

*Review*

## CHARACTERISTIC PATTERN OF INFLAMMATORY RESPONSE AND ITS ASSOCIATION WITH REDUCED SURVIVAL IN PATIENTS WITH COMMON SOLID CANCERS

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**Summary:** Anticipated survival is a major factor to be taken into consideration when deciding whether active intervention or palliation is appropriate in patients with advanced cancers. However, there are few reports on factors, which determine survival in advanced disease. It has been recognised for sometime that a proportion of patients with advanced cancer have an ongoing acute phase response, indicated by increased circulating concentrations of acute phase proteins such as C-reactive protein and decreased concentrations of albumin. However, the mechanism of the increase in C-reactive protein and decrease in albumin concentration is still not clear. Recent research has focused on these established prognostic factors in such cancer patients that include metastatic disease, involuntary weight loss, reduced albumin total protein concentrations, raised white blood cell count and reduced Karnofsky performance status. Reports also suggest that the acute phase response, as evidenced by an elevated C-reactive protein concentration may be a significant factor in the survival of patients with advanced cancers. Taken together, these parameters are associated with deterioration in the quality of life and reduced survival. Hence, the aim of this review and the discussed results of different studies was to examine and evaluate the importance of these factors in predicting the duration of survival of patients with advanced common solid cancers namely, lung, gastrointestinal and breast cancers.

**Keywords:** C-reactive protein, albumin, bronchogenic cancer, gastrointestinal cancer

### Introduction

In the modern industrialised world, where famine and pestilence are things of the past, cancer has become a new scourge. It may not be the commonest cause of death, usually occurring less frequently than heart disease, but it has the reputation of being usually a fatal condition for which effective treatments are few.

Cancer is a disorder of cell proliferation and differentiation and usually arises as the result of one

or more series of mutations in DNA, which may be either germline (inherited) or somatic (acquired during life) [1]. The rate of this depends on three factors: (1) the number of the cells that are actively dividing or moving through the cell cycle, (2) the cell cycle time, and (3) the number of the cells that are being lost [1]. As cancerous tumour cells are actively engaged in cycling, they seem to grow rapidly that often relates to the size of the cell pool. It has been shown that the cell cycle time of cancerous tissue cells is not necessarily shorter than that of normal cells; rather, cancer cells do not die on schedule [1].

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## Epidemiology

Much of the knowledge of human cancer has been derived from the epidemiological studies of different types of cancers. There are marked differences when comparing certain cancers within the Far East and some Eastern European countries. These differences are due to varying risk factors between populations, and the sophistication or otherwise of screening and cancer control programmes. In the European Union, approximately one in three contract the disease in their lifetime and one in four people die from cancer. In recent years, however, trends in cancer mortality appear to have changed, at least in some European countries. Data provided by the World Health Organisation were used to evaluate age specific incidence rates from 1969 through 1986 for lung, breast, colorectal and stomach cancers [2]. Over this period, recorded cancer incidence in persons aged 45 years and older in European countries studied has increased for lung and breast cancers in most age groups, while the decline in stomach cancer is substantial. Overall, the most noteworthy features of these data are:

- \* falling incidence of lung cancer in men, which contrasts with the increasing incidence in women and reflects the generally later adoption of the tobacco habit by successive cohorts of women, compared with men. It is projected that between 1986 and 2000 the annual number of registration of lung cancer may fall by 17% in men but may rise by 10% in women. Since more than 80% of lung cancers are attributable to tobacco, the opportunity for primary prevention is obvious.
- \* increasing number of registrations of breast cancer (in post-menopausal women) which is, at least partly, attributed to earlier diagnosis through the national breast screening programme.

- \* rise in incidence of cancer of the colon and rectum in males
- \* fall in incidence of stomach cancer in both sexes, a trend observed in many other countries.

## Aetiology

It is about 170 years since the first plan was proposed for determining the causes of cancer by studying its incidence in relation to such factors as occupation, sex, marital status, and so on. Only in the last 25 years has there been a concerted effort to collect statistics for many different regions of the world, and for a set of populations selected to represent as wide a range of environments and lifestyles as possible.

The expanding understanding of cell cycle regulation has identified putative oncogenes and tumour suppresser genes that may be involved in tumorigenesis. Also in the last few years, many studies have confirmed that growth factors not only promote tissue proliferation but also induce malignant transformation [3]. Mainly growth factors are defined as polypeptides that stimulate cell proliferation or differentiation by binding to high affinity cell membrane receptors. Over-expression of growth factors has been found in many human tumours and this phenomenon is often considered to be a cause of carcinogenesis [4].

Proto-oncogenes, present in all normal eukaryotic cells, play an important role in regulating their growth and differentiation. The dominantly acting proto-oncogenes control metabolic pathways that involve peptide growth factor and their receptors as well as post receptor signalling mechanisms. The genetic damage can affect the function of the proto-oncogenes so that it is expressed at wrong times or places in deleterious quantities or it may change the function of the protein encoded by the oncogene.

The damage may be chromosomal translocations, gene amplifications, or point mutations. Although much has been learnt about the mechanisms by which products of normal or mutated oncogenes may transform cells, the agents that initiate such disturbances (e.g., translocations) are largely unknown. As with many other cancers, ionising radiations and chemicals have been implicated as mutagenic agents that may start the process [5].

### **Socioeconomic Determinants of Cancer**

Social class differences in health are seen at all ages, with lower socio-economic groups having greater incidence of premature and low birth weight babies, heart disease, stroke, and some cancers in adults. Risk factors including lack of breast-feeding, smoking, physical inactivity, obesity, hypertension, and poor diet are clustered in the lower socio-economic groups [6]. Life styles not only play a crucial role in the aetiology of cancers but also in the survival following diagnosis [7]. Because it is at least a principle modifiable determinant, it can be assumed that cancer could be avoided, and cancer survival improved via improved lifestyle.

In most countries lung cancer incidence rates for men and women show a social class gradient, with those from higher social classes having a lower incidence than the lower social classes. The overall rates for men are more than twice those in women but in both sexes there are higher rates with increased deprivation category [8]. With respect to breast cancer, as well as many other cancers, the medically under served are not properly studied by many in the medical and academic research community, and they are attended by health care institutions that often don't have the resources necessary to ensure access to the best possible cancer screening, clinical follow up, diagnosis, and treatment [9]. Lerman and colleagues showed that psychological distress about

breast cancer had a significant impact on reducing annual mammography adherence among the women in the study who had less than a high school education [10]. Love in 1991 notes that a decision to seek care requires an understanding of the medical implications of symptoms and a belief in the benefits of diagnosis and treatment. Among some populations, particularly low-income and minority populations, fatalism about cancer and negativism about cancer therapy are widespread [11].

