Papers

Delays in the diagnosis of oesophagogastric cancer: a consecutive case series

Iain G Martin, Sheila Young, Henry Sue-Ling, David Johnston

Abstract

Objectives: To examine the time taken to diagnose oesophageal or gastric cancer, identify the source of delay, and assess its clinical importance

Design: Study of all new patients presenting to one surgical unit with carcinoma of the oesophagus or stomach.

Setting: University department of surgery in a large teaching hospital.

Subjects: 115 consecutive patients (70 men, mean age 66 years) with carcinoma of the oesophagus (27) or stomach (88).

Main outcome measures: Interval from the onset of symptoms to histological diagnosis, final pathological stage of the tumour, and whether potentially curative resection was possible.

Results: The median delay from first symptoms to histological diagnosis was 17 weeks (range 1 to 168 weeks). 25% (29/115) of patients had a delay of over 28 weeks (median 39 weeks). Total delay was made up of the following components: delay in consulting a doctor (29%), delay in referral (23%), delay in being seen at hospital (16%), and delay in establishing the diagnosis at the hospital (32%). No relation was found between delay in diagnosis and tumour stage in patients with gastric cancer, but for oesophageal cancer those with stage I and II disease were diagnosed within 7 weeks compared with 21 weeks ($P < 0.02$) for those with stage III and IV disease.

Conclusions: Long delays still occur in the diagnosis of patients with cancer of the stomach or oesophagus. Streamlined referral and investigation pathways are needed if patients with gastric and oesophageal carcinomas are to be diagnosed early in the course of the disease.

Introduction

The Japanese make strenuous efforts to diagnose cancer of the stomach and oesophagus at an early stage. Patients have wide en bloc resection of the primary tumour and its draining lymph nodes to achieve clear margins of resection, proximally, distally, and circumferentially (so called R0 resection). Operative mortality is about 2% and five year survival after resection for gastric cancer is 86% and for all patients who have resection 64%.[1] For patients with oesophageal cancer operative mortality is 4% and five year survival 30%.[2]

In Britain, however, both gastric and oesophageal cancer have been regarded as fatal diseases until recently. There is no screening programme, and even patients who develop suspicious symptoms such as weight loss, anaemia, dysphagia, and vomiting may remain undiagnosed for many months. When cancer of the stomach or oesophagus is finally diagnosed surgery is usually far less extensive than in Japan. Operative mortality is between 5%[3] and 15%[4] after resection and five year survival of gastric cancer is 5-10% for all cases and just 20-30% after resection.[5] The results for oesophageal cancer are even worse. In Yorkshire operative mortality was reported to be 13-15% and five year survival just 1-2% overall and 6-10% after resection.[6]

We have previously shown that when Japanese surgical methods were applied in Britain the five year survival of British patients with gastric cancer was similar to that of Japanese patients with the same stage disease.[3 5] The task, then, is to attempt to diagnose the disease in Britain at the earliest possible stage and to perform more radical resections. We describe the results of a study of 115 consecutive patients with gastric or oesophageal cancer who were referred to our department over 16 months, starting in January 1994. We examined the length of delay in diagnosis and the reasons.

Subjects and methods

One of us (SY) interviewed each patient at first presentation to our department. All data were verified by a second author (IGM). Dates were recorded according to the patients' recollection and cross referenced with the patients' notes. Details of the patient's first symptoms, the number of visits to the general practitioner before referral to hospital, and of any relevant drug treatment were recorded. We followed the patients' subsequent clinical course.

The time to diagnosis was measured from the date when the patient first experienced the symptoms that led to diagnosis. In the case of patients with long standing dyspepsia, this date was taken to be when the patient first noticed a significant change in these symptoms. The primary end point was the establishment of a histological diagnosis of malignancy and the second endpoint was the date when the patient had definitive surgery (if appropriate). The overall delay in weeks was

Academic Department of Surgery, Centre for Digestive Diseases, General Infirmary at Leeds, Leeds, LS1 3EX

Iain G Martin, *consultant surgeon*

Sheila Young, *research assistant*

Henry Sue-Ling, *consultant surgeon*

David Johnston, *professor of surgery*

Correspondence to: Mr Martin (I.G.MARTIN@leeds.ac.uk)

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Table 1 Stage of gastric and oesophageal tumours. Values are number (percentages) of patients

Tumour stage	Gastric cancer	Oesophageal cancer
I	20 (17)	1 (1)
II	7 (6)	6 (5)
III	33 (30)	14 (12)
IV	28 (24)	6 (5)
Total	88 (76)	27 (24)

recorded for each patient and divided into four periods:

1. The time from first symptoms to the patient first seeking medical advice.
2. The time from first seeking medical advice to referral for investigation by endoscopy or barium meal or for a hospital consultant's opinion.
3. The time from referral to first attendance at hospital for investigation or outpatient consultation.
4. The time from first attendance at hospital to establishment of a definitive histological diagnosis.

For patients who had surgery we also recorded the time from histological diagnosis to the operation.

Tumours were staged according to the 1987 TNM classification,[7 8] whenever possible from operative specimens.We used statistics appropriate for non-parametric data. Grouped data were compared by the Mann-Whitney U test, corrected for ties and small numbers.

Results

We recruited 115 patients (70 men and 45 women) over 18 months. Eighty eight patients had cancer of the stomach and 27 cancer of the oesophagus. Of the 88 gastric cancers, 27 were located predominantly in the upper third of the stomach, 33 mainly in the middle third, and 28 in the lower third, The median age of the patients when they first developed symptoms was 66 years (range 31 to 89 years).

The first symptoms or signs were dyspepsia or indigestion in 19 (17%), dysphagia in 41 (24%), abdominal or chest pain in 48 (28%), nausea or vomiting in 27 (16%), heartburn in 7 (4%), weight loss in 20 (12%), early satiety in 27 (16%), and anaemia in 19 (17%). Some patients experienced more than one symptom.

All patients had endoscopy and staging investigations (chest *x* ray film, abdominal ultrasonography, and thoracoabdominal computed tomography). Twenty one (18%) had stage I disease, 13 (11%) stage II disease, 47 (41%) stage III disease, and 34 (30%) stage IV disease (table 1).

Table 2 Median (interquartile range) diagnostic delays from first symptoms to histological diagnosis in weeks

Delay	All patients (n=115)	Oesophageal cancer (n=27)	Gastric cancer (n=88)
From first symptoms to seeing doctor	2.0 (1.0-7.7)	2.1 (1.1-12.4)	2.0 (0.9-5.5)
From seeing doctor to being referred to hospital for investigations or consultation	2.0 (0.0-6.3)	2.1 (0.0-4.4)	2.1 (0.0-7.5)
From being referred to being seen for consultation or investigation	2.0 (0.7-2.7)	1.4 (0.7-2.6)	2.0 (0.6-2.9)
From being seen at hospital to histological diagnosis	2.8 (1.2-6.6)	2.3 (1.4-6.7)	3.1 (1.0-5.8)
Total delay	17.1 (8.7-28.6)	17.1 (7.3-23.8)	17.3 (9.7-32.0)

Eighty (91%) of the patients with gastric cancer and 25 (92%) of the patients with oesophageal cancer were treated surgically. Of the surgical procedures, 78 (74%) were regarded as potentially curative resections, 24 (23%) were palliative resections, and three (3%) palliative bypasses or laparotomy.

The median delay from the onset of symptoms to a definitive histological diagnosis was 17.1 weeks for patients with gastric cancer and 17.3 weeks for patients with oesophageal cancer. Table 2 shows the breakdown of this delay. Overall, delay in consulting a doctor accounted for 29% of the total, delay in referral 23%, delay in being seen at hospital 16%, and delay in establishing the diagnosis at the hospital 32%.

Twenty nine patients experienced delays in diagnosis of more than 28 weeks, and among these the median delay was 39 weeks (43 weeks if the time to treatment is included). For these patients, delay in presenting to a doctor accounted for 18% of the overall delay, delay in being referred for investigation and treatment 33%, delay in being seen at the hospital for investigation or consultation 13%, and delay in establishing a histological diagnosis at the hospital 36%.

