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Original contribution

A review of the incidence of adenocarcinoma detected during surveillance for Barrett's esophagus☆

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Summary The objective of this study is to provide an up-to-date estimate of the incidence of adenocarcinoma detected during surveillance of Barrett's esophagus. Fifty-five longitudinal studies involving approximately 61 000 patients were reviewed. A general linear model analyses with Poisson link function was used to study how the number of cancer cases detected depended on study details. The studies seemed to follow the same statistical model, and the probability of developing Barrett's carcinoma during surveillance was found to depend on the following variables: how Barrett's metaplasia was defined, the number of patients studied, the mean time of follow-up, and the fraction of patients followed up for at least 5 years. The model derived from all the studies predicted that the per-person probability of developing cancer in 5 years of complete follow-up is approximately .0012.
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1. Introduction

It has become clear that finding adenocarcinoma (Barrett's carcinoma) is an uncommon event during surveillance for Barrett's esophagus, [1,2]. Nevertheless, it is frustrating to witness the presence of Barrett's carcinoma at first endoscopy, which is not so an uncommon event to those of us involved with Barrett's surveillance. Some have even reported that 95% of Barrett's carcinomas developed outside a surveillance program [2]. Because of these issues, because reports of the incidence of Barrett's carcinoma during surveillance have yielded variable results, and because follow-up biopsies for Barrett's esophagus comprise a significant workload for pathologists, here I undertake a brief review and analysis of data from 55 longitudinal surveillance studies of Barrett's esophagus. Altogether, this study uses data from approximately 61 000 patients.

2. Materials and methods

2.1. Study patients

The data for this study came from 55 previously reported longitudinal studies of Barrett's esophagus [3-51] (several studies were reported in one review). When a single institution reported their data several times, only the latest was used. Nevertheless, because some studies involved collaborations between several institutions and because the number of study

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Table 1 Summary of surveillance studies

Characteristics	Values
Publication year, median (range)	2002 (1984-2018)
No. of patients, mean (range)	1136 (26-16 330)
Years of follow-up, mean (range)	5.7 (2.7-17.3)
Fraction of patients followed up to 5 y, mean (range)	0.38 (0.15-0.75)
No. of cancer patients found, mean (range)	21 (0-337)
No. of studies defining Barrett's as intestinal	25
No. of studies defining Barrett's as columnar	30

Table 2 General linear model analysis of the number of patients developing cancer during surveillance of Barrett's esophagus

Variable	Coefficient	*P*
Intercept	−2.53	NA
Intestinal type	0.455	~0
No. of patients*	0.888	~0
Mean follow-up (y)	0.277	.031
Fraction followed to 5 y	−6.05	~0

Abbreviation: NA, not applicable.

patients used twice was not given, it is possible that a few patients appear more than once. Although the studies reported several outcomes during surveillance of Barrett's patients, the outcome targeted here is the occurrence of adenocarcinoma because this avoids diagnostic disagreements over the presence and grades of dysplasia. Studies were included if their patients had Barrett's metaplasia (either columnar or intestinal type) and if the time of follow-up began with the first endoscopy documenting Barrett's. Otherwise, there were no exclusion criteria. Altogether, the studies reported 61,371 surveillance patients including 1106 who developed adenocarcinoma. Other details are summarized in Table 1.

2.2. Statistical model

Because the number of cancer cases observed during surveillance is a counted phenomenon, the Poisson probability function is a natural one to use, and this was combined with a general linear model to study how the number of discovered cancer cases related to study details. Specifically, a general linear model with Poisson link function was used with S-PLUS software (MathSoft, Seattle, WA).

One factor often ignored in prior reviews of Barrett's surveillance studies was censoring, that is, when patients were followed up for varying periods. Although the degree of censoring was in general not reported, a few studies provided sufficient data to favor an exponential drop in the number of available patients with time [13,19,20,30,48]. Thus, for this analysis, an exponential model was used to estimate the fraction of patients available, *fa*, at a given time, *t*, as follows:

$$fa = \exp(-\beta^* \ t) \quad (1)$$

and β was estimated as the inverse of the mean follow-up.

3. Results

Altogether, 53 studies provided sufficient details for the general linear model analysis, and the results are shown in Table 2. The positive sign for the intestinal type coefficient implies that studies restricted to patients having documented intestinal type Barrett's esophagus at study entry found more cancer patients than did studies accepting any type of columnar epithelium. The positive signs for the coefficients for number of patients and mean follow-up time imply the expected results that studies with more patients and longer follow-up found more cancer patients. However, the negative coefficient sign for the fraction followed to 5 years implies that studies with a higher fraction followed to 5 years observed a *lower* incidence of cancer. In other words, those with more censoring observed a *higher* cancer incidence. The result reflects how cancer incidence is routinely defined, that is, as the ratio of the number of cancer cases to the product of number of patients × mean years of follow-up. Here, studies with higher fractions of patients followed up for at least 5 years yielded larger denominators and therefore lower incidences. This effect is illustrated in Fig. 1, which shows a plot of incidence on the *y*-axis versus the fraction followed for 5 years on the *x*-axis. The points come from the studies, and the line shows the trend for the data (lowess function in S-PLUS). The plot demonstrates that studies with a higher fraction followed had lower reported incidences.