### **Inflammatory Response to Tumours**

The notion that the inflammatory response has an adverse effect on survival of patients with cancer goes back to the work of Riesco [12], who demonstrated a relationship between curability and the total number of leucocytes in the peripheral blood in almost 600 patients treated for various forms of cancers. These findings indicated that the immunological activity of peripheral lymphocytes might be a favourable factor in the cure of cancer by conventional treatment though the underlying basis of these results however is as yet unclear. However it is known that the recruitment of neutrophils into inflammatory foci is a fundamental process observed in inflammation as recent evidence has demonstrated that neutrophils are capable of producing inflammatory cytokines. These reports are, however, mainly based on the findings obtained *in vitro*.

It has also been known for twenty years that following tumour recurrence and progression, a proportion of patients develop an acute-phase protein response [13-14] Weinstein and coworkers studied the acute phase protein response in order to determine whether they were specific products of metastatic tumour cells or whether they originated from the normal pathway of acute phase biosynthesis. About 300 patients with a broad spectrum of neoplastic diseases, including ten types of solid

tumours and three classes of haematological malignancies were studied retrospectively. They concluded that serum amyloid A and C-reactive protein concentrations are elevated in response to inflammation secondary to the neoplastic disease [15]. Moreover, the mediators of the acute phase protein response are also increased in cancer patients [16]. They alter the host metabolism in a way that may promote tumour growth [17], and gets involved in tumour progression and recurrence [18]. Whereas increased C-reactive protein has also been shown to be associated with recurrence and reduced survival in colorectal cancer reflecting metastatic potential of the tumour and its biologic aggressiveness [19-20]. Nozoe and coworkers reported that an increase in the preoperative circulating concentration of C-reactive protein was associated with reduced survival of patients undergoing curative colorectal cancer surgery [20].

Margaron and Soni, in a review suggested that a decrease in serum albumin concentrations is an almost inevitable finding in disease states, and is primarily mediated in the acute phase response by alterations in vascular permeability and redistribution. This change is not disease specific but marked changes that persist are generally associated with a poorer prognosis [21]. Ernst and group reported that *Helicobacter pylori* induce infiltration of the gastric mucosa by polymorphonuclear cells and macrophages, as well as T and B-lymphocytes. Paradoxically, this robust immune/inflammatory response cannot clear the infection thus leaves the host prone to complications resulting from chronic inflammation. One adverse consequence of this inflammatory response may be gastric cancer, as inflammation has been implicated in the development of intestinal metaplasia and mutations in oncogenes that precede the development of gastric adenocarcinoma [22].

In summary, the utility of the inflammatory response as a marker for the progression and survival of cancer appears to be of some promise. However, it is not clear whether in relation to survival, the response is the same in different tumour types.

### **Prognostic Factors in the Survival of Patients with Bronchogenic Cancer**

Lung cancer, of which non small cell lung cancer (NSCLC) constitutes about 80%, is the greatest cause of cancer related deaths world-wide. Mateva and coworkers demonstrated that early diagnosis of lung cancer is of crucial importance for surgery management and prognosis in lung cancer patients [23]. Unfortunately it usually presents late with advanced incurable disease for which treatment options are limited. Hence, anticipated survival is a major factor to be taken into consideration when deciding whether active intervention or palliation is appropriate in patients with lung cancer. However, few studies have addressed the prediction of survival in the lung cancer [24].

It has been recognised for sometime that a proportion of patients with malignancy have ongoing acute phase protein response, indicated by continuously increased circulating concentrations of C-reactive protein [25-26]. Moreover, reports have also documented an increase in circulating pro-inflammatory cytokine interleukin-6 in gastrointestinal [16] and lung cancer patients [27-28].

Metastatic disease, involuntary weight loss, increased concentrations of IL-6 and C-reactive protein; reduced circulating concentrations of albumin appear to be associated with poor nutritional status, impaired performance status and shorter survival [24]. It is reported that lung cancer patients who died within six months after diagnosis had significantly lower values of all nutritional parameters including

serum albumin and creatinine than those who survived more than six months. Patients with more abnormal parameters tended to have poorer survival rates [25].

We analysed the relationship between blood parameters measured at the time of sampling and within four weeks of diagnosis and survival duration in a cohort of 421 patients with bronchogenic cancer. At the time of analysis 399 patients (95%) were dead. From the time of sampling, blood parameters were available from 239 male patients and 182 female patients. The median (range) age at the time of diagnosis was 65 (39-95) and the median survival

from the day of sampling was 62 days (range 4-3147). Univariate analysis of the relationship between the variables measured and survival from the day of sampling is shown in Table-1. There was a significant relationship between 5 of the 7 variables assessed and survival. On multivariate analysis between all variables and survival from sampling, C-reactive protein concentration ( $p=0.0021$ ), albumin ( $p<0.0001$ ) and calcium ( $p=0.0021$ ) remained independent predictors of survival (Table-2). A negative correlation from the time of sampling was found between  $\log_{10}$  C-reactive protein and albumin concentrations ( $r=-0.517$ ,  $p=<0.0001$ ).

**Table 1.** Univariate analyses of the relationship between categorical variables and survival from sampling in bronchogenic cancer patients (n = 421).

Factors	n	Survival (Median)	(Days) (95%CI)	p-value (log rank)
Age < 60	127	128	(93-163)	0.0066
Age > 60	294	62	(47-77)	
Sex M	239	72	(52-92)	0.7765
Sex F	182	83	(55-111)	
CRP < 10	125	105	(58-152)	0.0132
CRP > 10	296	65	(49-81)	
TP < 62	161	54	(29-79)	0.001
TP > 62	260	87	(64-110)	
ALB < 35	138	38	(28-48)	<0.0001
ALB > 35	283	105	(82-128)	
Ca < 2.6	288	118	(84-152)	0.0001
Ca > 2.6	21	31	(19-43)	
Dep < 7	169	65	(34-96)	0.9717
Dep > 7	218	62	(43-81)	

