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Meta-Analysis of the Risk of Gastric Stump Cancer: Detection of High Risk Patient Subsets for Stomach Cancer after Remote Partial Gastrectomy for Benign Conditions[1]

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ABSTRACT

Controversy about gastric cancer risk after partial gastrectomy exists, especially in the United States. Therefore, we performed a meta-analysis to determine overall relative risk and weighted mean relative risk for subsets of postgastrectomy patients, define possible high risk patients suitable for surveillance, and assess for publication bias which would overestimate risk.

If 2 studies were excluded because of heterogeneity, overall relative risk (RR) for gastric stump cancer in 22 studies analyzed was 1.66 [95% confidence limits (CL), 1.54–1.79]. With these 2 studies included, the RR summarized with a random effects model to account for study heterogeneity was 1.46 (95% CL, 1.18–1.82). No obvious evidence of publication bias was detected. Patients 15 years or more postoperative had a weighted mean RR of 1.48 (95% CL, 1.31–1.67) and patients 5–14 years postoperative had a RR of 0.91 (95% CL, 0.71–1.17) (P = 0.026). Patients operated upon for gastric ulcer had a weighted mean RR of 2.12 (95% CL, 1.73–2.59) and patients with duodenal ulcers had a RR of 0.84 (95% CL, 0.66–1.05) (P = 0.001). The weighted mean RR for females was 1.79 (95% CL, 1.39–2.29) and for males 1.43 (95% CL, 1.27–1.62) (P = 0.074). For Billroth II gastrectomy the weighted mean RR was 1.60 (95% CL, 1.15–2.18) and for Billroth I gastrectomy 1.20 (95% CL, 1.01–1.42) (P = 0.220).

Although differences in risk between subsets of postgastrectomy patients seem to exist, recommendations concerning endoscopic surveillance await further studies of cost-benefit analysis.

INTRODUCTION

The preponderance of medical literature indicates an increased risk of gastric cancer after peptic ulcer surgery, and in Western Europe the operated stomach is considered a premalignant condition (1). However, controversy concerning cancer risk after partial gastrectomy still remains, especially in the United States where literature reports are less convincing (2, 3).

If gastric stump cancer is assumed to be a real phenomenon, the overall risk of cancer appears too low to justify large scale screening programs (4, 5). Although the prognosis of advanced gastric stump cancer is poor, survival improves dramatically with early detection as demonstrated by endoscopic biopsy screening programs (6–10). Therefore, endoscopic screening would be beneficial if high cancer risk subsets of postgastrectomy patients could be delineated. Unfortunately, most studies have lacked the statistical power to analyze various risk categories (11, 12).

Meta-analysis provides methodology to summarize overall risk by combining results from several studies (13–15). This report describes a meta-analysis of the existing literature concerning the relative risk of gastric stump cancer after partial gastrectomy. In the study, we assess the weighted mean log-relative risk of gastric stump cancer, provide possible explanations for discrepancies between studies, investigate evidence for publication bias (which overestimates the risk of cancer because negative studies are not published), and define higher risk patient subsets which may be suitable for surveillance.

MATERIALS AND METHODS

Gastric stump cancer is defined as an adenocarcinoma of the stomach occurring 5 years or more after gastric surgery for benign conditions (16). A minimal latency of 5 years is chosen to avoid spurious effects due to faulty diagnosis. The reports for meta-analysis were collected by a literature search by three of us (A. C. T., G. J. A. O., K. W. F. T.) on Medline from 1982–1988 and in the reference lists of the subsequent articles. The key words searched included "gastrectomy," "stomach neoplasms," "peptic ulcer," "ulcer surgery," "gastric carcinoma," "postoperative complications," "gastric remnant," "gastric stump," "postgastrectomy cancer." Only studies in the English or German language with risk appraisal were analyzed. The collected studies are listed in Table 1 (2, 3, 7, 11, 16–39). Several of these reports have been reviewed elsewhere (40).

