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Cost effectiveness of detecting Barrett's cancer

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Abstract

***Background*—Screening Barrett's oesophagus is controversial owing to a large variation in the reported incidence of neoplastic change and lack of evidence that screening improves tumour prognosis.**

***Aims*—To determine the incidence of Barrett's cancer, its cost of detection, and stage of disease at time of diagnosis.**

***Patients and Methods*—Data from our surveillance programme have been reviewed to assess the incidence of malignant change, tumour stage at diagnosis, and the cost per cancer detected.**

***Results*—166 patients had annual endoscopic surveillance. Six patients (five men) developed cancer – an incidence of one cancer per 59 male and 167 female patient-years of follow up. The screened group had a significantly earlier stage than a control group of unscreened cancers ($p<0.05$). The cost of detecting one cancer was £14 868 for men and £42 084 for women.**

***Conclusions*—The cost of screening for Barrett's cancer is high but may be justified on the basis of the high incidence of detecting early stage disease.**

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Keywords: Barrett oesophagus, cost-benefit analysis, cost effectiveness, oesophageal neoplasms, precancerous conditions.

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Barrett's oesophagus is a common acquired condition that predisposes to development of adenocarcinoma of the oesophagus.[1] It is usually related to acid reflux.[2] About 10% of patients having endoscopy for reflux symptoms will have Barrett's oesophagus.[3] Necropsy series suggest that 1% of the adult population develop Barrett's oesophagus.[4]

The relative risk of developing cancer with Barrett's oesophagus is difficult to measure. Prevalence rates of Barrett's cancer in the surgical literature that range from 10 to 46%[1 5] are gross overestimates of its true prevalence because benign disease tends to be asymptomatic.[6] Only one case in 20 is detected in life.[4] The most accurate method of measuring the risk of Barrett's cancer is therefore its incidence. Prospective endoscopic surveillance programmes provide the most accurate means of measuring the incidence, which has been estimated to be on average one cancer per 76 (range 48–175) patient-years of surveillance[7] (Table I).

Over the past decade, adenocarcinoma of the oesophagus has been increasing in contrast with a slight decline in the incidence of squamous cell carcinoma.[19 20] This may explain why the incidence of Barrett's cancer tends to be lower in the earlier reports in Table I. It is estimated that 64–86% of all adenocarcinomas of the oesophagus originate from Barrett's epithelium.[21 22] Short segment metaplasia may account for a large proportion of the remainder.[23]

Screening for adenocarcinoma in Barrett's oesophagus has been advocated with the aim of identifying early asymptomatic cancer.[24] Dysplasia often progresses from low to high grade and is still the most effective way of identifying those at highest risk of malignancy.[25] High grade dysplasia is associated with early invasive malignancy in 50–66% of cases and is considered by some surgeons to be an indication for surgery.[26 27] Resection of early stage adenocarcinoma or high grade dysplasia is associated with prolonged survival.[28] By contrast, lymph node positive disease is often not resectable, and resected cases have a low cure rate.[29]

Despite this, endoscopic surveillance is not universally undertaken. The reasons for this probably include cost factors, but also uncertainty about the 'pick-up' or case detection rate in an already elderly population. Furthermore, and in the current climate of evidence-based medicine, the proof that screen detected cancers have a better prognosis than those which have not been under surveillance is still lacking.

We have evaluated our experience of screening for Barrett's cancer. The aims were to determine the incidence of Barrett's cancer, to evaluate the effectiveness of surveillance in detecting curable, early stage cancers, and to estimate the case detection cost.

