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# Adenocarcinoma of the esophagogastric junction: characteristics of female patients and young adult patients based on a 12-year retrospective and prospective multicenter clinicoepidemiological cohort study in Japan

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## Abstract

**Background** Adenocarcinoma of the esophagogastric junction (AEGJ) is most common in men and the elderly, but the disease is becoming more common in female and young adult persons. We have investigated the clinicoepidemiological characteristics of female and young adult patients with AEGJ and the 12-year trends in the Kurashiki area for young adult patients with AEGJ.

**Methods** Patients diagnosed with AEGJ in 12 hospitals between January 2008 and December 2019 were included in this study. Patients were divided into three groups by age (young adult [≤50 years], middle-aged [51 to 70 years], and elderly [>70 years]). Factors associated with AEGJ such as obesity, smoking, hiatal hernia and male, which were reported in our previous study, were identified.

**Results** One hundred and eighty-eight AEGJ patients, including 36 females and 20 young adults, were characterized. There was no significant change in the annual incidence of AEGJ among female ($p$=0.078) and young adult patients ($p$=0.89). Female patients without any associated factors, accounting for 53% (19/36) of the female patients and young adult patients, had significantly more histologically undifferentiated cancers than patients with at least one associated factor (58% [11/19] vs. 30% [50/169], $p$=0.025) and middle-aged and elderly patients (60% [12/20] vs. 30% [25/83] vs. 28% [24/85], $p$ =0.026). Smoking was significantly less common in women than in men (8% [3/36] vs. 57% [87/152], $p < 0.01$). There were no significant differences between ages in the proportions of these associated factors.

**Conclusions** Histologically undifferentiated AEGJ cancers were more frequent in female patients without any associated factors and in young adult patients. Factors associated with AEGJ may differ between women and men, but they are similar in young adults and older adults. No increase in young adult patients with AEGJ was observed in the 12-year study.

**Keywords** Adenocarcinoma of the esophagogastric junction, Esophageal adenocarcinoma, Epidemiology, Female patients, Young adult patients

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## Background

Esophageal adenocarcinoma (EAC), including adenocarcinoma of the esophagogastric junction (AEGJ), occurs less frequently in Japan than in Western countries [1, 2]. However, in Japan as well as in Western countries, the incidence of AEGJ has been increasing [3, 4]. EAC is mainly associated with Barrett's esophagus (BE), gastroesophageal reflux disease (GERD), obesity, and smoking [5–7]. Guidelines of The American College of Gastroenterology recommend screening for BE in patients who have chronic GERD symptoms and at least three of the following risk factors: male, age >50 years, Caucasian, smoking, obesity, and a history of BE or EAC in a first-degree relative [8]. In contrast, an Asia-Pacific consensus states that BE does not deserve screening because of its low prevalence in the region [9]. In Japan, surveillance methods for AEGJ are not well established, and guidelines for evaluating high-risk patients are needed [9, 10]. Through large clinicoepidemiological studies, factors associated with AEGJ in Japanese patients, such as obesity, smoking, hiatal hernia, and male, have been identified, and they are similar to those of EAC patients in Western countries [11]. Thus, studies in Western countries have revealed that individuals with these risk factors can benefit from screening for early detection of EAC [12, 13]. Because EAC, including AEGJ is characterized by a predominantly male or elderly population [2, 6, 7, 11–13], screening can detect AEGJ at an early stage in these cohorts; on the other hand, a proportion of female patients and young adult patients may not be screened, making early detection in them difficult. Attention to esophageal symptoms in this population may need increased attention.

In recent years, the epidemiology of AEGJ in Japan and perhaps elsewhere, especially in women and young adults, may be changing because of major changes in the environment and society, such as the westernization of the diet and the decrease in *Helicobacter pylori* infection [14, 15]. Matsuno et al. [3] reported an increase in the incidence of EAC among women, although not as much as among men, between 1985 and 2014 in Osaka Prefecture. According to a study using data from three population-based cancer registries in Japan between 1993 and 2014, the incidence of EAC increased, especially in men aged 40-59 years [16]. In a large single-center, retrospective study by Sawas et al. [17], from 2009 to 2012 in the United States, young patients (≤50 years of age) with EAC accounted for about 15% of EAC. Lifestyle changes and rising obesity among women and young people may contribute to this epidemiological shift. However, there are few studies on the characteristics of female patients and young adult patients with AEGJ because of its low prevalence.

