RESEARCH ARTICLE

Editorial Process: Submission:09/11/2023 Acceptance:04/07/2024

Chronological Trend of Opportunistic Endoscopic Screening for Gastric Cancer and Atrophic Gastritis

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Abstract

Background: Opportunistic endoscopic screening for gastric cancer was initiated in 2004 at our institute. We investigated chronological trends in gastric cancer detection rates based on individual characteristics and atrophic gastritis prevalence. **Methods:** Overall, 15,081 asymptomatic individuals aged ≥40 years without a medical history of gastric cancer underwent first-time esophagogastroduodenoscopy in our institute between February 2004 and December 2017. We retrospectively investigated individual characteristics and endoscopic diagnoses by period (early period: 2004–2007, middle period: 2008–2012, and late period: 2013–2017), clarified the long-term detection rate and the characteristics of endoscopic screening-detected gastric cancer, and evaluated the relationship between gastric cancer and atrophic gastritis. **Results:** Gastric cancer detection rates in the early, middle, and late periods were 1.01% (76/7,503, men/women: 4,360/3,143, average age: 59.4 years, prevalence of atrophic gastritis: 72%), 0.69% (40/5,820, men/women: 3,668/2,152, average age: 56.8 years, prevalence of atrophic gastritis: 48%), and 0.46% (8/1,758, men/women: 1,083/675, average age: 58.7 years, prevalence of atrophic gastritis: 37%), respectively. Multivariate analysis revealed that male sex (odds ratio 1.92, 95% confidence interval 1.28-2.95), age ≥75 years (2.73, 95% CI 1.32-5.05), and atrophic gastritis (C1-C3: 2.21, 1.36-3.73, O1-O3: 5.36, 3.17-9.30) were significantly associated with the incidence of gastric cancer. **Conclusions:** The gastric cancer detection rate and atrophic gastritis prevalence have decreased over time. However, continuing endoscopic screening is important, especially for those at a high risk of developing gastric cancer complicated by severe atrophic gastritis.

Keywords: Gastric cancer- atrophic gastritis- endoscopy- upper gastrointestinal endoscopy- screening

Asian Pac J Cancer Prev, **25 (4)**, 1247-1255

Introduction

The incidence and mortality of gastric cancer in Eastern Asia are the highest worldwide, with more than half of the new cases and deaths occurring in Eastern countries [1]. Gastric cancer screening is effective in detecting gastric cancer at an early stage, where symptoms are minimal. Early treatment is expected to reduce gastric cancer mortality [2, 3]. In Japan, gastric cancer screening using upper gastrointestinal X-ray examination (UGI screening) began in the 1960s and has been introduced as a national program since 1983 [4-7]. The Japanese guidelines for gastric cancer screening recommended the use of UGI screening in 2005 based on several case-control and cohort studies [6-9]. In 2015, gastric cancer screening using endoscopy was included in the Japanese Guidelines for Gastric Cancer Screening [10]. The effectiveness of gastric cancer screening using endoscopy was based on a nested case-control study using data from the Korean National Cancer Screening Program for gastric cancer since 2002, which showed a 47% reduction in gastric cancer mortality in patients who underwent endoscopic screening compared with patients who had never been screened [11]. Furthermore, in 2016, gastric cancer screening was introduced into population-based screening in Japan and endoscopic screening was conducted in 48.0% (817/1,701) of municipalities [12]. Thus, gastric cancer screening using endoscopy may play an important role in reducing gastric cancer-related mortality in the future.

Opportunistic screening using endoscopy for gastric cancer was initiated in 2004 at our screening center, and all procedures were conducted by highly experienced endoscopists. Daily endoscopic examinations revealed

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a decrease in gastric cancer and atrophic gastritis caused by Helicobacter pylori (*H. pylori*) infection over time. In addition, *H. pylori* infection has been reported to decrease in younger adults [13, 14]. Therefore, we clarified the long-term results of the detection rate and characteristics of gastric cancer detected by endoscopic screening during this period and additionally evaluated the relationship between gastric cancer and atrophic gastritis, which is a risk factor for gastric cancer [15-17]. This study aimed to clarify the chronological trends in the detection rate and characteristics of gastric cancer and the relationship between atrophic gastritis and gastric cancer, using long-term data from asymptomatic individuals who underwent high-quality endoscopic screening.

