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Development and external validation of a head and neck cancer risk prediction model

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Abstract

Background: Head and neck cancer (HNC) incidence is on the rise, often diagnosed at late stage and associated with poor prognoses. Risk prediction tools have a potential role in prevention and early detection.

Methods: The IARC-ARCAGE European case–control study was used as the model development dataset. A clinical HNC risk prediction model using behavioral and demographic predictors was developed via multivariable logistic regression analyses. The model was then externally validated in the UK Biobank cohort. Model performance was tested using discrimination and calibration metrics.

Results: 1926 HNC cases and 2043 controls were used for the development of the model. The development dataset model including sociodemographic, smoking, and alcohol variables had moderate discrimination, with an area under curve (AUC) value of 0.75 (95% CI, 0.74–0.77); the calibration slope (0.75) and tests were suggestive of good calibration. 384 616 UK Biobank participants (with 1177 HNC cases) were available for external validation of the model. Upon external validation, the model had an AUC of 0.62 (95% CI, 0.61–0.64).

Conclusion: We developed and externally validated a HNC risk prediction model using the ARCAGE and UK Biobank studies, respectively. This model had moderate performance in the development population and acceptable performance in the validation dataset. Demographics and risk behaviors are strong predictors of HNC, and this model may be a helpful tool in primary dental care settings to promote prevention and determine recall intervals for dental examination. Future addition of HPV serology or genetic factors could further enhance individual risk prediction.

KEYWORDS

behaviors, demographics, epidemiology, head and neck cancer, laryngeal cancer, model, oral cancer, oropharyngeal cancer, risk, risk prediction

1 | INTRODUCTION

Head and neck cancers (HNC), comprising of cancers of the oral cavity (OCC), pharynx, and larynx, are the eighth most common cancer globally with over 800 000 cases and 400 000 deaths in 2020.[1,2] The incidence of HNC is increasing and projected to further rise by 30% by 2030.[3] Key risk factors include tobacco smoking and alcohol consumption, both alone and synergistically in combination.[4] Additionally, socioeconomic factors are important with those from lower socioeconomic groups having a greater risk and burden of disease.[5] The incidence of oropharyngeal cancers (OPC) are the most rapidly rising rapidly rising, which has been attributed to human papillomavirus (HPV) infection.[6–9] HNC often presents late, with the majority of global HNC cases being diagnosed at advanced stage (III or IV), which is associated with poorer outcomes and prognosis.[10–14]

Given the concurrent challenges of growing incidence and late-stage presentation, there has been an increased emphasis on the need for primary and secondary prevention strategies. Risk prediction models and tools have been proposed as having a potential role to help improve earlier detection and promote preventive interventions, such as referrals to smoking cessation services.[15] Risk prediction models for other diseases and cancer sites have already been utilized in primary care settings, for example the Q-risk and Q-cancer series of risk tools.[16,17] Assessment of clinical risk prediction tools has suggested they are beneficial in supporting clinical management and promoting behavioral change.[18,19]

However, there are a limited number of existing HNC risk tools that have been developed or translated into practice. A review of existing HNC risk models identified that many of the models did not undertake external validation (i.e., testing the model in a dataset that is independent from that within which the model was developed).[20] This external validation is now widely considered to be an essential feature of clinical risk model development, ensuring that the model is both reproducible and generalizable to other populations.[21–23] The growing number of large population-cohort studies offers new opportunities for developing and validating clinically applicable risk models.[24]

The aim of this research was to develop and validate a multivariable logistic-regression HNC risk prediction model that can accurately predict and quantify an individual's risk of overall HNC (OCC, OPC, and larynx) in the population. This model was designed as part of a primary prevention strategy with the intention of later conducting a feasibility study in primary dental care settings. We hypothesized that a HNC risk model developed using a dedicated HNC case–control study and externally validated in a large population cohort could achieve good predictive performance and generalizability in the population.

2 | METHODS

2.1 | Definitions and data sources

HNC cases were defined as squamous cell carcinomas of the oral cavity, pharynx, and larynx according to WHO International Classification of Disease-10 (ICD-10) codes and definitions (ICD-10 codes C00.3-C06, C09-C14, C32).[25,26] Cases of the salivary glands and the esophagus were excluded.

The Alcohol Related Cancers And Genetic susceptibility in Europe (ARCAGE) study was selected as the training dataset for the model.[27] ARCAGE is a large European multi-center case control study that was coordinated by the IARC, with 14 different sites across 11 nations.[28] The study recruited over 2000 Upper Aero-Digestive Tract (UADT) cancer cases and controls (age and sex matched) from 2002 to 2005.