Among the patients who had surgery there was a further median delay of 3.9 weeks before operation. However, as this extra delay did not alter the conclusions of any of the subsequent analyses and since not every patient had surgery, only the delay between the onset of symptoms and histological diagnosis is considered below.

General practitioners referred 51 patients immediately for investigations or consultation. The remaining 64 patients made further visits before being referred (16 made one further visit, 16 two further visits, 18 three further visits, and 14 patients four or more visits). Fifty five patients were given a prescription at the initial consultation: 23 for simple antacids, 19 for H_2 receptor antagonists, seven for proton pump inhibitors, and six for other drugs.

When patients were seen at the hospital the diagnosis was established within four weeks in 70 patients (61%) and within eight weeks for 88 (76%). For 17 patients the delay was between 12 and 87 (median 33) weeks.

Relations with delay in diagnosis

We found no significant relation between the nature of the first symptoms and delay in diagnosis. Even when dysphagia was the main first symptom the diagnosis was not made significantly more rapidly than in patients with less dramatic symptoms. Similarly no relation was found between diagnostic delay and tumour location. The median delay was 17 weeks for oesophageal carcinomas, 14 weeks for lesions of the upper stomach, 16 weeks for middle stomach lesions, and 22 weeks for antral and pyloric lesions.

Use of our open access endoscopy service reduced the delay in diagnosis. Overall the median delay for the 65 patients referred directly to the open access dyspepsia clinic was 14 weeks compared with 25 weeks for the 50 who were more conventionally referred ($P < 0.001$).

For patients with stomach cancer there was no clear relation between tumour stage and delay in diagnosis (fig 1). For oesophageal cancer, however, the median

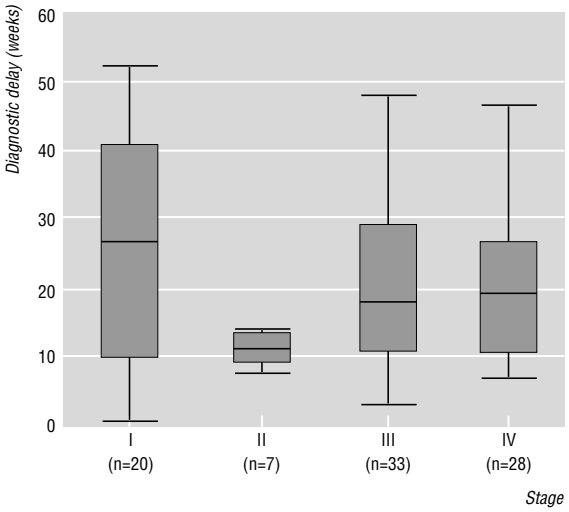

Fig 1 Relation between stage of gastric cancer and delays in establishing histological diagnosis (thick line=median, box=interquartile range, whiskers=full range)

delay was 6.7 weeks in patients with stage I and II disease but 20.9 weeks in those with stage III and IV disease ($P < 0.02$, fig 2[2]).

In patients with gastric cancer we found no relation between delay in diagnosis and the success of potentially curative resection (17.7 weeks for successful operations *v* 17.8 for unsuccessful). The relation was also non-significant for patients with oesophageal cancer (15 *v* 24 weeks, $P = 0.2$).

Discussion

Although our department has a well established open access endoscopy service, the median interval between first symptoms and histological diagnosis was 17 weeks and the median interval between first symptoms and definitive treatment 21 weeks. Furthermore, in a quarter of patients the median interval to diagnosis was 39 weeks and to treatment 43 weeks. Even though some patients had to visit their general practitioner several times before being referred for investigation, the longest delays were in hospital. It seems likely that the delays in other hospitals in Britain are likely to be similar if not longer.

We found that the patients were usually quick to seek medical advice for their symptoms. Much of the delay in diagnosis could therefore be avoided if general practitioners referred patients promptly for investigation and a sense of urgency was imparted to the hospital's diagnostic process.

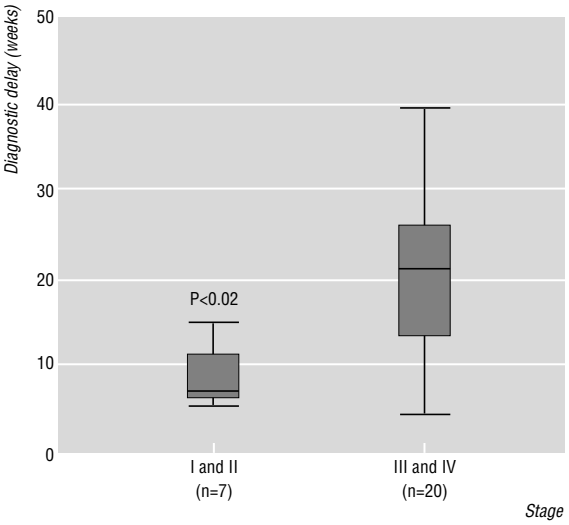

Fig 2 Relation between stage of oesophageal cancer and delays in establishing histological diagnosis (thick line=median, box=interquartile range, whiskers=full range)

Do long delays in diagnosis matter?

Delays in diagnosis are important because cancers grow continuously, albeit at differing rates. Decreasing the diagnostic delay should result in tumours being diagnosed at earlier stages, although no study (including this one) has shown a relation between short duration of symptoms and early tumour stage. In fact, both we and other authors have shown a trend in the other direction—that is, the longest symptomatic histories are often associated with the "earlier" tumours.[9 10] This is probably explained by the natural course of upper gastrointestinal tumours.

Early gastric cancer (tumour confined to the mucosa or submucosa irrespective of lymph node status) has a doubling time of between 1.5 and 10 years whereas "advanced" cancer has a doubling time of between 2 months and 1 year.[11 12] Most advanced cancers are still amenable to potentially curative resection, and the delays in diagnosis that we have found are equivalent to one or two doubling times of the tumour. If, instead of diagnosing patients when they have stage IV disease, with few five year survivors, we could diagnose them while they still had stage III disease with a five year survival of 30% or, better still, stage II disease with a five year survival of 70%,[3] the effect on overall survival would be marked. Since most patients present with advanced cancer, quicker treatment should mean patients have smaller tumours and lower stage disease, which has a greater chance of cure.

The other evidence which suggests that early diagnosis of gastric cancer matters is the changing pattern of presentation in Britain and elsewhere. Over the past 20 years we have seen the proportion of patients presenting with stage I disease increase fourfold.[3] Other centres that have adopted similar policies for the early investigation of dyspeptic patients have also reported similar proportions of patients with curable disease [13 14]; indeed evidence is accumulating from Birmingham that early investigation and prompt surgery can reduce mortality (M T Hallisey *et al*, first international gastric cancer congress, Kyoto, Japan, March 1995).

For oesophageal cancer we found a significant difference between the delay in diagnosis among patients with stage I and II disease compared with those with stage III and IV disease. However, this was based on fewer patients than we had for stomach cancer. At present early radical surgery provides the only hope of cure for most patients with oesophageal cancer.[2 15] The median delay was seven weeks for those with stage I and II cancer and 21 weeks for those with more advanced cancer, which suggests that prompt referral, investigation, and treatment are needed.

Key messages

- Survival of oesophagogastric cancer is most likely if the tumour is caught early
- The median delay in diagnosis for patients with oesophagogastric cancer was 17 weeks but 25% of patients had delays of more than 28 weeks
- For patients with oesophageal cancer this delay was associated with tumours of more advanced stage
- Patient delay in seeking medical help was relatively short; the biggest reductions in delays could be produced by streamlined referral and investigation.
- Open access endoscopy service reduced delays in diagnosis compared with standard referral

Can these delays be reduced or eliminated?

