

Relation between gastric cancer and previous peptic ulcer disease

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Abstract

Background—It is presently not well understood to what extent peptic ulcer and gastric cancer represent related diseases.

Aims—The objective of this study was to assess past occurrence of gastric and duodenal ulcers in patients with cancer of the gastric cardia or other parts of the stomach.

Methods—The association between peptic ulcer and gastric cancer was studied among patients followed up at hospitals of the US Department of Veterans Affairs. Two populations of 1069 subjects with cancer of the cardia and 3078 subjects with cancer of other parts of the stomach were compared with a control population of 89 082 subjects without gastric cancer. In multivariate logistic regressions, presence or absence of cancer served as the outcome variable, while age, sex, race, previous histories of gastric ulcer, duodenal ulcer, peptic ulcer site unspecified, gastric resection, or vagotomy served as modifier variables.

Results—Old age, non-white ethnicity, and male sex proved strong and independent risk factors for non-cardiac gastric cancer. A previous history of gastric, but not duodenal ulcer was associated with a significantly raised odd ratio of 1.53 (95% confidence interval: 1.24 to 1.87). Cancer of the cardia affected predominantly whites, and was relatively more common in men than non-cardiac gastric cancer. Past gastric ulcers exerted no significant influence (1.02, 0.67 to 1.56), while duodenal ulcers and peptic ulcer site unspecified were protective (duodenal ulcer: 0.68, 0.47 to 0.95; peptic ulcer disease: 0.66, 0.47 to 1.00). Partial gastrectomy was a risk factor for non-cardiac gastric cancer (1.86, 1.32 to 2.63), but not for cancer of the cardia (1.09, 0.54 to 2.20).

Conclusion—These epidemiological patterns might stem from underlying differences in the influences of gastritis and acid secretion on the development of the two cancer types.

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Keywords: adenocarcinoma of the oesophagus, Barrett's oesophagus, duodenal ulcer, epidemiology of peptic ulcer, gastritis, gastric cancer, gastric ulcer, *Helicobacter pylori*.

It is presently not fully understood to what extent peptic ulcer and gastric cancer represent related diseases.¹⁻³ Epidemiological studies seem to suggest that while a past history of

duodenal ulcer protects against the future development of gastric cancer, a past history of gastric ulcer may make a subject more susceptible to subsequent development of gastric cancer.⁴⁻⁶ Observational studies suffer from three common limitations.⁷⁻⁹ (1) Since gastric cancer has become a relatively rare disease, it is difficult to accumulate large enough number of patients that would assure a statistically powerful and unequivocal result. (2) A prospective follow up of patients with gastric ulcer and controls poses tremendous logistic problems, and in most studies the length of observation has been rather short. On the other hand, spread or regression of gastritis and the development of metaplasia are disease processes that evolve slowly over prolonged time periods. (3) Secondary to the short observation periods, it was difficult to discern true gastric ulcers from ulcerated cancers whose benignity was misdiagnosed initially.

The issue of relatedness between peptic ulcer and gastric cancer remains important, particularly after the discovery of *Helicobacter pylori* and the realisation that this bacterium plays an important part in the development of duodenal ulcer, gastric ulcer, as well as gastric cancer. The relation between a past history of peptic ulcer and gastric cancer would shed light on the mode of action exerted by *H pylori* on the gastroduodenal mucosa. A history of gastric ulcer resulting in an increased risk for gastric cancer would suggest that both diseases share a partly similar pathophysiology. Differences between risk factors for cancer in the cardia and other parts of the stomach would point at different mechanisms operating in the development of these two types of gastric cancer. Thus, the aim of this case control study was to compare the past occurrence of gastric and duodenal ulcer between case subjects with and control subjects without gastric cancer. Gastric cancer was divided into cancer of the cardia and other parts of the stomach. As partial gastrectomy represents a risk factor for the development of cancer in the gastric remnant, the number of gastric surgeries in the case and control populations were taken into account. The comparison of cancer cases and control subjects was carried out in the large computerised database of all hospitalised US military veterans that is maintained by the Department of Veterans Affairs (VA).

