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Mortality from upper gastrointestinal tumors in colorectal cancer screening patients

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ABSTRACT

Background and study aims Currently, gastric cancer screening is only cost-effective in countries with high incidence. Integrated screening, in which gastroscopy is performed in conjunction with colonoscopy, could help reduce the gastric cancer screening procedure burden in countries with low or intermediate incidence. However, there is a lack of population-based studies to identify high-risk groups.

Methods In this retrospective analysis of a colorectal cancer (CRC) screening program database, we used Cox proportional hazards model to identify an association of high- and low-risk finding (polyps ≥ 10 mm or with high-grade dysplasia) with time to death from upper gastrointestinal cancer (esophageal and gastric). We estimated the 10-year mortality of upper gastrointestinal tumors in different 10-year age groups, stratified by sex and polyp finding at colonoscopy.

Results We included 349,856 CRC screening colonoscopies in our study. The median follow-up time was 5.22 years (95% confidence interval [CI] 5.21–5.24 years). Of the participants, 4.5% had polyps ≥ 10 mm or with high-grade dysplasia (HGD). At the end of the study period, 384 deaths from upper gastrointestinal cancer had occurred. Aside from age and sex, we found the presence of high-risk polyps to be significantly associated with upper gastrointestinal cancer death (hazard ratio 1.54, 95% CI 1.06–2.25, P= 0.025).

Conclusions CRC screening participants with polyps < 10 mm and no HGD have a lower risk for mortality from upper gastrointestinal cancers compared with participants with polyps > 10 mm and HGD. Future studies will demonstrate whether integrated screening with additional gastroscopy is effective in CRC screening participants with large or highly dysplastic polyps.

Introduction

Globally, cancers of the digestive system, including malignancies of the upper and lower gastrointestinal tract, account for 18,5% of new cancers and 22.4% of cancer deaths [1]. Some 8.7% of all new cancers can be attributed to esophageal and stomach tumors, and 9.8% of all new cancers originate from the colon or rectum [1]. Many lifestyle habits and dietary patterns have been described as risk factors for both colorectal cancer (CRC) and upper gastrointestinal tumors. These include a low physical activity level, obesity, tobacco consumption, a high-caloric diet, and excessive alcohol intake [2, 3, 4, 5, 6, 7, 8]. Screening for CRC is recommended by many national and international societies, including the US Preventive Services Task Force (USPSTF) [9] and the European Union [10]. Notwithstanding the burden of disease, there is currently no population-wide screening program for upper gastrointestinal tumors in countries of the global West. Patients at high risk for esophageal adenocarcinoma due to long-standing history of gastroesophageal reflux disease (GERD), can undergo surveillance if symptoms persist for more than 5 years [11]. Likewise, to prevent development of squamous cell carcinoma (SCC) of the esophagus, patients at risk, such as those with a history of achalasia or diagnosis of head and neck cancer, are eligible for screening programs [12]. For the prevention of gastric cancer, screening the general population is not recommended in low-incidence settings; however, it is effective in countries with a large burden of new cases, such as Korea [13]. Infection with *Helicobacter pylori*, which precedes the majority of gastric adenocarcinomas, leads to chronic atrophic gastritis (CAG) [14]. CAG is a premalignant condition that can be detected during upper endoscopy [15]. Combining fecal immunochemical testing (FIT) with stool antigen tests for *H. pylori* has been proposed, but that strategy would only be useful in countries without primary colonoscopy screening [16]. In countries with intermediate incidence, gastric cancer screening can be performed in patients undergoing screening colonoscopy who have a certain risk profile, but data supporting this strategy are lacking [17]. The aim of this study was to investigate whether patients screened with colonoscopy who have high-risk polyp features experience higher mortality from upper gastrointestinal tumors so as to provide data for future integrated screening with upper gastrointestinal endoscopy together with colonoscopy.