The UK Biobank cohort study was selected for model validation. It has over 500 000 participants recruited from 2006 to 2010. Data included sociodemographic, behavioral, clinical, and genetic information. The UK Biobank is also linked to national cancer and death registries, which allows for ready identification of newly diagnosed and existing cases within the cohort.[29–31]

The HNC risk prediction model development and validation were conducted in accordance with the Transparent Reporting of a multivariable Prediction model for Individual Prognosis Or Diagnosis (TRIPOD) guidelines.[32] Ethical approval for secondary data analysis was obtained from the MVLS college ethics committee of the University of Glasgow (Project no: 200210024). The ARCAGE study had original ethical approval from IARC and local research ethics boards, while the UK Biobank received ethical approval from the North West Multicentre Research Ethics Committee (MREC).

2.2 | Model development in ARCAGE

Logistic regression modeling was used to compute odds ratios (ORs) and 95% confidence intervals (95% CI). Model discrimination was reported using the area under curve (AUC) values with 95% CIs and the calibration was reported using Spiegelhalter's Z statistic.[33] The model was designed for practicality in a primary care setting. Frequencies and means were also calculated for each variable. In addition, univariable logistic regression analysis was conducted and AUCs and ORs with 95% CIs were reported.

Three sequential strategies were used for variable predictor selection. First, a "black box" approach was used, which was essentially an agnostic logistic regression of all available variables in the ARCAGE study to identify key statistically significant variables. Following this, the logistic regression model was refined based upon existing evidence of HNC risk factors; models were constructed using HNC risk factors established by pre-existing literature including original ARCAGE study analyses.[34–42] The third and final strategy entailed finalizing the model informed by the black box and literature with variables that were (i) available in the UK Biobank and (ii) would be feasible for recording in a clinical setting (e.g., behaviors such as smoking and alcohol behaviors are relatively easy to assess and are recorded routinely at new patient or check-up examinations in primary dental care, while a food frequency questionnaire might prove difficult to include in such routine appointments). Forward selection was used to select variables, with backward selection also used as a quality check.

Descriptive statistics and univariable associations were described for the key variables considered for the model at the literature-informed stage. Variables that were not ultimately selected were excluded for the following reasons: failure to survive stepwise selection in a multivariable model; considered impractical to test in a primary dental care setting; or the variable lacked

TABLE 1 Descriptive, univariable, and multivariable results for key model development variables in the ARCAGE study.

Variable	Cases (n = 1926)	Controls (n = 2043)	p-value	Univariable odds ratio (95% CI)	Final model multivariable odds ratio (95% CI)
Oral cavity	490 (25.4%)				
Oropharynx	452 (23.5%)				
Larynx	670 (34.8%)				
Hypopharynx	184 (9.6%)				
Overlapping	130 (6.7%)				
Age, mean (±SD)	58.8 (±10.2) years	59.3 (±11.6) years	0.18	1.00 (0.99–1.00)	**1.01 (1.00–1.01)**
Sex			**<0.0001**		
Male	1584 (82.2%)	1552 (76.0%)		**1.47 (1.26–1.71)**	**0.71 (0.58–0.86)**
Female	342 (17.8%)	491 (24.0%)		Ref	Ref
Years of education			**<0.0001**		
16+ years	98 (5.1%)	196 (9.6%)		Ref	Ref
No education	35 (1.8%)	34 (1.7%)		**2.06 (1.21–3.50)**	**1.87 (1.02–3.45)**
1–3 years	53 (2.8%)	34 (1.7%)		**3.12 (1.90–5.11)**	**2.25 (1.27–3.96)**
4–6 years	285 (14.8%)	255 (12.5%)		**2.24 (1.66–3.00)**	**1.56 (1.12–2.018)**
7–9 years	439 (22.8%)	433 (21.2%)		**2.03 (1.54–2.67)**	**1.45 (1.07–1.97)**
10–12 years	491 (25.5%)	599 (29.3%)		**1.64 (1.25–2.15)**	1.31 (0.97–1.77)
13–15 years	165 (8.6%)	236 (11.6%)		**1.40 (1.02–1.91)**	1.24 (0.88–1.76)
Highest educational level			0.32		
Finished primary school	684 (35.5%)	548 (26.8%)		**2.23 (1.73–2.86)**	Not included[a]
Finished further school/clerks	1117 (58.0%)	1275 (62.4%)		**1.56 (1.23–1.98)**	Not included[a]
University degree/ manager	120 (6.2%)	214 (10.5%)		Ref	Not included[a]
Smoking status			**<0.0001**		
Never	158 (8.2%)	664 (32.5%)		Ref	Ref
Former	452 (23.5%)	700 (34.3%)		**2.71 (2.20–3.35)**	**1.92 (1.51–2.45)**
Current	1316 (68.3%)	679 (33.2%)		**8.15 (6.69–9.92)**	**5.20 (4.05–6.68)**
Smoking, pack years mean (±SD)	41.2 (±34.5)	21.6 (±33.7)	**<0.0001**	**1.03 (1.02–1.03)**	**1.01 (1.01–1.01)**
Alcohol drink status			**<0.0001**		
Never	111 (5.8%)	258 (12.6%)		Ref	Not included[a]
Former	309 (16.0%)	184 (9.0%)		**3.90 (2.93–5.20)**	Not included[a]
Current	1505 (78.1%)	1600 (78.3%)		**2.19 (1.73–2.76)**	Not included[a]
Alcohol drink frequency (%)			**<0.0001**		
Never	97 (5.0%)	238 (11.7%)		Ref	Ref
1/2 × a week or special occasions only	62 (3.2%)	107 (5.2%)		1.42 (0.96–2.10)	1.14 (0.74–1.76)
1–3 × a month	71 (3.7%)	179 (8.8%)		0.97 (0.68–1.40)	0.83 (0.55–1.24)
1/2 × a week	229 (11.9%)	408 (20.0%)		**1.38 (1.03–1.83)**	1.17 (0.84–1.62)
3/4 × a week	151 (7.8%)	185 (9.1%)		**2.00 (1.46–2.76)**	**1.49 (1.03–2.15)**
Daily or almost daily	866 (45.0%)	608 (29.8%)		**3.50 (2.70–4.52)**	**2.21 (1.63–2.99)**

