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Epidemiology of gallbladder cancer and trends in cholecystectomy rates in Scotland, 1968–1998

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Abstract

The aim of this study was to describe the epidemiology of gallbladder cancer in Scotland during the last 30 years. A secondary aim was to describe trends in cholecystectomy rates because it has been suggested that changing rates of cholecystectomy for benign gallbladder disease may be influencing the epidemiology of gallbladder cancer. A retrospective analysis of cancer registration and mortality (gallbladder cancer) and hospital discharge (cholecystectomy) data from Scotland in 1968–1998 was carried out. In Scotland the incidence of, and mortality from, gallbladder cancer have been falling in women since at least 1968, and in men since the late 1980s. Whilst overall survival remains poor, survival in older patients may have improved recently, and survival is better in patients from affluent areas. Cholecystectomy rates increased until 1977 then fell until the introduction of laparoscopic surgery caused them to return to the rates previously observed. The current declining incidence of gallbladder cancer in Scotland is probably, in part, related to the increasing cholecystectomy rates seen prior to 1977. Further studies addressing changes in stage at diagnosis and treatment provided are required to investigate the recent apparent improvement in survival of elderly gallbladder cancer patients.

Keywords: Cholecystectomy; Epidemiology; Gallbladder cancer; Incidence; Mortality; Scotland; Survival

1. Introduction

The aetiology of gallbladder cancer is incompletely understood. However, the main known modifiable risk factor for the disease is gallstones. Several case–control studies have identified gallstones as a risk factor [1–3], and cohort studies have shown that untreated gallstones confer an approximately 3-fold increase in the risk of gallbladder cancer [4,5].

Other previously demonstrated risk factors include increasing age, female gender [6], ethnic group (for example, Hispanics and American Indians in the United States (US)) [7], and a low educational level [1]. Other suggested risk factors, for example high parity [8], various dietary factors such as high total calorie intake [2,9], obesity [10], and chronic infection of the biliary tract [11] may be of independent significance, or may act through increasing the risk of gallstones.

Gallbladder cancer is a relatively uncommon malignancy in the United Kingdom (UK). However, worldwide, marked geographical variations in its incidence have been documented. Along with the UK, other Western and Northern European countries, North America and Australasia have a low incidence, whereas incidence is much higher in Central and Eastern Europe, Japan, and particularly South America [7,12].

Different secular trends in the incidence of gallbladder cancer have been noted in different countries. Over recent decades, the reported incidence has fallen in the US, Canada, Germany, Austria and Israel, whereas it has risen in Japan, China, India, Sweden, Finland and Italy [13–16]. The most recent studies to look at secular trends in gallbladder cancer in the UK have found that mortality fell over the 1970s and early 1980s [13,14].

The reasons for the observed secular trends are not well understood. However, given the importance of gallstones in the aetiology of gallbladder cancer, there has been considerable speculation about the role of

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changing rates of cholecystectomy for benign gallbladder disease [6,7,13]. Intuitively, increasing cholecystectomy rates may be expected to increase temporarily the reported incidence of gallbladder cancer as more early-stage cancers are found incidentally at operation. In turn, this might be expected to have a favourable impact on survival. Over many years, however, the incidence of and mortality from gallbladder cancer may be expected to fall as the people at the highest risk of developing the cancer, patients with gallstones, are removed from the population at risk.

This paper therefore aims to describe the epidemiology of gallbladder cancer in Scotland over the last 30 years, in terms of the trends in incidence, mortality and survival. A secondary aim is to consider this information in light of the changing cholecystectomy rates over the same time period.

2. Patients and methods

Data on registrations of gallbladder cancer for the years 1968–1996 were obtained from the Scottish Cancer Registry using the International Classification of Diseases (ICD) codes appropriate to the time period of diagnosis. The Scottish Cancer Registry is a national registry that aims to record all incident cases of cancer in the Scottish population, and the completeness and accuracy of the registry data as a whole have been shown to be high [17,18]. The study period started in 1968 as this was the first complete year for which Scottish cancer registration and death certification records used the ICD8 coding. The eighth revision of the ICD was the first to distinguish gallbladder cancer from other forms of biliary tract cancer.