Patients and methods

Study population and databases

CRC prevention by screening colonoscopy every 10 years starting at the age of 50 years for men and women is offered to every Austrian insured person. Alternatively, persons can opt for a guaiac-based fecal occult blood test at the age of 40 years and pursue colonoscopy in case of test positivity. Quality assurance is one of the main pillars of an effective screening program according to the US Multi-society Task Force and European Commission [18, 19]. Currently, Austria has a voluntary quality assurance program for endoscopists offering screening colonoscopy. Incentives for participation include regular performance feedback with benchmarking reports and endorsement by the Austrian Society for Gastroenterology and Hepatology. Endoscopists participating in the program agree to submit data on screening colonoscopies including polyp characteristics such as size and dysplasia grade and patient characteristics such as age and sex of screened participants. Data collection started in 2007 and is still ongoing. A database managed by the Austrian Main Association of Statutory Insurance Institutions (Österreichischer Dachverband der Sozialversicherungsträger) is used for storage of endoscopy data.

Data on gastric cancer death

Deaths in Austria are recorded by a national statistical agency, Statistics Austria. Causes of death are coded by the 10th WHO version of the International Classification of Diseases (ICD-10). We performed data linkage to the causes-of-death registry of study participants until December 2020.

Study design and definitions

This was a retrospective observational study. We included healthy CRC screening participants aged ≥ 50 years and ≤ 90 years. Because individuals with a history of inflammatory bowel disease or hereditary cancer syndromes are not eligible for average-risk CRC screening, they are not included in this study. Individuals with CRC at screening colonoscopy (index colonoscopy) were excluded. Between January 2007 and December 2020, 349,856 screening participants were included. Follow-up started at the first screening colonoscopy and ended at either death from upper gastrointestinal cancer or other causes. Follow-up (surveillance) colonoscopies were excluded. Participants were censored at the end of the study period in case no event was recorded. We considered deaths from upper gastrointestinal cancers as a death record using the codes “C15” (esophageal cancer) and “C16” (gastric cancer). We defined a high-risk polyp as any polyp ≥ 10 mm, serrated polyps with dysplasia, and adenomas with high-grade dysplasia. High-risk criteria were considered according to the classification by the European Society of Gastrointestinal Endoscopy (ESGE) [20, 21]. Currently, the ESGE does not include histologic features such as villous polyp components or traditional serrated histology as high-risk criteria, which is why we chose not to include these findings in the high-risk category.

Statistical analysis

Categorical variables were described by absolute and relative frequencies. Continuous variables were described by means and standard deviations, as well as by median and 25th and 75th percentiles. We calculated the rate of deaths for the variables sex, 10-year age groups, and polyp risk groups as the sum of deaths by the total person-years in each stratum. We estimated the probability of death from upper gastrointestinal tumors in screening participants with high-risk polyps and a colonoscopy without findings as the reference using a cause-specific Cox proportional hazards model. We included patient age as a categorical variable by 10-year age bands and patient sex in the model. For identifying an association of baseline characteristics of screening participants with upper gastrointestinal mortality,

a cause-specific Cox model with age as a continuous variable was computed. We tested the assumption of proportionality by calculating scaled Schoenfeld residuals. The associations of age, sex, and polyp risk group with time to upper gastrointestinal cancer death were reported as hazard ratios with 95% confidence intervals (Cis). We obtained estimates of upper gastrointestinal cancer death and 95% CIs at 10 years of follow-up for men and women of the different age categories from this model. All analyses were performed with R version 4.2.1. A significance level of $P < 0.05$ was set for statistical testing.

Results

Cohort characteristics

A total of 349,856 screening participants were included in the study. The median follow-up time was 5.22 years (95% CI 5.21–5.24 years) and the maximum follow-up time was 14 years. Of the study participants in the cohort, 51.3% were female (▶ **Table 1**), with a median age of 60.12 and a median age of male participants of 59.87. We observed 384 deaths from upper gastrointestinal cancers, of which 125 were attributed to esophageal cancers and 259 were considered deaths from gastric cancer. Rates of death from upper gastrointestinal tumors were higher in men, with 11.32 deaths from esophageal tumors per 100,000 person-years in male participants compared with 2.16 per 100,000 person-years in female participants. Men experienced 18.5 deaths from gastric cancer per 100,000 person-years, and the female rate of deaths per 100,000 person-years was 9.15.

Participant characteristics associated with upper gastrointestinal cancer death

We found that upper gastrointestinal cancer mortality was associated with male sex (hazard ratio [HR] 2.6; 95% CI 2.03–3.33), screening participant age at colonoscopy (HR 1.07, 95% CI 1.06–1.08). Having low-risk polyps at screening colonoscopy was not significantly associated with upper gastrointestinal cancer death (HR 1.23, 95% CI 0.95–1.58, P = 0.111); however, hazards for upper gastrointestinal cancer death were significantly higher for screening participants with high-risk polyps at colonoscopy (HR 1.5, 95% CI 1.03–2.18, P = 0.035) (▶ **Table 2**).

