ESOPHAGUS

Risk Factors in the Development of Esophageal Adenocarcinoma

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OBJECTIVES: **It is assumed that esophageal adenocarcinoma is the end result of a stepwise disease process that transitions through gastroesophageal reflux disease (GERD) and Barrett's esophagus. The aim of this study was to examine at what stage known risk factors exert their influence toward the progression to cancer.**

METHODS: **We enrolled 113 consecutive outpatients without GERD, 188 with GERD, 162 with Barrett's esophagus, and 100 with esophageal adenocarcinoma or high-grade dysplasia (HGD). All patients underwent a standard upper endoscopy and completed a standardized questionnaire about their social history, symptoms, dietary habits, and prescribed medications. We used adjusted logistic regression analysis to assess risk factors between each two consecutive disease stages from the absence of reflux disease to esophageal adenocarcinoma.**

RESULTS: **Overall, male gender, smoking, increased body mass index (BMI), low fruit and vegetable intake, duration of reflux symptoms, and presence of a hiatal hernia were risk factors for cancer/HGD. However, different combinations of risk factors were associated with different disease stages. Hiatal hernia was the only risk factor to be strongly associated with the development of GERD. For GERD patients, male gender, age, an increased BMI, duration of reflux symptoms, and presence of a hiatal hernia were all associated with the development of Barrett's esophagus. Finally, the development of cancer/HGD among patients with Barrett's esophagus was associated with male gender, smoking, decreased fruit and vegetable intake, and a long segment of Barrett's esophagus, but not with age, BMI, or a hiatal hernia.**

CONCLUSIONS: **While some risk factors act predominantly on the initial development of reflux disease, others appear to be primarily responsible for the development of more advanced disease stages.**

SUPPLEMENTARY MATERIAL is linked to the online version of the paper at http://www.nature.com/ajg

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INTRODUCTION

Esophageal adenocarcinoma has been increasing in the United States more than six-fold over the past three decades (1). The reasons for this steep increase are unknown. Several risk factors have been identified, including age, male gender, white ethnicity, history of reflux disease, a high body mass index (BMI), a low fruit and vegetable intake, the presence of a hiatal hernia, and the absence of *H. pylori* infection (2–7). Because each individual risk factor is common it has been difficult to identify a population at high risk for progression to cancer.

It is assumed that the development of esophageal adenocarcinoma follows a stepwise progression from no reflux disease to reflux disease, from reflux disease to Barrett's esophagus, and from Barrett's esophagus to cancer. This assumption is based on animal studies, in which pathological acid reflux was a prerequisite for the development of cancer (8). The assumption is further supported by population-based studies that found an association between reflux disease and esophageal adenocarcinoma (9–11). Barrett's esophagus is considered as a premalignant condition for the development of esophageal adenocarcinoma with an estimated

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annual transition rate to cancer between 0.12 and 0.5% (2,12–14). Although it is likely that reflux disease precedes Barrett's esophagus, and that Barrett's esophagus precedes cancer, only very few patients with reflux disease will progress to Barrett's esophagus and only few patients with Barrett's esophagus will ever progress to cancer.

Risk factors that have been identified for the overall progression to cancer, where the general population was used as the reference group, may pose a risk for an intermediary stage, but possibly less so for the final transition stage from Barrett's esophagus to cancer. It is not well known to what extent known risk factors are responsible for the development of different disease stages from the absence of reflux disease to cancer. In this study, we recruited a large group of patients with and without reflux disease, with Barrett's esophagus, and with esophageal adenocarcinoma who were referred for an endoscopy. We assessed the risk factors for different disease stages on the path to esophageal adenocarcinoma. The aim of this study was to examine which risk factors to what extent influence different disease stages, ranging from the absence of reflux disease to gastroesophageal reflux disease (GERD), Barrett's esophagus, and esophageal adenocarcinoma.