The aims of the study were to investigate the clinicoepidemiological characteristics of female and young adult AEGJ patients and the 12-year trends in the Kurashiki area for young adult patients with AEGJ.

## Methods

### Study design, setting, and participants

This multicenter study was conducted by the Kurashiki GERD Research Association, which consists of gastroenterologists from 12 hospitals, including one university hospital and 11 regional hospitals, in seven cities and three towns in western Okayama Prefecture. Esophagogastroduodenoscopy (EGD) is regularly performed at each hospital. Some patients voluntarily visited one of the 12 hospitals for digestive symptoms or health checkups, while others were referred by general practitioners; this inclusion of patients from multiple routes of entry helped avoid selective accumulation of cases at referral centers. Since over 90% of endoscopies in this area are performed at these 12 hospitals, this study is considered population based. During the period of this study, from 2008 to 2019 [18], the overall population gradually decreased from 793,000 in 2008 to 764,000 in 2019, but there was no change in the male-to-female ratio (0.92 to 0.93) and age distribution.

Data on AEGJ patients evaluated by EGD between January 01, 2008, and December 31, 2019 (12 years) were collected biennially through a questionnaire. All AEGJ patients newly identified during the study period were followed prospectively from January 01, 2009, to December 31, 2020, with the median follow-up period of 27 months (range: 1-145 months). Based on the results of EGD, endoscopic ultrasonography, computed tomography, and positron emission tomography/computed tomography, a treatment strategy was established according to guidelines edited by the Japan Esophageal Society [19], taking into account the patient's quality of life. The follow-up period was defined as the time from diagnosis to death from any cause or last hospital visit.

### Data collection

A survey form recorded the number of newly detected AEGJ cases and the patients' clinical characteristics was distributed to each institution. The content of the questionnaire used in this study was the same as that of the questionnaire used in our previous studies [11]. The study investigators provided detailed information from medical records, endoscopy reports, computed tomography findings, positron emission tomography findings, and pathology results of the cases during the 12-year study period. Patients with a prior diagnosis of AEGJ were excluded. Histologic diagnoses were made from endoscopic biopsies, endoscopic submucosal

dissection, or surgical resection by a certified pathologist at each hospital. Patients with benign esophageal disease, squamous cell carcinoma, neuroendocrine tumors, or metastatic lesions were excluded. BE was defined as columnar epithelium extending from the stomach to the esophagus in a continuous manner [19]. AEGJ was classified into three types according to Siewert's classification [20]: type I (adenocarcinoma of the distal esophagus, with tumor center 1-5 cm above the anatomic EGJ); type II (true carcinoma of the cardia with tumor center 1 cm above and 2 cm below the junction); and type III (subcardial carcinoma, with tumor center 2-5 cm below the EGJ, and infiltration of the EGJ and distal esophagus from below). In this study, types I and II AEGJ were defined as AEGJ and included in the study, whereas type III was defined as gastric cancer and excluded from the study.

### Characteristics of female AEGJ patients and young adult AEGJ patients

The patients were divided into three groups by age: ≤50 years of age defined as the young adults, 51 to 70 years of age defined as middle-aged, and >70 years of age defined as the elderly [17].

The following patient characteristics, based on our previous studies [11], were chosen for analysis: sex; age; symptoms at diagnosis; obesity (body mass index≥25 kg/m$^2$); smoking history (>20 pack-years); hiatal hernia; atrophy of the gastric mucosa according to the Kimura-Takemoto classification [21]; location (Siewert's type I or II); depth of cancer invasion (T1, invasion into the intra- or submucosa or ≥T2, invasion into the muscularis propria or deeper); and histological classification. In histological classification, undifferentiated type was defined as poorly differentiated adenocarcinoma and/or signet ring cell carcinoma; if even a little undifferentiated component was present, the tumor was considered undifferentiated type. In specimens from endoscopic submucosal dissection or surgery, the depth of cancer invasion was determined by pathological examination; in patients who did not undergo either of these resections, invasion was estimated clinically. Disease-specific survival, overall survival, and 5-year survival were calculated, and mortality was prospectively ascertained from questionnaire data. Long-term follow-up data, including survival data and cause of death, were collected retrospectively from each hospital's medical records.

This study was approved by the research ethics committee of the Kurashiki Central Hospital (approval number 2190), and informed consent was acquired with the opt-out method. All authors had access to the clinical data and approved the final version of the manuscript.