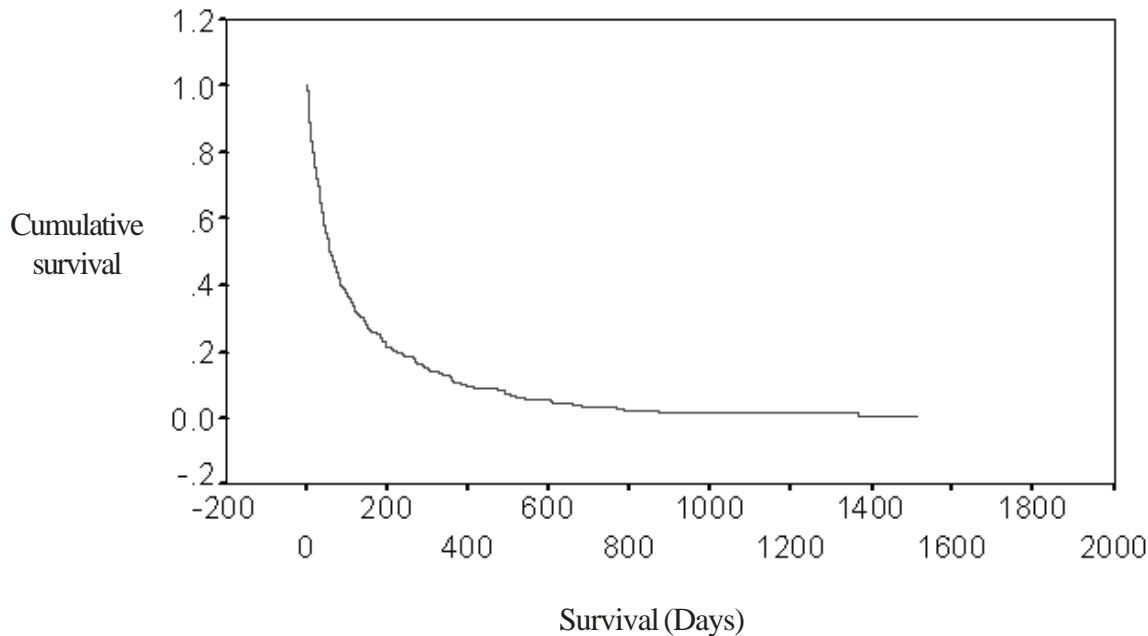
**Table 2.** Multivariate analyses of the relationship between continuous variables and survival from sampling in bronchogenic cancer patients (n=305).

	Hazard Ratio	p-value
*C-reactive protein	1.01 (1.00- 1.03)	0.0001
*Albumin (g/l)	0.93 (0.90- 0.95)	0.0001
*Calcium (mmol/l)	2.37 (1.57- 4.15)	0.0010

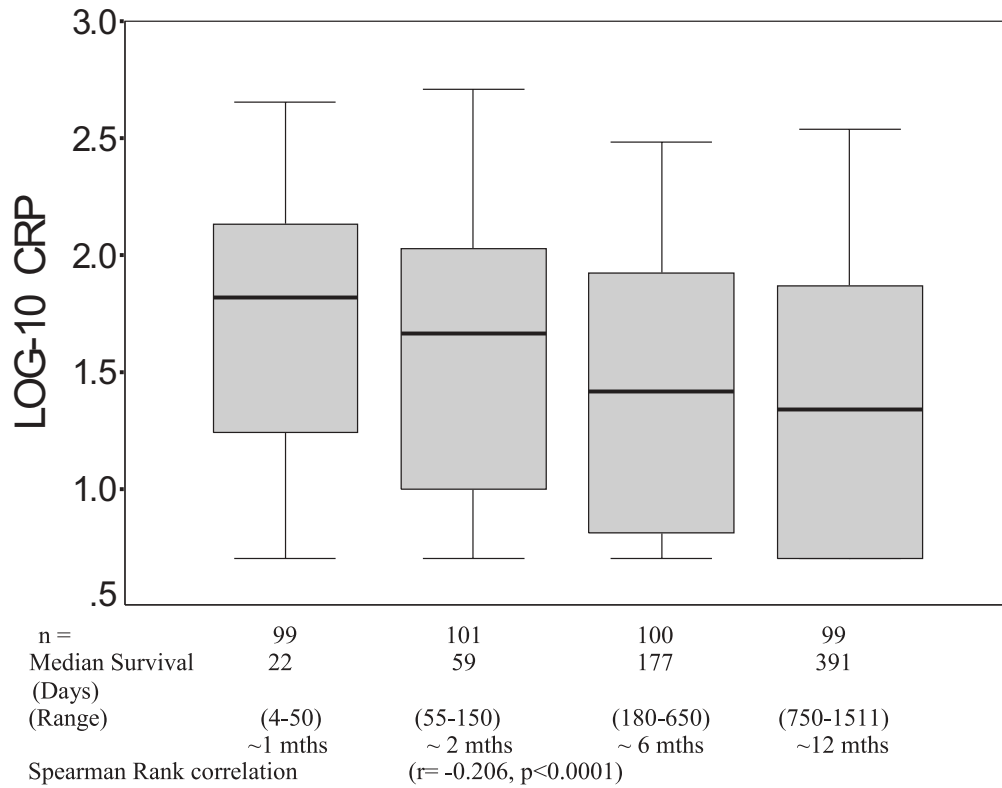
\* log<sub>10</sub>. All variables were treated as continuous, and the reported hazard ratios represent the relative risk for a unit increase in the prognostic variable. In the case of log<sub>10</sub> C-reactive protein concentration, this corresponds to a tenfold increase in C-reactive protein concentration. 95% confidence intervals for the hazard ratio are shown in brackets. Variables for which no hazard ratio is reported were excluded from the final Cox regression model.

In the present work, the majority of patients

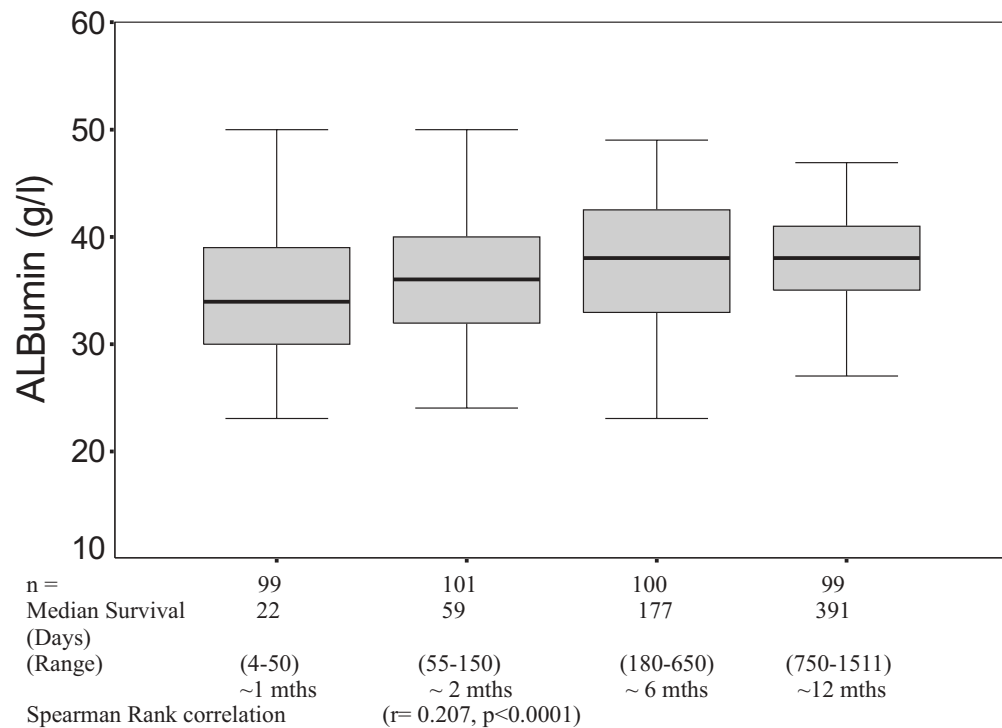
were followed up to death in contrast to previous studies where less than half of the patients were dead [15]. In general, bronchogenic cancer patients are diagnosed late, survival is approximately 8 months (ISD, 1998) and prognosis is poor. Extensive disease has been considered the most important prognostic factor in both small cell and non-small cell lung cancer. The median survival of the lung cancer patients diagnosed at advanced stages of the disease was 74 days and the 2-year survival was less than 10% [24]. Given that most of the patients in the present study did not survive more than 5 months it is likely that they were diagnosed at advanced stages of the disease (Fig. 1). The work demonstrated that the acute phase proteins, albumin and C-reactive protein were independently associated with survival (Figs 2,3). This is consistent with previous studies that have reported that increased circulating concentrations of C-reactive protein and decreased circulating concentrations of albumin are associated with poorer response to treatment and shortened survival in cancer patients [15,24,26,30]. The intensity of the inflammatory response in the patients