METHODS

Patients

We conducted a case–control study among consecutive patients undergoing a standard upper endoscopy with (i) esophageal adenocarcinoma or high-grade dysplasia (HGD) in Barrett's metaplasia, (ii) Barrett's esophagus without dysplasia or with low-grade dysplasia, (iii) GERD, and (iv) absence of reflux symptoms or esophagitis (no-GERD). The study was conducted at the three hospitals of the Charité University in Berlin, Germany, between December 2005 and August 2009. All patients were identified at the time of endoscopy, from medical records, or from the endoscopic database. The sample frame for the cancer/HGD group consisted of all 244 patients who were diagnosed with esophageal adenocarcinoma or HGD at the participating medical centers between July 2002 and January 2008. Potential participants for the Barrett group included 298 patients who were diagnosed with Barrett's esophagus without HGD between December 2005 and August 2009. Patient controls with GERD and no-GERD were selected from the endoscopic database of one of the hospitals during the same time period. To select a representative sample of GERD and no-GERD patients, we contacted every fifth consecutive patient who met inclusion and exclusion criteria. If we were unable to reach the patient after two attempts, then the next following patient in the database (i.e., the 10th patient) was contacted.

The diagnosis of Barrett's esophagus was based on its endoscopic appearance and a confirmatory pathology report. All pathology evaluations were carried out by two independent expert pathologists. Given the high risk of prevalent cancer or of progression to cancer (15,16) for patients with Barrett's esophagus and HGD, it was assumed that HGD and esophageal adenocarcinoma shared the same risk factors. The two findings were grouped together as done in previous studies (2,7,17).

Subjects in the GERD group included all patients who underwent an upper endoscopy for work-up of typical reflux symptoms or who were found to have reflux esophagitis (at least Savary-Miller stage 1 or Los Angeles classification grade A). Potential subjects for the no-GERD group included all those who underwent an upper endoscopy for reasons other than reflux disease. Exclusion criteria for the GERD and no-GERD groups included an American Society of Anesthesiologists (ASA) class >3 and a history of gastrointestinal surgery or malignancy. Patients who were identified as subjects for the no-GERD group, but who had esophagitis on upper endoscopy or who reported at least weakly reflux symptoms during the survey evaluation were subsequently adjudicated to the GERD group. Because potential study subjects were identified after completion of the endoscopy, some patients could not be contacted or had died by the time the survey was conducted. **Figure 1** details patient inclusion into the study. The study protocol was approved by the Institutional Review Board of the Charité University Hospitals.

Data collection

Potential study subjects were contacted by phone or during a subsequent clinic visit and asked to participate. Enrolled patients completed a standardized questionnaire about the history and duration of reflux symptoms, smoking history, dietary habits (time of largest meal, fruit and vegetable intake), BMI at the age of 40, history of diabetes mellitus, and infection with *Helicobacter pylori*. We extracted information on Barrett length, possible esophagitis, and hiatal hernia from the endoscopy report, and information on dysplasia from the pathology report. Medical records were also reviewed with regard to history of diabetes mellitus, and *H. pylori* infection. A patient was considered to have had a history of *H. pylori* infection if supported by medical records or reported by the patient. We also collected information on medication use (proton-pump inhibitors or histamine-2 receptor blocker, aspirin and other non-steroidal anti-inflammatory drugs and statins). Details about the onset of drug use and its relationship to the time of diagnosis of Barrett's esophagus or GERD were not available.

Statistical analysis

We examined the association between patient characteristics and different disease stages, ranging from the absence of reflux disease to cancer. We applied multivariate logistic regression analysis to calculate adjusted odds ratios (OR) with their 95% confidence interval (CI), using the statistical software Stata 11.0 (StataCorp LP, College Station, TX, USA). The regression model was developed based on the comparison between the cancer/HGD and the no-GERD groups. We included a pre-selected set of variables into the regression model (age, gender, BMI at age 40, and tobacco) and tested additional variables for significance. Only variables that maintained significance and changed the point estimates by >10% were included in the final model. We computed tests for trends after exclusion of missing data across categories of risk factors and for continuous variables using their continuous data values. Continuous variables were compared using the Student's *t*-test if normally distributed or the Mann–Whitney *U* test otherwise.