TABLE 1 (Continued)

Variable	Cases (n = 1926)	Controls (n = 2043)	p-value	Univariable odds ratio (95% CI)	Final model multivariable odds ratio (95% CI)
BMI kg/m^2, mean (±SD)	24.3 (±4.5)	26.2 (±4.4)	**<0.0001**	**0.91 (0.89–0.92)**	Not included[b]
Fruit consumption			0.54		
Never	69 (3.6%)	33 (1.6%)		Ref	Not included[b]
Once per month or less	69 (3.6%)	35 (1.7%)		0.94 (0.53–1.69)	Not included[b]
Several times per month	43 (2.2%)	17 (0.8%)		1.21 (0.60–2.43)	Not included[b]
Once per week	192 (10.0%)	104 (5.1%)		0.88 (0.55–1.43)	Not included[b]
Several times a week	550 (28.6%)	421 (20.6%)		**0.63 (0.41–0.96)**	Not included[b]
Once per day	481 (25.0%)	618 (30.3%)		**0.37 (0.24–0.57)**	Not included[b]
Several times per day	492 (25.6%)	799 (39.1%)		**0.30 (0.19–0.45)**	Not included[b]
Frequency of dental attendance			**<0.0001**		
Never	298 (15.5%)	174 (8.5%)		Ref	Not included[c]
Less than every 5 years	501 (26.0%)	389 (19.0%)		**0.75 (0.60–0.95)**	Not included[c]
Every 2–5 years	348 (18.1%)	402 (19.7%)		**0.51 (0.40–0.64)**	Not included[c]
At least every year	423 (22.0%)	820 (40.1%)		**0.30 (0.24–0.38)**	Not included[c]
Denture use			**<0.0001**		
Never	770 (40.0%)	1065 (52.1%)		Ref	Not included[a]
Ever	830 (43.1%)	739 (36.2%)		**1.55 (1.36–1.78)**	Not included[a]
HPV-16 negative	1078 (56.0%)	1252 (61.3%)	**<0.0001**	Ref	Not included[c]
HPV-16 positive	85 (4.4%)	5 (0.2%)		**19.73 (7.99–48.78)**	Not included[c]

Note: Statistical significance is highlighted in bold ($p < 0.05$).
[a]Not included for statistical reasons/variable inclusion.
[b]Not included for clinical practicality reasons.
[c]Not included due to no comparable variable or insufficient data in Biobank dataset.

sufficient data in the validation dataset. ORs and 95% CIs were calculated in multivariable logistic regression for the variables that were ultimately selected in the final model. A complete case analysis approach was adopted; variables with 10% or more missing data were be categorized or removed from model development altogether.[43,44]

2.3 | Model validation in UK Biobank

Cases were identified in the UK Biobank by adopting previous methods and code used by Burrows and colleagues, but matched according to our pre-defined list of ICD codes.[45] Cases with cancer diagnoses prior to 1st April 2007 (baseline assessment) were excluded (n = 61). If more than one cancer was diagnosed, the first chronological instance was taken to avoid duplication of cases (n = 285). Non-cancer patients were defined as

individuals with no cancer diagnosis (n = 383 442). Variables were formatted to match the formatting of the ARCAGE study variables that were selected during model development. A later attempt to stratify models by sex was also made.

