Risk Factors and Clinical Outcomes of Head and Neck Cancer in Inflammatory Bowel Disease: A Nationwide Cohort Study

Loes H. C. Nissen, MD,[,§§] Lauranne A. A. P. Derikx, PhD,[*] Anouk M. E. Jacobs, MD,[*] Carla M. van Herpen, PhD,[†] Wietske Kievit, PhD,[‡] Rob Verhoeven, PhD,[**] Esther van den Broek, PhD,[††] Elise Bekers, MD,[§] Tim van den Heuvel, MSc,[‡‡] Marieke Pierik, PhD,[‡‡] Janette Rahamat-Langendoen, PhD,[¶] Robert P. Takes, PhD,[‖] Willem J. G. Melchers, PhD,[¶] Iris D. Nagtegaal, PhD,[§] and Frank Hoentjen, PhD[*]; on behalf of the Dutch Initiative on Crohn and Colitis (ICC), Dutch Head and Neck Society, PALGA group, and IBD/HNC group*

Background: Immunosuppressed inflammatory bowel disease (IBD) patients are at increased risk to develop extra-intestinal malignancies. Immunosuppressed transplant patients show increased incidence of head and neck cancer with impaired survival. This study aims to identify risk factors for oral cavity (OCC) and pharyngeal carcinoma (PC) development in IBD, to compare clinical characteristics in IBD with the general population, and to assess the influence of immunosuppressive medication on survival.

Methods: We retrospectively searched the Dutch Pathology Database to identify all IBD patients with OCC and PC between 1993 and 2011. Two case-control studies were performed: We compared cases with the general IBD population to identify risk factors, and we compared cases with non-IBD cancer patients for outcome analyses.

Results: We included 66 IBD patients and 2141 controls with OCC, 31 IBD patients and 1552 controls with PC, and 1800 IBD controls. Age at IBD diagnosis was a risk factor for OCC development, Crohn's disease (CD; odds ratio [OR], 1.04; 95% confidence interval [CI], 1.02–1.07), and ulcerative colitis (UC; OR, 1.03; 95% CI, 1.01–1.06). For PC, this applied to UC (OR, 1.05; 95% CI, 1.01–1.06). IBD OCC cases showed impaired survival ($P = 0.018$); in PC, survival was similar. There was no effect of immunosuppression on survival. Human papillomavirus (HPV) testing of IBD cases revealed 52.2% (12/23) HPV-positive oropharyngeal carcinomas (OPCs).

Conclusion: This study shows that IBD is associated with impaired OCC survival. Higher age at IBD diagnosis is a risk factor for OCC development. We found no influence of immunosuppression on survival; 52.2% of OPC in IBD contained HPV.

Key Words: inflammatory bowel diseases, head and neck cancer, pharyngeal carcinoma, oral cavity carcinoma, immunosuppressive therapy

INTRODUCTION

Inflammatory bowel disease (IBD) is mainly diagnosed in young people and is characterized by chronic relapsing intestinal inflammation. The majority of IBD patients need long-term treatment with immunosuppressive medication to control the disease and prevent complications.[1,2] Furthermore, they have an increased risk of developing both intestinal and extra-intestinal malignancies (EIMs).[3] Immunosuppressive therapy can cause DNA damage and decrease immune surveillance, subsequently increasing EIM risk.[4–6] Reduced immune surveillance of the human papillomavirus (HPV), for example, is one of the contributing factors for the increased incidence of cervical cancer in patients with immunosuppression.[7–10]

HPV is associated with head and neck cancers (HNCs) as well, suggesting that immunosuppression use in IBD patients may also impact HNC risk in these patients. HPV-associated HNCs primarily occur in the (oro)pharynx of young patients[11] without a history of excessive exposure to alcohol and tobacco[12] and account for more than one-half of cancers of the oropharynx in the United States.[13] There is an

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From the*Inflammatory Bowel Disease Centre, Department of Gastroenterology and Hepatology, †Department of Oncology, ‡Department for Health Evidence, §Department of Pathology, ¶Department of Medical Microbiology, and ‖Department of Otorhinolaryngology, Radboud University Medical Centre, Nijmegen, the Netherlands;**Netherlands Cancer Registry/Netherlands Comprehensive Cancer Organization; ††Stichting PALGA, The Netherlands; ‡‡Department of Gastroenterology and Hepatology, Maastricht University Medical Centre, Maastricht, the Netherlands; §§Department of Gastroenterology and Hepatology, Jeroen Bosch Ziekenhuis, Den Bosch, the Netherlands

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Address correspondence to: Loes H. C. Nissen, MD, Inflammatory Bowel Disease Centre, Department of Gastroenterology and Hepatology, Radboud University Medical Centre, PO Box 9101, Code 455, 6500 HB Nijmegen, the Netherlands (loes.nissen@radboudumc.nl).

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approximately 2- to 4-fold increased risk of cancers of the oral cavity and oropharynx in patients infected with high-risk (oncogenic) HPV types. However, the reported prevalence seems to vary between countries. Recent studies on the prevalence in the Netherlands show lower prevalence.[14–16] In immunosuppressed transplant patients, the incidence of HNC is doubled compared with the general population.[17, 18] The outcome is worse in this group of immunosuppressed patients,[17, 19] which may be associated with high-dose immunosuppression.

Conflicting data on HNC risk in IBD are reported. Danish historical cohorts show no increased risk for lip, oral cavity, and pharyngeal cancer,[20, 21] while more recent US data show a standardized incidence ratio (SIR) for oral cancer of 9.77 (95% confidence interval [CI], 5.14–16.98)[22] in IBD patients. Various reports advocate regular oral screening.[23, 24] Currently, studies on risk factor for HNC development and HNC outcome in IBD patients are lacking. We hypothesized a worse outcome for oral cavity cancer (OCC) and pharyngeal cancer (PC) in IBD patients treated with immunosuppression in comparison with the general population.

In this study, we aimed to (1) identify risk factors in IBD patients that contribute to the development of OCC and PC and (2) compare the clinical characteristics, outcome, and survival of OCC and PC in IBD patients with the general population.