### Statistical analysis

Values are reported as means±standard error of the mean. Student's t-test or Mann-Whitney *U* test was used to compare the mean values of two groups. Chi-square test or Fisher's exact tests was used to compare percentages and assess the independence of qualitative variables between two groups or among three groups. The mean annual incidence of new cases (cases per 100,000 person years) was calculated from the number of AEGJ cases reported during the 12-year period, and the time trend of the incidence was assessed using the Cochrane-Armitage trend test. Disease-specific survival in each group was plotted with a Kaplan-Meier curve and compared by use of the log-rank test. Moreover, overall and 5-year survival rates were determined using the Kaplan-Meier method.

A $p$-value of <0.05 was considered statistically significant. EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), a graphic user interface for R (The R Foundation for Statistical Computing, Vienna, Austria), was used for statistical analysis.

## Results

### Patient characteristics

One hundred eighty-eight new cases of AEGJ were detected during the 12-year study period, of which 152 (81%) were men, with a mean age at diagnosis of 68.3±12.5 (range: 38-97) years, with a preponderance of men and the elderly, and 95 (51%) had no symptom at the diagnosis. Of the 188 cases, 20 (11%) were Siewert's type I AEGJ (including 2 cases of long segment BE), and 168 (89%) were Siewert's type II. Eighty-eight (47%) were T1, and 100 (53%) were ≥T2 (Table 1). No increasing trend in the annual incidence of new cases was noted ($p$=0.96) (Fig. 1).

### Characteristics of AEGJ in female patients

Women accounted for 36 (19%) of the included patients. The ages of female and male subjects were normally distributed. Mean age was 69.6±14.0 years for women and 68.0±12.2 years for men ($p$=0.49) (Table 2). There was no significant change in the annual incidence of females ($p$=0.078) and males ($p$=0.43) enrolled during the study period (Fig. 1). Smoking was much less common in women than in men (8% [3/36] vs. 57% [87/152], $p$ < 0.01). Between women and men, obesity (22% [8/36] vs. 34% [51/152], $p$=0.26), hiatal hernia (25% [9/36] vs. 41% [62/152], $p$=0.12), and Siewert's type I (6% [2/36] vs. 12% [18/152], $p$=0.38) were not significantly different. Histologically undifferentiated cancers were not significantly different between in women and in men (44% [16/36] vs. 30% [45/152], $p$=0.13). The depth of cancer invasion T1 was similar between women and men (50% [18/36] vs.

**Table 1** Characteristics of all patients

| Characteristics | All *n*=188 |
|---|---|
| Sex, *n* (%) | |
| Male | 152 (81) |
| Female | 36 (19) |
| Age at diagnosis, mean±SD, *yr* | 68.3±12.5 (range: 38-97) |
| Young adult (age ≤50 years), *n* (%) | 20 (11) |
| Symptoms at diagnosis, *n* (%) | |
| Absent | 95 (51) |
| Present | 84 (45) |
| Dysphagia/vomiting | 30 (16) |
| Heartburn/regurgitation | 25 (13) |
| Epigastric pain | 14 (7) |
| Anorexia/weight loss | 7 (4) |
| Anemia/bleeding | 3 (2) |
| Others | 5 (3) |
| Missing | 9 (5) |
| Siewert's type, *n* (%) | |
| Type I | 20 (11) |
| Type II | 168 (89) |
| Associated factors, *n* (%) | |
| Obesity (BMI≥25) | 59 (31) |
| Smoking | 90 (48) |
| Hiatal hernia | 71 (38) |
| Non-atrophic gastric mucosa (C1), *n* (%) | 92 (49) |
| Histology: undifferentiated type, *n* (%) | 61 (32) |
| Undifferentiated type / T1, *n* (%) | 12/88 (14) |
| Undifferentiated type / ≥T2, *n* (%) | 49/100 (49) |
| Depth of cancer invasion, *n* (%) | |
| T1 | 88 (47) |
| ≥T2 | 100 (53) |

*BMI* body mass index

46% [70/152], $p$=0.81) (Table 2). There was no significant difference in disease-specific survival between the sexes ($p$=0.74) (Fig. 2).