Materials and Methods

Study participants and design

This study was conducted using a database of 15,081 asymptomatic individuals aged 40 years and above who underwent first-time opportunistic screening using esophagogastroduodenoscopy (EGD) at the Cancer Screening Center of the National Cancer Center in Tokyo, Japan, from February 2004 to December 2017. Individuals with a medical history of gastric cancer were excluded. We retrospectively investigated the endoscopic diagnoses using endoscopic electronic records according to three periods (early period: 2004–2007, middle period: 2008–2012, and late period: 2013–2017). We determined the long-term detection rate of gastric cancer and evaluated the relationship between gastric cancer and atrophic gastritis. This study was approved by the Ethics Committee for Clinical Research of the National Cancer Center of Tokyo, Japan. We were permitted the use of anonymized data obtained from individuals who underwent endoscopic screening at our screening center. All individuals included in this study provided written informed consent.

Endoscopic procedures and diagnoses of gastric cancer and atrophic gastritis

All endoscopic procedures were performed by highly experienced endoscopists, all of whom were board-certified by the Japanese Gastrointestinal Endoscopy Society. As for endoscopic equipment, pethidine hydrochloride and/or propofol or midazolam were used as analgesic drugs with sedation according to the individual's preference, carbon dioxide was used for air supply since 2009, a traditional endoscope (GIF-H260; Olympus Corp., Tokyo, Japan) was used in the early and middle periods, and ultrathin endoscopes (EG-530NW, EG-580NW, EG-L580NW7; Fujifilm Corp., Tokyo, Japan) were used in the middle and late periods. Information regarding all gastric cancers, including histological diagnoses, was described in accordance with the Japanese Classification of Gastric Carcinoma (JCGC) [18]. The endoscopic extent of gastric atrophy was diagnosed according to the Kimura-Takemoto classification, which correlates with the histological degree of atrophic gastritis and is classified from C-0 to O-3 [19]. Patients with atrophic gastritis were considered to have a history of *H. pylori* infection.

Statistical analysis

Chi-squared test or Fisher's exact test was used for the analysis of categorical data, and Student's t-test and analysis of variance were used for continuous variables, with Bonferroni-Holm adjustment for multiple comparisons. Logistic regression was used to calculate the odds ratio (OR) for gastric cancer detection by comparing atrophy while adjusting for age, sex, and periods. All reported P-values were two-sided, and those under 0.05 were considered statistically significant. All statistical analyses were performed using the R software version 4.2.2 (The R Foundation for Statistical Computing, Vienna, Austria).

Results

Characteristics of individuals according to the period

Characteristics of the individuals by period are presented in Table 1. The mean age of the 7,503 individuals (4,360 [58.1%] men, 3,143 [41.9%] women) in the early period was 59.4 years, that of the 5,820 individuals (3,668 [63.0%] men, 2,152 [37.0%] women) in the middle period was 56.8 years, and that of the 1,758 individuals (1.083 [61.6%] men, 675 [38.4%] women) in the late period was 58.7 years.

Chronological trend of the detection rate and the characteristics of gastric cancer

The detection rate of gastric cancer was 1.01% (76/7,503) in the early period, 0.69% (40/5,820) in the middle period, and 0.46% (8/1,758) in the late period (Figure 1). The characteristics of gastric cancer detected by EGD according to the period are summarized in Table 2. There were no significant differences in sex, degree of atrophic gastritis, tumor location, depth of invasion, neoplasm size, histological type, or treatment strategy between the periods; however, the age and type of endoscope were significantly different. In the late period, there was a higher proportion of patients with early gastric cancer, differentiated-type adenocarcinoma, and patients who underwent endoscopic submucosal dissection (ESD) as the treatment strategy than in the other periods, although the differences were not statistically significant. The overall age-specific detection rate of gastric cancer showed a declining trend over time (Table 3). In addition, among different age groups, the detection rate of gastric cancer was as follows: 0.27% (8/2,911) for 40–49 years, 0.57% (28/4,948) for 50–59 years, 1.14% (64/5,614) for 60–69 years, 1.34% (20/1,492) for 70–79 years, and 3.45% (4/116) for those aged >80 years (Figure 2).