METHODS

Study Design

This study consisted of 2 retrospective case-control studies. Cases included IBD patients who developed OCC or PC and were selected through PALGA. PALGA is the national nationwide registry of cyto- and histopathology of the Netherlands.[25]

Case-Control Study 1 (I)

For the identification of risk factors for the development of OCC and PC in IBD patients, we compared IBD cases with HNC with IBD controls. Controls were randomly extracted from a population-based IBD cohort in the Netherlands (IBD South Limburg [IBDSL]).[26]

Case-Control Study 2 (II)

For the comparison of clinical characteristics and outcomes of OCC and PC between patients with and without IBD, we compared IBD cases with HNC with controls: patients with HNC from the general population. Controls were extracted from the Eindhoven Cancer Registry (ECR), a part of the

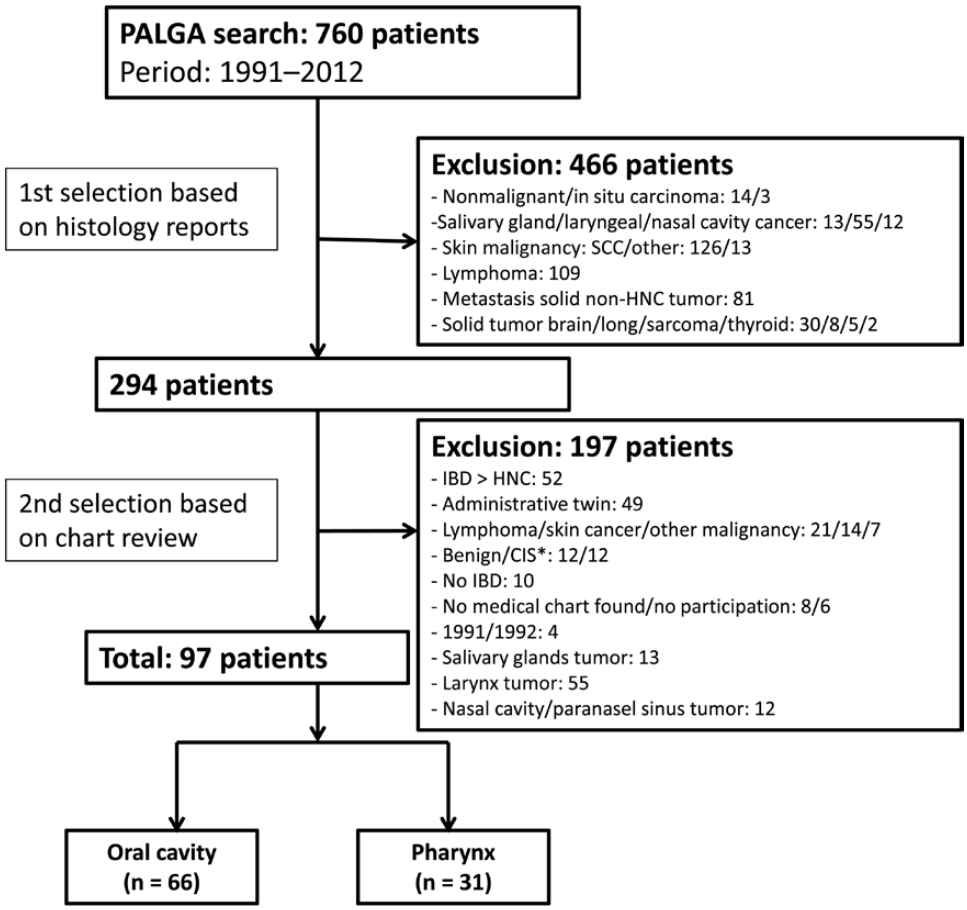

FIGURE 1. Flowchart case inclusion.

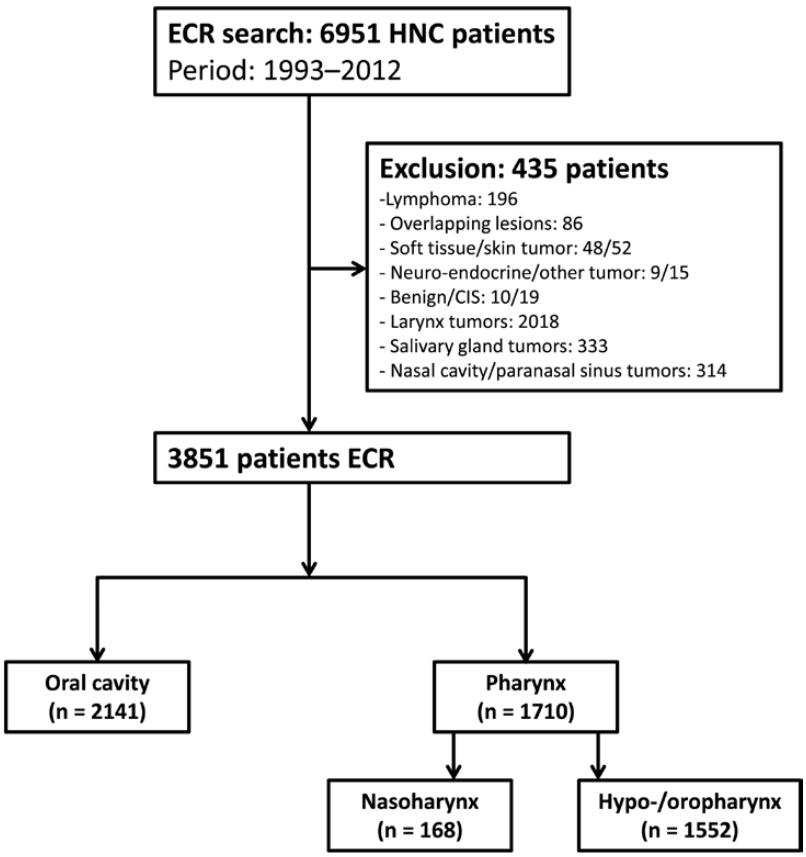

FIGURE 2. Flowchart ECR control (general population) inclusion.

Netherlands Cancer Registry (NCR). The study was approved by the Privacy Commission and Scientific Council of PALGA, by the Medical Ethics Review Committee of the Radboudumc, Nijmegen, the Netherlands (registration number 2013/211), and by the Medical Ethics Review Committee of the IBDSL.

