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Development and Internal Validation of a Lifestyle-Based Risk Prediction Model for 10-Year Incident Kidney Cancer in the 45 and Up Study

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Abstract

Purpose

Kidney cancer incidence continues to rise globally. Population-wide screening is not feasible due to low disease prevalence and risk of overdiagnosis, highlighting the need

for targeted, risk-stratified approaches. We aimed to develop and internally validate a lifestyle-based model to predict 10-year risk of kidney cancer.

Materials and Methods

Data were obtained from the Sax Institute's 45 and Up Study, a prospective cohort of adults aged ≥ 45 years recruited between 2006 and 2009 with linkage to the NSW Cancer Registry through to December 2019. Incident kidney cancer (ICD-10 C64) was defined as the first diagnosis after study enrolment. Candidate predictors included demographic, lifestyle, and clinical variables. A multivariable logistic regression model was developed using a 70% training set and evaluated in a 30% validation set. Model performance was assessed using discrimination (C-statistic), calibration, and decision curve analysis.

Results

Among 265,712 participants (mean follow-up 10.9 years), 1,010 incident kidney cancer cases were identified. Increasing age, male sex, obesity, hypertension, and diabetes were associated with higher risk, while vigorous physical activity was associated with lower risk. The model demonstrated moderate discrimination (C-statistic 0.68) and good calibration. At a predicted 10-year risk threshold of $\geq 1.0\%$, high-risk subgroups comprised approximately 4-5% of the population, with a 2.2- to 3.8-fold higher incidence. An eight-variable model incorporating smoking exposure demonstrated the strongest decision-analytic performance.

Conclusions

This population-based model using routinely available variables enables risk stratification in a low-incidence setting. Following external validation, it may support targeted prevention and risk-stratified screening strategies.

Keywords: 45 and up study, risk prediction; Kidney cancer; screening; decision curve analysis

Abbreviations

NSW - New South Wales

BMI - Body mass index

CHeReL - Centre for Health Record Linkage

NSWCR - New South Wales Cancer Registry

SURE - Sax Institute's Secure Unified Research Environment

SEIFA - Socioeconomic Indexes for areas

HR - Hazard Ratio

CI - Confidence Interval

1. Introduction

Kidney cancer represents the sixth most commonly diagnosed cancer in men and the tenth in women globally. [1 2] Incidence is rising, likely reflecting a combination of greater detection of incidental early-stage tumours and a growing prevalence of both established and emerging risk factors. In Australia, approximately 4,868 cases are projected in 2025, corresponding to a lifetime risk of 1 in 66[3]. Similar trends have been observed internationally, including in low- and middle-income countries, driven by increased exposure to modifiable risk factors and improved access to diagnostic services[4]. As a result the global burden of kidney cancer is projected to continue increasing [5].

Despite advances in treatment, a substantial proportion of patients present with advanced disease, and mortality remains significant, underscoring the need for improved strategies for early detection and prevention [4 6 7].

Earlier diagnosis may enable greater use of nephron-sparing approaches, including partial nephrectomy and ablative therapies, often delivered using minimally invasive techniques with curative intent. Preserving renal function may also reduce downstream cardiovascular morbidity associated with chronic kidney disease. [6 7] Accordingly,

early diagnosis and potential screening have been identified as key research priorities by patients, clinicians, and policymakers. [8-10]

Although interest in kidney cancer screening is increasing[11], no validated population-based screening programme currently exists. While kidney cancer fulfils several classical screening criteria, including a recognisable preclinical phase, frequent asymptomatic presentation, clinically meaningful morbidity, and effective treatment for early-stage disease, its relatively low incidence raises concerns regarding cost-effectiveness, overdiagnosis, and downstream harms. Consequently, population-wide screening is generally considered impractical, and attention has shifted towards targeted, risk-stratified approaches.

Risk prediction models represent a key enabling tool for such strategies. However, no kidney cancer risk model has been developed using Australian population data. The New South Wales 45 and Up Study provides a unique opportunity to address this gap.

In this study, we aimed to develop and internally validate a lifestyle-based model to predict 10-year risk of kidney cancer using data from the 45 and Up Study. By identifying individuals at increased risk, this model may support targeted prevention, personalised risk communication, and the future evaluation of risk-stratified screening strategies designed to reduce advanced disease while minimising potential harms.

2 Patients and Methods

2.1 Study population

Data were derived from the Sax Institute's 45 and Up Study, a large prospective cohort of 267,357 adults aged ≥ 45 years from New South Wales (NSW), Australia. The study design and recruitment procedures have been described previously. [12] In summary, participants were randomly sampled between 2006 and 2009 from the Services Australia (formerly the Department of Human Services) Medicare enrolment database, which provides near-complete population coverage, including citizens, permanent residents, and some temporary residents and refugees.

Participants completed a baseline questionnaire between January 2006 and December 2009, providing demographic, social, and lifestyle information, medical history, and consent for linkage to administrative health datasets

(<https://www.saxinstitute.org.au/our-work/45-up-study/questionnaires/>). Of the 267,357 participants, linkage was successfully completed for 266,333 individuals. After excluding those with prior kidney cancer and linkage errors, 265,712 participants were included in the analysis (Fig. 1).

Incident kidney cancer was defined as a first diagnosis of renal cell carcinoma (ICD-10 code C64) occurring after study enrolment. For the primary analysis, participants without kidney cancer whose follow-up was censored before 6 years were excluded to ensure sufficient observation time for reliable outcome ascertainment among event-free individuals. This approach reduces potential bias from early censoring while preserving sample size. Follow-up questionnaires were administered approximately every five years, and data access was provided via the Secure Unified Research Environment (SURE).

The 45 and Up Study was approved by the University of New South Wales Human Research Ethics Committee. This study was approved by the NSW Population and

Health Services Research Ethics Committee (2014/08/551) and conducted in accordance with the STROBE reporting guidelines.

2.2. Record linkage and outcome ascertainment

Baseline questionnaire data were probabilistically linked by the Centre for Health Record Linkage (CHeReL) to the NSW Cancer Registry (NSWCR), with linkage available through to 31 December 2019. The CHeReL probabilistic linkage method includes clerical review of uncertain matches and has an estimated false-positive rate of 0.5%.[13] (CHeReL; <http://www.cherel.org.au/>).

The NSWCR is a high-quality, population-based registry capturing all primary invasive cancers diagnosed among NSW residents (excluding non-melanoma skin cancer)[14].