Chronological trend of atrophic gastritis, detection rate, and the characteristics of gastric cancer according to the degree of atrophic gastritis

The prevalence of atrophic gastritis was 72% (5,430/7,503) in the early period, 48% (2,772/5,820) in the middle period, and 37% (655/1,758) in the late period (Figure 1). The proportion of individuals with atrophic gastritis according to age decreased over time except for those in their 80s (Table 3). The detection rate of gastric cancer according to the degree of atrophic

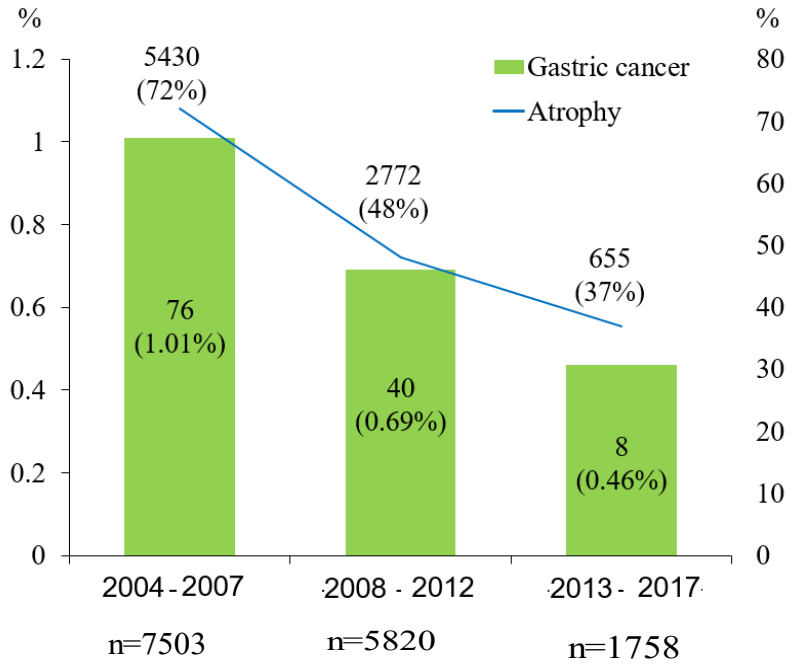

Figure 1. Chronological Trend of the Detection Rate of Gastric Cancer and Atrophic Gastritis

gastritis was 0.35% (22/6,224) for C0, 0.85% (59/6,953) for C1-C3, and 2.26% (43/1,904) for O1-O3 (Figure 3). The detection rate of gastric cancer significantly increased as gastric mucosal atrophy progressed (C0 vs. C1-3, p<0.001; C0 vs. O1-O3, p<0.001; C1-C3 vs. O1-O3, p<0.001). As for the histopathological findings, there were more differentiated-type gastric cancers than undifferentiated-type as the gastric mucosal atrophy progressed (C0: differentiated-type; 0.16% [10/6,224], undifferentiated-type; 0.19% [12/6,224], C1-C3: differentiated-type; 0.56% [39/6,953], undifferentiated-type; 0.29% [20/6,953], O1-O3: differentiated-type; 1.94% [37/1,904], undifferentiated-type; 0.32% [6/1,904]) (Figure 4).

Risk factors for gastric cancer

Multivariate analysis revealed that male sex (OR 1.92, 95% confidence interval [CI] 1.28-2.95), age ≥75 years (OR 2.73, 95% CI 1.32-5.05), and atrophic gastritis (C1-C3; OR 2.21, 95% CI 1.36-3.73, O1-O3; OR 5.36,

Table 1. Characteristics of the Individuals According to the Period

	2004-2007 (Early period) n=7,503	2008-2012 (Middle period) n=5,820	2013-2017 (Late period) n=1,758	P value
Sex, n, (%)				<0.001
Male	4,360 (58.1)	3,668 (63.0)	1,083 (61.6)	
Female	3,143 (41.9)	2,152 (37.0)	675 (38.4)	
Age, mean (SD), years	59.4 (8.2)	56.8 (9.9)	58.7 (10.7)	<0.001
Age, n (%)				<0.001
40-49	897 (12.0)	1,622 (27.9)	392 (22.3)	
50-59	2,750 (36.7)	1,664 (28.6)	534 (30.4)	
60-69	3,184 (42.4)	1,941 (33.4)	489 (27.8)	
70-79	624 (8.3)	561 (9.6)	307 (17.5)	
80-	48 (0.6)	32 (0.5)	36 (2.0)	
Atrophic gastritis, n (%)				<0.001
C0	2,073 (27.6)	3,048 (52.4)	1,103 (62.7)	
C1-C3	4,180 (55.7)	2,242 (38.5)	531 (30.2)	
O1-O3	1,250 (16.7)	530 (9.1)	124 (7.1)	
Type of endoscope, n (%)				<0.001
Traditional	7,503 (100)	3,439 (59.1)	0	
Ultrathin	0	2,381 (40.9)	1,758 (100)	

SD, standard deviation.

