Influences on pre-hospital delay in the diagnosis of colorectal cancer: a systematic review

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Colorectal cancer is a major global health problem, with survival varying according to stage at diagnosis. Delayed diagnosis can result from patient, practitioner or hospital delay. This paper reports the results of a review of the factors influencing pre-hospital delay – the time between a patient first noticing a cancer symptom and presenting to primary care or between first presentation and referral to secondary care. A systematic methodology was applied, including extensive searches of the literature published from 1970 to 2003, systematic data extraction, quality assessment and narrative data synthesis. Fifty-four studies were included. Patients' non-recognition of symptom seriousness increased delay, as did symptom denial. Patient delay was greater for rectal than colon cancers and the presence of more serious symptoms, such as pain, reduced delay. There appears to be no relationship between delay and patients’ age, sex or socioeconomic status. Initial misdiagnosis, inadequate examination and inaccurate investigations increased practitioner delay. Use of referral guidelines may reduce delay, although evidence is currently limited. No intervention studies were identified. If delayed diagnosis is to be reduced, there must be increased recognition of the significance of symptoms among patients, and development and evaluation of interventions that are designed to ensure appropriate diagnosis and examination by practitioners. British Journal of Cancer (2008) 98, 60–70. doi:10.1038/sj.bjc.6604096 www.bjcancer.com

Colorectal cancer is a major global health problem and the fourth most common cause of cancer death worldwide (Parkin et al., 2001). It is also a cancer the incidence of which continues to grow, particularly in developed countries (Parkin et al, 1999). Survival varies according to stage at diagnosis with 5-year survival falling from almost 90% for early cancers (Dukes A) to 15% for advanced tumours, when only palliative resection is possible (McArdle and Hole, 2002). In the majority of cases, primary care is the first point of contact for patients with lower gastrointestinal cancer symptoms, and colorectal cancer is not always an immediate diagnosis. Associated symptoms, including rectal bleeding and altered bowel habit, are common in primary care practice and as such, general practitioners (GPs) are required to differentiate between patients whose symptoms may be due to cancer and the much larger number of patients whose symptoms are attributable to benign, self-limiting illness.

The complexity surrounding identification of those patients requiring further investigation has led to the production of guidelines in many countries, all with the aim of encouraging earlier diagnosis (Benson et al, 2000; Department of Health, 2000; National Institute for Health and Clinical Excellence, 2005; Australian Cancer Network, 2006). In addition, patients too must determine whether a symptom warrants presentation to the health service or requires adoption of a wait and see approach. As such, delayed diagnosis of colorectal cancer can occur as a result of patient delay (the time between first noticing a symptom and first consulting a doctor), practitioner delay (between first consultation and referral) or hospital delay (between referral and diagnosis) (Nichols et al, 1981) and greater knowledge of the factors contributing to these phases is required if survival is to be increased. We conducted a systematic review of the factors that influence pre-hospital delay, that is, up to the point of referral.

MATERIALS AND METHODS

A worldwide review of the literature from 1970 to 2003 was conducted to identify the reasons for delay by patients in presentation with cancer symptoms and by practitioners in cancer detection and referral. Studies were identified from electronic databases (Medline, EMBASE, CINAHL, PsycINFO, Science Citation Index, Social Science Citation Index, International Bibliography of the Social Sciences, Proceedings First and Web of Science Proceedings), Cochrane Collaboration review groups, bibliographies, books, citations in identified articles and authors active in the field. Studies were selected if they focused on adult cancer and (1) the participants were individuals or groups of patients or primary care practitioners and (2) they evaluated factors associated with the interval between a patient first noticing...
a cancer symptom and presenting to primary care, or described an intervention designed to reduce that interval or (3) they evaluated factors associated with the time interval between the patient first presenting to primary care and being referred to secondary care, or described an intervention designed to reduce that interval. To identify factors associated with help-seeking and referral behaviour, studies that determined patient attitudes towards cancer awareness and presentation were also included, as were those which determined provider attitudes or behaviour towards cancer referral. Studies evaluating delay from presentation to treatment were not excluded until they were reviewed to ensure that they did not differentiate between stages in the delay cycle. Studies assessing the outcome of delay in terms of diagnosis, treatment or patient outcomes were excluded, as were those considering only the cost of interventions, validity of referral decisions or differences in referral periods.

Following the initial search, all references were independently assessed, and if subsequently eligible for inclusion, rated by two reviewers (SM, UM). Where differences of opinion occurred, papers were validated by a third reviewer (EM) and findings discussed until a consensus was reached. Previously developed scoring systems were extended and applied to assess the methodological adequacy of studies (Mitchell and Sullivan, 2001). Many used methodologies that did not lend themselves to such techniques; therefore, each included study was also assessed on the strength of the evidence it presented. We determined three grades of evidence: strong, moderate and insufficient.

Studies providing strong evidence were those with an adequate sample size, rigorous methods to ascertain data (i.e. not open to selection bias) and reporting statistically significant differences in relation to the delay-related factors identified (or using appropriate analytic techniques if qualitative). Studies providing moderate evidence had an adequate sample size, reported significant differences but used less rigorous methods to ascertain data or had an adequate sample size, used rigorous methods to ascertain data but used comparative analysis or reported only relevant descriptive statistics, without statistical testing of differences. Studies providing insufficient evidence had unclear or inappropriate methods to ascertain data and insufficient analysis. Where a study inferred results, the strength of its evidence was downgraded. The full methods used in this review have been described in detail elsewhere (Macdonald et al, 2006).

