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Original Article

Increased risk of esophageal squamous cell carcinoma in patients with squamous dysplasia: a nationwide cohort study in the Netherlands

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SUMMARY. **Squamous dysplasia is the histological precursor of esophageal squamous cell carcinoma (ESCC). The optimal management for distinct squamous dysplasia grades remains unclear because the corresponding risk of developing ESCC is unknown. We aimed to assess the ESCC risk in patients with esophageal squamous dysplasia in a Western country. This nationwide cohort study included all patients with esophageal squamous dysplasia, diagnosed between 1991 and 2020 in the Dutch nationwide pathology databank (Palga). Squamous dysplasia was divided in mild-to-moderate dysplasia (mild, low-grade, and moderate dysplasia) and higher-grade dysplasia (high-grade dysplasia, severe dysplasia, carcinoma in situ). ESCC were identified in Palga and the Netherlands Cancer Registry. The primary endpoint was diagnosis of *prevalent* (≤6 months) and *incident* (>6 months after squamous dysplasia) ESCC. In total, 873 patients (55% male, aged 68 years SD ± 13.2) were diagnosed with esophageal squamous dysplasia, comprising mild-to-moderate dysplasia (*n* = 456), higher-grade dysplasia (*n* = 393), and dysplasia not otherwise specified (*n* = 24). ESCC was diagnosed in 77 (17%) patients with mild-to-moderate dysplasia (49 *prevalent*, 28 *incident* ESCC) and in 162 (41%) patients with higher-grade dysplasia (128 *prevalent*, 34 *incident* ESCC). After excluding prevalent ESCC, the annual risk of ESCC was 4.0% (95% CI: 2.7–5.7%) in patients with mild-to-moderate dysplasia and 8.5% (95% CI: 5.9–11.7%) in patients with higher-grade dysplasia. All patients with squamous dysplasia, including those with mild-to-moderate dysplasia, have a substantial risk of developing ESCC. Consequently, endoscopic surveillance of the esophageal mucosa or endoscopic resection of dysplasia should be considered for patients with mild-to-moderate dysplasia in Western countries.**

KEY MESSAGES

What is already known on this topic?

- Squamous dysplasia is the histological precursor of ESCC and is divided in distinct grades, based on the proportion of the squamous epithelium with histopathological abnormalities.
- In Western countries, the optimal management for distinct squamous dysplasia grades remains unclear because the corresponding risk of developing ESCC is unknown.

What this study adds

The ESCC risk of patients with squamous dysplasia was increased for all patients with squamous dysplasia in a Western country; 2.1% for patients with mild dysplasia, 5.1% for low-grade dysplasia, and 5.2% for moderate dysplasia. Increasing grades of squamous dysplasia were associated with an increased ESCC risk.

How this study might affect research, practice, or policy

We recommend that endoscopic follow-up or treatment should be considered in all patients with esophageal squamous dysplasia in Western countries: 1) for patients with mild, low-grade, and moderate dysplasia, endoscopic surveillance with careful inspection with narrow band imaging or dye-based chromoendoscopy of the esophageal mucosa is indicated; and 2) for patients with high-grade dysplasia, severe dysplasia and carcinoma in situ adequate endoscopic staging and in case of suspected neoplasia endoscopic treatment should be performed.

KEY WORDS: **endoscopy, esophageal squamous cell carcinoma, squamous dysplasia.**

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INTRODUCTION

Over 85% of the esophageal cancers are esophageal squamous cell carcinoma (ESCC) worldwide.[1] In Western countries, the age-standardized incidence rate of ESCC ranged between 1.0 and 2.5 per 100.000 persons in 2018.[1] As most ESCC are detected in advanced and incurable stages, the 5-year survival rate of patients with ESCC is merely 22%.[2,3] The detection of ESCC at early stages is associated with a considerably better 5-year survival of 85–100%, as early-stage ESCC can potentially be treated curatively with endoscopic resection (ER).[2,3]

The cornerstone in detecting ESCC at early stages consists of the identification of high-risk patients for ESCC. An important group of high-risk patients are patients with esophageal squamous dysplasia, a histological precursor lesion of ESCC. Squamous dysplasia is defined as neoplastic alterations of the esophageal squamous epithelium, without invasion.[4] ESCC is thought to develop via the dysplasia-carcinoma cascade: from normal squamous epithelium via increasing grades of dysplasia to ESCC.[5,6] Adequate endoscopic detection and treatment of patients with squamous dysplasia allows for early detection of ESCC or can even prevent ESCC development.[7,8]

