

ORIGINAL ARTICLE

Risk of esophageal cancer in achalasia cardia: A meta-analysis

Clare L Gillies,[†] Affifa Farrukh,* Keith R Abrams[†] and John F Mayberry* 

*Department of Digestive Diseases, University Hospitals of Leicester NHS Trust and [†]Department of Health Sciences, University of Leicester, Leicester, UK

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Correspondence

Professor John Mayberry, Department of Digestive Diseases, Leicester General Hospital, Gwendolen Road, Leicester LE5 4PW, UK. Email: johnmayberry@yahoo.co.uk

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Abstract

Introduction: The association between cancer of the esophagus and achalasia has long been recognized. However, it has also been recognized that cancers themselves can give rise to achalasia-like syndromes. The risk of developing cancer is also a factor in assessing whether there is a potential role for surveillance in this disease. This paper uses published work to form the basis for a meta-analysis of the risk of developing esophageal cancer among patients with pre-existing achalasia.

Methods: This paper considered cancer risk reported in a range of studies of achalasia published over a 50-year period. Twenty-seven potential studies were identified. In 16 reports, it was possible to extract information on both length of follow-up and duration of achalasia so that person-years duration (PYD) could be calculated. The analysis was stratified between cancers identified in the first year after diagnosis of achalasia and cancers identified in subsequent years.

Results: From pooling the results of 16 studies, the incidence rate of esophageal cancer in achalasia patients was estimated to be 1.36 (95% CI: 0.56, 2.51) per 1000 person years. This is over 10 times higher than the general population incidence rates as reported by the IARC.

Conclusions: Therefore, our meta-analysis shows that achalasia is a major risk factor for the development of esophageal cancer. This is supported by the results from the time-stratified analysis. Incidence of esophageal cancer per 1000 person years was lower in the first year after diagnosis of achalasia than in subsequent years. This is strong evidence against the idea that achalasia may be induced by esophageal cancer instead of vice versa.

Introduction

An association between achalasia and esophageal cancer was first recognized as long ago as 1872.¹ The patient had experienced difficulty with swallowing for 40 years before the tumor developed. Several subsequent studies have suggested that the risk of developing squamous carcinoma of the esophagus for a patient with achalasia is somewhere between 3^{18,32} and 30%.^{2–4} In 1984, Chuong *et al.* questioned this association, and currently, the American Society for Gastrointestinal Endoscopy does not advocate surveillance in patients with achalasia because there is insufficient data from large well-conducted epidemiological studies.⁵ However, there is emerging pressure from some groups to introduce such an approach for the long-term management of this condition.⁶

The first purpose of this meta-analysis of studies conducted over the last 50 years was to establish the magnitude of the risk and to investigate how this changes with time following diagnosis. On the basis of such data, it then becomes possible to consider the potential efficacy of a screening program and the frequency with which endoscopic intervention would be needed for a surveillance program to be effective and from this the likely cost and cost effectiveness of such a program.⁷ Such a study will

not address the issue of the effectiveness of endoscopists in detecting early lesions—an area in which gastroenterologists and specialist pathologists have largely failed to prove themselves in the field of ulcerative colitis.⁸ However, in the case of achalasia, because of the enlarged nature of the esophagus, patients usually develop symptoms late and therefore present only at a stage of advanced malignancy, and so, the overall prognosis is poor. In this study, there was an opportunity to assess the magnitude of the risk of cancer and to consider whether surveillance could be of value. This needs to also be considered within the legal terms of what such a program would offer patients and at what risk.⁹

Methods

A literature review was carried out of both the English and non-English language literature using Medline. Twenty-seven potential studies were identified where patients with achalasia had been followed up and subsequent cancer incidence had been reported. Each paper was then reviewed, and their references were checked to identify further studies. Where possible, information was extracted on both length of follow-up and duration of achalasia so that person-years duration (PYD) could be

calculated. In addition, information was extracted on the number of cancers and whether the cancer developed within the first year after diagnosis of achalasia or in subsequent years.