### Characteristics of young adults

Of the 188 patients, 20 (11%) were young adults, 83 (44%) were middle-aged, and 85 (45%) were elderly (Table 3). There was no significant change in the annual incidence of AEGJ among young adult patients during the study period ($p$=0.89) (Fig. 3). All three age groups were predominantly male, with similar, statistically non-significant proportions of obesity, smoking, and hiatal hernia among the three groups. Of the 20 young adult patients, 7 had body mass index of 25 or more, 9 were smokers, and 8 had hiatal hernias. Non-atrophic gastric mucosa was significantly more common in young adult patients (90% [18/20]) than in middle-aged (57% [47/83]) and elderly (36% [31/85]) patients ($p$<0.01). Histologically undifferentiated cancers were also more common in the young adult patients (60% [12/20]) than in the middle-aged (30% [25/83]) and elderly (28% [24/85]) patients ($p$=0.026). The depth of cancer invasion ≥T2 was not significantly different between in young adult patients and in middle-aged and elderly patients (70% vs. 52% vs. 51%, $p$=0.29). The proportion of undifferentiated cancer among ≥T2 was not significantly different between young adult patients and middle-aged and elderly patients (79% vs. 47% vs. 42%, $p$=0.057) (Table 3). Five-year survival rates were 66.7%, 65.6%, and 48.3% in the young adult, middle-aged, and elderly groups, respectively. There was no statistically significant difference in disease-specific survival between the three age groups ($p$=0.11) (Fig. 4).

### Characteristics of patients without previously reported associated factors for AEGJ

Of the 188 patients, 19 (10%) had no associated factors (obesity, smoking, hiatal hernia and male). All these patients were women, accounting for 53% (19/36) of the female patients. The proportion of histologically undifferentiated cancers was significantly more in patients without any associated factors than in patients with at least one associated factor (58% [11/19] vs. 30% [50/169], $p$=0.025). However, there was no significant difference in the depth of cancer invasion ≥T2 between the two populations (63% vs. 52%, $p$=0.50) (Table 4).

Various treatments were used. Of the 188 patients with AEGJ, 60 underwent endoscopic submucosal resection and 95 underwent surgical resection. Only one patient in the young adult group received best supportive care, compared to 17 patients in the middle-aged and elderly groups (Table 5).

## Discussion

The major findings of this study were that young adult patients with AEGJ had significantly more histologically undifferentiated cancers than older patients, and that female patients without any associated factors such as obesity, smoking, and hiatal hernia also had significantly more undifferentiated cancers than patients with at least one associated factor. Although histologically undifferentiated cancers were more frequent in female and young adult patients, these patients may have been excluded from screening.

In addition, although this study was conducted over 12 years, the incidence of AEGJ patients did not increase in the Kurashiki area. Furthermore, because an increase in AEGJ in young people may lead to an increase in AEGJ in the future, we focused on young adults and found that young adult patients, like older patients, were mostly male and often had associated factors such as smoking

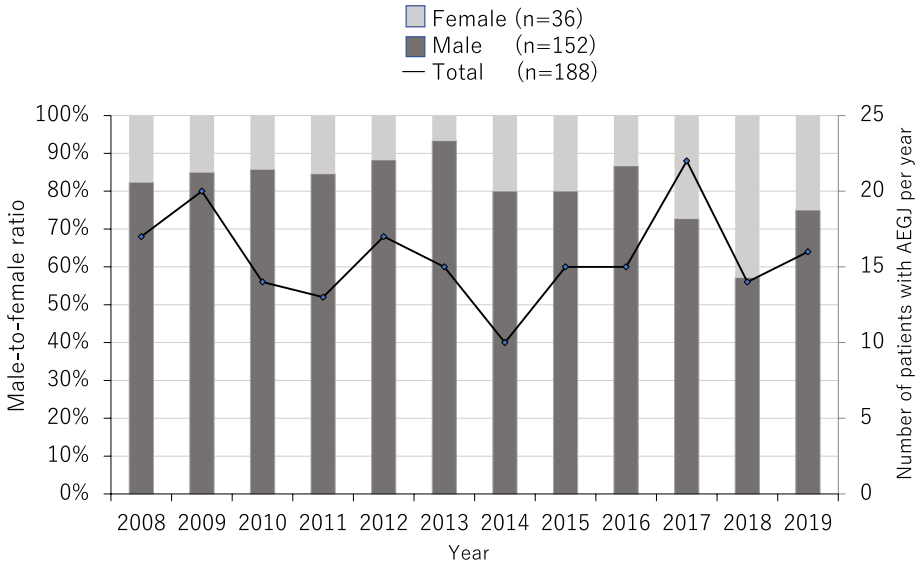


**Fig. 1** The male-to-female ratio and the number of patients with AEGJ over a 12-year period. No increasing trend in the annual incidence of new cases was noted (total: $p$=0.96, female: $p$=0.078, male: $p$=0.43, respectively, Cochrane-Armitage trend test). AEGJ, adenocarcinoma of the esophagogastric junction