Case Selection

For the identification of all IBD patients with HNC from January 1, 1993, until December 31, 2012, in the Netherlands, a search was performed in the national pathology database PALGA. PALGA has had nationwide coverage since 1991[25] and covers all academic and nonacademic Dutch pathology laboratories. Search terms for IBD included "ulcerative colitis" or "Crohn's disease" or "indeterminate colitis" or "chronic idiopathic inflammatory bowel disease." These terms were combined with search terms for HNC, including "head - neck" or "pharynx" or "mouth" or "oral cavity" or "lip" or "tongue" or "tooth" or "tonsil" or "adenoid."

An initial selection of cases was made based on pathology reports. Subsequently, medical charts were investigated for definitive inclusion or exclusion. All IBD patients with primary OCC and PC were included in this study. For this study, the exclusion criteria were OCC and PC in situ, lymphoma, diagnosis of IBD >3 months after OCC or PC diagnosis, OCC or PC diagnosis before 1993 or after 2012, and no confirmed diagnosis of IBD.

Case Control Study 1 (I): IBDSL Cohort Controls

To identify risk factors, we randomly included IBD controls diagnosed in the period 1991–2011 from the (population-based) IBDSL cohort.

The IBDSL cohort comprises adult IBD patients who were diagnosed between 1991 and 2011 in the South-Limburg area of the Netherlands. The South-Limburg region is a well-defined geographic region in the southeast of the Netherlands, with borders to Belgium and Germany and narrowly to the rest of the Netherlands in the north. Its geographic isolation results in a low net migration rate: 2.1 per 1000 inhabitants per year, favoring population research. A recent completeness check showed that 93% of all appropriate IBD patients from South-Limburg are currently registered in the IBDSL cohort. For detailed information on the IBDSL cohort, we refer to the cohort profile.[26]

One thousand eight hundred patients with an IBD diagnosis between 1991 and 2011 were randomly included, similar to our previous studies.[27–29] We chose an unmatched study design as we had a relatively large number of cases. This allowed us to adjust for possible confounders and avoid missing potential risk factors.

TABLE 1: Univariable Comparison of Potential Risk Factors Between IBD Patients With HNC (Cases) and IBDSL Controls

Variables	IBDSL	Oral Cavity	Missing	*P*	Pharynx	Missing	*P*
	n = 1800	n = 66			n = 31		
Median age at diagnosis, y	39.00	53.50	0/0	<0.01*	45.00	0/0	0.08
Female sex, No. (%)	983 (53.5)	22 (33.3)	0/0	<0.01*	12 (38.7)	0/0	0.10
Smoking (no; only CD patients), No. (%)							
Nonsmoker	253 (37.5)	9 (30.0)	1/122	0.45	0 (0.0)	3/122	<0.01*
Smoker	345 (51.2)	15 (50.0)			10 (90.9)		
Ex-smoker	76 (11.3)	6 (20.0)			1 (9.1)		
Alcohol use (current and past), No. (%)	-	46 (69.7)	-/5	-	17 (55.9)	-/11	-
Primary sclerosing cholangitis, No. (%)	13 (0.7)	1 (1.8)	4/20	0.36	0 (0.0)	10/20	0.10
IBD type, No. (%)							
Ulcerative colitis	1004 (55.8)	34 (52.4)	0/0	0.586	14 (46.7)	0/0	0.79
Crohn's disease	796 (44.2)	31 (47.7)			16 (53.3)		
Indeterminate colitis, No. (%)	0 (0.0)	1					
Ulcerative colitis, No. (%)[a]							
Proctitis (E1)	243 (24.4)	0 (0.0)	0/10	<0.01*	1 (7.7)	1/10	0.21
Left-sided colitis (E2)	472 (47.5)	17 (50.0)			7 (53.8)		
Pancolitis (E3)	279 (28.1)	17 (50.0)			5 (38.5)		
Crohn's disease, No. (%)[a]							
Ileum (L1)	223 (12.4)	5 9(16.1)	0/1	0.26	1 (7.1)	0/1	0.13
Colon (L2)	183 (10.2)	10 (32.3)			5 (35.7)		
Ileocolonic (L3)	389 (21.6)	16 (51.6)			8 (57.1)		
Upper digestive (L4) (yes)	65 (3.6)	6 (20.0)	1/60	0.04*	3 (23.1)	1/60	0.09
Stricturating (B2)	263 (14.6)	12 (40.0)	1/0	0.43	5 (38.5)	1/0	0.77
Penetrating (B3)	188 (10.4)	9 (30.0)	1/0	0.42	5 (38.5)	1/0	0.21
Medication, No. (%)							
5-aminosalicylates	1605 (89.2)	50 (87.7)	9/13	0.61	18 (81.8)	9/13	0.27
Steroids	1113 (61.8)	44 (77.2)	9/13	0.03*	16 (72.7)	9/13	0.33
Thiopurines	717 (39.8)	30 (52.6)	9/17	0.06	10 (45.5)	9/17	0.62
Methotrexate	95 (5.3)	1 (1.8)	9/10	0.36	0 (0.0)	9/10	0.63
Cyclosporin	26 (1.4)	3 (5.3)	9/10	0.06	0 (0.0)	9/10	1.00
Anti-TNF therapy	350 (19.4)	6 (10.5)	9/25	0.08	4 (18.1)	9/25	1.00
IBD-related surgery, No. (%)	1284 (71.7)	43 (65.2)	0/8	0.25	19 (63.3)	1/8	0.32
Median duration of follow-up since IBD diagnosis, y	7.00	9.00	0/30	0.01*	11.00	0/30	0.09

Smoking data of IBDSL only avaible for CD patients.
[a]According to the Montreal classification.

Case Control Study 2 (II): ECR Controls

For the comparison of clinical characteristics and outcome of HNC in IBD with the general population, controls with OCC and PC were identified from the ECR. The ECR is managed by the Netherlands Comprehensive Cancer Organisation (NCCO) and prospectively has been registering all newly diagnosed cancers in the Southeast of the Netherlands since 1989. It covers a region with 2.3 million inhabitants (about 15% of the Dutch population), including more than 95% of all cancers in this area (http://www.eindhovencancerregistry.nl). The search terms used in this registry were C00, C02, C03, C04, C05, C06, C09, C10, C11, C12, C13, and C14, according to the ICD-0, third edition.[30] We included all OPC and PC controls in the period from January 1, 1993, to December 31, 2012. In situ cancers and lymphomas were excluded.