Methods

Data source

The patient treatment file comprises a multitude of individual computerised data files. The

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data files are managed by the Department of Veterans Affairs (VA) central Automation Center at Austin, Texas. Permits to use the data and the computational facilities at Austin are granted to interested investigators by the Automation Center. All files containing medical information are available as SAS data files. The main files contain records of all inpatient treatments from all VA hospitals distributed throughout the United States. These files were started in 1970 and are available for each fiscal year since then. From 1970 until 1980, the 8th revision of the International Classification of Diseases (ICD-8) was used to code the medical information.¹⁰ Since 1981, the 9th revision of the International Classification of Diseases (ICD-9) and its Clinical Modification have been used.¹¹ In addition to five digit codes for each disease, the ICD contains codes for individual surgical and non-surgical procedures. Prior to 1984, surgical procedures were contained in the main files, since 1984 all procedures performed in the operating room are contained in separate procedural files.

Individual subjects can be identified in the database by their unique social security number. The main files contain the patients' demographic characteristics, such as age, race, sex, and place of residence. Besides the primary, the main files from 1970 until 1983 provided for the possibility to record four additional secondary diagnoses. Since 1984 number of potential secondary diagnoses has been raised to nine. Until 1983 five surgical procedures could be coded for each hospital stay, since then the number has been raised to five for each hospital day.

Extraction of case and control subjects

Veterans who were first diagnosed with gastric cancer (ICD-9-codes: 151.0-151.9) from 1990 until 1994, inclusive, were extracted from the patient treatment file, individual veterans being identified by their unique social security number. In the subsequent analyses, patients with ICD-9-code 151.0 (cancer of the cardia) were kept separately from patients with ICD-9-codes 151.1-151.9 (cancer of other parts of the stomach). From each annual file of the patient treatment file, each 30th patient was selected as a control subject. Patients with any previous discharge diagnosis of gastric cancer between 1970 and 1993 were excluded from the control group. Each case and control subject was followed up backward through the annual patient treatment files of previous years to accumulate all previous discharge diagnoses between 1970 until the diagnosis of gastric cancer. In the control subjects the date of recruitment served as the cut off date. Patient records were flagged if they carried the following primary or secondary diagnosis: gastric ulcer (ICD-9: 531.00-531.92 and ICD-8: 531.0-531.9), duodenal ulcer (ICD-9: 532.00-532.92 and ICD-8: 532.0-532.9), and peptic ulcer site unspecified (ICD-9: 533.00-533.92 and ICD-8: 533.0-533.9). The following diagnostic codes were used as indicators for a past history of gastric surgery: gastrojejunal

ulcer (ICD-9: 534.00-534.92 and ICD-8: 534.0-534.9) and postgastric surgery syndromes (ICD-9: 564.2 and ICD-8: 997.9). The procedural codes were searched for the occurrence of gastric resection: Billroth I gastrectomy (ICD-9: 43.6 and ICD-8: 46.2), Billroth II gastrectomy (ICD-9: 43.7 and ICD-8: 46.2), and other partial gastrectomy or gastroenterostomy (ICD-9: 43.81, 43.89 or 44.39 and ICD-8: 46.5). Various types surgery involving vagotomy were identified by the following codes: vagotomy not otherwise specified (ICD-9: 44.00 and ICD-8: 46.8), truncal vagotomy (ICD-9: 44.01), highly selective vagotomy (ICD-9: 44.02), other selective vagotomy (ICD-9: 44.03). Vagotomies are frequently performed with concomitant antrectomy or pyloroplasty (ICD-9: 44.2, 44.21, 44.29 and ICD-8: 46.1).

For each of the diagnostic codes mentioned above, its date of first and last appearance in an individual patient was recorded. Each procedural code was extracted with the corresponding date of surgery. Unless stated otherwise, all gastric ulcers that were diagnosed for the first time one year or less prior to the first diagnosis of gastric cancer (or date of recruitment in the controls) were excluded from the analysis. Similarly, all gastric surgery performed one year prior to cancer diagnosis or recruitment was ignored. The length of time between the first diagnosis of gastric cancer and the first or last mention of peptic ulcer was calculated. We also calculated the length of time between the first diagnosis of gastric cancer and the date of gastric surgery.