Narrative synthesis of findings was undertaken to identify key concepts and themes that were shared across individual studies.

RESULTS

The search strategy identified 28356 articles of which only 169 (0.6%) met the inclusion criteria and were subject to detailed review (Figure 1). Fifty-four papers were included in the final analysis. Cohen’s kappa was used to determine inter-rater reliability, that is, the level of concurrence between the two independent reviewers in relation to whether identified studies were considered eligible for detailed evaluation. Kappa co-efficient for agreement beyond chance was 0.52.

More than half of the included studies (n = 31) were carried out in Western Europe, over half of these in the UK. None employed a controlled trial methodology, with most involving review of medical records or structured interviews with patients. More than one-third investigated both patient and practitioner delay (n = 20), almost half studied patient factors only (n = 25) and the remainder studied practitioner factors only. Studies most commonly evaluated any colorectal cancer, with smaller numbers dealing specifically with cancer of the rectum (11%), colon (9%) or anus (4%). Twenty-six papers were assessed as providing strong evidence, 19 provided moderate evidence and 9 provided insufficient evidence.

Studies were comparatively small in size, involving between 17 and 2525 participants (mean 420; median 228). The period under study ranged from 3 months to 53 years. Although more than half of the studies considered practitioner-related delay factors, only five included primary care practitioners as subjects. In almost three-quarters of studies, participants were identified from secondary care (n = 38), and were either in-patients (39%), outpatient attendees (16%), a combination of the two (5%) or identified from hospital records (37%). Other sources used were cancer registries, census or other household directories and patient groups. Only 6 of the 54 studies recruited patients from primary care.

Delay intervals

Thirty-eight studies reported length of delay, either from patient recognition of symptoms to presentation (n = 36) or from presentation to practitioner referral (n = 24). This was reported in a non-standardised way, and less than half reported intervals in medians, despite delay times having typically skewed distributions. The most frequently used methods of deriving delay intervals were by structured patient interview or data abstraction from hospital records. Only five studies used primary care records (9%). Median patient delay ranged from 7 days to 5 months (Worden and Weisman, 1975; Turunen and Peltokallio, 1982; MacArthur and Smith, 1984; Funch, 1985; Robinson et al, 1986; Ratcliffe et al, 1989; Dent et al, 1990; Curless et al, 1994; Arbman et al, 1996; Porta et al, 1996; Mulcahy and O’Donoghue, 1997; Majumdar et al, 1999; Mariscal et al, 2001) and practitioner delay from 0 to 15 months (Turunen and Peltokallio, 1982; MacArthur and Smith, 1984; Funch, 1985; Ratcliffe et al, 1989; Mansson, 1990; Jones and Dudgeon, 1992; Curless et al, 1994; Arbman et al, 1996; Harris and Simson, 1998; Majumdar et al, 1999; Mariscal et al, 2001).

Factors influencing patient delay

Forty-four papers considered factors that influenced patient delay. Most (n = 41) identified factors that increased delay, whereas almost two-thirds (n = 27) identified factors that decreased delay (Figure 2).

Patient behaviour

The influence of symptom awareness, and more particularly patients’ interpretation of symptoms, was a common theme across studies. Non-recognition of the seriousness of symptoms (Worden
and Weisman, 1975; Holliday and Hardcastle, 1979; Rubin et al., 1980; Anon, 1982; Marshall and Funch, 1986; Mor et al., 1990; Prohaska et al., 1990; Byles et al., 1992; Curless et al., 1994; Porta et al., 1996; Roncoroni et al., 1999; Sladden et al., 1999; Young et al., 2000; de Nooijer et al., 2001; Cockburn et al., 2003), or lack of knowledge, either about the disease itself or about the availability of screening was a major contributor to increased delay (Anon, 1982, 1986; Camilleri-Brennan and Steele, 1999; Pullyblank et al., 2002; McCaffery et al., 2003). Patients who presented late tended to either deny their symptoms entirely, or redefine these in relation to benign disease (Worden and Weisman, 1975; Bain et al., 2002; Langenbach et al., 2003). Perhaps unsurprisingly, increased delay was also found for patients who were less worried about their symptoms (Dent et al., 1990) or who self-diagnosed or self-medicated before presenting to primary care (Funch, 1985; Dent et al., 1990; Tanum et al., 1991; Byles et al., 1992; Sladden et al., 1999; Cockburn et al., 2003) (Table 1).

The anxiety associated with recognising a potential cancer symptom was also a key factor in the decision to present. Fear that symptoms were indicative of cancer (Prohaska et al., 1990; Byles et al., 1992; de Nooijer et al., 2001), fear of investigations related to diagnosis of cancer (Langenbach et al., 2003) and fear of powerlessness (Worden and Weisman, 1975; McCaffery et al., 2003) made patients consult less quickly, although, for some, fear that a symptom might be a sign of cancer brought about more rapid presentation (Hackett et al., 1973; Dent et al., 1990; Sladden et al., 1999; de Nooijer et al., 2001).