Fig. 2 demonstrates how well the model of Table 2 fit the consolidated data. The *x*-axis provides the expected number

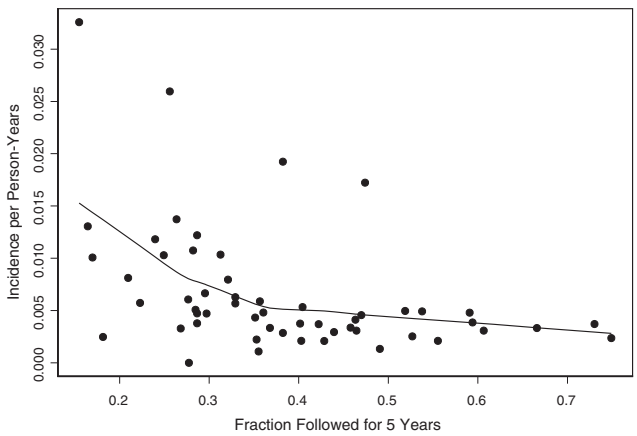

Fig. 1 A plot of the incidence per patient-years versus the estimated fraction of patients followed up for 5 years.

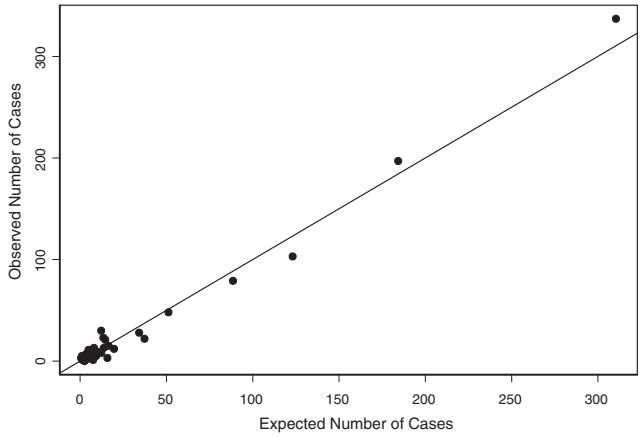

Fig. 2 A plot of expected number of cancer cases (*x*-axis) versus observed number of cancer cases (*y*-axis) for each study (each point on the plot). The line shows where perfect agreement should occur and demonstrates that all of the studies seem to follow this model.

of cancer cases predicted by the model, and the *y*-axis provides the number of cancer cases observed. The line shows where perfect agreement should occur. It demonstrates that despite the noise documented in Fig. 1, all of the studies seemed to follow the same statistical model.

Table 3 provides the model's estimate of number of cancer cases found at 5 and 10 years if 1000 patients were recruited at the beginning of the study and if censoring was such that 38% were followed up to 5 years (the estimated average across all the studies). The results demonstrate once again the population with intestinal metaplasia yielded more cancer cases and that longer follow-up resulted in more cases. Finally, the coefficients in Table 2 predict that the per-person probability of developing carcinoma in 5 years is approximately .0012 if the 5-year follow-up is complete.

Lastly, 23 of the 55 studies reported that some adenocarcinomas were found at the time of, or shortly after, the first endoscopy. For these studies, 63% of the cancer patients were found at the first endoscopy.

Table 3 Number of expected cancer patients per 1000 study patients

	Years of follow-up	
Barrett's definition	5	10
Intestinal	23	93
Columnar	15	59

NOTE. Entries are the number of expected cancer cases predicted by the model of Table 2. These results assume a starting group of 1000 study patients with 38% followed up for 5 years, which was the average across the studies used in the analysis.

4. Discussion

Many have observed that different surveillance studies of Barrett's esophagus reported different incidence rates of adenocarcinoma [41,52]. Although some have speculated that this variation was due to publication bias [1], this review and its analysis suggest that the variation is largely due to 4 factors: how Barrett's metaplasia was defined, the number of study patients, the length of follow-up, and the degree of censoring. After controlling for these 4 factors, the analysis here demonstrates that all the studies followed the same model that implies a uniform incidence of Barrett's carcinoma. Studies restricted to those with intestinal metaplasia found more cancer patients, and this result favors restricting the definition of Barrett's to specimens with intestinal-type epithelium. Studies with larger numbers of patients and longer follow-up also found more cancer patients. Furthermore, both the analyses of Table 2 and Fig. 1 demonstrate that studies with a higher fraction followed to 5 years reported a lower incidence of adenocarcinoma. Because most study patients do not develop adenocarcinoma, the result suggests that studies with less complete follow-up may have fewer cancer-free patients contributing to the denominators for calculating incidence. In other words, the patients who are doing well may be more difficult to follow up, and patients who develop adenocarcinoma, especially early in follow-up, may be easier to follow up. With complete follow-up to at least 5 years, the statistical model predicted a per-person probability of detecting cancer in 5 years of .0012, a rate so low as to favor less vigorous or more targeted surveillance. To my knowledge, this is the first study to address the importance of censoring in surveillance for Barrett's esophagus, and the results suggest that those undertaking longitudinal studies of Barrett's esophagus should take care to obtain complete follow-up of their study patients.

Finally, because 23 of the studies collectively found that 63% of the Barrett's carcinomas were found at first endoscopy, there may be a form of Barrett's carcinoma that evolves too quickly to be detected during surveillance.

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