Statistical analysis

Quantitative parameters, such as age and lengths of time, were expressed as mean values with their standard errors. For univariate comparisons of quantitative parameters between cases and controls, the *t* test was used. For univariate comparisons of qualitative parameters, such as sex and race, the χ^2 test was used. In the multivariate analysis, case and control subjects were compared by multivariate logistic regression using the LOGISTIC procedure of SAS.¹² Presence or absence of gastric cancer served as the outcome variable. Age, sex, race, and a previous history of gastric ulcer, duodenal ulcer, peptic ulcer site unspecified, gastric resection, or vagotomy served as modifier variables. The length of time between the last occurrence of various ulcer types and ulcer surgery were also considered in the model. The results of the analyses were expressed as odds ratios and their 95 per cent confidence intervals. An odds ratio was considered significant if its 95% confidence interval did not include unity.

Results

Of all patients discharged from VA hospitals between 1990 and 1994, 4147 patients were diagnosed for first time to have gastric cancer. A population of 89 082 patients discharged during the same period as the cancer cases

TABLE I Patient characteristics, veterans population 1990-1994

	Cancer of the stomach		
	Cardia (n=1069)	Body and other stomach (n=3078)	Control subjects (n=89 082)
Mean age (SD)	65 (9)	67 (10)	58 (15)
Sex (%)			
Female	4 (0)	24 (1)	2335 (3)
Male	1065 (100)	3054 (99)	86 747 (97)
Race (%)			
Non-whites	178 (17)	1344 (44)	23 769 (27)
Whites	891 (83)	1734 (56)	65 313 (73)
Ulcer history (%)			
Gastric ulcer	24 (2)	117 (4)	1756 (2)
Duodenal ulcer	31 (3)	121 (4)	3166 (4)
Peptic ulcer site unspecified	36 (3)	158 (5)	3933 (4)
Surgical history (%)			
Resection	10 (1)	45 (1)	632 (1)
Vagotomy	12 (1)	28 (1)	591 (1)
Any type of surgery	23 (2)	64 (2)	1016 (1)

served as controls (Table I). Compared with the control population, patients with both types of gastric cancer were significantly older than the control population: $t=22.608$, $p<0.001$ for cancer of the cardia; $t=47.252$, $p<0.001$ for other gastric cancer. The two cancer populations were strikingly different with respect to their sex and race distribution compared with each other and with the control population. Both cancer populations contained relatively more men than the control population ($\chi^2=22.224$, $df=1$, $p<0.001$ for cancer of the cardia; $\chi^2=39.715$, $df=1$, $p<0.001$ for other gastric cancer). Gastric cancer involving the cardia was especially common among whites ($\chi^2=53.975$, $df=1$, $p<0.001$), while other gastric cancers affected predominantly non-whites ($\chi^2=431.986$, $df=1$, $p<0.001$). Compared with controls, relatively more cases with non-cardiac gastric cancer had a past history of gastric ulcer ($\chi^2=49.125$, $df=1$, $p<0.001$). No such clustering of past gastric ulcers occurred in cancers of the cardia. The case and the control populations did not differ significantly with respect to a past history of duodenal ulcer or peptic ulcer site unspecified. Patients with non-cardiac gastric cancer had also undergone relatively more resective surgery than the control population ($\chi^2=22.085$, $df=1$, $p<0.001$).

Table II shows the temporal relation between the occurrence of peptic ulcer and gastric cancer. For each ulcer type, the average time difference between the first appearance of cancer diagnosis and the first or last appearance of ulcer diagnosis was calculated. In the control subjects, the time of recruitment

served as the cut off point. In both case populations alike, the time intervals between first gastric ulcer and gastric cancer were slightly (but not significantly) shorter than the ones between the first duodenal ulcer and gastric cancer. Only in patients with non-cardiac gastric cancer did the last gastric ulcer occur significantly later than the last duodenal ulcer ($t=2.621$, $df=236$, $p=0.009$). In all three populations, peptic ulcer site unspecified was diagnosed in closest temporal proximity with the cancer or cut off point. Overall, there was a large variation in the temporal relations between peptic ulcer and gastric cancer, and the length of time between last ulcer and cancer ranged between 0-24 years with respect to all ulcer types. On the average, gastric surgery had been performed 11.2 (SEM=0.8) years before the first diagnosis of gastric cancer.