10-year estimates of upper gastrointestinal cancer mortality

The estimated 10-year risk for upper gastrointestinal cancer death in female screening participants with high-risk polyps was 0.1%, 0.17%, 0.32%, and 0.66% for women aged 50 to 59, 60 to 69, 70 to 79 or 80 to 89 years, respectively, compared with 0.07%, 0.11%, 0.21%, and 0.43%, respectively, for women with a colonoscopy without findings (▶ **Fig. 1**). The estimates for men were higher across all age categories (▶ **Fig. 2**). For men having no polyps, the estimates were 0.17%, 0.28%, 0.53%, and 0.82% in the age categories 50 to 59, 60 to 69, 70 to 79, and 80 to 89 years, respectively. In men with high-risk polyps, the estimates were 0.26% 0.43%, 0.82%, and 1.10%, respectively (▶ **Table 3**). The estimates for the risk difference

▶ **Table 1** Study cohort.

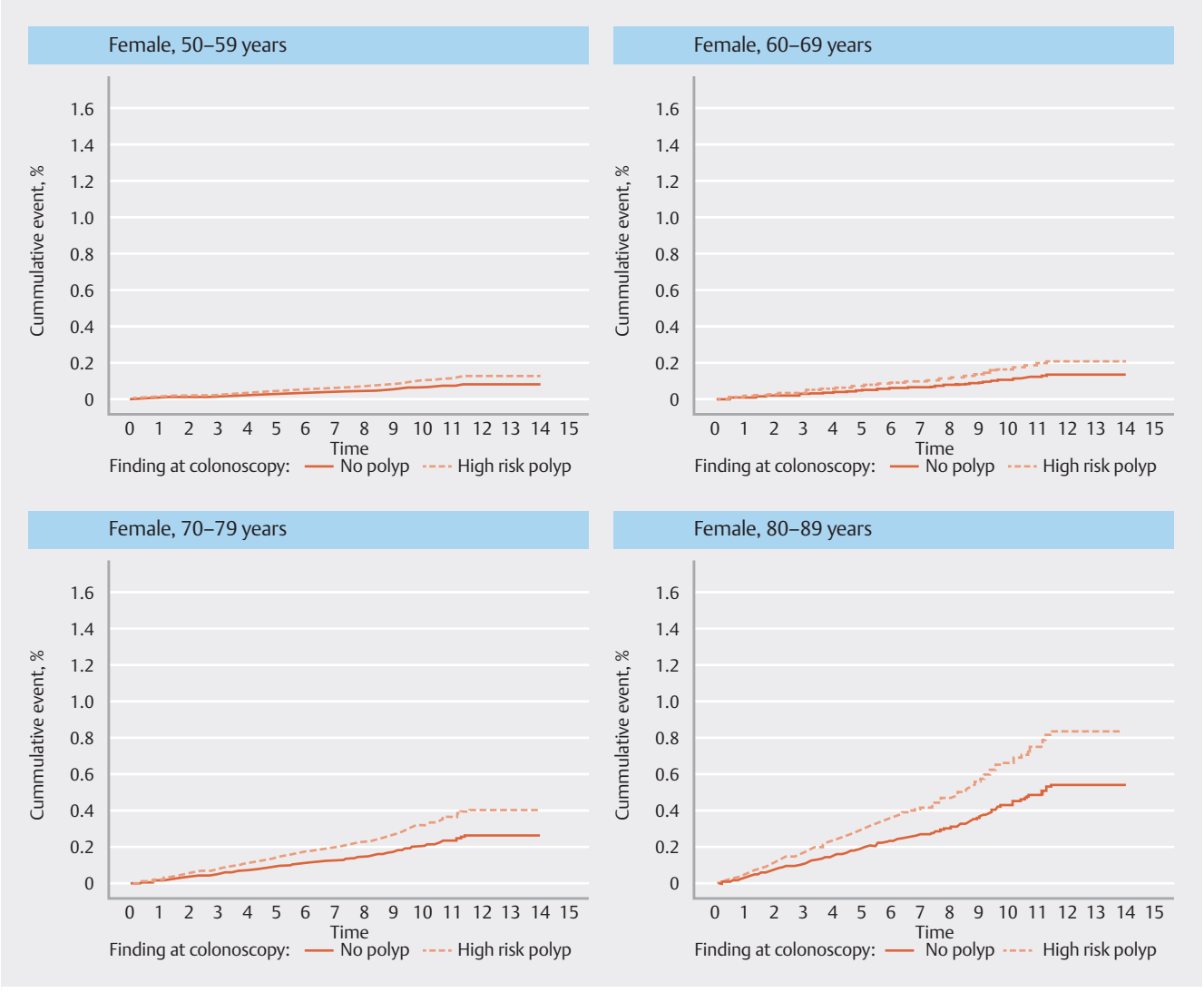
	Overall (N = 349,856)
Age	
▪ Mean (SD)	61.5 (8.57)
▪ Median [Q1, Q3]	60.0 [54.1,67.6]
Age group	
▪ 50–59 years	175038 (50.0%)
▪ 60–69 years	108845 (31.1%)
▪ 70–79 years	57583 (16.5%)
▪ 80–89 years	8390 (2.4%)
Sex	
▪ Female	179464 (51.3%)
▪ Male	170392 (48.7%)
Polyp finding	
▪ No polyps	204923 (58.6%)
▪ Low-risk polyps	129323 (37.0%)
▪ High-risk polyps	15610 (4.5%)
▪ Non-advanced adenoma	120506 (34.4%)
▪ Advanced adenoma	24435 (7.0%)