2.3. Exposure variables and outcome measures

Candidate predictors were selected a priori based on clinical relevance and prior literature. Variables considered included age, sex, body mass index (BMI in kg/m²; underweight: < 18.5, normal: 18.5 to < 25, overweight: 25 to < 30, or obese: ≥ 30), smoking exposure (including heavy smoking defined as ≥30 pack-years), hypertension, diabetes, socioeconomic status (SEIFA), area of residence, household income, Ancestry, region of birth, alcohol consumption, level of education, self-reported health and quality of life, and physical activity by session and time. Key predictors included in candidate models are detailed below.

2.4. Statistical analysis

Baseline characteristics were compared between participants with and without incident kidney cancer using the Mann–Whitney U test for continuous variables and χ^2 tests for categorical variables. A complete-case approach was used, with no

imputation for missing data. Age was used as the underlying time scale, with follow-up commencing at age at baseline and ending at age at kidney cancer diagnosis, death, or 31 December 2019, whichever occurred first. Proportional hazards assumptions were assessed using log–log plots; where violations were suspected, stratified models were explored. A logistic regression framework was used to estimate 10-year absolute risk, consistent with prior population-based cancer risk models and facilitating clinical interpretability. The cohort was randomly split into training (70%) and validation (30%) datasets. Given the large sample size and favourable events-per-predictor ratio (>10), this split-sample approach was considered appropriate and minimised the risk of overfitting[15-17].

Model performance was evaluated using discrimination (C-statistic with 95% confidence intervals), calibration (decile-based plots with LOWESS smoothing), and decision curve analysis across clinically relevant thresholds (0.1%–1.5%).

Five prespecified candidate models were evaluated:

- **Option 1 (6 variables):** age, sex, BMI, hypertension, diabetes, vigorous physical activity
- **Option 2 (7 variables):** Option 1 + alcohol intake
- **Option 3 (7 variables):** Option 1 + European ancestry
- **Option 4 (8 variables):** Option 2 + European ancestry
- **Option 5 (8 variables):** Option 2 + smoking exposure (<30 vs ≥30 pack-years)

Sensitivity analyses using full 10-year follow-up were also performed.

2.5 Final model specification

The final model was specified using a logistic regression framework:

$$\text{logit}(P) = \beta_0 + \beta_1(\text{age group}) + \beta_2(\text{sex}) + \beta_3(\text{BMI category}) + \beta_4(\text{hypertension}) \\ + \beta_5(\text{vigorous physical activity}) + \beta_6(\text{diabetes})$$

Predicted absolute risk was calculated as:

$$P = \frac{1}{1 + e^{-\text{logit}(P)}}$$

All analyses were conducted using Stata version 19.5 (StataCorp, College Station, TX, USA).

Results

Over a mean follow-up of 10.9 years, 1,010 incident kidney cancer cases were identified among 265,712 participants (646 men and 364 women). Baseline demographic and lifestyle characteristics of participants with and without incident kidney cancer are presented in Table 1.

Associations between selected sociodemographic and lifestyle factors and incident kidney cancer are summarised in Table 2. In multivariable analyses, higher kidney cancer risk was observed with increasing age, male sex, higher BMI, hypertension, smoking duration, European ancestry and diabetes. In comparison, while vigorous physical activity was associated with lower risk.

Model development and validation were conducted in a population-based cohort of 68,202-69,314 participants (depending on model specification), with 271-275 incident kidney cancer events observed over 10 years. The overall 10-year incidence was approximately 0.40% across all analyses.

Across five prespecified candidate models (6-8 predictors), discrimination in the validation dataset was moderate and similar, with minimal differences between specifications ($\Delta\text{AUC} < 0.01$; Table 3). Calibration was good across models, with no systematic over- or under-prediction across the clinically relevant range; minor deviations were observed at the highest predicted risks where event counts were

sparse. (Table 4) Decision curve analysis (DCA) in the full validation cohort demonstrated positive net benefit for all candidate models compared with screen-all and screen-none strategies across low threshold probabilities, consistent with the low baseline incidence of kidney cancer; Option 5 showed the highest net benefit (Table 5).

More meaningful differences emerged after risk stratification. At a predicted 10-year risk threshold of $\geq 1.0\%$, the high-risk subgroup comprised approximately 4-5% of the cohort, with a 2.2- to 3.8-fold increase in incidence and capture of approximately 9.6% to 16.6% of events, depending on model specification. (Supplementary Table 1a)

Event prevalence within these subgroups was approximately 3.6–3.8-fold higher than in the overall population, providing stable decision-analytic estimates. At a $\geq 1.5\%$ threshold, subgroups were very small ($\leq 0.5\%$) with sparse events, resulting in unstable estimates; this threshold was therefore considered exploratory (Supplementary Table 1b).

Given similar discrimination and calibration across candidates, the primary model was selected based on decision-analytic stability, risk stratification performance, clinical interpretability, and transportability.[18] (Supplementary Table 2) The two eight-variable models demonstrated the strongest performance at this threshold. Option 4 (including alcohol consumption and European ancestry) and Option 5 (including alcohol consumption and heavy smoking exposure ≥ 30 pack-years) each identified 45 kidney cancer events (16.6%) while classifying fewer than 5% of the cohort as high risk. Option 5 was selected as the preferred model, as it demonstrated robust performance without reliance on ancestry variables, supporting broader generalisability. Its smoking definition aligns with established lung cancer screening criteria, facilitating potential integration with risk-based screening frameworks.

Figure 2 summarises discrimination, calibration, and decision-curve performance of the final model in the validation cohort. Performance of alternative models is presented in supplementary figures 1A-D. Sensitivity analyses using 10-year follow-up censoring demonstrated similar findings (Supplementary Figures 2A-E).

Discussion

We developed and internally validated a kidney cancer risk prediction model using routinely available demographic and lifestyle factors from the prospective 45 and Up Study, a large Australian population-based cohort. The model demonstrated moderate discrimination and good calibration, comparable with international phenotypic models derived from European and UK cohorts[19-21], while benefiting from greater robustness due to a substantially larger number of incident kidney cancer cases.

Across candidate models, discrimination remained similar despite incremental addition of predictors, suggesting that a parsimonious set of variables captures most of the predictive signal. In contrast, decision-analytic performance differed more meaningfully, highlighting the importance of evaluating clinical utility beyond conventional discrimination metrics, particularly in low-incidence settings where small differences in classification can have meaningful implications.