If the delays in diagnosis and treatment are to be decreased we believe that two changes are needed. Firstly, patients with new onset dyspepsia or a change in long standing dyspepsia must be referred promptly and, secondly, hospital assessment must be speeded up. For patients with breast cancer, the "one stop" clinic at which a histological diagnosis is established at the first hospital visit is becoming the expected norm. Perhaps a similar service should be set up for gastroenterology. Open access clinics have already reduced the delay. Overall the median delay for the patients referred directly to the open access dyspepsia clinic was 14 weeks n compared with 25 weeks for those more conventionally referred. The median age of our patients was 66 years and only 23 were over 75 years, suggesting that most would be better served by direct referral to an open access service.

In conclusion we have shown that there is a median delay of 17 weeks from first symptoms to diagnosis in patients with upper gastrointestinal cancer. We believe this is clinically important because it probably represents one to two doubling times for most patients with gastric cancer. In patients with oesophageal cancer such delay is associated with worsening tumour stage and poorer prognosis. Early referral for investigation and prompt endoscopic assessment will produce the greatest reduction in these delays.

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Commentary: Japanese point of view

Takeshi Sano, Keiichi Maruyama

Department of Surgical Oncology, National Cancer Centre Hospital, Tokyo
Takeshi Sano, *Head of gastric division*
Keiichi Maruyama *Head of gastric division*

If you work in Japan the local government or the health department of your company will offer you a barium meal examination. You may choose to ignore this because you have no symptoms or because you had normal results the previous year. Suppose that later you feel epigastric discomfort for several days. Since there is no British-style general practice system in Japan you visit a private "gastrointestinal clinic" near your office (there are many of these in Japan, and no private insurance is needed). The doctor will ask whether you have taken breakfast and, if the answer is no, will suggest you have a gastroscopy in the clinic on that day. You may be frightened by the sudden offer, but you remember one of your colleagues who has recently undergone curative surgery for an early gastric cancer detected in the screening which you declined. The doctor examines your upper gastrointestinal tract meticulously, taking biopsy specimens, and may find an early gastric cancer.

The diagnosis of oesophagogastric cancer is often made before a patient attends hospital in Japan, and the patients are referred to hospital surgeons along with the endoscopic films and a copy of the pathology results. Surgeons try to attack the tumour as soon as possible especially in advanced disease.

Martin *et al* divided the total delay from onset of symptoms to surgical treatment into five stages. Each step took several weeks, making the total delay 21 weeks. This could be even longer in other parts of Britain where open access endoscopy is not available. In

Japan the middle three referral steps can be omitted or shortened, and the delay from the first medical consultation to histological diagnosis is usually less than two weeks.

The delay from onset of symptoms to treatment is a practical problem, and it could be reduced by improvements in the referral system. However, the concept of early diagnosis in Japan is different in that the emphasis is placed on diagnosis before symptoms occur. More than six million adults have radiological screening for gastric cancer every year. Although several problems have been identified, such as low cost-effectiveness and the significant false negative rate, more than 7000 new cases are diagnosed as a result of the screening programme every year. The oesophagus is also screened "in passing." The most important byproducts of the programme are widely available and easily accessed endoscopy services and a heightened public awareness of the disease. Most superficial oesophageal cancers and many early gastric cancers are incidentally found in the clinics during routine endoscopy for non-specific symptoms.

In the Japanese health care system many generous policies have been established without much consideration of the cost. The early detection of oesophagogastric cancer which is now possible in Japan may be one of the most important products of this strategy.

Commentary: Britain does better than Germany before patients reach hospital

J R Siewert, U Fink

Department of Surgery, Technische Universitat Munchen, Germany
J R Siewert, *head of department*
U Fink, *head, section of surgical oncology*

It is undisputed that a patient's prognosis is better the earlier the tumour stage is at the start of treatment. It is also undisputed that a tumour grows with time. Delay in the diagnosis of a tumour is therefore counterproductive, but does it also influence the prognosis of a patient?

Delays in diagnosis may reflect the natural course of the tumour, with tumours that have been diagnosed late developing slower than those detected earlier and vice versa. So far there is no clear proof that the extent of delay in the diagnosis is consistent with a worse prognosis. Martin *et al* found a correlation for oesophageal cancer but not gastric cancer and our own analysis could also not identify such a correlation.[1]

The specific problem when dealing with gastric carcinomas is that there is no typical symptom which brings the patient to the doctor. Theodor Storm, a German poet who died of gastric cancer, described his symptoms as "only a point, hardly a pain." Therefore it is understandable and unavoidable that some delay in diagnosis is caused by the patient. Only intensive education of the population and easy access to endoscopy might help to shorten the delay. A patient must have the opportunity to have endoscopy without all the bureaucratic hurdles and with the full freedom of choice of treatment later on. At present this is not possible in Germany. Patients must be referred to a specialist and the cost has to be reimbursed from the patient's health insurance. Obviously open access as described by Martin *et al* is better.

Table 1 Median delay in diagnosis (weeks) of gastric cancer in two prospective studies

	Leeds (n=88)	Munich[1] (n=100)
Pretreatment delay		
Total delay (first symptom to diagnosis)	17.3	32.0
Patient's delay (first symptom to visiting general practitioner)	2.0	12.0
Doctors' delay:		
First visit to histological diagnosis	NS	12.0
First general practice visit to hospital referral	2.1	11 (n=60)
First visit to private internal physician to hospital referral	NA	24 (n=32) (P=005)
Referral to hospital consultation	2.0	1.0 (n=58)
Consultation to histological diagnosis	3.1	1.0 (n=22)
Hospital delay (histological diagnosis to resection)	3.9	2.0

NS=not stated, NA=not applicable.

The importance of open access to endoscopy is proved by the long "doctors' delay." In Germany the delay is 12 weeks longer than that reported by Martin *et al* (table 1). Part of the problem is that a doctor is paid for the patient's treatment and not for the diagnosis. Therefore when a patient presents with epigastric discomfort doctors generally start by treating the symptoms. H_2 blockers and especially omeprazol and *Helicobacter pylori* eradication improve symptoms, and the need for further investigation is reduced or delayed. In Germany the doctor's delay in diagnosis is 11 weeks for a general practitioner but 24 weeks for an internal physician. A reward is needed for the discovery of an early carcinoma to strengthen the motivation of doctors in private practice.

At least in Germany the diagnostic delay stops as soon as the patient enters the clinic. From this point it is only one more week until the final diagnosis is made and treatment started. This is the only point where the situation in Germany is obviously better than in Great Britain, where one third of the time of delay is caused by the last phase in the hospital. In this respect the British system could be improved.

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Retrospective study of reasons for improved survival in patients with breast cancer in East Anglia: earlier diagnosis or better treatment?

Diane Stockton, Tom Davies, Nicholas Day, Jenny McCann

East Anglian Cancer Intelligence Unit, Department of Community Medicine, Institute of Public Health, University of Cambridge, Cambridge CB2 2SR

Diane Stockton, *university research associate*

Tom Davies, *director*

Jenny McCann, *university research associate*

Department of Community Medicine, Institute of Public Health, University of Cambridge, Cambridge CB2 2SR

Nicholas Day, *professor and director*

Correspondence to: Miss Stockton.

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Abstract

Objectives: To investigate the recent fall in mortality from breast cancer in England and Wales, and to determine the relative contributions of improvements in treatment and earlier detection of tumours.

Design: Retrospective study of all women with breast cancer registered by the East Anglian cancer registry and diagnosed between 1982 and 1989.

Subjects: 3965 patients diagnosed 1982-5 compared with 4665 patients diagnosed 1986-9, in three age groups 0-49, 50-64, ≥65 years, with information on stage at diagnosis and survival.

Main outcome measures: Three year relative survival rates by time period, age group, and stage; relative hazard ratios for each time period and age group derived from Cox's proportional hazards model, adjusted for single year of age and stage.

Results: Survival improved in the later time period, although there was little stage specific improvement. The proportion of early stage tumours increased especially in the 50-64 year age group, and adjustment for stage accounted for over half of the improvement in survival in women aged under 65 years.