Data on deaths from gallbladder cancer for the years 1968–1998 were obtained from the General Register Office (Scotland). Mid-year population estimates for Scotland for 1968–1998 were obtained from the Annual Reports of the Registrar General for Scotland. Annual, gender-specific, age-standardised incidence and mortality rates were calculated using direct standardisation to the European standard population [19]. Average annual gender- and age-specific incidence and mortality rates were calculated for the study period as a whole.

Persons diagnosed with gallbladder cancer during 1987–1996 were assigned to a 1991 census-based Carstairs deprivation quintile according to their postcode sector of residence at the time of diagnosis [20]. The Carstairs deprivation score is a small area indicator of socio-economic status based on the prevalence measured at the decennial census of four characteristics: overcrowding, male unemployment, social class and car ownership. Deprivation quintile one represents the most affluent areas of Scotland and deprivation quintile five the most deprived areas. To assess the relationship between gallbladder cancer and deprivation, average annual age-standardised incidence rates for the five deprivation quintiles were calculated. Linear regression on the log rates was used to assess trends in incidence across the quintiles [21].

All cause death data are supplied routinely to the Scottish Cancer Registry and are linked to cancer registration records using electronic probability matching to allow survival analysis to be performed [22]. One- and 5-year relative survival estimates following diagnosis of gallbladder cancer for patients aged less than 65 years and 65 years or over at the time of diagnosis were calculated for the five successive 5-year periods from 1971–1975 to 1991–1995, along with their 95% Confidence Intervals (CIs) [23]. Age differences and secular trends in survival were then assessed. Relative survival compares the survival of patients with the cancer of interest to survival of people of the same age, gender and, in this analysis, deprivation level in the general population who are free from cancer. To assess the relationship between survival and deprivation, the observed and relative survival for up to 5 years following diagnosis was calculated for patients from each deprivation quintile diagnosed during 1986–1995.

Data on cholecystectomies performed in Scottish hospitals between 1968 and 1998 were obtained from the Scottish Morbidity Record (SMR)01 dataset. An SMR01 record is generated each time a patient is discharged from a Scottish NHS hospital episode of care. Completeness and accuracy of recording of procedures performed during the hospital episode have been shown to be consistently high [24,25]. Separate codes allowing laparoscopic and open cholecystectomies to be distinguished were introduced during 1991; therefore, separate annual rates for laparoscopic procedures are only available from 1992 onwards.

3. Results

3.1. Incidence

In Scotland over the 29-year period 1968–1996, a total of 448 cases of gallbladder cancer were registered in males (an average of 15 per year) and 1288 were registered in females (an average of 44 per year). Overall, this represents less than 0.5% of all cancers (excluding non-melanoma skin cancers) registered. The incidence of gallbladder cancer in females has fallen over the study period as a whole. By contrast, the incidence in males was relatively steady over the 1970s and early 1980s, but has shown a decreasing trend since the late 1980s (Fig. 1). Due to the relatively small numbers of cases, annual age-specific incidence rates are unstable, but it appears that, in both genders, the decreases in incidence seen have been mainly due to falling age-specific

incidence rates in patients aged 65 years and over (data available on request).

Over the whole study period, incidence rates were extremely low in patients aged less than 40 years, but thereafter increased with increasing age. Incidence rates were higher in females than males at all ages (Fig. 2).

The incidence of gallbladder cancer in women showed a significant positive relationship with deprivation ($P = 0.02$). For cancers registered in the 10-year period 1987 to 1996, the 'best fit' age-standardised incidence rate in women in deprivation quintile 5 was 1.3/100 000, compared with 0.7/100 000 in women in deprivation quintile 1. Incidence in men showed a similar relationship with deprivation (Fig. 3), but this did not reach statistical significance.