Once the HNC cases within the cohort were identified, descriptive analysis, probability calculations and the subsequent logistic regression using the coefficients from ARCAGE were conducted. The methods used for reporting the performance during model development were repeated for the validation process. Model discrimination was reported using the area under the receiver operating curve (AUC) with 95% CIs and calibration was reported using Spiegelhalter's Z statistic.

Frequencies, means, and descriptive tests were also calculated for each variable, using two sample or Welch's two sample t-tests and chi-square or continuity corrected score tests for categorical data.

Model training and validation analyses were conducted using SAS v9.4 and R version 4.2.2.

3 | RESULTS

3.1 | Model development in ARCAGE

The ARCAGE study had 1926 HNC cases and 2043 controls for model development. A summary of the descriptive results of the study are summarized in Table 1. Cases and controls were broadly similar in terms of age and sex, as expected with the ARCAGE study matching controls by age-group and sex.

As consistent with the "black box" model and evidence from existing literature, male sex, increasing age, lower educational attainment (and virtually synonymous years of education), smoking, alcohol consumption frequency, and HPV-16 seropositivity (defined as a test of HPV-16 E6 MFI > 1000, or 3 out of 4 E-proteins greater than threshold values [HPV16 E1 > 200 MFI, HPV16 E2 > 679 MFI, HPV16 E6 > 484 MFI, HPV16 E7 > 548 MFI]) were associated with an increased HNC risk.[46] Regular dental visits, fruit and vegetable consumption, and increased BMI were associated with modest protective effects.

The ARCAGE study collected a detailed food frequency history which was deemed impractical to replicate in a clinically applied model, resulting in the decision to drop dietary variables from the final model. The BMI variable offered only a marginal improvement in prediction (AUC of 0.76), and there were concerns about conflicting evidence on the relationship between BMI and HNC risk from case–control studies and cohort studies—such that validating case–control derived data in a cohort would not improve prediction. Moreover, BMI was considered more challenging to accurately measure in some primary care settings (e.g., dental practices) where scales and stadiometers may not always be routinely available. This could also lead to potential recall biases and metric conversion challenges, impeding this variables utility. For these reasons, BMI was not included in further modeling.

Frequency of attendance at a dental practice was a statistically significant predictor of HNC risk. However, the UK Biobank had no comparable variable and participant data for dental practice attendance frequency, which was consequently dropped from the model selection.

HPV-16 serostatus data provided an increase in HNC prediction (AUC of 0.80, 95% CI = 0.79–0.82) and excellent calibration (Figure S3, Supporting Information). However, a number of the ARCAGE study participants lacked HPV serology ($n = 1549$, 39.0%). Furthermore, at the time of writing, 9695 UK Biobank participants were randomly sampled for HPV testing and subsequently, only a proportionately small proportion of our validation
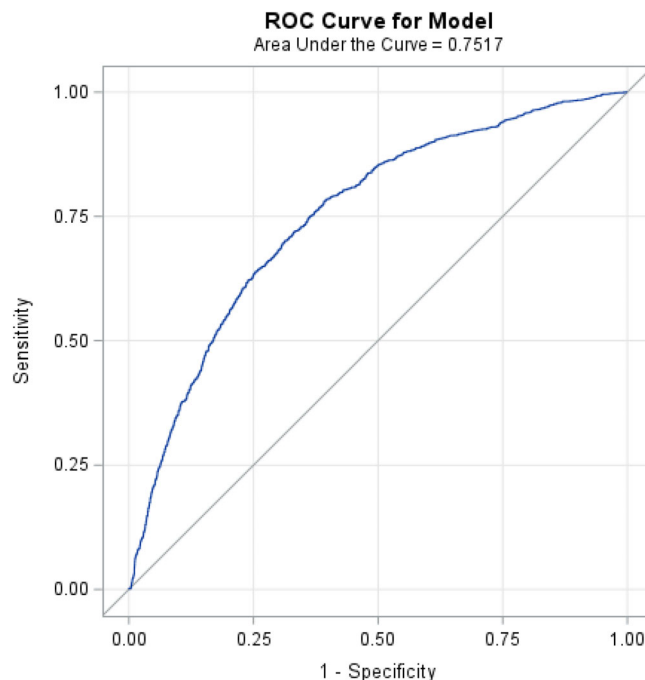

FIGURE 1   Receiver operating curve for final ARCAGE development model. [Color figure can be viewed at wileyonlinelibrary.com]

UK Biobank dataset sample ($n = 7238$, 1.9%) had HPV serology data available for analysis. Of these participants with HPV serology data, only four of the 1177 HNC cases had an HPV-positive serology test (0.3%)—making effective validation with this variable non-viable.