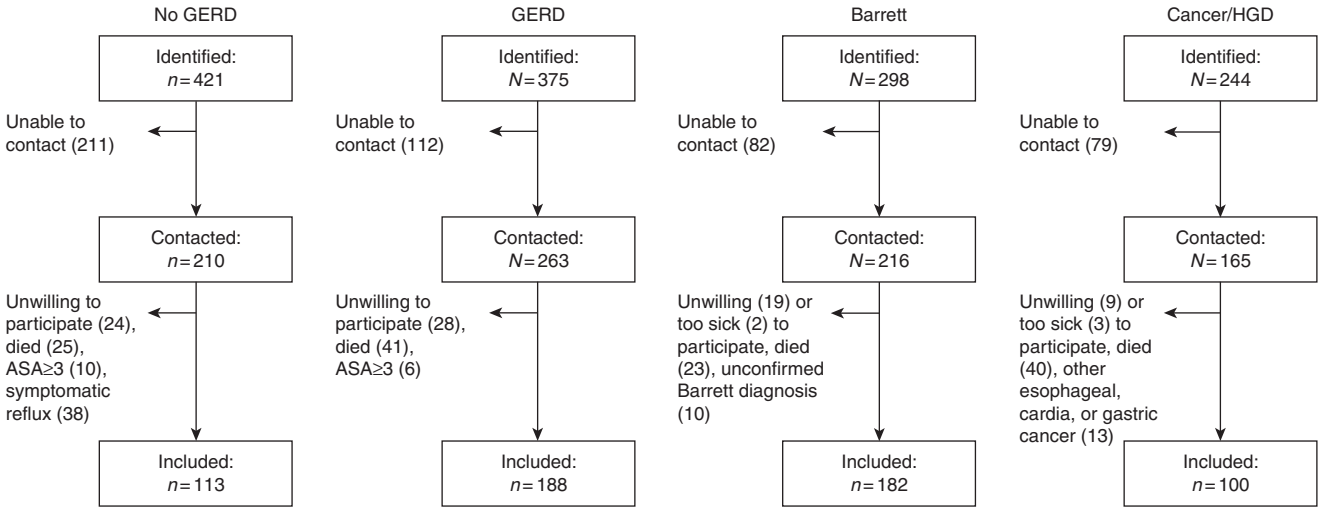

Figure 1. Flow chart. Selection and inclusion of study participants. ASA, American Society of Anesthesiologist classification; GERD, gastroesophageal reflux disease; HGD, high-grade dysplasia.

Categorical variables were compared using the Chi-squared test. Based on previous epidemiologic studies, we estimated that common risk factors such as male gender or presence of hiatal hernia would rise in increments of about 20% among the four study groups. Considering an α-error of 5%, a β-error of 20%, and depending on the prevalence rate in the comparison group, it was estimated that the individual groups should contain at least 100 subjects. Patient recruitment was stopped after 100 patients had been recruited into the cancer/HGD group.

RESULTS

Patient characteristics

A total of 1,338 patients were identified for all groups combined. Of these, 563 (42.1%) were included in the study (**Figure 1**), 113 patients into the no-GERD group, 188 patients into the GERD group, 162 patients into the Barrett group, and 100 patients into the cancer/HGD group. Inability to reach patients, unwillingness to participate, death, or meeting exclusion criteria were reasons for not including identified subjects. In the Barrett group, 11 (6.8%) had low-grade dysplasia and 67 (41.4%) had long-segment Barrett's esophagus ≥3 cm. Of the 100 patients in the cancer/HGD group, 75 had cancer and 25 HGD alone. All patients were of Caucasian ethnicity. Details of patient characteristics, endoscopy findings, and medications are summarized in **Table 1**.

The no-GERD and GERD groups showed similar patient characteristics. Patients with Barrett's esophagus were older, more often men, heavier, ate less fruits and vegetables, and had reflux symptoms for more years than GERD patients. Patients with cancer/HGD and Barrett's esophagus were similar with respect to age, BMI at age 40, and duration of reflux symptoms. However, cancer/HGD patients were more likely to be male, to be current or former smokers, reported reflux symptoms more often, and had a lower intake of fruits and vegetables compared with Barrett patients.