Data Extraction

Three authors (L.N., L.D., and A.J.) reviewed the medical charts of IBD cases, which were anonymized, and extracted data of both IBD and HNC diagnosis.

TABLE 2: Final Multivariable Logistic Regression Model After Adjustment for Confounders and Follow-up: Independent Risk Factors for HNC Development

Model	Variable	Coefficient β	Odds Ratio (95% CI)	*P*
Oral cavity				
Ulcerative colitis, all cases (n = 34)	Age at IBD diagnosis	0.03	1.03 (1.01–1.06)	<0.01
Ulcerative colitis	Male sex	1.03	2.79 (1.08–7.18)	0.03
Sensitivity analysis (n = 26)	Age at IBD diagnosis	0.05	1.05 (1.02–1.08)	<0.01
Crohn's disease	Age at IBD diagnosis	0.04	1.04 (1.02–1.07)	<0.01
All cases (n = 31)	Upper digestive (L4)	1.08	1.10 (1.04–1.17)	0.03
Crohn's disease	Age at IBD diagnosis	0.04	1.04 (1.02–1.07)	<0.01
Sensitivity analysis (n = 20)				
Oropharynx				
Ulcerative colitis, all cases (n = 12)	Age at IBD diagnosis	0.05	1.05 (1.00–1.09)	0.01
Ulcerative colitis	5-aminosalicylates	-4.03	0.02 (0.01–0.09)	<0.01
Sensitivity analysis (n = 9)				
Crohn's disease, all cases (n = 12)	No risk factors identified			
Crohn's disease Sensitivity analysis (n = 6)	No risk factors identified			

Data that were collected for the IBD cases included sex, date of birth, medical history, alcohol and smoking history, height, and weight. IBD variables that were collected: type of IBD based on histopathologic evaluation, date of IBD diagnosis, IBD phenotype (Montreal Classification),[31] presence of primary sclerosing cholangitis, IBD medication use (5-aminosalicylates, corticosteroids, thiopurines, methotrexate, calcineurin inhibitors, and anti-TNF therapy), period of therapy use, and number and type of surgery. IBD diagnosis was predicated on a combination of several criteria: clinical, endoscopic, histological, and radiographic criteria.[32] For IBD controls from the IBDSL, same variables were collected, although alcohol and smoking history were only partially available and duration of immunosuppressive medication was not available.

HNC characteristics for cases and controls included diagnosis date, location and tumor stage according the TNM classification (7th edition), previous HNC or radiation, differentiation grade, primary treatment, (local) recurrence, and overall survival.

IBD cases were encrypted and anonymously linked to the Dutch Cancer Registry database, for reasons of quality control and completion of collected HNC data.

HPV Detection and Genotyping

Sample preparation

We isolated DNA from formalin-fixed paraffin-embedded (FFPE) tissue samples (4 µM) with the EZ1 robot (Qiagen, Germany, with the DNA tissue kit of Qiagen) according to standard procedures (19). We used them for polymerase chain reaction (PCR) analysis. We included a negative water control with each batch of samples (10).

Immunohistochemistry

For immunostaining, we used an anti-p16 monoclonal antibody (clone G 175–405; BD Pharmi ngen, San Diego, CA, USA) with a 1:10 dilution. As positive control, we used cervical cancer tissue with high p16 expression. We scored the p16 immunohistochemistry positive in case there was strong nuclear and cytoplasmic staining present in more than 70% of the malignant cells. All other p16 immunohistochemistry patterns were scored as negative.

HPV-DNA detection and typing

For the broad-spectrum HPV-DNA amplification performance, we used a short PCR fragment assay (HPV SPF_{10}-$LiPA_{25}$, version 1; Labo Bio-medical Products B.V., Rijswijk, the Netherlands). This assay amplifies a 65-bp fragment of the L1 open reading frame of HPV genotypes.[33] For the HPV genotyping, we used a cocktail of 9 conservative probes in a micro titer hybridization assay, the DNA enzyme immunoassay (DEIA). The samples positive for HPV by DEIA were subsequently analyzed with the line probe assay (LiPA25) by reverse hybridization with type-specific probes (for HPV 6, 11, 16, 18, 31, 33, 34, 35, 39, 40, 42, 43, 44, 45, 51, 52, 53, 54, 56, 58, 59, 66, 68/73, 70, and 74). We inspected and interpreted the LiPA strips visually following the standardized reference guide. Phocine herpesvirus was used as an internal amplification control.

Statistics

For case-control studies 1 (I) and 2 (II), we assessed possible risk factors, HNC characteristics, and outcomes between cases and controls with a univariable analyses. We used a X^2 test or Fisher exact test (if suitable) to analyze categorical data. We used an independent Student *t* test or Mann-Whitney *U* test to

TABLE 3: Univariable Comparison of Oral Cavity Characteristics Between IBD Cases and Controls From the General Population With Oral Cavity