Conclusion: Over half of the drop in mortality in women aged under 65 years seems to be attributable to earlier detection of tumours, which has been observed since the mid-1980s. This could have resulted from an increase in breast awareness predating the start of the breast screening programme.

Introduction

In East Anglia in 1993 breast cancer accounted for almost 30% of all malignancies in women (excluding non-melanoma skin cancer) and was attributed as the cause of 591 deaths in a population of just over one million women. The cumulative risk to age 85 years of developing breast cancer is 11.2%—that is, about one in nine women will develop breast cancer by this age.

There has recently been much publicity regarding a reported drop in mortality from breast cancer in England and Wales in the 1990s.[1,2] Much of this recent fall may be due to improvements in treatment[1,2]—for example, more younger women with breast cancer being treated with tamoxifen and chemotherapy.

An alternative hypothesis is that tumours are being detected earlier, thus allowing more effective intervention. In 1986 there was much publicity about breast cancer after the publication of the Forrest report,[3] which listed guidelines for a national screening programme. The improvement in public awareness caused by the media coverage at this time could have led to the earlier detection of tumours.

Considering these two hypotheses, if improvements in treatment are the primary cause of the fall in mortality from breast cancer we would expect to see a corresponding fall in stage specific mortality. As the results of the overview of the trials on treatment of breast cancer show the main effect to be on early stage breast cancer,[4] one would expect, in particular, to see an overall improvement in survival from stage I and II breast cancers. If, alternatively, changing stage at diagnosis has been the main contribution to the fall in mortality we would expect to see little change in stage specific survival but a shift towards earlier stage at diagnosis. We investigated the relative contributions of improved treatment and earlier diagnosis on the observed reduction in mortality.

The reported drop in mortality began in the years 1989-90. We have, therefore, attempted to relate changes in mortality between the years 1985-8 and 1989-92 to characteristics of patients' tumours at diagnosis and also to the three year survival of women with cancers diagnosed on average three years earlier (that is, between the two time periods of four years—1982-5 and 1986-9). During the later time period there was considerable publicity surrounding breast screening, but the programme itself did not start in East Anglia until April 1989 and then began with the 60-64 year age group. Only 1.5% of cancers diagnosed in the later period had been detected through screening. Thus any changes in stage at presentation between the two time periods are unlikely to be the result of screening.

Subjects and methods

The ascertainment and quality of the data in the East Anglian cancer registry are high, and it is one of the few registries that collects stage information for breast cancer and performs active follow up of patients. All invasive breast cancers diagnosed between 1982 and 1989 and registered by the registry were identified. Active follow up of patients is carried out by the registry three years after diagnosis and then every five years until death, so vital status three years after diagnosis was known for almost all (99.4%) of the identified patients. All the cancers were staged by a clinical oncologist working in the registry.

In the period 1982-5 there were 3965 registered cases of invasive breast cancer, and of these, 14 (0.4%) patients had fewer than three years' follow up. In 1986-9 there were 4665 registered cases, and 36 (0.8%) patients had fewer than three years' follow up. Patients lost to follow up were entered into the analysis as censored cases. Some patients, especially elderly women, did not have enough information in the records for staging. These patients are included in the analysis as unstaged.

Mortality was directly standardised for age with the European standard population. The breast cancer

Table 1 Mortality from breast cancer (deaths per 100 000 woman years) by time period and age group, standardised to European standard population

Age group (years) and area	Time period		% Change
	1985-8	1989-92	
<50:			
East Anglia	10.1	9.1	–10
England and Wales	10.3	9.6	–9
50-64:			
East Anglia	86	79	–9
England and Wales	92	87	–9
≥65:			
East Anglia	164	176	7
England and Wales	163	164	0

mortality and population data used were obtained from the Office of Population Censuses and Surveys (OPCS). Relative survival estimates, with expected death rates obtained from OPCS life tables, were used to compare the two time periods by age group and stage.[5] An analysis of survival with adjustment for age and stage was carried out for each age group to compare the two time periods by using Cox's proportional hazards model.[6]

Treatment details were available for patients aged 50-69 years. These had previously been extracted from clinical notes and from the cancer registration details as part of the evaluation of the breast screening programme.

Results

Table 1 shows the change in mortality seen in East Anglia between 1985-8 and 1989-92. Corresponding rates for the whole of England and Wales are also given. The fall in East Anglia is comparable with that seen nationally and was confined to women under 65 years of age.

Table 2 Numbers (%) of patients diagnosed with breast cancer by time period, stage, and age group

Age group (years) and stage	Time period		% Change
	1982-5	1986-9	
< 50:			
I	281 (78)*	338 (84)*	
II	331	447	
III	93 (12)	91 (10)	
IV	33 (4)	39 (4)	
Unstaged	49 (6)	19 (2)	
Total	787	934	18.7
50-64:			
I	369 (70)*	491 (78)*	
II	471	622	
III	208 (17)	176 (12)	
IV	130 (11)	102 (7)	
Unstaged	31 (3)	36 (3)	
Total	1209	1427	18.0
≥ 65:			
I	335 (42)*	429 (51)*	
II	487	740	
III	428 (22)	459 (20)	
IV	142 (7)	220 (10)	
Unstaged	577 (29)	456 (20)	
Total	1969	2304	17.0

*Percentage for stage I and II combined.

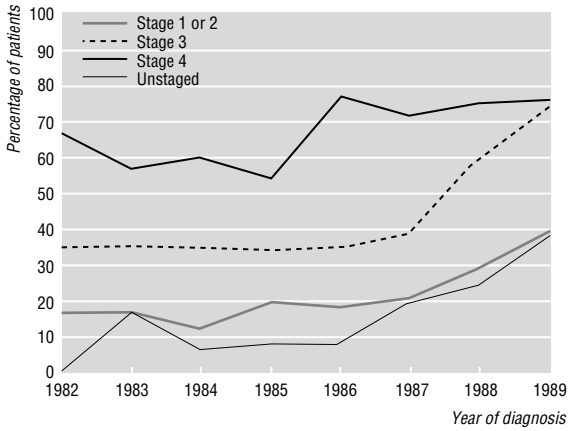

Fig 1 Percentage of patients diagnosed with breast cancer in first (1982-5) and second (1986-9) period by age group and stage

Table 2 and figure 1 show the distribution by age and stage of breast cancer cases diagnosed in the two time periods. In the age groups under 65 years there was a considerable increase in early (stage I and II) tumours. The odds ratio for being diagnosed as stage I or II in the later time period compared with the earlier was 1.5 in these younger women (see statistical appendix), representing a considerable stage shift. There was a relatively large proportion of unstaged tumours in women aged 65 years or over at diagnosis, so we could not determine whether the stage distribution had changed in this age group between the two time periods, and analysis of data relating to these women was difficult.

The percentage increases in the three age groups <50, 50-64, and ≥ 65 years were 18.7%, 18.0%, and 17.0%, respectively, suggesting that the effect of screening in the 50-64 year age group in the second time period has been minimal, despite a 28% increase in the number of cancers diagnosed in women aged 60-64 years (some of whom would have been invited for screening in 1989).

Estimates for relative survival at three years (that is, adjusted for all cause mortality; table 3) showed an overall improvement in survival of women diagnosed in 1986-9 compared with 1982-5. This improvement was largely confined to women under the age of 65 years; for women aged 65 years or over at diagnosis the change in survival was minimal, reflecting the absence of an effect on mortality in this age group. As expected, there was high survival in those with early stage tumours and poorer survival in those with stage III and IV tumours. There was little change in stage specific survival, however, particularly for stages I and II for which we would expect treatment to be most effective.