TABLE I *Reported incidence of Barrett's cancer*

Report	*No of patient-years*	*No of cancers*	*Incidence (per patient-year)*
Spechler* 1984[8]	350	2	1 in 175
Sprung 1984[9]	162	2	1 in 81
Cameron* 1985[10]	884	2	1 in 441
Sampliner 1985[11]	92	1	1 in 92
Achkar 1988[12]	166	1	1 in 166
Robertson 1988[13]	218	3	1 in 56
Van Der Veen* 1989[14]	681	4	1 in 170
Ovaska 1989[15]	166	3	1 in 55
Hameeteman 1989[16]	269	5	1 in 52
Skinner 1989[17]	145	3	1 in 48
Williamson 1991[18]	497	5	1 in 99

*Postal questionnaire; all other reports are endoscopic surveillance.

Methods

Patients

The databases of the gastrointestinal units at the Royal Liverpool and Broadgreen Hospitals were used to identify all patients with an endoscopic diagnosis of Barrett's oesophagus over a 12 year period between 1981 and 1992. Cross referencing with the pathological databases was then used to obtain histological confirmation of a columnar lined (Barrett's) oesophagus. Barrett's oesophagus was defined as columnar epithelium in biopsy specimens taken either at least 3 cm proximal to the gastro-oesophageal junction, or 0–3 cm from the gastro-oesophageal junction but showing intestinal metaplasia. The latter represents a short segment Barrett's oesophagus, which is known to have a significant risk of malignant change.[21 23] The gastro-oesophageal junction was defined to be where the saccular stomach and gastric folds end and the tubular and smoother oesophagus begins. Cases not fulfilling these criteria were excluded.

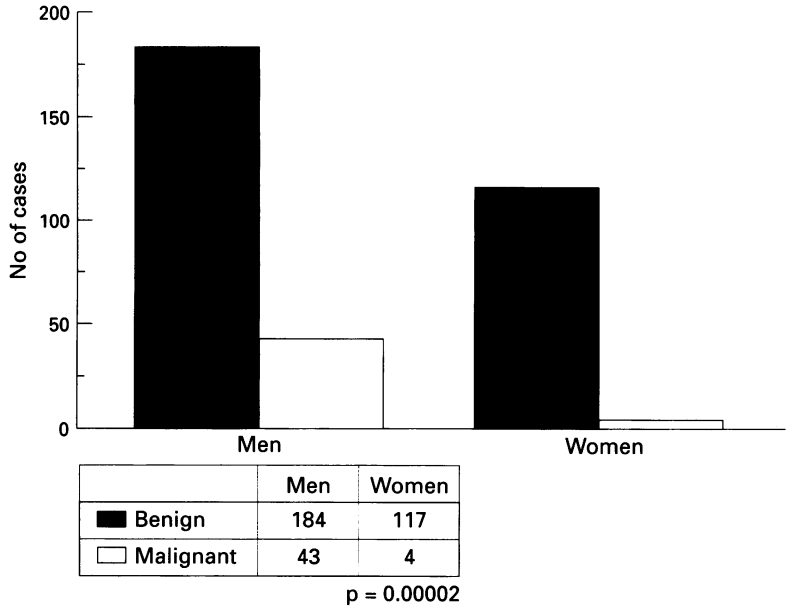

Figure 1: Sex distribution of all patients with a histological diagnosis of Barrett's oesophagus at initial endoscopy – benign and malignant.