Variable	IBD Patients	ECR Patients	Missing, No.	*P*
	n = 66	n = 2141	IBD/ECR	
Median age at diagnosis, y	60.50	65.00	0/0	0.02 *
Female sex, No. (%)	22 (33.3)	810 (37.8)	0/0	0.26
Tumor location, No. (%)				
Oral cavity	57 (86.4)	1506 (70.3)	0/0	<0.01*
Lip	9 (13.6)	635 (29.7)		
Histology, No. (%)				
SCC	62 (95.4)	2045 (96.5)	1/0	0.50
Differentiation, No. (%)				
Good	6 (12.2)	486 (27.5)	12/373	0.03*
Moderate	37 (75.5)	1013 (57.3)		
Poor	6 (12.2)	269 (15.2)		
Staging, No. (%)				
T stage oral cavity[a]				
T1	33 (60.0)	619 (42.0)	2/31	0.07
T2	12 (21.8)	401 (27.2)		
T3	3 (5.5)	115 (7.8)		
T4	7 (12.7)	340 (23.1)		
N stage oral cavity[a]				
N0	39 (74.2)	1270 (71.7)	2/80	0.87
N1	7 (11.3)	184 (10.4)		
N2	9 (14.5)	300 (16.9)		
N3	0 (0.0)	17 (1.0)		
M stage (yes) oral cavity[a]	1 (1.8)	17 (1.2)	1/121	0.51
TNM – stadium oral cavity, No. (%)				
Stadium I	27 (50.9)	454 (33.8)	4/162	0.05
Stadium II	7 (13.2)	231 (17.2)		
Stadium III	7 (13.2)	162 (12.1)		
Stadium IV	12 (22.6)	497 (37.0)		
TNM – stadium lip, No. (%)[a]				
Stadium I	7 (100.0)	248 (87.3)	2/351	1.00
Stadium II	0 (0.0)	20 (7.0)		
Stadium III	0 (0.0)	8 (2.8)		
Stadium IV	0 (0.0)	8 (2.8)		
Treatment, No. (%)				
Surgery (yes)	60 (90.9)	1834 (85.7)	0/0	0.23
Chemo (yes)	1 (1.5)	69 (3.2)	0/0	0.44
Radiotherapy (yes)	23 (34.8)	750 (35.0)	0/0	0.98
Previous malignancy, No. (%)	14 (21.2)	460 (21.5)	0/0	0.96

Abbreviations: OSCC, oral squamous cell carcinoma; SCC = squamous cell carcinoma.
[a]According to the 7th TNM edition.

analyze continuous data. We included variables with a *P* value of <0.1 in the univariable analyses in a multivariable model.

For case-control study 1 (I), a multivariable logistic regression model with backward sampling was performed. In this model, we adjusted for the follow-up duration (fixed variable). We defined follow-up as time since IBD diagnosis until the date of HNC diagnosis (for cases) or the end of follow-up or death (for controls). We made the model for CD and UC patients for the identification of independent risk factors for development of HNC. Because use of medication, especially in the distant

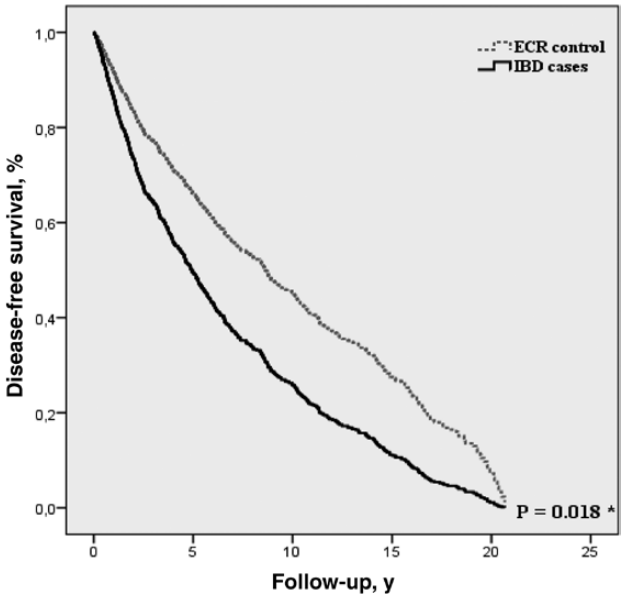

FIGURE 3. Oral cavity malignancy Kaplan-Meier survival curve.

past, may not be reliable and may differ from current treatment regimes, we did not include use of medication in the primary multivariable analysis. Therefore, we performed a second multivariable logistic regression analysis (which we called sensitivity analysis). These analyses included patients with an IBD diagnosis since 1991 in both the case and control groups. Medication use was included in this second logistic regression model.

For case-control study 2 (II), Kaplan-Meier survival curves were made, and we performed log-rank analysis. Subsequently, we performed confounder correction with a Cox regression model with forward sampling. We considered a covariate a confounder when the beta coefficient of the variable changed by 10% or more. As the clinical behavior (and TNM classification) is different for PC subsites (oro-, naso-, and hypopharynx), TNM stage and survival were analyzed separately.

We considered a P value of <0.05 statistically significant. All statistical analyses were performed with IBM SPSS statistics, version 20.0 (SPSS Inc, Chicago, IL, USA).

RESULTS

Cases and Controls

The initial PALGA search yielded 760 IBD and cancer cases. First, we excluded 466 patients who did not present with either an OCC or a PC (Fig. 1). Second, 197 patients were excluded who did not have confirmed IBD in their medical records, resulting in 31 patients with PC and 66 with OCC.

For case-control study I, 1800 IBD controls were randomly selected from the IBDSL. For case-control study II, we included 2141 patients with OCC and 1552 with a PC from the ECR (Fig. 2).

Case Control Study I: Risk Factors for OCC and PC Development in IBD Patients

OCC

The univariable comparison between IBD cases and IBDSL controls (Table 1) showed that cases were older at IBD diagnosis (median 53.5 vs 39.0 years; $P < 0.01$) and were more frequently male (66.7% vs 46.5%; $P < 0.01$). UC cases had more extensive disease (Montreal E3 disease: 50.0% vs 28.1%; $P < 0.01$), and CD patients had more frequent Montreal L4 disease (20.0% vs 3.6%; $P = 0.037$). IBD cases used more steroids compared with IBDSL controls (77.2% vs 66.8%; $P = 0.03$). We found no statistical difference in use of thiopurines (cases 52.6 % vs controls 39.8%; $P = 0.06$) and anti-TNF therapy (cases 10.5% vs controls 19.4%; $P = 0.08$).

In the multivariable logistic regression model, age at IBD diagnosis remained an independent risk factor to develop OCC in both UC (OR, 1.03; 95% CI, 1.01–1.06) and CD (OR, 1.04; 95% CI, 1.02–1.07) (Table 2). For CD, Montreal L4 disease (OR, 1.10; 95% CI, 1.04–1.17) was an additional risk factor.