At a predicted 10-yr risk threshold of $\geq 1.0\%$, the model identified a small subgroup (approximately 4–5% of the population) with a 2.2–3.8-fold higher incidence, capturing approximately 16% of incident cancers. Although absolute risk remains low, this degree of risk concentration is important from a screening perspective, where feasibility and cost-effectiveness depend on identifying subgroups with sufficiently elevated risk. These findings support the potential role of risk-stratified approaches over population-wide screening strategies.

Selection of the final model incorporating age, sex, body mass index, hypertension, diabetes, vigorous physical activity, alcohol consumption, and smoking exposure (≥ 30 pack-years) was guided by clinical interpretability, transportability, and decision-analytic performance. While a simpler six-variable model offered comparable discrimination and may serve as a pragmatic baseline model, the eight-variable model demonstrated more stable net benefit across clinically relevant thresholds and was therefore retained. The inclusion of heavy smoking is a practical strength, aligning with established lung cancer screening criteria [22] and facilitating potential integration with existing screening programmes. Avoidance of ancestry-dependent predictors may further enhance generalisability and equity across populations.

Population-wide screening for kidney cancer remains impractical due to low incidence and the risk of overdiagnosis and overtreatment. Screening is therefore more plausibly justified in carefully defined high-risk subgroups[23 24].

Lifestyle-based risk models provide a pragmatic and scalable approach to population-level risk stratification. Unlike models reliant on complex or non-modifiable predictors, the present model incorporates modifiable risk factors that are routinely assessed in primary care, including obesity, smoking, hypertension, diabetes, and physical activity. This enables individualised risk estimation, which may support behaviour change, enhance patient engagement, and complement broader prevention strategies[5 25].

Our findings are consistent with prior studies demonstrating modest discrimination of phenotypic models, reflecting the inherent challenge of predicting a relatively uncommon malignancy using lifestyle factors alone. Nonetheless, the model identified a clinically meaningful high-risk subgroup using readily available variables, providing a practical foundation for risk-stratified screening strategies.

Integrated screening approaches may offer a feasible pathway for implementation. The Yorkshire Kidney Screening Trial demonstrated the acceptability and feasibility of incorporating abdominal imaging into lung cancer screening programmes[26].

Individuals eligible for lung cancer screening represent a particularly relevant high-risk population, and integration of kidney cancer risk stratification into such frameworks may improve efficiency. More broadly, ‘piggy-backing’ kidney cancer detection onto existing screening platforms may enhance yield while minimising additional resource burden. In this context, the recent introduction of a national lung cancer screening programme in Australia[22] provides a timely opportunity to evaluate integrated screening strategies in shared high-risk populations, particularly older adults with a history of smoking.

However, formal economic evaluation is required to determine cost-effectiveness and sustainability, particularly in low-incidence settings.

This study has several strengths. It leverages a large, well-characterised population-based cohort with long-term follow-up and near-complete outcome ascertainment

through linkage to a state-based cancer registry, minimising misclassification and loss to follow-up. The use of decision curve analysis further strengthens clinical interpretation by linking predicted risk to potential screening decisions and clinical consequences.

Several limitations should be acknowledged. Exposure variables were self-reported at baseline and are subject to measurement error and misclassification, likely biasing estimates towards the null. The use of baseline exposures precludes dynamic risk updating and may underestimate long-term predictive performance. However, reliance on self-reported variables may also enhance feasibility, as risk could be estimated without requiring further investigations. The model does not incorporate genetic factors, family history, renal function, or circulating biomarkers, which may improve discrimination but would reduce scalability and implementation potential.

Their absence likely constrained the upper limit of predictive performance, reflecting the inherent difficulty of predicting kidney cancer using phenotypic variables alone. Future work incorporating these factors, along with longitudinal exposure updates, may further improve discrimination and clinical relevance.

External validation was not performed, and generalisability beyond this population remains to be established. Validation in independent cohorts is essential prior to clinical application. Nevertheless, the observed performance is consistent with externally validated international models, supporting the broader transportability of this modelling approach.

Despite these limitations, the model provides a clinically interpretable and scalable framework for identifying individuals at increased risk of kidney cancer. In practice, this may support personalised risk communication and targeted preventive strategies in primary care. For individuals exceeding higher risk thresholds, targeted imaging, most plausibly renal ultrasound, may be considered, while opportunistic integration with existing imaging pathways, including lung cancer screening[26], represents a promising future direction.

Conclusions

A kidney cancer risk prediction model derived from participants in the 45 and Up Study demonstrated moderate discrimination and good calibration plots with decision-analytic evaluation supporting its utility for population-level risk stratification in a low-incidence setting. Using routinely available demographic and clinical variables, the model provides a pragmatic scalable framework for identifying individuals at increased risk. Following external validation, it may support targeted prevention and risk-stratified screening strategies.

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Figure 1.

CONSORT-style flow chart of selection of 45 and Up Study participants for inclusion in the analysis