Presenting symptom and patient history

For the most part, patients who suffered from more serious symptoms such as obstruction or abdominal pain delayed less (Devlin et al., 1973; MacAdam, 1979; Rubin et al., 1980; MacArthur and Smith, 1984; Prohaska et al., 1990; Mulcahy and O’Donoghue, 1997; Majumdar et al., 1999; Young et al., 2000; Mariscal et al., 2001), whereas those experiencing either non-specific symptoms or more common symptoms, such as bleeding or altered bowel habit, delayed longer (Devlin et al., 1973; Galloway et al., 1984; Mor et al., 1990; Curless et al., 1994). There were, however, some patients for whom pain resulted in increased delay (Hackett et al., 1973; Nilsson et al., 1982; MacArthur and Smith, 1984; Prohaska et al., 1990). Those who recognised the symptom or who had previous experience of a symptom or of cancer itself tended to delay less (MacDonald and Freeling, 1986; Samet et al., 1988; Dent et al., 1990; Porta et al., 1996; Sladden et al., 1999). This was also the case for those with comorbidity (Ratcliffe et al., 1989; Mor et al., 1990; Porta et al., 1996; Mariscal et al., 2001) and those experiencing multiple symptoms (Mariscal et al., 2001).

A number of studies considered the relationship between presentation behaviour and cancer site. These demonstrated that those with cancer of the rectum were more likely to have delayed presentation (Devlin et al., 1973; Galloway et al., 1984; Prohaska et al., 1990; Mor et al., 1990; Porta et al., 1996; Sladden et al., 1999). By and large, patient age (Worden and Weisman, 1975; MacAdam, 1979; McDermott et al., 1981; Turunen and Peltokallio, 1982; Pitlik and Poticha, 1983; Galloway et al., 1984; MacArthur and Smith, 1984; Marshall and Funch, 1986; Robinson et al., 1986; Samet et al., 1988; Dent et al., 1990; Mor et al., 1990; Prohaska et al., 1990; Marble et al., 1992; Kempainen et al., 1993; Curless et al., 1994; Arbman et al., 1996; Porta et al., 1996; Mulcahy and O’Donoghue, 1997; Majumdar et al., 1999; Young et al., 2000; Mariscal et al., 2001).

Patient characteristics

Social networks and support were identified as being a potentially important factor in reducing delay, when patients either sought advice from or made decisions based on the experience of others (Holliday and Hardcastle, 1979; MacAdam, 1979; MacArthur and Smith, 1984; Samet et al., 1988; Camilleri-Brennan and Steele, 1999; Roncoroni et al., 1999; Sladden et al., 1999). By and large, patient age (Worden and Weisman, 1975; MacAdam, 1979; McDermott et al., 1981; Turunen and Peltokallio, 1982; Pitlik and Poticha, 1983; Galloway et al., 1984; MacArthur and Smith, 1984; Marshall and Funch, 1986; Robinson et al., 1986; Samet et al., 1988; Dent et al., 1990; Mor et al., 1990; Prohaska et al., 1990; Marble et al., 1992; Kempainen et al., 1993; Curless et al., 1994; Arbman et al., 1996; Porta et al., 1996; Mulcahy and O’Donoghue, 1997; Majumdar et al., 1999; Young et al., 2000; Mariscal et al., 2001).
| Author(s) | Location | Study type | Participants | Cancer site | Factors which increase delay | Factors which decrease delay | No impact on delay | Evidence |
|-----------|----------|------------|--------------|-------------|-----------------------------|-----------------------------|-------------------|----------|
| Devlin et al (1973) | England | Retrospective observational | 310 patients (aged 30–95, 53% men, 47% women) | Rectum | Symptom type – altered bowel habit, bleeding | Symptom type – abdominal or anorectal pain | Worry; incapacitated by symptoms; acknowledgment of cancer | Moderate |
| Hackett et al (1973) | USA | Prospective observational | 125 patients (aged 19–59, 38% men, 62% women); 22% with colon cancer | Colon | Non-recognition of symptom seriousness; denial; powerlessness; comorbidity; fatigue | Age; sex; marital status; socioeconomic status; family history | Strong |
| Worden and Weisman (1975) | Massachusetts, USA | Prospective observational | 200 patients (58% men, mean age 66; 42% women mean age 67) | Colorectal | Non-recognition of symptom seriousness | Advice from social network | Moderate |
| Holliday and Hardcastle (1979) | England | Prospective observational | 128 patients (55% men, mean age Rectum 61; 45% women, mean age 59) | Colorectal | Non-recognition of symptom seriousness | Age; sex; social isolation; frequency of consulting | Moderate |
| MacAdam (1979) | England | Prospective observational | 150 patients (79% with colon/rectal cancer), 105 GPs | Colon, rectum | Cancer site – rectum | Cancer site – colon; symptom type Rectum – abdominal pain, bleeding | Age; sex; symptom type | Moderate |
| Rubin et al (1980) | Israel | Prospective observational | 100 patients (aged 36–85, mean age 64; 66% men, 34% women) | Colorectal | Non-recognition of symptom seriousness | Symptom type – abdominal pain, weakness | Age; sex | Strong |
| McDermott et al (1981) | Australia | Retrospective observational | 1228 patients (55% men, mean age Colon, rectum 40+; 45% women, mean age 59) | Colorectal | Non-recognition of symptom seriousness; lack of knowledge; lack of routine screening | Symptom type – pain, bleeding, bowel disturbance | Insufficient |
| Anon (1982) | USA | Cross-sectional | 804 members of the public (aged 40+) | Colorectal | Non-recognition of symptom seriousness | Age; < 50; sex – male | Moderate |
| Nilsson et al (1982) | Sweden | Retrospective observational | 284 patients (aged 20–99; 52% men, 48% women) | Colorectal | None | | Moderate |
| Turunen and Peltokallio (1982) | Finland | Retrospective observational | 100 patients (45% men, 55% women | Colorectal | None | | Moderate |
| Pitlik and Potsha (1983) | Illinois, USA | Retrospective observational | 826 patients (31 aged < 40; 45% men, 55% women) | Colorectal | Age – younger | | Moderate |
| Galloway et al (1984) | Scotland | Retrospective observational | 481 patients (92.5% aged 50+; 50% Colorectal men, 50% women) | Colorectal | Age – younger; symptom type – rectal bleeding | | Strong |
| MacArthur and Smith (1984) | England | Prospective observational | 127 patients | Colorectal | Symptom type – weight loss, rectal pain; Other life events; feeling better; self-treatment | Symptom type – abdominal pain, nausea; advice from social network | Strong |
| Funch (1985) | Washington, USA | Prospective observational | 294 patients (aged 18–85; 49% men, 51% women) | Colorectal | Lack of awareness of screening; lack of knowledge | | Insufficient |
| Anon (1986) | USA | Cross-sectional | 2525 members of the public (aged 40+) | Colorectal | None | | Insufficient |
| MacDonald and England Freeling (1986) | England | Cross-sectional | 171 GP patients (aged 55+; 50% men, 50% women) | Colorectal | Sex – male; cancer site – rectum (female)/colon (male); non-recognition of symptom seriousness | Recognition of symptoms; symptom type – bleeding | Age; education | Moderate |
| Marshall and Funch (1986) | USA | Prospective observational | 306 patients (aged 18–85; 50% men, 50% women) | Colorectal | None | | Moderate |
| Robinson et al (1986) | Israel | Retrospective observational | 445 patients (54% men, 46% women) | Colorectal | None | | Moderate |
| Samet et al (1988) | New Mexico, USA | Prospective observational | 800 patients (aged 65 – 100, mean 72); 28% with colorectal cancer | Colorectal | Race – white Hispanic; sex – male; income – lower | Previous cancer diagnosis; regular check-ups | Age; sex; availability of vehicle; social support; participation in screening | Strong |
| Ratcliffe et al (1989) | England | Prospective observational | 332 patients (aged 30 – 100, mean 70; 51% men, 49% women) | Colorectal | Family history; cancer site – rectum | Comorbidity – diverticular disease | Strong |
| Dent et al (1990) | Australia | Prospective observational | 93 patients with rectal bleeding (aged 35–85, median 55; 54% men, 46% women), 58 GPs | Colorectal | Consulting non-medical professional; self-treatment; less worry (self-diagnosis); education level – lower | Previous rectal bleeding; regularly checking toilet paper or faeces; worry that bleeding means cancer | Age; sex; social support; income; ethnicity; occupation | Strong |
Table 1 (Continued)