SD, standard deviation.

▶ **Table 2** Multivariable cause-specific Cox proportional hazards model demonstrating the association of CRC screening participants sex, age and whether polyps were detected at screening or not. Estimates are expressed as hazard ratios (HRs) with 95% confidence intervals (CIs).

Characteristic	HR	95% CI	P value
Sex			
▪ Female	—	—	
▪ Male	2.58	2.01, 3.30	< 0.001
Age group			
▪ 50–59 years	—	—	
▪ 60–69 years	1.65	1.32, 2.07	< 0.001
▪ 70–79 years	3.17	2.44, 4.12	< 0.001
▪ 80–89 years	6.60	4.50, 9.69	< 0.001
Polyp finding			
▪ No polyps	—	—	
▪ Low-risk polyps	1.25	0.97, 1.60	0.089
▪ High-risk polyps	1.54	1.06, 2.25	0.025

CI, confidence interval; HR, hazard ratio.



▶ **Fig. 1** Estimated probability of upper gastrointestinal cancer death (esophageal and gastric cancer) for female CRC screening participants in different age groups stratified by finding at colonoscopy (no polyps or high-risk polyps).

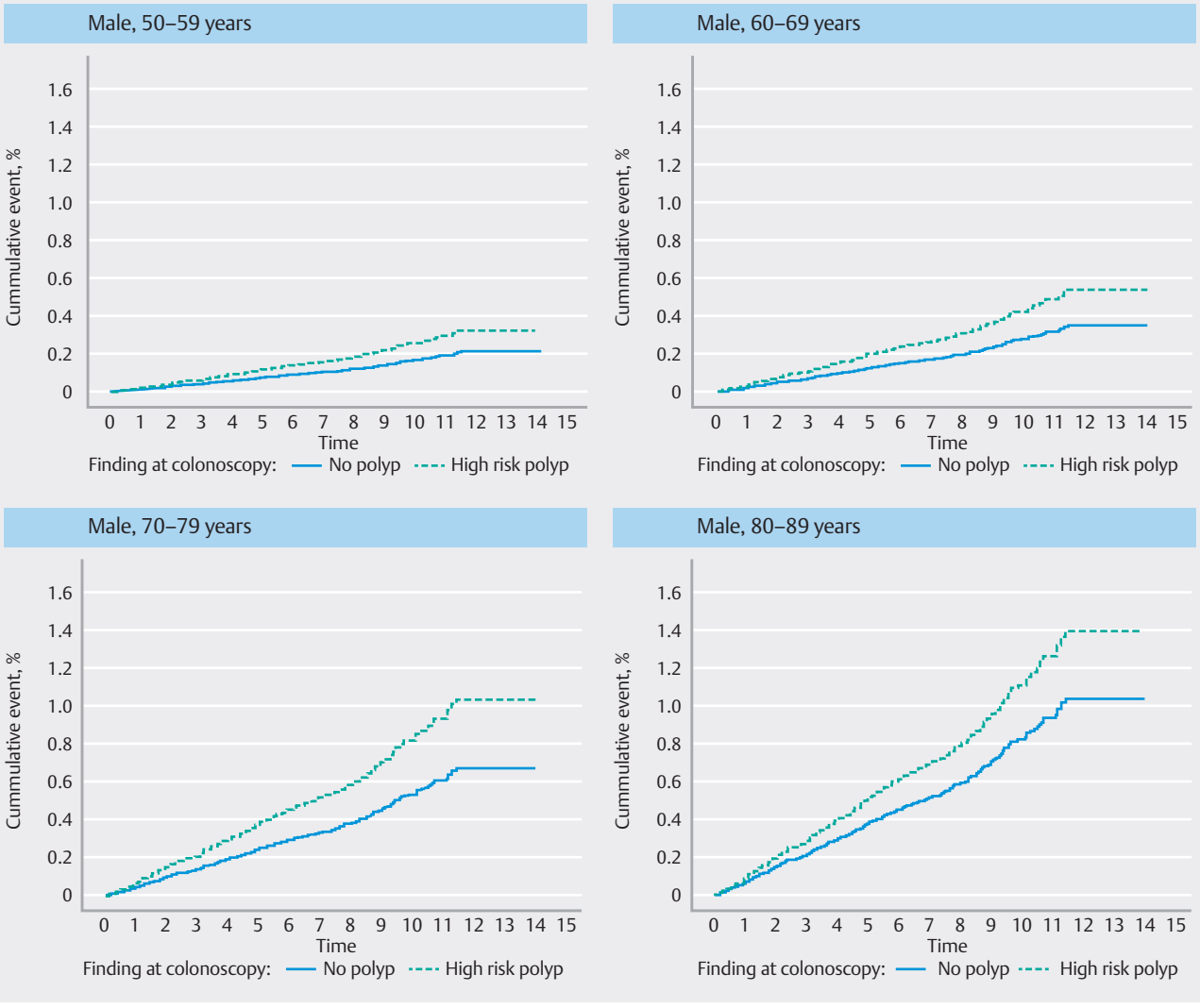
in upper gastrointestinal cancer death between men and women with high-risk polyps was largest in the age category 70 to 79 years (HR 0.50%; 95% CI 0.29–0.71), ▶**Table 4**). However, the absolute risk difference for upper gastrointestinal cancer death between men and women with no polyp was largest in the age category 80–89 years (absolute risk difference 0.39%; 95% CI 0.23–0.59). Table 1 s shows deaths per 100,000 person-years by age group, sex, and polyp finding.

Discussion

