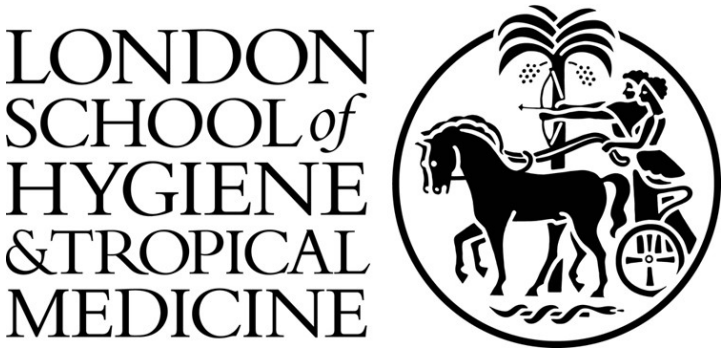

Exploring age inequalities in the management and survival of colorectal cancer patients

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Declaration

I, Sara Benitez Majano, confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

This is a research paper style thesis. Two papers have been published and one is being prepared for peer-review. Two further papers in preparation are included in the thesis. I am the lead and corresponding author of all the papers included. I carried out the literature review, data preparation for analysis, data analysis, and drafted the manuscripts included in the thesis. Co-authors provided feedback on statistical methods, had access to results and contributed to their interpretation, critically reviewed the manuscripts, and approved the submitted versions.

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Thesis abstract

Background

Cancer survival in England is poorer than in other comparable countries. Older cancer patients generally have less evidence-based treatment, and poorer survival than younger patients. This is often attributed to the increasing presence of comorbidity with age. Concerns exist, particularly in England, that age-related differences in cancer outcomes arise because of clinical decision-making based on chronological age alone. This study aims to examine the impact of age on having optimal cancer management for colorectal cancer (CRC).

Methods

Using population-based cancer registration records of 139,457 CRC patients diagnosed in Denmark, England, Norway and Sweden during 2010-2012, I estimate and compare age-standardised stage-specific three-year net survival, and the likelihood of receiving radical surgery by age and stage. Then, focusing on the 99,942 patients diagnosed in England, I quantify how far age-related differences in patient management are mediated by comorbidity and the diagnostic route, using causal mediation.

Findings

In comparison with Denmark, Norway and Sweden, CRC patients in England had lower three-year net survival. There was an age gradient in the proportion treated at each stage of disease in England, which was not as evident in the other countries. Analyses focusing on patients without evidence of comorbidity in England and Denmark showed a similar trend. In England, the proportion of patients with evidence of receiving a full investigation and surgical treatment decreased with age. The age differential was partly mediated by the diagnostic route, but not by comorbidity.

Interpretation

These findings suggest that the CRC survival deficit in England can be attributed partly to under-management of older patients. Complex interactions between biological, attitudinal and contextual factors may be behind these findings. Raising the proportion of patients receiving optimal management to the levels observed in comparable countries would improve CRC outcomes, provided that adequate post-operative and long-term care are also available.

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List of abbreviations and acronyms

ACPGBI	Association of Coloproctology of Great Britain and Ireland
ASA	American Society of Anaesthesiologists physical status classification system
ADL	Activities of daily living
CCI	Charlson Comorbidity Index
CGA	Comprehensive Geriatric Assessment
CI	Confidence interval
CME	Complete mesocolic excision
CRC	Colorectal cancer
CT	Computed tomography
CWT	Cancer Waiting Times Monitoring Data Set
DCCG.dk	Danish Colorectal Cancer Group
DE	Direct Effect(s)
DSI	Diagnostic and staging investigation
EP	Emergency Presentation
FIT	Faecal immunochemical test
gFOBT	Guaiac faecal occult blood test
HES	Hospital Episode Statistics
IADL	Instrumental activities of daily living
IE	Indirect Effect(s)
IMD	Index of Multiple Deprivation
Ma	Mediator a, first mediator
Mb	Mediator b, second mediator
Mc	Mediator c, third mediator
MRI	Magnetic resonance imaging
NBOCA	National Bowel Cancer Audit
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NCCR	Norwegian Colorectal Cancer Registry
ONS	Office for National Statistics
RS	Resectional surgery
RtD	Routes to Diagnosis
SCRCR	Swedish ColoRectal Cancer Registry
SES	Socioeconomic status
TME	Total mesorectal excision
UN	United Nations
UK	United Kingdom
WHO	World Health Organization

Chapter 1: Background

1.1 Introduction

Cancer patients in England have poorer outcomes than in other high-income countries.[1-3] Results from international comparisons of cancer survival have stimulated cancer policy in England, and other countries, with the aim of 'closing the gap' in cancer survival.[4]

Significant efforts have been invested into understanding the origins of these disparities, especially between comparable high-income countries with universal health care coverage, such as Australia, Canada, Denmark, England, Norway and Sweden. Delays in diagnosis that lead to advanced stage disease, which is more difficult to treat and cure, as well as geographic and socioeconomic inequalities in access to care have been proposed as explanations of the international differences in cancer survival.[2,3,5,6] Differences in stage distribution between countries partly explain international differences in cancer survival.[6,7] The survival deficit in England in comparison with other developed countries, however, seems to be driven by lower stage-specific survival. In a recent international population-based comparison, colon and rectal cancer patients in England had lower survival at each Dukes stage than patients in Sweden and Norway (rectal cancer only), with the largest differences seen in patients in the age group 75-99 years.[5] These differences in stage-specific survival suggest that cancer management varies between countries, and possibly more so for older patients.

Cancer is currently the leading cause of death, ahead of cardiovascular disease, in several European countries, including Denmark, Norway and the United Kingdom,[8] and it is a main contributor to disease burden in people aged 60 and over.[9] It is estimated that by 2030, 76% of cancers in men and 70% in women will occur in people over the age of 65 years.[10] Nonetheless, older cancer patients frequently have fewer diagnostic and staging procedures and less evidence-based treatment than younger patients.[9] There is substantial uncertainty on how best to manage cancer in older patients. They are under-represented in clinical trials, hence, the use and effectiveness of many clinical interventions in the older population is frequently not supported by scientific evidence.[11,12] Adequate interventions in older patients are complicated by concomitant chronic conditions, frailty, and potentially deficient access to adequate care.[9,10,13]

As the population ages, the proportion of people who are 65 years or older is growing. In the UK, the proportion of the population aged 65 years or older was 17.8% in 2015 and is projected to reach nearly a quarter of the population by 2045.[14] This demographic trend

poses great challenges to health care systems, and in particular, for the provision of care of chronic conditions, such as cancer, to meet the needs of older people.[9,10]

In this study, I examine the impact of increasing age on the likelihood of having optimal cancer management, in an international comparison (between Denmark, England, Norway and Sweden) and within England, focusing on colorectal cancer (CRC). I hypothesise that differences in the management of older patients may help explain the international differences in population-based cancer survival, beyond what would be explained by the presence of comorbidity.

1.2 Colorectal cancer epidemiology

Progression from pre-malignant lesions, adenomatous polyps, to cancer takes approximately ten to fifteen years, and is affected by both environmental and genetic factors that result in abnormal cell regulation and tumour growth.[15] Potentially modifiable risk factors including physical inactivity, unhealthy diet, and smoking, which help to explain the association between low socioeconomic status and increased incidence of colorectal cancer.[16,17] There is evidence indicating that potentially modifiable risk factors such as physical inactivity, consumption of red meat, processed meat, and folate are associated with colon cancer but not rectal cancer, and that genetic mutations vary between the two sub-sites.[18,19]

Globally, colorectal cancer is the second most common cancer in women and the third most common cancer in men.[20] It was the second most common cancer diagnosis in women and men in Denmark, UK, Norway and Sweden in 2012.[20] Standardised incidence rates however vary between the countries, with higher CRC incidence in Denmark and Norway than in the UK and Sweden. In 2012, there were 45.9 diagnoses in men and 35.7 diagnoses in women per 100,000 persons in Denmark, with the corresponding figures of 42.6 and 35.8 in Norway.[20] In contrast, the numbers were 36.8 in men and 24.5 in women in the UK, 32.2 and 26.5 in Sweden, for the same calendar year.[20] In Norway, the incidence of colorectal cancer has reportedly increased in men in recent years, particularly in lower socioeconomic groups, and probably in relation to increasing exposure to risk factors such as consumption of alcohol and processed meats.[21] Using cancer incidence data for the period 2005-2014 (Denmark, Norway and Sweden) and 2004-2013 (UK), it was recently projected that age-standardised incidence rates (per 100,000 person-years) in 2018 were higher in Norway and Denmark than in the UK and Sweden.[22]

1.3 Diagnostic and staging investigation of colorectal cancer

The aim of mass screening for colorectal cancer is to reduce incidence and mortality through diagnosis of asymptomatic – early stage – tumours and removal of pre-malignant lesions. Organised mass screening programmes have been introduced in many European countries in the last two decades, with large variation in terms of implementation and coverage.[23] In Denmark, a feasibility pilot study in the Copenhagen county started in 2005 offering screening with biennial guaiac faecal occult blood test (gFOBT) to residents aged 50 to 74 years;[24] the national screening programme was then rolled out in 2014.[25] In England, the national Bowel Cancer Screening Programme (BCSP) was introduced in 2006, offering screening with biennial gFOBT to persons aged 60-69.[26] A gradual extension of the eligibility age range to 74 years started in 2009.[27] In 2013, the English BCSP introduced a new screening test: a one-off rectosigmoidoscopy at age 55 years.[28] In 2018, the faecal immunochemical test (FIT) started to replace gFOBT in England because of its higher sensitivity and expected acceptance and uptake.[29,30] In Norway, a regional pilot study started in 2012 offering screening (with either FIT, or flexible sigmoidoscopy) to residents of Østfold, Akershus and Buskerud counties aged 50-74 years old. Currently, the Norwegian Directorate of Health is planning to start the national colorectal cancer screening programme in 2019, offering FIT or colonoscopy to residents aged 55 years.[31] Similarly, a national bowel cancer screening programme is due to start in Sweden in 2019, offering FIT to residents aged 50 to 74 years,[32] following regional screening programmes in Stockholm and Gotland counties.[24]

Uptake of screening is highly variable and generally below target: 45.4% in the Copenhagen county, Denmark; 52.4% in England; and 65% in the Stockholm and Gotland counties in Sweden.[24] Variation in uptake partly depends on the type of test used. Most screening programmes use non-invasive stool tests that identify small amounts of blood in stool samples. The faecal immunochemical test is associated with higher uptake as it involves one stool sample and no dietary restrictions, in comparison with the gFOBT that requires sampling of multiple bowel movements per screening and dietary restrictions due its poor-to-moderate sensitivity.[33] Screening with invasive imaging techniques such as colonoscopy generally have even lower uptake than non-invasive tests.[24] Deprivation and age gradients in screening uptake for colorectal cancer have been described, with older patients and those of lower socioeconomic status less likely to participate.[34,35]

Besides screening, the pathway from suspicion of cancer to a colorectal cancer diagnosis may be through primary care, referral from other health care specialists, or through an emergency admission. With the publication of the first National Cancer Plan in England in 2000, cancer-

specific referral routes were introduced along with waiting time targets to avoid delays in cancer diagnosis. The two-week wait referral route demands rapid referral of patients with suspected cancer to secondary care.[4] Patients diagnosed through an emergency presentation generally have poorer cancer outcomes than those diagnosed through other routes.[36-38] Comparable measures to avoid delays in cancer diagnosis have been introduced in several other countries. In Denmark, a law setting up a maximum wait of two weeks between a cancer diagnosis and treatment was introduced in 2001.[39] Additional measures were introduced in 2007 including a maximum wait of two days between GP referral and specialist appointment, and public reporting of waiting times throughout the cancer patient pathway.[39] Rapid referral routes were introduced in Norway and Sweden in 2016, reportedly influenced by the Danish experience.[40]

Once in secondary care, patients may have more than one investigation to confirm or exclude a colorectal cancer diagnosis. According to current clinical guidelines in England, colonoscopy should be offered to all patients with suspected colorectal cancer, unless contraindicated due to major comorbidities, in which case flexible sigmoidoscopy followed by a barium enema, or computed tomographic colonography should be performed.[41] Patients with confirmed colorectal cancer should be offered clinical investigations for staging, including computed tomography (CT) scans of chest, abdomen and pelvis. Patients with suspected rectal cancer, should additionally be offered Magnetic Resonance Imaging (MRI) of the primary tumour, and further trans-anal ultrasound if deemed amenable to local excision through MRI, or if MRI is contraindicated.[41] The European Registration of Cancer Care (EURECCA) multidisciplinary consensus conference on tumours of the colon and rectum found large consensus about the elective imaging work-up to diagnose and stage colon cancer in several European countries (including Denmark, England, Norway and Sweden among others) in their first meeting in 2012.[42] For rectal cancer, there was large consensus for most imaging tests, except for the use of digital rectal examination and endo-rectal ultrasound following MRI.[42]

Determining disease extension is important to determine patient eligibility for specific treatment options, with either curative or palliative intent. The International Union for Cancer Control's TNM classification of malignant tumours categorises colorectal tumours according to the extension of the disease, based on three components: primary tumour (T), regional lymph nodes (N) and distant metastasis (M).[43] Two classifications are defined for each tumour: a pre-treatment clinical classification drawn from imaging tests, biopsy or endoscopy, and/or physical examination; and a pathological classification, following histopathological assessment of the primary tumour, regional lymph nodes, and of distant

metastases. Different combinations of the T, N and M components (pathological and/or clinical) are used to define categories of summary stage.

1.4 Overview of treatment of colorectal cancer

Treatment options are mostly determined by the extension of the disease. Potentially curative treatment of colorectal tumours generally involves surgery with or without additional therapies. The aim of surgery for colorectal cancer is to remove the tumour and its lymphatic drainage.

The colon and rectum have different location, blood supply, lymphatic drainage and innervation, therefore they have different treatment and outcomes.[19] Total or partial colectomy, or removal of the colon, with its associated blood supply and lymphatic drainage has been the standard surgery for colon cancer for decades.

The location of rectal tumours within a confined space, the pelvic cavity, means that a complete surgical removal is a challenging task. Historically, results of rectal cancer surgery have been poor in terms of residual disease and recurrence.[44,45] In view of the high recurrence rates, in the early 20th century, English surgeon William Miles devised an extensive surgical procedure (named abdominoperineal resection, APR) to remove the rectum, rectosigmoid, along with their lymphatic drainage and blood supply, mesorectum (fatty tissue surrounding the rectum), plus the anus and levator ani muscles, to cover the upward, downward, and lateral spread of rectal tumours. Though oncologic outcomes were improved, perioperative mortality and associated morbidity was high, and the procedure was generally deemed too risky for patients older than 60 years or with concomitant conditions.[45] With advances in medical technologies such as anaesthesia and blood transfusion, APR eventually became the standard care for rectal cancer, and most later surgical developments in rectal cancer focused on developing less radical procedures, preserving sphincter function, while maintaining oncologic outcomes (e.g. Hartmann's procedure and [low] anterior resection).[45] By the late 1970s however, recurrence rates were still high at around 30%,[46] and it was recognised that circumferential margins were likely to be compromised with a blunt excision of the mesorectum by hand.[45,46] The concept of total mesorectal excision (TME) was introduced by English surgeon Richard (Bill) Heald working at Basingstoke District Hospital in the late 1970s.[47] He postulated that high recurrence rates were a result of leaving mesorectal residue rather than extension outside the mesorectum.[48] TME is based on the embryological development of the bowel, and entails sharp dissection under direct vision in the embryological plane (between the visceral fascia covering the mesorectum and the parietal pelvic fascia lining the retroperitoneum) to remove the tumour

and mesorectum en bloc.[45,46,49] Recurrence rates decreased sharply with TME, to 4% at 5 years postoperatively, over a 13-year period.[50] Heald's experience was reproduced in other institutions[51] and in the mid-1990s, TME was introduced in Scandinavian countries and in The Netherlands by workshops, tutoring and video demonstrations.[49] Although the technique was developed in the UK, it was adapted earlier in the Scandinavian countries than in England.[6] Currently, TME is the gold-standard surgical technique for rectal cancer, however, it remains a challenging and demanding procedure that requires a high degree of specialisation and skill.[49]

The TME principle of dissection in the embryological plane and intact removal of the bowel and surrounding mesenterium (mesocolon) was later applied to colon cancer (denoted complete mesocolic excision, CME) by Hohenberger and colleagues in Germany with good outcomes in terms of reduced recurrence rates (from 6.5% to 3.5%) and 5-year survival (from 82.1 to 89.1%).[52] The use of CME for colon tumours is more variable than TME for rectal cancer.

The use of additional therapies for non-metastatic rectal tumours is determined by the risk of local recurrence. Since before the adoption of TME, preoperative radiation has been part of the standard treatment of locally-advanced rectal tumours in most European countries,[41,42,53,54] however, practice varies between and within countries.[42] In Norway, preoperative chemo-radiotherapy with delayed surgery is the norm, whereas in Sweden the standard is to have a short course of radiotherapy preoperatively.[55] The use of radiotherapy for rectal cancer is highly variable within England.[56] Currently, there is an ongoing debate on whether the benefit of (neo)adjuvant therapy is relevant for most CRC patients, in view of the advances in surgical resection techniques in the last decades, namely TME and CME.[57] Adjuvant chemotherapy is generally recommended for stage III/IV colon cancers.[42]

1.5 Measures of health status

An important determinant of cancer treatment, along with disease extension, is the patient's overall health status and concomitant, pre-existent chronic conditions (comorbidity)[58]. The term 'multimorbidity' refers to the existence of two or more chronic conditions.[58] Several summary measures of comorbidity and multimorbidity have been proposed, validated and used in epidemiological research.[59] The commonly used Charlson Comorbidity Index (CCI) ranks specific chronic conditions based on their associated risk of death;[60,61] specific conditions are given weights based on age-standardised relative risks of death at one year in hospitalised patients with selected conditions, then added to obtain a composite score.[61] This assumes that the relationship between concomitant conditions is additive instead of

multiplicative (i.e. there is no synergy between them), and that the risk of death associated with the indexed conditions remains valid with current clinical practice.

In surgical settings, several indices or scales are used to stratify patients' ability to tolerate surgery (operative risk). The American Society of Anaesthesiologists physical status classification system (ASA) was introduced in the early 1940's to stratify the physical state of patients in the preoperative period for statistical analyses (from no organic pathology to emergency surgery in patients with extreme systemic disorders that are a threat to life regardless of the type of treatment).[62] In the 1941 publication, Meyer Sakland proposed the six classes of physical state, acknowledging that this was one of the many factors to be considered to assess operative risk (including the planned surgical procedure, skills of the surgeon, postoperative care, and the patient's history with anaesthesia).[62] It is however frequently used for grading the preoperative health of surgical patients, and as a 'predictor' of risk of surgical complications and outcomes, because of its simplicity and its reported association with surgical outcomes.[63,64] The ASA system has been criticised for its low discriminatory power, and low inter-observer consistency,[65,66] and there is varying opinion on its value to risk-stratify patients in the preoperative period.[67]

Other risk prediction indices have been developed specifically for the preoperative setting. The physiological and operative severity score for the enumeration of mortality and morbidity (POSSUM) was developed for the preoperative assessment of patients to plan and standardise the quality (and level) of care in the UK.[68] It uses 12 physiological variables (including systolic blood pressure, pulse, electrocardiogram and serum levels of sodium and potassium, among others) to predict 30-day mortality and morbidity after surgery. It was later revised and modified (and named Portsmouth POSSUM or P-POSSUM) to make better predictions of in-hospital mortality.[69] Although it was developed for surgical audit in a UK setting, it has been found to be a good risk predictor in some settings,[70] though not in others.[71]

Specific to cancer, 'performance status' scales are used in clinical settings to assess the general well-being and degree of independence of cancer patients, and to help determine eligibility for (and tolerance to) specific treatments.[72,73] There are several scoring systems, with the most frequently used being the Karnofsky performance score (KPS, which has 11 levels ranging from 0 to 100, with the highest indicating no evidence of disease, and the lowest death),[74] and the Eastern Cooperative Oncology Group (ECOG) score, also called WHO or Zubrod score (with five levels from 0 to 4, with the highest indicating death and the lowest used for asymptomatic patients).[75] Both KPS and ECOG scales were developed to monitor

patients' ability to carry out normal activities and self-care during clinical trials for chemotherapeutic drugs,[74,75] and currently they are also used to assess operative risk.[76] The scores are not based on a standard questionnaire but on the clinician's impression about the autonomy of the patient, making them easy to use without detailed questioning.[76] Some authors argue, however, that performance status scales lack sensitivity for the older cancer population, especially those with multimorbidity and or functional deficits.[77,78]

Besides multimorbidity, older people may also develop frailty, defined as an age-associated clinical syndrome characterised by a decline in function in several physiologic systems, causing vulnerability to adverse health outcomes.[79-81] In 2001, Linda Fried and colleagues proposed a frailty phenotype as a standardised definition of frailty and demonstrated its predictive validity for adverse outcomes in two US cohorts from the Cardiovascular Health Study.[81] The characteristic included in the frailty phenotype include unintentional weight loss, muscle mass loss, weakness (measured as grip strength), exhaustion (self-report), slowness (walking speed), and low activity (kilocalories per week). Three or more of those characteristics would identify a frail patient.[81] Several other operational definitions of frailty have been proposed, including the clinical frailty scale from the Canadian Study of Health and Aging (which uses 70 variables to define seven levels of the scale, from very fit to severely frail).[82] The concept of frailty has recently expanded from its origins in epidemiological research into clinical practice, where it has the added benefit (additional to identifying 'high risk patients) that it allows the identification of patients whose physical decline is still reversible.[80,83]

Frailty (and multimorbidity) can lead to disability or dependency in carrying out essential tasks for self-care and for living independently.[79] Disability is thus partly determined by the wider environment, because it is about an individual being able to carry out tasks that are expected within a physical and sociocultural environment (at home, work, etc.).[84] The same limitation in function may have different levels of disability depending on the expectation of others (such as family members and service providers), and on the physical environment (barriers or assistance for physical access, for instance). Disability is generally assessed with questionnaires of activities of daily living (ADL, assessing ability to bathe, dress, ambulate, and use the toilet) or instrumental ADL (IADL, ability to perform domestic tasks, such as housework, cooking and shopping).[85]

Because older patients are at risk of having multimorbidity, frailty, and/or disability, comprehensive geriatric assessment (CGA) techniques have been suggested as better multidimensional tools to plan and deliver medical, rehabilitative and psychosocial care.[86] In

the oncology setting, CGA has been used to monitor and predict side effects from chemotherapy, and mortality. More recently, the international Preoperative Assessment of Cancer in the Elderly (PACE) project produced a CGA tool focused on the surgical cancer patient. PACE incorporates several tools used for surgical risk assessment (including ECOG performance status, ASA, P-POSSUM, ADL, mini mental state (MMS), and Satariano's modified index of comorbidities, among others).[78] Aspects relating to frailty and disability (PS and ADL) were particularly associated with 30-day morbidity.[78] A 2018 review of the literature reporting the use of CGA for prediction of postoperative complications in gastrointestinal cancers found six studies (two from Norway, and one each from Korea, Poland, US, and Singapore). The meta-analysis showed that CCI score of three or higher, polypharmacy (defined as five drugs per day or more), and ADL dependency were important predictors of postoperative complications.[87] One of the Norwegian studies compared the predictive value of elements of different CGA and ECOG performance status in a cohort of colorectal cancer patients, and found that severe comorbidity, dependency (IADL), depression and malnutrition were the most important predictors of postoperative complications and early mortality.[88]