**Table 2** Characteristics of patients by sex

| Characteristics | Female *n*=36 (19%) | Male *n*=152 (81%) | *p*-value |
|---|---|---|---|
| Age at diagnosis, mean±SD, *yr* | 69.6±14.0 | 68.0±12.2 | 0.49 |
| Siewert's type, *n* (%) | | | 0.38 |
| Type I | 2 (6) | 18 (12) | |
| Type II | 34 (94) | 134 (88) | |
| Associated factors, *n* (%) | | | |
| Obesity (BMI≥25) | 8 (22) | 51 (34) | 0.26 |
| Smoking | 3 (8) | 87 (57) | < 0.01 |
| Hiatal hernia | 9 (25) | 62 (41) | 0.12 |
| Non-atrophic gastric mucosa (C1), *n* (%) | 19 (53) | 73 (48) | 0.74 |
| Histology; undifferentiated type, *n* (%) | 16 (44) | 45 (30) | 0.13 |
| Depth of cancer invasion, *n* (%) | | | 0.81 |
| T1 | 18 (50) | 70 (46) | |
| ≥T2 | 18 (50) | 82 (54) | |

*BMI* body mass index

and obesity. These findings suggest that AEGJ is a cancer caused by environmental influences.

It is unclear why undifferentiated cancer is more frequent in female patients without any associated factors and young adult patients. However, two types of AEGJ have been reported [22, 23]: Nunobe *et al.* [23] reported that AEGJ with and without intestinal metaplasia in the background mucosa differed in clinicopathological features, including the presence of undifferentiated components, phenotypic expression, and lymph node metastasis, and that AEGJs without intestinal metaplasia had undifferentiated components more frequently than those with intestinal metaplasia. Furthermore, it was shown that AEGJs without intestinal metaplasia were more frequent in patients under the age of 60 [23]. Although this study did not examine the presence or absence of intestinal metaplasia, a possible reason why undifferentiated cancer is more common in female patients without any associated factors

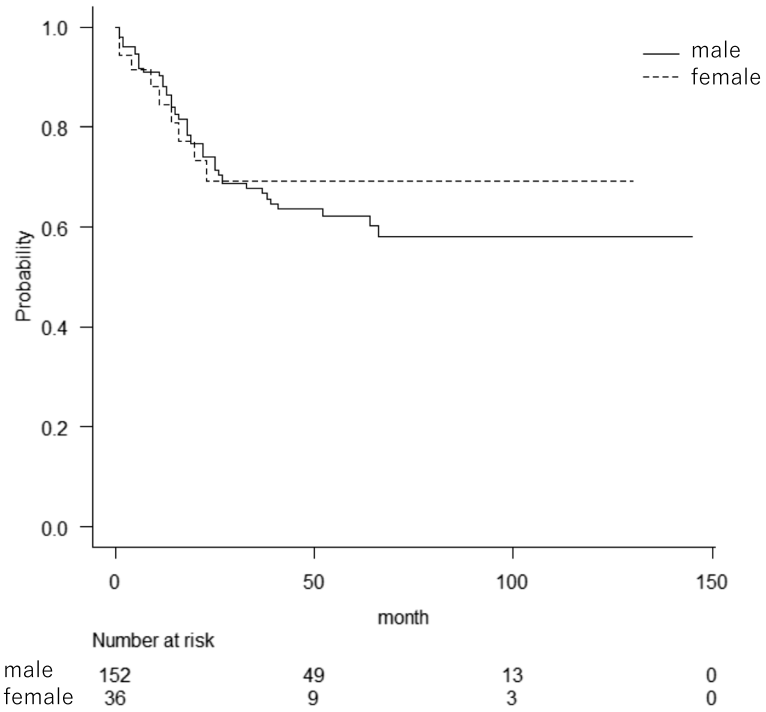


**Fig. 2** Disease-specific survival time in months comparing female and male patients. There was no significant difference in disease-specific survival between the sexes ($p$=0.74, log-rank test)