| Author(s) | Location | Study type | Participants | Cancer site | Factors which increase delay | Factors which decrease delay | No impact on delay | Evidence |
|-----------|----------|------------|--------------|-------------|-----------------------------|-----------------------------|-------------------|----------|
| Mor et al (1990) | Rhode Island, USA | Prospective observational | 625 patients (aged 45–90; 31% men, 69% women), 46% with colorectal cancer | Colorectal | Non-recognition of symptom seriousness; age – younger; symptom type – bleeding, altered bowel habit | Comorbidity | Strong |
| Prohaska et al (1990) | Washington, USA | Prospective observational | 254 patients (48% men; 52% women) | Colon, rectum | Non-recognition of symptom seriousness; symptom type – rectal pain; too busy; fear | Symptom type – abdominal pain; Age; income | Strong |
| Tanum et al (1991) | Norway | Retrospective observational | 117 patients (aged 35–91; 21% men, 79% women) | Anus | Self-treatment | | Insufficient |
| Byles et al (1992) | Australia | Cross-sectional | 1211 members of public (aged 40+; 49% men, 51% women), 20% with rectal bleeding | Rectum | Non-recognition of symptom seriousness; embarrassment; fear | Self-diagnosis | Moderate |
| Marble et al (1992) | Connecticut, USA | Retrospective observational | 100 patients (aged 14–40, mean 36; 50 aged 49–86, mean 70) | Colorectal | Age – younger | | Strong |
| Kemppainen et al (1993) | Finland | Retrospective observational | 178 patients (aged 27–97, mean 91; 44% men, 56% women) | Colorectal | Age and sex – male < 65, female 80+ | | Moderate |
| Vines et al (1993) | Italy | Prospective observational | 330 patients, 29% with colon cancer (58% men, 42% women) | Colon | Education level – higher | | Strong |
| Curless et al (1994) | England | Prospective observational | 273 patients (aged 25–53, median 68; 56% men, 44% women) | Colorectal | Presentation with non-specific symptoms; non-recognition of symptom seriousness | | Strong |
| Arblman et al (1996) | Sweden | Retrospective observational | 554 patients (aged 30–95; 51% men, mean age 70; 49% women, mean age 72), 39% with rectal, 61% with colon cancer | Colon, rectum | Cancer site – rectum; | Presenting as emergency | Age | Strong |
| Porta et al (1996) | Spain | Prospective observational | 183 patients (mean age 67; 66% men, 34% women) | Colorectal | Age – older; sex – male; literacy; social class – lower; unemployment; recognition of symptom seriousness | | | |
| Mulcahy and O'Donoghue (1997) | Ireland | Prospective observational | 777 patients (aged 26–92, mean 68; 54% men, 46% women) | Colorectal | Non-recognition of symptom seriousness | | | |
| Camilleri-Brennan and Steele (1999) | Scotland | Cross-sectional | 1004 adult members of the public (mean age 50, 40% men, 60% women) | Colorectal | Lack of knowledge<sup>a</sup> | Experience through social network<sup>a</sup> | | Moderate |
| Majumdar et al (1999) | North Carolina, USA | Retrospective observational | 194 patients (aged 15–95, mean 66; 53% men, 47% women) | Colorectal | Symptom type – weight loss | Symptom type – obstruction | Age; sex; cancer site | Strong |
| Roncoroni et al (1999) | Italy | Prospective observational | 100 patients (aged 38–89; 54% men, 46% women) | Colorectal | Non-recognition of symptom seriousness | Advice from social network | | Strong |
| Sladden et al (1999) | Australia | Cross-sectional | 903 GP attenders (aged 50+, mean 64; 51% men, 49% women) | Rectum | Non-recognition of symptom seriousness; self-treatment; previous rectal bleeding; sex – male | Blood in toilet; advice from social network; worry that bleeding means cancer | | Strong |
| Young et al (2000) | The Netherlands | Prospective observational | 23 patients (mean age 52; 43% men, 57% women), 26% with colon cancer, 10 GPs | Colon | Sex – male; non-recognition of symptom seriousness | | | |
| de Nooijer et al (2001) | Australia | Qualitative interviews | 217 patients (aged 59–74, mean 65; 59% men, 41% women), 73% with colon cancer | Large bowel | Education level – higher | Comorbidity; symptom type – pain; Age; sex; availability of vehicle; bleeding; first presenting at hospital; multiple symptoms | | Strong |
| Mariscal et al (2001) | Spain | Prospective observational | | | | | | |
Factors influencing practitioner delay