Thus, the final prediction model included age, sex, socioeconomic status via categories of years of education, smoking status, smoking pack years, alcohol consumption status, and alcohol consumption frequency (Table 1).

Age was associated with an increased risk association with each year. Females were at an increased risk of HNC versus their male counterparts, which may be attributable to matching. Increased risks for HNC were observed for: low relative to a high number of years in education; current (and former) smoker relative to never smoking status; increased number of pack years relative to zero; and a high frequency of alcohol consumption relative to never drinking alcohol.

The final risk prediction model for development (Figure 1) had an AUC of 0.75 (95% CI, 0.74–0.77). The results of Spiegelhalter's Z test for calibration (-0.603, $p = 0.55$) suggest the model was calibrated.

3.2 | Model validation in UK Biobank

Descriptive statistics of the validation population are summarized in Table 2. Following data management procedures (Figure 2) there were 384 616 participants that

TABLE 2 UK Biobank cohort study descriptive statistics results.

Variable	UK Biobank cohort (%), $n = 384\ 616$	HNC cases (%), $n = 1177$	Univariable odds ratio (95% CI)	p-value
Oral cavity	NA	490 (25.4%)		
Oropharynx	NA	452 (23.5%)		
Larynx	NA	670 (34.8%)		
Hypopharynx	NA	184 (9.6%)		
Overlapping	NA	130 (6.7%)		
Age, years, mean (±SD)	55.6 (±8.1)	58.3 (±7.1)	**1.05 (1.04–1.05)**	**<0.0001**
Sex				**<0.0001**
Female	208 740 (54.3%)	313 (26.6%)	Ref	
Male	175 876 (45.7%)	864 (73.4%)	**3.29 (2.89–3.74)**	
Years of education (%)				**<0.0001**
0: No education	376 (0.1%)	0	<0.001 (<0.001 to >999.999)	
1: <1–3 years	320 (0.1%)	1 (0.1%)	1.28 (0.18–9.15)	
2: 4–6 years	243 (0.1%)	2 (0.2%)	3.39 (0.84–13.70)	
3: 7–9 years	3258 (0.8%)	20 (1.7%)	**2.56 (1.61–3.97)**	
4: 10–12 years	180 575 (46.9%)	646 (54.9%)	**1.47 (1.29–1.67)**	
5: 13–15 years	44 908 (11.7%)	130 (11.1%)	1.19 (0.97–1.45)	
6: 16+ years	154 936 (40.3%)	378 (32.1%)	Ref	
Smoking status (%)				**<0.0001**
Never	214 642 (55.8%)	326 (27.7%)	Ref	
Former	127 382 (33.1%)	524 (44.5%)	**2.72 (2.36–3.12)**	
Current	40 355 (10.5%)	316 (26.9%)	**5.19 (4.44–6.06)**	
Smoking pack years, mean (±SD)	6.5 (±14.2)	19.8 (±26.4)	**1.03 (1.03–1.03)**	**<0.0001**
Alcohol drink frequency (%)				**0.02**
0: Never	31 494 (8.2%)	127 (10.8%)	Ref	
1: 1/2 × a week or special occasions only	44 257 (11.5%)	86 (7.3%)	**0.48 (0.37–0.63)**	
2: 1–3 × a month	43 477 (11.3%)	78 (6.6%)	**0.44 (0.34–0.59)**	
3: 1/2 × a week	99 803 (25.9%)	290 (24.6%)	**0.72 (0.58–0.89)**	
4: 3/4 × a week	88 527 (23.0%)	233 (19.8%)	**0.65 (0.53–0.81)**	
5: Daily or almost daily	75 820 (19.7%)	358 (30.4%)	1.17 (0.96–1.44)	

Note: Statistical significance is highlighted in bold ($p < 0.05$).

were available for model validation. Within this, there were 1177 HNC cases, of which the largest proportion were cases of the oropharynx ($n = 453$, 38.5%).

Upon external validation, the final risk prediction model (Figure 3) had an AUC of 0.62 (95% CI, 0.61–0.64). The results of Spiegelhalter's Z test (-0.013, $p = 0.99$) suggested that the model has acceptable calibration.[33]

3.3 | Sensitivity analysis

An attempt to account for potential HPV-associated OPC cases was made by trialing the same model for OCC and

Laryngeal cases only (Figure S1). However, this only yielded a marginal improvement in discriminative performance in the validation dataset with an AUC of 0.63 (95% CI, 0.60–0.65).

Similarly, a model was created using exclusively UK participants in ARCAGE to account for potential heterogeneity associated with the multi-national nature of the study; ARCAGE UK centers used population controls, while other centers used hospital patient controls. On validation, this also offered limited discriminative performance (Figure S2) with an AUC of 0.52 (95% CI, 0.51–0.54) in the UK Biobank.