Three literature reports were excluded because the relative risk could not be estimated from the data presented (17, 23, 29); one study (30) had too small a sample size (13) and two studies (33, 37) did not fulfill the assumption of sample homogeneity ($P < 0.01$). This assumption states that all studies under investigation are measuring the same risk estimate so that differences between estimates are due to random error (13). Homogeneity was tested by comparing the relative risk of each study with the summary relative risk from all other studies by χ^2 (13). Of the remaining 22 reports, 4 were case-control studies and 18 were longitudinal cohort studies. In the 22 studies used, 827 cases of gastric stump cancer occurred. When 95% CL[4] were unavailable in the original publications, this statistic was calculated from the estimated risks using a method by Woolfe (41) for odds ratios from unmatched case-control studies and a technique by Ederer and Mantel (42) for the cohort studies. Risk estimates were transformed logarithmically for approximation to a normal distribution. Thus, independent of the study type, the standard error of the logarithm of the RR could be used to measure statistical uncertainty (13, 43). This was accomplished by logarithmic transformation of these three quantities and then calculation of the average distance between logarithm RR and upper and lower limits and division by 1.96 (43). Results were depicted in a funnel display plotting logarithm of RR against a measure of precision (standard error of logarithm of RR) (13, 14, 43).

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[4] The abbreviations used are: CL, 95% confidence limits; RR, relative risk.

Table 1 *Twenty-eight literature reports on the risk of gastric cancer after remote peptic ulcer surgery*

	Cohort studies		
Author (Ref.)	Estimated relative risk	95% CL[a]	Average follow-up (yr)
Viste *et al.* (36)	2.1	1.7–2.6	28.4
Lundegardh *et al.* (39)	1.0	0.8–1.2	25–33
Krause (24)	2.2	1.4–3.3	24.3
Loscos *et al.* (35)	2.2	1.8–2.7	23.8
Clark *et al.*[b] (30)	4.4	0.0–17.0	22–27
Offerhaus *et al.* (11)	1.8	0.8–2.1	>20.0
Tokudome *et al.*[b] (33)	0.2	0.1–0.4	<20.0
McLean and Ross (2)	0.8	0.3–1.5	18.9
Fischer *et al.* (31)	1.2	0.7–2.1	18.0
Schafer *et al.* (3)	0.8	0.1–2.8	<18.0
Hirohata (27)	1.5	0.5–3.0	<18.0
Arnthorsson *et al.* (38)	1.2	0.8–1.6	17.0
Asano *et al.*[b] (37)	0.3	0.2–0.5	13.1
Kuhlmayer and Rokitansky (22)	1.9	1.3–2.6	?
Helsingen and Hillestad (16)	2.1	1.1–3.8	?
Griesser and Schmidt (25)	1.6	1.3–2.0	?
Hilbe *et al.* (26)	1.5	1.1–2.1	?
Domellof and Janunger (7)	1.4	0.8–2.3	?
Peitsch and Becker (28)	2.4	1.6–3.6	?
Watt *et al.* (32)	3.3	1.8–6.3	?
Caygill *et al.* (34)	1.8	1.3–2.2	?
Denck and Salzer[b] (23)	Insufficiently informative		
Welvaart and Warnsinck[b] (29)	Insufficiently informative		
Vitek *et al.*[b] (17)	Insufficiently informative		
Stalsberg and Taksdal (18)	2.9	1.8–5.3	
Kivilaakso *et al.* (19)	1.8	0.6–5.5	
Papachristou *et al.* (20)	3.0	1.5–6.2	
Sandler *et al.* (21)	0.7	0.3–1.6	

[a] 95% Confidence limits (when confidence limits were lacking in the original publication they were calculated, see text; Refs. 41 and 42).
[b] Excluded from meta-analysis; see text.

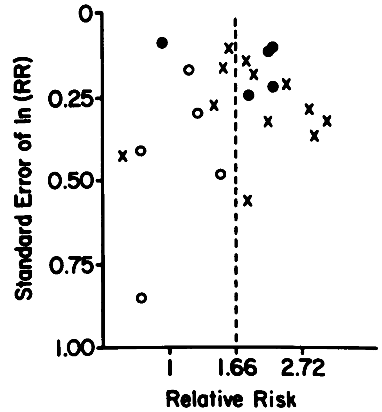

Fig. 1. Funnel plot of RR of gastric stump cancer (on logarithmic scale) according to standard error of logarithm (*ln*) of RR for studies with a mean follow-up of ≥20 years (●), 20 years (○), and follow-up not specified or case-control study (x), calculated on 22 studies summarized in Table 1. -----, weighted relative risk of pooled data.

The literature suggests that the risk of gastric stump cancer only increases after a latency of >15–20 years postoperatively. Therefore, studies were distinguished on the basis of average duration of patient follow-up and study type (<20 years follow-up, ≥20 years follow-up, and case-control studies or studies with an unspecified duration of follow-up). Also, the weighted mean of all the above 22 study results with 95% CL was calculated using as weight the inverse variance or precision of the results, *i.e.*, $1/SE^2$. Moreover, different risk factors were assessed for statistical significance by Z statistic comparison of the weighted mean relative risk for stump cancer of subsets of postgastrectomy patients (13).