Twenty-nine papers considered factors that influence practitioner delay. More than three-quarters \((n = 24)\) identified factors that increased delay and less than half \((n = 12)\) factors that decreased delay (Figure 3).

Practitioner behaviour

The most commonly identified themes associated with delayed referral related to initial diagnosis and activity of the practitioner. Misdiagnosis, occurring either through treating patients symptomatically or attributing symptoms to a health problem other than colorectal cancer, resulted in increased time to referral (Spasov, 1978; Holliday and Hardcastle, 1979; Rubin et al, 1980; Zaichuk, 1980; Nilsson et al, 1982; Turunen and Peltokallio, 1982; Funch, 1985; Dixon et al, 1990; Mannson, 1990; Edwards et al, 1991; Harris and Simson, 1998; Roncoroni et al, 1999; Young et al, 2000). In addition, failure to examine the patient, usually rectal examination (Spasov, 1978; Holliday and Hardcastle, 1979; Rubin et al, 1980; Zaichuk, 1980; Turunen and Peltokallio, 1982; MacArthur and Smith, 1984; Dixon et al, 1990; Mannson, 1990; Tanum et al, 1991; Kemppainen et al, 1993; Roncoroni et al, 1999; Young et al, 2000; Langenbach et al, 2003), or receiving negative or false negative test results (Funch, 1985; Kemppainen et al, 1993; Harris and Simson, 1998) contributed to the delay. One qualitative study suggested that early presentation on the part of the patient could actually increase delay (Marshall and Funch, 1986; Porta et al, 1990; Turunen and Peltokallio, 1982) and that increased delay and less than half \((n = 12)\) factors that decreased delay (Figure 3).

Presenting symptom

Although the nature of symptoms will undoubtedly have contributed to referral decisions, it was difficult to reach definitive conclusions about their influence. For some patients, experiencing pain resulted in more rapid referral (Mariscal et al, 2001), whereas for others this had no impact (Young et al, 2000). Similarly, presenting with rectal bleeding could lead both to a more rapid (Sladden and Thomson, 1998; Mariscal et al, 2001) or more delayed outcome (Rubin et al, 1980; Mannson, 1990; Edwards et al,
Clinical Studies

1991). Evaluation of the impact of tumour site on referral decision demonstrated that patients with rectal cancers were less likely to experience delay than those with colon cancers (MacAdam, 1979; Marshall and Funch, 1986; Robinson et al., 1986; Ratcliffe et al., 1986; Sladden and Thomson, 1998), and there is some evidence of an association between delay and an extensive number of factors concentrated around four emergent themes: symptoms, patient history, patient characteristics and behaviour.

Patient history
Consultation patterns related to obtaining a diagnosis were also found to be of relevance, with those patients, often women, who frequently consulted their general practitioner following a non-conclusive initial visit, more likely to experience delayed referral (MacAdam, 1979; Turunen and Peltokallio, 1982; Marshall and Funch, 1986). Similarly, those lacking continuity of care could also suffer delay, although a second opinion might precipitate referral (Bain et al., 2002). Patients with co-existing disease were likely to be referred more quickly (Mariscal et al., 2002). Patients with co-existing disease were likely to be referred more quickly (Mariscal et al., 2002). Patients with co-existing disease were likely to be referred more quickly (Mariscal et al., 2002).

Patient characteristics
There was some evidence relating to the impact of certain patient characteristics on practitioners’ referral patterns. Older patients were more likely to be referred more quickly (Nilsson et al., 1982; Turunen and Peltokallio, 1982; Pitlik and Poticha, 1983; Robinson et al., 1986; Sladden and Thomson, 1998), and there is some evidence of an association between delay and social class, with those from the lower end of the socioeconomic spectrum experiencing a longer wait to referral (MacArthur and Smith, 1984). There was however, no conclusive relationship between patient sex and referral delay (Turunen and Peltokallio, 1982; Marshall and Funch, 1986; Robinson et al., 1986; Arbman et al., 1996).