The pathological assessment of squamous dysplasia can be challenging and currently two classification systems are used worldwide: a three-tiered and two-tiered classification.[4,9] Both classifications are based on the proportion of the squamous epithelium with histopathological abnormalities.[4,9] The three-tier system is predominantly used in Asian countries and classifies squamous dysplasia in mild, moderate, and severe dysplasia.[9] In an Asian study with 13.5 years of endoscopic surveillance, the risk of neoplastic progression was up to 24% for mild dysplasia, 50% for moderate dysplasia, and 74% for severe dysplasia.[9–14] However, it is unknown whether this risk of ESCC can be generalized to patients with squamous dysplasia in Western countries, as the incidence of ESCC differs strongly between Western and Asian countries.[1]

In Western countries, the World Health Organization advises to use the two-tiered classification with low- and high-grade dysplasia to increase the level of inter-observer agreement among pathologists.[4,15] Current guidelines in Western countries advocate that ER should be performed for high-grade dysplasia and ESCC limited to the mucosa, but it remains controversial whether endoscopic surveillance or treatment is indicated for low-grade dysplasia.[16] The optimal management for distinct squamous dysplasia grades remains unclear because the corresponding risk of developing ESCC for each distinct grade of squamous dysplasia is unknown. We, therefore, aimed to assess the ESCC risk in patients with squamous dysplasia in a Western country.

METHODS

Study design and patients

We performed a nationwide, retrospective study including all patients diagnosed with esophageal squamous dysplasia between January 1991 and December 2020 in the Netherlands. Patients were identified via the Dutch nationwide pathology databank (Palga).[17] The development of ESCC in included patients was identified from Palga and the Netherlands Cancer Registry (NCR; nationwide registry of all cancers). All patient data were coded and anonymized by a third trust party and, therefore, no informed consent was needed. This study was approved by the Medical Ethical Review Committee of the Erasmus Medical Centre (MEC-2022-0274). The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a priori approval by the institution's Human Research Committee.

Palga search

The Palga database contains all Dutch pathology reports with nationwide coverage since 1991, linked to an encrypted individual patient identification number and diagnostic code.[17] The diagnostic code reflects the location, type, and histopathological diagnosis of the tissue sample (e.g. esophagus × biopsy × low-grade dysplasia). The Palga database was searched for the diagnostic codes for dysplasia and atypia in the esophagus (search details are described in Supplementary Table S1). Inclusion criteria were all diagnostic codes for squamous dysplasia in the esophagus. Exclusion criteria were dysplasia in a Barrett's esophagus or columnar epithelium, dysplasia located in the stomach and patients with previous or simultaneous (i.e. in the pathology specimen of the same date) esophageal cancer, and patients developing esophageal adenocarcinoma.

Histopathological definitions

Squamous dysplasia is characterized by the presence of both cytological and architectural atypia.[4] Characteristics of cytological atypia include cell enlargement, pleomorphism, hyperchromasia, loss of polarity, and overlapping. Architectural atypia is defined as abnormal maturation of the epithelium. The grade of dysplasia is based on the proportion of the squamous epithelium with pathological abnormalities.[4,9] Mild, moderate, and severe dysplasia are limited to the lower third, middle third and three thirds of the squamous epithelium (Fig. 1).[9] Low-grade dysplasia is defined as mild cytological atypia confined to the lower half of the squamous epithelium.[4] High-grade dysplasia is characterized by severe cytological atypia or the presence of mild cytological atypia in more

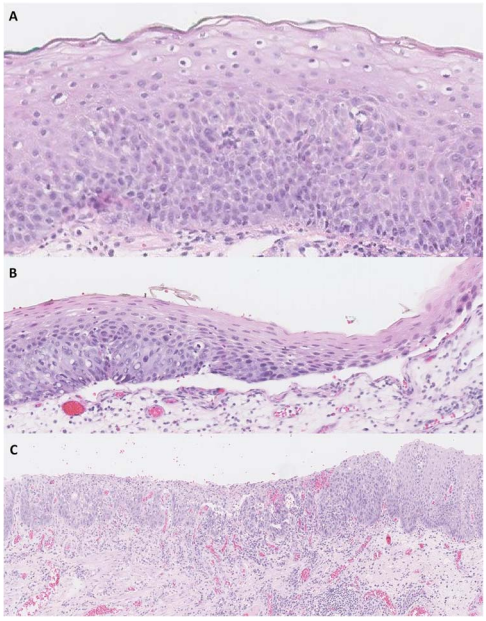

Fig. 1 Distinct grades of squamous dysplasia in the esophagus. (A) Mild dysplasia with dysplastic cells limited to the lower third of the squamous epithelium. (B) Moderate dysplasia with dysplastic cells limited to the middle third of the squamous epithelium. Both image (A) and (B) are referred to as low-grade dysplasia in the two-tiered classification. (C) Severe dysplasia with dysplastic cells extending to the full thickness of the squamous epithelium (hematoxylin-eosin staining, original magnification ×100 in A and B and ×50 in C).