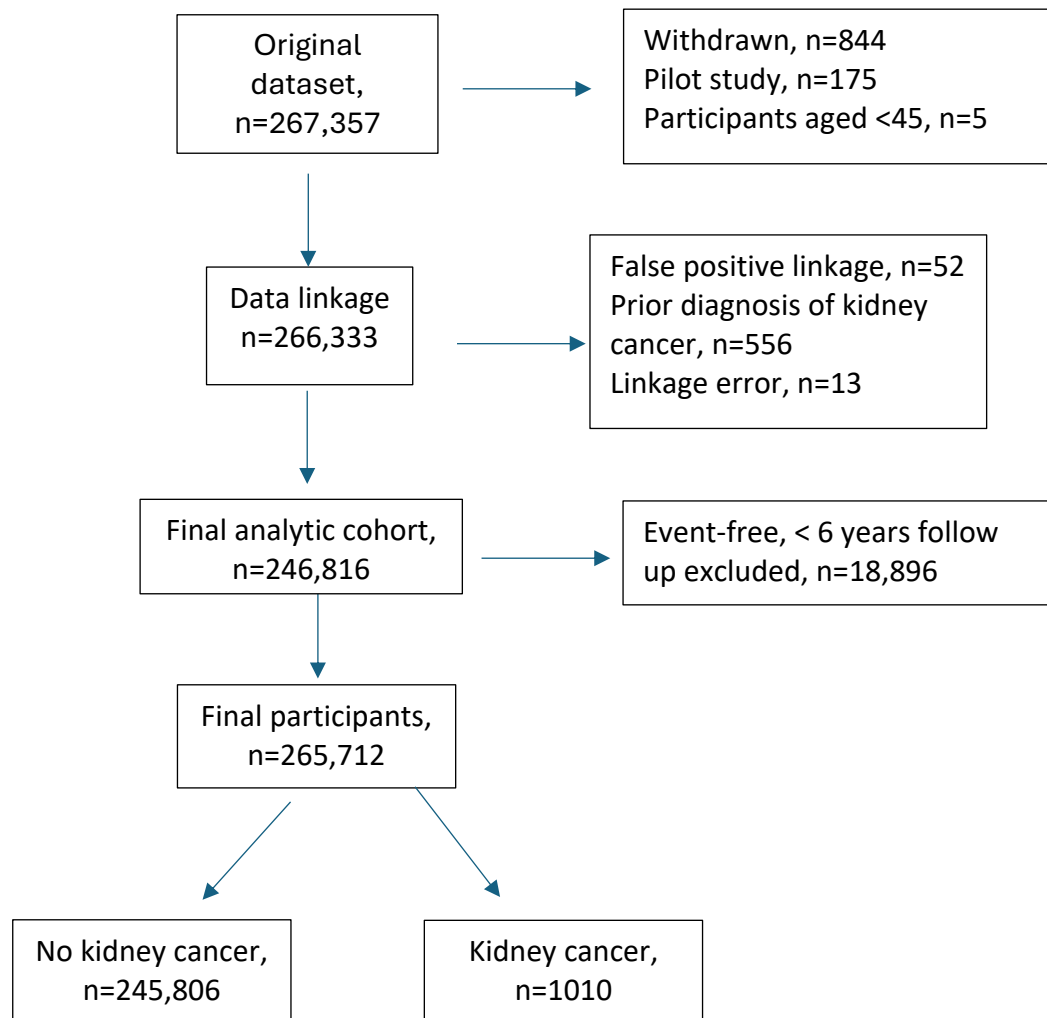
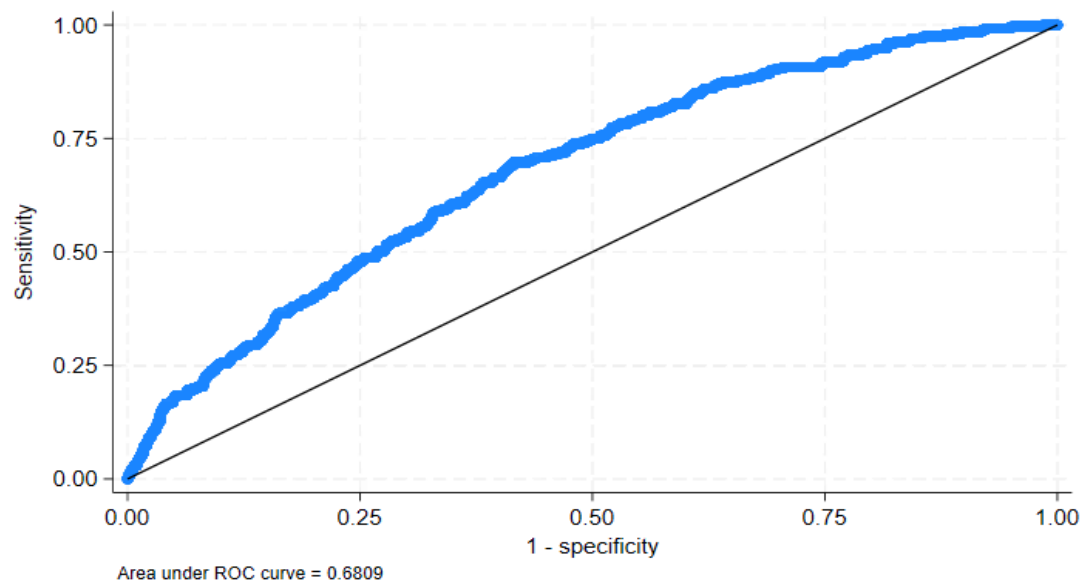


Figure 2.

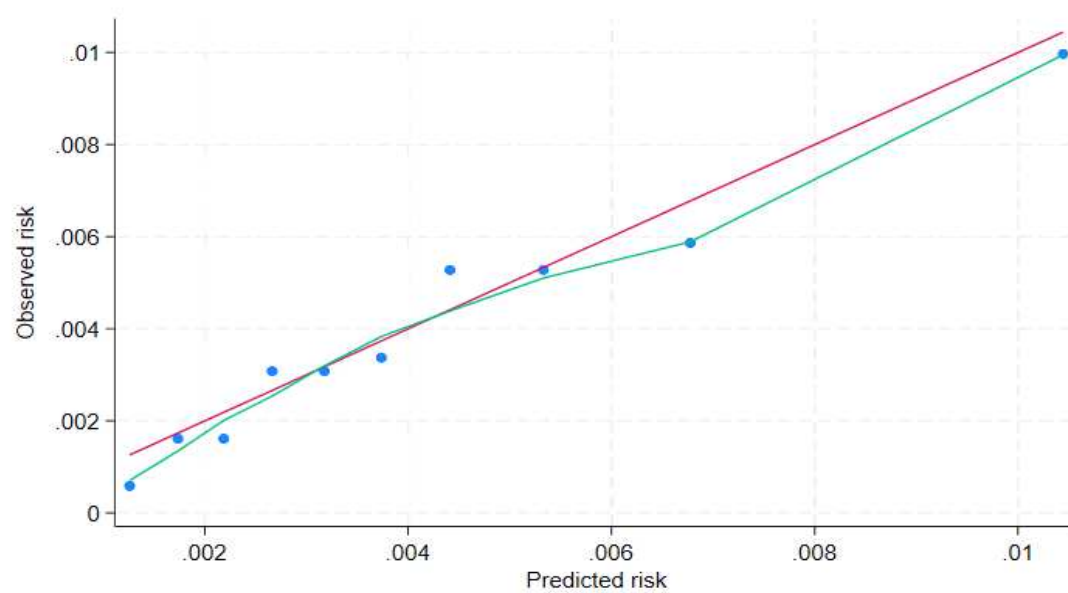
Performance of kidney cancer risk prediction model in the validation cohort.