**Figure 1.** Survival from sampling in bronchogenic cancer patients.



**Figure 2.** Relationship between log C-reactive protein and survival (quartile) in bronchogenic cancer patients.



**Figure 3.** Relationship between albumin and survival (quartile) in bronchogenic cancer patients.

of the present study was greater and may account for the poorer survival in bronchogenic cancer. In the present study, the relationship between deprivation and poorer survival was of borderline significance on univariate analysis and lost on multivariate analysis. However, there was a trend towards a greater number of patients from low socio-economic status in the group, which developed an acute phase response, suggesting that deprivation is not a primary factor in the poorer survival of bronchogenic cancer patients and that the tumour-host inflammatory response may be important. Irrespective, the magnitude of the inflammatory response is associated with reduced survival in patients with advanced bronchogenic cancer.

### **Prognostic Factors in the Survival Of Patients with Gastrointestinal Cancer**

Patients with early gastrointestinal cancer may produce no symptoms at all or present with non-specific symptoms that may not be obvious while patients with advanced gastrointestinal cancer may exhibit the symptoms and signs of cancer anorexia, progressive weight loss and an insidious erosion of their body cell mass [31-32]. The condition progresses in a relentless manner and contributes greatly to the reduced survival seen in these patients.

Although many studies have addressed the prediction of survival in the early stages of gastrointestinal cancer [33] there are few reports on factors, which determine survival in advanced disease. The factors that determine survival of advanced gastrointestinal cancer patients are ill understood. Recent work suggests that activation of the host's own proinflammatory cytokine network may be important [34]. It is, therefore, of interest that one of the key metabolic changes induced by proinflammatory cytokines is the hepatic acute phase protein response and C-reactive protein is often increased in advanced malignancy [25,32]. Moreover, increased circulating C-reactive protein

is associated with increased energy expenditure and a shortened duration of survival in some types of gastrointestinal cancer patients [20].

A decrease in circulating albumin concentrations is an almost inevitable finding in disease states. Albumin is the principal negative acute phase reactant and a reduction in the concentration of this protein is an established marker of poor prognosis in malignancy [35]. Although, albumin concentration is a prognostic indicator in certain malignant diseases, its value in patients with gastrointestinal cancer remains unclear [36]. Studies of many populations, comprising healthy subjects and patients with gastrointestinal cancer, albumin concentration was found to be inversely related to mortality risk in a graded manner over its entire range; the estimated increase in the odds of death ranges from 24% to 56% for each 2.5 g/l decrement in serum albumin concentration [37].

In a cohort of patients with gastrointestinal cancer, the relationships between blood parameters measured at the time of sampling and survival duration were analysed. A total of 334 patients were studied of which 106 were gastric cancer and 228 were colorectal cancer patients. At the time of analysis 173 patients (50%) were dead.

In gastric cancer patients, blood parameters were available from 65 male patients and 41 female patients. The median range of the age at the time of diagnosis was 62 (29-90) and the median survival from the day of sampling was 116 days (range 6-1551) On multivariate analysis between all variables and survival from sampling, albumin ( $p < 0.0001$ ) remained independent predictors of survival (Table-3). No results in the cohort fell within four weeks of diagnosis. In colorectal cancer patients, on multivariate analysis between all variables and survival from sampling C-reactive protein ( $p = 0.0021$ ), albumin ( $p < 0.0001$ ) and total protein ( $p = 0.0002$ ) and phosphate ( $p = 0.0336$ ) remained

independent predictors of survival (Table-4). The numbers of cases falling within four weeks of diagnosis were too small to allow meaningful analysis. Taken together, in gastrointestinal cancer patients from the time of sampling, on multivariate analysis between all variables and survival from sampling, C-reactive protein ( $p < 0.0001$ ); albumin ( $p < 0.0001$ ); total protein ( $p = 0.0031$ ) and tumour type ( $p = 0.0022$ ) remained independent predictors of survival (Table-5). There were significant inverse correlations between log-10 C-reactive protein and albumin ( $r = -0.586$ ,  $p < 0.0001$ ) and between log-10 C-reactive protein and total protein ( $r = -0.353$ ,  $p < 0.0001$ ).

**Table 3.** Multivariate analyses of the relationship between continuous variables and survival from sampling in gastric cancer patients (n=67).

	Hazard Ratio	p-value
*Albumin (g/l)	0.869 (0.086- 0.912)	<0.0001

\* log10. All variables were treated as continuous, and the reported hazard ratios represent the relative risk for a unit increase in the prognostic variable. Variables for which no hazard ratio is reported were excluded from the final Cox regression model.

**Table 4.** Multivariate analyses of the relationship between continuous variables and survival from sampling in colorectal cancer patients (n=172).

	Hazard Ratio	p-value
*C-reactive protein (mg/l)	1.00 (1.01-1.02)	0.0001
*Albumin (g/l)	0.906 (0.87- 0.94)	<0.0001

\* log10. All variables were treated as continuous, and the reported hazard ratios represent the relative risk for a unit increase in the prognostic variable. In the case of log10 C-reactive protein concentration, this corresponds to a tenfold increase in C-reactive protein concentration. 95% confidence intervals for the hazard ratio are shown in brackets. Variables for which no hazard ratio is reported were excluded from the final Cox regression model.

There was a significant reduction in survival in the patients with an acute phase response (CRP > 10mg/l) (median 120 days) compared with those patients with CRP < 10mg/l (median 408 days).

**Table 5.** Multivariate analyses of the relationship between continuous variables and survival from sampling in gastrointestinal cancer patients.