than half of the squamous epithelium.[4] Carcinoma in situ (CIS) is defined as the presence of dysplastic cells throughout the full thickness of the squamous epithelium, without invasion.[9] If squamous dysplasia could not be graded, because of biopsy size or orientation, this is referred to as dysplasia not otherwise specified (NOS).[9]

Data collection

From Palga, anonymized pathology reports with conclusions and microscopic assessment were collected from 5 years before the diagnosis squamous dysplasia and all follow-up reports till July 2022. We extracted the following characteristics for all included patients: sex, age, year of squamous dysplasia, number of endoscopies with biopsies and time intervals, and date of last follow-up or the diagnosis of ESCC. The time interval between squamous dysplasia and ESCC diagnosis was divided in *prevalent* (within 6 months) and *incident* (> 6 months). For patients with ESCC, the following characteristics were collected from the NCR; age at ESCC diagnosis, histopathological characteristics, and location of ESCC (cervical; <18 cm from the incisors, upper third; 18–24 cm from the incisors, middle third; 24–32 cm from the incisors, lower third; 32–40 cm from the incisors, and overlap; between two parts of the esophagus). The TNM stage of ESCC and treatment strategy (on 31 January 2021) were also assessed.

Study endpoints

The primary endpoint of this study was the proportion of patients with squamous dysplasia that were subsequently diagnosed with ESCC. Secondary endpoints included 1) the risk of ESCC for distinct grades of squamous dysplasia, 2) the time between first squamous dysplasia diagnosis and the detection of ESCC, and 3) characteristics and outcomes of patients with squamous dysplasia and subsequent ESCC.

Statistics

Descriptive statistics are presented as means with standard deviations (SD), medians with inter-quartile ranges (IQR) and counts with percentages, according to the nature of the data. For sub-group analyses, patients with mild, low-grade, and moderate dysplasia were combined in the group mild-to-moderate dysplasia and patients with high-grade dysplasia, severe dysplasia, and CIS were combined in the group higher-grade dysplasia. Sub-groups were compared using the X^2 test. The percentage annual risk of ESCC was calculated with number of events divided by number of patient years at risk, multiplied by 100. Cox proportional hazards analyses were performed to identify and quantify potential risk factors for the detection of ESCC and were presented as hazard ratios (HR) with 95% confidence intervals (CI). The statistical package (survminer) in R was used for the cumulative incidence plot. Two-side P-values <0.05 were considered significant. Analyses were performed in IBM SPSS for Windows version 28 (SPSS Inc) and R version 4.2.2 (The R Foundation Statistical Computing, Vienna, Austria).

RESULTS

Patients

The Palga search identified 9.687 patients with dysplasia in esophageal pathology specimen between January 1991 and December 2020 in the Netherlands (Figure S1). After review of pathology reports, 873 patients with a confirmed first diagnosis of squamous dysplasia in the esophagus were included. The mean age of included patients was 68.0 years (SD ±13.2) and 55.1% was male.

Baseline characteristics of squamous dysplasia

The baseline grade of dysplasia of included patients was mild ($n = 179$), low-grade ($n = 80$), moderate ($n = 197$), high-grade ($n = 77$), and severe ($n = 244$) dysplasia, and CIS ($n = 72$) (Table 1). In 79/197 patients with moderate dysplasia, the grade of dysplasia could be divided into low-grade (69.6%) and high-grade dysplasia (30.4%), based on complete pathology reports. Squamous dysplasia was diagnosed

Table 1 Baseline characteristics of included patients with esophageal squamous dysplasia.

Characteristic	Total cohort	Mild-to-moderate dysplasia	Higher-grade dysplasia
No. of patients	**873**	**456**	**393**
Sex, male	481 (55.1%)	255 (55.9%)	213 (54.2%)
Age, years	68 (SD ± 13.2)	66 (SD ± 13.6)	71 (SD ± 12.2)
Year of diagnosis			
1991–2000	237 (27.2%)	139 (30.5%)	92 (23.4%)
2000–2010	296 (33.9%)	146 (32.0%)	142 (36.1%)
2010–2020	340 (38.9%)	171 (37.5%)	159 (40.5%)

Data presented as *n* with (%) or mean with standard deviation (SD). Patients with mild ($n = 179$), low-grade ($n = 80$), and moderate dysplasia ($n = 197$) were combined in the group mild-to-moderate dysplasia. Patients with high-grade dysplasia ($n = 77$), severe dysplasia ($n = 244$), and CIS ($n = 72$) were combined in the group higher-grade dysplasia. The total cohort ($n = 873$) also included patients with baseline squamous dysplasia NOS ($n = 24$).