For comparison of pooled summaries of various risk categories of patients, only studies sufficiently informative on these subsets were used. No heterogeneity was found among these subsets. Seven studies were used for comparison of the pooled data for males and females (11, 16, 24, 34, 36, 38, 39). Only a comparison of Billroth I and Billroth II gastrectomies could be made, and 4 informative studies were available (24, 31, 34, 39). Insufficient data prevented the assessment of risk associated with other peptic ulcer surgical procedures, *i.e.*, vagotomy or gastroenterostomy. The importance of the underlying disease or indication for the initial procedure (gastric *versus* duodenal ulcer) was evaluated from the pooled data of 3 studies (16, 34, 39).

The risk of gastric stump cancer depends on the duration of postoperative interval (1, 11, 39). Interestingly, the first 15 years postoperatively may have a decreased incidence of gastric stump cancer. Therefore, the pooled data from 4 studies (11, 34, 38, 39) with specification of postoperative intervals <15 years and ≥15 years were compared. The 15-year cutoff was dictated by the intervals used in these studies.

To provide an estimate including the two studies not meeting criteria for homogeneity, an overall relative risk was also calculated with a random effects model by the weighted noniterative procedure as described by DerSimonian and Laird (44). This model incorporates heterogeneity among studies into the analysis of the overall relative risk.

RESULTS

Fig. 1 shows the funnel display of the relative risks (on logarithmic scale) according to the standard errors of the logarithm of RR of the 22 studies available for the present meta-analysis. A distinction is made between studies with an average duration of follow-up of ≥20 years, a follow-up of <20 years, and case-control studies or studies with an unknown duration of follow-up. The dashed line indicates the summary relative risk for gastric stump cancer by weighted average approach (weighted mean RR, 1.66; 95% CL, 1.54–1.79). The relative risk calculated with a random effects model to adjust for heterogeneity was 1.46 (95% CL, 1.18–1.82).

A statistically significant difference in mean relative risks was noted for patients operated on for duodenal ulcers (RR, 0.84; 95% CL, 0.66–1.05) compared with gastric ulcers (RR, 2.12; CL 95%, 1.73–2.59) ($P = 0.001$) and for patients with 5–14 years of postoperative follow-up (RR, 0.91; 95% CL, 0.71–1.17) compared to patients with ≥15 years of follow-up (RR, 1.48; CL 95%, 1.31–1.67) ($P = 0.023$).

Differences in sex or procedure type were not statistically significant. The RR for males was 1.43 (95% CL, 1.27–1.62) and for females 1.79 (95% CL, 1.39–2.29). The weighted mean relative risk for Billroth II gastrectomy was 1.60 (95% CL, 1.15–2.18) and for Billroth I gastrectomy 1.20 (95% CL, 1.01–1.42). Table 2 summarizes the results of the pooled data for patient subgroups.

DISCUSSION

Although meta-analysis is a useful statistical tool to answer clinical inquiries by pooling literature data, some differences among individual studies which contribute to the observed results will remain unquantified (13). Despite these limitations, the present meta-analysis makes important observations in the understanding of gastric stump cancer.

This study confirms an increased relative risk of gastric stump cancer in patients with partial gastrectomy. No obvious evidence of overestimation of cancer risk by publication bias was detected. If publication bias did exist, a gap in the lower left side of the funnel display due to a lack of studies published with negative results would be expected (43).

The risk of cancer in the gastric remnant occurs after a long latency. The relative risk of stump cancer after a postoperative interval of ≥15 years was significantly higher than the first 14 years postoperatively. Many investigators have reported a trend toward increased risk with longer latency after surgery (11, 18, 21, 34, 36, 39). Moreover, a long cancer-free interval corre-

Table 2 *Summary of the results of meta-analysis in 22 reports on the risk of gastric stump cancer for total study population and subsets of postgastrectomy patients*

	Weighted mean relative risk	95% CL	*P* value[a]	Refs. for pooling data
Total study population	1.66	1.54–1.79		Table 1
Males *vs.* females	1.43	1.27–1.62	0.074	11, 16, 24, 34, 36, 38, 39
	1.79	1.39–2.29		
Billroth II *vs.* Billroth I	1.60	1.15–2.18	0.220	24, 31, 34, 39
	1.20	1.01–1.42		
Gastric ulcer *vs.* duodenal ulcer	2.12	1.73–2.59	0.001	16, 34, 39
	0.84	0.66–1.05		
Postoperative interval 5–14 yr *vs.* ≥15 yr	0.91	0.71–1.17	0.026	11, 34, 38, 39
	1.48	1.31–1.67		

[a] *P* value of significance by *Z* statistic, two-tailed.

sponds with our screening program experience, since all the stump cancers were detected after a postoperative interval of >20 years (10). As noted by others (1, 11, 39), the long cancer-free latency explains discrepancies between studies; almost all studies with a mean follow-up of ≥20 years reported an increased risk of gastric stump cancer (Fig. 1, Table 1).