PC

We included 31 IBD cases with PC: 25 with oropharyngeal carcinoma (OPC) and 6 with hypopharyngeal carcinoma (HPC) (Fig. 1). The univariable comparison between cases and IBDSL controls only showed a difference in tobacco use in CD patients (100% vs 62.5%; $P < 0.01$). We found no differences in use of medication: thiopurines $P = 0.62$ (cases 45.5% vs controls 39.8%) and anti-TNF $P = 1.00$ (cases 18.1% vs controls 19.4%).

In the multivariable logistic regression model (Table 2), no risk factors remained for CD. For UC, age at IBD diagnoses was an independent risk factor (OR, 1.05; 95% CI, 1.08–1.06).

The sensitivity analysis revealed a protective effect of 5-aminosalicylates for OPC in UC patients (OR, 0.02; 95% CI, 0.01–0.09) (Table 2).

Case-Control Study II: OCC and PC Cases vs ECR Controls

OCC

IBD cases had a lower median age at OCC diagnosis (60.5 vs 65.0 years; $P = 0.02$) compared with controls (Table 3). OCC cases had less frequent well-differentiated tumors (12.2% vs 27.5%; $P = 0.03$), and there was a trend toward a lower TNM stage ($P = 0.05$). Overall survival was similar in the univariable analysis ($P = 0.30$) (Supplementary Fig. 1). However, adjusted for confounders, IBD cases showed worse survival ($P = 0.02$) (Fig. 3). Immunosuppressive therapy did not negatively affect overall survival following OCC ($P = 0.43$) (Supplementary Fig. 1).

TABLE 4: Univariable Comparison of Pharynx Carcinoma Characteristics Between IBD Cases and Controls From the General Population With Pharynx Carcinoma

Variable	IBD Patients	ECR Patients	Missing, No.	*P*
	n = 31	n = 1552	IBD/ECR	
Oropharynx and hypopharynx				
Median age at diagnosis, y	59.00	61.00	0/0	0.65
Female sex, No. (%)	12 (38.7)	432 (27.8)	0/0	0.22
Tumor location, No. (%)				
Nasopharynx	0 (0.0)	158 (9.4)	0/23	0.09
Oropharynx	25 (80.6)	1095 (64.9)		
Hypopharynx	6 (19.4)	434 (25.7)		
Histology, No. (%)				
SCC	30 (96.8)	1459 (94.0)	1/93	1.00
Differentiation, No. (%)				
Good	2 (9.1)	88 (6.9)	9/275	0.69
Moderate 11 (50.0)	725 (56.8)			
Poor	9 (40.9)	464 (36.3)		
Oropharynx, No. (%)				
T stage[a]				
T1–T2	18 (75.0)	505 (47.5)	0/33	0.02*
T3–T4	7 (25.0)		557 (52.5)	
N stage[a]				
N0	12 (50.0)	363 (34.8)	0/25	0.49
N1	3 (12.5)	160 (15.3)		
N2	8 (33.3)	469 (45.0)		
N3	1 (4.2)	51 (4.9)		
M stage (yes)[a]	1 (4.2)	44 (4.4)	1/55	0.96
TNM – stadium, No. (%)[a]				
Stadium I –II	9 (37.5)	222 (21.6)	1/65	0.06
Stadium III–IV	15 (62.5)	808 (78.2)		
Hypopharynx				
T stage, No. (%)[a]				
T1	0 (0.0)	39 (9.3)	1/14	0.51
T2–T3	4 (80.0)	231 (55.0)		
T4	1 (20.0)	150 (35.7)		
N stage, No. (%)[a]				
N0	4 (80.0)	109 (26.7)	1/1	0.11
N1	1 (20.0)	75 (18.3)		
N2	0 (0.0)	188 (46.0)		
N3	0 (0.0)	37 (9.0)		
M stage (yes)[a]	0 (0.0)	24 (6.0)	1/34	1.00
TNM – stadium, No. (%)[a]				
Stadium I	0 (0.0)	11 (2.6)	1/18	0.03*
Stadium II–III	4 (80.0)	109 (26.2)		
Stadium IV	1 (20.0)	296 (71.2)		
Oropharynx and hypopharynx treatment, No. (%)				
Surgery (yes)	14 (46.7)	348 (22.4)	1/0	<0.01*
Chemo (yes)	2 (6.7)	276 (17.8)	1/0	0.15
Radiotherapy (yes)	22 (73.3)s	1235 (79.6)	1/0	0.40
Previous malignancy, No. (%)	12 (41.4)	342 (22.0)	2/0	0.01*

Abbreviation: SCC, squamous cell carcinoma.
[a]According to the 7th TNM edition.

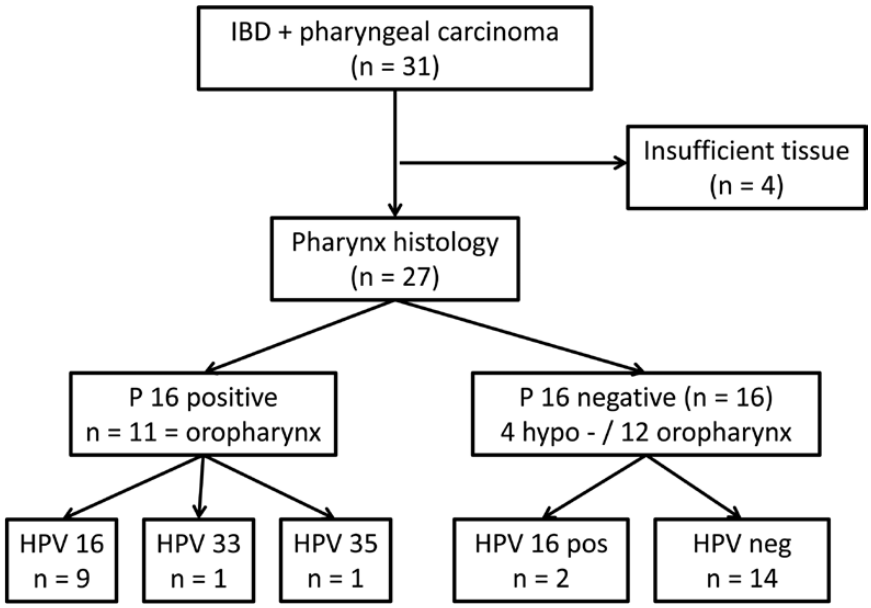

FIGURE 4. Pharyngeal cancer histopathology.