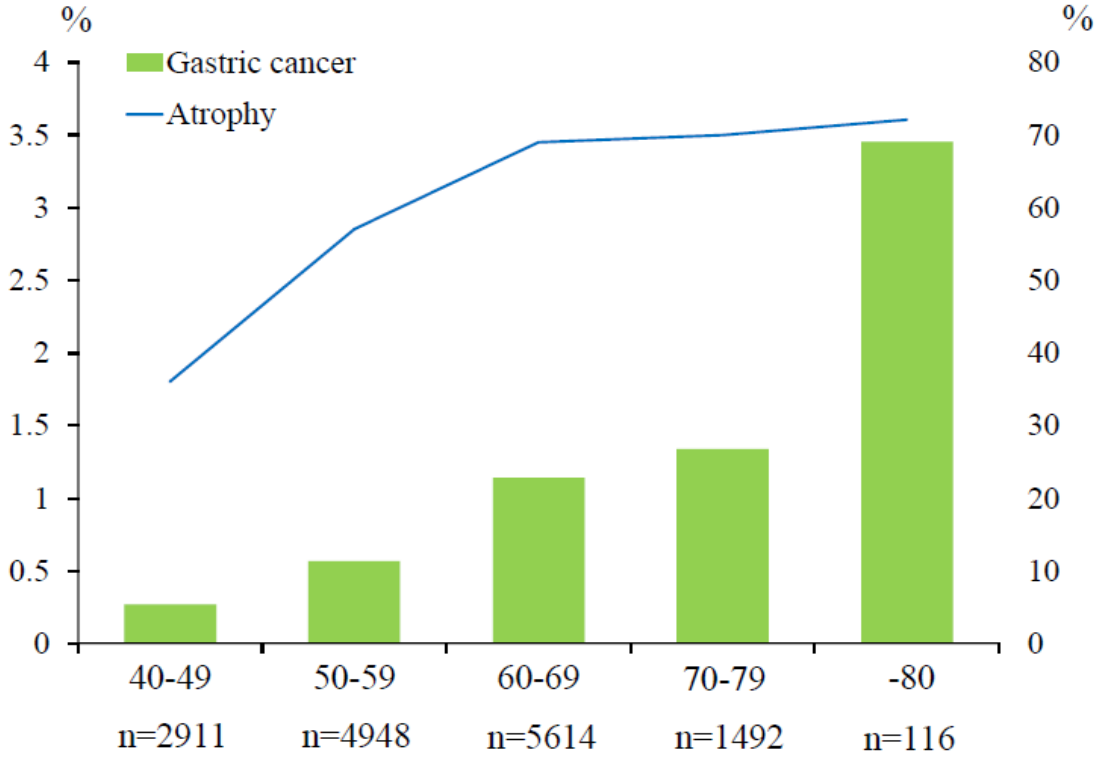

Figure 2. The Detection Rate of Gastric Cancer and Atrophic Gastritis by Age

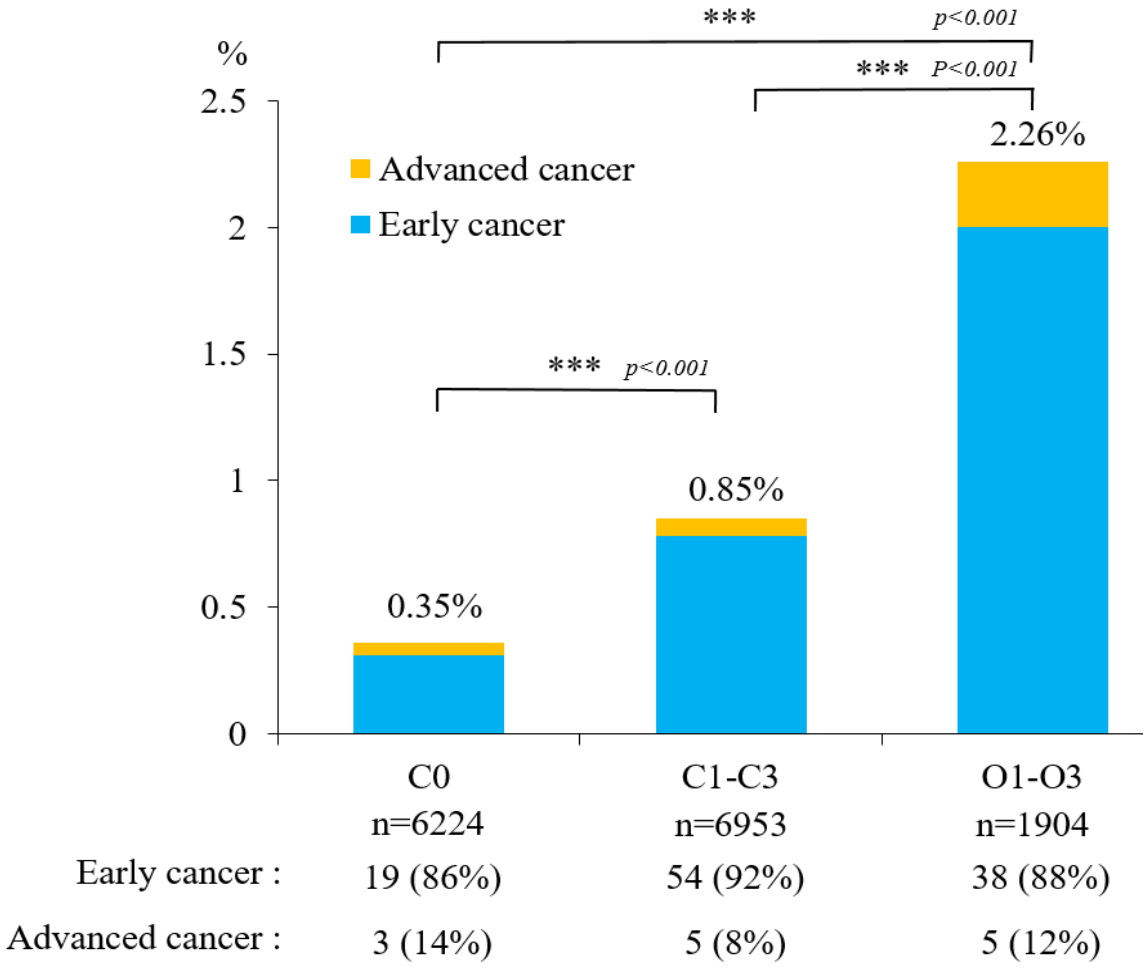

Figure 3. The Detection Rate of Gastric Cancer According to the Degree of the Atrophic Gastritis

Table 2. Characteristics of Gastric Cancer Detected by Esophagogastroduodenoscopy According to the Period

	Gastric cancer detected by EGD n=124 (0.82%)			P value
	2004-2007 (Early period) n=76 (1.01%)	2008-2012 (Middle period) n=40 (0.69%)	2013-2017 (Late period) n=8 (0.46%)	
Sex, n (%)				0.24
Male	59 (77.6)	31 (77.5)	4 (50.0)	
Female	17 (22.4)	9 (22.5)	4 (50.0)	
Age, years, mean (SD) (%)	62.9 (7.7)	62.1 (8.7)	70.1 (8.7)	0.04
Atrophic gastritis, n (%)				
C0	11 (14.5)	9 (22.5)	2 (25.0)	0.72
C1-C3	36 (47.4)	19 (47.5)	4 (50.0)	
O1-O3	29 (38.2)	12 (30.0)	2 (25.0)	
Type of endoscope, n (%)				<0.001