	Hazard Ratio	p-value
*Albumin (g/l)	0.88 (0.85- 0.92)	<0.0001
*C-reactive protein (mg/l)	1.00 (1.01-1.01)	<0.0001
*Albumin (g/l)	0.906 (0.87- 0.94)	<0.0001
*Total protein (g/l)	1.04 (1.01-1.06)	0.0031
*Tumour type (G/C)	0.58 (0.42-0.82)	0.0022

\* log10. All variables were treated as continuous, and the reported hazard ratios represent the relative risk for a unit increase in the prognostic variable. In the case of log10 C-reactive protein concentration, this corresponds to a tenfold increase in C-reactive protein concentration. 95% confidence intervals for the hazard ratio are shown in brackets. Variables for which no hazard ratio is reported were excluded from the final Cox regression model.

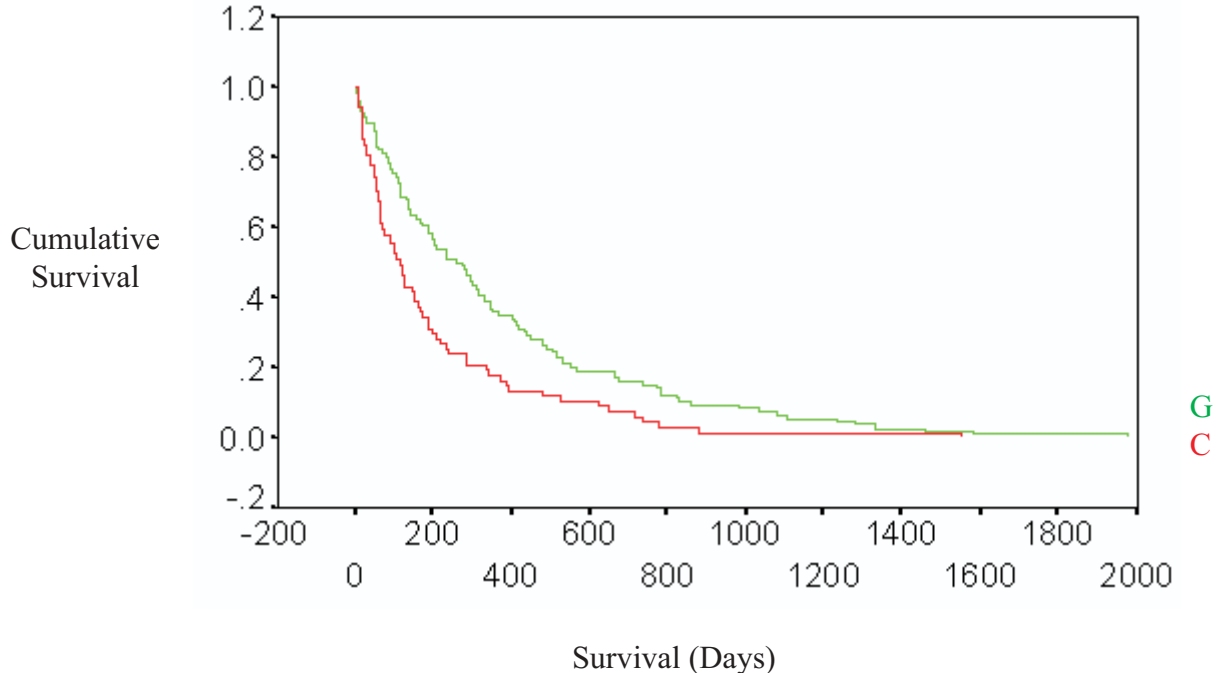
In general, the acute phase proteins are defined as circulating proteins that increase in concentration by 25% or more in the first 7 days following tissue damage. Some proteins, such as albumin and total protein, demonstrate a reduction in circulating concentrations during the acute phase response, and are often referred to as negative acute phase proteins [39]. Of the proteins that increase, C-reactive protein is most commonly used to assess the magnitude of the inflammatory response in humans. The present study represents a snapshot view of a dynamic process of deteriorating nutritional status and function in gastrointestinal cancer patients. The main criteria

for inclusion into the study were diagnosis of gastrointestinal cancer and data on inflammatory markers and therefore assessment was at that point in the disease course. However, other sampling points for example, the date of diagnosis or hospitalisation is subject to similar limitations. One of the difficulties in assessing the contribution of inflammatory response to survival in such patients is measurement of the extent of disease where dissemination to multiple organ sites has occurred. Given that both gastric and colorectal cancer patients in the present study did not survive more than approximately 8 months and 20 months respectively, it is likely that they were diagnosed at advanced stages of the disease (Fig. 4).

Tumour site is an important determinant of survival along with inflammatory response in

gastrointestinal cancer. To determine the influence of tumour type on survival in gastrointestinal patients, we analysed the data accordingly and it is clear that patients with gastric cancer have survived less compared with colorectal cancer. Considering tumour type and survival in gastrointestinal patients, the effect on survival has been variously reported. In the present study tumour type was significantly associated with survival. However, we did not have information on the stage of disease. Therefore, in the absence of tumour staging it would appear that tumour type is an important prognostic factor.

The relationship between deprivation and poorer survival was of borderline significance on univariate analysis and lost on multivariate analysis. Although the prognostic significance of the socio-economic status of patients of gastrointestinal cancer



**Figure 4.** Survival from sampling in gastric (G) and colorectal (C) cancer patients.

has been demonstrated [7] the mechanisms by which the socio-economic status influence prognosis are still ill understood. Recently, McLeod suggested that deprivation did appear to influence long term survival and treatment in gastrointestinal patients [39].

In this very study we have demonstrated both in gastric and colorectal cancer patients, that the presence of an inflammatory response (either an increase in C-reactive protein or a decrease in albumin and total protein concentrations) are associated with reduced survival. Similar results have been obtained by Zaloudik and associates in colorectal cancer suggesting that response to therapy was poorer and prognosis worse with increased C-reactive protein and decreased circulating albumin concentrations [40].