Despite the recent availability of multidisciplinary tools to assess the health status of patients and their suitability for (cancer) treatment, these are not widely used in clinical practice. The ASA classification and performance status scale are the tools more easily and frequently used in clinical practice, and the Charlson Comorbidity Index is one most frequently used in epidemiologic research, despite their known disadvantages. The presence of comorbidity, frailty and/or disability may determine the options for cancer treatment and affect cancer outcomes in the short and longer term.[89] Suboptimal management of cancer in older patients is usually attributed to their observed health status and associated risks, which may outweigh potential benefits of procedures indicated by clinical guidelines.[59,90] Although less intensive cancer treatment in older patients may sometimes be justifiable, there are concerns that, particularly in England, age-related disparities in cancer care and outcomes also arise because of clinical decision-making based on chronological age rather than biological age.[13,34,91]

1.5 Cancer management in older patients

Suboptimal management of chronic conditions in older patients has been extensively described in the literature.[89,92,93] Previous studies have found that older cancer patients may be under-treated, even if chronological age alone is not a contraindication for treatment.[12,92-95] Even those patients with resectable disease seem to be less likely to be treated than younger patients.[96]

There are many physiological changes in relation to age, such as atrophy of muscle cells in the cardiovascular, respiratory and musculoskeletal systems, reduced function of liver and kidneys, neuronal loss, among others.[97] These factors may affect body functioning and tolerance to stressors, including disease and clinical interventions to control them. Additionally, older patients tend to have more concomitant chronic conditions than younger people, and it is generally presumed that poor cancer outcomes in older patients relate to their comorbidities and how these influence cancer management and outcomes.[59,93]

Besides comorbidity, older patients have higher prevalence of cognitive impairment, depression, decreased mobility and may also lack social support.[98,99] Patients with cognitive impairment are more likely to under-report pain.[12] Beliefs that "good patients don't complain" may be more prevalent in older patients than in younger ones.[12]

Furthermore, there is significant uncertainty about the benefit of medical procedures for diagnosing, staging and treating cancer in older patients. Despite the need for scientific evidence to justify medical interventions in older cancer patients, they are generally excluded from clinical trials. This is usually justified by the frequent presence of multimorbidity in older patients that may compromise the generalisability of the findings, but it has the effect of reducing the evidence-base for the management of older patients. This may be impeding older patients from getting adequate cancer care because in order to justify the risks, the benefits must outweigh them, and the evidence of this benefit is often lacking. In general, clinical guidelines tend to focus on single illnesses, and health services are overall organised around younger patients who present one disorder or a limited episode of illness.[98]

Suboptimal management of cancer in older patients may be guided by best clinical intentions to protect people from unnecessary interventions that may worsen their quality of life with little impact on survival; or because postoperative care may be inadequate for those requiring additional support, who tend to be old. Health professionals may be less confident in treating older patients and less willing to offer aggressive treatment to patients with insufficient social support.[13]

Whatever the cause, there are concerns that the needs of older cancer patients are not being met, and that chronological age is informing clinical decision-making rather than biological age.[10,13,91,92,100] There is some debate as to whether the suboptimal management of older cancer patients is due to age-differentiated behaviour or age discrimination/ageism.[101,102] Discrimination may refer to the "unjust of prejudicial treatment of different categories of people", or to the "recognition and understanding of the difference between one thing and

another".[103] Arguably, the second form of discrimination is inherent and needed in clinical practice.[104]

'Ageism', a term first used by US psychiatrist Robert Butler, is a process of discrimination and negative stereotyping against people because of their chronological age.[105] Ageism and age discrimination are often used interchangeably, but some make the distinction between ageism as the attitude (stereotypes and presumptions) which may lead to a set of actions, which are known as age discrimination. Pessimistic attitudes towards older patients in the clinical setting may be held by healthcare professionals and patients themselves. Negative views of ageing held by patients and their carers may have a negative impact on their health, as it is likely to impact their behaviours, such as healthy eating, smoking, drinking, and health-seeking behaviour.[92,102] A recent study found that perceiving life expectancy to be longer was associated with higher participation in bowel cancer screening.[106] Health professionals may make assumptions about patients' potential tolerance of treatment and their preferences, and there is a danger of under-treating healthy older patients who have a long life expectancy and who may benefit from cancer treatment.

1.7 Study Aim

The aim of this study is to examine the impact of increasing age on the likelihood of having optimal management of colorectal cancer, and on cancer outcomes.

To address the question "*Are older patients in England under-managed in comparison with older patients in other countries, and in comparison with younger patients in England?*", different endpoints in the pathway of management of colorectal cancer patients are examined in each of the objectives.

A comparison of cancer management and survival between Denmark, England, Norway and Sweden is undertaken because these countries have similar wealth and coverage of their health systems, and because they have high-quality cancer registries with comparable available data on patient characteristics, cancer management, and outcomes at population level.

1.8 Objectives

1) To estimate and compare stage-specific net survival between Denmark, England, Norway and Sweden.

2) To determine and compare the effect of age on receiving surgical treatment for colorectal cancer in Denmark, Norway and Sweden, and to quantify the proportion

of under-treatment that could be avoided if patients in England were managed as in the best-performing country.

3) To explore the role of comorbidity in explaining international differences in surgical management of colorectal cancer, focusing on Denmark and England.

4) To examine the effect of age on receiving a complete staging investigation for colorectal cancer and to explore how this relationship is mediated by comorbidity and the diagnostic route in England.

5) To examine the effect of age on receiving optimal treatment for colorectal cancer and explore how this relationship is mediated by comorbidity and the diagnostic route in England.

1.9 Theoretical framework and outline of thesis

Understanding whether some patients may benefit from more aggressive management is imperative for improving cancer outcomes. In this study, I explore age inequalities in cancer management as potential determinants of colorectal cancer outcomes. I address the main research question through an international comparison of stage-specific survival and surgical treatment of colorectal cancer patients by age and, when possible, level of comorbidity; followed by a closer examination of the age inequalities in CRC management within England. Lastly, I provide a contextual interpretation of the quantitative findings.

To compare the clinical characteristics of patients by age and country, I develop and apply several algorithms to derive information on the relevant clinical characteristics and endpoints (stage at diagnosis, completeness of staging investigation, and potentially curative surgery), in a standardised and harmonised manner. These are described, along with other materials and methods, in Chapter 2.

Chapters 3 and 4 encompass the main quantitative analyses carried out for this thesis. In general, these analyses focus on individual-level biological characteristics as determinants of individual-level health outcomes, while making statistical adjustments for socioeconomic and contextual variables. The statistical analyses presented in these chapters are, hence, mainly guided by the biomedical theory of disease distribution.[107] Specifically, in Chapter 3, I compare the management and survival of colorectal cancer patients between Denmark, England, Norway and Sweden, addressing objectives 1, 2 and 3. In Chapter 4, I address objectives 4 and 5, by examining some of the potential underlying mechanisms behind the age inequalities in colorectal cancer management within England.

In Chapter 5, I present a summary of the main findings; followed by a contextual interpretation and implications of this work, reflecting on the potential benefit of 'alternative' epidemiologic theories of disease distribution to understand and potentially address health inequalities in follow-up work.

Chapter 2: Overview of methods

2.1 Data sources

Information on all colorectal cancer patients diagnosed in England between 2010 and 2012 was extracted from national population-based cancer registration (NCR) records. Individual tumour NCR records of patients diagnosed in England were linked to the National Bowel Cancer Audit (NBOCA)[108] data, Hospital Episode Statistics (HES)[109] in-patient and out-patient records, Cancer Waiting Times Monitoring Data Set (CWT)[110] and to the Routes to Diagnosis (RtD) dataset. Individual NCR records of tumours diagnosed in Denmark were linked to the Danish Colorectal Cancer Group (DCCG.dk) database for additional clinical information.[111] Norwegian NCR data are routinely linked to the Norwegian Colorectal Cancer Registry (NCCR), a specialised registry that contains detailed clinical information on all CRC patients nationwide.[112] The Swedish Colorectal Cancer Registry provided clinical data on patients diagnosed with colorectal adenocarcinoma in Sweden;[113] its coverage for the study period was over 98%.[114]

2.1.1 Specialised colorectal cancer registries

Rectal cancer has historically been associated with high recurrence rates, morbidity and poor survival. After the introduction of TME as the gold-standard surgical technique to remove rectal cancer, clinicians in several countries established clinical databases to monitor and audit surgical outcomes of rectal cancer patients.

In Denmark, the Danish Colorectal Cancer Group of the Danish Surgical Society (DCCG.dk) established a national database in 1994 aiming to improve the quality of diagnosis and treatment of patients with rectal cancer.[111] Since 2001 this database has also included all patients diagnosed with colon cancer.[111] The DCCG.dk database includes all adult patients diagnosed with colorectal adenocarcinomas referred to a surgical department in Denmark.

Following smaller clinical audits of bowel cancer patients in England,[115] the Association of Coloproctology of Great Britain and Ireland (ACPGBI) initiated the National Bowel Cancer Audit (NBOCA) project in 2003 as a joint initiative with the National Clinical Audit Support Programme (NCASP).[116] It aims to measure the quality of care and survival of patients with colorectal cancer in England and Wales, and it is currently delivered jointly by the ACPGBI, the Royal College of Surgeons Clinical Effectiveness Unit, and NHS Digital.[117]

The Norwegian Rectal Cancer project was initiated in 1993 aiming to improve rectal cancer outcomes, by introducing TME surgery, and establishing a registry for quality control: the

Norwegian Rectal Cancer Registry (NRCR).[112] In 2007, the NRCR was broadened to include colon cancer patients, forming the Norwegian Colorectal Cancer Registry (NCCR).[112]

The Swedish Rectal Cancer Registry started in 1995 to monitor outcomes of all patients with rectal adenocarcinoma in Sweden.[118] From 2007, the coverage of the registry was widened to include patients diagnosed with colon adenocarcinoma, forming the Swedish ColoRectal Cancer Registry (SCRCR).[119]

The data collected by these specialised registries or clinical audits are regularly analysed and fed back to health care providers, and contribute to the standardisation and quality assurance of care.[1,120]

2.1.2 Additional data sources for England

Given that the coverage of the NBOCA dataset was not 100% complete during the study period (86% in 2011-2012),[121] English NCR records were also linked to additional data sources to reduce missing information on the main clinical variables. The Hospital Episode Statistics is an administrative dataset that records information on all clinical procedures, performed in NHS Hospitals, it contains information on outpatient, inpatient and emergency admissions.

The Cancer Waiting Times Monitoring Data Set records information on patients who are referred to secondary care for suspicion of cancer, and who are offered treatment within the NHS.[122] It is used to monitor cancer waiting times targets from referral in primary care to specialist evaluation, from referral to treatment, and from decision to treat to treatment receipt.

2.2 Ethical and data access approvals

Access and use of the English datasets for this study is covered by the Health Research Authority ethical (13/LO/0610) and statutory (PIAG 1-05(c)/2007) approvals to the LSHTM Cancer Survival Group. For the international comparison, this study is covered by approvals from the UK Health Research Authority (reference ECC 3-04(i)/2011), the National Health Service Research Ethics Service (11/LO/0331), and the London School of Hygiene & Tropical Medicine (LSHTM, 12171). These approvals were reviewed and accepted by the LHSTM Research Governance Committee in August, 2018 as appropriate for this Research Degree Project. Additional local approvals were sought for the international data sources: a Data Processing Agreement with the Danish Cancer Society and approval from the Danish Data Protection Agency was established for using the DCCG.dk data; a Data Disclosure Agreement with the Cancer Registry of Norway for using the Norwegian data; and ethical approval from the Regional Ethical Committee in Uppsala for the Swedish data.

2.3 Variable definitions

Information on date of birth, date of diagnosis, last day of follow-up, and vital status was extracted from national population-based cancer registry records. The main exposure variable *age* was calculated as the difference between the date of cancer diagnosis and the date of birth. Different age categories and age as a continuous variable were explored and used for specific analyses (detailed in the Results section).

Socioeconomic status of patients diagnosed in England was represented by the income domain of the Index of Multiple Deprivation[123] of the Lower Layer Super Output Area (LSOA) of residence (~1,500 inhabitants), categorised into five categories of deprivation according to the quintiles of the national distribution of the LSOA-level deprivation scores.

Information on *comorbidity* recorded in the six years previous to the colorectal cancer diagnosis was derived from HES records for English cancer patients. A detailed description of the algorithm for obtaining comorbidity information from HES records has been described by Maringe and colleagues.[124] The individual diagnoses included were ischaemic heart disease, heart failure, stroke, peripheral vascular disease, peptic ulcer, chronic kidney disease, chronic obstructive pulmonary disease, chronic liver disease, diabetes mellitus, dementia, para/hemiplegia, human immunodeficiency virus infection, morbid obesity and previous cancer diagnoses. Ideally, the information in the comorbidity variable should reflect the overall health status of patients, that is, both in relation to their cancer (how cancer affects different systems and organs) and in relation to their pre-existing chronic conditions.

Information on comorbidity for patients diagnosed in Denmark was readily available in the DCCG.dk database, as the Charlson Comorbidity Index. This variable was derived by DCCG.dk staff using diagnoses made in the 10 years previous the colorectal cancer diagnosis and excluding those made in the three months before the cancer diagnosis. Information on individual disease diagnoses and durations was not available. Information on comorbidity was not available from the Norwegian and Swedish data sources included in this study, therefore these countries were not included in the analysis by comorbidity status (Section 3.3).

Information on *route to diagnosis* of patients diagnosed in England was extracted from the Routes to Diagnosis (RtD) dataset. This dataset includes a variable that assigns each tumour one of several predefined routes to diagnosis using the algorithm developed and described by Elliss-Brookes and colleagues.[37]

2.3.1 Stage at diagnosis

A hierarchical algorithm was developed and applied for these analysis, updating and extending a previous stage algorithm[125] to derive information on disease extension, defined by the Union for International Cancer Control (UICC) TNM classification of malignant tumours,[43] from multiple data sources. In summary, each tumour is assigned a single TNM summary stage from individual pathological and clinical T, N and M components. The algorithm gives priority to pathological confirmation of the tumour, lymph node extension, and distant metastases (if positive), over clinical TNM components. Stage was categorised as missing when there was not sufficient information from individual T, N and M components to derive summary stage.

The description of the algorithm and its application to colorectal and lung tumours was published in the British Journal of Cancer in 2016.[126] This work was also presented as a poster at the PHE Cancer Data and Outcomes conference in Manchester, June, 2016; and at the UICC World Cancer Congress, Paris, 2016. The stage algorithm was applied to all the datasets used for the analyses presented in Chapters 3 and 4.

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SECTION A – Student Details

Student ID Number	376763	**Title**	Ms
First Name(s)	Sara		
Surname/Family Name	Benitez Majano		
Thesis Title	Exploring age inequalities in the management and survival of colorectal cancer patients		
Primary Supervisor	Dr Sarah Walters		

If the Research Paper has previously been published please complete Section B, if not please move to Section C.

SECTION B – Paper already published

Where was the work published?	British Journal of Cancer		
When was the work published?	June, 2016		
If the work was published prior to registration for your research degree, give a brief rationale for its inclusion			
Have you retained the copyright for the work?*	**Yes**	Was the work subject to academic peer review?	**Yes**

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For multi-authored work, give full details of your role in the research included in the paper and in the preparation of the paper. (Attach a further sheet if necessary)	I was the lead author of this paper. I planned the study, developed the algorithm presented in the paper, carried out the analysis, and prepared the draft of the paper. Co-authors provided feedback and input on the development of the algorithm, and on the manuscript.

SECTION E

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Deriving stage at diagnosis from multiple population-based sources: colorectal and lung cancer in England

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Background: Stage at diagnosis is a strong predictor of cancer survival. Differences in stage distributions and stage-specific management help explain geographic differences in cancer outcomes. Stage information is thus essential to improve policies for cancer control. Despite recent progress, stage information is often incomplete. Data collection methods and definition of stage categories are rarely reported. These inconsistencies may result in assigning conflicting stage for single tumours and confound the interpretation of international comparisons and temporal trends of stage-specific cancer outcomes. We propose an algorithm that uses multiple routine, population-based data sources to obtain the most complete and reliable stage information possible.

Methods: Our hierarchical approach derives a single stage category per tumour prioritising information deemed of best quality from multiple data sets and various individual components of tumour stage. It incorporates rules from the Union for International Cancer Control TNM classification of malignant tumours. The algorithm is illustrated for colorectal and lung cancer in England. We linked the cancer-specific Clinical Audit data (collected from clinical multi-disciplinary teams) to national cancer registry data. We prioritise stage variables from the Clinical Audit and added information from the registry when needed. We compared stage distribution and stage-specific net survival using two sets of definitions of summary stage with contrasting levels of assumptions for dealing with missing individual TNM components. This exercise extends a previous algorithm we developed for international comparisons of stage-specific survival.

Results: Between 2008 and 2012, 163 915 primary colorectal cancer cases and 168 158 primary lung cancer cases were diagnosed in adults in England. Using the most restrictive definition of summary stage (valid information on all individual TNM components), colorectal cancer stage completeness was 56.6% (from 33.8% in 2008 to 85.2% in 2012). Lung cancer stage completeness was 76.6% (from 57.3% in 2008 to 91.4% in 2012). Stage distribution differed between strategies to define summary stage. Stage-specific survival was consistent with published reports.

Conclusions: We offer a robust strategy to harmonise the derivation of stage that can be adapted for other cancers and data sources in different countries. The general approach of prioritising good-quality information, reporting sources of individual TNM variables, and reporting of assumptions for dealing with missing data is applicable to any population-based cancer research using stage. Moreover, our research highlights the need for further transparency in the way stage categories are defined and reported, acknowledging the limitations, and potential discrepancies of using readily available stage variables.

Stage at diagnosis is a key predictor of cancer survival (Richards, 2009). Differences in stage are believed to be one of the main drivers of disparities in cancer survival between and within regions (Sant *et al*, 2003). England is known to lag behind in cancer survival in comparison to other comparably wealthy countries with a universal health system (Coleman *et al*, 2011). Part of this

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survival differential is presumably due to a poorer stage distribution of cancer cases in England (Sant *et al*, 2003; Walters *et al*, 2013b). In the past couple of decades, many resources have been invested in improving cancer outcomes through identifying and treating cancer at an earlier stage (Richards, 2009; Department of Health, 2011).

Research examining national and international temporal and geographical patterns in cancer outcomes is usually based on population-based cancer registry data, which have historically lacked information on stage. Further granularity of information is required to understand in depth the effect of stage on cancer outcomes at the population level and to monitor and evaluate cancer policy and changes in clinical practice. Recent efforts by Public Health England (PHE) and the National Cancer Registration Service have driven an improvement in availability of stage information for cancers diagnosed in England (McPhail *et al*, 2015). The national aim is for at least 70% of cancer patients to be staged at diagnosis (Health and Social Care Information Centre, 2015).

Clinical or surgical quality assurance programmes, also called clinical audits, have been developed as instruments to ensure clinical quality standards of health-care providers (van Gijn *et al*, 2010). Clinical audits contain detailed clinical data, including information on diagnostic investigations, stage at diagnosis, and treatment for cancer (van Gijn *et al*, 2012). Besides helping clinical specialists improve their practice, clinical audits offer a rich, complementary source of clinical data for population-based cancer research.

Comparability of stage information from different sources has been a controversial issue, especially when making international or temporal comparisons, as clinical protocols, data collection methods, coding practices, and tumour classification systems may vary between geographies and time periods (Walters *et al*, 2013a). Inconsistencies may also occur between different sources of information from the same country.

We describe an algorithm to derive stage at diagnosis from different sources, based on a series of hierarchical rules applied on both the data sources and the individual stage variables from the TNM classification (Sobin *et al*, 2009). This extends the algorithm proposed and used by Walters *et al* (2013a) for the International Cancer Benchmarking Partnership module 1 study. The algorithm is illustrated for colorectal and lung cancer.

MATERIALS AND METHODS

Data sources. The National Cancer Registry data provides information on date of birth, sex, vital status, date of death, tumour site, and morphology (Office for National Statistics, 2015).

The Cancer Analysis System (CAS) is a national database administered by the National Cancer Intelligence Network of PHE. It combines the National Cancer Registry data with data from other sources (Health and Social Care Information Centre, 2015) and holds information on main tumour features, socio-demographic characteristics, stage, and treatment dates.

The National Clinical Audit Programme comprises multiple clinical audits to monitor and evaluate health-care practice on specific conditions, benchmark performance, and inform patients and the general public of current standards of care in different medical specialties (Healthcare Quality Improvement Partnership, 2015). Cancer clinical audits contain information on patient referral, diagnostic investigations, pretreatment staging, treatment, pathology evaluations, posttreatment follow-up, and outcomes. Information is collected at the hospital level and its accuracy and completeness should, in principle, be ensured by relevant clinicians before submission to the Audit (Scott *et al*, 2014). The National Bowel Cancer Audit Project (NBOCAP) was developed to collate detailed clinical bowel cancer data by the Association of Coloproctology of Great Britain in 2001 (Health and Social Care Information Centre, 2014). The Lung Cancer Audit Database (LUCADA) was developed by the Royal College of Physicians Intercollegiate Lung Cancer Group in 2002 and started collecting lung cancer data nationally in 2005 (Royal College of Physicians, 2015). Figure 1 summarises the sources of information for the stage algorithm.

Data linkage. Individual colorectal and lung cancer records from the ONS National Cancer Registry data were linked to the CAS records of the same cancers diagnosed between 2008 and 2012. It followed a two-part strategy, linking records at the patient level using an eight-level hierarchy based on the availability of information on NHS number, date of birth, sex, and postcode and linking records at the tumour level by tumour site and diagnosis date. Of the 163 915 colorectal cancer cases (ICD-10 C18-C19) in the ONS National Cancer Registry data diagnosed in England during the study period, 158 953 (96.97%) linked to a CAS record and 121 707 (74.25%) linked to an NBOCAP record. For lung cancer (ICD-10 C33-C34), there were 168 158 tumours diagnosed in England during the study period. Of these, 167 236 (99.45%) linked to a CAS record and 131 540 (78.22%) linked to a LUCADA record.

The staging algorithm. The algorithm is based on rules of the Union for International Cancer Control TNM classification of malignant tumours. The TNM classification was developed in the 1950s as an international standard for classifying malignant tumours by anatomical extent (Sobin *et al*, 2009). It aims to provide an unambiguous grouping of cancer cases for clinicians to make standardised and consistent decisions for adequate disease management.