Cox's proportional hazards ratios comparing the risk of death within three years after diagnosis of breast cancer in 1986-9 with 1982-5 were calculated overall and for each age group (table 4). There was a significant ($P<0.01$) improvement in survival in the later time period when we examined it overall (that is, not taking age or stage into account). This improvement remained after adjustment for single year of age, but when adjustments for stage were also made almost all the improvement disappeared. Thus, adjustment for stage accounted for almost all of the improvement in survival. When we made comparisons specific for age

Table 3 Percentages of patients (95% confidence intervals) surviving three years from diagnosis (relative survival estimates)

Stage and age group (years)	Time period 1982-5	Time period 1986-9	% Change
Overall:			
<50	78 (75 to 81)	82 (79 to 85)	4
50-64	75 (72 to 77)	81 (79 to 83)	6
≥65	72 (69 to 74)	73 (70 to 75)	1
I:			
<50	94 (91 to 97)	93 (90 to 96)	–1
50-64	95 (92 to 97)	94 (92 to 97)	–1
≥65	98 (93 to 102)	100 (97 to 104)	2
II:			
<50	80 (76 to 84)	83 (80 to 87)	3
50-64	83 (79 to 86)	84 (81 to 87)	1
≥65	89 (84 to 93)	85 (81 to 89)	–4
III:			
<50	53 (42 to 63)	60 (50 to 71)	7
50-64	55 (48 to 63)	65 (58 to 73)	10
≥65	67 (61 to 73)	61 (56 to 67)	–6
IV:			
<50	25 (10 to 41)	36 (21 to 52)	11
50-64	22 (15 to 29)	22 (14 to 30)	0
≥65	31 (22 to 40)	25 (18 to 31)	–6
Unstaged:			
<50	55 (41 to 70)	58 (33 to 82)	3
50-64	69 (51 to 86)	83 (68 to 97)	14
≥65	54 (48 to 59)	58 (52 to 64)	4

Table 4 Cox's proportion hazards ratios[6] (95% confidence intervals) comparing patients diagnosed in 1986-9 with those diagnosed in 1982-5

Detail	Hazard ratio (95% CI)
All subjects:	
Overall	0.87 (0.80 to 0.94)**
Adjusted for year of age	0.89 (0.82 to 0.95)**
Adjusted for year of age and stage	0.97 (0.90 to 1.05)
<50 Years:	
Adjusted for year of age	0.82 (0.67 to 1.02)
Adjusted for year of age and stage	0.90 (0.73 to 1.12)
50-64 Years:	
Adjusted for year of age	0.75 (0.64 to 0.88)**
Adjusted for year of age and stage	0.90 (0.77 to 1.06)
≥65 Years:	
Adjusted for year of age	0.96 (0.90 to 1.06)
Adjusted for year of age and stage	1.02 (0.92 to 1.10)

**Represents significance at the 1% level.

group the difference in survival between time periods was again considerably smaller in each age group after adjustment for stage and was not significant. For the two younger age groups, in which there were few unstaged tumours, adjustment for stage accounted for more than half the improvement in survival.

Discussion

In East Anglia mortality from breast cancer has fallen in much the same way as it has done nationally. This was not caused by a fall in incidence; indeed this has been rising. The most likely explanations are that treatment has improved and that women are presenting at an earlier stage.

The King's Fund guidelines published in 1986 suggested various treatment protocols that could reduce mortality.[7] In particular, they recommended use of tamoxifen; possibly the increased use of tamoxifen may

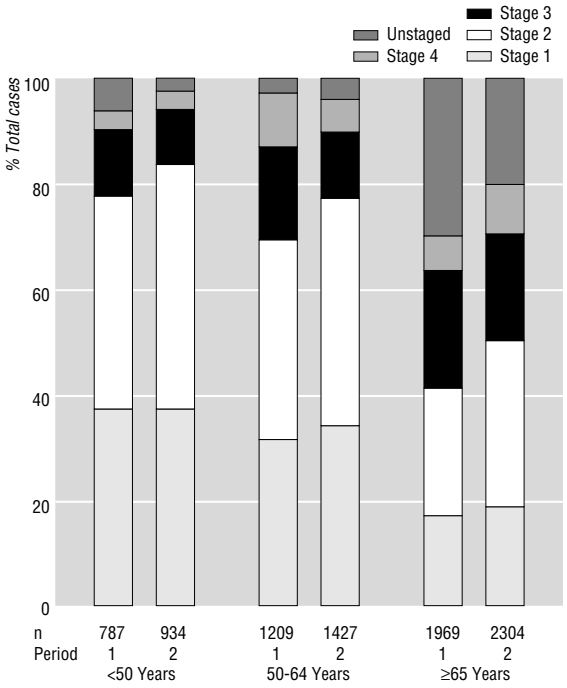

Fig 2 Percentage of patients aged 50-69 diagnosed with breast cancer who were receiving hormone treatment

be the major contributor in the improvement of treatment.[1] Figure 2 shows the proportion of women in East Anglia aged 50-69 years who received tamoxifen as part of their primary treatment. A clear rise in use in women with early stage cancers is seen. The proportion of patients receiving tamoxifen treatment in East Anglia is low in comparison with that reported in south east England,[8] Edinburgh,[9] and Yorkshire.[10] Although we believe there may have been some under-reporting of use in East Anglia, however, we see no reason why under-reporting should not be consistent over the study period and do not believe it could account for the total difference in reported use between East Anglia and other areas of the United Kingdom.

In stage I and II tumours the 10 year relative hazard of death for patients with breast cancer who are using tamoxifen is 0.7.[4] In the period covered by the data, tamoxifen use has increased in these women from 17% to 30%. Given that the improvement in survival is 30% in those being treated with tamoxifen, however, the overall improvement in survival in this age group would be only 4% and probably less over three years. There has been no significant improvement in stage specific survival in the women aged 50-64 years for early stage cancers (see tables 3 and 4), and it therefore seems unlikely that tamoxifen has improved survival significantly. As the number of patients being treated with tamoxifen in East Anglia increases in line with other regions it is hoped there will be more of a treatment effect. Similar results, showing no improvement in prognosis with increased use of treatment modalities, were found recently in the south eastern Netherlands.[11]

The incidence of breast cancer has been rising in East Anglia, with the annual rate of rise increasing from 1986 and then again from 1989. All of the increase in incidence is in stage I and II tumours. Rea-

Key messages

- There has been a similar reduction in mortality from breast cancer in East Anglia and in England and Wales
- Survival has improved in later years
- There has been no significant improvement in survival for specific stages of disease
- There has been a shift to earlier diagnosis of tumours since the mid-1980s; this explains over half of the improvement in survival
- Reduction in mortality does not seem to be due to improved treatment

sons for this increase in incidence of early stage tumours from 1986 onwards are unclear. Screening cannot be the cause because it did not start until 1989. The increase could, however, be due to a general increase in breast awareness (with the publication of the Forrest report) causing a reduction in tumour size at diagnosis and hence a decline in mortality from breast cancer.[12]

In conclusion, earlier diagnosis probably accounts for more than half the improvement in survival in women aged under 65 years. The causes of the rest of the improvement are not clear but probably involve improved and more extensively used effective treatment. Together with the activity of the screening programme these should result in further reductions in mortality from breast cancer in the future.

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Conflict of interest: None.

Appendix

Table A1 Calculation of odds ratio

	Group 1 (stage I or II)	Group 2 (stage III, IV, unstaged)
Group 1 (1986-9, aged <65)	P_1(n=1898)	P_0(n=463)
Group 2 (1982-5, aged <65)	Q_1(n=1452)	Q_0(n=544)

Odds ratio=$P_1Q_0P_0Q_1$=1898×554/463×1452=1.54.

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Size at birth and blood pressure: cross sectional study in 8-11 year old children

Stephanie J C Taylor, Peter H Whincup, Derek G Cook, Olia Papacosta, Mary Walker

Abstract

Objective: To identify which patterns of fetal growth, represented by different measurements of size at birth, are associated with increased blood pressure in children aged 8-11 years.

Design and setting: School based, cross sectional survey conducted in 10 towns in England and Wales in 1994.

Subjects: 3010 singleton children (response rate 75%) with physical measurements and information on birth weight from parental questionnaires. Hospital birth records were examined for 1573.

