Gastric cancer risk after vagotomy

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Abstract

The risk of gastric cancer after vagotomy for benign gastric and duodenal disease was examined in a population based cohort of 7198 patients operated on during 1971-79 and followed up until 1988. After exclusion of the first year of follow up there were 34 cases of gastric cancer compared with 25.6 expected (standardised incidence ratio (SIR)=1.33; 95% confidence intervals (CI) 0.92 to 1.86). Separate analyses by duration of follow up, sex, age at operation, underlying diagnosis, and operative procedures did not show any significant increased or decreased risk of gastric cancer in any of the subgroups. In conclusion, decreased gastric acid secretion after vagotomy does not increase the risk of gastric cancer in the first 10 years after operation or in the subgroup followed up for 10-18 years. A longer follow-up is needed before an excess risk can be excluded.

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Medical and surgical treatment of peptic ulcer disease has undergone dramatic changes during the last few decades. In Sweden, partial gastrectomy was standard treatment until about 20 years ago. Highly selective vagotomy, introduced in 1971, rapidly replaced gastric resection as the preferred surgical procedure in the early 1970s. Concomitantly, the number of patients operated on for peptic ulcer has decreased.¹

Little is known about the longterm effects in humans of permanent or intermittent inhibition of gastric acid secretion. It is well established that partial gastrectomy with Billroth II gastrojejunostomy for gastric ulcer entails an increased risk of cancer in the gastric remnant about 20 years after the operation.²⁻⁷ The increase in risk, however, does not seem to be related primarily to acid reduction as there is no risk increase after Billroth I gastroduodenostomy.²

Pharmacologically induced hypochlorhydria has been shown to be associated with increased gastric bacterial growth, reduction of nitrate to nitrite, and increased concentration of carcinogenic *N*-nitroso compounds in the gastric juice.⁸⁻⁹ Although the corresponding effects seem to be absent after vagotomy without resection,¹⁰ vagotomy has consistently been shown to enhance experimental carcinogenesis in the stomach in various animal species.¹¹⁻¹⁸ Vagotomised juxtapyloric ulcer patients followed up longitudinally showed a statistically significant increase in the prevalence and degree of chronic body gastritis,¹⁹ and dysplasia may be a common finding after

vagotomy.²⁰⁻²¹ Furthermore, pernicious anaemia, a condition characterised by gastric atrophy, achlorhydria, and hypergastrinaemia, is associated with a considerably increased risk of gastric cancer.²²

Any increase in cancer risk after vagotomy may therefore have implications for the longterm treatment with potent drugs for inhibition of gastric acid secretion. Evaluation of any gastric cancer risk after the use of these drugs is limited by the number of longterm users with sufficient treatment duration.²³ In contrast, large number of patients who have been subjected to vagotomy are now available with up to almost 20 years of observation. In these patients, as in medically treated patients, the gastric acid secretion is reduced, albeit not abolished, and the secretion of gastrin, a hormone with trophic effects on the stomach mucosa, is slightly increased.²⁴ Hence, studying vagotomy patients may shed light on the effects of longterm inhibition of gastric acid on gastric cancer risk.

Patients and methods

THE COHORT

In 1965 the Swedish National Board of Health and Welfare began receiving annual reports from all inpatient medical institutions in Sweden and recorded data on individual hospital admissions and discharges in an inpatient registry. At the start, six of the 25 counties in Sweden were included. This registration expanded successively to cover 85% of the Swedish population by 1979. Besides the national registration number,²⁵ a unique personal identifier given to all Swedish residents, each record contains data on place of residence, hospital department, surgical procedures, and up to eight discharge diagnoses. Since 1969, these diagnoses are recorded according to the 8th revision of the International Classification of Diseases. All records in the inpatient registry between the years 1971 to 1979 that mentioned a vagotomy procedure were considered for inclusion in the study.