The anatomical extent of disease is based on the assessment of three components: the extent of the primary tumour (T), the presence and extent of metastases to regional lymph nodes (N), and the presence of distant metastases (M). For each tumour, two classifications are defined: a pretreatment clinical classification (c), drawn from physical examination, imaging tests, endoscopy, or biopsy; and a pathological classification (p), after histopathological assessment of the primary tumour, removal and assessment of lymph nodes, and microscopic evaluation of distant metastases.

The TNM classification goes through periodic prospective and retrospective evaluations that lead to the development and publication of improved editions. The Fifth and Sixth Editions were published in 1997 and 2002, respectively (Sobin and Wittekind, 1997, 2002), followed by the current Seventh Edition, in effect since 2010 (Sobin *et al*, 2009). Possibly the biggest change between the latest editions was the elimination of the category Mx, previously used to denote that distant metastases could not be assessed (Sobin *et al*, 2009). This category is now considered inappropriate as clinical assessment of metastases may be based solely on physical examination (cM). Pathological Mx (pMx) may be misinterpreted and overused by pathologists when they have access to histological material to assess pT and pN, but not for pM, a frequent situation after surgery for resection of the primary tumour (Sobin and Compton, 2010). The deletion of this category encourages the use of M0 when metastasis cannot be proven and should facilitate the completeness of stage grouping.

Hierarchies of data sources and stage variables. A hierarchy of data sources was established for different types of information to avoid inconsistencies, given that information could potentially come from a maximum of three data sets. The ONS National Cancer Registration data was our preferred data set for main person and basic tumour characteristics such as date of birth, vital

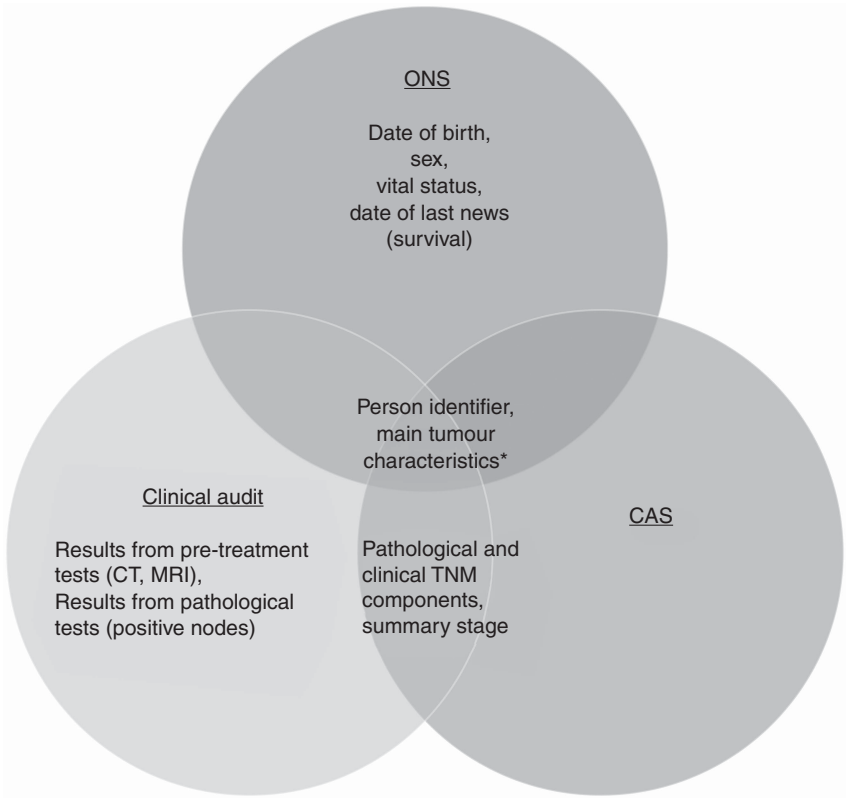

Figure 1. Sources of data for deriving stage for colorectal and lung cancer, England, 2008–2012. *Main tumour characteristics include ICD-10 topography codes, histology, behaviour, and date of diagnosis. Abbreviations: CAS = Cancer Analysis System; CT = computarised tomography scan; MRI = magnetic resonance imaging; ONS = Office for National Statistics Cancer Registration Dataset.

status, deprivation quintile, topography, and morphology of the primary tumour. This decision was based on their established quality-control processes to verify this information and to be consistent with official national cancer statistics (Office for National Statistics, 2015). Clinical audits were the preferred source for detailed clinical data such as pretreatment diagnostic investigations, dates and results of medical interventions, and staging resulting from these. Staging information from CAS was used if missing or invalid from the clinical audit.

The algorithm can be divided into two parts for descriptive purposes. The first part entails deriving individual T, N, and M components from all available sources of pathological and clinical stage information. Once individual T, N, and M components have been ascertained, the second part of the algorithm applies TNM definitions for stage grouping, to obtain the overall grouped TNM stage (I, II, III, IV). Two different strategies for deriving TNM stage grouping are described depending on the acceptable level of missing information from individual T, N, and M components.

Deriving individual T, N, and M components. We used a set of rules to treat potentially discordant information from different sources to derive overall individual T, N, and M components from different types of variables in the data sets following TNM classification rules.

The pathological TNM classification uses information from clinical TNM and complements it using additional information from pathological evaluation (Sobin *et al*, 2009). Pathological TNM should therefore be the most complete source of staging information, at least for T and N. In our data sets, there was information for pathological and clinical individual T, N, and M components from the clinical audits and CAS plus staging information from additional variables (Table 1). We gave priority to the pathological variables over clinical ones for T and N, but cM was prioritised over pM (Walters *et al*, 2013a). Although distant metastases are not generally evaluated during surgery for resection of the primary tumour (Sobin and Compton, 2010; Walters *et al*, 2013a), pathological confirmation of metastases, from a biopsy, for example, was given priority over a negative or inconclusive result from a clinical/imaging test.

Our algorithm allowed results from medical tests and diagnostic procedures to inform individual clinical T, N, and M components when missing or with a value of zero. Similarly, records of the presence of metastases in specific organs or of regional lymph node involvement were used to inform cM or pN, respectively. Information in these additional variables was used as evidence of local, regional, and/or distant extension of disease when positive but did not rule out their presence. For example, if there was evidence of distant metastases from one of these additional variables, this replaced the value of cM to cM1; however, if there was no evidence of metastasis in that variable, it did not change the value of cM to cM0, allowing the algorithm to keep looking for information in subsequent variables.

In addition to the clinical and pathological T, N, and M components, CAS reports a third type of staging information that may come from either pathological or clinical data and may use the highest value of a particular component for a given tumour or be directly flagged by the registry. This 'integrated' stage information was used only when exhausting all other possible sources because its algorithm was not fully documented.

We used an additional step for determining the M component to account for the fact that, although the categories Mx and pM0 do not exist in the Seventh Edition of the TNM classification, their use is still common practice: If M was still missing after looking in all potential sources, and there was indirect evidence of a clinical examination, that is information on both clinical T and N, M was assumed to be M0. Once an individual overall T, N, or M

Table 1. Sources of valid T, N, and M components: completeness of variables and contribution to final staging

	Data sets		Colorectal		Lung	
Variables	**Audit**	**CAS**	**Completeness count (%)**	**Contribution count (%)**	**Completeness count (%)**	**Contribution count (%)**
T component						
pT	●		32 648 (19.9)	32 017 (19.5)[a]	15 427 (9.2)	15 427 (9.2)
Serosal involvement or perforation	●		5209 (3.2)	710 (0.4)	NA	NA
pT		●	77 997 (47.6)	52 761 (32.2)	14 933 (8.9)	5970 (3.6)
cT	●		48 204 (29.4)	16 113 (9.8)	107 171 (63.7)	89 265 (53.1)
Result from MRI	●		22 056 (13.5)	2295 (1.4)	NA	NA
cT		●	5773 (3.5)	754 (0.5)	7952 (4.7)	1217 (0.7)
iT		●	104 047 (63.5)	11 358 (6.9)	91 917 (54.7)	11 437 (6.8)
Missing T component				47 907 (29.2)		44 842 (26.7)
N component						
pN	●		32 666 (19.9)	32 518 (19.8)[a]	15 177 (9.0)	15 177 (9.0)
Count of positive lymph nodes	●		14 523 (8.9)	310 (0.2)	NA	NA
pN		●	74 212 (45.3)	49 351 (30.1)	15 180 (9.0)	6914 (4.1)
Count of positive lymph nodes		●	35 695 (21.8)	4656 (2.8)	3511 (2.1)	841 (0.5)
cN	●		50 108 (30.6)	16 141 (9.9)	107 300 (63.8)	88 336 (52.5)
Result from MRI	●		20 387 (12.4)	1319 (0.8)	NA	NA
cN		●	6576 (4.0)	1261 (0.8)	8085 (4.8)	1274 (0.8)
iN		●	101 453 (61.9)	9574 (5.8)	91 693 (54.5)	11 349 (6.7)
Missing N component				48 785 (29.8)		44 267 (26.3)
M component						
cM	●		51 542 (31.4)	50 548 (30.8)[a]	107 057 (63.7)	107 057 (63.7)
Distant metastasis	●		17 890 (10.9)	8727 (5.3)	NA	NA
Result from liver CT	●		75 714 (46.2)	1064 (0.6)	NA	NA
cM		●	13 212 (8.1)	6548 (4.0)	8987 (5.3)	1894 (1.1)
pM	●		10 333 (6.3)	3248 (2.0)	10 845 (6.4)	648 (0.4)
pM		●	10 936 (6.7)	4170 (2.5)	9675 (5.8)	2944 (1.8)
iM		●	67 948 (41.5)	18 800 (11.5)	92 930 (55.3)	14 197 (8.4)
Clinical examination				3294 (2.0)		3056 (1.8)
Missing M component				67 516 (41.2)		38 362 (22.8)
Summary stage[b]						
pStage	●		30 239 (18.4)[c]	2206 (1.3)[c]	16 946 (10.1)	20 (<0.01)
cStage	●		80 036 (48.8)[c]	1098 (0.7)[c]	105 410 (62.7)	485 (0.3)
pStage		●	4351 (2.7)	38 (<0.01)	2117 (1.3)	41 (<0.01)
cStage		●	508 (0.3)	5 (<0.01)	679 (0.4)	7 (<0.01)
iStage		●	57 596 (35.1)	1189 (0.7)	85 267 (50.7)	1520 (0.9)
Stage		●	108 105 (66.0)[d]	4003 (2.4)[d]	NA	NA
Total				163 915		168 158

Abbreviations: CAS = Cancer Analysis System; M = metastases; MRI = magnetic resonance imaging; N = lymph nodes; NA = not available; T = tumour. Colorectal and lung cancer diagnoses in England, 2008–2012. Prefixes: p: pathological; c: clinical; i: integrated (origin may be pathological, clinical, highest value, or simply flagged by the registry).

[a]Some zero values for this variable are replaced by positive values in the next step of the algorithm, where the contribution to final staging is made. Therefore, completeness of this variable does not equal its contribution to final staging.

[b]Summary stage variables contribute to non-restrictive strategy only.

[c]Dukes stage from Audit.

[d]Dukes stage from CAS.

component was populated at a specific step of the algorithm, there was generally no need to look further for information of that particular component in subsequent steps of lower priority.

Deriving the grouped TNM stage. After ascertaining individual – and unique – T, N, and M values to each tumour, the second part of the algorithm followed TNM classification definitions to categorise different combinations of T, N, and M values into TNM stage groupings. This part of the algorithm starts by examining M. Generally, for most cancer sites, including colorectal and lung, a positive M value effectively represents the maximum value of TNM stage grouping, stage IV, independently of the values of N and T. Similarly, once a positive M has been excluded, and there is a positive N, the algorithm assigns a TNM stage III to the tumour, independently of the value of T. The algorithm then evaluates subsequent subcategories in a descending order (stages II and I).

To manage the missing information within N and/or M, we applied two different strategies to derive overall stage based on the algorithm for deriving stage described by Walters *et al* (2013a). The most conservative of the two approaches, the restrictive strategy, is stricter in the sense that all three components need to be present to derive the grouped stage. In contrast, the non-restrictive strategy allows for the interpretation of missing information as an absence of metastases to the lymph nodes (N) or to distant organs (M). Additionally, after exhausting all possibilities of deriving the grouped TNM stage from individual T, N, and M components, the algorithm moves on to using the pathological and clinical summary stage information. The restrictive strategy differs in that we ignore the grouped stage variables, given that we cannot verify individual T, N, and M components from these.

The staging algorithm applied to colorectal cancer. Both CAS and NBOCAP use the Fifth Edition of the TNM classification (Sobin and Wittekind, 1997), following guidance from the Royal College of Pathologists (Health and Social Care Information Centre, 2014). The definition of node involvement changed in later editions, specifically in that evaluation of satellite mesenteric

tumour deposits use a size criterion in the Fifth Edition, while the Sixth and Seventh Editions use a shape criterion to determine the presence of mesenteric lymph node involvement (Doyle and Bateman, 2012). Subdivisions of stage categories have been added, and definitions of T4a and T4b have been reversed in the Seventh Edition (Sobin *et al*, 2009). Except for the lymph node definition change, none of the changes affect definitions of overall stage grouping categories.

NBOCAP data allowed for single tumours to have several treatment records. These records may hold conflicting information on pathological T, N, and M components, presumably measured at different points in the treatment journey. Therefore, the first part of the algorithm applied to colorectal cancer was to establish a hierarchy of NBOCAP treatment records based on their closeness to diagnosis date. As a general rule, only records with treatment procedures dated within 30 days before or after the date of diagnosis were eligible to contribute with information on pathological T, N, and M components. This was to avoid assigning values of TNM associated with restaging and/or disease progression to what we define as stage at diagnosis. Of these records with procedures dated between the ±30-day window from diagnosis, the closest one to the date of diagnosis would be given priority over information contained in subsequent treatment records, assuming it contained a valid code for that variable. In cases where multiple records of one tumour had the same procedure dates, the one with lowest values of individual T, N, and M components would be given priority, following a general rule of the TNM classification (Sobin *et al*, 2009, p. 9). Information in subsequent treatment records would only be used if such information was missing in the previous one. Information on individual clinical T, N, and M components from NBOCAP was the same in all treatment records of any single tumour, as in CAS. Additional variables with information on colorectal cancer-specific staging are listed in Table 1. The full procedure to derive individual T, N, and M components of stage for colorectal cancer is detailed in Supplementary Appendix Figures S1–S3.

The second part of the algorithm for deriving overall stage grouping using the non-restrictive strategy used additional information from the colorectal cancer-specific Dukes classification. As the Dukes classification is not directly equivalent to specific combinations of individual T, N, and M components, TNM summary stage variables from CAS were given priority over Dukes staging, in the same order as individual T, N, and M variables (pathological, followed by clinical and integrated). The second part of the colorectal cancer stage algorithm is summarised in Figures 2 and 3.

The staging algorithm applied to lung cancer. The first part of the algorithm remains as described above, except that there were no additional variables to inform individual T, N, and M components in LUCADA (See Supplementary Appendix Figures S6–S8).

The main challenge in adapting the algorithm to lung cancer was the substantive modifications between the Sixth and Seventh Editions of the TNM classification (Goldstraw *et al*, 2007): definitions of some individual components of T and M as well as of some categories of the stage grouping have changed (Mirsadraee *et al*, 2012). We derived TNM stage grouping following definitions of the Sixth and Seventh Editions of the TNM classification separately. Most of these changes do not affect the overall TNM stage grouping, therefore we chose to apply definitions of the current Seventh Edition of TNM classification for the whole study period (see Supplementary Appendix Figures S4 and S5).

Statistical analyses. We estimated age-standardised 5-year net survival, stratified by stage, including a missing stage category, for patients diagnosed in England between 2008 and 2012 and followed up until end of 2013. Net survival represents survival with cancer as the only potential cause of death by factoring out mortality from other causes (expected mortality) (Pohar Perme *et al*, 2012). Within the relative survival setting in which causes of death are not available, the expected mortality was provided by life tables from the England general population, namely, life tables by age, sex, calendar year, and deprivation (London School of Hygiene & Tropical Medicine, 2015). Net survival was estimated with the non-parametric Pohar-Perme estimator (Pohar Perme *et al*, 2012) implemented in the Stata program *stns* (Clerc-Urmès *et al*, 2014). We used the complete approach for survival analysis, as used for national cancer survival statistics (Office for National Statistics, 2015). We used the International Cancer Survival Standard weights for age standardisation, which categorises age into five groups (15–44, 45–54, 55–64, 65–74, and 75–99 years of age) (Corazziari *et al*, 2004). We compared 5-year net survival between both versions of the staging algorithm (restrictive and non-restrictive) for each cancer.

RESULTS

The proportion of cases with valid information on individual T and N components was comparable between cancer sites (Table 1). Completeness of valid information on the M component varied significantly between colorectal and lung cancer (41.2% *vs* 22.8% missing M component, respectively Table 1). Of the 163 915 primary malignant colorectal tumours, 92 778 (56.6%) had valid stage using the restrictive strategy and 137 429 (83.8%) using the non-restrictive strategy. Of the 168 158 primary lung cancer cases, 128 866 (76.6%) had stage information with the restrictive strategy, *vs* 135 666 (80.7%) with the non-restrictive strategy. Completeness of derived stage improved over time for both cancer sites, as did the difference in stage completeness between the restrictive and non-restrictive strategies (Table 2).

Distribution of stage differed between strategies for colorectal cancer (Table 2). Assuming equivalence between values of zero and missing for N and M, as in the non-restrictive strategy, decreased dramatically the overall missingness of TNM stage grouping for colorectal cancer and affected the overall stage distribution. For instance, 25 431 (27.4% of data with observed stage) tumours were classified as stage III using the restrictive strategy and increased to 41 537 (30.2% of data with observed stage) using the non-restrictive strategy, mainly owing to the assumption of equivalence between missing and zero value of M in the first part of the algorithm. This difference was less pronounced for lung cancer, because of better completeness of the individual M component (Table 1). Lung cancer stage distribution was comparable between strategies (Table 2).

Using summary stage, variables in the non-restrictive strategy did not considerably improve the completeness of stage for either cancer site, indicating that most cases had fairly complete T, N, and M information before reaching this step or had all stage variables missing.

Age-standardised 1-year net survival for colorectal cancer was significantly lower using the non-restrictive strategy for all stages, particularly for the missing stage category. Differences in lung cancer survival between the two strategies were negligible (Table 3; Supplementary Appendix Figure S9). These figures reflect the differences between both strategies and how incomplete the individual stage components are.

DISCUSSION

This paper describes an algorithm to derive stage from multiple data sources. Recording of stage is now one of the

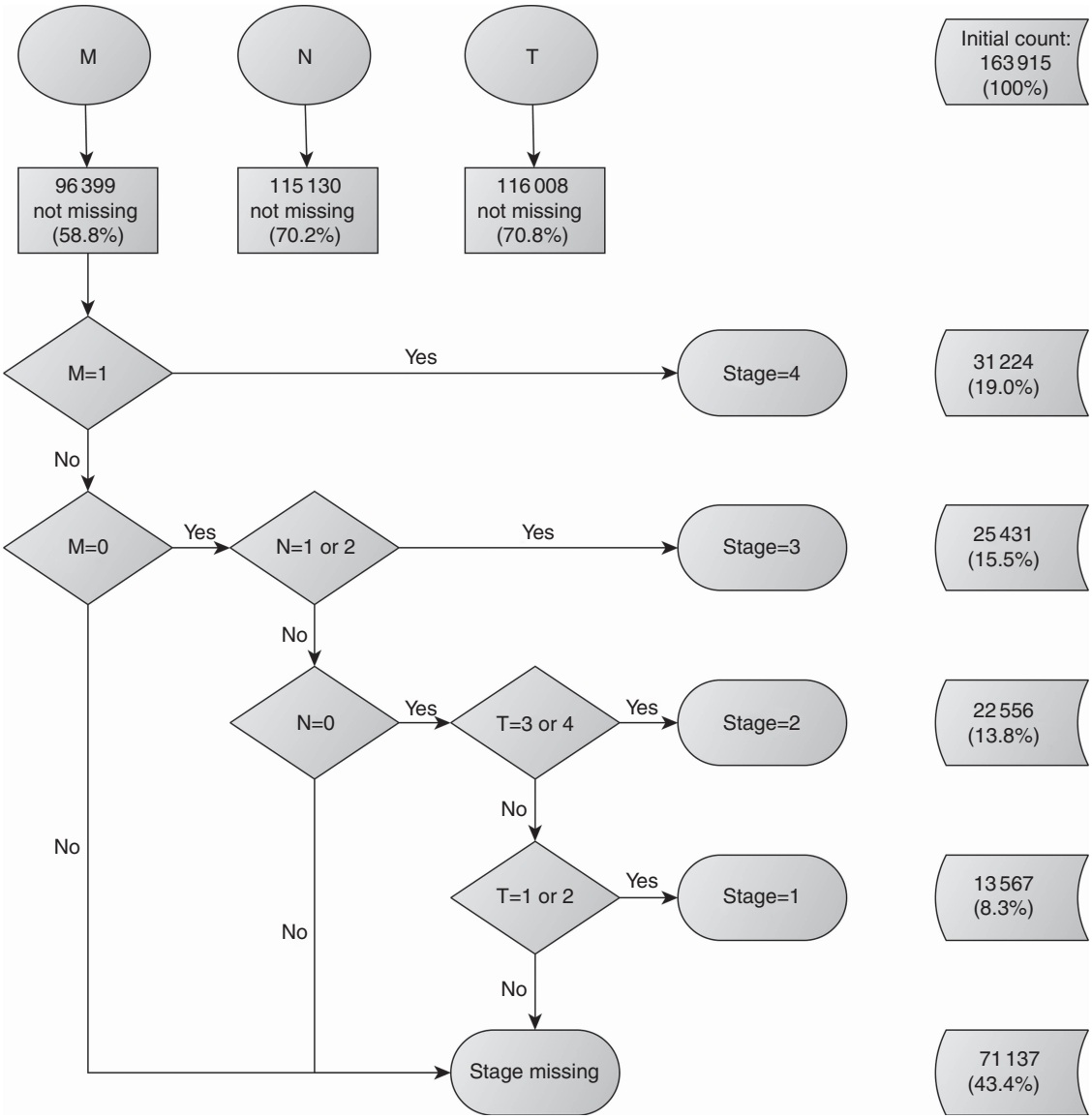

Figure 2. Deriving stage for colorectal cancer using the restrictive strategy, England, 2008–2012. Abbreviations: T = tumour; N = lymph nodes; M = distant metastases.

Clinical Commissioning Group Outcome Indicators in England. However, it is rarely reported how this information is collected and then integrated into stage categories. We aim to adopt a standard approach to derive stage from multiple sources using a series of hierarchical rules. We have adapted it to specific cancer sites to illustrate its generalisability and highlight some data and cancer-specific issues.