PC

Despite a lower T stage (T1–T2: 75.0% vs 47.5%; $P = 0.02$) (Table 4) in IBD patients with OPC, comparable TNM stage ($P = 0.06$) and survival ($P = 0.50$) were found compared with controls. Immunosuppressive therapy did not negatively affect overall survival following OPC ($P = 0.10$ and $P = 0.07$) (Supplementary Fig. 2A). We found no difference in survival between HPV-positive and -negative OPCs ($P = 0.45$).

IBD patients with HPC (n = 6) had a lower TNM stage ($P = 0.03$) (Table 4) and better overall survival compared with the general population ($P = 0.01$) (Supplementary Fig. 2B).

Both OPC and HPC cases underwent surgery more frequently (46.7% vs 22.4%; $P < 0.01$) (Table 4).

Histopathology and HPV Analysis

We obtained tissue from 48 of 66 identified OCC cases for further analyses. All cases were squamous cell carcinomas, and 5 of 48 tumors (10.4%) were p16 positive, suggesting the possibility of HPV-related cancers. Subsequent HPV testing of these 5 cases revealed 3 cases with HPV 16 infection and 2 cases without HPV detection. In addition, we obtained tissue from 27 of 31 PC patients for further analyses (Fig. 4). The p16-positive cases (n = 11) were all HPV positive and were all oropharyngeal of origin. Of the OPC, 12 of 23 (52.2%) were HPV positive, most HPV 16 (10/12; 83.3%). In 8 of 12 HPV-positive cases, we were informed about medication use: 6 used immunosuppressive therapy before HNC diagnosis (4/6 at least thiopurines).

DISCUSSION

In this nationwide study, we found that IBD patients with OCC have impaired survival compared with the general population, adjusted for TNM stage. Higher age at IBD diagnosis was a risk factor for OCC development in IBD and for PC in UC. Proximal CD localization was another risk factor for OCC development. Furthermore, we found that 52.2% of IBD-associated oropharyngeal cancers were HPV positive compared with 30% in the general Dutch population. Immunosuppression did not impact the survival of patients with HNC in IBD.

We showed that 52.2% of the OPCs in IBD were HPV positive, which is in line with the reported prevalence of HPV-positive OPCs in the (international) general population.[34] However, the reported prevalence seems to vary between countries, and in recent studies on the prevalence in the Netherlands, lower figures (30 %) have been reported.[14–16] Differences in HPV prevalence between IBD patients with and without immunosuppression could not be determined due to the limited number of cases. In the general population, patients with HPV-positive tumors have better outcomes, but in IBD cases, no difference in survival was observed. As OPC incidence is increasing, mainly due to the increased incidence of HPV-positive OPCs, the potential impact of prophylactic HPV vaccines is of interest.[35, 36] This especially applies to immunosuppressed patients on thiopurine therapy, as reduced immunosurveillance may cause persisting HPV infections.

In line with colorectal cancer in IBD, OCC in IBD arises at a younger age (median, 60.5 vs 65.0 years; $P = 0.021$) and has an impaired prognosis.[3] Furthermore, immunosuppressive therapy may promote tumor progression and impair survival.[6, 37] However, we found no difference in tumor stage and overall survival in our cohort regardless of immunosuppression use. More specifically, thiopurines, methotrexate, and anti-TNF therapy did not impact risk of HNC or outcomes after treatment for HNC. These results must be interpreted with caution due to

the limited number of IBD patients with HNC. Furthermore, clinicians fear the negative impact of immunosuppression on cancer outcomes; thus immunosuppression may only be used in patients with a favorable risk profile. Finally, Penn[38] showed that the risk of recurrence for (renal) transplant patients is highest in the first 2 years after malignancy diagnosis. Our data may have been influenced by wide variations in the commencement of immunosuppressive therapy after cancer diagnosis.

We indentified 2 risk factors for HNC development in IBD: first, proximally localized disease in CD patients (Montreal L4, including oral cavity inflammation; OR, 1.103; 95% CI, 1.040–1.170; $P = 0.028$). This may be related to upper gastrointestinal IBD-related inflammation. Furthermore, we identified older age at IBD diagnosis as a risk factor for both OCC and PC development. This is an interesting observation that is in line with other cancer types in IBD,[27, 39] although our study does not provide an explanation for this observation.

To date, this is the largest systematically collected series of OCC and PC in IBD patients. However, our study also comes with several limitations, such as its retrospective nature. Especially in cases who were enrolled in early years, it was challenging to collect accurate and complete information. Therefore, we also performed a sensitivity analysis, enrolling only cases diagnosed with IBD after 1990. This did not show immunosuppressive therapy as a risk factor for OCC or PC development. Second, we used 3 different databases that were constructed in different ways to address our hypothesis. Our data search was retrospective, while the IBDSL and the cancer registry (including ECR) collect prospectively. Unfortunately, there is no single database available that could have answered our research questions sufficiently. Third, in heavy smokers, there is a 5- to 25-fold increased risk of cancer, in comparison with nonsmokers. This relation seems dose dependent. The relative risk to develop HNC due to alcohol also seems dose dependent. A compounded effect was found for the combination of tobacco smoking and alcohol consumption. Unfortunately, these important data on tobacco and alcohol use were incomplete for the ECR and IBDSL. Only smoking data for Crohn's disease patients were available. In univariable analyses, smoking emerged as a risk factor for PC, but not in multivariable analyses. This may be due to the limited numbers.

As HPV presence is correlated inversely with tobacco (and alcohol) consumption and is an important risk factor especially for (oro)pharyngeal cancer, this would provide important additional information. Unfortunately, these data were not available for the IBDSL and ECR controls.

Finally, for several variables in the analyses, there are missing values. For these variables, results should be interpreted cautiously, as no firm conclusions can be drawn.

Some authors[22, 24] have suggested oral screening for all IBD patients, especially those who are starting immunosuppression. As the incidence of HNC in IBD in general is low and no well-defined premalignant lesions analogous to cervical intraepithelial neoplasia in cervical cancer have been established yet, we would recommend increased awareness for HNC in IBD rather than active screening, especially in elderly onset IBD.