In Table III, the temporal relation between gastric and duodenal ulcer was analysed in those patients who had been diagnosed with both ulcer types. About two thirds of all gastric ulcers preceded or coincided with the first diagnosis of duodenal ulcer. This pattern was observed in cases with any type of gastric cancer and controls alike ($\chi^2=1.726$, $df=4$, $p=0.786$).

The outcome of the multivariate logistic regressions are contained in Table IV. In keeping with the results of the univariate analyses, old age, male sex, and white ethnicity proved strong and independent risk factors for the occurrence of cancer involving the gastric cardia. A past history of gastric ulcer exerted no significant influence, while a past history of duodenal ulcer or peptic ulcer site unspecified reduced the risk for cancer of the cardia by 42% or 44%, respectively. No other factor was associated with a significant influence.

In the multivariate analysis of non-cardiac gastric cancer, age and sex again proved significant risk factors. Old age appeared a stronger and male sex a weaker risk factor than in cardiac cancer. Non-white ethnicity and a past history of gastric ulcer both increased significantly the risk for gastric cancer outside the cardia. A past history of duodenal ulcer exerted a protective influence that failed, however, to reach statistical significance. Partial gastric resection was also associated with a significantly increased risk. Other factors considered in the multivariate analysis did not affect the occurrence of gastric cancer in a significant fashion.

A variety of additional analyses were done to test the robustness of the multivariate analyses. Besides the gastric ulcers listed in Table I, the first occurrence of additional 32 and 275 gastric ulcers was diagnosed in the patients

TABLE II Temporal relation between peptic ulcer and gastric cancer

Ulcer type	Number	First occurrence*		Last occurrence*	
		Mean	SEM	Mean	SEM
Gastric ulcer					
Cancer of cardia	24	8.4	1.4	7.2	1.4
Cancer of body and other stomach	117	8.3	0.6	5.7	0.6
Control subjects	1756	8.1	0.1	7.3	0.1
Duodenal ulcer					
Cancer of cardia	31	8.7	1.3	8.6	1.3
Cancer of body and other stomach	121	9.3	0.8	8.3	0.8
Control subjects	3166	8.2	0.1	6.9	0.1
Peptic ulcer site unspecified					
Cancer of cardia	36	7.0	1.0	3.0	0.7
Cancer of body and other stomach	158	6.5	0.4	3.9	0.4
Control subjects	3933	6.2	0.1	3.8	0.1

*Numbers refer to years.

TABLE III Temporal relation between gastric and duodenal ulcer

	GU 1st	DU=GU	DU 1st	Total
Cancer of the stomach				
Cardia	2	1	3	6
Body and other stomach	6	6	6	18
Control subjects	180	74	132	386

TABLE IV Risk factors for gastric cancer

Variable	Odds ratio	95% Confidence intervals	Wald (χ^2)	p Value
<i>Cancer of the cardia (ICD-Code 151.0)</i>				
Age*	1.38	1.32 to 1.45	184.3816	0.0001
Male sex	6.51	2.44 to 17.41	13.9534	0.0002
White ethnicity	1.60	1.36 to 1.89	32.3799	0.0001
Gastric ulcer	1.02	0.67 to 1.56	0.0088	0.9254
Duodenal ulcer	0.68	0.47 to 1.00	3.9017	0.0482
Peptic ulcer site unspecified	0.66	0.47 to 0.94	5.3967	0.0202
Gastric resection	1.09	0.54 to 2.20	0.0536	0.8170
Vagotomy	1.89	0.97 to 3.69	3.4555	0.0630
<i>Cancer of the stomach (ICD-Codes 151.1-151.9)</i>				
Age*	1.69	1.64 to 1.74	1222.7250	0.0001
Male sex	2.58	1.72 to 3.87	20.8977	0.0001
White ethnicity	0.39	0.36 to 0.42	632.8373	0.0001
Gastric ulcer	1.53	1.24 to 1.87	16.2356	0.0001
Duodenal ulcer	0.89	0.73 to 1.08	1.3687	0.2420
Peptic ulcer site unspecified	0.94	0.79 to 1.12	0.5128	0.4739
Gastric resection	1.86	1.32 to 2.63	12.5484	0.0004
Vagotomy	0.80	0.52 to 1.24	0.9720	0.3242

*Increase in risk ratio per 10 years.