Another model, including denture use offered little improvement in performance (AUC of 0.77, 95% CI,
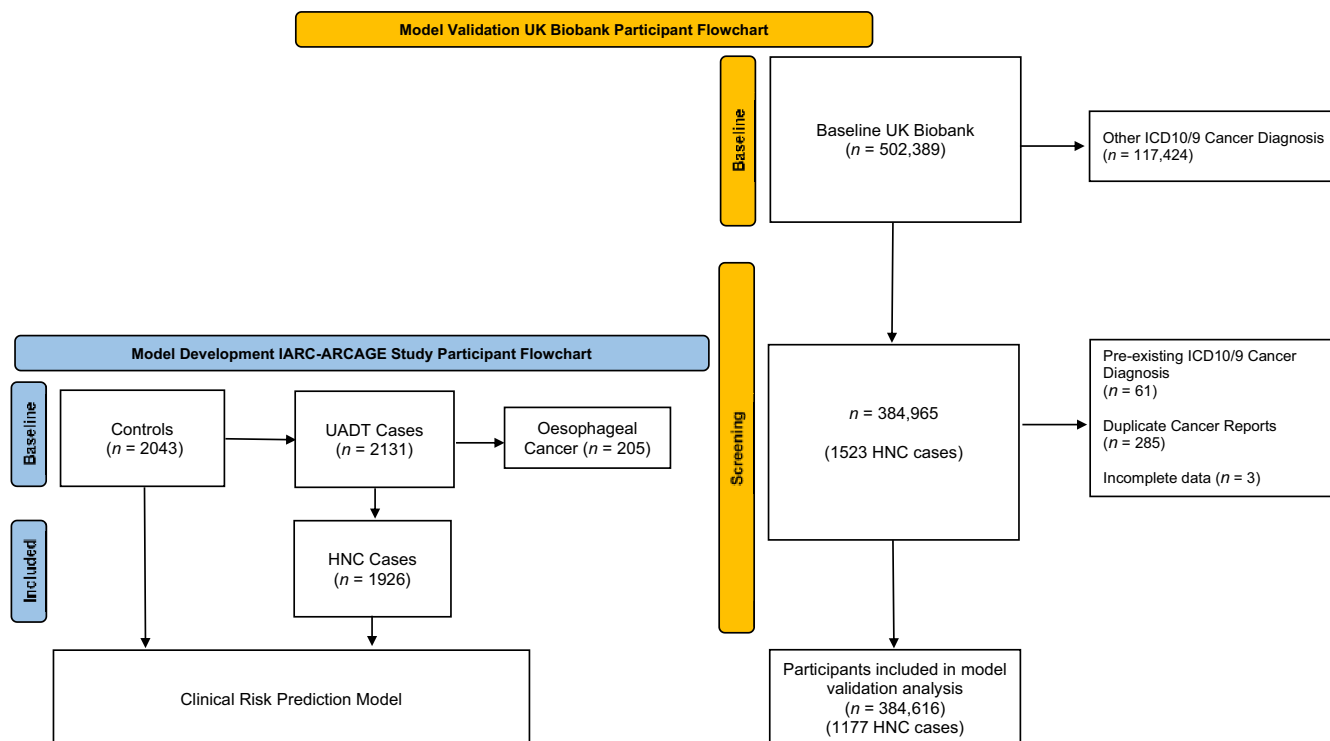
Model Validation UK Biobank Participant Flowchart

Baseline

Baseline UK Biobank
(n = 502,389) → Other ICD10/9 Cancer Diagnosis
(n = 117,424)

Model Development IARC-ARCAGE Study Participant Flowchart

Baseline

Controls
(n = 2043) → UADT Cases
(n = 2131) → Oesophageal Cancer (n = 205)

Screening

n = 384,965
(1523 HNC cases) → Pre-existing ICD10/9 Cancer Diagnosis
(n = 61)

Duplicate Cancer Reports
(n = 285)

Incomplete data (n = 3)

Included

HNC Cases
(n = 1926)

Clinical Risk Prediction Model

Participants included in model validation analysis
(n = 384,616)
(1177 HNC cases)

FIGURE 2 ARCAGE and UK Biobank participant flowchart. [Color figure can be viewed at wileyonlinelibrary.com]