DISCUSSION
The importance of colorectal cancer in terms of its burden to society is well established; the benefits of presentation and diagnosis early in the course of the disease are clear. Yet although early diagnosis is desirable, it is also difficult and delays can occur at various points in the process. Understanding why delay occurs is the first step to reducing it. This paper presents a comprehensive, systematic review of the literature relating to the reasons for patient and primary care delay in the diagnosis of colorectal cancer. We found evidence of an association between delay and an extensive number of factors concentrated around four emergent themes: symptoms, patient history, patient characteristics and behaviour.

A strength of this review is the inclusion of studies in any language, reducing the potential for bias introduced by the exclusion of papers published in non-English language journals, which may be more inclined to show negative results (Egger et al., 1997). The main limitation of the review relates to substantial heterogeneity between included studies. The nature of the topic and variability in study quality and reporting made it neither possible nor appropriate to pool data for meta-analysis. Rather, we graded study evidence by the robustness of its methodology and analysis, allowing us to weight each study in our composite assessment of delay-related factors. A previous systematic review of delay in breast cancer concluded that most studies were of poor quality and that the strength of evidence was inadequate to inform development of strategies to shorten delay (Ramirez et al., 1999).

Half of all studies included in this review provided strong evidence in relation to the factors they reported, and a further third provided moderate evidence. It is encouraging to note that most of these papers have been published since 1990; almost half in the last decade. Furthermore, we identified considerably more evidence than previous narrative and systematic reviews conducted as part of evidence-based guidelines (Carter and Winslet, 1998; Scottish Intercollegiate Guidelines Network, 2003).

One important finding of this review centres on the complex relationship between presentation behaviour and presenting symptoms. The evidence suggests that if delay is to be reduced, what is important is not simply patients’ awareness of symptoms but rather their recognition and understanding of the potential seriousness of those symptoms. The implications of this are not
## Table 2  Practitioner associated delay factors