In this study, we investigated deaths from upper gastrointestinal tumors in a CRC screening cohort. We found that there was an association of deaths from gastric cancer and esophageal cancer with participant sex, age, and whether high-risk polyps were detected at screening colonoscopy.

Gastric cancer screening is cost-effective and has consistently been associated with a reduction in gastric cancer incidence in many populations in the global East [22]. The global distribution of gastric cancer might be attributable to a higher prevalence of infections with cytotoxin-associated gene A (cagA) strains of *H. pylori* in these countries, one of the main risk factors for gastric cancer. European countries, especially Central and Western countries such as Austria, currently have no population-based screening program for upper gastrointestinal cancers, owing to a low overall incidence of these conditions and a decline in gastric cancer incidence and mortality [23].

Aside from chronic infections with *H. pylori*, several risk factors have been described to be involved in the pathogenesis of non-cardia gastric tumors. Smoking has consistently been associated with an increase in gastric cancer risk, especially the non-cardia gastric type [24]. In addition, a low intake of fruit as well as a high body mass index (BMI) has been associated with gastric cancer risk, reflecting the importance of diet in the pathogenesis of this condition [25, 26].



▶ **Fig. 2** Estimated probability of upper gastrointestinal cancer death (esophageal and gastric cancer) for male CRC screening participants in different age groups stratified by finding at colonoscopy (no polyps or high-risk polyps).