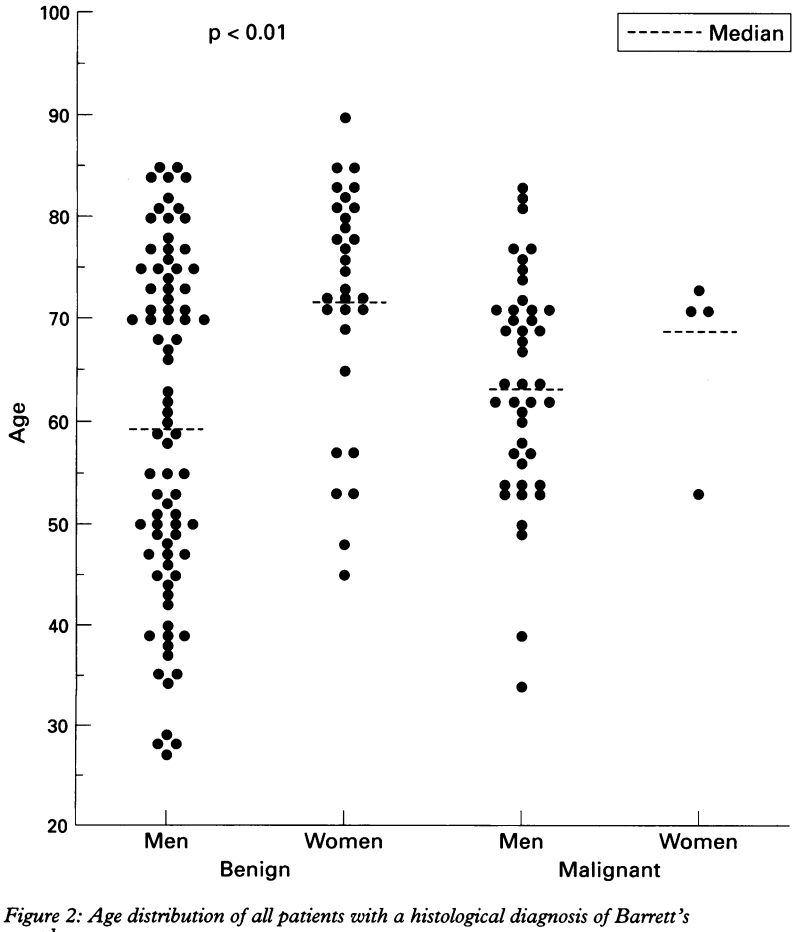

Figure 2: Age distribution of all patients with a histological diagnosis of Barrett's oesophagus.

Methods

Patient details, extent of Barrett's oesophagus, duration of endoscopic surveillance, and eventual outcome were all noted. Over a similar time period, patients presenting de novo with adenocarcinomas of the oesophagus arising in Barrett's epithelium were used to act as a control group. Patients who had suspicious symptoms or endoscopic signs of cancer at presentation and who were confirmed as having a Barrett's cancer within a year were not regarded as having screen detected cancers. Only those tumours that had been resected were used in the comparison, resulting in accurate staging in both groups but at the risk of reducing the impact of screening by excluding unresectable stage III and IV disease in the control group. The International Union Against Cancer TNM classification of malignant tumours was used to stage the oesophageal cancers.[30]

The calculation of the cost of surveillance was made on the basis that the average patient had annual endoscopy at which two biopsy specimens were taken and a single outpatient visit.

Statistical techniques used included Mann-Whitney U test, Poisson interval tests, and Yates's corrected χ^2 test as appropriate.

Results

Age and sex

Barrett's oesophagus was identified in 348 patients. Of these, 47 patients also had adenocarcinoma present. As shown in Figure 1, 61% of the benign cases were men, whereas 91% of the malignant cases were men ($p<0{\cdot}005$, χ^2 test).

In Figure 2, men with benign disease had a bimodal distribution with median age of 58·5 (range 27–84); and women had a unimodal distribution with a median age of 73 (range 35–92) ($p<0{\cdot}05$). The average age of male (66 years, range 34–92) and female (71 years, range 53–73) patients with tumours did not differ from those with metaplasia without malignant change.

