identical methods, independently validating these six predictions models. To date, the validation of QCancer® (colorectal) [4], QCancer® (ovarian) [7] and QCancer® (gastro-oesophageal) [8] to predict the risk of undiagnosed colorectal, ovarian and gastro-oesophageal cancer, respectively. Accordingly, the descriptions of the methods used in the subsequent papers are substantially the same.

Before contemplating whether a prediction model could be considered for clinical use, it is important to evaluate the statistical characteristics and demonstrate transportability in data not used in the developing the prediction model, ideally by independent investigators [9–11]. This entails evaluating the prediction model as defined in the original study development study, considering no additional predictors and no modifications to outcome and predictor definitions [9,11,12].

The aim of this article is to describe the results from an independent evaluation of QCancer® (Renal) on a different large dataset of general practice records in the United Kingdom not used to derive the prediction model.

2. Methods

2.1. Cohort selection

Study participants were patients registered between 01 January 2000 and 30 June 2008 and recorded on the THIN database (http://www.thin-uk.com/). The same exclusion criteria as the original development paper were adopted [1]. Patients were excluded if they had a prior diagnosis of renal tract cancer, were registered less than 12 months with the general practice, had invalid dates, were under the age of 30 years or were aged 85 years or over. Entry to the cohort was defined as the same as the original development study [1] as the latest of (1) the study start date, (2) the date the patient registered with the practice and, for those patients with red flag symptoms (e.g., haematuria, abdominal pain, weight loss, appetite loss, and anaemia), and (3) the date of the first recorded onset of any red flag symptom within the study period.

2.2. Outcome measures

The outcome measure was defined as for the original development study [1], except there was no linkage to death records and based solely on what was recorded on the patient records. Diagnosis of renal tract cancer was defined as incident diagnosis of cancer of the bladder, kidney, ureter or urethra during the 2 years after study entry. Patients without the outcome were censored at the earliest of the date of death, date of leaving the practice study or 2 years of follow-up. As noted in the original study developing QCancer® (Renal), a 2-year period was used as this was assumed to be the time period during which existing renal tract cancers are likely to become clinically evident [1,13].

2.3. Statistical analysis

The 2-year estimated risk of renal tract cancer for every patient in the THIN cohort was calculated using QCancer® (Renal) risk score (http://www.qcancer.org/renal). Observed 2-year renal tract cancer risks were obtained using the method of Kaplan–Meier. Multiple imputation using all predictors plus the outcome variable and censoring status was used to replace missing values for smoking status [14]. This involves creating multiple copies of the data and imputing the missing values with sensible values randomly selected from their predicted distribution. Ten imputed data sets were generated and results from analyses on each of the imputed data sets were combined using Rubin's rules to produce estimates and confidence intervals that incorporate the uncertainty of imputed values [15]. Smoking status was derived from combining two risk factors; (1) whether the patient was a non-smoker, ex-smoker or current smoker and (2) amount of cigarettes smoked, defined as light (<10 cigarettes/day), moderate (10–19 cigarettes/day) or heavy (≥20 cigarettes/day).

Predictive performance of the QCancer® (Renal) risk score on the THIN cohort was assessed by examining measures of calibration and discrimination. Calibration refers to how closely the predicted 2-year renal tract cancer risk agrees with the observed 2-year renal tract cancer risk. This was assessed for each tenth of predicted risk, ensuring 10 equally sized groups, and each 5-year age category by plotting observed proportions versus predicted risk.

Discrimination is the ability of the risk score to differentiate between patients who experience an event during the study period and those who do not. This measure is quantified by calculating the *c*-statistic [16]; a value of 0.5 represents chance and 1 represents perfect discrimination. We also calculated the *D*-statistic [17] and R^2-statistic [18] that are measures of discrimination and explained variation respectively and are tailored towards censored survival data. The *D*-statistic is a measure of prognostic separation of survival curves and is closely related to the standard deviation of the prognostic index (the linear component from the Cox model). The R^2 (explained variation) is the proportion of total variation in the outcome that is explained by the prediction model, ranging from 0 to 100%.

All statistical analyses were carried out in *R* (version 2.14.1) [19] and the ICE (multiple imputation) procedure in Stata (version 11.2) [20].

3. Results

Between 01 January 2000 and 30 June 2008, 2,145,133 eligible patients from 364 general practices in the United Kingdom were