Endoscopy showed a hiatal hernia more often in GERD than in no-GERD patients and in Barrett patients more often than in GERD patients. Non-significantly fewer patients with cancer/HGD had a hiatal hernia than Barrett patients. The length of Barrett's esophagus was available in 157 Barrett patients and 75 cancer/HGD patients. It was significantly longer in patients with cancer/HGD compared to patients with Barrett's esophagus alone. The prevalence of *H. pylori* infection was not significantly different among the four patient groups.

Proton-pump inhibitors/H2A use was more common in the GERD group compared with the no-GERD group and more common in the Barrett group compared with the GERD group or the cancer group. There were no differences among the four groups regarding their use of statins or non-steroidal anti-inflammatory drugs other than aspirin.

Risk factors associated with the development of esophageal adenocarcinoma

Overall, male gender, history of smoking, and the presence and size of a hiatal hernia were strong risk factors for esophageal adenocarcinoma/HGD when compared with patients without reflux disease in the adjusted analysis. Increasing BMI at age 40 showed a small, but significant association with esophageal adenocarcinoma (P trend = 0.034) with an OR of 1.21 for obese as compared with normal-weight patients (**Figure 2**; **Supplementary Table 2a Appendix**). A high intake of fruit and vegetables of at least four portions per day showed a strong protective effect (OR 0.25, 95% CI 0.07–0.83). Similarly, *H. pylori* infection appeared to be protective (OR 0.50, 95% CI 0.23–1.09). Duration of smoking, a history of diabetes, or timing of the largest meal during the day was not associated with esophageal adenocarcinoma/HGD.

Risk factors associated with the development of GERD in patients without GERD

Presence of a hiatal hernia was the only risk factor to be significantly associated with GERD (OR 3.62, 95% CI 2.15–6.09), and

Table 1. Patient characteristics

Variable	No GERD (1) *n*=113	GERD (2) *n*=188	Barrett's esophagus (3) *n*=162	Cancer/HGD (4) *n*=100	*P* (1 vs. 2)	*P* (2 vs. 3)	*P* (3 vs. 4)
Patient characteristics							
Age, mean years (s.d.)	62.3 (10.1)	61.0 (9.4)	63.4 (11.4)	64.7 (9.7)	0.256	**0.038**	0.336
Male gender, %	51	49	72	87	0.688	**<0.001**	**0.004**
Smoking, ever, %	61	64	64	84	0.630	0.916	**0.001**
DM, %	16	20	17	17	0.355	0.395	0.944
BMI, mean (s.d.)	25.2 (5.2)	26.3 (5.3)	27.1 (3.9)	25.5 (4.6)	0.077	0.097	**0.002**
BMI age 40, mean (s.d.)	24.7 (4.2)	24.8 (3.9)	25.9 (4.2)	26.3 (3.6)	0.842	**0.008**	0.490
Fruit/vegetable, mean servings/day (s.d.)	2.2 (1.0)	2.2 (1.0)	1.9 (0.9)	1.7 (0.8)	0.742	**0.012**	**0.045**
Largest meal at night, %	50	43	48	52	0.215	0.409	0.432
Heartburn frequency, % >3×/week	NA	45	45	58	NA	0.977	**0.050**
Heartburn duration, mean (s.d.)	NA	10.7 (9.9)	17.3 (14.0)	20.0 (14.0)	NA	**<0.001**	0.124
Endoscopy							
Hiatus hernia, % present	25	54	76	64	**<0.001**	**<0.001**	0.062
Length of Barrett segment, mean (s.d.)	NA	NA	3.2 (2.9)	5.1 (3.9)	NA	NA	**<0.001**
Long segment Barrett, %	NA	NA	43	66	NA	NA	**0.001**
Helicobacter pylori, %	31	40	30	23	0.118	0.064	0.281
Medications							
PPI/H2B, %	39	63	78	61	**<0.001**	**0.003**	**<0.001**
Aspirin, %	46	46	51	45	0.965	0.355	0.312
NSAIDs, %	32	34	39	34	0.152	0.884	0.634
Statins, %	26	24	31	25	0.736	0.115	0.261