Surveillance data

Only 166 of the 301 patients (55%) with no evidence of cancer at presentation entered the

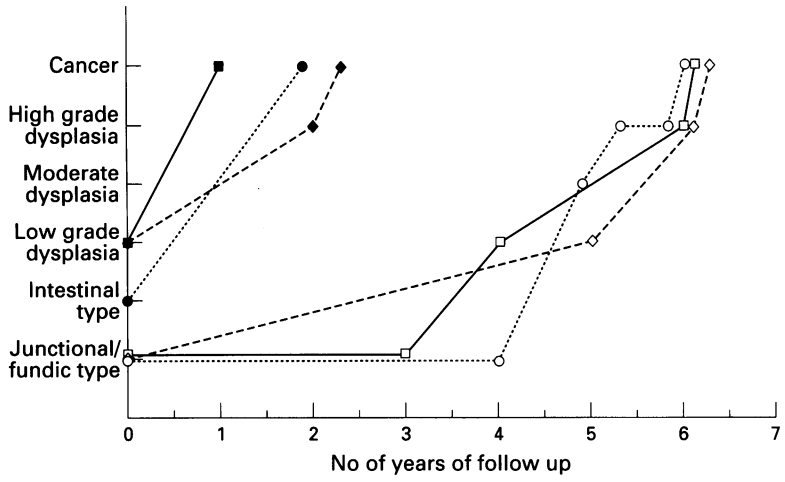

Figure 3: Histological progression to malignancy in the six screen detected tumours.

prospective surveillance programme. Of those patients who were not screened, 79 were excluded because they were unfit for major surgery; 52 were excluded either by consultants who did not routinely screen Barrett's oesophagus or by errors in follow up and only three patients actually refused endoscopic surveillance. One hundred and eight (65%) male and 58 (35%) female patients who entered the surveillance programme were screened for a total of 294 and 167 patient-years, respectively. Most patients were, in fact, recruited in the past five years as the importance of Barrett's oesophagus as a premalignant condition has made endoscopists more vigilant in looking for its presence. Many patients were elderly and died of unrelated causes or were subsequently excluded because they had become unfit for surgery. This explains why, in a 12 year surveillance programme, the mean length of follow up was only 2·7 years for men and 2·9 years for women.

Adenocarcinoma of the oesophagus developed in five men and one woman. The histological progression to cancer is shown in Figure 3. One of these six patients had developed dysphagia, the other five having no significant symptoms that would have normally warranted endoscopy. The incidence or risk of developing cancer was one cancer detected per 59 male or 167 female patient-years of surveillance. Not included are four other patients who had oesophagectomies after screening had discovered high grade dysplasia on random biopsies. Owing to practical difficulties, we have not looked to see if any of the non-screened patients developed Barrett's cancer.

Comparison of screened and unscreened cancers

All six patients with screen detected cancers had oesophagogastrectomy. Table II shows the stage of disease in the screened group after resection compared with 25 unscreened consecutively resected group of patients with Barrett's cancers. There were no sex differences between the two groups. The mean age of the surveillance detected cancers was 67·5 compared with 62·6 for the unscreened group

TABLE II *Stage of cancer after resection in the screened and unscreened groups. Node negative versus node positive (p=0·2 Fisher's exact test)*

Stage	*Unscreened*	*Screened*	
0	1	1	Lymph node negative
I	0	2	
IIA	11	2	
IIB	3	0	Lymph node positive
III	3	1	
IV	7	0	
Total	25	6	

(p=0·05 Mann-Whitney *U* test). However, there was no difference in ages between those who did not develop cancer in the surveillance group and the unscreened cancer group. According to the UICC classification of disease, stage 0 is defined as carcinoma in situ. This was recorded for two patients (one screened and one unscreened) who had unequivocal invasive cancer on preoperative endoscopic biopsy but, at most, had high grade dysplasia or carcinoma in situ in the resection specimen. Both these patients had had preoperative chemotherapy as part of a national trial.

An important finding from this study was that surveillance detected cancers were more likely to be node negative than unscreened cancers. Unfortunately, by excluding unresectable advanced stage tumours from the control group, this did not quite reach statistical significance.