The mechanism thought to underlie the increased risk of stomach cancer is production of *N*-nitroso carcinogens in the gastric remnant. These compounds are generated from nitrate and nitrite by gastric bacteria which have overgrown from postoperative hypochlorhydria. In addition, gastric reflux of bile with increased level of bile acids may play a role (40). The increasing risk of gastric stump cancer with duration of postoperative period suggests a dose-response relationship and supports this mechanism of carcinogenesis.

Also, an association between initial surgical indication and subsequent risk of stomach cancer was detected. Patients who underwent surgery for gastric ulcer seem at higher risk for stump cancer. This relationship may be explained by gastric mucosal atrophy which already exists in gastric ulcer patients at the time of the initial operation in contrast to the duodenal ulcer patients (45).

Although not statistically significant, a higher relative risk of stump cancer was observed in females than in males and after Billroth II than Billroth I gastrectomy. The risk of other surgical procedures could not be assessed, but vagotomies and gastroenterostomies for peptic ulcer have had increased risk of stomach cancer (18, 32, 34, 36). In animal experiments, the frequency of gastric cancer varied with surgical procedure and increased with associated bile reflux (46).

At first glance, the overall risk of gastric stump cancer, being slightly higher than the general population, seems unimpressive. However, closer examination reveals that postgastrectomy patients had no increased relative risk of gastric cancer during the first 15 years after surgery. Yet, the risk seems to increase steadily with each additional 5-year period of follow-up (7, 11, 18, 19, 21, 34, 36, 38, 39). In several reports, the risk of stump cancer is >4-fold higher than the general population in patients ≥25 years postoperatively (11, 18, 21, 34, 36).

In conclusion, this meta-analysis reveals differences in relative risk between subsets of postgastrectomy patients. The postoperative interval appears to be a significant risk factor. Also, the type of ulcer which prompted surgery may be important. Screening studies of postgastrectomy patients utilizing endoscopic biopsy of the gastric stump have been effective in detecting early gastric cancer (7–10, 47, 48), a lesion considered curable by surgical resection (49). Although large-scale screening programs of all postgastrectomy patients seem unjustified (4, 5), surveillance of high risk patient subsets may constitute an appropriate medical care strategy. Recommendations concerning this approach await cost-benefit analysis.