- **Option 5:** 8 Variables: age, sex, BMI, hypertension, diabetes, VPA, alcohol, smoking (≥ 30 pack-years)

(A) Discrimination assessed using receiver operating characteristic (ROC) analysis.

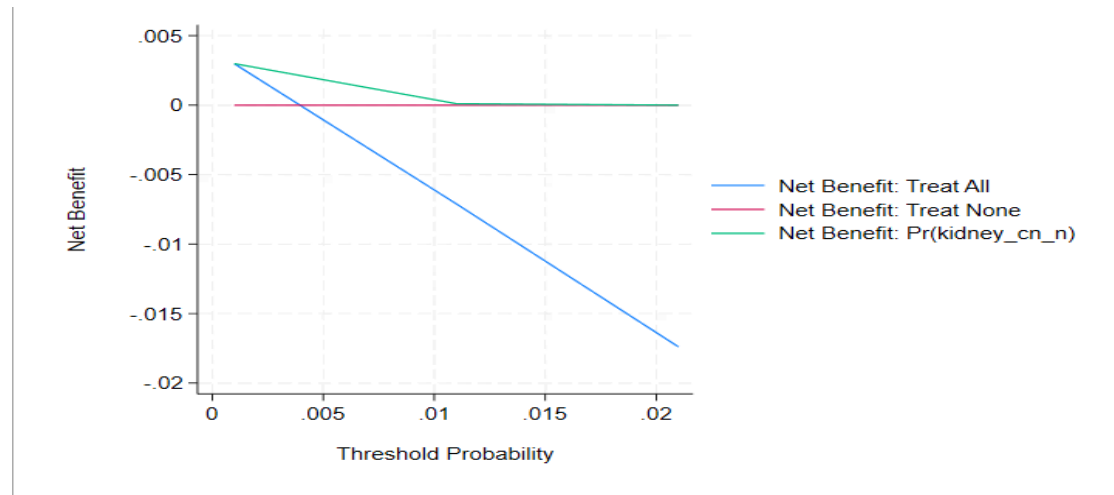


(B) Calibration plot comparing predicted and observed 10-year kidney cancer risk.

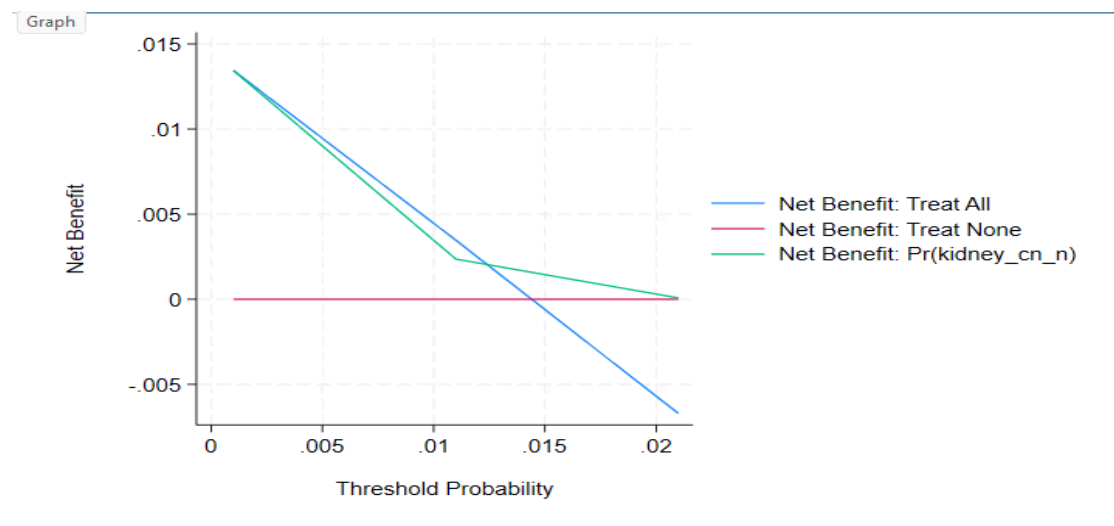


(C) Decision curve analysis (DCA) demonstrating net benefit across clinically relevant risk thresholds in (i) the entire validation cohort and (ii-iii) risk-stratified subgroups defined by predicted 10-year risk thresholds.

C1. Entire Test Population (N=68,203, Events=271, Prevalence=0.40%)



C2. High-Risk Subgroup $\geq 1.0\%$ (N=3,118, Events=45, Prevalence=1.44%)



C3. High-Risk Subgroup $\geq 1.5\%$ (N=350, Events=6, Prevalence=1.71%)

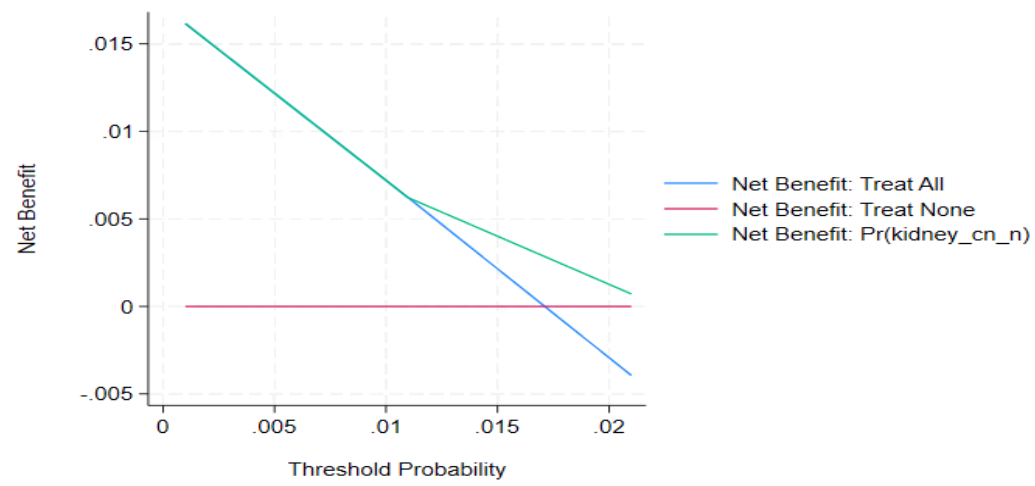


Table 1. Baseline demographic and lifestyle factors in relation to kidney cancer incidence in participants in the New South Wales 45 and Up Study (2006-2019)