After excluding those with an erroneous national registration number through linkage to the national Death and Emigration Registry²⁶ and the Swedish population registry there was a total of 8292 patients who had had a vagotomy during the period 1971 to 1979 and were thus potentially eligible. We excluded 386 patients with a cancer diagnosis, 343 patients who had a vagotomy combined with a partial or total gastrectomy, 120 patients who had an operation for a gastrojejunal ulcer, 191 patients who died postoperatively, and finally 54 patients who emigrated from Sweden the

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TABLE I Standardised incidence ratios (SIR) for gastric cancer 1–18 years after vagotomy, by duration of follow up, sex, diagnosis at operation, surgical procedure, and age at operation

	No	Person years	Observed	SIR	95% CI
All patients	7198	73 837	34	1.3	0.92 to 1.86
Sex:					
Male	5356	54 689	25	1.2	0.78 to 1.77
Female	1842	19 148	9	1.9	0.87 to 3.61
Diagnosis at operation:					
Gastric ulcer	1190	11 349	6	1.1	0.42 to 2.49
Duodenal ulcer	4836	50 717	22	1.3	0.82 to 1.99
Other gastric disorders	804	11 771	6	1.7	0.61 to 3.62
Other diseases	368				
Surgical procedure:					
Vagotomy with drainage	1863	18 136	11	1.1	0.57 to 2.03
Vagotomy without drainage	5335	55 701	23	1.5	0.92 to 2.17
Age at operation (y):					
<50	3704	41 249	5	1.4	0.46 to 3.33
50–60	1887	19 708	14	1.8	0.96 to 2.94
≥60	1607	12 880	15	1.1	0.59 to 1.75
Follow up after operation (y):					
1–4		26 930	11	1.3	0.66 to 2.36
5–9		30 281	16	1.5	0.86 to 2.45
10–14		15 283	7	1.2	0.47 to 2.40
15–18		1 344	0	0	0 to 5.87

same year as the operation. Thus, the cohort included a total of 7198 patients. Table I shows the distribution of the cohort members by sex, diagnosis at discharge, operative procedures, and age. The mean age at operation was 49.1 years, and the mean age at diagnosis of gastric cancer was 65.6.

To assess the possible association between the underlying disease and cancer risk the patients were grouped into four mutually exclusive categories: gastric ulcer, duodenal ulcer, other gastric diseases, and other diseases. In separate analyses patients who had a vagotomy with a drainage procedure (gastrojejunostomy or pyloroplasty) were grouped together and compared with those subjected to a selective proximal vagotomy only.

FOLLOW UP

Record linkage, based on the national registration number, to the national Death and Emigration Registries²⁶ gave information on the date of death or emigration through 1988. The Swedish Cancer Registry,²⁷ founded in 1958, was used to ascertain all incident cancers diagnosed in the cohort from start of follow up until the end of 1988. The time of observation was calculated from the registration date of operation until the diagnosis of gastric cancer, death, emigration or the end of the observation period (31 December 1988).

The expected number of cancers was calculated by multiplying the number of person years for each sex by age specific cancer incidence rates for each five year age group and calendar year of observation. These expected rates were derived from the study population – that is, the total Swedish population. For the main analyses, we used a one year latency period between the date of operation and calculation of the observed and the expected number of cancers. The aim of this approach was to eliminate or reduce a possible impact of selection bias. Such bias occurs when patients in whom cancer symptoms or an overlooked malignant ulcer lead to an operation for ulcer disease. The stratified analyses were carried out by the time since operation, sex, diagnosis

at time of operation, surgical procedures, and the age at operation.

STATISTICAL METHODS

Standardised incidence ratios (SIR), the ratio of the observed to expected number of cancers, and 95% confidence intervals (CI) were calculated on the assumption that the observed number of cancers followed a Poisson distribution.²⁸

Results

After excluding the first year after operation a total of 34 gastric cancers were diagnosed during the follow up compared with 25.6 expected (SIR=1.33; 95% CI 0.92 to 1.86) (Table I). All cancers were histopathologically confirmed. Neither surgical procedures or the various diagnoses at operation were associated with any appreciable differences in relative risk. Although women and patients under the age of 60 had a slightly increased risk of gastric cancer, they did not significantly differ from that of the background population (Table I). When examined by duration of follow up, risks tended to be lower in the second half of follow up compared with the first nine years (Table II).

Discussion

The absence of a statistically significant risk increase in this large population based cohort with more than 70 000 person years of observation may seem reassuring. Especially as our results are in contrast with published works so far: in five studies ranging from 209 to 1643 patients, up to a 3.3-fold death risk from gastric cancer was seen.^{3 21 29–31} The frequent addition of drainage procedures to the vagotomies, and the possibility of surveillance bias in these studies make comparisons with this study difficult. Unoperated duodenal ulcer disease is, however, generally considered to protect against gastric cancer.³² Therefore, a risk close to that seen in the general population may, in fact, reflect an increased risk among duodenal ulcer patients. The role of *Helicobacter pylori* requires some consideration. It is generally accepted that this infection is closely associated with peptic ulcer.³³ There is also accumulating evidence that the infection is positively and independently associated with risk of gastric cancer.^{34–39} As vagotomy seems to have no impact on the infection,⁴⁰ the *Helicobacter* associated risk of gastric cancer probably persists even after operation. Whether or not the *Helicobacter pylori* state is a determinant for the likelihood of being operated – and thus a potential confounder – is largely unknown. It is, however, highly unlikely that an important association between vagotomy and gastric cancer has been concealed in this study through negative confounding by *Helicobacter pylori* state – that is, that the prevalence of the infection would have been lower among surgical cases than in the general population.