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REFERENCES

1. Carter, D. C. Cancer after peptic ulcer surgery. Gut, *28:* 921–923, 1987.
2. McLean Ross, A. H., Smith, M. A., Anderson, J. R., and Small, W. P. Late mortality after surgery for peptic ulcer. N. Engl. J. Med., *307:* 519–522, 1982.
3. Schafer, L. W., Larson, D. E., Melton, L. J., Higgins, J. A., and Ilstrup, D. M. The risk of gastric carcinoma after surgical treatment for benign ulcer disease. A population based study in Olmsted County, Minnesota. N. Engl. J. Med., *309:* 1210–1213, 1983.
4. Logan, R. F. A., and Langman, M. J. S. Screening for gastric cancer after gastric surgery. Lancet, *2:* 667–670, 1983.
5. Sonnenberg, A. Endoscopic screening for gastric stump cancer—would it be beneficial? A hypothetical cohort study. Gastroenterology, *87:* 489–495, 1984.
6. Zuerlein, N., Denzler, T., and Schenken, J. R. Cancer arising in the gastric stump. Occurrence following resection for benign peptic ulcer disease. Arch. Pathol. Lab. Med., *109:* 958–960, 1985.
7. Domellöf, L., and Janunger, K. G. The risk for gastric carcinoma after partial gastrectomy. Am. J. Surg., *134:* 581–584, 1977.
8. Schrumpf, E., Stadaas, J., Myren, J., Serck-Hanssen, A., Anne, S., and Osnes, M. Mucosal changes in the gastric stump 20–25 years after partial gastrectomy. Lancet, *2:* 467–469, 1977.
9. Stokkeland, M., Schrumpf, E., Serck-Hanssen, A., Myren, J., Osnes, M., and Stadaas, J. Incidence of malignancies of the Billroth II operated stomach. A prospective follow-up. Scand. J. Gastroenterol. Suppl., *16:* 169–171, 1981.
10. Offerhaus, G. J. A., vd Stadt, J., Huibregtse, K., and Tytgat, G. N. J. Endoscopic screening for malignancy in the gastric remnant: the clinical significance of dysplasia in gastric mucosa. J. Clin. Pathol., *37:* 748–754, 1984.
11. Offerhaus, G. J. A., Tersmette, A. C., Huibregtse, K., *et al.* Mortality caused by stomach cancer after remote partial gastrectomy for benign conditions: forty years of follow up of an Amsterdam cohort of 2633 post-gastrectomy patients. Gut, *29:* 1588–1590, 1988.
12. Rehner, M., and Peters, K. Statistische Beurteilungsprobleme. *In:* K. Dahm and M. Rehner (eds.), Das Karzinom im Operierten Magen Stuttgart, pp. 41–48. Georg Thieme Verlag, 1975.
13. Greenland, S. Quantitative methods in the review of epidemiologic literature. Epidemiol. Rev., *9:* 1–30, 1987.
14. Light, R. J., and Pillemer, D. B. Summing up: the science of reviewing research. Cambridge, MA: Harvard Unversity Press, 1984.
15. Berlin, J. A., and Chalmers, T. C. Meta-analysis of branched chain amino acids in hepatic encephalopathy. Gastroenterology, *97:* 1043–1045, 1989.
16. Helsingen, N., and Hillestad, L. Cancer development in the gastric stump after partial gastrectomy for ulcer. Ann. Surg., *143:* 173–179, 1956.
17. Vitek, J., Vrubel, F., and Zejda, V. Primare Magenstumpfkarzinome an Ulcusresezierten. Zentralbl. Chir., *88:* 246–253, 1963.
18. Stalsberg, H., and Taksdal, S. Stomach cancer following gastric surgery for benign conditions Lancet, *2:* 1175–1177, 1971.
19. Kivilaakso, E., Hakkiluoto, A., Kalima, T., and Sipponen, P. Relative risk of stump cancer following partial gastrectomy. Br. J. Surg., *64:* 336–338, 1977.
20. Papachristou, D. N., Agnanti, N., and Fortner, G. J. Gastric carcinoma after treatment of ulcer. Am. J. Surg., *139:* 193–196, 1980.
21. Sandler, R. S., Johnson, M. D., and Holland, K. L. Risk of stomach cancer after gastric surgery for benign conditions. A case-control study. Dig. Dis. Sci., *29:* 703–708, 1984.