	Total N=265712 (%)	No Kidney cancer N=264702 (%)	Kidney Cancer N=1010 (%)	P value
Age at recruitment				<.001
1. 45-49	34823 (13.1)	34746 (13.1)	77 (7.6)	
2. 50-59	88183 (33.2)	87924 (33.2)	259 (25.6)	
3. 50-69	73690 (27.7)	73307 (27.7)	383 (37.9)	
4. 70-79	42030 (15.8)	41849 (15.8)	181 (17.9)	
5. ≥80	26986 (10.2)	26876 (10.2)	110 (10.9)	
Sex				<.001
Male	123167 (46.4)	122521 (46.3)	646 (64.0)	
Female	142545 (53.7)	142181 (53.7)	364 (36.0)	
Socioeconomic status				
1. Quintile 1 (Least disadv.)	54826 (20.6)	54645 (20.6)	181 (17.9)	0.196
2. Quintile 2	44350 (16.7)	44183 (16.7)	167 (16.5)	
3. Quintile 3	49395 (18.6)	49216 (18.6)	179 (17.7)	
4. Quintile 4	55737 (21.0)	55504 (21.0)	233 (23.1)	
5. Quintile 5 (Most disadv.)	54362 (20.5)	54141 (20.5)	221 (21.9)	
6. Missing/Invalid	7042 (2.7)	7013 (2.7)	29 (2.9)	
Area of residence 1				
1. Major Cities	138642 (52.2)	138092 (52.2)	550 (54.5)	0.160
2. Inner Regional	92393 (34.8)	92071 (34.8)	322 (31.9)	
3. Outer Regional/Remote	29749 (11.2)	29631 (11.2)	118 (11.7)	
4. Missing/Invalid	4928 (1.9)	4908 (1.9)	20 (2.0)	
Area of residence 2				
1. Major Cities	138642 (52.2)	138092 (52.2)	550 (54.5)	0.306
2. Others	122142 (46.0)	121702 (46.0)	440 (43.6)	
3. Missing	4928 (1.9)	4908 (1.9)	20 (2.0)	
Income per year				<.001
1. < \$19,999	52225 (19.7)	51996 (19.6)	229 (22.7)	
2. \$20,000-\$39,999	46436 (17.5)	46236 (17.5)	200 (19.8)	
3. \$40,000-\$69,999	46910 (17.7)	46725 (17.7)	185 (18.3)	
4. ≥\$70,000	62619 (23.6)	62436 (23.6)	183 (18.1)	
5. Missing / Invalid	57522 (21.7)	57309 (21.7)	213 (21.1)	
Ancestry European				

1. No	233804 (88.0)	232935 (88.0)	869 (84.0)	0.056
2. Yes	31906 (12.0)	31765 (12.0)	141 (16.0)	
3. Missing	2 (0)	2 (0)	0 (0)	
Region of birth				0.004
1. AUS/NZ	204135 (76.8)	203377 (76.8)	758 (75.1)	
2. Asia	9355 (3.5)	9331 (3.5)	24 (2.4)	
3. UK Ireland & Europe	41640 (15.7)	41446 (15.7)	194 (19.2)	
4. Others	10582 (4.0)	10548 (4.0)	34 (3.4)	
Hypertension				<.001
1. No	164139 (61.8)	163682 (61.8)	457 (45.3)	
2. Yes	101573 (38.2)	101020 (38.2)	553 (54.8)	
Overall health				<.001
1. Excellent	38800 (14.6)	38696 (14.6)	104 (10.3)	
2. Very Good	94666 (35.6)	94328 (35.6)	338 (33.5)	
3. Good	86533 (32.6)	86158 (32.6)	375 (37.1)	
4. Fair	30724 (11.6)	30583 (11.6)	141 (14.0)	
5. Poor	5609 (2.1)	5593 (2.1)	16 (1.6)	
6. Missing	9380 (3.5)	9344 (3.5)	36 (3.6)	
Quality of life				0.189
1. Excellent	59773 (22.5)	59572 (22.5)	201 (19.9)	
2. Very Good	93866 (35.3)	93502 (35.3)	364 (36.0)	
3. Good	71279 (26.8)	70986 (26.8)	293 (29.0)	
4. Fair	22487 (8.5)	22400 (8.5)	87 (8.6)	
5. Poor	4282 (1.6)	4270 (1.6)	12 (1.2)	
6. Missing	14025 (5.3)	13972 (5.3)	53 (5.3)	
Education				0.058
1. No school certificate or other qualification	31128 (11.7)	30985 (11.7)	143 (14.2)	
2. School or intermediate certificate	58433 (22.0)	58213 (22.0)	220 (21.8)	
3. Higher school or leaving certificate	25953 (9.8)	25855 (9.8)	98 (9.7)	
4. Trade or apprenticeship / Certificate or diploma	84429 (31.8)	84107 (31.8)	322 (31.9)	
5. University degree or higher	61326 (23.1)	61123 (23.1)	203 (20.1)	
6. Missing/invalid	4443 (1.7)	4419 (1.7)	24 (2.4)	
Marital status				0.399
1. Single	16661 (6.3)	16596 (6.3)	65 (6.4)	
2. Married / Living with partner	198343 (74.7)	197609 (74.7)	734 (72.7)	