ROC Curve for Model
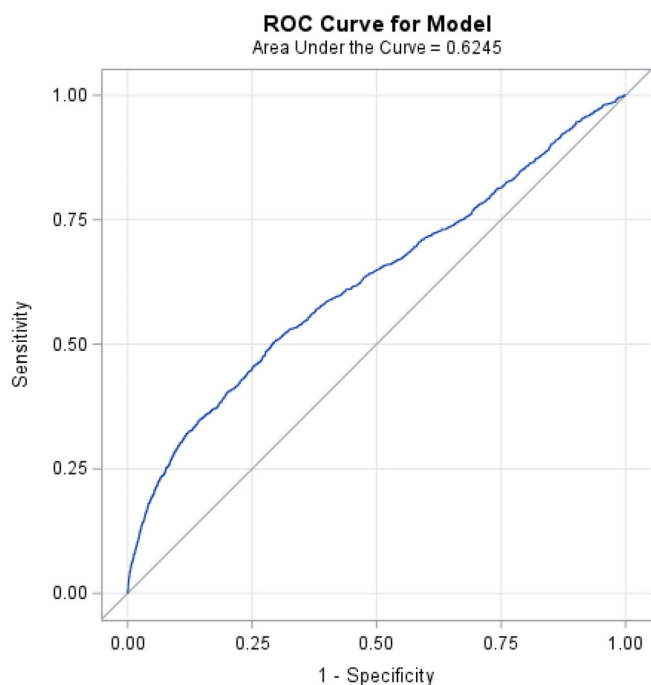Area Under the Curve = 0.6245

FIGURE 3 Receiver operating curve for the validation of the HNC risk prediction model in the UK Biobank. [Color figure can be viewed at wileyonlinelibrary.com]

0.75–0.78) and had limited discrimination upon validation (AUC = 0.61, 95% CI, 0.59–0.63) (Figures S4 and S5).

4 | DISCUSSION

We developed a risk prediction model for all HNC sites using two separate sources—a European multi-center HNC case–control study for model development and a UK population-based cohort study for model validation. The model performed well in the developmental dataset. Upon validation, the AUC results show that while the model can predict individual risk of HNC, its discriminative ability is acceptable, but more limited, in the UK Biobank. Similar findings were observed when the model was developed from OCC and laryngeal subsites, and exclusively UK participants. The models were calibrated, with nonsignificant results for Spiegelhalter's Z test suggestive that we can accept the null hypothesis that models were well calibrated.

Two other HNC risk models have made use of these study datasets. Budhathoki and colleagues recently developed multiple models stratified by subsite using pooled data from five separate studies including data from the ARCAGE and UK Biobank studies. The models included epidemiological risk factors, HPV serostatus, polygenic risk scores (PRS) and combinations of these.[47] Our model took a different approach, opting ultimately for feasibility and practicality of use by predicting overall HNC risk using epidemiological predictors that could readily be captured in a clinical setting, as opposed to the site and gender specific models created by Budhathoki and

colleagues.[47] These epidemiology models performed marginally better than our model using demographic and behavioral factors. However, interestingly, the variable selection was largely similar. The models were also well calibrated. The discrepancy in performance could perhaps be explained by the larger sample size from the pooled studies used by Budhathoki et al. for both model development and validation via randomly splitting the dataset rather than using an independent external validation dataset as conducted by our study.[47] The models using HPV serostatus were highly predictive of OPC but seemingly less predictive for overall HNC risk, as consistent with our findings. Similarly, the models using a combination of epidemiological and PRS had good predictive performance. However, the use of models incorporating these factors is not as feasible to replicate in primary care and community settings at present.

Another HNC risk prediction model developed by McCarthy and colleagues using the UK Biobank splits the dataset geographically for development and validation.[48] This model used demographic predictors, in addition to smoking and alcohol consumption status, BMI, exercise levels, and daily fruit/vegetable consumption.[48] The model had good calibration and marginally improved, but relatively limited, discriminative performance with an AUC of 0.64. The performance of this model, like ours, could perhaps be explained by the sole use of the UK Biobank as a validation dataset and use of epidemiological predictors.

Notably, following our evaluation of this, we opted to exclude BMI due to temporal variability on its risk relationship in the literature. The relationship between BMI and HNC risk may be subject to temporal variation depending on the time point assessed. There is an existing body of evidence derived from case–control analyses, including that of the ARCAGE study, suggestive of a lower BMI being associated with an increased HNC risk.[49–51] While some of these studies assessed BMI estimate at mid-life (e.g., at age 30 years), longitudinal cohort studies show either an increased or no clear HNC risk with higher BMI over a longer period[52–55] which is more similar to the risk relationship for many other cancers where an increased BMI is associated with increased inflammatory burden, various comorbidities, and subsequent cancer risk.[55,56]