Only 16 of the 27 studies identified provided sufficient information to establish the total number of cancers detected and for overall PYD to be calculated. Sufficient detail was provided in 12 of the 16 studies to identify whether cancer was diagnosed in the first year after diagnosis of achalasia or in later years. Figure 1 gives a break down of the data extraction process. Many of the studies, especially when stratified, reported zero cases of cancer. A continuity correction of 0.5 was added to the zeros so that a meta-analysis model in which the log incidence rate was assumed to be approximately normally distributed could be applied. As an alternative to using a continuity correction, the data were also modeled directly using a Bayesian Poisson regression meta-analysis, which has the advantage of allowing all the uncertainty associated with the between-study heterogeneity to be included.

The analysis was stratified between cancers identified in the first year after diagnosis of achalasia and cancers identified in subsequent years. This was because it was important to identify cases in which the cancer may have developed prior to a diagnosis of achalasia or where patients had been inappropriately diagnosed with achalasia when, in fact, they were suffering from esophageal cancer. Stratifying the analysis also enabled some assessment of how the risk of cancer changes with time since diagnosis.

Results

Table 1 lists the characteristics of the studies included in the meta-analyses. Most of the studies used were carried out in Europe, although studies from the United States, South America, and Australia were also included. Table 2 documents the studies that were excluded and the reasons for doing so. The time period covered by the studies varied widely; some started as early as the 1930s, while others ran into the 1990s. All studies covered a time period of at least 10 years. The size of the studies also varied, with the number of achalasia cases investigated ranging from 43 to 1062. Mean age of study participants was not always reported, but it has been included in Table 1 where the figures were available. Chagas disease is an infective disease comparable to achalasia but only found in Latin America. Two of the studies in this meta-analysis were carried out in Argentina and Chile, where the achalasia cases followed up could, in fact, be potentially misdiagnosed Chagas cases. Fortunately, both these studies tested all participants for Chagas disease to try and identify any such cases. The Argentinian study found only 2 cases of Chagas among their 242 patients, whereas the Chilean study found 15 cases of Chagas among the 100 patients they followed up. As these are a small proportion of the study samples, and the data for the true achalasia patients could not be separated out from the study results, these studies, and consequently a few Chagas cases, were retained in the meta-analysis.