3. Widowed / Divorced / Separated	49100 (18.5)	48898 (18.5)	202 (20.0)	
4. Missing	1608 (0.6)	1599 (0.6)	9 (0.9)	
BMI				<.001
1. Under & Normal weight	93528 (35.2)	93296 (35.3)	232 (23.0)	
2. Overweight & Obese	151832 (57.1)	151126 (57.1)	706 (69.9)	
3. Missing / Invalid	20352 (7.7)	20280 (7.7)	72 (7.1)	
Smoking				0.009
1. Never	149746 (56.4)	149217 (56.4)	529 (52.4)	
2. Ever	114053 (42.9)	113578 (42.9)	475 (47.0)	
3. Missing/Invalid	1913 (0.7)	1907 (0.7)	6 (0.6)	
Smoking intensity				0.012
1. 0<10 cigs/day	19194 (7.2)	19128 (7.2)	66 (6.5)	
2. ≥10 to <20 cigs/day	36281 (13.7)	36146 (13.7)	135 (13.4)	
3. ≥20 cigs/day	55048 (20.7)	54786 (20.7)	262 (25.9)	
4. Missing / Invalid	155189 (58.4)	154642 (58.4)	547 (54.2)	
Smoking duration				0.048
1. 0<30 years	64022 (24.1)	63777 (24.1)	245 (24.3)	
2. ≥30 years	43538 (16.4)	43337 (16.4)	201 (19.9)	
3. Missing / Invalid	158152 (59.5)	157588 (59.5)	564 (55.8)	
Alcohol				0.434
1. Non-drinker	86796 (32.7)	86457 (32.7)	339 (33.6)	
2. 1-4	52640 (19.8)	52436 (19.8)	204 (20.2)	
3. >4-7	37970 (14.3)	37825 (14.3)	145 (14.4)	
4. >7-10	26423 (9.9)	26341 (10.0)	82 (8.1)	
5. >10	56860 (21.4)	56640 (21.4)	220 (21.8)	
6. missing	5023 (1.9)	5003 (1.9)	20 (2.0)	
Drinking frequency				0.617
1. Non-drinker	86796 (32.7)	86457 (32.7)	339 (33.6)	
2. 1-3	69105 (26.0)	68839 (26.0)	266 (26.3)	
3. 4-7	102690 (38.7)	102316 (38.7)	374 (37.0)	
4. missing	7121 (2.7)	7090 (2.7)	31 (3.1)	
Self reported diabetes				<.001
1. No	241926 (91.1)	241062 (91.1)	864 (85.5)	
2. Yes	23786 (9.0)	23640 (8.9)	146 (14.5)	
Physical activity sessions per week				0.589
1. 0 Sessions	15658 (5.9)	15587 (5.9)	71 (7.0)	
2. <5 sessions	41007 (15.4)	40847 (15.4)	160 (15.8)	
3. 5-<10 sessions	89524 (33.7)	89180 (33.7)	344 (34.1)	
4. 10-<15 sessions	63241 (23.8)	63016 (23.8)	225 (22.3)	

5. 15-<20 sessions	22663 (8.5)	22572 (8.5)	91 (9.0)	
6. ≥20 sessions	28106 (10.6)	28003 (10.6)	103 (10.2)	
7. Missing / Invalid	5513 (2.1)	5497 (2.1)	16 (1.6)	
Walking sessions per week				0.9916
1. 0 Sessions	40945 (15.4)	40791 (15.4)	154 (15.3)	
2. <10 sessions	184736 (69.5)	184030 (69.5)	706 (69.9)	
3. 10-<20 sessions	24518 (9.2)	24422 (9.2)	96 (9.5)	
4. ≥20 sessions	9823 (3.7)	9785 (3.7)	38 (3.8)	
5. Missing/invalid	5690 (2.1)	5674 (2.1)	16 (1.6)	
Moderate sessions per week				0.575
1. <5 Sessions	167546 (63.1)	166900 (63.1)	646 (64.0)	
2. 5-<10 sessions	73726 (27.8)	73456 (27.8)	270 (26.7)	
3. ≥10 sessions	18750 (7.1)	18672 (7.1)	78 (7.7)	
4. Missing/invalid	5690 (2.1)	5674 (2.1)	16 (1.6)	
Vigorous sessions per week				0.0026
1. 0 Sessions	159631 (60.1)	158968 (60.1)	663 (65.6)	
2. <5 Sessions	74142 (27.9)	73897 (27.9)	245 (24.3)	
3. ≥5 sessions	26249 (9.9)	26163 (9.9)	86 (8.5)	
4. Missing/invalid	5690 (2.1)	5674 (2.1)	16 (1.6)	
Physical activity total time per week				0.2191
1. <75 minutes	17639 (6.6)	17558 (6.6)	81 (8.0)	
2. 75-<150 minutes	6726 (2.5)	6702 (2.5)	24 (2.4)	
3. 150-<300 minutes	13260 (5.0)	13211 (5.0)	49 (4.9)	
4. 300-<450 minutes	11687 (4.4)	11632 (4.4)	55 (5.5)	
5. ≥450 minutes	206079 (77.6)	205310 (77.6)	769 (76.1)	
6. Missing/Invalid	10321 (3.9)	10289 (3.9)	32 (3.2)	
Walking total time per week				0.6382
1. <60 minutes	81833 (30.8)	81500 (30.8)	333 (33.0)	
2. 60-<120 minutes	45823 (17.3)	45646 (17.2)	177 (17.5)	
3. 120-<180 minutes	36267 (13.7)	36140 (13.7)	127 (12.6)	
4. 180-<240 minutes	25105 (9.5)	25019 (9.5)	86 (8.5)	
5. 240-<300 minutes	15710 (5.9)	15648 (5.9)	62 (6.1)	
6. ≥300 minutes	50653 (19.1)	50460 (19.1)	193 (19.1)	
7. Missing/invalid	10321 (3.9)	10289 (3.9)	32 (3.2)	
Moderate total time per week				0.0338
1. 0 minutes	79633 (30.0)	79341 (30.0)	292 (28.9)	
2. <150 minutes	40936 (15.4)	40800 (15.4)	136 (13.5)	
3. 150-<300 minutes	82524 (31.1)	82207 (31.1)	317 (31.4)	
4. ≥300 minutes	10321 (3.9)	10289 (3.9)	32 (3.2)	
5. Missing/invalid	79633 (30.0)	79341 (30.0)	292 (28.9)	
Vigorous total time per week				0.0001
1. 0 minutes	155153 (58.4)	154498 (58.4)	655 (64.9)	

2. <75 minutes	40264 (15.2)	40148 (15.2)	116 (11.5)
3. 75-<150 minutes	24202 (9.1)	24107 (9.1)	95 (9.4)
4. ≥150 minutes	35772 (13.5)	35660 (13.5)	112 (11.1)
5. Missing/invalid	10321 (3.9)	10289 (3.9)	32 (3.2)
Moderate + Vigorous total times (MET-h/week) combined			0.2181
1. <7.5 hour	79089 (29.8)	78757 (29.8)	332 (32.9)
2. 7.5-<15 hours	40405 (15.2)	40255 (15.2)	150 (14.9)
3. 15-<22.5 hours	30204 (11.4)	30103 (11.4)	101 (10.0)
4. 22.5-<30 hours	21994 (8.3)	21905 (8.3)	89 (8.8)
5. ≥30 hours	83699 (31.5)	83393 (31.5)	306 (30.3)
6. Missing/Invalid	10321 (3.9)	10289 (3.9)	32 (3.2)