Studies developing risk models for other cancers (including colorectal and renal cancers) in the UK Biobank have shown variability in performance.[57,58] Most models showed limited to reasonable (AUC > 0.60) levels of discrimination within the UK Biobank, with similarly varying levels of calibration. The variables selected for our model and those considered for selection, but not ultimately chosen, chime with the existing literature on HNC epidemiology. Demographic factors including age, sex, and socioeconomic status are well established predictors of HNC.[34,59,60] Our model performance metrics are also supportive of these findings. Similarly, smoking and alcohol consumption have also been shown to be highly predictive of HNC both in the literature and within our model, these also having clear dose relationships.[4]

The extent of missing HPV data in the UK Biobank (98.1%) and limited number of HPV-positive HNC cases meant accurate validation of an HPV model was not viable. Furthermore, our model was designed with the intention to be non-invasive for feasibility testing in a clinical setting, so our variables were chosen with the practicalities of this in mind. However, there is undoubtedly future scope for HPV status to be used for risk prediction of OPC, especially as technology and testing methods continue to improve. This is evidenced by a recent cohort study that was undertaken in Hamburg, where population HPV antibody testing and follow-up were used in order to inform risk stratification and investigations. This allowed the investigators to detect HPV positive OPC cases at an earlier stage.[61] Suggestions for any further modeling would be to utilize HPV serology status data (ideally with the development of a "rapid" test that could be used in primary care) for use in a separate OPC risk model, as conducted by Budhathoki et al. or Tota et al.[47,62] However, as stated, this was out of the scope of this project. While genomic or HPV biomarkers could improve the predictive accuracy of a risk model, their inclusion limits the utility of a tool in primary care settings with limited time/resources. There may be evidence to suggest that given the heterogeneity of subsites (and their relevant risk factors) included in HNC, future models should stratify by subsite. However, high-risk behaviors (such as smoking and alcohol) and sociodemographic predictors are generalizable across all HNC subsites, even among people with HPV-positive tumors. This approach also becomes more challenging for less common subsites where fewer cases for analysis are available (e.g., hypopharynx).

Another notable HNC risk prediction model was the HANRC V.2 tool developed by Tikka and colleagues.[63] This model had excellent performance and has seen use in secondary and tertiary care settings.[64,65] However, the model focuses on clinical signs and symptoms of HNC, many of which are associated with existing or advanced stage disease. In contrast, our model was designed with the specific complementary intention of primary prevention activity in a dental care setting, where at the time of writing, no such tool exists. Thus, what sets this model apart was its deliberate design with ease of use in primary care at the forefront, achieved through the integration of

robust yet readily accessible predictors that could inform preventive dialogues and inform recall activity.

This study had some strengths. We used a large, multinational HNC-focused case–control study that allowed for the selection of robust and predictive variables to assess HNC risk. The pooling of participants allowed for more accurate estimates of risk and greater generalizability, than a UK-based study alone. The use of a large UK-based population cohort as a validation dataset allowed for high-quality model validation. All of these analyses were also conducted in accordance with TRIPOD guidelines. Our model also faced some limitations. First, the cases were age-category and sex matched in the ARCAGE case–control study. This could have potentially weakened or altered the associations between two key demographic predictors (as observed with sex, where being female was associated with an increased HNC risk multivariably). However, despite this, the model fared well in the development stages. Stratification by sex yielded modest improvements in male predictive performance upon validation but at the cost of female predictive performance (data not shown).

There is also evidence to suggest that, comparatively, participants in the UK Biobank are less socioeconomically deprived than the general population.[66] Thus, the "healthy volunteer" effect associated with large volunteer cohorts may have also attenuated the performance of the model in the validation dataset, as previously observed leading to underestimation of the strength of associations between exposures and outcomes.[67] Finally, one of the major limitations and challenges of this analysis was the matching of predictor variables between the studies – first the variable (or a similar variable) had to exist and second it had to exist in sufficient quantity within both datasets. In some instances, this resulted in the exclusion of otherwise potentially viable variables, most notably HPV-16 serostatus and frequency of dental attendance. However, the comparative heterogeneity of the studies also served as a strength—it ensured the total number of variables was kept minimal and truly served to test the generalizability of the model.

5 | CONCLUSIONS

We have developed and externally validated a HNC risk model using the ARCAGE and UK Biobank studies respectively. This model had good performance in the development study and had a fair level of performance in the UK Biobank validation dataset. Ultimately, demographics and behaviors are strong predictors of HNC; however, these factors alone cannot reliably predict individual risk with a high degree of accuracy. Future incorporation of further biomarkers such as HPV-16 serostatus

or high-risk genetic variants could enhance the model prediction. The developed model still has potential to be feasibility tested and adapted for use as a clinical decision support tool in the primary care settings (including dental practices)—informing patient recall intervals and prompting preventive interventions.

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Additional supporting information can be found online in the Supporting Information section at the end of this article.