| Author(s) | Location | Study type          | Participants | Cancer site          | Factors which increase delay                                                                 | Factors which decrease delay                                                                 | No impact on delay                                                                 | Evidence     |
|-----------|----------|---------------------|--------------|----------------------|-----------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------|--------------|
| Spasov (1978) | Russia | Retrospective observational | 382 patients | Rectum | Initial misdiagnosis; inadequate investigation; inadequate examination                          | Adequate examination; Accurate tests                                                      | Patient age – < 50; patient sex – female; initial misdiagnosis; failure to examine; frequent attendance by patient | Unable to determine            |
| Holliday and Hardcastle (1979) | England | Prospective observational | 200 patients (58% men, mean age 66; 42% women mean age 67) | Colorectal | Failure to examine; initial misdiagnosis; inappropriate referral                             | Adequate examination; Accurate tests                                                      | Patient age – < 50; patient sex – female; initial misdiagnosis; failure to examine; frequent attendance by patient | Moderate        |
| MacAdam (1979) | England | Prospective observational | 150 patients (79% with colon(rectum, colon, rectum cancer), 105 GPs | Colorectal | Cancer site – colon                                                                            | Adequate examination; Accurate tests                                                      | Patient age – < 50; patient sex – female; initial misdiagnosis; failure to examine; frequent attendance by patient | Moderate        |
| Rubin et al (1980) | Israel | Retrospective observational | 100 patients (aged 36 – 85, mean 64; 66% men, 34% women) | Rectum | Initial misdiagnosis; failure to examine; symptom type – bleeding                             | Adequate examination; Accurate tests                                                      | Patient age – < 50; patient sex – female; initial misdiagnosis; failure to examine; frequent attendance by patient | Strong         |
| Zaichuk (1980) | Russia | Retrospective observational | 55 patients | Rectum | Failure to examine; initial misdiagnosis                                                     | Adequate examination; Accurate tests                                                      | Patient age – < 50; patient sex – female; initial misdiagnosis; failure to examine; frequent attendance by patient | Unable to determine            |
| Nilsson et al (1982) | Sweden | Retrospective observational | 284 patients (aged 20 – 99; 52% men, 48% women) | Colorectal | Patient age – < 50; patient sex – male; initial misdiagnosis; failure to examine; frequent attendance by patient | Adequate examination; Accurate tests                                                      | Patient age – < 50; patient sex – female; initial misdiagnosis; failure to examine; frequent attendance by patient | Insufficient    |
| Turunen and Peltokallio (1982) | Finland | Prospective observational | 100 patients (45% men, 55% women) | Colorectal | Patient age – 50; patient sex – female; cancer site – colon; frequent attendance by patient | Adequate examination; Accurate tests                                                      | Patient age – < 50; patient sex – female; initial misdiagnosis; failure to examine; frequent attendance by patient | Moderate        |
| Piltuk and Poticha (1983) | Illinois, USA | Retrospective observational | 826 patients (31 aged < 40, 45% men, 55% women) | Colorectal | Patient age – younger                                                                         | Adequate examination; Accurate tests                                                      | Patient age – < 50; patient sex – female; initial misdiagnosis; failure to examine; frequent attendance by patient | Moderate        |
| MacArthur and Smith (1984) | England | Prospective observational | 127 patients | Colorectal | Failure to examine; patient social class – lower                                               | Symptom type – constipation                                                               | Patient age – < 50; patient sex – female; initial misdiagnosis; failure to examine; frequent attendance by patient | Strong         |
| Funch (1985) | Washington, USA | Prospective observational | 294 patients (aged 18 – 85; 49% men, 51% women) | Colorectal | Patient age – < 50; patient sex – female; cancer site – colon; frequent attendance by patient | Adequate examination; Accurate tests                                                      | Patient age – < 50; patient sex – female; initial misdiagnosis; failure to examine; frequent attendance by patient | Moderate        |
| Marshall and Funch (1986) | Washington, USA | Prospective observational | 396 patients (aged 18 – 85; 50% men, 50% women) | Colorectal | Patient age – < 50; patient sex – female; cancer site – colon; frequent attendance by patient | Adequate examination; Accurate tests                                                      | Patient age – < 50; patient sex – female; initial misdiagnosis; failure to examine; frequent attendance by patient | Strong         |
| Robinson et al (1986) | Israel | Retrospective observational | 445 patients (54% men, 46% women) | Colorectal | Patient age; sex                                                                                | Adequate examination; Accurate tests                                                      | Patient age – < 50; patient sex – female; initial misdiagnosis; failure to examine; frequent attendance by patient | Strong         |
| Ratcliffe et al (1989) | England | Retrospective observational | 332 patients (aged 30 – 100, mean 70; 51% men, 49% women) | Colorectal | Cancer site – rectum                                                                            | Adequate examination; Accurate tests                                                      | Patient age – < 50; patient sex – female; initial misdiagnosis; failure to examine; frequent attendance by patient | Strong         |
| Dixon et al (1990) | England | Retrospective observational | 376 patients (aged 31 – 91, median 67) referred by 151 GPs | Colorectal | Initial misdiagnosis; failure to examine; inaccurate tests                                     | Adequate examination; Accurate tests                                                      | Patient age – < 50; patient sex – female; initial misdiagnosis; failure to examine; frequent attendance by patient | Insufficient    |
| Mansson (1990) | Sweden | Retrospective observational | 42 patients (aged 45 – 92; 43% men, 57% women) | Colorectal | Initial misdiagnosis; failure to examine; inaccurate tests                                     | Adequate examination; Accurate tests                                                      | Patient age – < 50; patient sex – female; initial misdiagnosis; failure to examine; frequent attendance by patient | Moderate        |
| Edwards et al (1991) | Wales | Retrospective observational | 22 patients (aged 45 – 81, mean 63; Anus 50% men, 50% women) | Anus | Failure to examine; inadequate tests                                                           | Adequate examination; Accurate tests                                                      | Patient age – < 50; patient sex – female; initial misdiagnosis; failure to examine; frequent attendance by patient | Moderate        |
| Tanum et al (1991) | Norway | Retrospective observational | 117 patients (aged 35 – 91; 21% men, 79% women) | Anus | Failure to examine; inadequate tests                                                           | Adequate examination; Accurate tests                                                      | Patient age – < 50; patient sex – female; initial misdiagnosis; failure to examine; frequent attendance by patient | Moderate        |
| Jones and Dudgeon (1992) | England | Retrospective observational | 245 GPs, 1465 patients (> 300 with colon cancer) | Colon | Cancer site – colon                                                                             | Adequate examination; Accurate tests                                                      | Patient age – < 50; patient sex – female; initial misdiagnosis; failure to examine; frequent attendance by patient | Moderate        |
| Kemppainen et al (1993) | Finland | Retrospective observational | 178 patients (aged 27 – 97, mean 91; 44% men, 56% women) | Colorectal | Failure to examine; inaccurate tests                                                           | Adequate examination; Accurate tests                                                      | Patient age – < 50; patient sex – female; initial misdiagnosis; failure to examine; frequent attendance by patient | Moderate        |
| Arbin et al et al (1996) | Sweden | Retrospective observational | 554 patients (aged 30 – 93; 51% men, mean age 70; 49% women, mean age 72), 39% with rectal and 61% with colon cancer | Colorectal | Patient sex – female                                                                            | Adequate examination; Accurate tests                                                      | Patient age – < 50; patient sex – female; initial misdiagnosis; failure to examine; frequent attendance by patient | Strong         |
| Harris and Simson (1998) | England | Retrospective observational | 17 patients (aged 43 – 86, mean 72; Colorectal 59% men, 41% women) | Rectum | Initial misdiagnosis; inadequate tests                                                          | Adequate examination; Accurate tests                                                      | Patient age – < 50; patient sex – female; initial misdiagnosis; failure to examine; frequent attendance by patient | Moderate        |
| Sladden and Thomson (1998) | Australia | Cross-sectional | 68 GPs (aged 32 – 67; median 44) | Rectum | Patient age – older; symptom type – blood in toilet; no visible cause; multiple episodes of bleeding | Adequate examination; Accurate tests                                                      | Patient age – < 50; patient sex – female; initial misdiagnosis; failure to examine; frequent attendance by patient | Strong         |
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Table 2 (Continued)

| Author(s) | Location | Study type | Cancer site | Factors which increase delay | Factors which decrease delay | Evidence |
|-----------|----------|------------|-------------|-----------------------------|-----------------------------|----------|
| Roncoroni et al (1999) | Italy | Prospective | Colorectal | Initial misdiagnosis; failure to examine | Presenting symptom | Strong |
| Young et al (2000) | Australia | Prospective | Colorectal | Initial misdiagnosis; failure to examine | Presenting symptom | Strong |
| Martin et al (2000) | Spain | Prospective | Colorectal | Initial misdiagnosis; failure to examine | Presenting symptom | Strong |
| Ban et al (2002) | Scotland | Qualitative | Colorectal | Initial misdiagnosis; failure to examine | Presenting symptom | Strong |
| Crichton et al (2002) | England | Descriptive | Colorectal | Initial misdiagnosis; failure to examine | Presenting symptom | Strong |
| Ecclesley et al (2003) | England | Prospective | Colorectal | Initial misdiagnosis; failure to examine | Presenting symptom | Strong |
| Langenbach et al (2003) | Germany | Qualitative | Colorectal | Initial misdiagnosis; failure to examine | Presenting symptom | Strong |