with cardiac and non-cardiac gastric cancer, respectively, during the year preceding the first diagnosis of gastric cancer. The corresponding number of first diagnosed gastric ulcers in the control population was 733. If these ulcers were included in the regression analysis of non-cardiac gastric cancer, the odds ratio associated with gastric ulcer rose to 2.97 (95% confidence interval: 2.58 to 3.40). On the other hand, extending the exclusion period for gastric ulcers preceding non-cardiac cancer from one year up to five years left the outcomes of the multivariate analysis largely unchanged. The odds ratio of gastric ulcer with three year exclusion period was 1.48 (1.17 to 1.86) and with five year exclusion 1.50 (1.15 to 1.94). Gastric surgery represents a known risk factor for the development of gastric cancer. The multivariate analysis adjusts for the contribution of individual factors. Nevertheless, to rule out completely any possible interaction between peptic ulcer and subsequent ulcer surgery, the regression analysis was repeated with only those ulcers that had not been treated subsequently by gastric surgery. In case of non-cardiac gastric cancer, this measure failed to alter the odds ratio associated with gastric ulcer (OR=1.50, 1.15 to 1.94) or duodenal ulcer (OR=0.90, 0.74 to 1.09) in any substantive way. In cardiac cancer, the odds ratios changed to (OR=0.98, 0.61 to 1.58) for gastric ulcer and (OR=0.72, 0.48 to 1.07) for duodenal ulcer.

Discussion

This study showed an increased risk for non-cardiac cancer associated with rising age, non-white ethnicity, and male sex. These findings are in agreement with previously reported epidemiological patterns of gastric cancer in the United States.¹³ Moreover, the study showed that a past history of gastric, but not duodenal ulcer was associated with an increased risk for gastric cancer outside the cardia. Our results leave little doubt that gastric ulcer was truly associated with an increased risk for gastric cancer, because even after the exclusion of all gastric ulcers up to five years prior to the first cancer diagnosis the odds ratio remained significantly increased. Although the majority

of gastric ulcers first diagnosed in close temporal proximity to the subsequent diagnosis of gastric cancer may be suspicious for misdiagnosed malignant ulcers, this explanation becomes less probable the further back in time one moves from the initial diagnosis of gastric cancer. Gastric resection resulted in an increased risk for non-cardiac gastric cancer. This finding is consistent with many previous reports that have shown an increased risk for gastric stump cancer after gastric resection, the risk rising with the length of the time since surgery.¹⁴⁻¹⁶ In striking contrast with cancer involving the body and the antrum of the stomach, cancer of the cardia affected predominately whites. Cancer of the cardia was also relatively more common in men than the other types of gastric cancer. A history of gastric ulcer exerted no significant influence and duodenal ulcer or peptic ulcer site unspecified were both protective. Gastric surgery exerted no significant influence on its occurrence.

Part of the epidemiological correlation between gastric and duodenal ulcer relates to an underlying infectious gastritis in both diseases.¹⁷ Over time, the gastritis may spread from the antrum to the rest of the stomach. As the area of the acid secreting mucosa decreases, the duodenal ulcer tends to burn out and the patient becomes more susceptible to gastric ulceration.¹⁸ Further progression of the gastritis and development of extensive intestinal metaplasia may then lead to gastric cancer. However, this hypothetical sequence is somewhat at odds with the results of this study, as well as those of previous studies. Firstly, all published series of peptic ulcer contained a fraction of patients who presented with both ulcer types at the same time or even with a duodenal ulcer diagnosed subsequently to a gastric ulcer.^{7, 19-20} Secondly, although the last gastric and duodenal ulcers occurred on average 5.7 and 8.3 years, respectively, before the diagnosis of non-cardiac gastric cancer, the time difference between the two diagnoses ranged anywhere between 0 and 24 years. Large series of patients have been accumulated, in whom gastric and duodenal ulcers or at least scars thereof were found concomitantly with the cancer.²¹⁻²² These findings would suggest that the hypothesis regarding the temporal sequence of the three diseases is too simplistic or that it applies only to a fraction of the patient population.