3.2. Mortality

In Scotland over the 31-year period 1968–1998, a total of 397 deaths from gallbladder cancer occurred in males (an average of 13 per year) and 1149 occurred in females (an average of 37 per year). As would be expected for a highly lethal tumour, the secular trends in mortality from gallbladder cancer closely mirror the trends in incidence. It is notable, however, that mortality rates have fallen more steeply than incidence: whereas mortality

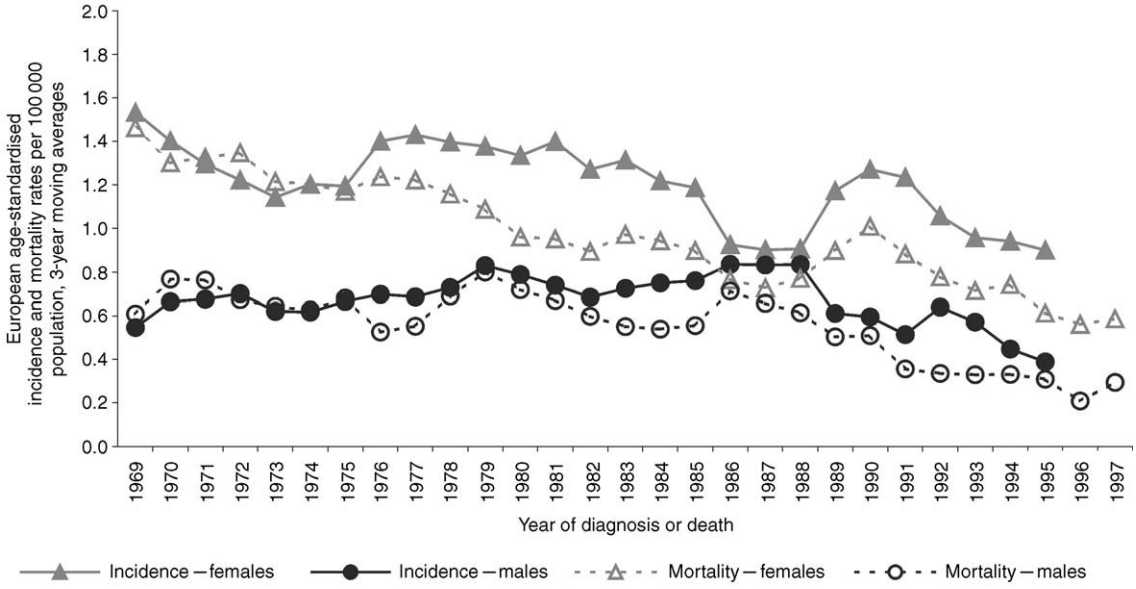

Fig. 1. Secular trends in incidence and mortality rates of gallbladder cancer, Scotland 1968–1998. Note that the 3-year moving averages are displayed to minimise the effect of year-to-year random fluctuation in the rates.