The cost of an endoscopy in 1992 was £80 according to the financial department at the Royal Liverpool Hospital, with biopsies there is an additional cost of £40 and an outpatient visit is an extra £60 – a total of £180 per endoscopy. The 166 screened patients had a total of 653 endoscopies in 461 patient years of surveillance – an average of 1·4 endoscopies per patient per year. Thus the screening cost per patient per year is 1·4×180=£252. From the incidence data the cost of detecting a single cancer in a male patient is 59×252=£14 868 and in a woman is 167×252=£42 084.

Discussion

Risk factors – age and sex

Male sex has been confirmed to be associated with higher cancer risk. While the male to female ratio of patients with metaplasia is generally about 3:2,[6 12 18] the ratio in patients with Barrett cancers ranges from 5:1 to 29:1[5 11 31] – 10:1 being about average. Previous series suggest that this effect is determined by heavy smoking and alcohol consumption in the male patients; malignant change is associated with a significant smoking history in over 90% of cases.[8 32]

We noticed a bimodal age distribution for men with benign Barrett's oesophagus. Young men who presented with symptoms in their 20s and 30s may represent a childhood Barrett's subgroup, which has been shown to be much more common in boys than girls.[33] Borrie and Goldwater also noticed this bimodal distri-

bution and proposed a double aetiology for Barrett's oesophagus.[34] Our data support this view.

There are reports of adenocarcinomas occurring in patients with Barrett's oesophagus as young as 11 – a fact which has led to the recommendation of surveillance from the age of 10.[35] We excluded children from our study, and the youngest patient with Barrett's cancer was a man aged 34, so we agree that young men with Barrett's oesophagus represent a subgroup who should be considered at high risk and should benefit the most from endoscopic surveillance.

Previous surgery

Antireflux surgery is known not to be protective against subsequent development of malignancy as there are now numerous reports of cancers occurring many years after successful surgery.[14 36–38] One of our screen detected cancers had also developed 12 years after having a symptomatically successful antireflux procedure, suggesting that malignant change is independent of continued gastro-oesophageal reflux (acid or alkaline). Complete regression of Barrett's oesophagus after surgical or medical treatment is rare and the presence of unknown co-carcinogens means that continued surveillance is necessary.

It is of interest that one of our patients had had a previous polyagastrectomy for peptic ulceration 10 years before the development of his screen detected cancer. Biliary reflux may have been an important factor in the cause of cancer in this case. Others have also noticed previous gastric surgery to be common in patients presenting with Barrett's cancer.[10 14]

Interval cancers

Interval cancers are possible and may prove to be of a more aggressive type than one presenting with a more insidious onset. One of our screen detected cancers had symptoms suggestive of cancer before endoscopic diagnosis. He had decided to wait for his annual endoscopy before seeking attention and after resection was found to have a stage III tumour. The patient's previous screening endoscopy was performed before the introduction of four quadrant biopsies at two centimetres of Barrett's epithelium as recommended previously.[24] It is possible that had he had more detailed sampling, dysplasia might have been detected and early signs of malignant change acted upon before lymph node metastases developed. We are currently recommending that patients with low and moderate grade dysplasia be rebiopsied after three months of treatment with a proton pump inhibitor.[39] This sampling method has also been used so that even patients with high grade dysplasia have been safely followed up for up to nine years.[40 41]

In a recent report on the cost effectiveness of screening for Barrett's cancer,[42] assumptions about incidence and natural history of Barrett's cancer were made. Their decision making analysis recommends surveillance every three, four, or even five years. This is based on the assumption that unscreened cancers have a resection rate of 49% – which seems very high, and a resection rate of only 75% for screened cancers – which is much lower than our 100% resection rate. Of more importance is that they assume only a 64% five year survival for screen detected cancers. As we have already pointed out, there are no data to support this assumption. Finally, they assume that cancer develops over four to five years but in 50% of our cases, cancer was detected after fewer than two years (Fig 3). A screening strategy of endoscopy every three or more years is therefore likely to increase the number of interval cancers.