In conclusion, we found that IBD patients with OCC may have reduced survival compared with the general population. Proximal disease localization in CD is a risk factor for OCC development. The majority (52.2%) of IBD-associated oropharyngeal cancers were HPV positive. Immunosuppression did not impact incidence and survival of HNC in IBD.

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APPENDIX

A: PALGA Group

E.E.C. de Jonge (Groene Hart Ziekenhuis, Gouda), R. Natte (Hagaziekenhuis, Den Haag) E.W.P. Nijhuis (Onze Lieve Vrouwe Gasthuis, Amsterdam), C. Peutz-Kootstra (Maastricht University Medical Center, Maastricht), J.J.T.H. Roelofs (Amsterdam Medical Center, Amsterdam), S.M. Willems (University Medical Center Utrecht, Utrecht), A.P. Willig (Laurentius Hospital, Roermond).

B: IBD and HNC Group

A.A. van Bodegraven (Vrije University Medical Centre, Amsterdam), A.C.I.T.L. Tan (Canisius Wilhelmina Hospital, Nijmegen), J.J. Meeuse (Hospital Rivierenland, Tiel), A.E. van der Meulen–de Jong (Leiden University Medical Centre, Leiden), B. Oldenburg (University Medical Centre Utrecht, Utrecht), B.C.A.J. Loffeld (Zuwe Hofpoort Hospital, Woerden), B.M. Durfeld (Hospital Group Twente, Almelo), C.J. van der Woude (Erasmus Medical Centre, Rotterdam), D.L. Cahen (Amstelland Hospital, Amstelveen), G. D'Haens (Academic Medical Centre, Amsterdam), D. Janik (Ommelander Hospital Group, Delfzijl), W.G.M. Mares (Hospital Gelderse Vallei, Ede), L.P.L. Gilissen (Catharina Hospital, Eindhoven), F.L. Wolters (VieCuri, Venlo), G. Dijkstra (University Medical Centre Groningen, Groningen), G.W. Erkelens (Gelre Hospital, Apeldoorn), T.J. Tang (IJsselland Hospital, Capelle aan den IJssel), R. Breumelhof (Diakonessenhuis, Utrecht), H.J.T. Smalbraak (Lievensberg Hospital, Bergen op Zoom), J.C. Thijs (Hospital Bethesda, Hoogeveen), J.H. Voskuil (Hospital Tjongerschans, Heerenveen), J.P. Kuyvenhoven (Kennemer Gasthuis, Haarlem), J. Vecht (Isala, Zwolle), M.C.M. Rijk (Amphia Hospital, Breda), J.M. Janssen (Onze Lieve Vrouwe Gasthuis, Amsterdam; Boven IJ Hospital, Amsterdam), J.T. Sarneel (Admiraal De Ruyter Hospital, Middelburg), J.W.M. Tjhie-Wensing (Elkerliek Hospital, Helmond), J.Y.L. Lai (Groene Hart Hospital, Gouda; Langeland Hospital, Zoetermeer),

L.T. Vlasveld (Hospital Bronovo, Den Haag), L.E. Oostenbrug (Atrium Medical Centre, Heerlen), M. Gerretsen (Diaconessenhuis Meppel, Meppel), M.A. Van Herwaarden (Deventer Hospital, Deventer), N. Mahmmod (Sint Antonius, Nieuwegein), M.G.V.M. Russel (Medical Spectrum Twente, Enschede), M.J.A.L. Grubben (Sint Elisabeth Hospital, Tilburg), M.K. Vu (Rijnland Hospital, Leiderdorp), M.L. Verhulst (Máxima Medical Centre, Eindhoven), P. Dewint (Van Weel – Bethesda Hospital, Dirksland; Maasstad Hospital, Rotterdam), P.C.F. Stokkers (Sint Lucas Andreas Hospital, Amsterdam), P.J. Bus (Laurentius Hospital, Roermond), P.J. Wismans (Havenziekenhuis, Rotterdam), P.W.E. van der Haeck (Refaja Hospital, Stadskanaal), R.J.L. Stuyt (Haga Hospital, Den Haag), R.N.M. Zeijen (Vlietland Hospital, Schiedam), R.P.M. Dahlmans (Sint Jans Gasthuis, Weert), S. Vandebosch (ZorgSaam Zeeuws-Vlaanderen, Terneuzen), T.E.H. Romkens (Jeroen Bosch Hospital, Den Bosch), W. Moolenaar (Medical Center Alkmaar, Alkmaar), W.R. ten Hove (Diaconessenhuis Leiden, Leiden), H. Boot (Antoni van Leeuwenhoek Hospital Amsterdam), K. van der Linde (Medical Center Leeuwarden, Leeuwarden), P. Wahab (Rijnstate Hospital, Arnhem), S.Y. de Boer (Slingeland Hospital, Doetinchem), K. Thurnau (Ropcke Zweers Hospital, Hardenberg) W.J. Thijs (Martini Ziekenhuis, Groningen), D.F.G.M. Josemanders (Reinier de Graaf Groep, Delft), R.L. West (Sint Franciscus Gasthuis, Rotterdam), M.J. Pierik (Maastricht University Medical Center, Maastricht), A.C.T.M. Depla (Slotervaart Hospital, Amsterdam), E.T.P. Keulen (Orbis Medical Center, Sittard), W.A. de Boer (Bernhoven Hospital, Uden), A.H.J. Naber (Tergooi Hospital, Hilversum), J.R. Vermeijden (Meander Medical Center, Amersfoort), R.C. Mallant-Hent (Flevo Hospital, Almere), R. Beukers (Albert Schweitzer Hospital, Dordrecht), P.C.J. Ter Borg (Ikazia Hospital, Rotterdam), E.C.R. Halet (Franciscus Hospital, Roosendaal), K.F. Bruin (Twee Steden Hospital, Tilburg), R.K. Linskens (Sint Anna Hospital, Geldrop), W. Bruins Slot (Spaarne Hospital, Hoofddorp).

SUPPLEMENTARY DATA

Supplementary data are available at *Inflammatory Bowel Diseases* online.

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