Main outcome measures: Systolic and diastolic blood pressure at age 8-11 years.

Results: In the whole group birth weight was inversely related to systolic pressure (regression coefficient − 1.48 mm Hg/kg; 95% confidence interval − 2.20 to − 0.76) after adjustment for current body size. There was no significant association between birth weight and diastolic pressure. The association with systolic pressure was much stronger in girls (− 2.54 mm Hg/kg; − 3.60 to − 1.48) than in boys (− 0.64 mm Hg/kg; − 1.58 to 0.30), with a significant difference between the sexes (P = 0.006). Among the other neonatal measures, head circumference and placental weight were inversely associated with subsequent blood pressure in girls, and placental ratio (placental weight:birth weight) was positively associated with blood pressure in boys. Neither ponderal index at birth nor length:head circumference ratio was related to blood pressure in either sex.

Conclusions: In these contemporary children the association between birth weight and blood pressure was apparent only in girls. There was no evidence that measures of size at birth, which may be related to nutrition at critical periods of pregnancy (thinness at birth or shortness in relation to head circumference), are related to blood pressure in the offspring.

Cardiovascular Research Group, Department of Primary Care and Population Sciences, Royal Free Hospital School of Medicine, London NW3 2PF

Stephanie J C Taylor, *honorary research fellow in public health medicine*

Peter H Whincup, *senior lecturer in clinical epidemiology*

Olia Papacosta, *research statistician*

Mary Walker, *honorary research fellow*

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Department of Public Health Sciences, St George's Hospital Medical School, London SW17 0RE
Derek G Cook, *reader in epidemiology*
Correspondence to: Dr Taylor (staylor@rfhsm.ac.uk).

Introduction

It has been proposed that events occurring before birth may influence the risk of cardiovascular disease in later life.[1] Associations between small size at birth and increased risk of adult cardiovascular mortality have been described,[2 3] and there is strong evidence of an inverse association between birth weight and later blood pressure in both adults and children.[4] The mechanism underlying this association is unknown, but fetal undernutrition at critical periods of intrauterine development may produce a permanent increase in blood pressure by a process known as "programming."[5 6] The "fetal origins" hypothesis suggests that undernutrition in the first, second, or third trimester may result in a symmetrically small baby; a thin, light baby; or a baby with a normal birth weight who is short in relation to its head circumference; and that these particular patterns of size at birth may be related to raised blood pressure.[7] It has also been proposed that babies with large placentas, especially when associated with low birth weight, are at particular risk of hypertension in later life.[8] Few studies, however, have actually examined the associations between different measures of size at birth or placental size and blood pressure in contemporary children. Here we present a population based study of these associations in 8-11 year old children.

Subjects and methods

Sampling procedures—Details of the study design and methods have been presented elsewhere.[9] The study was based on 10 towns, five with exceptionally high adult cardiovascular mortality (Wigan, Burnley, Port Talbot, Rochdale, and Rhondda) and five with exceptionally low adult cardiovascular mortality (Esher, Chelmsford, Leatherhead, Bath, and Tunbridge Wells). In each town we selected a stratified random sample of 10 junior schools. Fifty children from the upper two years of each school were invited to attend for measurement.

Survey procedures—All the relevant local research ethics committees approved the study and informed, written parental consent was obtained. Low and high mortality towns were visited alternately between April and November 1994. All measurements were made by one of two pairs of trained field nurses.

Blood pressure and other physical measurements—Two seated blood pressure measurements were carried out on the right arm by using a Dinamap 1846SX automated oscillometric monitor (Critikon, United States),[10 11] which was calibrated daily and compared with a mercury column sphygmomanometer weekly. There was no evidence of measurement drift during the study. A single cuff size was used to ensure the minimum cuff bladder width to arm circumference ratio recommended by the American Heart Association[12] was met for 89% of the study population. The oldest 40% of the children were also asked to provide a blood sample after the application of local anaesthetic cream. Heights were measured to the last complete millimetre by using a portable stadiometer (CMS). Weights were measured to the last complete 0.1 kg by using an electronic weighing scale (Soehnle) with the children in light clothing without shoes. Blood samples were taken after the physical measurements were completed.

Parental questionnaire and birth records—Parents were sent a detailed questionnaire that included questions on the child's birth weight, place of birth, gestation, siblings, parents' occupations, and mother's height. Social class was coded from parental occupation by using the Office of Population Censuses and Surveys classification of occupations (1980). Consent to examine birth records was also requested, and these records were sought at every hospital in which 20 or more study children (5% of the study children in each town) had been born. Details extracted from birth records included weight, head circumference, and length at birth, placental weight, and the mother's antenatal blood pressures. Birth records were not sought for children born at home.

Statistical methods—All data were analysed with the SAS system statistical software package (SAS Institute, North Carolina). Ponderal index (weight/height^3) was used as a measure of weight for height at 8-11 years because it was independent of both height and age in these data; it was also used as a measure of thinness at birth. Placental ratio (placental weight:birth weight) and shortness for head size (birth length:head circumference) were used when appropriate. Systolic and diastolic blood pressures were based on the average of two readings. Multiple linear regression was used to adjust associations between blood pressure and birth weight (as well as other indices) for structural and confounding variables. Body measures at birth and in childhood were included as continuous variables or fitted in fifths or thirds, when appropriate, by using linear regression techniques. All models included adjustment for sex, town, and who measured the blood pressure as categorical variables and age as a continuous variable. An adjustment for the slightly higher mean blood pressures seen in children anticipating blood tests (even after adjustment for age) was fitted as a categorical variable.

Results

After invitation 3728 children participated in the study, and 3719 had a complete set of measurements (response rate 75%). Questionnaires including data on birth weight were returned for 3181 children (85% of participants); 3010 of these children were singleton births and only 39 (1.2%) were home births. Permission to examine birth records was granted for 3107 children (98% of those returning questionnaires), and, of these, 2350 children (76%) were born in local hospitals. Birth records for 1573 of the 2350 children described above were located. Subjects were excluded from analyses of placental weight and placental ratio if birth records stated that the placenta was incomplete (64 children). Table 1 shows the characteristics of the 3010 study children and of the subset with birth records retrieved. There were no significant differences between the mean ages, birth weights, anthropometric measurements, and blood pressures in these two groups. There were significant differences between the sexes: the boys were thinner and lighter at 8-11 years and were heavier, longer, and had greater head circumferences at birth. In the 1550 children with birth weights from both questionnaire and birth records the

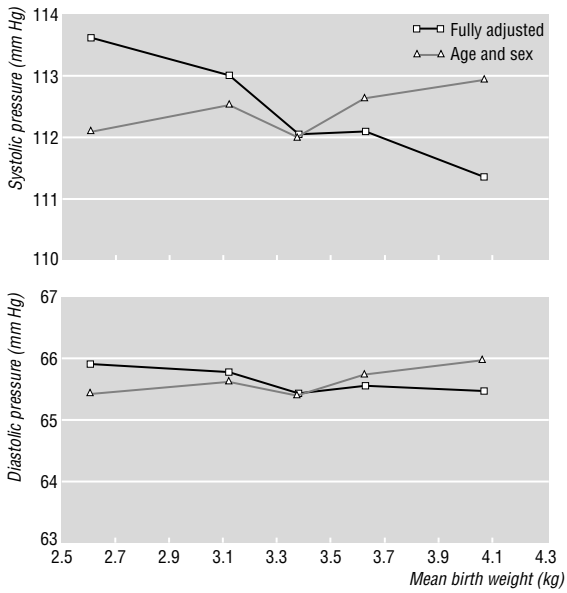

Fig 1 Association between birth weight and systolic and diastolic blood pressure showing effect of adjustment for current body build

Table 1 Mean measurements in children in full dataset and in subset with data from birth records