Abbreviations: SD (standard deviations), BMI (Body mass index), MET (metabolic equivalent of task)

Table 2. Unadjusted and adjusted analysis for risk of kidney cancer by selected sociodemographic and lifestyle factors in the 45 and Up Study (2006-2019)

	Unadjusted model				Adjusted model**			
	HR	LCI	UCI	p-value	HR	LCI	UCI	p-value***
Sex				<0.0001				<0.0001
Male (ref)	1				1			
Female	0.47	0.41	0.53		0.49			
Hypertension				<0.0001				<0.0001
1. No	1				1.78			
2. Yes	1.86	1.65	2.1					
BMI				<0.0001				<0.0001
1. Under & Normal weight	1				1			
2. Overweight & Obese	1.89	1.64	2.19		1.56	1.35	1.81	
3. Missing / Invalid	1.31	0.98	1.74		1.23	0.93	1.64	
Smoking				0.0389				0.0415
1. < 30 years	1				1			
2. ≥30 years	1.21	1.05	1.44		1.05	0.93	1.18	
3. Missing/Invalid	0.9	0.78	1.04		1.2	0.83	1.74	
Ancestry European				0.018				0.0227
1. No	1				1			
2. Yes	1.23	1.04	1.46		1.22	1.03	1.45	

Alcohol				0.311				0.0001
1. Non drinker	1.01	0.86	1.2		1.09	0.92	1.29	
2. 1-4	1				1			
3. >4-7	0.95	0.77	1.17		0.96	0.78	1.18	
4. >7-10	0.79	0.62	1.02		0.71	0.55	0.91	
5. >10	1	0.84	1.21		0.77	0.64	0.93	
6. Missing/Invalid	1.08	0.68	1.63		1.14	0.73	1.77	
Self reported diabetes								
1. No	1			<0.0001	1			<0.0001
2. Yes	2.04	1.74	2.39		1.59	1.36	1.88	
Physical activity total time per week								
1. <75 minutes	1			0.0238	1			0.0951
2. 75-<150 minutes	0.78	0.51	1.19		0.78	0.51	1.19	
3. 150-<300 minutes	0.75	0.53	1.06		0.75	0.53	1.05	
4. 300-<450 minutes	0.94	0.67	1.3		0.93	0.67	1.29	
5. ≥450 minutes	0.72	0.58	0.9		0.76	0.61	0.95	
6. Missing/Invalid	0.63	0.42	0.93		0.69	0.46	1.03	
Moderate total time per week								
1. 0 minutes	1			0.0031	1			0.0413
2. <150 minutes	0.81	0.68	0.95		0.82	0.7	0.97	
3. 150-<300 minutes	0.72	0.59	0.88		0.77	0.63	0.95	
4. ≥300 minutes	0.77	0.66	0.91		0.84	0.71	0.99	
5. Missing/invalid	0.68	0.48	0.97		0.76	0.53	1.08	
Vigorous total time per week								
1. 0 minutes	1			0.0005	1			0.0001
2. <75 minutes	0.72	0.59	0.86		0.7	0.58	0.84	
3. 75-<150 minutes	0.96	0.78	1.18		0.99	0.8	1.22	
4. ≥150 minutes	0.75	0.61	0.91		0.74	0.61	0.9	
5. Missing/invalid	0.77	0.54	1.08		0.81	0.58	1.15	

Moderate + Vigorous total times (MET-h/week) combined							
1. <7.5 hour	1			0.0254	1		0.149
2. 7.5-<15 hours	0.9	0.75	1.08		0.93	0.77	1.12
3. 15-<22.5 hours	0.76	0.61	0.94		0.8	0.65	1
4. 22.5-<30 hours	0.95	0.76	1.19		1.02	0.82	1.28
5. ≥30 hours	0.81	0.69	0.94		0.87	0.75	1.01
6. Missing/Invalid	0.74	0.52	1.05		0.82	0.57	1.16

* Age at diagnosis was the underlying time variable.

** Multivariate analysis was adjusted for age, sex, hypertension, smoking and BMI.

*** p value was generated excluding missing/invalid

Table 3. Comparative performance of candidate kidney cancer risk prediction models

Model specifications and discrimination

Model (Option)	Predictors	No. of variables	Validation cohort (N)	Events	Baseline incidence	AUC
1	Age, sex, BMI, hypertension, diabetes, VPA	6	69,314	275	0.40%	0.677
2	Option 1 + alcohol	7	68,203	271	0.40%	0.679
3	Option 1 + European ancestry	7	69,313	275	0.40%	0.678
4	Option 2 + European ancestry	8	68,202	271	0.40%	0.679
5 (Primary)	Option 2 + heavy smoking (≥30 pack-years)	8	68,203	271	0.40%	0.681

Table 4. Calibration (validation cohort)

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Model	Calibration performance
Option 1	Good agreement with observed risk; minor tail deviations
Option 2	Good; no material improvement over Option 1
Option 3	Good; similar to Option 1
Option 4	Good; similar to Option 2
Option 5	Good; no systematic over- or under-prediction

Table 5. Decision curve analysis in the entire validation cohort across candidate kidney cancer risk prediction models

Model (Option)	Predictors	Validation cohort (N)	Events	Baseline prevalence	Threshold probability range*	Net benefit vs treat-none	Net benefit vs treat-all	Overall DCA interpretation
1	Age, sex, BMI, hypertension, diabetes, VPA	69,314	275	0.40%	~0.2-2.0%	Positive	Positive	Provides modest clinical utility across low thresholds
2	Option 1 + alcohol	68,203	271	0.40%	~0.2-2.0%	Positive	Positive	Similar to Option 1; no material improvement
3	Option 1 + European ancestry	69,313	275	0.40%	~0.2-2.0%	Positive	Positive	Comparable to Option 1; no clear advantage
4	Option 2 + European ancestry	68,202	271	0.40%	~0.2-2.0%	Positive	Positive	Slightly higher net benefit at upper low-risk thresholds
5 (Primary)	Option 2 + smoking (<30 vs ≥30 pack-years)	68,203	271	0.40%	~0.2-2.0%	Consistently positive	Consistently positive	Greatest and most stable net benefit across thresholds

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