**Table 3** Characteristics of young adult patients compared to middle-aged, and elderly patients

| Characteristics | Young adult group *n*=20 (11%) | Middle-aged group *n*=83 (44%) | Elderly group *n*=85 (45%) | *p*-value |
|---|---|---|---|---|
| Sex, *n* (%) | | | | 0.50 |
| Male | 15 (75) | 70 (84) | 67 (79) | |
| Female | 5 (25) | 13 (16) | 18 (21) | |
| Siewert's type, *n* (%) | | | | 0.32 |
| Type I | 3 (15) | 11 (13) | 6 (7) | |
| Type II | 17 (85) | 72 (87) | 79 (93) | |
| Associated factors, *n* (%) | | | | |
| Obesity (BMI≥25) | 7 (35) | 30 (36) | 22 (26) | 0.33 |
| Smoking | 9 (45) | 46 (55) | 35 (41) | 0.16 |
| Hiatal hernia | 8 (40) | 32 (39) | 31 (36) | 0.93 |
| Non-atrophic gastric mucosa (C1), *n* (%) | 18 (90) | 47 (57) | 31 (36) | < 0.01 |
| Histology; undifferentiated type, *n* (%) | 12 (60) | 25 (30) | 24 (28) | 0.026 |
| Undifferentiated type / ≥T2, *n* (%) | 11/14 (79) | 20/43 (47) | 18/43 (42) | 0.057 |
| Depth of cancer invasion, *n* (%) | | | | 0.29 |
| T1 | 6 (30) | 40 (48) | 42 (49) | |
| ≥T2 | 14 (70) | 43 (52) | 43 (51) | |

*BMI* body mass index

and in young adult patients may be that these patients have more AEGJs without intestinal metaplasia.

There was no significant difference in the depth of cancer invasion and survival between the young adult, middle-aged, and elderly patients; however, numerically more patients in the young adult group than in the older groups had depth of cancer invasion ≥T2 at the time of diagnosis. There are three possible reasons for

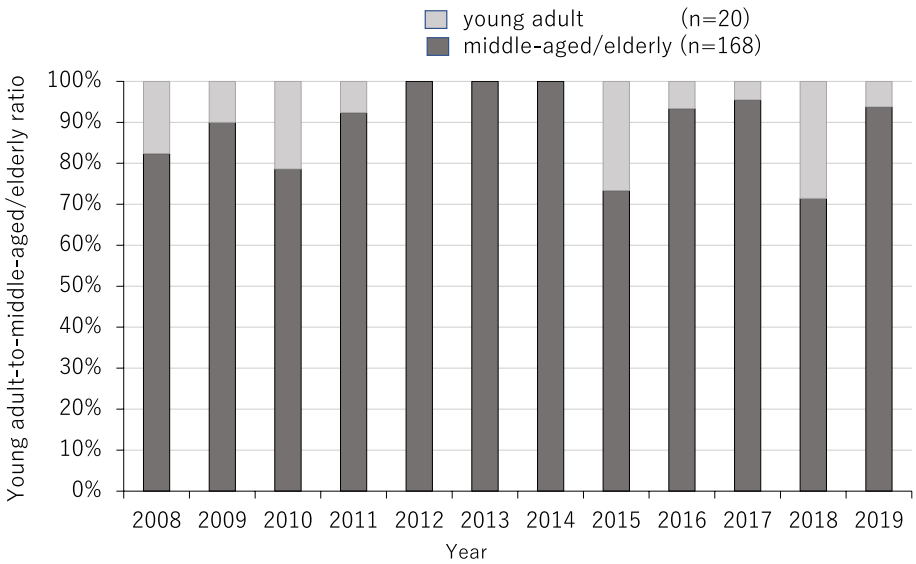


**Fig. 3** The young adult-to-middle-aged/elderly ratio over a 12-year period. No increasing trend in the annual incidence of new cases was noted (young adult group: $p$=0.89, Cochrane-Armitage trend test). AEGJ, adenocarcinoma of the esophagogastric junction