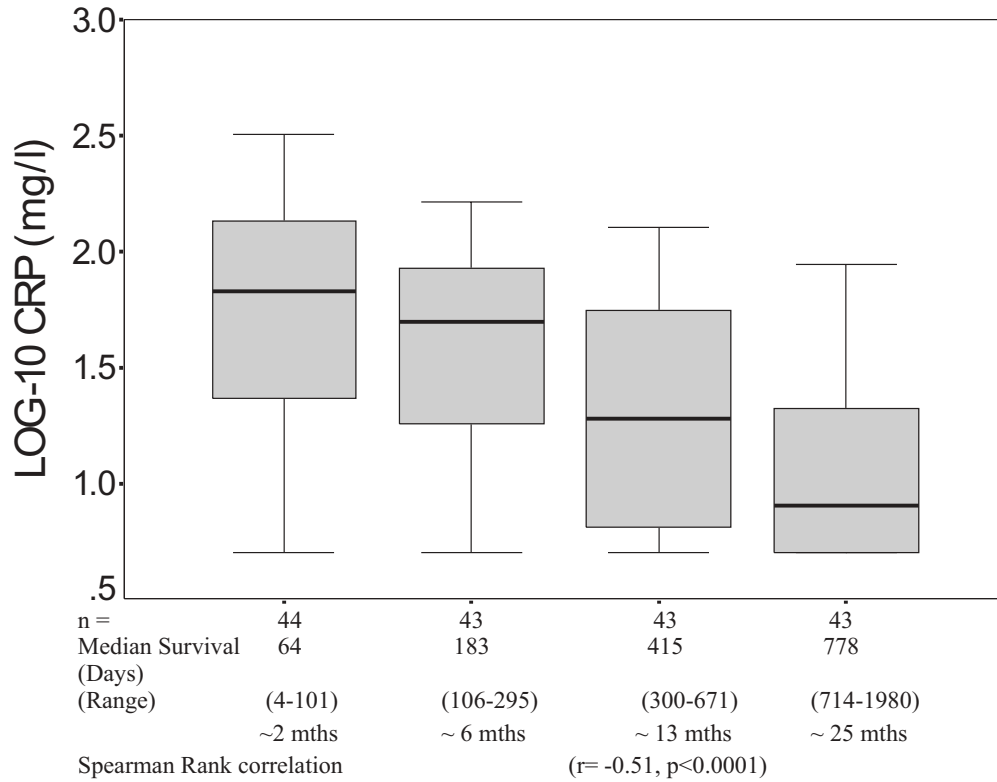
Due to the variability in the sampling period we were able to demonstrate that, as the intensity of inflammatory response increased the poorer was the outcome and especially nearer to death the intensity of the inflammatory response increased significantly (Figs.5,6). This is also consistent with, Goransson and coworkers who reported that high preoperative C-reactive protein and low albumin concentrations correlated to the “overall” tumour burden, exhibiting early recurrence and worse prognosis [41]. The mechanism whereby an inflammatory response reduces survival of gastrointestinal cancer patients is still unclear. However it has been demonstrated that the magnitude of the acute phase response is related to the rate of loss of body cell mass [31]. Moreover, there is evidence that the presence of an inflammatory response stimulates tumour growth in colorectal [19-20] and gastric cancer [42]. Therefore, the impact of an inflammatory response on survival may be due to increased loss of metabolically active tissue and increased tumour growth ultimately compromising outcome. Irrespective of the results, the present study demonstrates that the majority of such patients with gastrointestinal cancer have an inflammatory response

and the extent and persistence of that response is associated with the duration of survival.

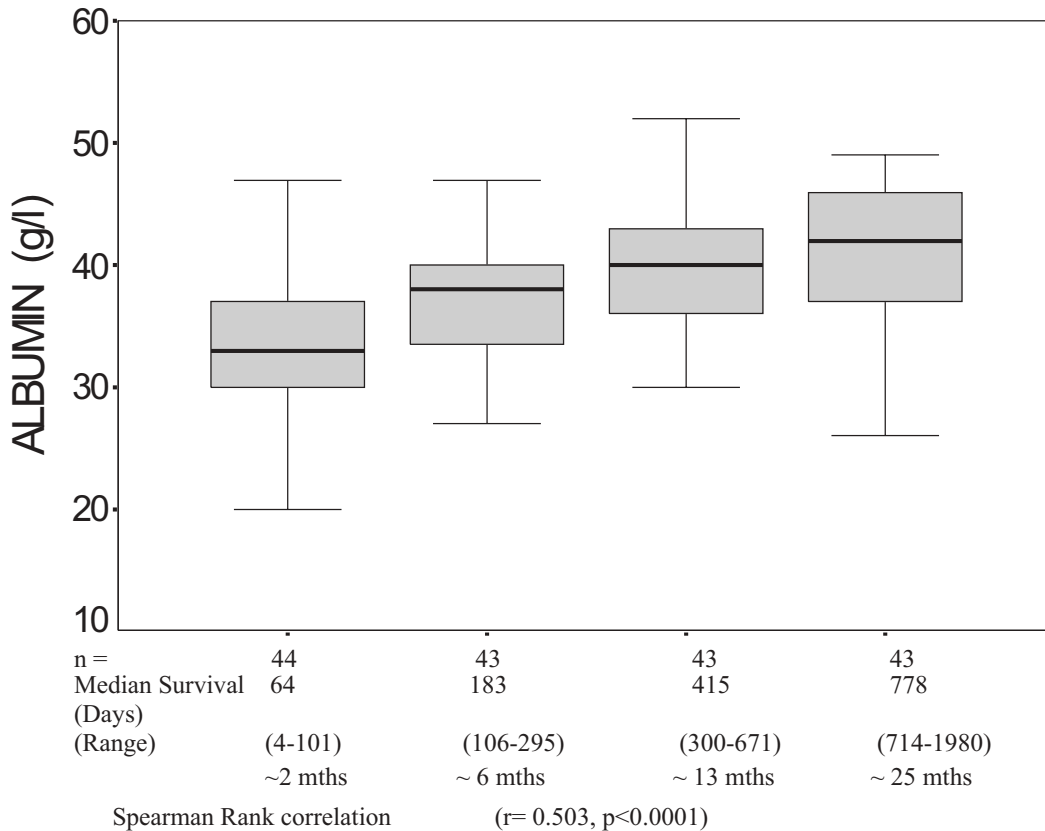
### **Prognostic Factors in the Survival of Patients with Advanced Breast Cancer**

Breast cancer constitutes about 25% of the female cancer burden and is the greatest cause of cancer related deaths among women after lung cancer. For any women, free from other life threatening disease, the theoretical risk of developing breast cancer up to the age of 74 is approximately 8%. Well-established breast cancer risk factors include older age, a family history of breast cancer, early menarche, late age at first childbirth, late age at menopause, history of benign breast disease and exposure to ionising radiations. The natural history of breast cancer has not been fully elucidated and therefore there remains uncertainty over prognosis. More recently there have been reports that markers of acute phase response such as albumin and interleukin-6 are also associated with reduced survival [43]. Moreover, these inflammatory markers were found to predict a poorer response to chemo-endocrine therapy as well as survival in metastatic breast cancer [43]. There is relationship between socio-economic deprivation and poorer survival in women with breast cancer. At the same time differences in survival from breast cancer by socio-economic deprivation category cannot be accounted for by differences in tumour stage [44].

In a cohort of patients with breast cancer, survival was examined from both sampling and diagnosis and blood parameters measured at the time of sampling were used in the analysis of results. A total of 120 patients were studied. At the time of analysis 73 patients (60%) were dead. From the time of sampling, blood parameters were available from 120 female patients. The median (range) age at the time of diagnosis was 59 (30-90) and the median survival from the day of sampling was 247 days (range 2-1891).