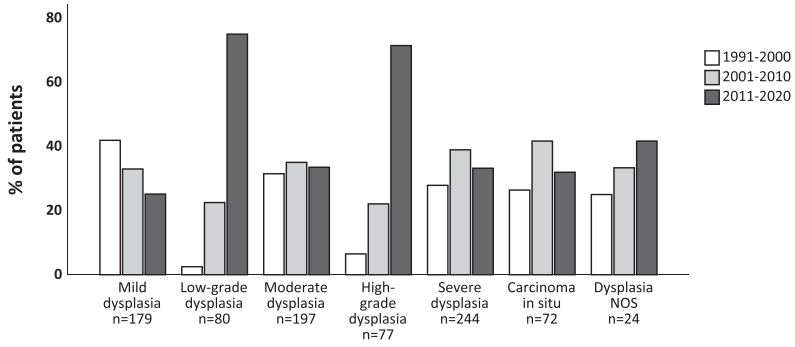

Fig. 2 The proportion of patients with distinct grades of squamous dysplasia during recent decades. For patients with dysplasia NOS, grading of squamous dysplasia was not possible, due to biopsy size or orientation. Most cases of low- (75.0%) and high-grade dysplasia (71.4%) were diagnosed between 2011 and 2020 ($P < 0.001$).

between 2020 to 2010 (38.9%), 2000 to 2010 (33.9%), and 1991 to 2000 (27.2%). Most cases of low-grade (75.0%) and high-grade dysplasia (71.4%) were diagnosed between 2011 and 2020 (Fig. 2) ($P < 0.001$).

Treatment strategies for baseline mild, low-grade, and moderate dysplasia

The cohort included 456 patients with mild-to-moderate dysplasia of which 57.0% of the patients underwent endoscopic re-assessment with histopathology or treatment. This was performed after a median of 12 weeks (IQR 6–29). During the first endoscopic-reassessment, ESCC was detected in 5.1%, 1.8%, and 12.8% of patients with baseline mild, low-grade, and moderate dysplasia, respectively (Fig. 3). The median histopathological follow-up time was 10 months (IQR 3–42) and patients received a median of 2 (IQR 1–4) endoscopies. Thirteen (2.8%) patients with mild-to-moderate dysplasia were treated with primary ER ($n = 12$; 2.6%) or surgery ($n = 1$; 0.2%). The ER and surgery specimens showed mild-to-moderate dysplasia ($n = 6$), higher-grade dysplasia ($n = 5$), and ESCC ($n = 2$). The remaining patients (43.0%) had no histopathological follow-up.

Treatment strategy for baseline high-grade dysplasia, severe dysplasia, and CIS

A total of 71.5% of 393 included patients with higher-grade dysplasia underwent endoscopic re-assessment with histopathology or treatment. The initial endoscopic re-assessment was performed after a median of 5 weeks (IQR 2–10) and revealed mild-to-moderate dysplasia (5.0%), higher-grade dysplasia (39.6%), and ESCC (32.7%). Patients underwent a median of 2 endoscopies (IQR 1–4) during the follow-up till the diagnosis of ESCC or last follow-up. 71 (18.1%) patients with higher-grade dysplasia underwent treatment with ER (9.7%), surgery (4.3%), or chemotherapy and/or radiotherapy (4.1%). Pathological assessment of ER and surgery specimens showed no dysplasia ($n = 1$), mild-to-moderate dysplasia ($n = 1$), higher-grade dysplasia ($n = 25$), and ESCC ($n = 28$). In the remaining patients (28.5%), no histopathological follow-up was available.

Association between increasing grades of dysplasia and risk of ESCC

ESCC was diagnosed in 28.4% of included patients with baseline squamous dysplasia. Table 2 depicts the proportions of patients diagnosed with ESCC, according to their distinct grades of baseline squamous dysplasia. Increasing grades of dysplasia were associated with a significantly increased risk of ESCC ($P < 0.001$) (Table 3). Patients with moderate dysplasia had a significantly increased risk of ESCC compared with mild dysplasia (HR 2.40, 95% CI: 1.35–4.29) and a showed a trend towards an increased risk compared with low-grade dysplasia (HR 1.71,