Traditional	76 (100)	24 (60.0)	0 (0.0)	
Ultrathin	0 (0.0)	16 (40.0)	8 (100)	
Tumor location, n (%)				0.85
Upper	9 (11.8)	5 (12.5)	1 (12.5)	
Middle	41 (53.9)	25 (62.5)	4 (50.0)	
Lower	26 (34.2)	10 (25.0)	3 (37.5)	
Depth of invasion, n (%)				0.9
Early cancer (T1a, T1b)	67 (88.2)	36	8 (100.0)	
Advanced cancer (≥T2)	9 (11.8)	4	0 (0.0)	
Neoplasm size, mm, mean±SD	22.9±17.6	21.4±23.0	10.4±6.8	0.88
Histological type, n (%)				0.14
Differentiated type	50 (65.8)	28 (70.0)	8 (100.0)	
Undifferentiated type	26 (34.2)	12 (30.0)	0 (0.0)	
Treatment starategy, n (%)				0.05
ESD	38 (50.0)	25 (62.5)	8 (100.0)	
Surgery	36 (47.4)	14 (35.0)	0 (0.0)	
Chemotherapy	0 (0.0)	1 (2.5)	0 (0.0)	
Observation	1 (1.3)	0 (0.0)	0 (0.0)	
Unknown	1 (1.3)	0 (0.0)	0 (0.0)	

EGD, esophagogastroduodenoscopy; SD, standard deviation; ESD, endoscopic submucosal dissection.