22. Kühlmayer, R., and Rokitansky, O. Das Magenstumpfkarzinom als Spätproblem der Ulcuschirurgie. Langenbecks Arch. Chir., *278:* 361–375, 1954.
23. Denck, H., and Salzer, G. 21 Jahre Ulcuscirurgie an der Klinik Denk in Wien 1933–1954. VI Teil. Die Fragen der Karzinomgefahrdung des Ulcuskranken und Magenresezierten. Gastroenterologia, *88:* 94–109, 1957.
24. Krause, U. Late prognosis after partial gastrectomy for ulcer. A follow-up study of 361 patients operated upon from 1905 to 1933. Acta Chir. Scand., *144:* 341–354, 1957.
25. Griesser, G., and Schmidt, H. Statistische Erhebungen uber die Haufigkeit des Karzinoms nach Magenoperation wegen eines Geschwursleidens. Med. Welt., *35:* 1836–1840, 1964.
26. Hilbe, G., Salzer, G. M., Hussl, H., and Kutschera, H. Die Karzinomgefahrdung des Resektionsmagens. Langenbecks Arch. Klin. Chir., *323:* 142–153, 1968.
27. Hirohata, T. Mortality from gastric cancer and other causes after medical or surgical treatment for gastric ulcer. J. Natl. Cancer Inst., *41:* 895–908, 1968.
28. Peitsch, W., and Becker, H. D. Frequency and prognosis of gastric stump-cancer. Frontiers Gastrointest. Res., *5:* 170–177, 1979.
29. Welvaart, K., and Warnsinck, H. M. The incidence of carcinoma of the gastric remnant. J. Surg. Oncol., *21:* 104–106, 1982.
30. Clark, C. G., Ward, M. W. N., McDonald, A. M., and Tovey, F. I. The incidence of gastric stump cancer. World J. Surg., *7:* 236–240, 1983.
31. Fischer, A. B., Graem, N., and Jensen, O. M. Risk of gastric cancer after Billroth II resection for duodenal ulcer. Br. J. Surg., *70:* 552–554, 1983.
32. Watt, P. C. H., Patterson, C. C., and Kennedy, T. L. Late mortality after vagotomy and drainage for duodenal ulcer. Br. Med. J., *288:* 1335–1338, 1984.
33. Tokudome, S., Kono, S., Ikeda, M., *et al.* A prospective study on primary gastric stump cancer following partial gastrectomy for benign gastroduodenal diseases. Cancer Res., *44:* 2208–2272, 1984.
34. Caygill, C. P. J., Hill, M. J., Kirkham, J. S., and Northfield, T. C. Mortality from gastric cancer following gastric surgery for peptic ulcer. Lancet, *1:* 929–931, 1986.
35. Loscos, J. M., del Olmo, A. G., Nisa, E., Baki, W., Nazal, R., and Ramirez-Armengol, J. A. Cancer of the gastric stump. Gastrointest. Endosc., *32:* 75–77, 1986.
36. Viste, A., Bjornestad, E., Opheim, P., *et al.* Risk of carcinoma following gastric operations for benign disease. A historical cohort study of 3740 patients. Lancet, *2:* 502–505, 1986.
37. Asano, A., Mizuno, S., Sasaki, R., Aoki, K., Yokoyama, H., and Yokoyama, Y. The long-term prognosis of patients gastrectomized for benign gastroduodenal diseases. Jpn. J. Cancer Res., *78:* 337–348, 1987.
38. Arnthorsson, Tulinius, H., Egilsson, V., Sigvaldason, H., Magnusson, B., and Thorarinsson, H. Gastric cancer after gastrectomy. Int. J. Cancer, *42:* 365–367, 1988.
39. Lundegardh, G., Adami, H.-O., Helmick, C., Zack, M., and Meirik, O. Stomach cancer after partial gastrectomy for benign ulcer disease. N. Engl. J. Med., *319:* 195–200, 1988.
40. Offerhaus, G. J. A., Tersmette, A. C., Tersmette, K. W. F., Tytgat, G. N. J., Hoedemaeker, P. J., and Vandenbroucke, J. P. Gastric, pancreatic, and colorectal carcinogenesis following remote peptic ulcer surgery. Review of the literature with the emphasis on risk assessment and underlying mechanism. Modern Pathol., *1:* 352–356, 1988.
41. Woolfe, B. On estimating the relation between blood group and disease. Ann. Hum. Genet., *10:* 251–253, 1955.
42. Ederer, F., and Mantel, N. Confidence limits on the ratio of two Poisson variables. Am. J. Epidemiol., *100:* 165–167, 1974.
43. Vandenbroucke, J. P. Passive smoking and lung cancer: a publication bias? Br. Med. J., *296:* 391–392, 1988.
44. DerSimonian, R., and Laird, N. Meta-analysis in clinical trials. Contr. Clin. Trials, *7:* 177–188, 1986.
45. Schrager, J., Spink, R., and Mitra, S. The antrum in patients with duodenal and gastric ulcers. Gut, *8:* 497–508, 1967.
46. Kobori, O., Shimizu, T., Maeda, M., *et al.* Enhancing effect of bile and bile acid on stomach tumorigenesis induced by *N*-methyl-*N'*-nitro-*N*-nitrosoguanidine in Wistar rats. J. Natl. Cancer Inst., *73:* 853–861, 1984.
47. Greene, F. L. Neoplastic changes in the post-gastrectomy stomach: results of an eight-year endoscopic screening program (Abstract). Gastrointest. Endosc., *35:* 153, 1989.
48. Offerhaus, G. J. A., vd Stadt, J., Huibregtse, K., Tersmette, A. C., and Tytgat, G. N. J. The mucosa of the gastric remnant harboring malignancy. Histological findings in the biopsies of 504 asymptomatic patients 15–46 years after partial gastrectomy with the emphasis on non-malignant lesions. Cancer (Philadephia), *64:* 698–703, 1989.
49. Itoh, H., Oahata, Y., Nakamura, K., Nagata, T., Mibu, R., and Nakayama, F. Complete ten-year post-gastrectomy follow-up of early gastric cancer. Am. J. Surg., *158:* 14–16, 1989.

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