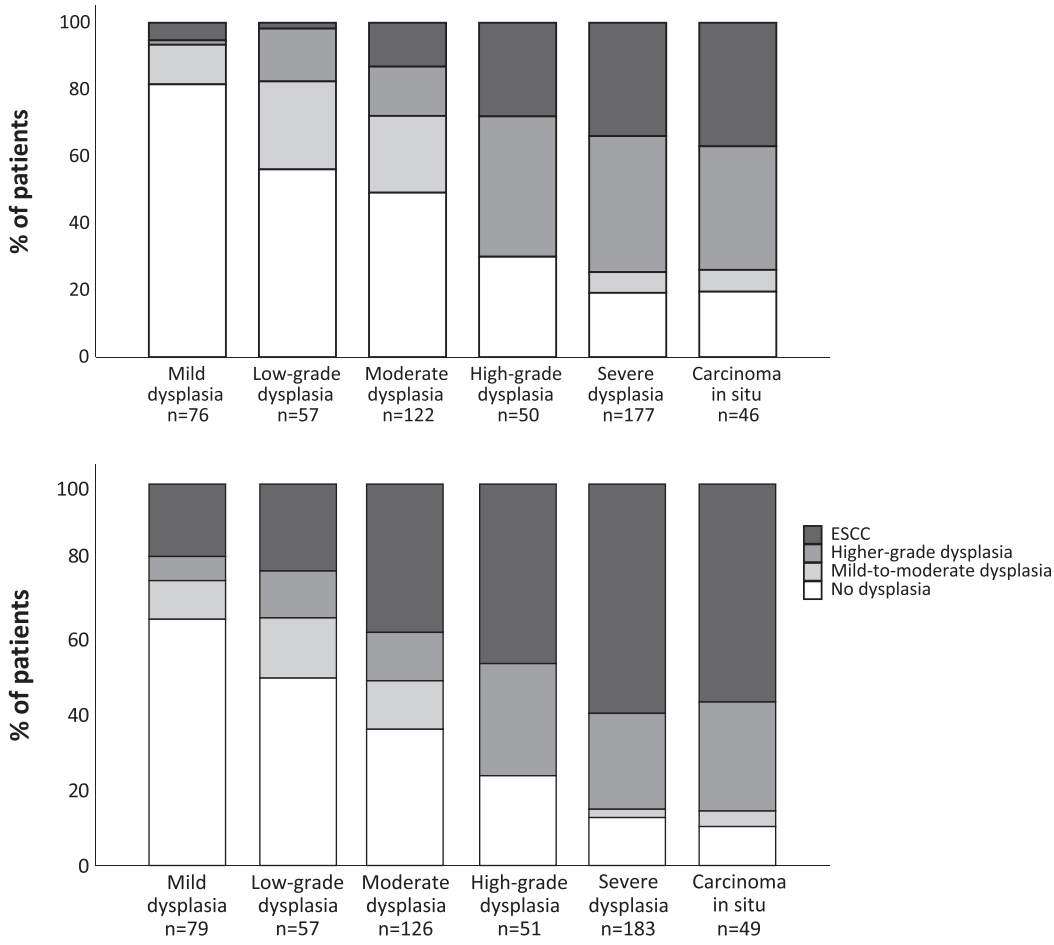

Fig. 3 Most advanced lesion detected during first endoscopic re-assessment and complete follow-up in patients with distinct grades of squamous dysplasia at baseline. Data presented in groups according to the grade of confirmed first squamous dysplasia diagnosis. (A) shows the most advanced lesion detected during first endoscopic re-assessment. Patients with dysplasia NOS as first dysplasia diagnosis ($n = 24$) or detected during first endoscopic re-assessment ($n = 11$) are not shown. The median time to first endoscopic re-assessment with histopathology was 17, 12, 11, 4, 5, and 6 weeks for patients with mild, low-grade, moderate, high-grade, and severe dysplasia, and CIS, respectively. (B) shows the most advanced lesion detected during complete follow-up. (B) contains seven patients with a clinical diagnosis of ESCC without pathology confirmation, based on data from the Netherlands cancer registry. The median follow-up time was 20 months for mild dysplasia, 10 months for low-grade dysplasia, 7 months for moderate dysplasia, 4 months for high-grade dysplasia, 2 months for severe dysplasia, and 5 months for CIS.

95% CI: 0.93–3.16). Patients with low-grade dysplasia had a tendency towards an increased risk to develop higher-grade dysplasia, compared with patients with mild dysplasia (HR 3.10, 95% CI: 0.98–9.80), but the results were not significant. Baseline high-grade dysplasia was associated with a significantly increased risk of ESCC, compared with mild (HR 3.64, 95% CI: 1.91–6.94) and low-grade dysplasia (HR 2.59, 95% CI: 1.32–5.10). The risk of ESCC between patients with baseline moderate dysplasia and high-grade dysplasia did not differ significantly (HR 0.66, 95% CI: 0.41–1.08). Results were consistent after adjusting for sex, age, year of first dysplasia diagnosis, primary treatment strategy, and time to first endoscopic re-assessment (Table 3, Supplementary Table S2).