In our example, the use of TNM Fifth Edition for colorectal cancer is justified to facilitate comparability of temporal trends (Royal College of Pathologists, 2014). There is a perceived increase in interobserver variability when assigning lymph node status using the shape criterion of the Seventh TNM Edition, rather than the size criterion of the Fifth Edition (Doyle and Bateman, 2012; Royal College of Pathologists, 2014). In England, the RPC recognises that some multidisciplinary teams – from which Clinical Audit stage data may be collected – use the Seventh Edition of TNM to stage colorectal cancers and that it might be requested in particular cases, such as those enrolled in clinical trials. There was poor individual information of the TNM edition used for staging colorectal cancer in the data sets we used. Given that there were some codes that are valid in TNM Seventh but not in TNM Fifth, we remain uncertain that all cases were staged using the Fifth Edition of TNM. There is conflicting evidence on the effect of using different editions of the TNM classification on the final staging (Nagtegaal *et al*, 2011; Doyle and Bateman, 2012). Nonetheless, comparing categories using different TNM editions may lead to stage migration, complicating comparisons of stage-specific outcomes. In contrast, the lung cancer data sets, in particular the Clinical Audit data, consistently reported an individual indicator of the edition of TNM used.

Distribution of colorectal cancer stage and stage-specific survival differed between strategies to define summary stage. Survival was lower for all stage categories using the non-restrictive strategy. Imputing all cases with missing M and/or N to a value of zero, as in the non-restrictive strategy, relies on very strong assumptions and may lead to misclassification, biased stage-specific survival estimates, and overly narrow variances. The missing stage categories contain a mixture of various stages, even though on average their prognosis is poorer than observed stage. The real stage distribution within the missing categories is different between strategies, as is their survival. The survival discrepancy between strategies was negligible for lung

cancer. This is because there was more complete information on individual M component for lung (77.2%) than for colorectal cancer (58.8%). The restrictive approach is more conservative and keeps open, when necessary, the possibility of using specific approaches to deal with missing data, such as multiple imputation (White *et al*, 2011).

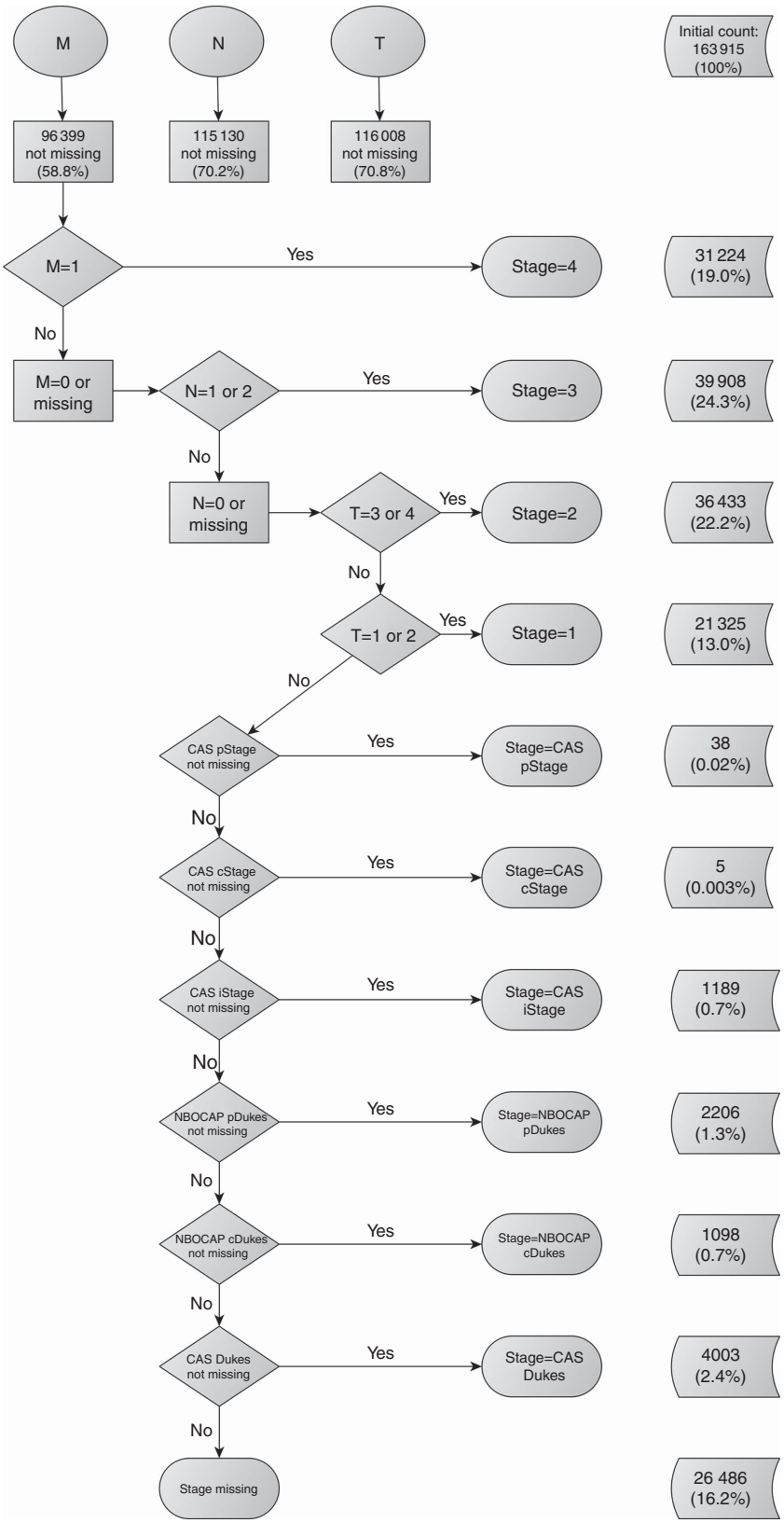

Figure 3. Deriving stage for colorectal cancer using the non-restrictive strategy, England, 2008–2012. Abbreviations: CAS = Cancer Analysis System; cDukes = clinical Dukes staging; cStage = clinical TNM stage; iStage = integrated TNM stage; M = distant metastases; N = lymph nodes; NBOCAP = National Bowel Cancer Project; pDukes = pathological Dukes staging; pStage = pathological TNM stage; T = tumour.

Table 2. Overall stage grouping by cancer, year of diagnosis, and staging strategy

	Year of diagnosis					
	2008 count (%*)	2009 count (%*)	2010 count (%*)	2011 count (%*)	2012 count (%*)	Total count (%*)
Colorectal cancer						
Non-restrictive strategy						
Missing stage	6996 (22.1)	6408 (19.8)	5114 (15.7)	4777 (14.3)	3191 (9.4)	26 486 (16.2)
Observed stage	24 630 (77.9)	25 939 (80.2)	27 518 (84.3)	28 708 (85.7)	30 634 (90.6)	137 429 (83.8)
I	3774 (15.3)	4159 (16.0)	4602 (16.7)	5043 (17.6)	5803 (18.9)	23 381 (17.0)
II	7631 (31.0)	7612 (29.3)	7764 (28.2)	7944 (27.7)	8195 (26.8)	39 146 (28.5)
III	7890 (32.0)	8212 (31.7)	8495 (30.9)	8508 (29.6)	8432 (27.5)	41 537 (30.2)
IV	5335 (21.7)	5956 (23.0)	6657 (24.2)	7213 (25.1)	8204 (26.8)	33 365 (24.3)
Restrictive strategy						
Missing stage	20 948 (66.2)	19 360 (59.9)	15 071 (46.2)	10 749 (32.1)	5009 (14.8)	71 137 (43.4)
Observed stage	10 678 (33.8)	12 987 (40.1)	17 561 (53.8)	22 736 (67.9)	28 816 (85.2)	92 778 (56.6)
I	1046 (9.8)	1434 (11.0)	2333 (13.3)	3637 (16.0)	5117 (17.8)	13 567 (14.6)
II	2175 (20.4)	2684 (20.7)	4169 (23.7)	5883 (25.9)	7645 (26.5)	22 556 (24.3)
III	2759 (25.8)	3455 (26.6)	4839 (27.6)	6408 (28.2)	7970 (27.7)	25 431 (27.4)
IV	4698 (44.0)	5414 (41.7)	6220 (35.4)	6808 (29.9)	8084 (28.1)	31 224 (33.7)
Total	31 626	32 347	32 632	33 485	33 825	163 915
Lung cancer						
Non-restrictive strategy						
Missing stage	11 498 (35.9)	8242 (25.0)	5622 (16.8)	3938 (11.4)	2441 (6.9)	31 741 (18.9)
Observed stage	20 509 (64.1)	24 765 (75.0)	27 846 (83.2)	30 463 (88.6)	32 834 (93.1)	136 417 (81.1)
I	2888 (14.1)	3560 (14.4)	3713 (13.3)	4092 (13.4)	4871 (14.8)	19 124 (14.0)
II	1303 (6.4)	1661 (6.7)	2221 (8.0)	2509 (8.2)	2764 (8.4)	10 458 (7.7)
III	6338 (30.9)	7204 (29.1)	7030 (25.2)	7211 (23.7)	7623 (23.2)	35 406 (26.0)
IV	9980 (48.7)	12 340 (49.8)	14 882 (53.4)	16 651 (54.7)	17 576 (53.5)	71 429 (52.4)
Restrictive strategy						
Missing stage	13 661 (42.7)	10 143 (30.7)	7321 (21.9)	5121 (14.9)	3046 (8.6)	39 292 (23.4)
Observed stage	18 346 (57.3)	22 864 (69.3)	26 147 (78.1)	29 280 (85.1)	32 229 (91.4)	128 866 (76.6)
I	2223 (12.1)	2952 (12.9)	3237 (12.4)	3781 (12.9)	4703 (14.6)	16 896 (13.1)
II	1060 (5.8)	1455 (6.4)	2030 (7.8)	2383 (8.1)	2696 (8.4)	9624 (7.5)
III	5357 (29.2)	6434 (28.1)	6531 (25.0)	6894 (23.5)	7437 (23.1)	32 653 (25.3)
IV	9706 (52.9)	12 023 (52.6)	14 349 (54.9)	16 222 (55.4)	17 393 (54.0)	69 693 (54.1)
Total	32 007	33 007	33 468	34 401	35 275	168 158

Note: %*: Percentages for stages I to IV represent the proportion of observed stage data, excluding observations with missing stage. Colorectal and lung cancer diagnoses in England, 2008–2012.

Table 3. Age-standardised estimates of 1- and 5-year net survival by cancer, stage, and staging strategy

Stage	Non-restrictive staging strategy NS (CI)	Restrictive staging strategy NS (CI)
Colorectal cancer		
One-year net survival		
I	0.979 (0.976, 0.981)	0.982 (0.978, 0.985)
II	0.936 (0.933, 0.939)	0.949 (0.945, 0.952)
III	0.880 (0.877, 0.883)	0.898 (0.893, 0.902)
IV	0.495 (0.489, 0.501)	0.510 (0.504, 0.515)
Missing	0.605 (0.599, 0.612)	0.777 (0.774, 0.780)
Five-year net survival		
I	0.952 (0.944, 0.960)	0.957 (0.945, 0.969)
II	0.849 (0.843, 0.855)	0.861 (0.852, 0.871)
III	0.638 (0.632, 0.645)	0.665 (0.655, 0.674)
IV	0.152 (0.146, 0.157)	0.158 (0.152, 0.164)
Missing	0.414 (0.406, 0.423)	0.619 (0.614, 0.624)
Lung cancer		
One-year net survival		
I	0.843 (0.837, 0.848)	0.852 (0.846, 0.858)
II	0.685 (0.675, 0.695)	0.693 (0.683, 0.704)
III	0.431 (0.425, 0.437)	0.439 (0.433, 0.445)
IV	0.182 (0.179, 0.185)	0.183 (0.180, 0.186)
Missing	0.256 (0.250, 0.262)	0.298 (0.293, 0.303)
Five-year net survival		
I	0.542 (0.531, 0.554)	0.541 (0.529, 0.554)
II	0.325 (0.310, 0.340)	0.325 (0.309, 0.341)
III	0.099 (0.094, 0.104)	0.100 (0.095, 0.105)
IV	0.025 (0.024, 0.027)	0.026 (0.024, 0.028)
Missing	0.093 (0.088, 0.098)	0.125 (0.120, 0.130)

Abbreviations: CI, confidence interval; NS, net survival. Diagnoses in England, 2008–2012.

A particular limitation arises when applying the algorithm for staging tumours receiving neoadjuvant therapy. Pathological stage components are collected after neoadjuvant treatment, thus downgrading may occur. This issue may be addressed by making specific rules to deal with such tumours. This was not possible in our data given that information on neoadjuvant therapy is missing in the vast majority of cases from all available sources. Differences in aggressiveness of diagnostic investigation may also affect the comparability of stage-specific outcomes (Allemani *et al*, 2013).

We acknowledge potential limitations and have discussed the data issues and our assumptions. We encountered several issues in relation to coding of stage variables, inconsistencies in use of editions of TNM classification, conflicting stage information for single tumours, and a high proportion of missing data. We believe these may arise in other settings and data sets and have tried to address them in a transparent way, useful for other users of cancer staging information.

We have applied the algorithm to two cancer sites in a single country but aim for the hierarchical rules to be adaptable for other cancer sites and data sources in different countries, as the issue of inconsistently defined and reported stage categories is widespread in the current population-based cancer research (Ciccolallo *et al*, 2005; Walters *et al*, 2013a). The outcome will depend heavily on the quality of the specific data source but the general approach of prioritising information of highest quality, reporting sources of individual TNM variables, and reporting of assumptions when dealing with missing or inconsistent data is relevant to any cancer research using stage information. Descriptive results such as reported in Tables 1 and 2 are helpful

in understanding the origins of summary stage and the reasons for shifts in stage distributions.

Validity of the information contained in cancer records remains a general issue. We believe it should be mandatory to have a relevant clinician at the health-care provider level ensuring that data collected are complete and truly reflect the information clinical decisions are based on. For each cancer case, it should be clear what classification was used to assign stage variables. As skilled clinicians are needed to collect and use stage information to make adequate medical decisions, there is also the need of people with standardised skills for recording and compiling of clinical information from medical records. The National Health System should make an effort to train and support such a workforce. Complete and accurate stage information is essential to assess cancer control policy and to understand inequalities in cancer management and cancer survival, at both national and international levels. We encourage cancer registries and health-care providers to clearly document the process for deriving stage grouping and reporting any data quality checks to validate this information. This information should be readily available for researchers.

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CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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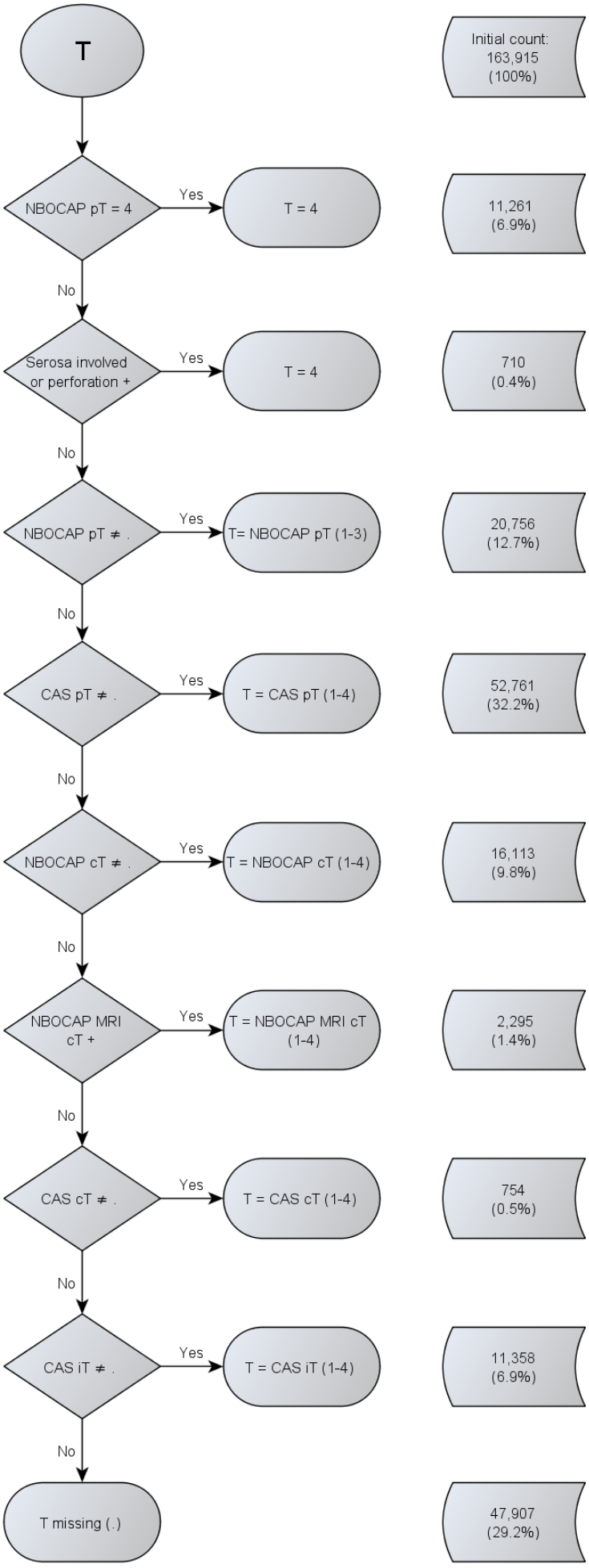
Supplementary Information accompanies this paper on British Journal of Cancer website (http://www.nature.com/bjc)

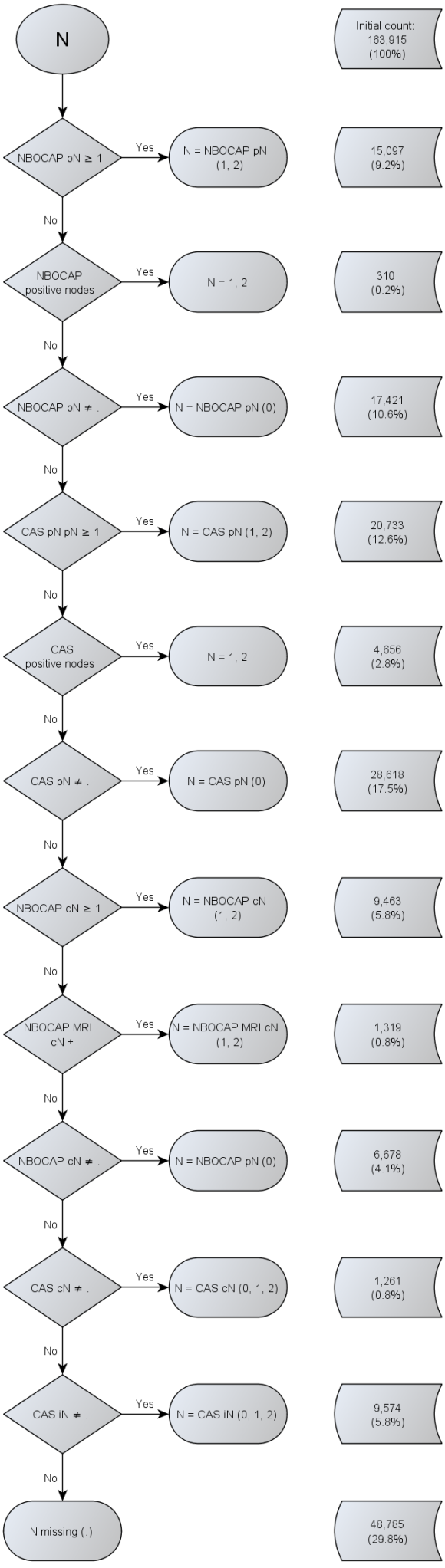
Supplementary Web-Appendix

Contents

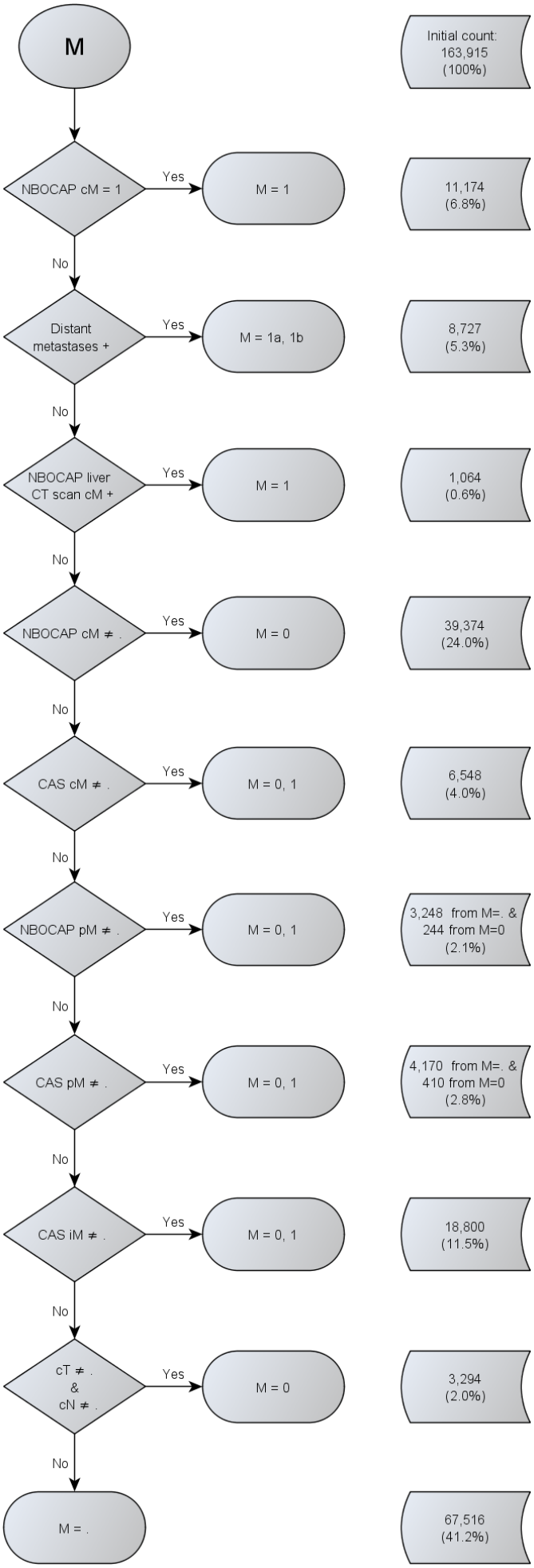
Web-Appendix Figure 1. Deriving T component of TNM stage for colorectal cancer, England, 2008-2012.