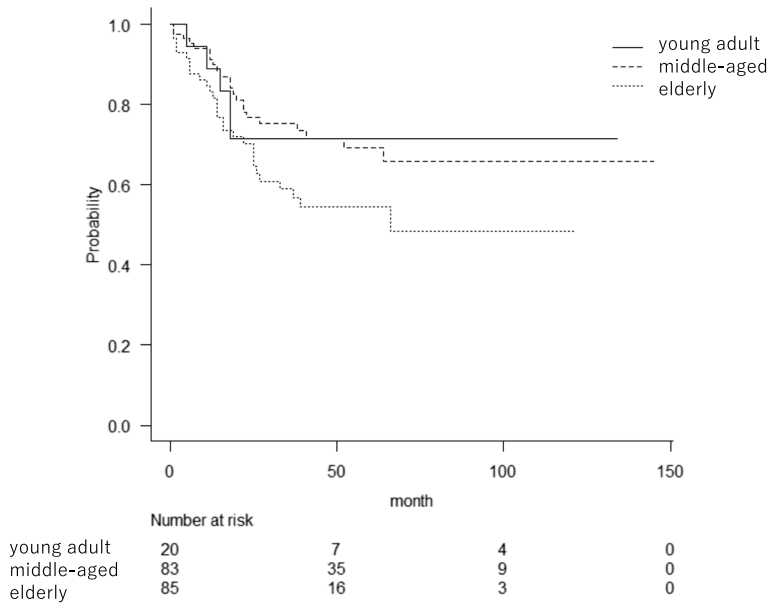


**Fig. 4** Disease-specific survival time in months comparing young adult, middle-aged, and elderly patients. There was no significant difference in disease-specific survival among the three age groups ($p$=0.11, log-rank test)

this difference. First, people aged ≤50 years have fewer screening opportunities than those aged >50 years, and young people often do not seek medical attention until symptoms appear. Second, young adults have more undifferentiated cancers, which may invade more deeply. Third, different genetic factors are involved in the three groups [7, 24, 25]. A multicenter retrospective study by Ishihara et al. [26] revealed that poorly differentiated tumor was an independent predictor of metastasis of EAC or AEGJ. Furthermore, Sawas et al. [17] reported that young adult patients with EAC had lower rates of BE and intestinal metaplasia than older patients, and that young adult patients had more advanced tumors at presentation and shorter survival. Since young adults are usually not eligible for screening, AEGJ in them is rarely detected during routine screening. Accordingly, detecting

**Table 4** Characteristics of patients without any associated factors

| Characteristics | Patients without any associated factors *n*=19 (10%) | Patients with at least one associated factor *n*=169 (90%) | *p*-value |
|---|---|---|---|
| Sex, *n* (%) | | | |
| Male | 0 | 152 (90) | |
| Female | 19 (100) | 17 (10) | |
| Siewert's type, *n* (%) | | | 0.70 |
| Type I | 1 (5) | 19 (11) | |
| Type II | 18 (95) | 150 (89) | |
| Associated factors, *n* (%) | | | |
| Obesity (BMI≥25) | 0 | 59 (35) | |
| Smoking | 0 | 90 (53) | |
| Hiatal hernia | 0 | 71 (42) | |
| Non-atrophic gastric mucosa (C1), *n* (%) | 6 (32) | 86 (51) | 0.18 |
| Histology; undifferentiated type, *n* (%) | 11 (58) | 50 (30) | 0.025 |
| Depth of cancer invasion, *n* (%) | | | 0.50 |
| T1 | 7 (37) | 81 (48) | |
| ≥T2 | 12 (63) | 88 (52) | |

*BMI* Body mass index

**Table 5** Treatment strategy for AEGJ by depth of cancer invasion and age

| Depth of cancer invasion | ESD with/without surgical resection | Surgical resection with/without adjuvant chemotherapy | Chemotherapy with/without radiotherapy | BSC |
|---|---|---|---|---|
| T1 | | | | |
| Young adult group, *n (%)* | 6 (100) | 0 | 0 | 0 |
| Middle-aged/elderly groups, *n (%)* | 54 (66) | 28 (34) | 0 | 0 |
| ≥T2 | | | | |
| Young adult group, *n (%)* | 0 | 9 (64) | 4 (29) | 1 (7) |
| Middle-aged/elderly groups, *n (%)* | 0 | 58 (67) | 11 (13) | 17 (20) |
| Total, *n (%)* | 60 (32) | 95 (51) | 15 (8) | 18 (9) |

*AEGJ* adenocarcinoma of the eophagogastric junction, *ESD* endoscopic submucosal resection, *BSC* best supportive care

AEGJ early in young adults is especially important for the success of curative resection in them. Although there was no apparent increase in young adult AEGJ patients during the 12-year study period, non-atrophic gastric mucosa was significantly more common in young adults than in the older patients. These findings suggest that AEGJ associated with the non-atrophic gastric mucosa is more common in young adults than AEGJ associated with atrophic gastritis due to *H. pylori.* This is one of two distinct etiologies of AEGJ that have been reported [27, 28]. Given the decrease in *H. pylori* infection [14, 15] and the associated increase in non-atrophic gastric mucosa, future trends in AEGJ among young adults should be carefully monitored.