Prevalent and incident ESCC

Prevalent ESCC was diagnosed in 181/873 (20.7%) patients and incident ESCC in 67/692 (9.7%) patients (Table 2, Fig. 4). Incident ESCC was detected after a median of 23 months (IQR 11–49). After excluding patients with prevalent ESCC, the annual ESCC risk was 2.1%, 5.1%, and 5.2% per patient-year for patients with mild, low-grade, and moderate dysplasia (Table 2) with a total of 701.3 patient-years of follow-up. The risk for both prevalent and incident ESCC increased with increasing grades of baseline squamous dysplasia (Table 2, Supplementary Table S3). Multivariable analyses, adjusted for sex and age, showed similar results.

Characteristics of ESCC

Patients diagnosed with ESCC had a mean age at diagnosis of 69.0 years (SD ± 10.7) and 56.0% was male (characteristics of prevalent and incident ESCC are shown in Supplementary Table S4). The tumor stage of ESCC was low (0–II) in 48.4% and high (III–IV) in 27.5%. Distant metastases at time of

Table 2 The proportion of patients with distinct grades of baseline squamous dysplasia diagnosed with prevalent and incident ESCC.

Baseline grade of dysplasia	No. of patients	No. of patients diagnosed with ESCC	Prevalent ESCC	Incident ESCC[1]	Annual ESCC risk per PY [1]	PY at risk[1]
Mild dysplasia	179	15 (8.4%)	9 (5.0%)	6 (3.5%)	2.1%	279.7
Low-grade dysplasia	80	13 (16.3%)	8 (10.0%)	5 (6.9%)	5.1%	97.3
Moderate dysplasia	197	49 (24.9%)	32 (16.2%)	17 (10.3%)	5.2%	324.4
High-grade dysplasia	77	24 (31.2%)	18 (23.4%)	6 (10.2%)	8.9%	67.5
Severe dysplasia	244	110 (45.1%)	92 (37.7%)	18 (11.8%)	7.5%	239.7
Carcinoma in situ	72	28 (38.9%)	18 (25.0%)	10 (18.5%)	10.6%	94.6
Dysplasia NOS [2]	24	9 (37.5%)	4 (16.7%)	5 (25.0%)	10.1%	49.6
Total cohort	873	248 (28.4%)	181 (20.7%)	67 (9.7%)	5.8%	1152.7

Data presented as *n* with (%). ESCC were divided in prevalent (≤ 6 months) and incident (>6 months) after baseline diagnosis of squamous dysplasia. [1]Calculated for patients at risk of ESCC at 6 months after baseline squamous dysplasia ($n = 692$). [2]Grading of squamous dysplasia was not possible, due to biopsy size or orientation. ESCC, esophageal squamous cell carcinoma; NOS, not otherwise specified, PY, patient-years.

Table 3 Risk factors associated with the detection of ESCC in patients with distinct grades of squamous dysplasia ($n = 873$).

	No. of ESCC/total no. of patients	Univariate HR	95% CI	*P*	Adjusted HR	95% CI	*P*
Sex							
Male	139/481	Reference	—		Reference	—	—
Female	109/392	0.96	0.75–1.24	0.765	0.91	0.71–1.17	0.460
Age (years)	248/873	1.02	1.01–1.03	<0.001	1.02	1.00–1.03	0.009
Year of first dysplasia diagnosis							
1991–2000	50/237	Reference	—	—	Reference	—	—
2000–2010	101/296	1.43	1.02–2.00	0.040	1.37	0.98–1.94	0.069
2010–2020	97/340	1.22	0.87–1.72	0.251	1.19	0.83–1.70	0.340
Grade of baseline dysplasia							
Mild dysplasia	15/179	Reference	—	—	Reference	—	—
Low-grade dysplasia	13/80	1.40	0.67–2.95	0.373	1.29	0.60–2.75	0.513
Moderate dysplasia	49/197	2.40	1.35–4.29	0.003	2.23	1.25–3.99	0.007
High-grade dysplasia	24/77	3.64	1.91–6.94	<0.001	2.96	1.52–5.77	0.001
Severe dysplasia	110/244	5.33	3.10–9.15	<0.001	4.70	2.72–8.11	<0.001
Carcinoma in situ	28/72	4.07	2.17–7.62	<0.001	3.43	1.82–6.49	<0.001
Dysplasia NOS	9/24	2.43	1.06–5.55	0.036	2.34	1.02–5.34	0.045