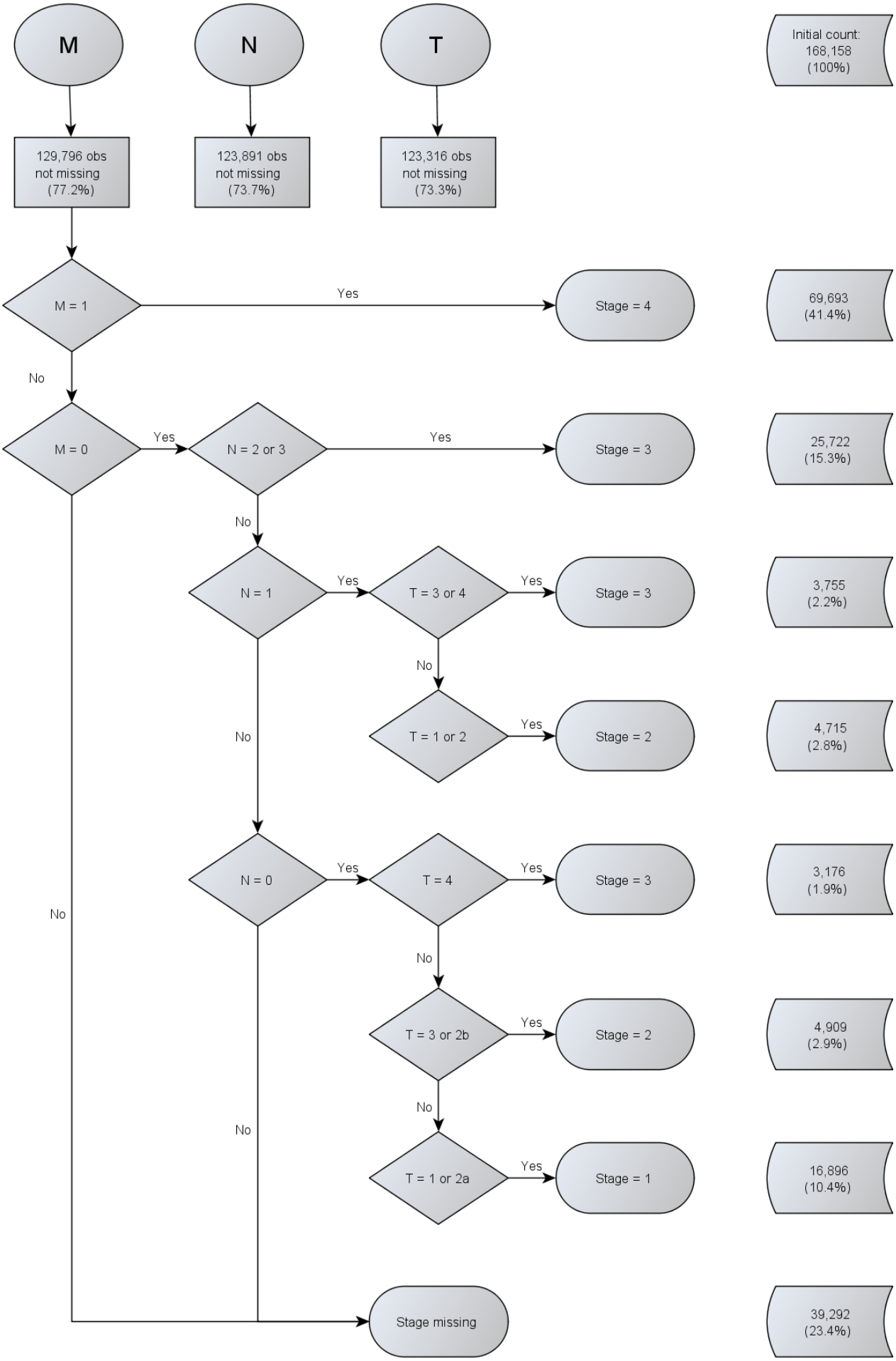
Web-Appendix Figure 2. Deriving N component of TNM stage for colorectal cancer, England, 2008-2012.



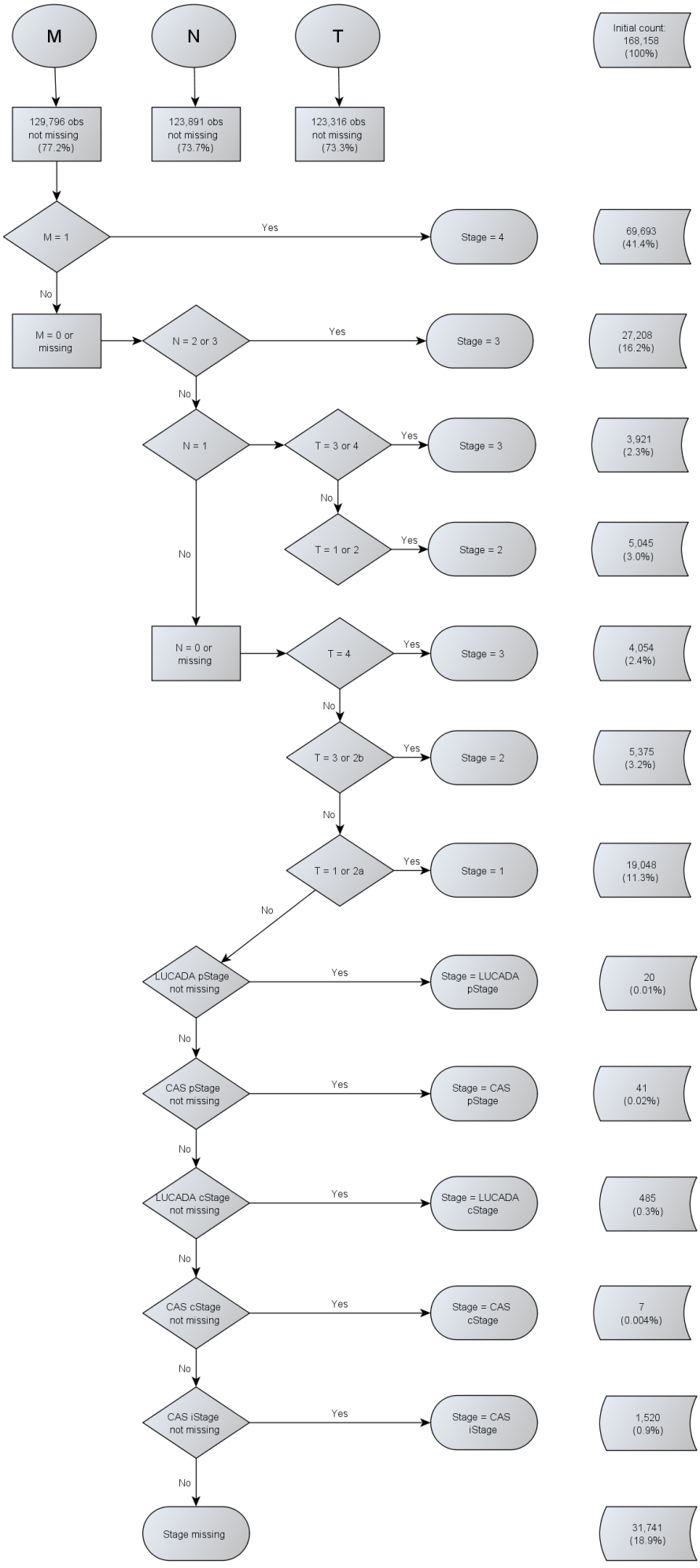
Web-Appendix Figure 3. Deriving M component of TNM stage for colorectal cancer, England, 2008-2012.



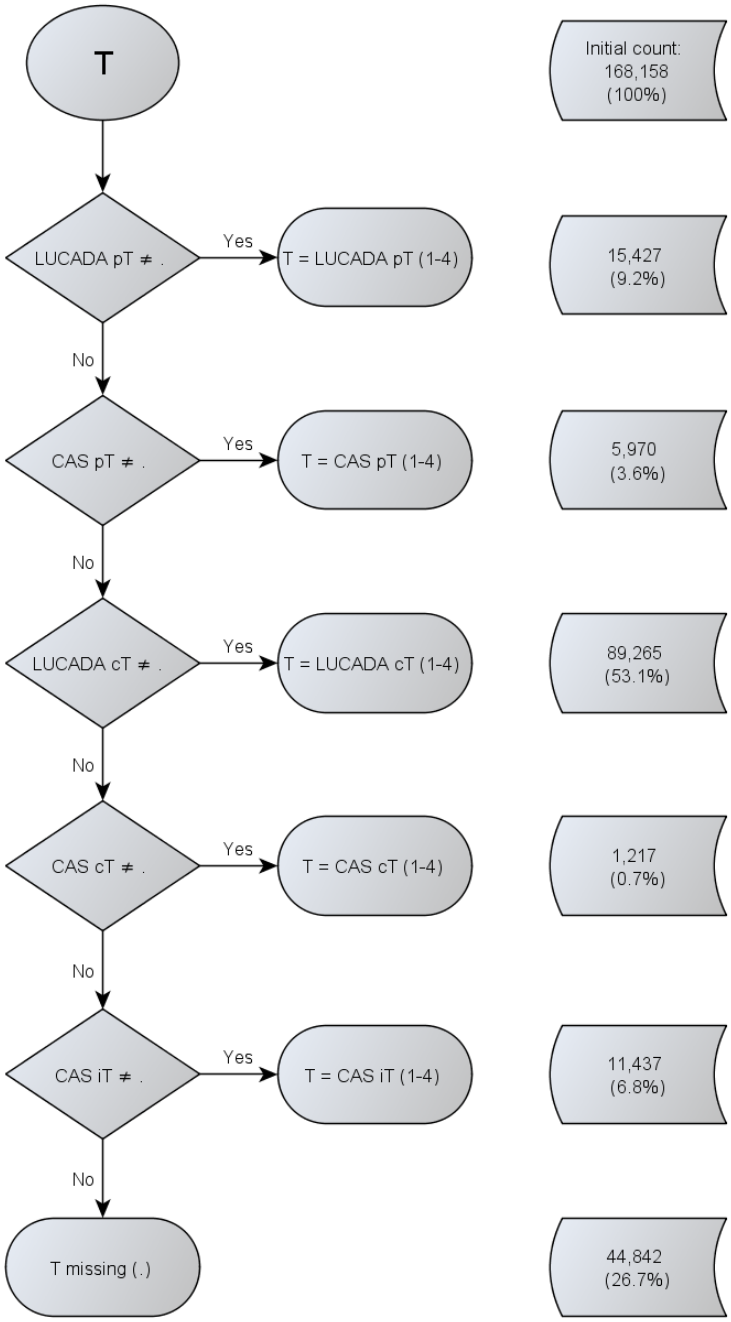
Web-Appendix Figure 4. Deriving TNM stage for lung cancer using the restrictive strategy, England, 2008-2012.



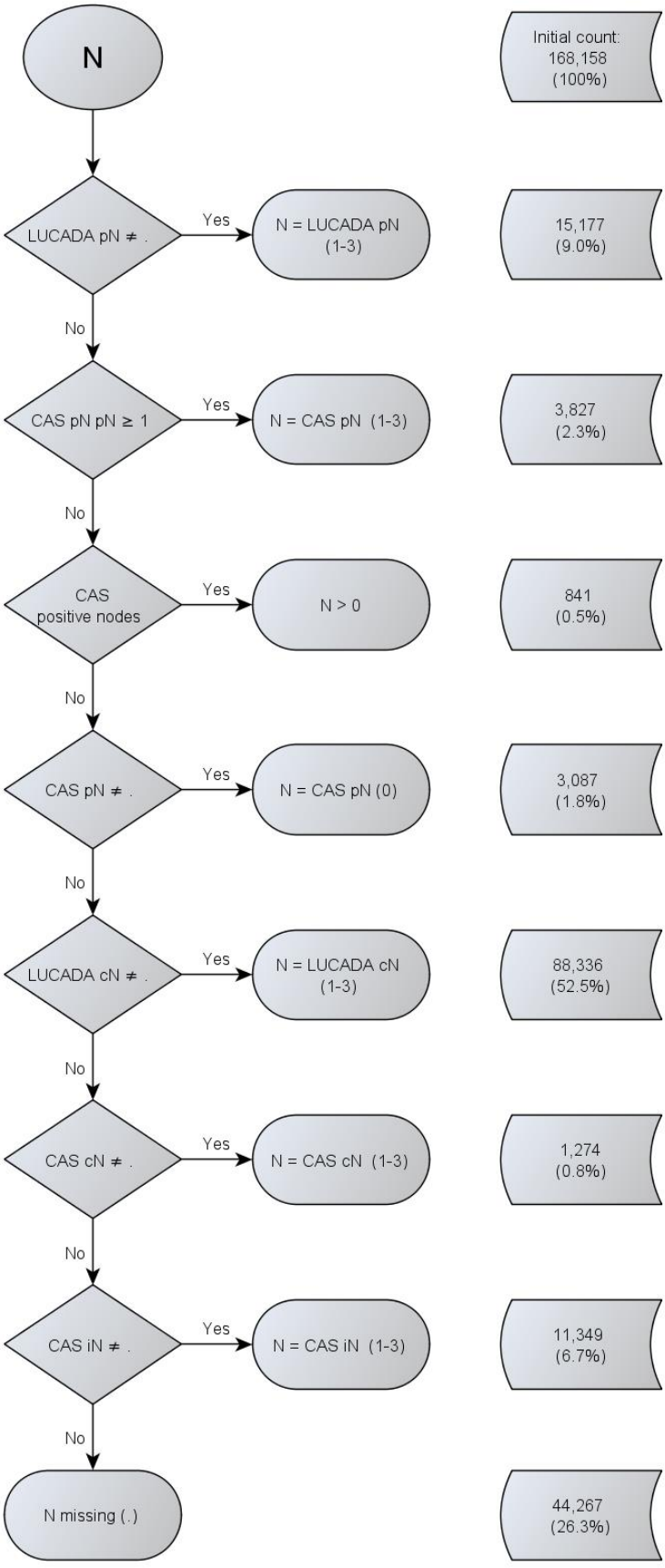
Web-Appendix Figure 5. Deriving TNM stage for lung cancer using the non-restrictive strategy, England, 2008-2012.



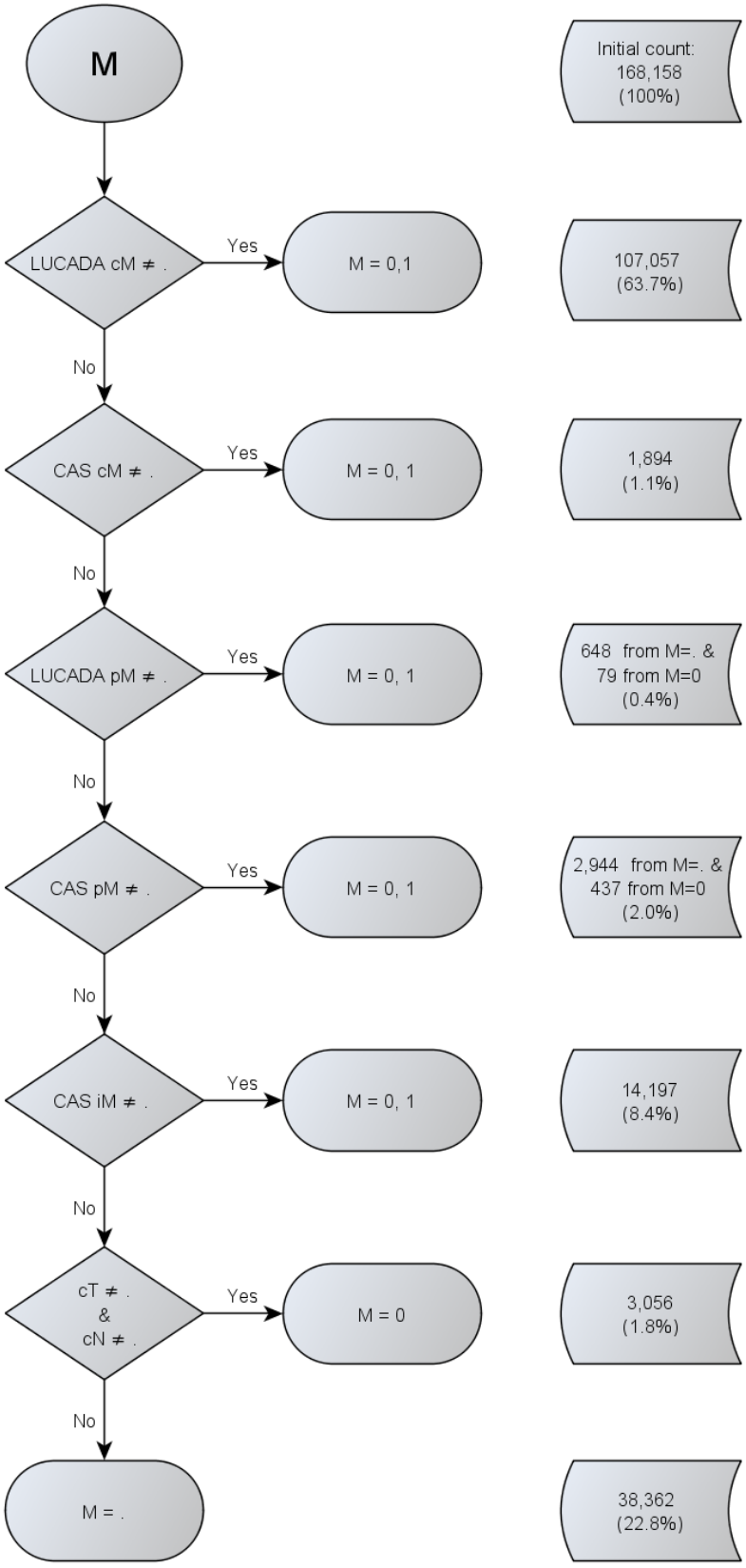
Web-Appendix Figure 6. Deriving T component of TNM stage for lung cancer, England, 2008-2012.



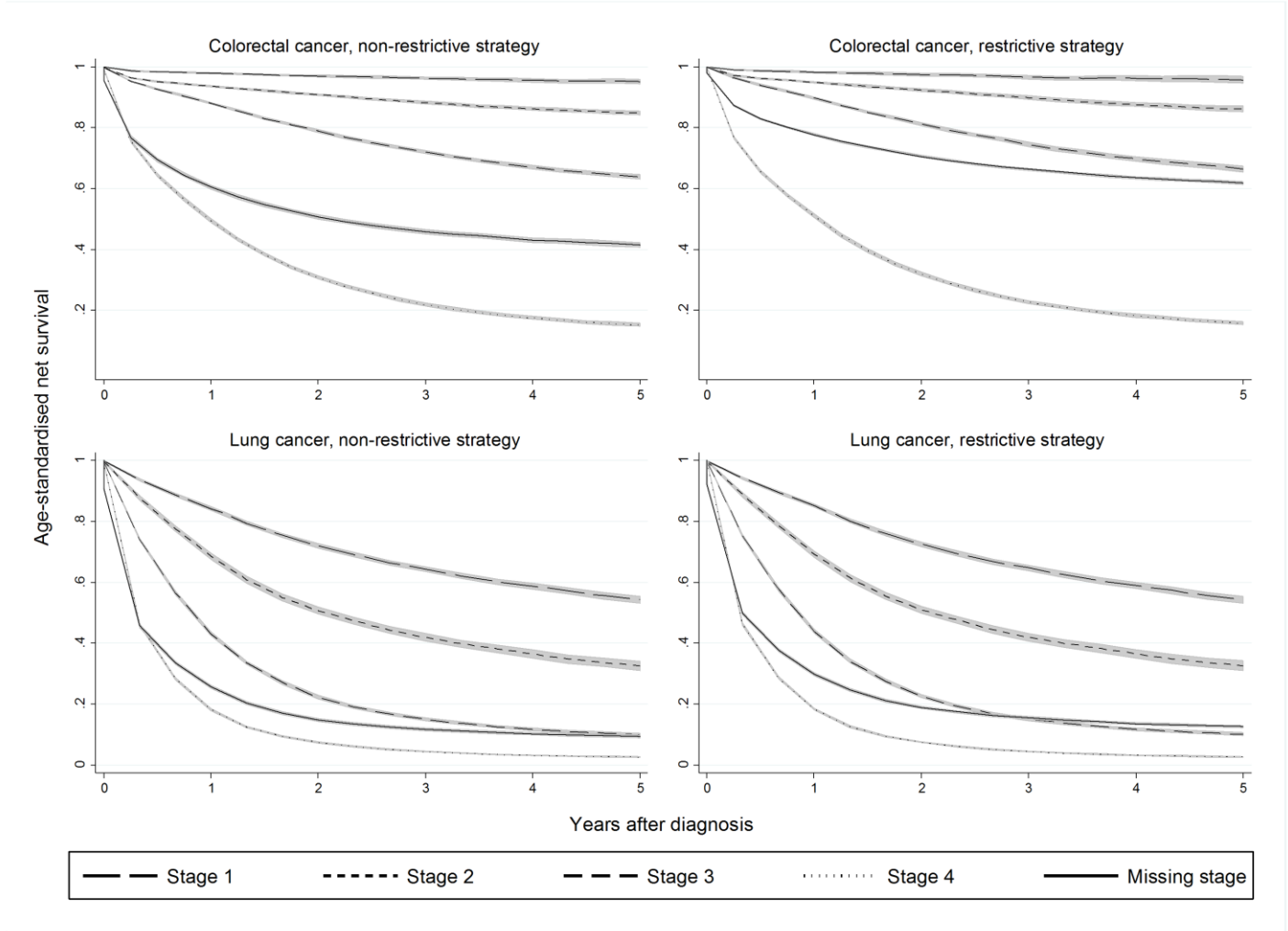
Web-Appendix Figure 7. Deriving N component of TNM stage for lung cancer, England, 2008-2012.



Web-Appendix Figure 8. Deriving M component of TNM stage for lung cancer, England, 2008-2012.



Web-Appendix Figure 9. Age standardised net survival by TNM stage, England 2008-2012



Notes:

T: Tumour component of TNM stage
NBOCAP: National Bowel Cancer Project
pT: Pathological T
%: Percent
+: Positive
≠: Not equal to
.: Missing
CAS: Cancer Analysis System
cT: Clinical T
MRI: Magnetic Resonance Imaging
iT: Integrated T
N: Lymph nodes component of TNM stage
pN: Pathological N
≥: Greater than or equal to
cN: Clinical N
iN: Integrated N
M: Distant Metastases component of TNM stage
cM: Clinical M
CT: Computerised Tomography scan
pM: Pathological M
iM: Integrated M
pStage: Pathological TNM Stage
cStage: Clinical TNM Stage
iStage: Integrated TNM Stage
LUCADA: Lung Cancer Audit Database

2.3.2 Additional information on stage

With recent improvements in the availability of stage information in population-based data sources, the first research paper of this thesis focuses on setting and updating general hierarchical rules to derive stage information in a transparent and reproducible manner for research purposes. In summary, the stage algorithm presented in the BJC paper (Section 2.3.1) has two dimensions. The first one provides some general rules to maximise the staging information available from multiple data sources, and potentially multiple records per patient. The second dimension of the stage algorithm focuses on deriving a single TNM summary stage.