Gastric cancer of the body and the antrum on one hand and gastric cancer of the cardia on the other hand seem to constitute two different disease entities. Cancer of the cardia is frequently associated with Barrett's epithelium, which represents a severe form gastro-oesophageal reflux disease. Reflux disease characterised by ulcerations, strictures, or Barrett's epithelium is more common among men than women and whites than non-whites.²³ In the present analysis, a similar distribution by sex and ethnicity was also revealed by cancer of the cardia. Gastro-oesophageal reflux disease results from the corrosive action of the acidic refluente on the oesophageal

mucosa. Long term infection with *H pylori* leads to multifocal atrophic gastritis and loss of gastric acidity, which could protect the patient against reflux disease and possibly also against adenocarcinoma originating from Barrett's epithelium. Such mechanisms could underlie the missing influence of gastric ulcer or even the protective influence of duodenal ulcer and peptic ulcer site unspecified on cardiac cancer. On the other hand, the multifocal atrophic gastritis related to *H pylori* predisposes the patient to gastric ulcer, as well as gastric cancer in the body or antrum.²⁴⁻²⁵ No such clear cut relation exists between this type of gastritis and duodenal ulcer.²⁶

Cancers of the cardia and other parts of the stomach show opposing time trends. While the incidence rates of cancer in the gastric body or antrum have notably decreased, those of cardiac cancer have increased during the same period.^{13 17 27-31} In the United States, the most pronounced rise and fall of cardiac and non-cardiac cancers, respectively, affected white men; the rise and fall were less noticeable among non-whites.³² Again, these time trends are consistent with the contention that infection with *H pylori* determines the epidemiological pattern of both types of gastric cancer. The recent improvements in hygiene and socioeconomic status decreased the infection rates of *H pylori* in the general population. As the improvements benefited whites more than non-whites, gastric cancer rates have decreased primarily in whites. During the same time, the population wide decrease in *H pylori* induced atrophic gastritis and its associated hypochlorhydria increased the general susceptibility for reflux disease, Barrett's oesophagus, and adenocarcinoma of the cardia. Other factors, such as changes in dietary habits, may have also contributed to these temporal changes.³³

In relying on the patient treatment file for conducting the present research project, it is important to consider several shortcomings of this large database. Like all large databases, the patient treatment file is limited in capturing all pertinent health care activity in individual patients. For instance, no records exist to record diagnoses made outside of the Veterans Affairs system, and our analysis may underestimate the true frequency of previous peptic ulcers. Oesophagogastroduodenoscopy and upper gastrointestinal x rays are frequently performed as outpatient procedures. Our inability to record outpatient activity could have introduced a systematic error to both groups of case and control subjects. As individual veterans received part of their medical care as outpatients or outside VA facilities altogether, the time sequence of diagnoses, as they appear in the computerised database, may not necessarily reflect their true temporal relation. On the other hand, the different influences of gastric and duodenal ulcer on various types of gastric cancer rules out a simple selection or detection bias as an explanation for the observed findings.

Lastly, our database deals exclusively with US military veterans. This population consists primarily of male subjects with low family

income and increased exposure to environmental risk factors, for instance, *H pylori* infection or smoking. Their health behaviour and medical care are different from those of other Americans. In general, their health awareness and concern about prevention may be less developed than in the whole US population. On the other hand, very similar odds ratios were reported in a recent study from Sweden.³⁴ A history of duodenal ulcer reduced the cancer risk by 40%, while that of gastric ulcer increased the cancer risk twofold. In contradistinction with the case control design of the present study, Hansson and coworkers followed a cohort of ulcer patients over a time period of 9.1 years. The minor differences between the results of the study by Hansson and ours could be explained by the fact that he did not consider a breakdown of cancers by different gastric sites. The similar findings observed by two independent groups suggest that the relation between peptic ulcer and gastric cancer apply to different populations alike and that these associations would be shown also by future studies, irrespective of the particular study design chosen by the investigators.

In summary, the results of this study clearly show cancers involving the gastric cardia or other parts of the stomach to represent two opposites of a spectrum of gastric cancer. Cardiac cancer affects mostly white men. A previous ulcer history does not influence its occurrence, if anything, it might protect against its development. On the other hand, cancer in other parts of the stomach affects mostly non-whites, male predominance is less striking than in cardiac cancer, and a past history of gastric ulcer confers an increased risk. These patterns might stem from underlying differences in the influences of gastritis and acid secretion on the development of the two cancer types.

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