TABLE II Standardised incidence ratios (SIR) for stomach cancer 1–18 years after vagotomy, by duration of follow up, sex, diagnosis at operation, surgical procedure, and age at operation

	1–9 Years after operation			10–18 Years after operation		
	Observed	SIR	95% CI	Observed	SIR	95% CI
All	27	1.4	0.94 to 2.08	7	1.1	0.42 to 2.17
Sex:						
Males	18	1.2	0.69 to 1.84	7	1.3	0.52 to 2.67
Female	9	2.6	1.18 to 4.89	0	0	0 to 2.96
Diagnosis at operation:						
Gastric ulcer	6	1.5	0.55 to 3.26	0	0	0 to 2.95
Duodenal ulcer	16	1.3	0.75 to 2.12	6	1.3	0.49 to 2.90
Other gastric disorders						
Other diseases	5	1.9	0.62 to 4.49	1	1.1	0.03 to 6.19
Surgical procedure:						
Vagotomy with drainage	9	1.2	0.56 to 2.34	2	0.8	0.09 to 3.03
Vagotomy without drainage	18	1.6	0.92 to 2.45	5	1.2	0.38 to 2.74
Age at operation:						
<50	4	1.8	0.50 to 4.65	1	0.8	0.02 to 4.28
50–59	10	1.8	0.88 to 3.37	4	1.6	0.43 to 4.05
≥60	13	1.1	0.61 to 1.96	2	0.7	0.08 to 2.59

In this study the standardised incidence ratios were consistently above unity, one to nine years after operation and for women there was even a significantly increased risk. Although we discarded cancer cases that occurred within one year of the operation, misdiagnosed cancers at time of operation may still have an impact on the rates during the first nine years after operation. Moreover, as the latency period for gastric cancer may be several decades^{41 42} a reliable risk estimate after 10–30 years is needed to establish or reject a causative association. As Table I shows, the number of patients with sufficient observation time is clearly too small for firm conclusions.

Misclassification of the exposure (vagotomy) may also entail underestimation of the relative risk. The validity of data in the inpatient registry has been evaluated in a random sample of admissions.⁴³ Codes for surgical procedures were missing in 7.8% (almost half of which were for minor semi-invasive or auxiliary procedures combined with correctly recorded main procedures), and erroneous in 1.8%. Although there is a possibility that, for example, some drainage procedures were not recorded, or that some vagotomies were performed on previously operated stomachs without a diagnosis of gastrojejunal ulcer, the degree of misclassification is of such a low magnitude that it probably has not seriously affected the risk estimates. The cancer cases in this cohort were ascertained through record linkage with the Swedish Cancer Registry. With accuracy of more than 95%⁴⁴ there is little reason to believe that our results were seriously flawed especially as such misclassification should be non-differential.

There is a reasonable concordance between the findings in this study and the results of investigations aimed at assessing risks associated with the use of H₂ antagonists.^{45–48} These studies do not provide evidence for a carcinogenic effect after acid inhibition, but they all show an excess gastric cancer incidence during the first years after treatment, almost certainly because of misdiagnosed cancer cases. In a recent Danish study, however, an increased longterm risk was seen for women.⁴⁸ The comparison of vagotomy with longterm pharmacological acid inhibition is probably inappropriate, as even with highly selective

vagotomy (without drainage), there is a progression of gastritis that seems to exceed that seen during cimetidine maintenance treatment.¹⁹ Moreover, there is some evidence that cimetidine may have an anti-tumour effect.^{49–53} On the other hand, the increased intragastric N-nitrosation, as seen during treatment with antisecretory drugs^{8 9} may constitute less of a problem in vagotomised patients.¹⁰

In conclusion, although our results in this study are reassuring, longer follow up is needed before an increased risk for gastric cancer after vagotomy and presumably after longterm medical treatment with H₂ blockers can with confidence be ruled out.

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