95% CI 3.17-9.30) were significantly associated with the incidence of gastric cancer (Table 4).

Discussion

This study included long-term data from gastric cancer screenings using high-quality endoscopy. We investigated the chronological trends in opportunistic endoscopic screening for gastric cancer and the relationship between gastric cancer and atrophic gastritis. The detection rate of gastric cancer has been decreasing with time. It was 1.01% in the early period, 0.69% in the middle period, and 0.46% in the late period. Simultaneously, the prevalence of atrophic gastritis has decreased over time from 72% in the early period and 48% in the middle period to 37% in the late period at our screening center. The overall age-specific gastric cancer detection rate also showed a declining trend over time. A decrease in the proportion of atrophic gastritis was also observed in each age group over time, except for those in their 80s. This is consistent with the decreasing trend in the prevalence of *H. pylori* infection [13, 14]. A previous report highlighted a similar declining trend over time in relation to atrophic gastritis. The report indicated that the prevalence of atrophy in the antrum and corpus was significantly lower in the 2010s (33%, 19%, respectively) compared to the evaluation conducted in either the 1970s (98%, 82%) ($p < .001$) or the 1990s (80%, 67%) ($p < .001$) [20]. Furthermore, it is noteworthy that the detection rates of gastric cancer as well as atrophic gastritis have decreased almost by half in the last decades. The decrease in *H. pylori* infection rates, along with improved environmental hygiene, was thought to have led to a decrease in atrophic gastritis incidence and associated gastric cancer.

However, the detection rate of gastric cancer in data from our screening center consistently surpassed that observed in the general population across all time periods. There are several possible explanations for this finding.

Table 3. The Number of Individuals with Gastric Cancer or Atrophic Gastritis by Period and Age

	2004-2007 (Early period)			2008-2012 (Middle period)			2013-2017 (Late period)		
	n	GC	AG	n	GC	AG	n	GC	AG
Male (years)									
40-49	369	2 (0.54)	218 (59.1)	1004	2 (0.20)	311 (31.0)	241	0 (0.0)	54 (22.4)
50-59	1,566	14 (0.8)	1078 (68.8)	1072	5 (0.47)	493 (46.0)	331	0 (0.0)	105 (31.7)
60-69	1,980	33 (1.67)	1546 (78.1)	1199	16 (1.33)	731 (61.0)	315	1 (0.32)	156 (49.5)
70-79	414	8 (1.93)	338 (81.6)	371	7 (1.89)	240 (64.7)	175	3 (1.71)	100 (57.1)
80-	31	2 (6.45)	27 (87.1)	22	1 (4.55)	19 (86.4)	21	0 (0.0)	12 (57.1)
Total	4,360	59 (1.35)	3207 (73.6)	3668	31 (0.85)	1794 (48.9)	1,083	4 (0.37)	427 (39.4)
Female (years)									
40-49	528	2 (0.38)	273 (51.7)	618	2 (0.32)	169 (27.3)	151	0 (0.0)	23 (15.2)
50-59	1,184	5 (0.42)	837 (70.7)	592	4 (0.68)	250 (42.2)	203	0 (0.0)	49 (24.1)
60-69	1,204	9 (0.75)	932 (77.4)	742	3 (0.40)	426 (57.4)	174	2 (1.15)	77 (44.3)
70-79	210	1 (0.48)	170 (81.0)	190	0 (0.0)	125 (65.8)	132	1 (0.76)	72 (54.5)
80-	17	0 (0.0)	11 (64.7)	10	0 (0.0)	8 (80.0)	15	1 (6.67)	7 (46.7)
Total	3,143	17 (0.54)	2223 (70.7)	2152	9 (0.42)	978 (45.4)	675	4 (0.59)	228 (33.8)
All (years)									
40-49	897	4 (0.45)	491 (54.7)	1622	4 (0.25)	480 (29.6)	392	0 (0.0)	77 (19.6)
50-59	2,750	19 (0.69)	1915 (69.6)	1664	9 (0.54)	743 (44.7)	534	0 (0.0)	154 (28.8)
60-69	3,184	42 (1.32)	2478 (77.8)	1941	19 (0.98)	1157 (59.6)	489	3 (0.61)	233 (47.6)
70-79	624	9 (1.44)	508 (81.4)	561	7 (1.25)	365 (65.1)	307	4 (1.30)	172 (56.0)
80-	48	2 (4.17)	38 (79.2)	32	1 (3.13)	27 (84.4)	36	1 (2.78)	19 (52.8)
Total	7,503	76 (1.01)	5430 (72.4)	5820	40 (0.69)	2772 (47.6)	1,758	8 (0.46)	655 (37.3)