Results were obtained with univariate and multivariate Cox proportional hazards analyses. Two-side *P*-values <0.05 were considered statistically significant. In multivariate analyses, results were adjusted for sex, age, and grade of baseline dysplasia. For patients with dysplasia NOS, grading of squamous dysplasia was not possible, due to biopsy size or orientation. Data are presented as HR with 95% CI with the detection of ESCC as outcome. CI, confidence interval; ESCC, esophageal squamous cell carcinoma; HR, hazard ratio; NOS, not otherwise specified.

diagnosis were detected in 8.9% of patients. In total, patients with ESCC were treated with ER (14.9%), surgery (35.1%), and chemo-/radiotherapy (47.6%). The median survival after ESCC diagnosis was 25 months (IQR 10–75).

DISCUSSION

Squamous dysplasia is the histological precursor of ESCC and is divided in distinct grades, based on the proportion of squamous epithelium with histopathological abnormalities. In Western countries, the risk of ESCC for these distinct grades of dysplasia is unknown and, consequently, optimal management remains unclear. We performed a nationwide, retrospective study on the risk of ESCC in patients with distinct grades of esophageal squamous dysplasia in the Netherlands. In our study, all patients with squamous dysplasia, including patients with mild, low-grade, and moderate dysplasia, had a substantially increased risk of developing ESCC. Therefore, endoscopic surveillance or treatment should be considered for all patients with squamous dysplasia in Western countries.

The currently published studies on squamous dysplasia and the associated risk of ESCC originate from Asian countries.[9–11,13,14] These studies report a cumulative 5-year incidence of ESCC ranging from 1% to 24% for patients with mild dysplasia, 5% to 50% for moderate dysplasia, and up to 100% for severe dysplasia and CIS.[9–11,13,14] In rural areas of China, one-time endoscopic screening and treatment in case of dysplasia resulted in both a decreased incidence and mortality of ESCC in residents aged 40–69 years, compared with controls.[18,19] These findings confirm that in Asian

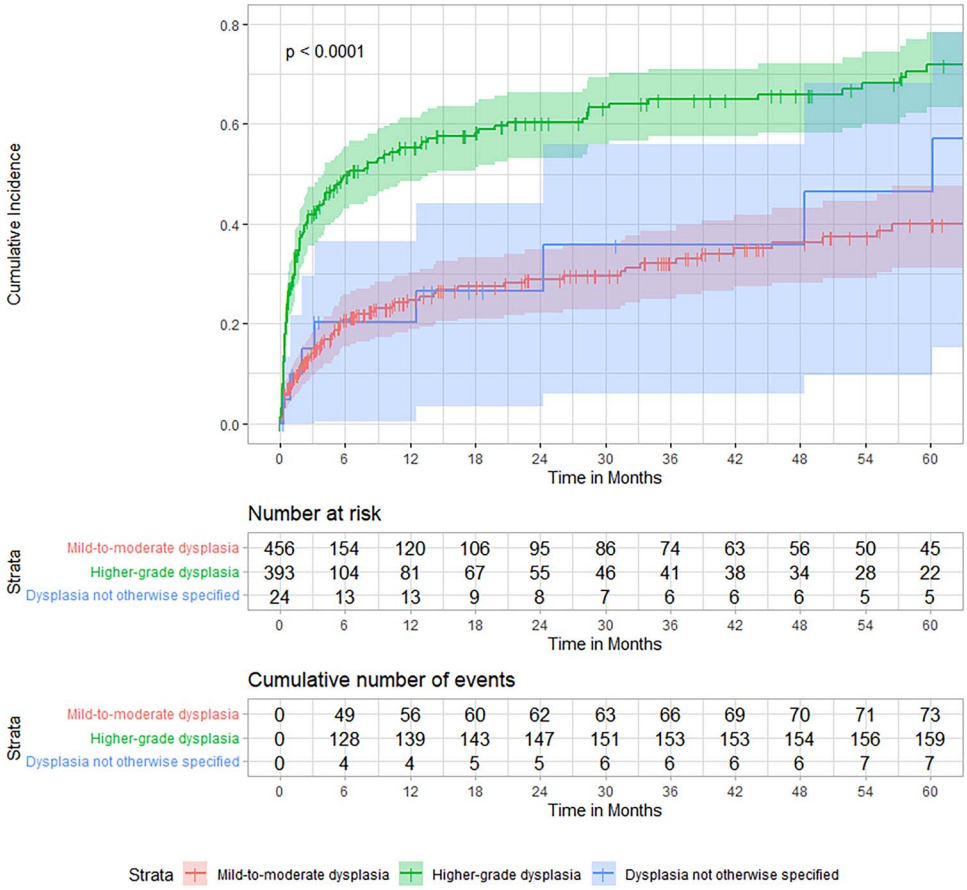

Fig. 4 Cumulative incidence of esophageal squamous cell carcinoma in 873 patients with baseline squamous dysplasia. Data are shown for patients with mild-to-moderate dysplasia ($n = 456$), higher-grade dysplasia ($n = 393$), and dysplasia NOS ($n = 24$). Logrank test between groups: $p < 0.001$.