In the case of CRC diagnoses in England, during the study period (2010-2012), stage information was available from the NBOCA dataset and from the national cancer registry (CAS, Cancer Analysis System). NBOCA allowed multiple records per patient, each of them corresponding to an individual "treatment record". There might be conflicting information on individual pathological T, N, and M components in different treatment records of the same patient, as these could have been measured at different points during the treatment journey, for instance, before and after radiotherapy. To avoid assigning TNM values associated with restaging and/or disease progression, the first rule of the stage algorithm is to focus on information from treatment records with procedures dated within ±30 days from the cancer diagnosis date. In the case of multiple treatment records within the ±30-day window, priority is given to the stage information in the record closest to the date of diagnosis. In the case of multiple treatment records with the same treatment date, priority is given to the record with the lower (valid) value of pathological T (or N, when the value of T is the same between records with the same date, and so on), following a general rule specified in the 7th Edition of the TNM Classification.[43] This series of rules ensures that the same order of records is used consistently, and minimises the potential effect of re-staging of tumours.

To derive a single TNM summary stage, the stage algorithm gives priority to pathological over clinical information, except for the M component, where clinical evidence of distant metastases, cM1, supersedes the absence of pathological evidence of metastases, pM0. The paper describes two strategies to derive TNM summary stage, namely the 'restrictive' and 'non-restrictive strategy'. In essence, the difference between the two strategies is the handling of missing information on the M component of TNM stage. The 'restrictive' strategy makes no assumption of missing M information, while the 'non-restrictive' strategy assumes that missing information on M indicates absence of metastases, or M0. The restrictive

strategy therefore results in a higher proportion of missing information than with the non-restrictive strategy. The choice of strategy may influence stage-specific survival, as M status is a strong determinant of cancer outcomes. In the example presented in the BJC publication,[126] stage-specific 5-year survival is slightly poorer for colorectal and lung cancer patients in each of the (I-IV) stage categories using the non-restrictive strategy than with the restrictive strategy. For fair comparisons, the same strategy for deriving stage needs to be used across populations.

The choice of strategy to derive summary TNM stage depends on the research question, choice of analysis, and on the procedure to handle missing information. Different to previous editions, the 7th edition of TNM does not include the Mx category indicating undetermined M status.[43] This is to avoid inconsistencies in the use and interpretation of the Mx category, and the "unintended consequence of preventing stage grouping by cancer registries".[127] Instead, the TNM 7th edition recommends using the M0 category when there is no evidence of metastatic disease. This results in no missing information on M, because patients are considered M0 unless proven otherwise (by clinical examination for clinical M, and/or pathological confirmation for pathological M).[127] The 'non-restrictive' strategy of the stage algorithm effectively introduces this TNM 7th edition rule, regardless of the actual edition used at the cancer registry: it assigns M0 to patients without pathological (pM1) nor clinical evidence of metastases (cM1). This is important, especially for international comparisons of cancer outcomes, because registries may adhere to different editions of the TNM Classification. For instance, following recommendations from the Royal College of Pathologists, English registries follow the 5th edition of TNM, while other registries, such as those in Norway, adhere to the 7th edition of TNM. In order to harmonise the definition of stage, and improve the comparability of stage-specific results, I used the 'non-restrictive' strategy to derive stage in all datasets included in the international comparison of CRC treatment and survival presented in Section 3. Results are shown for the missing stage categories of each country in the web-appendix of the Lancet Oncology publication.[128] Cautious interpretation is needed when comparing cancer outcomes in the stage category because the reasons for having stage missing (or the 'missingness mechanisms') likely differ between the countries, and so the characteristics of patients in this category.

For the England-specific analyses presented in Section 4, I used the 'restrictive' strategy to derive stage, thus making no assumptions about missing M information. This was to avoid using two different strategies to deal with missing data, as I used single stochastic imputation with chained equations to handle missing information on stage (and on the diagnostic route).

This strategy assumes that the missingness mechanism is missing at random, meaning that there may be systematic differences between the observed and the missing values, but that these differences may be explained by other observed variables.[129] This is a sensible assumption when focusing on the English data. The other variables included in the multiple imputation models for stage included treatment status, completeness of diagnostic and staging investigations, the Nelson-Aalen indicator (of the cumulative hazard rate of death), age, sex and deprivation quintile.

It is worth recognising that the completeness and quality of stage information in the English registries has substantially improved over time.[130] With increasing efforts to improve the completeness of stage in cancer registration, the case-mix and characteristics of patients who remain in the missing stage category likely change, as well as their survival. Even with best efforts to collect and register, a (hopefully small) proportion of patients will remain unstaged: because they were too ill to be investigated and/or died soon after diagnosis. These patients will have poorer prognosis than those who are missing stage because of 'administrative' reasons (patients who were staged in the clinical setting, but whose stage information is not recorded in cancer registration because of administrative issues). As 'administrative' reasons of missing stage information become less prevalent due to efforts to improve registration, the comparability of the missing stage category between countries with a small proportion of patients with missing stage likely improves.

2.3.3 Diagnostic and staging investigations

Another algorithm was developed for this project to obtain information on *staging investigations* from HES and NBOCA records. The HES dataset contains information on in-patient and out-patient diagnoses and medical procedures performed within the National Health System. A single patient may have multiple observations, one for each hospital episode, and multiple diagnoses and procedures per episode. The OPCS Classification of Interventions and Procedures 4.7, an NHS Fundamental Information Standard for the classification of interventions and procedures performed in NHS hospitals in England is used to classify medical procedures.

OPCS-4.7 is used to code the relevant procedures in HES records, using NHS guidance on data collection for diagnostic waiting times, and covering all imaging and endoscopic tests recommended for investigating colorectal tumours by current English clinical guidelines.[131] Individual hospital episodes with any of the OPCS-4.7 codes for each of the staging procedures performed in the three months prior to and/or after the cancer diagnosis were

first flagged. In cases where there were multiple OPCS-4.7 codes for the same procedure, priority was given to codes that were considered more specific than others, and to those performed closest to the date of the cancer diagnosis. This information summarised into several variables each staging procedure recommended by clinical guidelines (chest tomography, abdominal tomography, pelvic tomography, pelvic magnetic resonance imaging, colonoscopy, and CT colonography).[41] Information on staging investigations derived from the HES data was then complemented with information from NBOCA.

2.3.4 Potentially curative surgery

For patients diagnosed in England, information on *surgical treatment procedure* and *date of surgery* was derived from HES and NBOCA records, following an algorithm similar to the one for deriving information on staging investigation. OPCS-4.7 codes for cancer-directed surgeries that are generally used with potential curative intent were identified using the OPCS-4.7 full list of codes.[132] Codes for cancer-directed diagnostic, palliative and/or non-resectional symptom-alleviating procedures, such as colonoscopy without resection, colostomy, and colonic stents were excluded. The final list of valid OPCS codes included all those listed in the Lancet Oncology Commission on Global Cancer Surgery 2015 publication and classed as surgical procedures needed to treat colorectal cancer.[133] Additionally, I included some less specific codes for certain procedures (such as H10.9, Unspecified excision of sigmoid colon). Relevant procedures performed within one month before and nine months after the colorectal diagnosis were identified. This time window allows the identification of relevant surgical procedures performed before the official date of diagnosis, (which could be, for instance, the date of the pathology report, which would be dated after the surgical procedure). Additionally, the time window allows the identification of delayed surgical procedures following neoadjuvant chemo-radiotherapy therapy, which may have been in use in some hospitals during the study period.[134] The information on surgical procedures was then summarised into several variables by extent of resection and/or topography (e.g.: total proctocolectomy, total colectomy, anterior resection, rectosigmoidectomy, hemicolectomy, local excision, etc.). Of these categories, the most extensive procedure was chosen. Local excisions were considered radical for stage I tumours only. Information on surgical treatment was extracted from NBOCA when no information was available in HES records.

For patients diagnosed in Denmark, Norway and Sweden, information on surgical procedures and the date they were performed was extracted from National Colorectal Cancer Registries following the same criteria above with regards to time from diagnosis, and valid procedures.

2.3.5 Chemotherapy and Radiotherapy

Information on chemotherapy and radiotherapy status were derived from NBOCAP and CWT records when available for patients diagnosed in England.

For patients diagnosed in Denmark, Norway and Sweden, information on chemotherapy, radiotherapy and dates was extracted from the National Colorectal Cancer Registries following the same criteria above with regards to time from diagnosis, and valid procedures.

2.4 Overview of statistical methods

2.4.1 Causal assumptions and direct acyclic graphs

To study age inequalities in cancer management, I have made assumptions about the relationships between the different factors explored as determinants of the outcome(s):

- A person's age at presentation, the main exposure of all analyses included in this thesis, affects the likelihood of having comorbidity, of being diagnosed following an emergency presentation, as well as the likelihood of having a complete diagnostic and staging investigation, of having resectional surgery, and ultimately affects that person's chances of surviving.
- A person's comorbidity status, affects the likelihood of being diagnosed through an emergency presentation, having a complete investigation, receiving treatment, and surviving.
- A person's diagnostic route (emergency or not) affects their chances of being fully investigated, being treated for their cancer, and surviving.
- Receiving resectional surgery determines a person's survival.
- All the relationships above are confounded by patients' socioeconomic status and sex.
- Additionally, the relationship between comorbidity, diagnostic route, completeness of the investigation, treatment status, and survival may be confounded by system factors, such as the quality of care provided in hospitals.
- The effect of age on different factors may reflect other mechanisms, such as attitudinal factors

These assumptions are graphically summarised in a directed acyclic graph in Figure 2.1

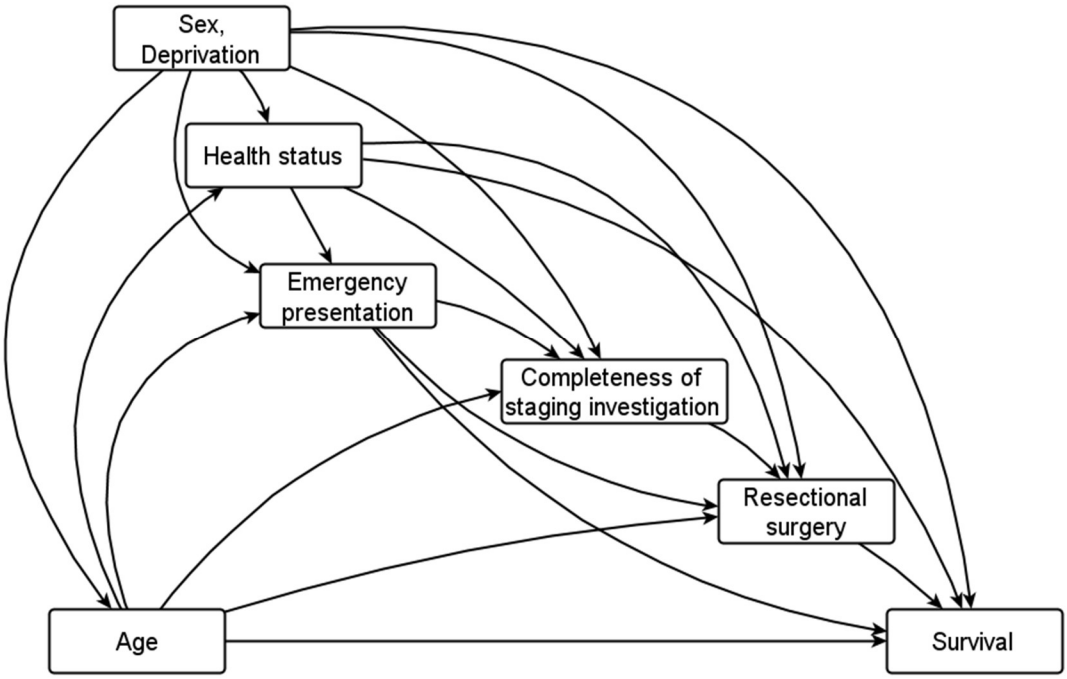


Figure 2.1: Assumed causal relationship between age and colorectal cancer outcomes
Age affects survival directly and by several mechanisms (mediators), including health status, the diagnostic route (emergency presentation or not), completeness of the staging investigation and by resectional surgery status. Age is assumed to affect the other health outcomes directly, too (health status, diagnostic route, investigation and surgery). Variables sex and deprivation are assumed to potentially confound all the relationships.

Directed acyclic graphs (DAGs) are a useful tool to illustrate the assumed causal relationships between the variables considered in the analysis. A DAG is a graphical model that uses unidirectional arrows to represent the prior knowledge that we have regarding the relationships between the variables before the analysis.[135] DAGs have theoretical and mathematical underpinnings, but without parametric assumptions.[136] Although DAGs do not make assumptions about the distribution of the variables or shapes of the associations, they contain assumptions about causal relations. For instance, the absence of an arrow between two variables represents the assumption of no direct link between those two variables.[136] The presence of an arrow between two variables is however not deterministic; it implies that we are not making an assumption of independence between the variables.

DAGs facilitate the identification of different types of variables, which is informative for the analysis plan and variable adjustment.[137] For instance in figure 2.1, deprivation is a confounder of the relationship between age at presentation (main exposure) and the ultimate endpoint (or outcome) survival; or deprivation affects age at presentation and survival, and is not in the causal pathway between those two variables. The variable 'health status' is a mediator of the relationship between age and survival because it is associated with both, and lies in the causal pathway between them.

2.4.2 Net survival

For the first objective, the international comparison of stage-specific net survival, I estimated and compared net survival between Denmark, England, Norway and Sweden up to 3 years after diagnosis, using the complete approach.[138] Net survival represents survival that would be seen if cancer were the only potential cause of death. It therefore excludes the force of mortality due to other causes. Net survival can be estimated in the relative survival setting and the cause-specific setting. The cause-specific setting requires information on the underlying causes of death, so non-cancer causes are censored in the analysis.[139] Reliable information on causes of death is not generally available in cancer registry records, therefore the relative survival setting is preferred. In the relative survival setting, information on non-cancer mortality hazard is provided by life tables for the general population (by country, sex, age in complete years, calendar year, and deprivation information if available). For the survival analyses presented in this thesis, I used life tables prepared by the Cancer Survival Group, London School of Hygiene and Tropical Medicine.[140]

In both settings, survival estimation can be biased by informative censoring. Informative censoring occurs when patients are censored (they stop being at risk of experiencing the outcome) in a non-random manner, and their mortality hazard is different from that of patients who remain at risk. Informative censoring is likely because older cancer patients are more likely to die due to non-cancer causes in comparison to younger patients, thus to be censored, but they are also more likely to die of cancer than younger patients (who tend to remain in the risk set).[139] The Pohar-Perme estimator of net survival takes into account this informative censoring, thus providing unbiased estimation of net survival.[141]

Net survival, is useful for international comparisons of survival, because it effectively accounts for differences in the background mortality between populations. To obtain age-standardised stage-specific net survival by country, I used a multivariate modelling approach to estimate the excess mortality hazard due to colorectal cancer and predicted survival by country, disease stage and age group (defined by the International Cancer Survival Standard population for age-standardisation)[142] using the strcs Stata command.[143] A weighted average of these age-group specific estimates provided age-standardised net survival estimates to account for differences in the age distribution of patients between the countries. Additionally, I used a non-parametric approach (Pohar-Perme)[141] to estimate net survival for all stages combined in the international comparison, and stage-specific survival in England to validate the algorithm to derive stage, using the stns Stata command.[144]

2.4.3 Regression models and predictions

For the first part of the second objective, I estimated the probability of receiving radical surgery using multivariate logistic regression models. Models were developed for each disease stage and initially included country, age, and sex. I kept the main effects of these exposure variables and important interactions between country and age a priori, and added other interactions on the basis of the likelihood ratio test.

To quantify the proportion of under-treatment that could be avoided if patients in England were managed as in the best-performing country (second part of objective 2), I used a standardisation technique, applying the coefficient of the best performing country (from the logistic regression models described above) to the other countries, to assess the hypothetical change in the probability of receiving radical surgery if patients had been treated as in the best performing country, given their observed characteristics.

For the third objective, I explored the role of comorbidity in explaining the probability of receiving radical surgery using similar multivariate logistic regression models to those used for the second objectives, additionally including a comorbidity variable, and/or stratifying by comorbidity level (defined by categories of the Charlson Comorbidity Index). Additionally, I estimated the rate of decrease in the probability of receiving radical surgery by age for each stage and country included in this sub-analysis, by comparing the slopes of the country-specific probability functions (derivatives).

2.4.4 Mediation analysis

For objectives 4 and 5, I used causal mediation analysis to examine the mechanisms by which age determines the likelihood of receiving an incomplete diagnostic and staging investigation and treatment for colon and rectal cancer in England. The general objective of mediation analysis is to split the total effect of an exposure on an outcome into mediated (indirect) and not mediated (direct) effects.[145] For example, in the analysis for objective 4, age at presentation (the main exposure) may influence the completeness of staging investigations (outcome) directly, and/or indirectly through comorbidity (mediator): comorbidity is determined by age, and the completeness of staging investigations is determined by the comorbidity level.

Traditional approaches to carry out mediation analysis are prone to biased results,[145-147] but recent methodologic advances have shown how to examine the decomposition of total effect into indirect and direct effects, even within complex scenarios like this.[146]

The causal mediation setting relies on the counterfactual framework in which several hypothetical scenarios of interest are compared. In these 'alternative worlds', researchers 'intervene' on (or change the level of) the exposure and mediator(s) in the whole study population and contrast all the potential outcomes with of different levels of exposure and mediator(s), conditional on the confounders.

A simplified example to describe the process for identifying direct and indirect effects for objective 5 (examining the effect of age on receiving optimal CRC surgical, and explore how this relationship is mediated by comorbidity and the diagnostic route in England): Let *age* be the main exposure variable (with levels old/young), *comorbidity* (with levels Yes/No) be the mediator, and *treatment* (with levels Yes/No) be the outcome. For obtaining direct causal effects, we compare the outcome of interest (*treatment*) between two scenarios: one in which everyone is *old* and another in which everyone is *young*, and in both, *comorbidity* is assumed to be distributed as if everyone was young. Comparably, the indirect effects are estimated comparing another set of scenarios in which everyone is *old*, but their *comorbidity* distribution is either as observed among the *old* or as if observed among the *young*. In other words, we ask two legitimate questions:

1. Which *treatment* would be given, in comparison to the *young*, if the *old* had the *comorbidity* of the *young*? – direct effect of age
2. Which *treatment* would be given, in comparison to the *old* with no *comorbidity*, to the *old* with *comorbidity*? – effect of age mediated by comorbidity

In the analyses, I consider whether the health status of patients (given by their comorbidity level and underlying disease stage), and/or their diagnostic route are mechanisms that explain age differences in the completeness of diagnostic investigation (objective 4), and in receiving radical surgery for colorectal cancer (objective 5) using a parametric g-computation procedure, as described by Daniel and colleagues.[148]

I used Stata software (releases 14 or 15) for all statistical analyses.[149,150]

The next two Chapters (3 and 4) cover the main quantitative analyses applying the methods described in this Chapter to research questions addressing the specific objectives of this project.

Chapter 3: International comparison of survival and stage-specific surgical treatment of colorectal cancer patients

3.1 Introduction

Population-based cancer survival is an important measure of the effectiveness of healthcare systems in managing cancer.[151] International comparisons of population-based cancer survival have historically shown that patients in England (and the UK) have poorer survival than patients in other European[2,152,153] and other high-income countries with universal access to healthcare.[3,154] This survival deficit has driven cancer policy in England since the publication of the first National Cancer Plan in 2000, which aimed to improve cancer survival in England to match that of the best-performing countries.[4]

Proposed causes of the survival differences include advanced stage at diagnosis, delays between onset of symptoms and diagnosis, and treatment.[155] Reported deficits in stage-specific colorectal cancer indicate that suboptimal cancer management in England may also have a role in explaining poorer cancer survival in England.[5] Evidence also suggests that the international differences in colorectal cancer survival may be wider in the older age group.[5]

Previous work from the International Cancer Benchmarking Partnership (ICBP) found poorer stage distribution of colorectal tumours in Denmark, and poorer stage-specific survival in England, suggesting deficits in early diagnosis in Denmark and in treatment in England.[5] Recent reports have shown that cancer survival in Denmark is improving and is now closer to that seen in Norway and Sweden; whereas cancer survival in England, though improved, still lags behind.[1,156] In both countries, cancer policy has focused on early diagnosis initiatives. Denmark and England introduced expedited referral routes in the early 2000s to avoid delay in diagnosis and improve cancer outcomes. In England, cancer waiting time targets were introduced, for instance, from primary care referral to treatment receipt. Waiting time targets, however, do not consider the type of treatment received. The waiting time target between referral and treatment receipt is equally met when undergoing resectional surgery, or receiving pain control. Although important, timing to (diagnosis and) treatment is not the only determinant of cancer outcomes.

I hypothesise that differential management of older cancer patients may be another contributing factor to the 'survival gap' between England and better performing countries. To examine this, first, I present a recent comparison of colorectal cancer survival in England, Denmark, Norway and Sweden for all patients and by disease stage, using data from national,

population-based colorectal cancer registries in each of the countries. Then, I compare the proportion (and probability) of patients receiving potentially curative treatment, specifically surgery to remove the primary tumour, by age and stage. Finally, to account for differences in comorbidity and its associated operative risk, I present a sub-analysis exploring the role of comorbidity in determining treatment receipt in a comparison between Denmark and England.

3.2 Surgical treatment and survival from colorectal cancer in Denmark, England, Norway, and Sweden

This section addresses objectives 1 and 2 of this research degree project: To estimate and compare stage-specific net survival between Denmark, England, Norway and Sweden; and to determine and compare the effect of age on receiving surgical treatment for colorectal cancer in Denmark, Norway and Sweden, quantifying the proportion of under-treatment that could be avoided if patients in England were managed as in the best-performing country.

The research for this section has been reported in the paper entitled "Surgical treatment and survival from colorectal cancer in Denmark, England, Norway, and Sweden: a population-based study", which was published in the peer-review journal The Lancet Oncology in December, 2018.[128] The findings were also presented at the Union for International Cancer Control World Cancer Congress, Kuala Lumpur, 2018. Earlier findings were presented at the European Society for Medical Oncology Congress, Madrid, 2017.

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RESEARCH PAPER COVER SHEET

Please note that a cover sheet must be completed for each research paper included within a thesis.

SECTION A – Student Details

Student ID Number	376763	**Title**	Ms
First Name(s)	Sara		
Surname/Family Name	Benitez Majano		
Thesis Title	Exploring age inequalities in the management and survival of colorectal cancer patients		
Primary Supervisor	Dr Sarah Walters		

If the Research Paper has previously been published please complete Section B, if not please move to Section C.

SECTION B – Paper already published

Where was the work published?	The Lancet Oncology		
When was the work published?	December, 2018		
If the work was published prior to registration for your research degree, give a brief rationale for its inclusion			
Have you retained the copyright for the work?*	**Yes**	Was the work subject to academic peer review?	**Yes**

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Stage of publication	Choose an item.

SECTION D – Multi-authored work

For multi-authored work, give full details of your role in the research included in the paper and in the preparation of the paper. (Attach a further sheet if necessary)	I was the lead author of this paper. I co-planned the study with my supervisors, carried out the literature review, data preparation, analyses, and prepared the draft of the paper. Co-authors provided feedback and input on the data preparation, analyses, interpretation and on the paper drafts.