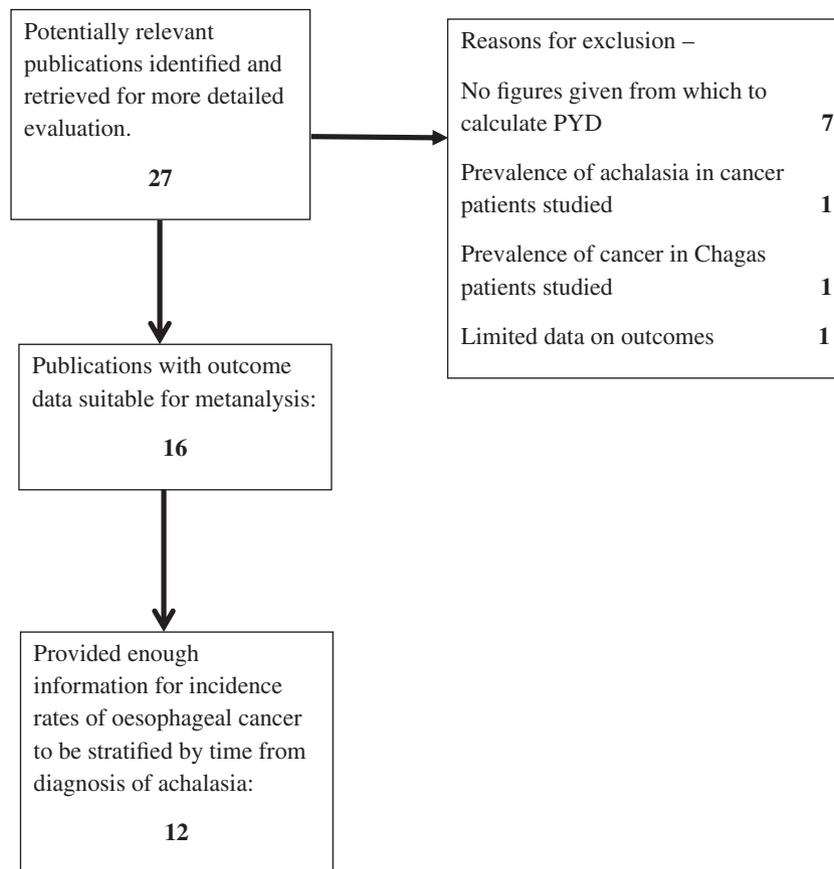


Figure 1 Flow diagram.

Table 1 Characteristics of studies used in the meta-analysis

Study	Period	Country	Number of Cases (cancers)	Mean age (SD)	Age range
Aggestrup <i>et al.</i> ¹⁰	1949–1964	Denmark	146 (10)	46 [†]	4–83
Arber <i>et al.</i> ¹¹	1973–1983	Israel	162 (0)	47.7 (18.3)	2–85
Barrett ¹²	1935–1964	England	120 (7)	—	4–84
Chuong <i>et al.</i> ⁵	1971–1981	USA	100	53.1	41–89
Corti <i>et al.</i> ¹³	1970–1990	Argentina	242 (8)	61.3	41–76
Csendes <i>et al.</i> ¹⁴	1973–1987	Chile	100 (3)	42	13–18
Ellis ³	1933–1948	England	69 (7)	—	12–59
Malthaner <i>et al.</i> ¹⁵	1964–1983	Canada	52 (0)	43.7	22–67
Mattioli <i>et al.</i> ¹⁶	1955–1991	Italy	185 ²⁸	41.5	4–76
Meijssen <i>et al.</i> ¹⁷	1973–1988	Netherlands	195 (3)	52	—
Perrachia <i>et al.</i> ¹⁸	1967–1988	Italy	244 (1)	—	—
Pierce <i>et al.</i> ¹⁹	1954–1969	USA	110	—	—
Russell <i>et al.</i> ²⁰	1979–1989	Australia	43	49 [†]	13–86
Sandler <i>et al.</i> ²¹	1964–1989	Sweden	1062 (24)	57.2	—
Streitz <i>et al.</i> ²²	1970–1992	USA	241 (3)	—	—
Wychulis <i>et al.</i> ²³	1935–1967	USA	1318 (7)	—	—

[†]Median.

Table 2 Studies not included in the meta-analysis of cancer risk in achalasia

Author	Date	Country	Cases	Mean age	Range	Follow-up (months)	Cancers
Overlap with studies in analysis							
Ruffato <i>et al.</i> ²⁴	1978–2002	Italy	174	57 (median)	7–83	93	4
Leeuwenburgh <i>et al.</i> ²⁵	1975–2006	Netherlands	448	51	4–92	107	15
Zaninotto <i>et al.</i> ²⁶	1980–1992	Italy	228	—	—	220	4
Other studies							
Khan <i>et al.</i> ²⁷	1987–2003	Pakistan	300	40	17–72	192	0
West <i>et al.</i> ²⁸	1971–1994	Netherlands	125	—	—	144	6
Brucher <i>et al.</i> ²⁹	1982–1998	Germany	124	49	9–91	67	4
Harris <i>et al.</i> ³⁰	1991–1998	England	40	38 (median)	15–84	17	3
Gugulski <i>et al.</i> ³¹	1961–1992	Poland	252	41	15–81	138	0
Liu <i>et al.</i> ³²	1979–2000	China	176	32.9	—	168	3