**Figure 5.** Relationship between log C-reactive protein and survival (quartile) in gastrointestinal cancer patients.



**Figure 6.** Relationship between albumin and survival (quartile) in gastrointestinal cancer patients.

Univariate analysis of the relationship between the variables measured and survival from the day of sampling is shown in Table-6. There was a significant relationship between 3 of the 8 variables assessed and survival. On multivariate analysis between all variables and survival from sampling, C-reactive protein concentration ( $p=0.0021$ ) and total protein concentration ( $p=0.0818$ ) remained independent predictors of survival (Table 7). No results in the cohort fell within four weeks of diagnosis. There were significant inverse correlations between  $\log_{-10}$  C-reactive protein and albumin ( $r=-0.576$ ,  $p<0.0001$ ) and between  $\log_{-10}$  C-reactive protein and total protein ( $r=-0.374$ ,  $p<0.0001$ ). There was a significant reduction in survival in the patients with an acute phase response (C-reactive protein greater

than 10mg/l) (median 100 days) compared with those patients with C-reactive protein less than 10mg/l (median 410 days). There was no difference in DEPCAT between these groups. All patients were followed up to death in contrast to previous studies. Given that most of the patients in the present study did not survive more than 36 months, it is likely that they were diagnosed at advanced stages of the disease (Fig. 7).

The present study demonstrated that the presence of an inflammatory response (either an increase in C-reactive protein or a decrease in albumin) is associated with reduced survival. These results are consistent with previous reports, which suggested increased concentrations of acute phase

**Table 6.** Univariate analyses of the relationship between categorical variables and survival from sampling in breast cancer patients (n = 421).

Factors	n	Survival (Median)	(Days) (95%CI)	p-value (log rank)
Age < 60	67	409	(65-653)	0.5498
Age > 60	53	329	(233-425)	
CRP < 10	52	625	(252-998)	0.0037
CRP > 10	68	179	(0-373)	
TP < 62	46	231	(63-399)	0.0532
TP > 62	74	576	(261-891)	
ALB < 35	28	115	(54-176)	<0.0001
ALB > 35	92	576	(338-814)	
Ca < 2.6	113	372	(127-617)	0.8575
Ca > 2.6	6	409	(0-1077)	
Phos < 1.4	84	637	(433-841)	0.7573
Phos > 1.4	8	372	(66-678)	
Dep < 7	53	585	(1-1169)	0.4006
Dep > 7	43	505	(0-1079)	

**Table 7.** Multivariate analyses of the relationship between continuous variables and survival from sampling in breast cancer patients (n=172).

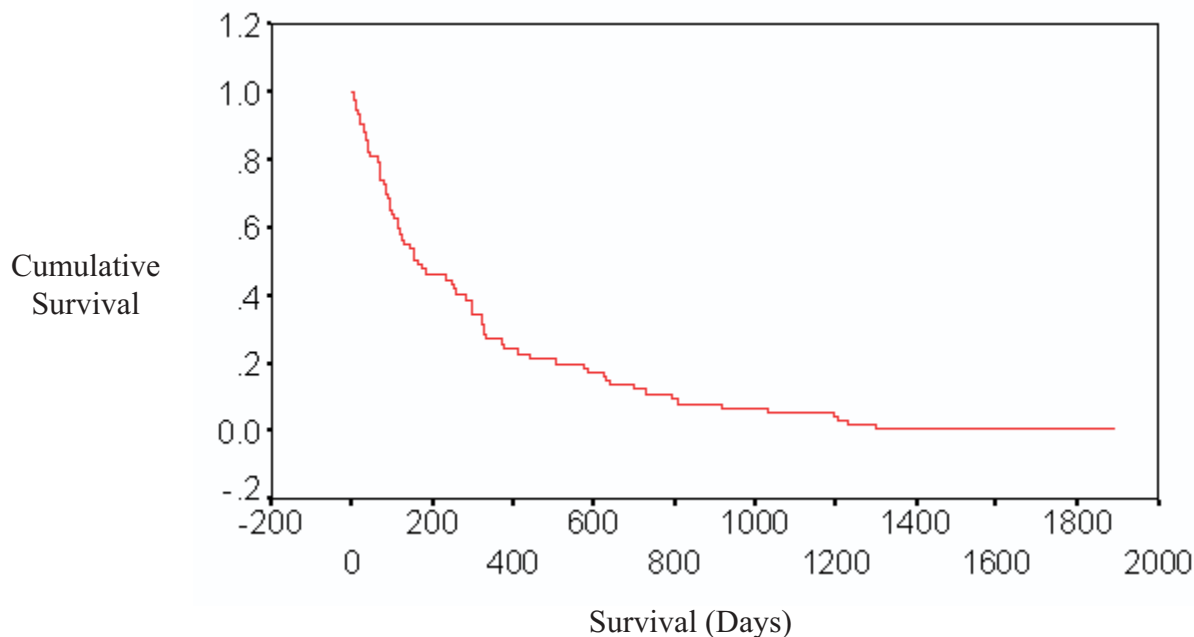
	Hazard Ratio	p-value
*C-reactive protein 1.00 (mmol/l)	(1.01-1.01)	0.0021

\* log10. All variables were treated as continuous, and the reported hazard ratios represent the relative risk for a unit increase in the prognostic variable. In the case of log10 C-reactive protein concentration, this corresponds to a tenfold increase in C-reactive protein concentration. 95% confidence intervals for the hazard ratio are shown in brackets. Variables for which no hazard ratio is reported were excluded from the final Cox regression model.

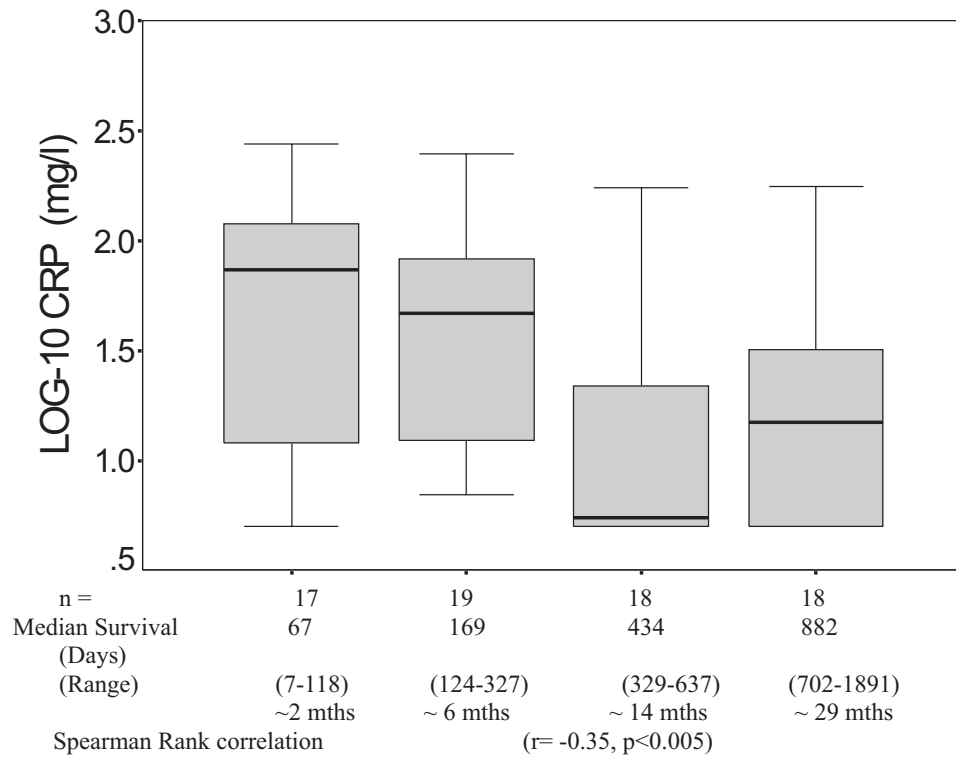
reactants (interleukin-6 and C-reactive protein) and decreased concentrations of albumin are associated with a poorer response to treatment and shortened survival in breast cancer patients [36,43]. Heys and associates surveyed nearly 80 patients with advanced