SECTION E

Student Signature	
Date	25th February 2019

Supervisor Signature	
Date	

Surgical treatment and survival from colorectal cancer in Denmark, England, Norway, and Sweden: a population-based study

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See Comment page 6

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Summary

Background Survival from colorectal cancer has been shown to be lower in Denmark and England than in comparable high-income countries. We used data from national colorectal cancer registries to assess whether differences in the proportion of patients receiving resectional surgery could contribute to international differences in colorectal cancer survival.

Methods In this population-based study, we collected data from all patients aged 18–99 years diagnosed with primary, invasive, colorectal adenocarcinoma from Jan 1, 2010, to Dec 31, 2012, in Denmark, England, Norway, and Sweden, from national colorectal cancer registries. We estimated age-standardised net survival using multivariable modelling, and we compared the proportion of patients receiving resectional surgery by stage and age. We used logistic regression to predict the resectional surgery status patients would have had if they had been treated as in the best performing country, given their individual characteristics.

Findings We extracted registry data for 139 457 adult patients with invasive colorectal adenocarcinoma: 12 958 patients in Denmark, 97 466 in England, 11 450 in Norway, and 17 583 in Sweden. 3-year colon cancer survival was lower in England (63·9%, 95% CI 63·5–64·3) and Denmark (65·7%, 64·7–66·8) than in Norway (69·5%, 68·4–70·5) and Sweden (72·1%, 71·2–73·0). Rectal cancer survival was lower in England (69·7%, 69·1–70·3) than in the other three countries (Denmark 72·5%, 71·1–74·0; Sweden 74·1%, 72·7–75·4; and Norway 75·0%, 73·1–76·8). We found no significant differences in survival for patients with stage I disease in any of the four countries. 3-year survival after stage II or III rectal cancer and stage IV colon cancer was consistently lower in England (stage II rectal cancer 86·4%, 95% CI 85·0–87·6; stage III rectal cancer 75·5%, 74·2–76·7; and stage IV colon cancer 20·5%, 19·9–21·1) than in Norway (94·1%, 91·5–96·0; 83·4%, 80·1–86·1; and 33·0%, 31·0–35·1) and Sweden (92·9%, 90·8–94·6; 80·6%, 78·2–82·7; and 23·7%, 22·0–25·3). 3-year survival after stage II rectal cancer and stage IV colon cancer was also lower in England than in Denmark (stage II rectal cancer 91·2%, 88·8–93·1; and stage IV colon cancer 23·5%, 21·9–25·1). The total proportion of patients treated with resectional surgery ranged from 47 803 (68·4%) of 69 867 patients in England to 9582 (81·3%) of 11 786 in Sweden for colon cancer, and from 16 544 (59·9%) of 27 599 in England to 4106 (70·8%) of 5797 in Sweden for rectal cancer. This range was widest for patients older than 75 years (colon cancer 19 078 [59·7%] of 31 946 patients in England to 4429 [80·9%] of 5474 in Sweden; rectal cancer 4663 [45·7%] of 10 195 in England to 1342 [61·9%] of 2169 in Sweden), and the proportion of patients treated with resectional surgery was consistently lowest in England. The age gradient of the decline in the proportion of patients treated with resectional surgery was steeper in England than in the other three countries in all stage categories. In the hypothetical scenario where all patients were treated as in Sweden, given their age, sex, and disease stage, the largest increase in resectional surgery would be for patients with stage III rectal cancer in England (increasing from 70·3% to 88·2%).

Interpretation Survival from colon cancer and rectal cancer in England and colon cancer in Denmark was lower than in Norway and Sweden. Survival paralleled the relative provision of resectional surgery in these countries. Differences in patient selection for surgery, especially in patients older than 75 years or individuals with advanced disease, might partly explain these differences in international colorectal cancer survival.

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Introduction

Colorectal cancer is among the three most common cancer diagnoses and causes of cancer death in women and men in Denmark, Norway, Sweden, and the UK.[1] The deficit in survival from colorectal cancer seen in Denmark and England compared with that of Norway and Sweden[2–4] might be explained partly by differences in disease stage distribution, arising from delays in diagnosis.[5] The variations in stage-specific survival also suggest differences in treatment.[5]

Research in context

Evidence before this study

To identify previous population-based international comparisons of colorectal cancer survival and treatment, we searched PubMed for articles published between Jan 1, 1980, and Jan 31, 2018, using the terms "population-based", "cancer", "survival", "treatment", "international", "colorectal OR colon OR rectum", without language restrictions. We manually searched the 95 references retrieved. In total, 22 articles assessed colorectal cancer outcomes in at least one of the countries included in our study. Additionally, we examined secondary references, national and international clinical guidelines, and other national reports for information on colorectal cancer management. Previous research showed that colorectal cancer survival was lower in England and Denmark than in other high-income countries with similar health-care coverage. The deficit in survival was partly explained by a more advanced stage distribution in Denmark and, potentially, by suboptimal care in England. Analysts who did this research pointed to the need for research into differences in stage-specific treatment between these countries.

Added value of this study

We used national population-based clinical data to compare stage-specific survival of patients diagnosed with primary colorectal adenocarcinoma in Denmark, England, Norway, and Sweden between 2010 and 2012, and to assess whether the international survival differences could be explained by differences in patient care. We considered stage-specific survival differences in relation to the proportion of patients who received resectional surgery. We showed that net survival up to 3 years after colon cancer was substantially lower in England and Denmark than in Norway and Sweden, and survival from rectal cancer was lower in England than in the other three countries. International differences were wider for patients with more advanced disease stage. The probability of receiving resectional surgery paralleled the survival outcomes, with patients in England substantially less likely to receive resectional surgery than in the other three countries. We also found a steep declining age gradient in the probability of receiving resectional surgery in England, which was less noticeable or not evident in the other countries.

Implications of all the available evidence

These findings have important policy implications, showing that the colorectal cancer survival deficit in England can be attributed partly to shortfalls in treatment. Patients older than 75 years, in particular, are less likely to receive surgery than patients with the same characteristics in Denmark, Norway, and Sweden. We highlight the need for more patient data on comorbidities, frailty, and additional therapies to understand these differences better.

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The primary treatment for colorectal cancer is surgical removal of the main tumour or tumours and affected tissues. Total mesorectal excision became the standard surgery for rectal cancer in Denmark, Norway, and Sweden in the mid-1990s[6–8] and some years later in England.[9] This technique entails the removal of the rectum and surrounding tissues, including lymph nodes and fascia,[10] and requires particular surgical training and skills to secure good results. The surgical principle of resection in the embryological plane, which is used in mesorectal excision, was later applied to colon cancer surgery, with favourable results in terms of recurrences and survival.[11,12]

Preoperative (neo-adjuvant) or postoperative (adjuvant) radiotherapy or chemotherapy can be used to reduce the risk of recurrence and treat micrometastases.[13,14] The decision to treat patients with colorectal cancer with neo-adjuvant or adjuvant therapy depends on the extent of disease and risk of recurrence. In general, clinical guidelines do not recommend additional therapy for early-stage colon tumours or rectal tumours treated with surgery with adequate resection margins.[13–15] The use of neo-adjuvant or adjuvant therapy for stage II or III tumours is variable between—and within[16]—countries, particularly for rectal tumours.[17]

We used population-based data from national colorectal cancer registries to estimate stage-specific and age-standardised net survival at 3 years of patients diagnosed with colorectal cancer in Denmark, England, Norway, and Sweden, and to compare the proportions of patients receiving resectional surgery in those countries by patient and tumour characteristics.

Methods

Study design and data sources

In this population-based study, we included all patients aged 18–99 years diagnosed with primary, invasive colorectal adenocarcinomas from Jan 1, 2010, to Dec 31, 2012. Patients diagnosed by their death certification alone and patients with records with invalid date sequences were excluded.[18] In Denmark, England, and Norway, we extracted data from population-based national cancer registries. By linking individual patient records in Denmark to the Danish Colorectal Cancer Group database,[19] additional clinical information was available for 11746 (90·7%) patients registered with colorectal adenocarcinomas in the Danish National Cancer Registry. Similarly, 97185 (99·7%) English national cancer registry records for patients with colorectal cancer were linked to at least one of the National Bowel Cancer Audit data, Hospital Episode Statistics inpatient and outpatient records, and the Cancer Waiting Times Monitoring Data Set. Norwegian national cancer registry data are routinely linked to the Norwegian Colorectal Cancer Registry, a specialised registry that contains detailed clinical information on all patients with colorectal cancer nationwide.[8] The Swedish

For more on the **Danish Colorectal Cancer Group** see http://www.DCCG.dk

For the **National Bowel Cancer Audit** see https://www.nboca.org.uk/

For the **Hospital Episode Statistics** see https://www.digital.nhs.uk/data-and-information/data-tools-and-services/data-services/hospital-episode-statistics

For the **Cancer Waiting Times Monitoring Data Set** see https://digital.nhs.uk/data-and-information/data-collections-and-data-sets/data-collections/cancerwaitingtimescwt

For the **Norwegian Colorectal Cancer Registry** see https://www.kreftregisteret.no/en/The-Registries/Clinical-Registries/Colorectal-Cancer-Registry/

For more on the **Swedish Colorectal Cancer Registry** see https://www.cancercentrum.se/samverkan/cancerdiagnoser/tjocktarm-andtarm-och-anal/tjock--och-andtarm/kvalitetsregister/

Colorectal Cancer Registry provided clinical data on patients with colorectal cancer in Sweden;[7] its coverage for the study period was near complete.[20] Definitions of clinical variables (site, stage, or treatment) were agreed with in-country clinicians and specialised cancer registry staff to reconcile differences in coding between the various data sources. The data specifications were agreed in advance with other countries through a prespecified data protocol. Some further discussions with clinicians and registry staff were held to understand and reconcile differences in coding and clinical practices in those countries.

All patients included in this study were followed up from time of diagnosis until death or until Dec 31, 2014, whichever occurred first. Last vital status was assessed by linking data to national death registry records.

Procedures

Colon cancer was defined by topographical codes C18.0–C19.9 and rectal cancer by codes C20.0–C20.9 of the International Classification of Diseases for Oncology, 3rd edition.[21] Tumours located 15 cm or less from the anal verge were considered rectal cancers. Tumours with morphological codes for non-adenocarcinoma were excluded from analyses.

See Online for appendix

We applied consistent quality control measures to all records (appendix pp 1–2).[18] In cases of multiple tumours diagnosed at the same site within 6 months of each other, we retained the date of diagnosis of the first tumour; where stage and type of surgery were inconsistent between records (n=327, 0·23%), we selected the most advanced stage and most extensive surgery. For all patients with record of more than one surgery, we selected the most extensive surgery.

Disease extent (stage), as defined by the Union for International Cancer Control TNM classification of malignant tumours, was characterised by applying a hierarchical algorithm previously described.[22] Priority was given to pathological confirmation of tumour, lymph node extension, and distant metastases (if positive), over clinical TNM components. During 2010–12, Denmark and England used the 5th edition of TNM in their colorectal cancer registries, whereas the 7th edition was used in Norway and Sweden. There is broad comparability between the main stage categories among these TNM editions.[22]

We defined resectional surgery as the surgical removal of the primary tumour, irrespective of the intent and outcome of surgery, done within 9 months of diagnosis. Information regarding surgery for each patient was extracted from the specialised registry data for Denmark, Norway, and Sweden. For England, we derived this information from Hospital Episode Statistics and National Bowel Cancer Audit records, by identifying relevant codes from the Classification of Intervention and Procedures of the Office of Population Censuses and Surveys (OPCS), version 4.7 (OPCS 4.7),[23] a standard classification of procedures done in National Health Service (NHS) hospitals in England. Local excisions were considered radical for stage I tumours alone. Non-resectional procedures that were purely diagnostic or symptom-alleviating (eg, stoma) were not considered as resectional surgery. In Denmark and England, surgical status was categorised as missing when patients were registered in the national cancer registry but were not recorded in the specialised colorectal cancer registry (or in Hospital Episode Statistics for England). We calculated the potential range of the proportion of patients that might have had resectional surgery in Denmark and England, first assuming that all patients with missing data were treated and then assuming that they were all untreated. We then estimated upper and lower limits of the probable distribution of resectional surgery in each of these countries.

Information regarding radiotherapy and planned chemotherapy within 6 months of diagnosis was extracted from colorectal cancer registry data in Denmark, Norway, and Sweden, and from National Bowel Cancer Audit and Cancer Waiting Times records in England.

We hold approvals from the UK Health Research Authority (reference ECC 3–04(i)/2011), the National Health Service Research Ethics Service (11/LO/0331), and the London School of Hygiene & Tropical Medicine (LSHTM, 12171). We have a data processing agreement with the Danish Cancer Society and approval from the Danish Data Protection Agency to use data from the Danish Colorectal Cancer Group; a data disclosure agreement with the Cancer Registry of Norway to use the Norwegian data; and ethical approval from the Regional Ethical Committee in Uppsala to use the Swedish data. Data preparation and analyses were done at the London School of Hygiene & Tropical Medicine. Data were extracted and transferred with a standard data structure protocol and file transmission procedure, in line with the CONCORD programme for the global surveillance of cancer survival.[24]

Outcomes

Our primary aim was to assess the estimated age-standardised net survival up to 3 years after diagnosis by country and disease stage and the estimated probability of patients receiving resectional surgery by stage and age in each country. We also estimated the hypothetical change in the probability of receiving resectional surgery that patients would have had if they had been treated as in the best performing country, given their individual characteristics.

Statistical analysis

We compared the demographic and clinical characteristics of patients with colorectal cancer diagnosed in Denmark, England, Norway, and Sweden, including patients' age, sex, and disease stage. We estimated net survival up to 3 years after diagnosis by country and disease stage, using the complete approach.[25] Net survival controls for the hazard of death from other causes

	Colon tumours				Rectal tumours			
	Denmark	England	Norway	Sweden	Denmark	England	Norway	Sweden
Mean age, years (SD)	71·9 (11·3)	72·4 (12·0)	72·6 (11·9)	72·7 (11·5)	69·5 (11·5)	70·0 (12·2)	69·9 (12·2)	70·3 (11·9)
Age group, years								
18–54	660 (7·7%)	5700 (8·2%)	656 (7·9%)	863 (7·3%)	481 (11·0%)	3109 (11·3%)	346 (11·1%)	626 (10·8%)
55–64	1480 (17·3%)	11 818 (16·9%)	1345 (16·1%)	1796 (15·2%)	935 (21·3%)	5936 (21·5%)	679 (21·8%)	1102 (19·0%)
65–74	2841 (33·2%)	20 403 (29·2%)	2441 (29·3%)	3653 (31·0%)	1502 (34·2%)	8359 (30·3%)	946 (30·4%)	1900 (32·8%)
75–84	2567 (30·0%)	21 942 (31·4%)	2670 (32·0%)	3907 (33·1%)	1107 (25·2%)	7289 (26·4%)	809 (26·0%)	1580 (27·3%)
85–99	1019 (11·9%)	10 004 (14·3%)	1227 (14·7%)	1567 (13·3%)	366 (8·3%)	2906 (10·5%)	331 (10·6%)	589 (10·2%)
Sex								
Men	4160 (48·6%)	37 279 (53·4%)	4087 (49·0%)	5875 (49·8%)	2670 (60·8%)	17 700 (64·1%)	1836 (59·0%)	3421 (59·0%)
Women	4407 (51·4%)	32 588 (46·6%)	4252 (51·0%)	5911 (50·2%)	1721 (39·2%)	9899 (35·9%)	1275 (41·0%)	2376 (41·0%)
Disease stage at diagnosis*								
Stage I	839 (10·7%)	7413 (12·8%)	972 (13·0%)	1462 (13·0%)	793 (20·7%)	5674 (24·4%)	705 (26·0%)	1247 (23·3%)
Stage II	2723 (34·7%)	17 524 (30·3%)	2482 (33·2%)	3648 (32·5%)	1032 (27·0%)	5014 (21·6%)	659 (24·3%)	1264 (23·6%)
Stage III	2036 (25·9%)	17 258 (29·8%)	1931 (25·9%)	3436 (30·6%)	1062 (27·8%)	7520 (32·4%)	645 (23·8%)	1551 (29·0%)
Stage IV	2256 (28·7%)	15 679 (27·1%)	2081 (27·9%)	2670 (23·8%)	935 (24·5%)	5026 (21·6%)	699 (25·8%)	1294 (24·2%)
Unknown stage	713 (8·3%)	11 993 (17·2%)	873 (10·5%)	570 (4·8%)	569 (13·0%)	4365 (15·8%)	403 (13·0%)	441 (7·6%)
Received resectional surgery†	6040 (70·5%)	47 803 (68·4%)	6023 (72·2%)	9582 (81·3%)	2982 (67·9%)	16 544 (59·9%)	2064 (66·3%)	4106 (70·8%)
Received radiotherapy‡	134 (1·6%)	2097 (3·0%)	109 (1·3%)	54 (0·5%)	1182 (26·9%)	11 299 (40·9%)	1321 (42·5%)	2935 (50·6%)
Received chemotherapy‡§	3272 (38·2%)	18 640 (26·7%)	1654 (19·8%)	2525 (21·4%)	2060 (46·9%)	8484 (30·7%)	931 (29·9%)	1404 (24·2%)
Unknown treatment status¶	949 (11·1%)	214 (0·3%)	0 (0·0%)	0 (0·0%)	263 (6·0%)	67 (0·2%)	0 (0·0%)	0 (0·0%)
Total	8567 (100%)	69 867 (100%)	8339 (100%)	11 786 (100%)	4391 (100%)	27 599 (100%)	3111 (100%)	5797 (100%)

Data are n (%), unless otherwise specified. *Proportions of total number of patients with known stage. †Defined as surgery to remove the primary tumour within 9 months of diagnosis, excluding diagnostic and palliative procedures. ‡Received within 6 months of diagnosis; sources and completeness of information on chemotherapy or radiotherapy varied greatly between countries, with a high proportion of missing information in England. §Planned chemotherapy in Norway and Sweden. ¶Proportion of patients not registered in specialised colorectal cancer registries (or Hospital Episode Statistics, Cancer Waiting Times Monitoring Data Set for England).

Table 1: **Characteristics of patients diagnosed with colorectal adenocarcinoma, 2010–12**

(background mortality) and is suitable for use in international comparisons of survival because background mortality differs between countries. In the absence of reliable information on the cause of death, the background mortality hazard was provided by life tables for the general population defined by country, sex, single year of age, and year.[26] We used a multivariable modelling approach to estimate the excess mortality hazard (ie, due to colorectal cancer) and predict net survival. Survival models were stratified by country and disease stage. We used a model selection strategy to test for non-linearity and time dependence of the effects of sex and age on the excess mortality hazard and their interactions.[27] Survival was predicted by age group, defined by the International Cancer Survival Standard. We used International Cancer Survival Standard weights to produce a weighted average of the survival estimates (age-standardisation), to allow for differences between countries in the age distribution of the population of patients with cancer.[28] We used the Stata command strcs to fit flexible parametric survival models on the log-hazard scale.[29]

We used multivariate logistic regression models to compare the probability of receiving resectional surgery between countries. Models were developed for each disease stage and initially included country, age, and sex. We started with a full, saturated model that included main effects and all potential interactions. The main effects and important interactions between country and age were kept a priori, and we considered other interactions on the basis of the likelihood ratio test. Non-linearity was assessed by comparing the model with age as a categorical variable against a model with age as a continuous variable. If categorical age was chosen, the non-linear effect of age was modelled by use of a restricted cubic spline variable. Subsequently, we applied the model coefficients of the best performing country to individuals from the other countries, to assess the hypothetical change in the probability of receiving resectional surgery if patients had been treated as in the best performing country, given their observed characteristics. We used Stata 15 software for all statistical analyses.[30]

	Colon tumours				Rectal tumours			
	Denmark	England	Norway	Sweden	Denmark	England	Norway	Sweden
Median follow-up time, years (IQR)	2·5 (0·9–3·5)	2·4 (0·7–3·5)	2·5 (1·1–3·7)	2·7 (1·4–3·7)	2·7 (1·5–3·7)	2·6 (1·4–3·6)	2·8 (1·9–3·8)	2·8 (1·8–3·8)
1-year net survival (95% CI)								
All stages	80·3 (79·5–81·0)	78·2 (77·9–78·5)	80·9 (80·1–81·6)	83·9 (83·3–84·5)	85·5 (84·5–86·5)	84·6 (84·2–85·0)	87·4 (86·0–88·6)	87·6 (86·7–88·5)
Stage I	97·1 (95·6–98·1)	98·7 (97·8–99·2)	98·2 (96·4–99·1)	100 (100·0–100·0)	98·0 (95·8–99·1)	98·8 (98·2–99·1)	98·4 (95·9–99·4)	99·8 (99·6–99·9)
Stage II	94·5 (93·4–95·4)	94·9 (94·6–95·3)	95·5 (94·4–96·3)	96·8 (96·1–97·4)	95·3 (93·9–96·3)	94·6 (93·8–95·3)	99·8 (99·8–99·8)	97·5 (96·1–98·4)
Stage III	87·8 (86·4–89·2)	87·5 (87·1–88·0)	89·3 (87·8–90·6)	90·7 (89·7–91·6)	90·0 (87·9–91·7)	91·1 (90·4–91·8)	93·9 (92·3–95·2)	93·6 (92·1–94·8)
Stage IV	52·9 (51·3–54·5)	48·4 (47·8–49·1)	57·3 (55·4–59·1)	51·9 (50·2–53·6)	61·6 (59·3–63·9)	60·0 (58·9–61·0)	66·6 (63·8–69·2)	61·5 (59·4–63·6)
Unknown stage	62·8 (60·2–65·4)	62·2 (61·3–63·0)	58·0 (55·0–60·8)	78·9 (76·1–81·4)	78·9 (75·9–81·6)	72·7 (71·6–73·8)	75·2 (71·8–78·2)	83·1 (80·4–85·5)
2-year net survival (95% CI)								
All stages	71·9 (71·0–72·8)	69·9 (69·5–70·2)	73·9 (73·0–74·8)	76·7 (75·9–77·5)	78·2 (76·9–79·4)	76·2 (75·7–76·8)	80·3 (78·6–81·8)	79·8 (78·6–81·0)
Stage I	96·2 (94·3–97·5)	98·2 (97·1–98·9)	98·2 (96·4–99·1)	99·5 (97·2–100·0)	97·0 (93·9–98·6)	97·8 (96·9–98·4)	98·4 (95·9–99·4)	99·8 (97·5–100·0)
Stage II	92·3 (90·9–93·5)	92·7 (92·2–93·2)	94·7 (93·4–95·7)	95·3 (94·3–96·2)	93·0 (91·1–94·5)	90·3 (89·2–91·3)	98·9 (98·0–99·4)	95·1 (93·2–96·4)
Stage III	81·4 (79·6–83·1)	80·1 (79·5–80·7)	82·1 (80·2–83·8)	84·0 (82·7–85·3)	83·0 (80·2–85·4)	82·9 (81·9–83·9)	88·2 (85·7–90·3)	86·8 (84·9–88·6)
Stage IV	34·4 (32·8–36·1)	30·5 (29·9–31·1)	41·9 (39·9–44·0)	33·6 (31·8–35·3)	42·4 (39·9–44·9)	39·7 (38·6–40·8)	49·6 (46·6–52·4)	39·8 (37·7–42·0)
Unknown stage	53·2 (50·4–56·0)	52·8 (51·9–53·8)	49·8 (46·6–52·8)	73·0 (69·8–75·9)	72·0 (68·4–75·2)	63·5 (62·1–64·7)	64·2 (60·3–67·9)	77·1 (73·9–79·9)
3-year net survival (95% CI)								
All stages	65·7 (64·7–66·8)	63·9 (63·5–64·3)	69·5 (68·4–70·5)	72·1 (71·2–73·0)	72·5 (71·1–74·0)	69·7 (69·1–70·3)	75·0 (73·1–76·8)	74·1 (72·7–75·4)
Stage I	95·6 (93·4–97·0)	97·8 (96·6–98·6)	98·2 (96·4–99·1)	99·3 (96·0–99·9)	96·3 (92·4–98·2)	96·9 (95·6–97·8)	98·4 (95·9–99·4)	99·3 (95·7–99·9)
Stage II	90·6 (88·9–92·0)	91·0 (90·4–91·5)	94·3 (93·0–95·4)	94·1 (92·8–95·1)	91·2 (88·8–93·1)	86·4 (85·0–87·6)	94·1 (91·5–96·0)	92·9 (90·8–94·6)
Stage III	76·3 (74·1–78·4)	74·1 (73·3–74·8)	76·3 (74·0–78·4)	78·4 (76·8–79·9)	77·2 (73·9–80·1)	75·5 (74·2–76·7)	83·4 (80·1–86·1)	80·6 (78·2–82·7)
Stage IV	23·5 (21·9–25·1)	20·5 (19·9–21·1)	33·0 (31·0–35·1)	23·7 (22·0–25·3)	30·4 (28·0–32·9)	27·1 (26·0–28·2)	38·5 (35·5–41·4)	26·7 (24·7–28·8)
Unknown stage	47·4 (44·5–50·2)	47·0 (45·9–48·0)	45·2 (42·0–48·4)	69·7 (66·3–72·9)	67·3 (63·3–70·9)	57·2 (55·8–58·6)	56·7 (52·4–60·8)	73·2 (69·8–76·3)

Table 2: **Age-standardised net survival of patients diagnosed with colorectal adenocarcinoma, 2010–12**

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the manuscript. The corresponding author had full access to all the data in the study, and the final responsibility for the decision to submit for publication.