▶ **Table 3** Estimated 10-year rate of upper gastrointestinal cancer deaths in female and male screening participants across age groups and grouped by screening colonoscopy finding (no polyp or high-risk polyp).

Male screening participants	Estimated rate of upper gastrointestinal deaths (%)		Female screening participants	Estimated rate of upper gastrointestinal deaths (%)	
	No polyp	High-risk polyp		No polyp	High-risk polyp
50–59 years	0.168 (0.13–0.206)	0.259 (0.155–0.362)	50–59 years	0.065 (0.048–0.082)	0.1 (0.059–0.142)
60–69 years	0.278 (0.214–0.342)	0.428 (0.252–0.603)	60–69 years	0.108 (0.08–0.135)	0.166 (0.097–0.235)
70–79 years	0.532 (0.399–0.665)	0.819 (0.479–1.157)	70–79 years	0.207 (0.153–0.26)	0.318 (0.188–0.448)
80–89 years	0.819 (0.479–1.157)	1.104 (0.675–1.532)	80–89 years	0.43 (0.25–0.608)	0.661 (0.287–1.034)

Esophageal cancer is histologically divided into esophageal adenocarcinoma and esophageal SCC. Although smoking, GERD, and obesity have been linked to tumorigenesis of esophageal adenocarcinoma, alcohol and tobacco consumption is more frequently observed in individuals with esophageal SCC [8, 24]. For both gastric and esophageal carcinoma, men are at higher risk of the disease than women. Despite an overall reduction in global prevalence, sex disparities in gastric cancer incidence have increased from a difference in age-standardized rate (ASR) of 1.86 to 2.20 since 1990 [26]. This trend is ob-

▶ **Table 4** Risk difference for estimated mortality from upper gastrointestinal tumors between men and women as calculated by age category.

	Risk difference (%)	
Age group	**No polyp**	**High-risk polyp**
50–59 years	0.103 (0.082–0.124)	0.159 (0.096–0.22
60–69 years	0.17 (0.134–0.207)	0.262 (0.155–0.368)
70–79 years	0.325 (0.246–0.405)	0.501 (0.291–0.709)
80–89 years	0.389 (0.229–0.549)	0.443 (0.388–0.498)

served in the older population, where the absolute difference in risk increased steadily, while the difference in the population aged < 40 years is negligible [26]. Estimates for esophageal cancer incidence and mortality are four-fold as high for men as for women [27]. However, in a cohort of GERD patients, Barret's esophagus (BE) was not more prevalent in men than in women [28]. For CAG, sex-specific differences are inconsistent, and mostly marginal [15]. This highlights the impact of gender on the occurrence of cancer, but not precancerous conditions.

Detection of high-risk polyps is more frequent in CRC screening participants with a high BMI, high alcohol intake, those with a low physical activity level and those who are smoking [29, 30, 31]. In our cohort, we found that the risk for upper gastrointestinal cancers was higher in CRC screening participants with high-risk polyps. We defined polyps ≥ 10 mm or with high-grade dysplasia in line with the current post-polypectomy guideline from the ESGE [20]. The presence of high-risk polyps in screening participants might reflect unfavorable lifestyle choices linked to malignant conditions besides CRC.

Given the good colorectal screening uptake, it was proposed to supplement screening colonoscopy with gastroscopy. However, in many non-Asian countries, there are still uncertainties about the cost-effectiveness of this approach, given the low incidence of gastric neoplasms. A cost-utility study by Areia and colleagues found that a screening gastroscopy would be cost-effective in countries with intermediate incidence of gastric cancer combined with a screening colonoscopy after a positive FIT compared with a stand-alone gastroscopy screening [17]. The ICER of an add-on gastroscopy every 5 or 10 years was reported to be 15,407€/quality-adjusted life-year (QUALY) and €30,908€/QUALY in a population with an ASR of 13.1 cases per 100,000 person-years [17].