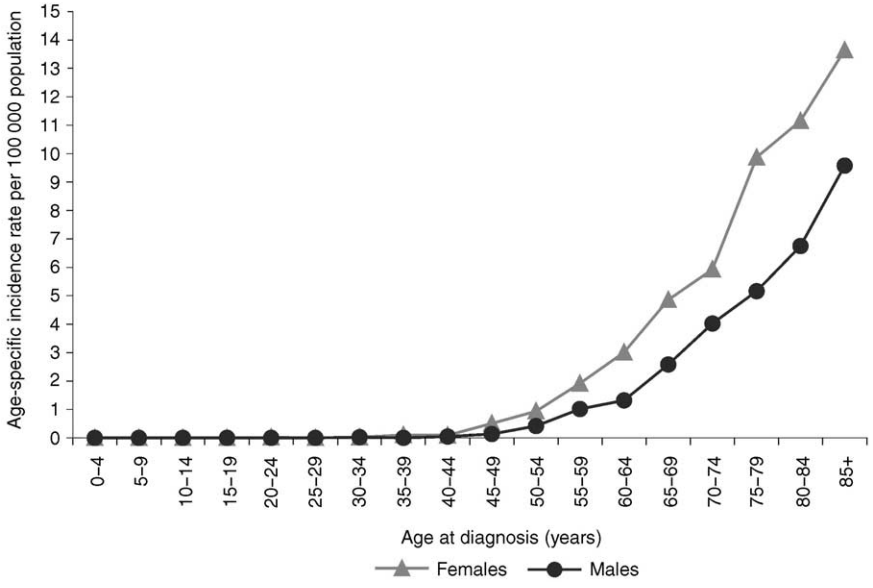

Fig. 2. Incidence of gallbladder cancer by age and gender, Scotland 1968–1996.

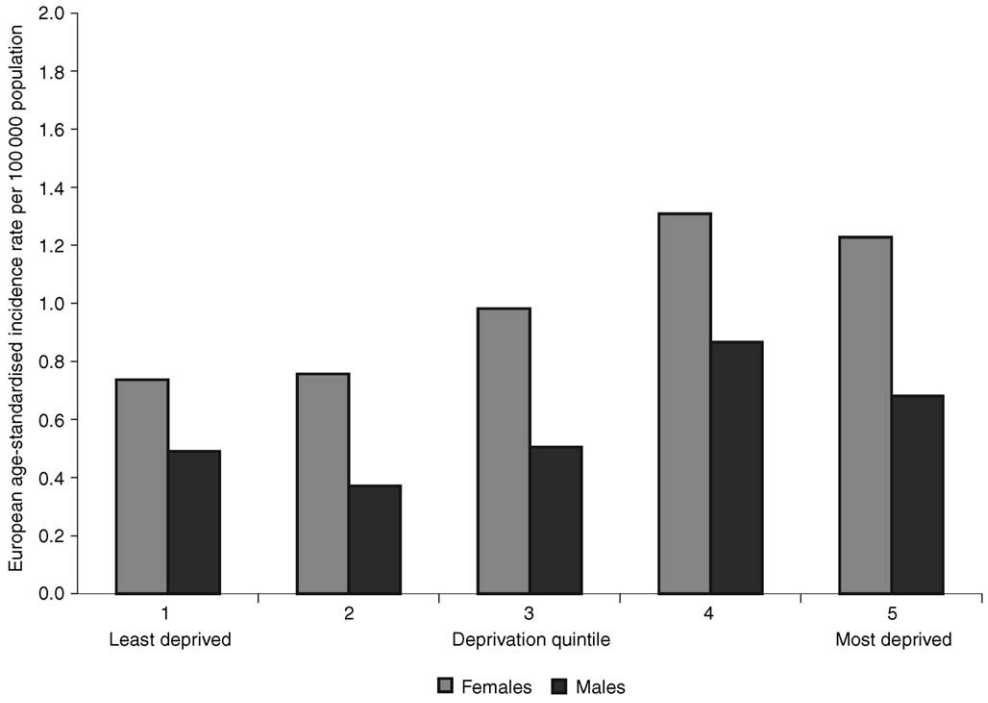

Fig. 3. Incidence of gallbladder cancer by deprivation, Scotland 1987–1996.

and incidence were very similar in the early part of the study period, latterly mortality rates have been lower than incidence (Fig. 1).

3.3. Survival

Overall gallbladder cancer carries a poor prognosis. Relative survival at 1, 3 and 5 years for all patients diagnosed in Scotland between 1991 and 1995 was 20, 12 and 6%, respectively.