Of the two methods used for fitting the meta-analyses models, it was thought that the Bayesian approach, as opposed to the normal approximation, would give the most accurate results. The results from the normal approximation would be slightly inflated due to the use of a continuity correction, and the Bayesian model also has the advantage of allowing for all the uncertainty associated with the between-study heterogeneity. Therefore, it is the results from the Bayesian model that are reported in Table 3. The drawback of the Bayesian model is that the confidence intervals of estimates from individual studies are shrunken as the model draws information from all the studies to estimate the confidence intervals. Therefore, for the purposes of the forest plot (Fig. 2), the normal approximation model was used. Figure 2 shows the forest plots. Sixteen studies had information on number of esophageal cancer cases for the whole time period after diagnosis of achalasia. For 12 studies, the cancer cases could be divided into those occurring in the first year after diagnosis of achalasia and those occurring in subsequent years. Generally, there was a higher incidence rate of esophageal cancer in subsequent years. Therefore, risk of esophageal cancer was increased in patients who had lived with achalasia for more than 1 year.

Table 3 reports the results of the Bayesian meta-analysis. The pooled incidence rate of esophageal cancer in achalasia patients was 1.36 (95% CI: 0.56, 2.51) per 1000 person-years. When results were stratified by time since diagnosis of achalasia, it could be seen that incidence rates were lower in the first year after diagnosis when compared to subsequent years, 0.71 (95% CI: 0.00, 4.71) compared to 1.55 (0.60, 2.53) per 1000 person-years, respectively. Table 4 reports the population incidence rates of esophageal cancer in regions of the world where the studies used in this meta-analysis were based. The confidence intervals for the pooled estimates for all years and > 1 year, do not include any of the population estimates; this shows that the incidence of

Table 3 Incidence of esophageal cancer in patients with achalasia, estimated from the Bayesian Poisson regression meta-analysis

Data used	Studies (n)	Incidence rate (95% credibility intervals)
All years	16	1.36 (0.56, 2.51)
<Year 1	13	0.71 (0.00, 4.71)
>Year 1	13	1.55 (0.60, 2.53)

Rates are per 1000 person-years.