Variables	Mean (SD) for all children* (n=3010)	Subset with data from birth records	
		No	Mean (SD)
Blood pressure (mm Hg):			
Systolic	112.4 (11.3)	1573	112.4 (11.3)
Diastolic	65.6 (7.0)	1573	65.7 (7.0)
Age (years)	10.46 (0.65)	1573	10.45 (0.64)
Height (cm)	141.2 (7.4)	1573	141.0 (7.3)
Weight (kg)	35.96 (8.09)	1573	36.99 (8.00)
Ponderal index (kg/m$^{3)}$	12.68 (1.93)	1573	12.73 (1.93)
Birth weight (g):	3350 (530)		
Questionnaire		1573	3360 (540)
Birth records	—	1563	3360 (520)
Head circumference (cm)	—	1465	34.7 (1.5)
Length (cm)	—	1446	52.2 (3.1)
Placental weight (g)†	—	1382	628.6 (141.3)
Placental ratio†	—	1366	0.19 (0.03)
Ponderal index at birth	—	1434	23.91 (3.71)
Head circumference:length ratio at birth	—	1444	0.67 (0.04)

*Singleton births only.
†Incomplete placentas excluded.

agreement between the two measures was close (mean (SD) difference 1.7 g (117.9 g); correlation coefficient 0.98). In 1508 (97.3%) of these children the difference between the two weights was less than 200 g.

Data on birth weight from parental recall and blood pressure

Figure 1 summarises the association between birth weight and blood pressure with the corresponding multiple linear regression coefficients in table 2. When we adjusted for age and sex alone there was no apparent association between birth weight and systolic blood pressure. Current body size, however, was a potential confounder of the association between birth weight and blood pressure (table 3), both height and ponderal index being related not only to blood pressure but also to birth weight. When we made adjustments to birth weight:blood pressure for height and ponderal index an inverse association between birth weight and systolic blood pressure became apparent; there was a fall in systolic blood pressure at 8-11 years of about 1.5 mm Hg for every kilogram increase in birth weight (fig 1, table 2). Even after we adjusted for current body size there was only a weak inverse association between birth weight and diastolic blood pressure, and this was not significant. Further adjustments for room temperature, number of siblings, maternal height, gestational age, maternal blood pressure during pregnancy, and social class did not alter these associations substantially (not shown).

Because the inverse association between birth weight and systolic blood pressure was apparent only after adjustment for height and ponderal index, all further analyses were adjusted for these two variables. There was no suggestion that the association between birth weight and blood pressure differed at different childhood heights (not shown). This remained true when the sexes were examined separately. The association did decrease slightly with increasing ponderal index, but this effect was seen only in the girls (not shown).

The association between birth weight and blood pressure seemed to be similar in children born at term and preterm (before 37 weeks' gestation), although in the smaller preterm group the association was not sig-

Table 2 Associations between birth weight and blood pressure in singleton born children of 8-11 years summarised as regression coefficients (b), also showing these associations by gestation and by sex

Detail	Adjustment*	Systolic blood pressure			Diastolic blood pressure		
		b (SE) (mmHg/kg)	P value	P value for difference between b	b (SE) (mmHg/kg)	P value	P value for difference between b
All subjects (n=3010)	Age and sex	0.41 (0.38)	0.28	—	0.24 (0.24)	0.31	—
	Full†	–1.48 (0.36)	0.0001		–0.35 (0.24)	0.14	
Difference when analysed by gestational age							
Subjects born at term (≥37/40)‡ (n=2691)	Full†	–1.39 (0.40)	0.0005	0.56	–0.45 (0.26)	0.09	0.83
Subjects born before term (<37/40) (n=139)	Full†	–1.16 (0.64)	0.07		–0.40 (0.43)	0.35	
Difference when analysed by sex							
Girls (n=1442)	Full†	–2.54 (0.53)	0.0001	0.006	–0.88 (0.35)	0.01	0.04
Boys (n=1568)	Full†	–0.64 (0.47)	0.17		0.07 (0.31)	0.83	

*All regression coefficients also adjusted for observer, anticipated venepuncture, and town.
†Adjustment for age, sex, current height, and current ponderal index.
‡Gestational age not available for 180 subjects.

Table 3 Correlation coefficients for study measures and birth weight in 3010 singleton births, birth weight from parental recall

Detail	Systolic blood pressure	Diastolic blood pressure	Height	Ponderal index
Diastolic blood pressure	0.59*			
Childhood height	0.30*	0.16*		
Childhood ponderal index	0.32*	0.16*	0.005	
Birth weight	0.01	0.02	0.18*	0.09*

*P<0.0001.

nificant (table 2). Analysis by sex revealed that the association seemed to be concentrated in the girls and very weak or absent in the boys. Test results for a sex difference in the association were significant for both systolic and diastolic pressure.

Data from birth records

Birth weight—Because of the clear sex difference in the association found in the whole dataset, data on the subset of children whose birth records were retrieved were analysed separately by sex. Table 4 presents the associations between the different birth measurements and blood pressure at 8-11 years, adjusted for height and ponderal index, along with the results of formal tests for differences in the regression coefficients (b) between the sexes. Again birth weight was inversely associated with blood pressure in the girls rather than the boys. The strength of the association was weaker in this subset, and this remained the case when these associations were re-examined in the same children by using their parentally recalled birth weights (b −1.20 mm Hg kg; 95% confidence interval −2.64 to 0.24 for systolic blood pressure in girls; −0.16 mm Hg kg; −1.44 to 1.12 for boys).

Head circumference and length at birth—Among the girls, head circumference at birth showed a significant inverse association with systolic blood pressure at 8-11 years and a weak, non-significant inverse association with diastolic blood pressure (table 4). Head circumference and birth weight, however, were closely correlated ($r=0.64$; $P<0.0001$), and we could not differentiate their relative importance in relation to subsequent blood pressure in the girls. An increase of 1SD in either of these two measures (the standard regression effect) resulted in a fall in systolic blood pressure of about 1 mm Hg. Length at birth, which was also strongly correlated with birth weight ($r=0.56$; $P<0.0001$), also tended to be inversely associated with both systolic and diastolic blood pressure in the girls, although these associations were not significant. Among the boys, none of these simple birth measures was related to blood pressure, although formal evidence of sex interaction was weak (table 4).

Ponderal index at birth and birth length:head circumference ratio—Neither of the two ratio birth measures examined (ponderal index and length:head circumference ratio) showed any consistent significant association with blood pressure in either sex.

Placental weight and placental ratio—Among the girls, placental weight showed a significant inverse association with systolic blood pressure, but it was also closely correlated with birth weight ($r=0.58$; $P<0.0001$), and the association between placental weight and blood pressure became non-significant when birth weight was included in the model (not shown). Placental ratio did not seem to be related to blood pressure in the girls. In the boys placental weight and placental ratio tended to be positively related to blood pressure; associations between placental weight and diastolic blood pressure and placental ratio and systolic blood pressure were significant despite the absence of an association bewteen birth weight and blood pressure in the boys. The association between placental weight and blood pressure was unchanged by the addition of birth weight into the model (not shown). Tests for interaction suggested that the associations between placental weight and blood pressure were significantly different in the two sexes (table 4).

Relative importance of current body size and birth weight on childhood blood pressure—We compared the relative strengths of the associations between systolic blood pressure and current size or birth weight by examining their standard regression effects. At 8-11 years an increase of 1SD in birth weight, childhood height, or childhood ponderal index was associated with a change in systolic blood pressure of −0.8 (−1.2 to −0.4), 3.4 (2.9 to 3.8), and 3.4 (3.1 to 3.8) mm Hg, respectively. Similar results were found when the unit of comparison was the interquartile range rather than the SD and also when these analyses were confined to the girls.