During the early part of the study period, survival tended to be poorer in patients aged 65 years or over compared with younger patients. However, older patients diagnosed between 1991 and 1995 showed a substantial increase in survival (particularly 1-year survival) compared with that seen in earlier time periods, hence survival in the two age groups became comparable (Table 1). However, it should be noted that, as the survival analysis is based on small numbers of cases, the associated CIs are wide.

For patients diagnosed between 1986 and 1995, relative survival for up to 5 years following diagnosis was better for patients from deprivation quintile 1 than for patients from deprivation quintiles 2–5, with the survival advantage of patients from affluent areas being most marked at 1 year following diagnosis (Fig. 4).

3.4. Cholecystectomies

In Scotland over the 31-year period 1968–1998, a total of 36 854 cholecystectomies were performed on males (an average of 1189 per year) and 107 802 were performed on females (an average of 3477 per year). The cholecystectomy rate in males and females increased from 1968 to a peak in 1977 then declined until

Table 1
Survival after diagnosis of gallbladder cancer, Scotland 1971–1995

	Age at diagnosis (years)	Time period of diagnosis				
		1971–1975	1976–1980	1981–1985	1986–1990	1991–1995
Percentage 1-year relative survival (95% CI)	<65	21.1 (12.9–30.7)	13.8 (7.2–22.6)	17.9 (9.7–28.1)	15.2 (7.6–25.4)	24.0 (14.2–35.1)
	⩾65	3.8 (1.9–6.7)	6.4 (4.0–9.5)	7.1 (4.6–10.5)	7.5 (4.6–11.2)	18.9 (13.6–24.8)
Percentage 5-year relative survival (95% CI)	<65	8.9 (3.9–16.5)	7.9 (3.2–15.2)	9.1 (3.7–17.6)	7.0 (2.3–15.3)	5.0 (1.3–12.5)
	⩾65	1.9 (0.6–4.4)	2.3 (1.0–4.7)	0.5 (0.1–2.3)	1.6 (0.4–4.5)	6.3 (3.1–10.9)

95% CI, 95% Confidence Interval.

1990/1991. Over the early 1990s, the rate increased again to reach levels just below those of 1977, then stabilised. The laparoscopic cholecystectomy rate in males and females increased from 1992 to 1996, then stabilised. In 1998, 72% of all cholecystectomies performed were laparoscopic (Fig. 5). Note that the apparent low operation rate in 1982 was probably due to industrial action affecting the completeness of SMR01 returns for that year.

Over the study period, cholecystectomy rates were extremely low in patients aged less than 20 years then increased with increasing age to reach a peak at 70–74 years in males and 60–64 years in females, then decreased with increasing age thereafter. Cholecystectomy rates were higher in females than males at all ages (data not shown).

4. Discussion

4.1. Incidence

This study has demonstrated that the reported incidence of gallbladder cancer in Scotland has fallen in