BMI, body mass index; DM, diabetes mellitus; GERD, gastroesophageal reflux disease; H2B, histamine-2 receptor blocker; HGD, high-grade dysplasia; NSAIDs, non-steroidal anti-inflammatory drugs; PPIs, proton-pump inhibitors.
Bold entries represent *P* values that are significant.

the OR increased with the size of the hernia (P trend < 0.001). A large hiatal hernia increased the OR four times compared with patients without a hiatal hernia (OR 4.23, 95% CI 2.03–8.81). No other risk factors were identified (**Figure 2**; **Supplementary Table 2b Appendix**). Specifically, we did not find a high BMI or a low fruit and vegetable intake to be associated with an increased risk for reflux disease. Presence of *H. pylori* infection did not appear to protect against GERD.

Risk factors associated with the development of Barrett's esophagus in patients with GERD

Age appeared to be a strong risk factor for the development of Barrett's esophagus among GERD patients (P trend = 0.027) (**Figure 2**; **Supplementary Table 2c Appendix**). GERD patients older than 75 years were three times more likely to develop Barrett's esophagus than GERD patients younger than 55 years (OR 2.96, 95% CI 1.34–6.51). Male gender was also a strong risk factor. Men with GERD had a 2.7 higher OR of developing Barrett's esophagus than women (OR 2.71, 95% CI 1.70–4.32). Furthermore, there was a significant association between increasing BMI and Barrett's esophagus (P trend = 0.014), with a non-significant doubling of the OR for obese compared with normal-weight patients (OR 1.99, 95% CI 0.88–4.50). Although high fruit and vegetable intake were protective in univariate analysis, the effect was not significant in the adjusted analysis. Heartburn duration was strongly associated with Barrett's esophagus (P trend = 0.004). Heartburn duration of at least 20 years was associated with 2 .4-fold higher OR of developing Barrett's esophagus than a heartburn duration of <10 years (OR 2.41, 95% CI 1.34–4.31). Frequency of heartburn was not associated with the development of Barrett's esophagus. Presence of a hiatal hernia was strongly associated with Barrett's esophagus (OR 2.43, 95% CI 1.50–3.94) among GERD patients, with a significant trend between size and effect (P trend = 0.001). *H. pylori* infection was not associated with the development of Barrett's esophagus in patients with GERD.

Risk factors associated with the development of cancer/HGD in patients with Barrett's esophagus

Male gender, but not age was strongly associated with the development of cancer/HGD in Barrett patients (**Figure 2**; **Supplementary**