countries, endoscopic surveillance or treatment is warranted for patients with all grades of squamous dysplasia. Unfortunately, comparisons between Asian and Western populations are difficult, caused by the large differences in ESCC incidence between these countries and, therefore, also differences in screening, surveillance, and treatment strategies.[1]

In the current study, we report on prevalent and incident ESCC separately, attempting to distinguish patients with a potentially underlying baseline ESCC, from patients developing ESCC during the follow-up. Prevalent ESCC were diagnosed in one fifth of included patients and up to 16% of patients with baseline mild, low-grade, and moderate dysplasia. A part of the patients with prevalent ESCC potentially had a visible suspicious lesion during endoscopy without histopathological confirmation. In others, the pathology report of dysplasia may have resulted in an additional endoscopy with ER, during which the diagnosis ESCC was established.

The pathological assessment of esophageal squamous dysplasia can be challenging and may be subject to interobserver variability and sampling bias. To decrease interobserver variability in Western countries, the two-tiered classification into low-grade or high-grade dysplasia was introduced in the 5th edition of the WHO classification.[4] In line with the introduction of the two-tiered classification, low- and high-grade dysplasia were diagnosed more frequently in this study during recent years. Nevertheless, we found that both the three-tiered (mild, moderate, and severe dysplasia) and two-tiered classification are currently used in the Netherlands. In line with the recommendation of the WHO, we think that one uniform classification for patients with squamous dysplasia, used by all pathologists in Western countries, would be desirable. Standardized advice for distinct grades of squamous dysplasia with indications for endoscopic surveillance and treatment, will promote exchangeability and comparability of scientific data and may help to improve the outcomes of patients with squamous dysplasia.

Sampling bias, when biopsies do not adequately reflect the grade of dysplasia, can be caused by several endoscopic and histopathological factors. Endoscopic factors include for example the experience of the endoscopist and the number, chosen location, and depth of the biopsies. Histopathological factors include a lack of orientation and presence of other histopathological abnormalities such as

active inflammation in case of reflux- or candida esophagitis. The occurrence and clinical relevance of sampling bias is confirmed by previous studies, which reported a discordance of the grade of squamous dysplasia of up to 45% between biopsy and corresponding ER specimen.[20–22] The study of Chen et al. (2022) reported on 202 patients with low-grade dysplasia in biopsies, of which the corresponding ER specimen showed high-grade dysplasia in 33% of patients.[21] These results are in line with the proportion of prevalent ESCC of 20.7% detected in our current study, and emphasize the importance of adequate endoscopic (re-)assessment with representative biopsies and accurate pathological assessment.

This nationwide cohort study is one of the first Western studies reporting on the ESCC risk in patients with squamous dysplasia, but has some inherent limitations. The current study was based on characteristics available in the Palga and NCR databases. The Palga database contains pathology reports from clinical practice. The NCR contains certain characteristics of patients diagnosed with ESCC, but clinical data, including medical history, symptoms of dysphagia and odynophagia, and endoscopy characteristiscs such as the presence, size, and macroscopic appearance of lesions, are not available. Endoscopic assessment and follow-up or treatment strategies were performed upon clinician's expert opinion and daily clinical practice, and no pathology slides were reassessed. No histopathological follow-up was available in a substantial proportion of included patients (i.e. 42% of patients with mild-to-moderate dysplasia and 31% of patients with higher-grade dysplasia), which may have resulted in an underestimation of the risk of ESCC.

In conclusion, all patients with esophageal squamous dysplasia in Western countries, including those with mild, low-grade and moderate dysplasia, have a substantial risk of developing ESCC. Consequently, endoscopic surveillance of the esophageal mucosa or ER of dysplasia should be considered for patients with mild-to-moderate dysplasia in Western countries. For patients with high-grade dysplasia, severe dysplasia and CIS, adequate endoscopic staging and in case of suspicion for neoplasia, aggressive treatment is required as ESCC is already present in a substantial proportion of patients.

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ETHICS APPROVAL

This study was approved by the Medical Ethical Review Committee of the Erasmus Medical Centre (MEC-2022-0274).

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