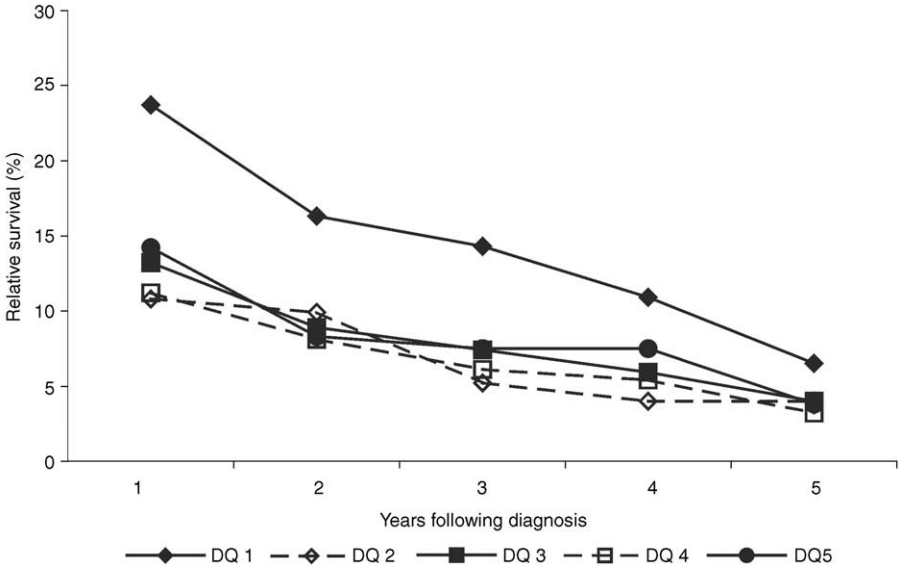

Fig. 4. Survival after diagnosis of gallbladder cancer by deprivation, Scotland 1986–1995. DQ, deprivation quintile.

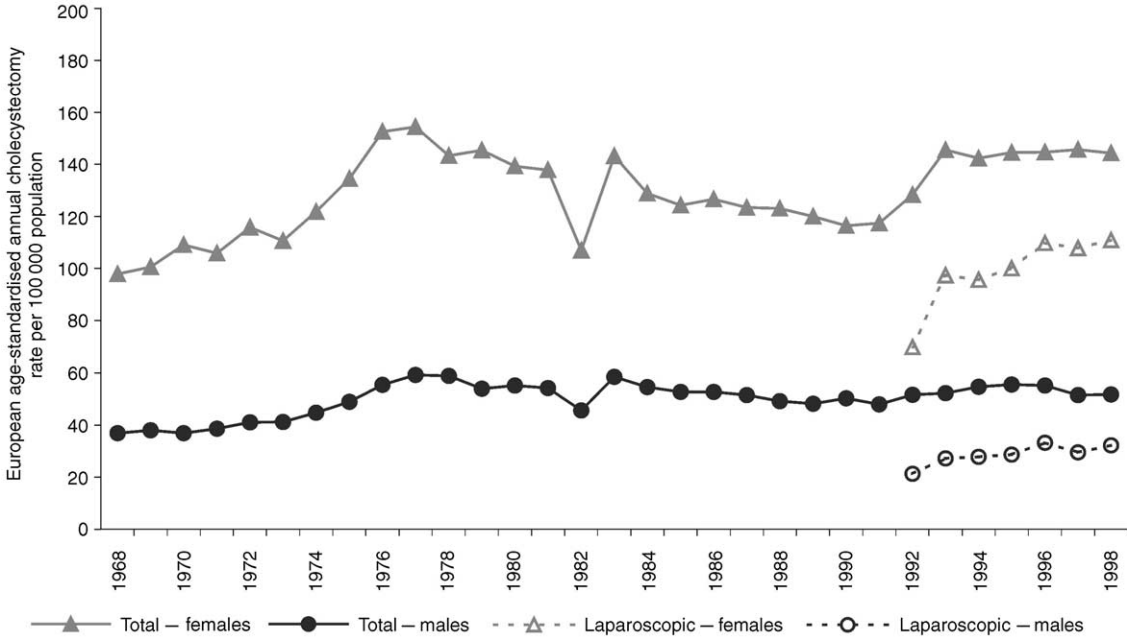

Fig. 5. Secular trends in cholecystectomy rates, Scotland 1968–1998.

women since at least the late 1960s and in men since the late 1980s. It is likely that the observed fall in incidence is real rather than artefactual. Although advanced gallbladder cancer may be confused clinically with extrahepatic bile duct cancer, there is no evidence of the falling incidence of gallbladder cancer being due to a diagnostic shift between these two cancers, as the reported incidence of extrahepatic bile duct cancer in Scotland has not shown any consistent trend over the study period (data not shown).