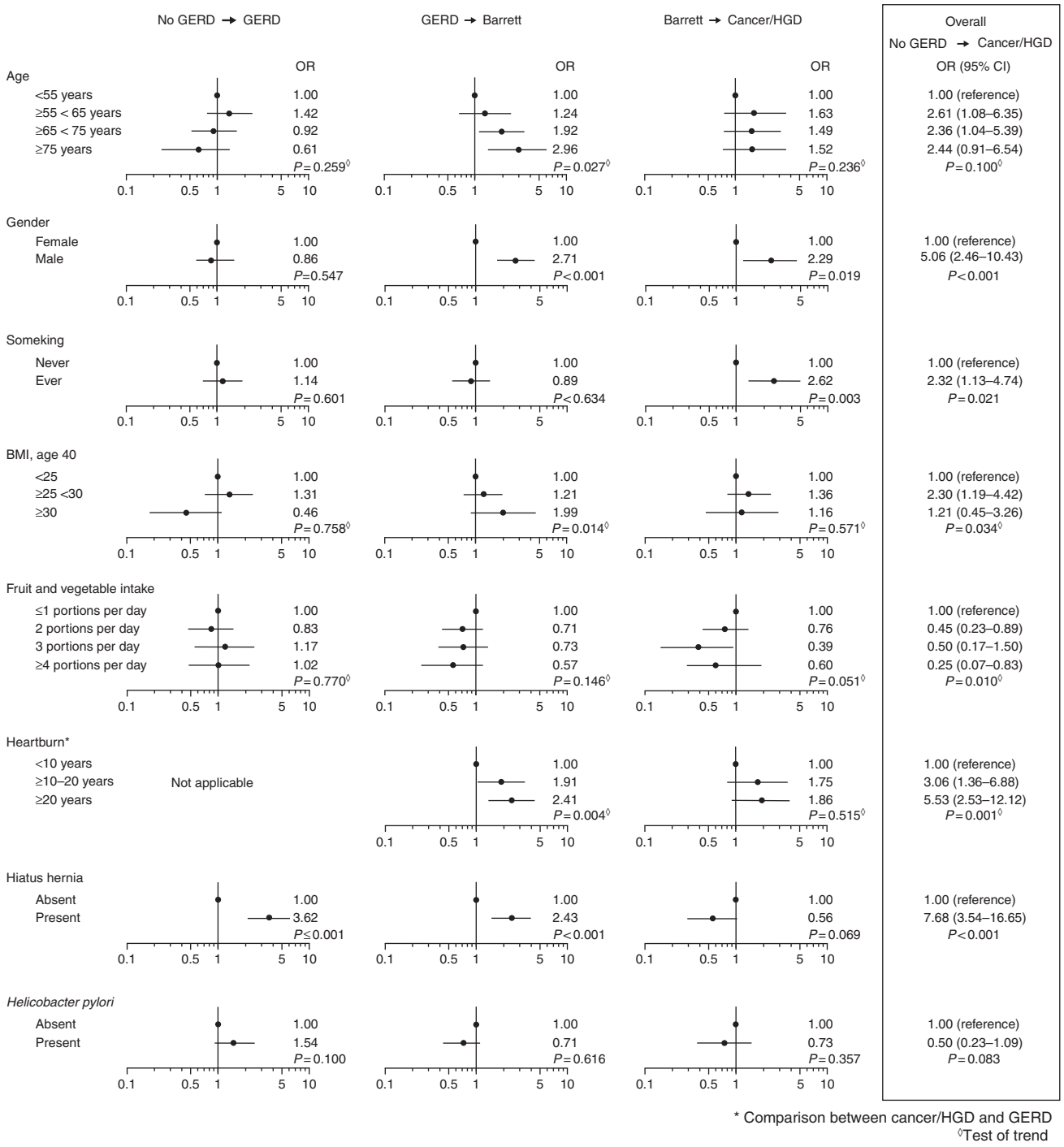

Figure 2. Effect of varying factors on the progression from the absence of reflux disease (no GERD) to reflux disease (GERD) to Barrett's esophagus to esophageal adenocarcinoma/high-grade dysplasia (cancer/HGD). Risks are expressed as odd ratios (OR) with 95% confidence interval (CI) adjusted for age, gender, history of smoking, and body mass index at age 40. BMI, body mass index; GERD, gastroesophageal reflux disease; HGD, high-grade dysplasia.

Table 2d Appendix). Cancer/HGD patients were twice more likely to be male than patients with Barrett's esophagus alone (OR 2.29, 95% CI 1.15–4.59). Smoking also appeared to be a strong risk factor. Any history of smoking was associated with a 2.6-fold odds (OR 2.62, 95% CI 1.38–4.99), whereas duration of smoking or years since smoking cessation exerted no significant influence. A high fruit and vegetable intake appeared to be protective with a dose–response effect (P trend = 0.051), although the OR among highest fruit and vegetable consumers were not significantly reduced in adjusted analysis (OR 0.60, 95% CI 0.19–1.91). Duration or frequency of reflux symptoms or the presence of a hiatal hernia was not associated with cancer/HGD. However, increasing

Barrett length was associated with the development of cancer/HGD in Barrett patients. Patients with a long-segment Barrett's esophagus had a 2.7 higher OR of developing cancer/HGD than those with a short-segment Barrett's esophagus (OR 2.69, 95% CI 1.48–4.88). For every 1 cm increase in Barrett length, the OR increased by 19% (OR 1.19, 95% CI 1.09–1.30). *H. pylori* infection did not appear to significantly reduce the risk of progression to cancer/HGD.