GC, gastric cancer; AG, atrophic gastritis.

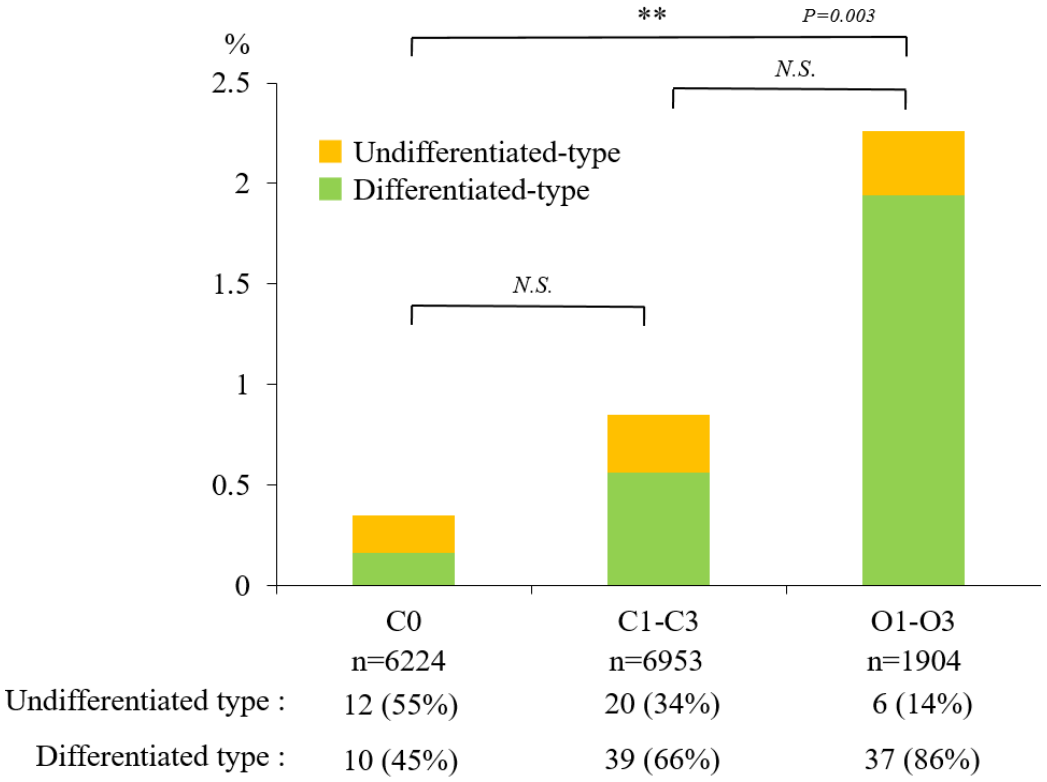

Figure 4. Detection Rates of Differentiated and Undifferentiated Adenocarcinomas According to the Degree of Atrophic Gastritis

Table 4. Risk Factors for Gastric Cancer

Variables	OR (95%CI)
Sex (male vs. female)	1.92 (1.28-2.95)
Age ≥75 years (vs. <75 years)	2.73 (1.32-5.05)
Atrophic gastritis C1-C3 (vs. C0)	2.21 (1.36-3.73)
Atrophic gastritis O1-O3 (vs. C0)	5.36 (3.17-9.30)
Middle period (vs. early period)	0.85 (0.52-1.34)
Late period (vs. early period)	0.61 (0.22-1.59)
Ultrathin endoscope (vs. traditional endoscope)	0.98 (0.51-1.84)

OR, odds ratio; CI, confidence interval

First, we systematically observed the inside of the stomach to map the entire stomach and avoided blind spots [21-24]. Second, we double-checked the endoscopic images at our center. Third, all endoscopic screenings were performed by well-trained endoscopists who were experts in endoscopic screening for gastric cancer.