This study has also demonstrated a positive relationship between material deprivation and the incidence of gallbladder cancer, presumably due to a higher exposure to risk factors in deprived groups. There is conflicting evidence as to whether gallstones are more common in people from deprived areas [26,27], and it is unknown whether deprived people with gallstones are less likely to undergo cholecystectomy than affluent people. However, it is known that other putative risk factors for gallbladder cancer, such as high parity and obesity, are more common in deprived groups.

4.2. Survival

Gallbladder cancer continues to have a poor prognosis. The poor survival of Scottish patients found in this study is comparable to that reported previously from Australia [28] and France [29]. The survival advantage of patients from affluent areas, and the recent improvement in survival of elderly patients, noted in this study, are difficult to interpret without additional information about factors known to influence the chance of survival, in particular stage at diagnosis and treatment given.

Stage at diagnosis is currently not recorded on the Scottish Cancer Registry for gallbladder cancer, hence investigating whether the stage distribution of gallbladder cancers is shifting in Scotland will require further detailed local studies. With regard to treatment for gallbladder cancer, there have been no major advances in treatment options over the time period of this study: surgery remains the mainstay of treatment. There is, however, an increasing trend for surgeons to deal more aggressively with cases of gallbladder cancer found incidentally at cholecystectomy. Again, further local studies will be required to determine whether, for example, re-operating to clear the gallbladder bed is having an impact on survival.

4.3. Relationship between cholecystectomy rates and incidence of gallbladder cancer

As previously mentioned, there has been much speculation in the literature about the relationship at a population level between cholecystectomy rates and the incidence of gallbladder cancer. One of the main strengths of this study is that in addition to information on the incidence of gallbladder cancer in Scotland since 1968, it also provides population-based information on cholecystectomy rates over the same time period. Cholecystectomy rates in Scotland were found to increase steeply from at least the late 1960s until the mid-1970s, then gradually decline again until 1990/1991. Over the early 1990s, they then rose again before stabilising at a level just below that seen in the mid-1970s.

In Scotland, no clear temporal association is evident between cholecystectomy rates and gallbladder cancer incidence since 1968. The calendar periods of highest rates of cholecystectomy do not correspond consistently to the periods of highest incidence of, or more favourable survival from gallbladder cancer, suggesting that the incidental discovery of malignant neoplasms following cholecystectomy for presumed benign disease is uncommon and has probably not played a major part in shaping the observed trends in gallbladder cancer. However, the rise in cholecystectomy rates to the mid-1970s may well have contributed to the more recent fall in cancer incidence (representing a 'lag time' of approximately 15–20 years), although definitive conclusions cannot be drawn from the data available. The relationship between cholecystectomy and gallbladder cancer may also be obscured to some extent by temporal changes in the prevalence of other known and unknown risk factors.

Ideally, it would have been preferable to calculate the incidence of gallbladder cancer in the population that has not undergone a cholecystectomy, rather than in the total population as we have done for this study. This would show how the incidence of gallbladder cancer is changing in the population actually at risk of the disease, and would allow a more definitive assessment of whether changing rates of cholecystectomy are responsible for the changing incidence of gallbladder cancer that we have identified at the total population level. Similar work to this has been carried out to examine whether increasing hysterectomy rates are responsible for changes in the incidence of endometrial and cervical cancers [30], but a similar approach has not been previously taken with gallbladder cancer. Unfortunately, this approach would require accurate yearly estimates of the proportion of people in different age groups who have had a cholecystectomy: these estimates are currently not available from routine statistics or, to our knowledge, from special surveys.

5. Conclusions

In summary, this paper has shown that the incidence of gallbladder cancer in Scotland has declined over recent years, and that this decline may, in part, be related to increasing cholecystectomy rates prior to the

mid-1970s. In addition, we have shown that patients from deprived areas have both a higher incidence of gallbladder cancer and a poorer survival from the disease than patients from affluent areas. Finally, there is some evidence that short-term survival in elderly patients with gallbladder cancer has improved recently, and additional studies looking at possible changes in stage at diagnosis and treatment provided are required to investigate this finding further.

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