DISCUSSION

In the present study, we examined risk factors associated with different disease stages in the development of esophageal adenocarcinoma. We found that different combinations of risk factors were associated with separate disease stages. Hiatal hernia was the only risk to be strongly associated with the development of GERD. Hiatal hernia, male gender, old age, increased BMI, and duration of reflux symptoms were all associated with the development of Barrett's esophagus in patients with GERD. Finally, male gender, smoking, decreased intake of fruit and vegetables, and increasing length of Barrett's esophagus were all associated with the progression to esophageal cancer in patients with Barrett's esophagus.

It has long been known that esophageal adenocarcinoma is more common in the elderly and in white men (3). In concordance with prior observations, our results suggest that rising age increases the risk for developing Barrett's esophagus (18). However, we did not find that age alone was associated with further progression from Barrett's esophagus to cancer (19). The observation that esophageal adenocarcinoma tends to occur in the elderly may be therefore primarily related to the development of the underlying Barrett's esophagus. Our results also confirm prior observations of a male predominance in both, Barrett's esophagus and esophageal adenocarcinoma. We found that male gender more than doubled the risk for patients with GERD to develop Barrett's esophagus, and further doubled the risk for Barrett patients to develop cancer of HGD.

Although smoking has been shown to be a risk factor for esophageal adenocarcinoma, doubling of its overall risk (4), it is unknown at what stage smoking actually exerts most of its influence (20,21). Our results indicate that smoking has no effect on the development of GERD or the transition from GERD to Barrett's esophagus. However, smoking appears to increase the risk for the progression from Barrett's esophagus to cancer. Similar results were reported in several European studies (22–25), but are in contrast with one prior US study (7). A recently published cohort study by Coleman *et al.* (25) found a doubling hazard ratio for former or current smokers as compared with never smokers. Similar to our study their study also failed to find any association with the length of smoking history.

Our study confirms prior case–control studies that showed an association between an increased BMI and the risk for esophageal adenocarcinoma (5). While there is a general consensus that overweight and obesity increase the risk for the development of reflux disease (5), we failed to confirm this association in our own study population. This may be related to an underlying lesser variation of the BMI in a German population with fewer overweight patients. The effect of a high BMI on the progression to Barrett's esophagus and cancer is still being debated (24,26,27). We found a strong association between an increased BMI and the progression from reflux disease to Barrett's esophagus, but not from Barrett's esophagus to cancer. These results suggest that obesity mediates its risk for esophageal adenocarcinoma primarily through the development of Barrett's esophagus. It should be noted, however, that we did not assess central obesity or intra-abdominal fat as separate risk factors. Although central obesity has been suggested to be a more important risk measure than BMI, there have been no data to show that central obesity increases the risk of transition from Barrett's esophagus to cancer (27–29).

Case–control studies have shown a protective dose-dependent influence of fruit and vegetable intake on the development of esophageal adenocarcinoma (6,30–32), which may be mediated through the effect of antioxidants (33). Our results confirm prior studies in showing its lack of influence on the development of GERD (34). In contrast with a prior study by Kubo *et al.* (35),we did not find that a high intake of fruit and vegetables protected against the development of Barrett's esophagus. The lack of effect in our study may be related to fewer study participants and a different assessment of dietary habits. The study by Kubo *et al.* asked for dietary habits within the year before Barrett diagnosis, while our study assessed dietary habits at age 40 introducing the higher potential of recall bias. With respect to the progression to cancer, our study suggests that a high fruit and vegetable intake may have a protective effect against the development of cancer in patients with Barrett's esophagus.

H. pylori infection has been reported to decrease the risk of Barrett's esophagus (36) and its progression to cancer, possibly as a result of reduced acid secretion in *H. pylori*-associated corpus predominant gastritis (37). Although our results did not reveal a statistically significant association, we observed an overall trend suggesting some protective influence on both the progression to Barrett's esophagus and to cancer.