ESGE currently recommends surveillance gastroscopy only in patients with a history of atrophic gastritis [32]. The American Society for Gastrointestinal Endoscopy suggests repeated gastroscopy in high-risk patients, like those with a relevant family history and some ethnic backgrounds [33]. Likewise, screening for esophageal cancer is only recommended for patients with a certain risk profile [11, 12]. However, there is no further characterization of high-risk patients in the general population. Although Barrett's esophagus is a recognized premalignant condition of esophageal adenocarcinoma, only a small proportion of patients might benefit from surveillance endoscopy [34]. For *H. pylori*-positive patients, eradication therapy appears to be more effective in patients without dyspepsia symptoms or those with premalignant gastric conditions such as CAG, intestinal metaplasia, or gastric dysplasia [35]. Aside from age, male sex appeared to be the strongest risk factor for upper gastrointestinal cancer death. The estimated risk difference in upper gastrointestinal cancer mortality between men and women increased in older age groups. In the high-risk polyp group, the risk difference between men and women was larger across all age groups (95% CI 0.159%; 0.096–0.22 and 95% CI 0.443%; 0.388–0.498%) compared with screening participants with no polyps (95% CI 0.103%; 0.082–0.124 and 95% CI 0.389%; CI 0.229%-0.549%).

In this study, we found that patients with high-risk polyps had a higher risk for mortality from tumors of the upper gastrointestinal tract (HR 1.54, 95% CI 1.06–2.25, $P = 0.025$). Age, sex, and presence of high-risk polyps, therefore, might serve as tools for risk stratification to assign patients to screening for upper gastrointestinal diseases. A possible approach for dual colonoscopy and gastroscopy screening could be to perform gastroscopy in patients in whom high-risk polyps were found. Because the classification of high-risk patients is only fully available when the histologic report is available, the additional gastroscopy could be performed when patients are recalled for a surveillance colonoscopy visit. A study of a Taiwanese cohort found that patients with gastric cancer had a significantly lower risk for cancer-specific mortality when a gastroscopy had been performed recently, as compared with those for whom the examination dated back more than 5 years [36]. This demonstrates that a single gastroscopy has an impact on patient outcome, due to possible early detection of neoplastic lesions or premalignant conditions. Further studies are needed that determine the efficacy in specific risk groups and Western populations.

Our study has limitations. We could not obtain comorbidities or common risk factors for upper gastrointestinal malignancy in this cohort such as smoking status, BMI, or alcohol consumption in the screening participants. This would have helped to further stratify risk for upper gastrointestinal conditions based on a risk score itself, instead of using high-risk polyps as the surrogate. Prospective studies in CRC screening participants that assess common risk factors are needed [3, 4, 5, 6, 7]. In addition, symptoms in screening participants were not available. Previous studies have demonstrated that symptoms such as dysphagia can help detect upper gastrointestinal malignancy in a primary care population [37]. Our assessment of cancer mortality outcomes relied on the location of the primary tumor according to the ICD-10 classification. Therefore, we did not stratify by tumor type, and have no information on the underlying histology of the tumor. The entity of the tumor might give important insights for further subgroup analyses. For example, the risk of esophageal adenocarcinoma in this cohort might differ from that for SCC, given that common risk factors differentially affect both conditions [37]. Likewise, the risk for cardia and non-cardia gastric cancer is differentially attributed to an infection with *H. pylori*. Because we could only link the data to the ICD-10 code death registry, we have no in-

formation about cancer stage at diagnosis of CRC. The strengths of this study is its size because this is the first large study of a CRC screening population investigating mortality from upper gastrointestinal cancers. We were able to link mortality data from 349,856 individuals.

Conclusions

We conclude that in a CRC screening cohort, some participant characteristics are associated with mortality from upper gastrointestinal tumors. Further studies will examine modifiable risk factors that lead to the increasing risk of upper gastrointestinal cancers in high-risk polyp participants and whether these features will be useful to select individuals who need preventive measures in the upper gastrointestinal tract.

Conflict of Interest

MT has advised for Abbvie, Albireo, BiomX, Boehringer Ingelheim, Falk, Gilead, Genfit, Hightide, Intercept, Jannsen, MSD, Novartis, Phenex, Pliant, Regulus, Siemens, and Shire, has received grants/research support from Albireo, Alnylam, Cymabay, Falk Pharma, Gilead, Intercept, MSD, Takeda, and UltraGenyx, has received speaker's fees form BMS, Falk Foundation, Gilead, Intercept, Madrigal, MSD and Roche, has received travel grants from AbbVie, Falk Foundation, Gilead, Intercept, Janssen and Roche, the Medical Universities of Graz and Vienna have filed patents on medical use of norUDCA and is listed as co-inventor. All other authors have no conflict of interest to declare.

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