breast cancer and measured the circulating concentrations of acute phase proteins C-reactive protein and albumin in serum taken prior to commencement of treatment and followed them for approximately 31 months and reported that reduced concentrations of albumin were independent prognostic indicators for a poorer survival in patients with advanced breast cancer [36].

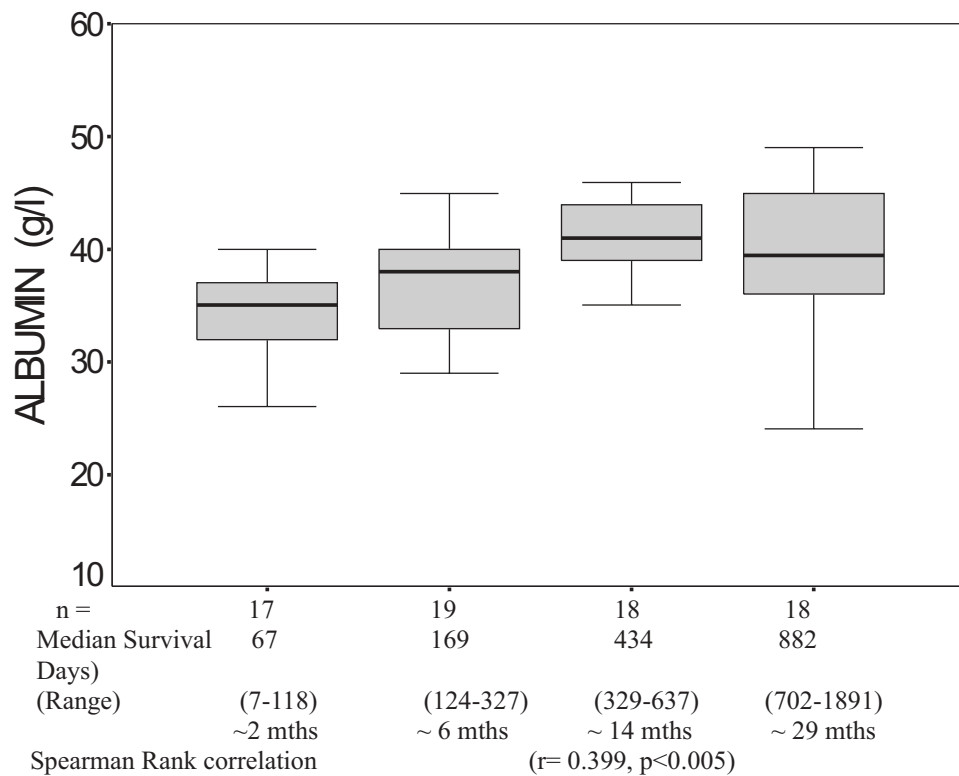
Moreover, due to the variability in the sampling period we were able to demonstrate that as the intensity of inflammatory response increased the poorer was the outcome and especially nearer to death the intensity of the inflammatory response increased significantly (Figs. 8,9). This has not been previously demonstrated in advanced breast cancer patients. Furthermore, the results demonstrated that the relationship between C-reactive protein and albumin together with C-reactive protein alters as breast cancer patients approached death.



**Figure 7.** Survival from sampling in breast cancer patients.



**Figure 8.** Relationship between log C-reactive protein and survival (quartile) in breast cancer patients.



**Figure 9.** Relationship between albumin and survival (quartile) in breast cancer patients.

Although the prognostic significance of the socio-economic status of patients of breast cancer has been demonstrated [44], the relationship between deprivation and poorer survival did not come out significant on either univariate analysis or on multivariate analysis. This may have been due to the small number of patients in the present cohort. Carnon and coworkers suggested that differences in survival from breast cancer by socio-economic deprivation category could not be accounted for by differences in tumour stage. Other possible explanations, such as differences in treatment or in host response, should be investigated [45]. It may be that inflammatory response is important in this observation.

## Conclusion

We have described a characteristic pattern of inflammatory response (increased C-reactive protein, decreased albumin) and their association with reduced survival in bronchogenic, gastric, colorectal and breast cancers. This would suggest a uniform host response to common solid tumours in the advanced stages of the disease. On multivariate analysis, with tumour type as a covariable it was of interest that the survival for a given magnitude of C-reactive protein, albumin was similar in gastrointestinal and breast tumours. In contrast, survival of bronchogenic cancer was shorter. The basis of this difference is not clear. Given the majority of patients with advanced cancer appear to die with respiratory failure secondary to infection. It may be that the shorter duration of survival in the bronchogenic cancer patients was due to the earlier presentation of such symptoms. The ratio of C-reactive protein/ albumin increases with reducing survival suggesting that the inflammatory response increases in importance when survival is taken into account regarding bronchogenic, gastrointestinal and breast cancers. With respect to early disease there is evidence in gastrointestinal and lung cancer to suggest that the interval between diagnosis of the

primary tumour and metastasis is shorter in patients with detectable serum C-reactive protein concentration [41]. Given that the median survival was approximately a year or less in all of the tumours examined it is likely that the majority of patients had advanced cancer at the time of observation. Taken together, this would indicate that C-reactive protein concentrations might be useful for “staging” cancer patients with disease progression. The importance of the inflammatory response in the survival of cancer patients has important implications both in the evaluation of new markers of disease severity [46] and in the interpretation of studies of treatment in cancer [47]. The review along with the inborn experimental result of described studies demonstrated that the majority of patients with advanced breast, gastric, colorectal and lung cancer have incidence of an inflammatory response and the extent of that response is associated with duration of survival. It is clear from the results that there is some variability in the response of these inflammatory mediators to different tumour types, and consequently the prediction of survival. Also the relationship between albumin, C-reactive protein and survival is consistent with concept that the presence of on-going inflammatory response hastens the subsequent death of patients with advanced cancer. Hence, anticipated survival is a major factor to be taken into consideration when deciding whether active intervention or palliation is appropriate in patients with advanced cancers.

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