Our study has several limitations. A large number of the initially selected participants could not be contacted and included into the final study population (**Figure 1**). Although we could not gather sufficiently detailed information to assess whether there were any substantial differences between participants and non-participants, the basic demographic characteristics (age, gender, BMI, and reflux symptoms) of our study population were similar to those reported in previous cohort or population-based studies (24,25,38), except for a slightly larger proportion of men in our GERD group than typically seen in this age group (38). Furthermore, we asked about weight and dietary habits at age 40, introducing the possibility of a recall bias. The direction of its effect can go both ways, depending on how much a patient (particularly a cancer patient) believes the risk factor is associated with the diagnosis. In our analysis, recall bias may have increased the variation around the estimate.

It also needs to be mentioned that our no-GERD group does not represent an asymptomatic population. These patients had an endoscopy for other reasons. While they did not have esophagitis or typical reflux symptoms some patients in this group may have had atypical symptoms that would have been revealed by an

abnormal pH study. This limitation likely leads to an underestimation of the observed effects.

Our results should be viewed as hypothesis generating. Our study examined the influences of various risk factors by comparing each two consecutive disease stages. Ideally, a large cohort of asymptomatic (no-GERD) patients should be followed over long time to understand transitions and risks along the assumed disease stages to cancer. Because such study would be impractical and extremely difficult to carry out, we have to rely on results from cross-sectional studies. It is plausible that seemingly intermediary stages (GERD and Barrett's metaplasia) may present themselves at the onset as the most severe and final stage of reflux disease (40). ORs that were determined for different disease stages, therefore, indicate an epidemiologic risk association rather than a time-dependent progression among different disease stages. Although a time-dependent progression may be truly mediated by different sets of risk factors, it could also be that combinations of different risk factors or varying strengths of individual risk factors govern the outcome from the beginning onwards. According to the second possibility, such patterns of risk factors would function more like as a set of switches that lead toward its pre-determined end point from the onset and within a short time period. Our cross-sectional study design does not allow us to differentiate between these varying possibilities for the natural progression to cancer.

In general, the strength of association calculated for individual risk factors depends on the type of comparison groups and their individual sizes. Some risk factors may appear weak or insignificant when contrasted with the findings of previous investigators. However, when we compared esophageal adenocarcinoma patients with controls without GERD (rather than Barrett's esophagus), the pattern changed with most ORs increasing in size or changing their level of significance. Because of the high number of exclusions our control group without GERD turned out to be smaller than anticipated. A larger control population might have rendered a larger number of risk factors statistically significant.

In conclusion, our study shows that different sets of risk factors are associated with different disease stages in the development to esophageal adenocarcinoma. While some risk factors act predominantly on the initial development of reflux disease, others are associated with more advanced disease stages, such as Barrett's esophagus or esophageal adenocarcinoma. Our results suggest that different combinations or varying strengths of individual risk factors may govern the final outcome from the onset. Alternatively, it is also possible that a gradual progression through different stages of disease severity may be mediated by the consecutive and time-dependent action of varying risk factors.

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CONFLICT OF INTEREST

Guarantor of the article: Heiko Pohl, MD.

Specific author contributions: Study concept, design, analysis and interpretation of data, drafting of the manuscript, critical revision of the manuscript for important intellectual content, and statistical analysis: Heiko Pohl; acquisition of data, critical revision of the manuscript for important intellectual content, and technical support: Katharina Wrobel; acquisition of data and critical revision of the manuscript for important intellectual content: Christian Bojarski, Winfried Voderholzer, and Thomas Rösch; analysis and interpretation of data, critical revision of the manuscript for important intellectual content, and statistical analysis: Amnon Sonnenberg; critical revision of the manuscript for important intellectual content: Daniel C. Baumgart.

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Study Highlights

WHAT IS CURRENT KNOWLEDGE

- ✓ Several risk factors for esophageal adenocarcinoma have been identified.
- ✓ It is not known at what stage in the progression to cancer risk factors exert their effect.

WHAT IS NEW HERE

- ✓ Different combinations of risk factors appear to be associated with different disease stages from the absence of reflux disease to esophageal adenocarcinoma.

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