Without difficulty. For the majority of patients presenting to primary care, symptoms such as rectal bleeding and change in bowel habit are attributable to benign, self-limiting illness. Interpretation of these symptoms as benign will therefore usually be correct. However, for the minority of patients whose symptoms are due to colorectal cancer, delays if long enough may lead to more advanced stage disease and less chance of cure. Thus, considerable emphasis must be placed on highlighting the potentially significant nature of symptoms, despite their commonality. The challenge lies in achieving a suitable balance, which targets the appropriate population without creating undue fear, overburdening primary care services with patients seeking reassurance or clogging up scarce investigative services. This is particularly important given the paradoxical relationship that can exist between delay and fear of a potential cancer symptom.

Although some patients denied their symptoms or re-defined them in relation to benign disease, self-diagnosis and self-treatment were common themes across studies. This may go some way to explaining why patient delay was found to be greater for rectal than for colon cancers. It is likely that many people will associate rectal bleeding with haemorrhoids or some other benign ano-rectal problem. Embarrassment may deter presentation. As such, patients may not attend with the symptom until it becomes problematic; thus for example, the presence of pain reduces delay. Interestingly, patients with comorbidity also delayed less, perhaps due to their already frequent attendance in practice and the ease with which new problems could then be discussed.

The most common reasons for practitioner delay related to initial misdiagnosis and insufficient examination. This is in keeping with findings from previous reviews of delay in cancer diagnosis and is similar to those reported for hospital-related delay (Goodman and Irvin, 1993; Potter and Wilson, 1999). Lower gastrointestinal symptoms are common in patients presenting to primary care and the challenge of appropriate referral is a significant one. The complexity surrounding identification of those patients requiring further investigation has led to the production of several guidelines, all with the aim of facilitating earlier diagnosis. Implicit within these is examination, either to determine whether the patient has an abdominal or rectal mass, or to confirm the existence of a benign explanation. Yet, this review suggests that at least a quarter of patients and perhaps as many as three quarters do not receive a rectal examination (Holliday and Hardcastle, 1979; Rubin et al., 1980; Nilsson et al., 1982; Turunen and Peltokallio, 1982; MacArthur and Smith, 1984; Dixon et al., 1990; Kemppainen et al., 1993; Roncoroni et al., 1999; Young et al., 2000; Langenbach et al., 2003). The full impact of the use of referral guidelines is not yet clear; there is some evidence to suggest that they may reduce delay, but the strength of that evidence to date is limited. Furthermore, we found no intervention studies related to reducing patient or practitioner delay for colorectal cancer. Consequently, the impact of existing initiatives, such as guidelines, must be investigated further.

The NHS is currently rolling out a bowel cancer screening programme; it commenced in England and is due to achieve nationwide coverage by 2009 (http://cancerscreening.org.uk/bowel). The programme targets men and women aged 60 – 69 (50 – 74 in Scotland) and offers biennial screening via home faecal occult blood test kits. The full impact of the programme on patients’ response to bowel symptoms is likely to be complex and will require evaluation. Nonetheless, it is likely that such screening will have some influence on pre-hospital delay, possibly through raising awareness of bowel symptoms and their potential seriousness, with consequent earlier presentation.

However, the bowel screening programme is aimed at detecting early stage disease in asymptomatic patients. Consequently, delays caused by some factors identified in this review, such as fear of cancer, denial of symptoms, initial practitioner misdiagnosis or failure to fully examine patients with rectal bleeding, will most
likely be unaffected by the screening programme. Furthermore, a negative screening result may give patients false reassurance if they subsequently develop symptoms, an occurrence that has already been found to contribute to practitioner delay (Funch, 1985; Kemppainen et al., 1993; Harris and Simson, 1998).

The findings from this review would suggest that the way ahead, although clear, is also complex. If we are to reduce delay in the pre-hospital phase of colorectal cancer diagnosis, we must address two main areas. Firstly, we must overcome the dilemma faced by patients, that of when to categorise nonspecific symptoms as non-serious. Attributing symptoms to benign disease may be entirely appropriate and as such, difficult to influence. Achieving this may include public education, but it is also likely to involve greater awareness of how symptoms are interpreted in the context of pre-existing disease, patient experience, social circumstances and life priorities. Such focus, away from ensuring recognition of symptoms and towards improving understanding of symptoms, will in turn require a shift in thinking on the part of the medical and research communities.

Secondly, we must influence the circumstances under which practitioners decide that further examination, investigation and referral are appropriate. This may require changes to existing guidelines, whereby physical examination and laboratory investigation are made explicit rather than implicit in the decision to refer. It may also require a change in practice, resulting in physical examination of all those who present with lower gastrointestinal symptoms, regardless of age, previous history or symptom duration. The initiation of such changes may already be underway, and indeed the recently published NICE Referral Guidelines for Suspected Cancer, which this review was intended to inform, now explicitly state that digital rectal examination should always be carried out in patients with unexplained lower GI symptoms (National Institute for Health and Clinical Excellence, 2005). What is certain is that pre-hospital delay in colorectal cancer is avoidable and it must be addressed if outcomes and survival are to be improved.

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