Regarding the characteristics of gastric cancers detected by EGD, there were no significant differences in sex, degree of mucosal atrophy, location, macroscopic type, depth of invasion, neoplasm size, or histology of gastric cancers between the periods. The use of ESD as a treatment strategy has increased over time. The first reason for this is ESD has been covered by medical insurance since 2006 and is generally performed all over Japan. Second, high-definition white-light endoscopy and careful examination may have enabled the early detection of gastric cancers.

According to age groups, the detection rate of gastric cancer increased as patients got older (0.27% for 40-49 years, 0.57% for 50-59 years, 1.14% for 60-69 years, 1.34% for 70-79 years, and 3.45% for over 80 years). This could be related to the increased prevalence of atrophic gastritis in elderly patients. Interestingly, the detection rate of gastric cancer for those in their 80s was three times higher than that of those in their 60s despite the almost same prevalence of atrophic gastritis. Long-term atrophic gastritis can increase the occurrence of gastric cancer. In addition, the accumulation of aberrant DNA methylation, linked to both aging and *H. pylori* infection, may serve as an epigenetic driver in the process of carcinogenesis [25-27]. Gastric cancer incidence has been decreasing over time; however, the detection rate of gastric cancer in elderly individuals remains high. Therefore, endoscopic screening should be carefully performed in elderly individuals.

In terms of the relationship between gastric cancer and the degree of atrophic gastritis, the detection rate of gastric cancer increased significantly as gastric mucosal atrophy progressed (0.35% for C0, 0.85% for C1-C3, and 2.26% for O1-O3). This result was consistent with that of a previous study that reported that patients with severe atrophic gastritis were at a particularly high risk of gastric cancer [15]. Furthermore, the proportion of differentiated gastric cancer increased as the gastric mucosal atrophy progressed. This was also consistent with a previous report that revealed that severe atrophic gastritis is a high-risk factor for differentiated gastric cancer [15, 28, 29]. In contrast, undifferentiated gastric cancer occurred more frequently in patients without atrophic gastritis than in those with severe atrophic gastritis. As *H. pylori* infection decreases in the future, an increase in the proportion of undifferentiated gastric cancers is anticipated. Therefore, it is important to evaluate the existence and degree of atrophic gastritis to identify high-risk individuals for gastric cancer and recognize the characteristics of gastric cancer occurring in each degree of gastric mucosal atrophy during endoscopic screening.

Atrophic gastritis, older age, and male sex were found to be risk factors for gastric cancer. Severe atrophic gastritis (O1-O3) was the greatest risk factor for gastric cancer. Therefore, endoscopic screening should be carefully performed in patients with these risk factors. In addition, no significant differences were observed in the detection rates of gastric cancer according to endoscope type. Therefore, there appears to be no effect of endoscope type on the lower rate of gastric cancer detection in the later period of the study.

This study has several limitations. First, this was a retrospective study conducted at a single center; however, it provided valuable data that verified the majority of asymptomatic individuals. Second, the demographics and number of individuals in each period were different, and lifestyle and family history were not examined (e.g., family history of gastric cancer, alcohol intake, smoking status etc). Third, *H. pylori* infection status was not examined, but endoscopic evaluation for atrophic gastritis was performed. Fourth, we did not exclude patients who underwent endoscopic screening at other hospitals prior to undergoing screening at our center.

In conclusion, the detection rate of gastric cancer and prevalence of atrophic gastritis have decreased over time. However, it is important to continue endoscopic screening, especially for those at a high risk of developing gastric cancer complicated by severe atrophic gastritis.

Author Contribution Statement

K.N. collected the data, performed statistical analysis, and drafted the manuscript. Y.M., H.T., and T.S. performed statistical analysis. E.S., I.H., and M.M. collected the clinical data. Y.K., N.K., Y.S., and T.M. designed the study and edited the manuscript. All authors have read and agreed to the published version of the manuscript..

Acknowledgements

Funding statement

This study was supported by the National Cancer Center Research and Development Fund (30-A-16, 2021-A-18).

Ethics approval statement

This study was approved by the Ethics Committee for Clinical Research of the National Cancer Center in Tokyo, Japan (No. 2016-166).

Data availability statement

Due to the nature of this research, participants in this

study did not agree for their data to be shared publicly; thus, supporting data are not available.

Patient consent statement

All individuals included in this study provided written informed consent.

Conflict of interest disclosure

The authors declare no potential conflict of interest.

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