Discussion

In this study we observed an inverse association between birth weight and systolic blood pressure, but this was concentrated in the girls and hardly apparent in the boys. The studies of data from birth records sug-

Table 4 Relations between birth measurements and blood pressure at 8-11 years in boys and girls separately summarised as regression coefficients (b)*

	Girls					Boys					P values for difference in b between sexes	
	Systolic			Diastolic		Systolic			Diastolic			
Detail	No	b (SE)	P value	b (SE)	P value	No	b (SE)	P value	b (SE)	P value	Systolic	Diastolic
Birth weight (kg)	734	−1.42 (0.74)	0.05	−0.34 (0.49)	0.51	829	−0.14 (0.67)	0.83	0.38 (0.45)	0.39	0.19	0.28
Head circumference (cm)	691	−0.61 (0.26)	0.02	−0.13 (0.18)	0.46	774	−0.001 (0.24)	0.99	0.14 (0.16)	0.40	0.09	0.26
Length at birth (cm)	677	−0.17 (0.14)	0.20	−0.15 (0.09)	0.10	770	0.06 (0.11)	0.57	−0.003 (0.07)	0.97	0.16	0.20
Ponderal index (kg/m^3) at birth	668	−0.008 (0.10)	0.93	0.09 (0.07)	0.19	766	−0.03 (0.10)	0.80	0.10 (0.07)	0.14	0.90	0.92
Ratio of length (cm) to head circumference (cm)	676	1.38 (4.55)	0.76	−3.84 (3.05)	0.21	768	2.99 (4.27)	0.48	−1.57 (2.87)	0.58	0.79	0.58
Placental weight (kg)	646	−7.74 (3.03)	0.01	−1.79 (2.01)	0.37	736	4.27 (2.50)	0.09	3.21 (1.66)	0.05	0.002	0.05
Ratio of placental weight (kg) to birth weight (kg)	637	−5.75 (11.86)	0.63	0.92 (7.79)	0.91	729	21.39 (10.74)	0.05	12.45 (7.06)	0.08	0.09	0.27

All multiple regression models adjusted for age, sex, observer, venepuncture, town, height, and ponderal index.
*Units of regression coefficients are mm Hg/unit of measurement.

gested that, among the girls only, three highly correlated measures—birth weight, head circumference, and placental weight—were inversely associated with blood pressure. Neither ponderal index at birth nor length:head circumference ratio showed any association with blood pressure in either sex. Placental weight, which was strongly correlated with birth weight in both sexes, was inversely associated with blood pressure in girls but tended to be positively associated in the boys, and placental ratio was also positively associated with blood pressure in boys.

This population based study included children with a wide range of birth weights and social circumstances. In agreement with the results of previous research[13] the validity of parental recall in this study was good. Although the association between birth weight and blood pressure seemed slightly weaker in the subgroup with data from birth records when it was compared with that in the full group of study children, mean birth weights and physical measurements between the two groups were similar, suggesting that the selection of children with birth record data was not biased with respect to these variables. As we relied on birth measures taken in various hospitals, differences in measuring techniques will inevitably have introduced some error,[14] which should be predominantly random. The consistent overestimation of systolic blood pressure by the Dinamap,[11] although influencing comparisons with other studies, should not have affected estimates of differences within the study population.

Relations to other studies

Birth weight and blood pressure—As in other studies of children,[4] adjustment for the effect of current size was necessary before the association between birth weight and blood pressure became apparent. This adjustment is justified in children because while childhood body size seems to confound the association, in adulthood this confounding is less apparent.[8] The strength of the association between birth weight and blood pressure seen in the present study was weaker than that in our earlier study of children of a similar age[15] and of comparable strength to those in 5-7 year old children.[16 17] This study, therefore, does not support our earlier suggestion of amplification of the association during the first decade.[15] The greater strength of the association in girls at this age has been suggested by two previous studies[18 19] and remains unexplained. The inverse association is not seen in adolescents,[4-21] and this may be because blood pressure tracking is perturbed as a result of rapid growth during this period.[22] Our study, which found stronger associations among girls, who were closer to puberty than the boys,[23] does not support this theory. Furthermore, there is no evidence that body build is acting as a stronger confounder of the association in girls as correlation coefficients relating childhood height and ponderal index to birth weight and blood pressure were similar in both sexes.

Other measurements of size at birth and blood pressure—Several previous studies have looked at measures of neonatal size other than birth weight and later blood pressure[24-30]; five of these looked at the associations in children.[24-26 28 30] Head circumference tended to be inversely related to systolic blood pressure in two studies,[25 29] but the associations between other measures of size at birth (including length,[25 28-30] ponderal index,[25-29] and head circumference:length ratio[25 27]) and subsequent blood pressure have all proved more inconsistent. Only one[31] of five subsequent studies[15 25 29 32] has confirmed the original finding of the highest subsequent blood pressures arising in light babies with big placentas.[8] Our findings on placental weight and placental ratio are in agreement with the results of Barker's study on placental weight[8] but only among the boys in whom no association between birth weight and blood pressure was observed. In the present study, apart from birth weight and univariate measures of size (particularly head circumference), associations between other measures of size at birth and blood pressure were weak and inconsistent.

Implications

These data on the associations between size at birth and blood pressure in contemporary children raise important questions about the fetal origins hypothesis. Firstly, they do not support the possibility of amplification during the second half of the first decade. Secondly, at 8-11 years the association is almost entirely restricted to the girls; a finding that is unlikely to be an artefact of adolescence. Thirdly, the finding that, although birth weight is related to subsequent blood pressure other more complex measures of fetal growth such as ponderal index at birth or head circumference:length ratio are not related, does not provide support for the programming of blood pressure at critical periods in the second and third trimesters. Finally, the association between birth weight and blood pressure at 8-11 years is much smaller than the effect of current size on blood pressure, suggesting that childhood obesity (currently increasing in prevalence[33]) remains a more important determinant of blood pressure in children. The association may be amplified with increasing age and may be increasingly concentrated among subjects with the greatest current body mass.[34] Our finding that the association was significantly stronger among girls with lower ponderal indices, however, does not favour this suggestion. Longitudinal studies of contemporary children growing into adulthood are needed to examine the consistency of associations with age and to assess the relative importance of fetal factors and current obesity in the determination of blood pressure and in adolescence and early adult life.

Conclusions

Our data confirm the existence of an inverse association between birth weight and blood pressure in singleton born children at 8-11 years of age. There seems, however, a clear sex difference in this association, with the effect being concentrated in the girls and extremely weak in the boys. Only highly correlated, one dimensional measures of size at birth seem to show any association with blood pressure in contemporary children. More sophisticated ratio measures of fetal growth do not seem to be related to subsequent childhood blood pressure. The association between placental weight and placental ratio and blood pressure in children at this age is inconsistent. These findings do not support the suggestion that programming in the second and third trimesters results in identifiable patterns of neonatal size that are associated with an increased risk of raised blood pressure.

Key messages

- This study confirms the well established inverse association between birth weight and childhood blood pressure, but there seems to be a strong difference between the sexes towards the end of the first decade of life—the association being strong in girls and weak or absent in boys
- Only highly correlated, simple measures of size at birth seem to be associated with blood pressure in girls; more complex measures of size at birth, including ponderal index and shortness in association to head circumference, are not associated with childhood blood pressure in either sex at 8-11 years
- The association between placental weight and placental ratio and blood pressure in children of 8-11 years is inconsistent
- These findings do not support the hypothesis that fetal undernutrition "programmes" raise blood pressure in the second and third trimesters
- Current body size is a much more important determinant of blood pressure in childhood than size at birth

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ONE HUNDRED YEARS

The prevention of hereditary diseases

A number of unmarried women of New York have formed a society for the prevention of hereditary diseases. They have registered a solemn vow not to marry any man whose family is tainted with consumption, insanity, alcoholism, or other heritable disease. This is a step in the right direction, and if the example of these wise virgins is widely followed by their sisters, and if eligible bachelors show an equally enlightened zeal for the healthfulness of posterity, they will have done something for the betterment of the race. But if it comes to a conflict between Cupid and Hygeia, the betting, we fear, will not be on the latter. Love, which laughs at locksmiths, will think little of snapping the frail link of a vow which has no sanction but the opinion of a small band of enthusiasts. (*BMJ* 1897;i:417.)