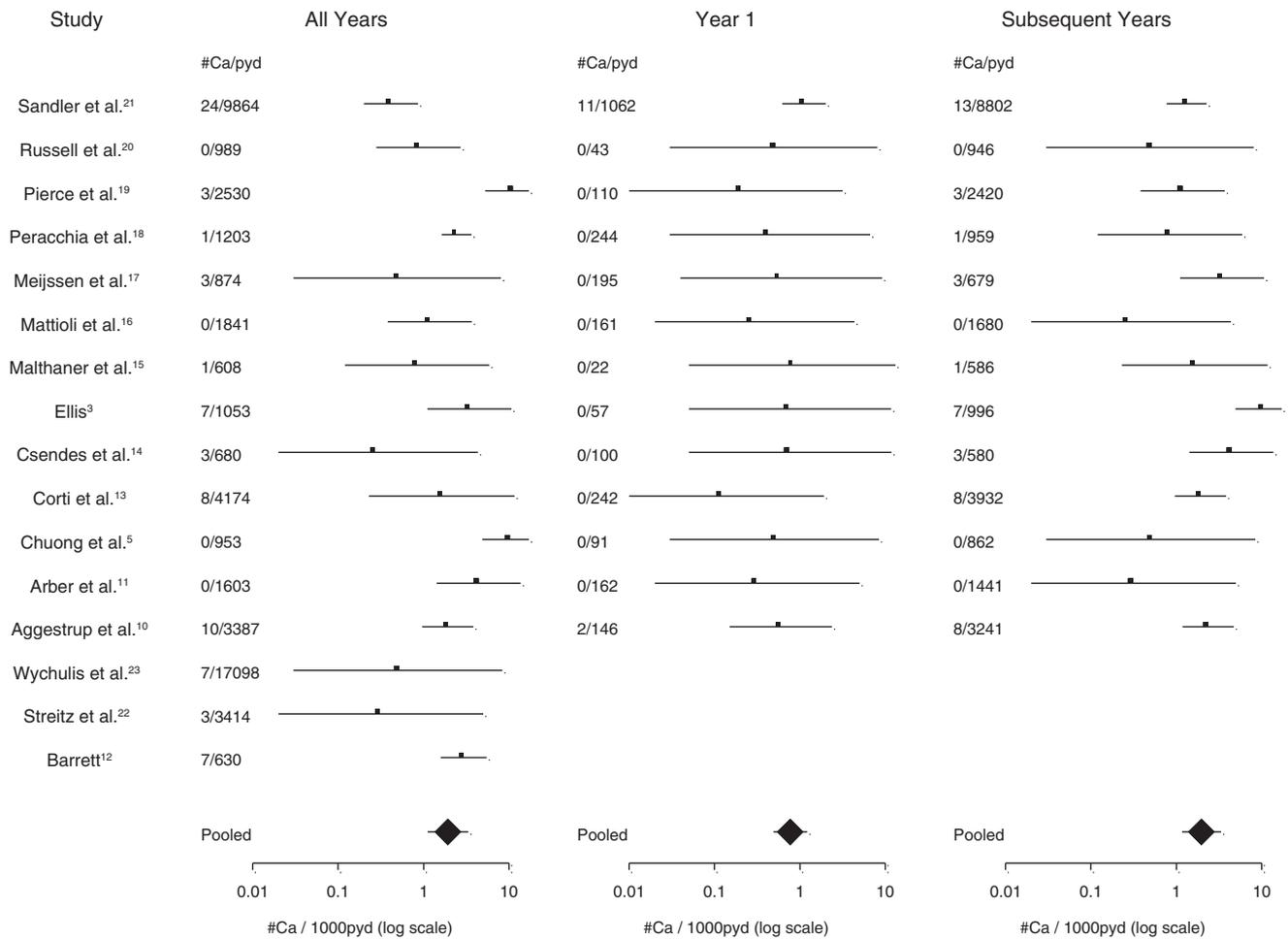


Figure 2 Meta-analysis of esophageal cancer occurrence stratified by time since diagnosis.^{1–3,6–8,12,22–26,29,30,32}

esophageal cancer in the achalasia patients included in this meta-analysis were significantly higher than those of general populations ($P < 0.05$). The pooled incidence for <1 year after diagnosis of achalasia was not significantly different from the population estimates reported in Table 4. This is probably due to limited data resulting in wide confidence intervals.

Discussion

From pooling the results of 16 studies, the incidence rate of esophageal cancer in achalasia patients was estimated to be 1.36 (95% CI: 0.56, 2.51) per 1000 person-years. This is over 10 times higher than the general population incidence rates as reported by

the IARC. Therefore, our meta-analysis shows that achalasia is a major risk factor for the development of esophageal cancer. This is supported by the results from the time-stratified analysis. Incidence of esophageal cancer per 1000 person-years was lower in the first year after diagnosis of achalasia than in subsequent years. This is strong evidence against the idea that achalasia may be induced by esophageal cancer instead of vice versa. The data do not allow an analysis of whether treatment of achalasia reduces cancer risk, although risk seems to increase with duration of disease. Until this question is addressed, it will not be possible to advocate routine surveillance.

It is important to remember that the achalasia patients in this meta-analysis may not be directly comparable to general populations. The majority of the studies included had a mean age of participants in the 40s or 50s. This is fairly comparable to a westernized population, although it is accepted that age is a possible confounder. Unfortunately, as age was poorly reported in these studies, it was impossible to calculate standard morbidity ratios, which would have accounted for any confounding effects of age.

Incidence rates of esophageal cancer have changed over time, and in this study, we have compared incidence in patients from as early as the 1930s with the general population figures from

Table 4 Incidence of cancer of the esophagus per 1000 person-years

Region	Male	Female
World	0.09	0.04
Northern Europe	0.07	0.07
Northern America	0.06	0.02
South America	0.06	0.02

Figures from GLOBOCAN.³²

1990. Although esophageal cancer is on the increase,³² this cannot explain why incidence rates have been found to be so much higher in these studies of achalasia patients.

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