Another noteworthy point in this study is that patients without any associated factors for AEGJ accounted for 53% of the female patients. Furthermore, this study is characterized by a much lower prevalence of smoking among women than among men (8% vs 57%). Given that smoking prevalence among Japanese women is one-fourth that of Japanese men [29], it is possible that the incidence of AEGJ in women is not as influenced by smoking as it is in men. On the other hand, a pooled analysis of the association between smoking and EAC in white men and women revealed that the risk of EAC in sex-specific analyses was not significantly different [30]. This difference from ours may be due to race. A modeling study [31] found that the incidence of EAC was much lower in women of all ages with weekly GERD than in men without weekly GERD, suggesting that risk factors for AEGJ may differ by sex. The reason for this sex difference in the incidence of EAC is unclear; but two recent studies have suggested that sex hormones are involved [32, 33], whereas a prospective cohort study conducted in

the United Kingdom found no association between circulating sex hormones and EAC [34].

In contrast, there were no significant differences by age in the proportions of associated factors such as obesity, smoking and hiatal hernia, suggesting that the factors associated with AEGJ are similar in young adults and older people. Saito et al. [16] reported that the increased incidence of EAC among young men was due to the increased rate of obesity in men and the decreased rate of *H. pylori* infection in Japan, which supports our results. Importantly, *H. pylori* infection has little effect on the incidence of AEGJ in young adults, but obesity, smoking, and hiatal hernia may be involved in the development of AEGJ even in young adults. Because some patients with these associated factors develop AEGJ, EGD as a screening for AEGJ may detect AEGJ in people with these associated factors, especially in young adults.

This study has several limitations. First, the number of AEGJ cases was small. However, we believe that this study is valuable because it is a multicenter study of a low-incidence disease over a 12-year period. Since the incidence of AEGJ is still low in Japan, especially among women and young adults, larger, longer-term prospective studies should be conducted to accumulate more cases. Second, the definition of AEGJ in the international literature is historically complex; AEGJ shares important epidemiological features with EAC, with several important risk factors being associated with both conditions [35]. Although the distinction between AEGJ and EAC is not clear, some studies combine these two cancers into a single category [30] or aggregate EAC patients on the basis of Siewert's classification [24]. EAC occurs primarily in the lower third of the esophagus, with approximately three quarters of all adenocarcinomas being found in the distal esophagus [5]. Since we defined AEGJ as Siewert's type I and II and excluded type III, AEGJ in this study can be considered EAC in many aspects, including epidemiology and risk factors. Third, obesity, smoking, hiatal hernia, and male were defined as factors associated with AEGJ on the basis of our previous study [11]. Because these factors have been recognized as factors associated with EAC or risk factors for EAC in other studies [12, 13], we considered it appropriate to use them as factors associated with AEGJ. Fourth, we examined gastric mucosal atrophy instead of *H. pylori* infection. Since bile reflux into the gastric antrum can cause inflammation and mucosal atrophy with or without *H. pylori* infection, C-1 was classified as "non-atrophic gastric mucosa" according to the Kimura-Takemoto classification [21]. Finally, if even a few undifferentiated components were histologically present, it was classified as undifferentiated cancer. Because unresectable advanced cancer was diagnosed histologically only by biopsy, the possibility that undifferentiated components were present in other parts of the tumor cannot be ruled out.

## Conclusions

Histologically undifferentiated cancers were more frequent in female patients with AEGJ without any associated factors and in young adult patients with AEGJ. Factors associated with AEGJ may differ between women and men, but may be similar in young adults and older adults. No increase in young adult patients with AEGJ was observed in the 12-year study.

#### Abbreviations

| | |
|---|---|
| EAC | Esophageal adenocarcinoma |
| AEGJ | Adenocarcinoma of the esophagogastric junction |
| BE | Barrett's esophagus |
| GERD | Gastroesophageal reflux disease |
| EGD | Esophagogastroduodenoscopy |

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#### Authors' contributions

All authors contributed to the study conception and design. Conceptualization: KM, NM and KH. Data curation: KM, NM, TW and YS. Data analysis: KM, NM and KH. Writing-original draft preparation: KM; writing-review and editing: NM, MM and KH. Supervision: KH. All authors reviewed the manuscript.

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#### Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

## Declarations

#### Ethics approval and consent to participate

Informed consent was obtained via an opt-out option on the website. This study was conducted after obtaining approval from the research ethics committee of the Kurashiki Central Hospital (approved number 2190) by conducting the opt-out method and excluding those who rejected. None of the participants rejected.

#### Consent for publication

Not applicable.

#### Competing interests

The authors declare no competing interests.

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