Cost effectiveness analysis

Our study has shown an incidence of malignant change in Barrett's oesophagus that is of a similar order of magnitude to that in the previously reported series (Table I). Our incidence was 2·8 times higher for men. In the above mentioned series, the number of cancers detected has never been greater than five and many detected only two or three cases. The 95% confidence limits for the actual incidence will therefore vary enormously. We detected six cases of Barrett's cancer and our 95% confidence limits for incidence are also quite wide, ranging from 1:25 to 1:181 for men and 1:30 to 1:6600 (Poisson distribution).[43]

Case detection cost is dependent on the incidence of malignant change in the screened group.[42] Our costings are based on the observed incidence and estimated values for the cost of endoscopy, biopsy, and an outpatient visit. In a previous study by Achkar and Carey in 1988 case detection cost was estimated to be $62 000.[12] Their calculation is based on the detection of a single cancer occurring during a 31 month follow up of a very small group of patients. As we have shown with our figures, the confidence limits for this figure will have such a wide range that this case detection cost may not be very accurate. Indeed, by combining our data with all the other reported screen detected cancers, we have calculated a mean incidence of 1:75 with 95% confidence intervals of 1:55 to 1:112 (Poisson distribution).[43] (We excluded three studies because they were conducted by postal questionnaire and may have firstly, overdiagnosed Barrett's oesophagus – which is common in our experience – and secondly, missed early asymptomatic tumours, both of which tend to underestimate the true incidence.[8 10 14]) The combined 95% confidence interval of case detection costs are therefore between 55×252= £13 860 and 11×2252=£28 224. It is recognised that our estimated figures may be very different from the costs in other units around the country.

Our figure of £14 868 per male cancer detected is similar to the £12 000 figure from Nottingham[7] and is in the more cost effective end of this range. This figure may be even lower as four men in the surveillance group had

surgery for high grade dysplasia before they progressed any further and were therefore not classified as screen detected cancers. The estimated cost of detecting a female cancer still compares favourably with the costs of screening for other malignancies. For example, when faecal occult blood testing is used the cost per life saved from colorectal cancer is $225 000,[44] and mammography for breast cancer has been estimated to cost up to £1 000 000.[45]

Cost effectiveness analysis needs to take into account many factors other than incidence and stage at time of detection. Screening should only be contemplated in patients who are potentially fit for oesophageal resection. In the elderly population the potential increase in life expectancy by detecting early oesophageal cancer is limited. In terms of life-years gained there will be a less favourable comparison with other cancers such as colorectal and breast cancer which often develop at a younger age. Money spent on screening, however, may be partially offset against savings of the high cost of adjuvant and palliative treatments required in more advanced cases. Recent research aimed at identifying those at particularly high risk may ultimately help to reduce costs.[46]

We have shown that screening is effective in identifying tumours at a curable stage. We would like to emphasise that unresectable advanced tumours were not included in the control group because they cannot be accurately staged. Their inclusion would have increased the strength of our statistical analysis. All five of our asymptomatic Barrett's cancers were node negative and had potentially curative resections. We believe that there has only been one other report comparing stage of disease between a screened and unscreened group of Barrett's cancers.[36] In this report the screened group also had better stage of disease compared with the unscreened group (p=0·006).

In conclusion, screening should only be contemplated in the younger patients who are potentially fit for oesophageal resection. In our experience, only patients with the intestinal type of metaplasia are at risk of dysplasia and cancer and all others should not be screened. Successful medical or surgical treatment of gastro-oesophageal reflux disease should not necessarily exclude patients from a surveillance programme. Regular endoscopic surveillance of high risk groups will be more cost effective. These include the male sex, those with established dysplasia of any grade, and may include patients who smoke heavily, develop Barrett's oesophagus at a young age, have had previous gastric surgery, or have long segment disease.

It is clear that although this is one of the largest studies of this type, the numbers of screen detected cancers are still very low. Large multicentred prospective surveillance programmes are required to determine accurately the cost per life year saved.

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