Results

We included information from 139 457 patients diagnosed with colorectal adenocarcinoma in England, Denmark, Norway, and Sweden in our analyses. The distribution by topographical site varied slightly between countries. The age distribution of patients was similar between countries, with patients with rectal cancer being younger than patients with colon cancer overall (table 1). Median follow-up was similar between countries (table 2). Disease stage was known for 11 676 (90·1%) of 12 958 patients in Denmark, 81 108 (83·2%) of 97 466 in England, 10 174 (88·9%) of 11 450 in Norway, and 16 572 (94·3%) of 17 583 in Sweden. In patients with known disease stage, the proportion diagnosed with stage I–III colon cancer was higher in Sweden than in England,

Norway, and Denmark; for rectal cancer, the proportion diagnosed with stage I–III rectal cancer was higher in England than in Sweden, Denmark, and Norway (table 1).

3-year age-standardised net survival from colon cancer was higher in Sweden and Norway than in Denmark and England. Rectal cancer survival was consistently higher than that for colon tumours in the study countries. 3-year survival from rectal cancer was generally similar between Denmark, Norway, and Sweden, and lower in England (table 2).

Net survival decreased with the increase in disease stage (table 2, figure 1). Age-standardised 3-year survival for stage I tumours was higher than 95% in all countries for both colon and rectal cancers. 3-year survival for patients with stage II tumours was about 90% or higher in all countries, although survival for patients with rectal or colon cancer in England and colon cancer in Denmark was notably lower than for patients in Sweden or Norway. Although generally higher than 75%, survival for patients with stage III colon and rectal cancer was lower in England than in Norway and Sweden up to 3 years after diagnosis, and in Denmark 1 year after diagnosis. Survival from stage IV colon cancer was consistently lowest in England and highest in Norway, reaching

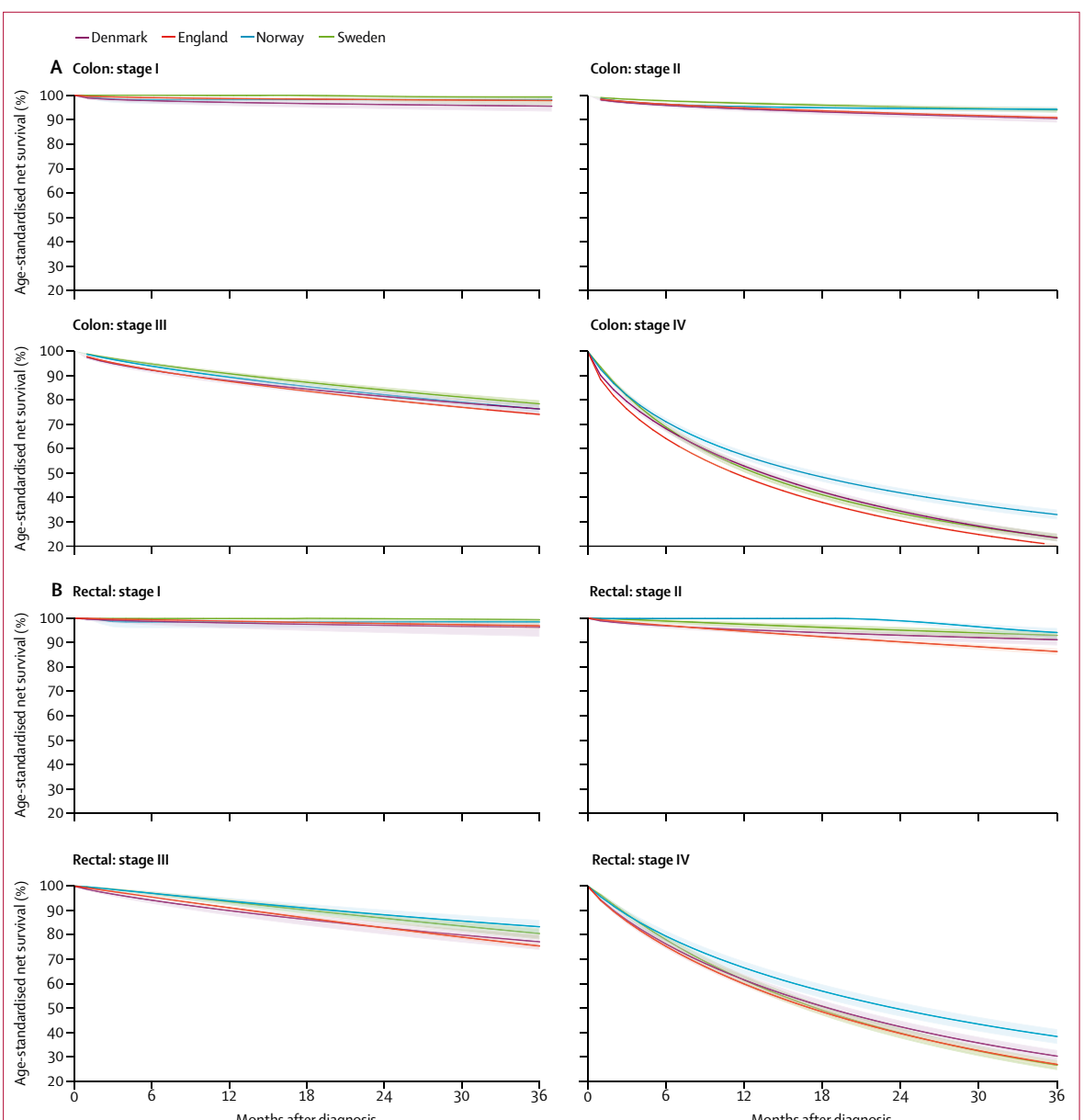

Figure 1: **Age-standardised stage-specific survival for colon (A) and rectal (B) adenocarcinoma diagnosed in 2010–12**
Shaded areas represent 95% CI of survival estimates.

	Colon tumours				Rectal tumours			
	Denmark	England	Norway	Sweden	Denmark	England	Norway	Sweden
Age group, years								
18–54	463 (70·2%)	4233 (74·3%)	495 (75·5%)	712 (82·5%)	371 (77·1%)	2065 (66·4%)	248 (71·7%)	465 (74·3%)
55–64	1091 (73·7%)	8951 (75·7%)	990 (73·6%)	1442 (80·3%)	705 (75·4%)	4083 (68·8%)	499 (73·5%)	860 (78·0%)
65–74	2077 (73·1%)	15 541 (76·2%)	1844 (75·5%)	2999 (82·1%)	1072 (71·4%)	5733 (68·6%)	664 (70·2%)	1439 (75·7%)
75–84	1818 (70·8%)	14 834 (67·6%)	1974 (73·9%)	3255 (83·3%)	698 (63·1%)	3962 (54·4%)	510 (63·0%)	1090 (69·0%)
85–99	591 (58·0%)	4244 (42·4%)	720 (58·7%)	1174 (74·9%)	136 (37·2%)	701 (24·1%)	143 (43·2%)	252 (42·8%)
Sex								
Men	2917 (70·1%)	25 649 (68·8%)	2925 (71·6%)	4711 (80·2%)	1843 (69·0%)	10 820 (61·1%)	1239 (67·5%)	2427 (70·9%)
Women	3123 (70·9%)	22 154 (68·0%)	3098 (72·9%)	4871 (82·4%)	1139 (66·2%)	5724 (57·8%)	825 (64·7%)	1679 (70·7%)
Disease stage at diagnosis								
Stage I	752 (89·6%)	6916 (93·3%)	836 (86·0%)	1328 (90·8%)	741 (93·4%)	5100 (89·9%)	605 (85·8%)	1122 (90·0%)
Stage II	2528 (92·8%)	16 438 (93·8%)	2189 (88·2%)	3541 (97·1%)	928 (89·9%)	3958 (78·9%)	556 (84·4%)	1145 (90·6%)
Stage III	1849 (90·8%)	15 555 (90·1%)	1688 (87·4%)	3282 (95·5%)	900 (84·7%)	5289 (70·3%)	539 (83·6%)	1361 (87·7%)
Stage IV	882 (39·1%)	6263 (39·9%)	1158 (55·6%)	1356 (50·8%)	307 (32·8%)	1293 (25·7%)	331 (47·4%)	376 (29·1%)
Unknown stage	29 (4·1%)	2631 (21·9%)	152 (17·4%)	75 (13·2%)	106 (18·6%)	904 (20·7%)	33 (8·2%)	102 (23·1%)
Total	6040 (70·5%)	47 803 (68·4%)	6023 (72·2%)	9582 (81·3%)	2982 (67·9%)	16 544 (59·9%)	2064 (66·3%)	4106 (70·8%)

Data are n (%). Resectional surgery defined as surgery to remove the primary tumour within 9 months of diagnosis, excluding diagnostic and palliative procedures.

***Table 3*: Proportion of patients diagnosed with colorectal adenocarcinoma in 2010–12 that received resectional surgery by age, sex, and disease stage**

20·5% for England and 33·0% for Norway at 3 years. For stage IV rectal cancer, survival was lowest in Sweden and England (26·7% in Sweden and 27·1% in England) and highest in Norway (38·5%) at 3 years (figure 1).

The overall proportion of patients who received resectional surgery was higher for colon than for rectal cancer in all countries (table 1). We could not establish the surgical status of some patients in Denmark because they were not registered in the Danish Colorectal Cancer Group database (949 [11·1%] of 8567 patients with colon cancer and 263 [6·0%] of 4391 patients with rectal cancer). Patients with colorectal cancer who were not registered in the Danish Colorectal Cancer Group database were more likely to have advanced stage disease or missing stage information and be slightly older than patients registered in the database. Data on surgery were unavailable for 0·3% of patients with colorectal cancer in England because their national cancer registry records could not be linked to the additional databases (Hospital Episode Statistics, National Bowel Cancer Audit, or Cancer Waiting Times). We report here analyses of the patients with known surgical status. The proportion of patients receiving resectional surgery was highest in Sweden and lowest in England, for both types of cancer (table 1).

The proportion of patients treated with resectional surgery was lower in individuals aged 75 years or older than in younger patients in each country, and international differences in resectional surgery use widened with increasing age of patients (table 3). The share of patients aged 75 years or older with colon cancer with evidence of resectional surgery varied from 19 078 (59·7%) of 31 946 patients in England to 4429 (80·9%) of 5474 in Sweden. In patients aged 75 years or older with rectal cancer, the share of those with resectional surgery varied from 4663 (45·7%) of 10 195 patients in England to 1342 (61·9%) of 2169 in Sweden. Sweden had the highest proportion of patients treated with resectional surgery for colon cancer, for each age group. For rectal cancer, Norway and Sweden had the highest proportions of resectional surgery for all but the youngest age group, where Denmark had the highest proportion of patients treated. England had the lowest proportion of patients treated with resectional surgery for rectal cancer in all age groups and for colon cancer in the two oldest age groups (table 3).

To account for differences in disease stage distribution, we examined the proportion of patients treated by stage and age group (figure 2). The proportion of patients with colon cancer with evidence of resectional surgery for each stage and age group was mostly similar between the four countries for stages I and II and in patients aged 75 years or younger. A higher proportion of patients younger than 85 years with stage I colon cancer in England had resectional surgery than in other countries. However, we observed a steep decline in the proportion of patients that had surgical treatment in the older age categories in England for each disease stage and for both types of cancer, which was not evident in the other countries (figure 2). For instance, a higher proportion of patients received resectional surgery for stage I colon tumours in the 75–84 age group than in the 85 and older age group in all countries, but the absolute difference between these age groups was 18·0% in England

compared with 2·9–5·5% in the other countries. A similar pattern was noted in the other disease stage categories. The proportion of patients with colon cancer aged 85 years and older with evidence of resectional surgery was consistently highest in Sweden for each disease stage as compared with the other three countries.

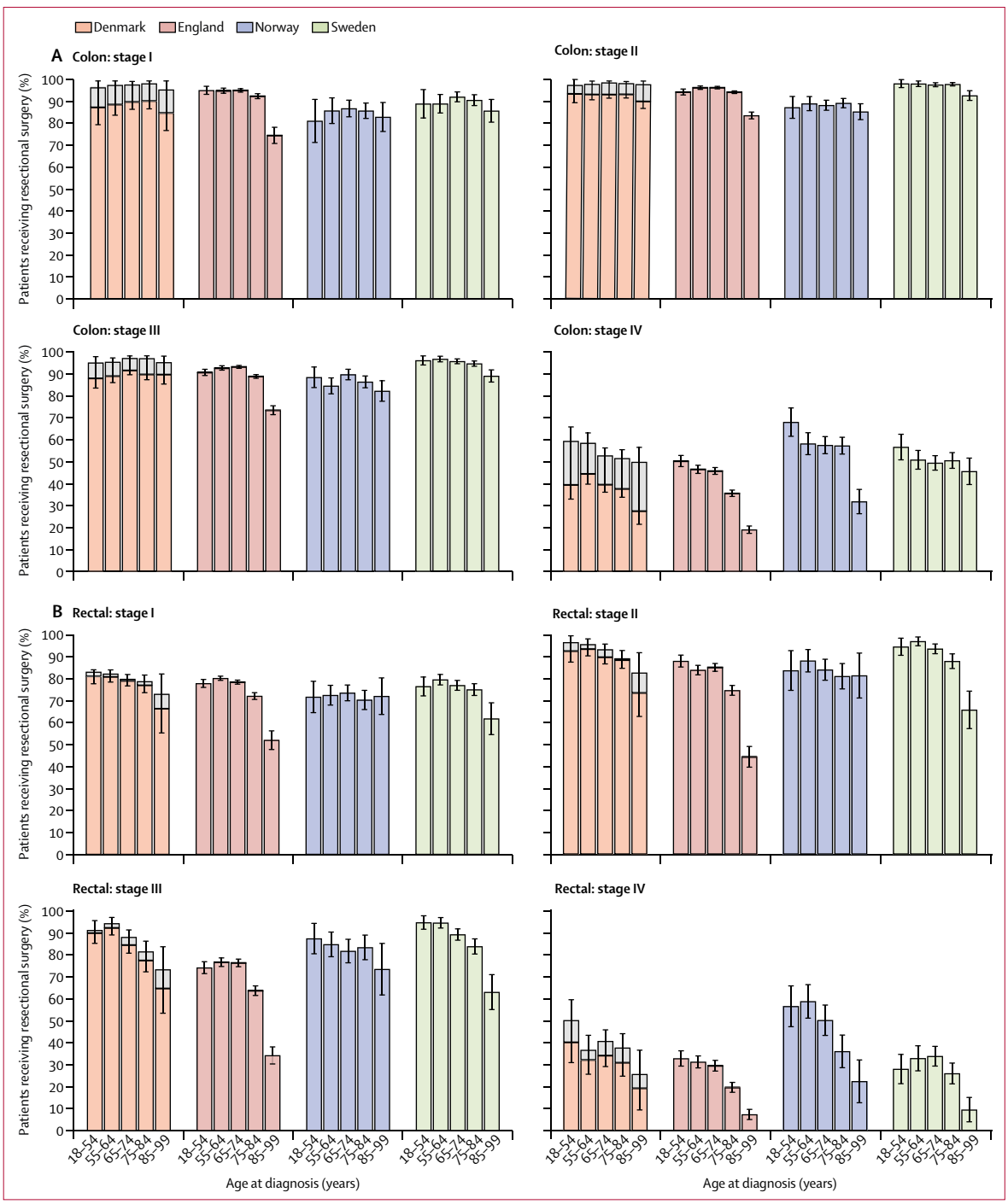

Figure 2: **Proportion of patients who underwent resectional surgery for colon (A) and rectal (B) adenocarcinoma by disease stage at diagnosis and age group, for diagnoses 2010–12**

Error bars are 95% CI. Resectional surgery is defined as surgery to remove the primary tumour within 9 months of diagnosis, excluding diagnostic and palliative procedures. Information on surgical status was available for all patients in Norway and Sweden. Information on surgery was missing for some patients in Denmark and for a small proportion of patients in England: light grey areas represent the proportion of patients with unknown surgical status by stage and age group; overall height of the bars shows the proportion of patients that would receive surgery if all patients with missing treatment data had surgical treatment.

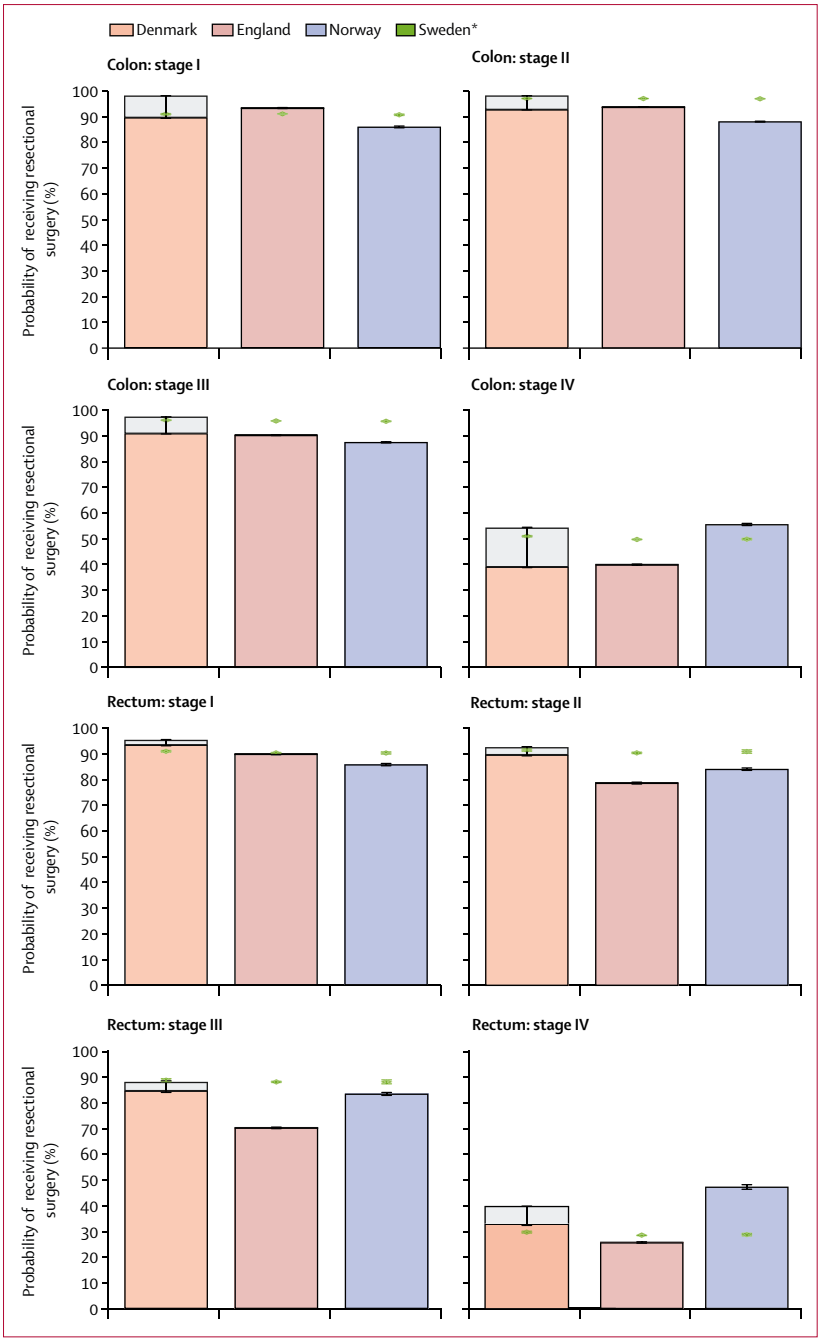

Figure 3: **Predicted probability of receiving resectional surgery by patient characteristics (age and sex) and tumour characteristics (stage at diagnosis)**

Error bars are 95% CI. Resectional surgery is defined as surgery to remove the primary tumour within 9 months of diagnosis, excluding diagnostic and palliative procedures. *Predicted probabilities of patients receiving resectional surgery by applying the coefficients of the Swedish logistic model to the cohorts of patients in each country, on the basis of the country-specific distributions of patient characteristics. Light grey areas at the top of the bars for Denmark and England represent the proportion of patients with unknown surgical status by stage and age group. The overall height of the bars shows the proportion we would observe if all patients with missing treatment data had received surgery.

Among patients younger than 85 years with rectal cancer who were diagnosed with stage I or II disease, we observed no significant differences in the likelihood of being treated with resectional surgery in any of the four countries. However, for patients with rectal cancer diagnosed with stage III–IV disease, the proportion treated was lower in England than in the other countries in our study, particularly in the oldest age groups (figure 2). We observed an age gradient in the proportion of patients receiving resectional surgery with all rectal cancer stages in Denmark, England, and Sweden, with lower proportions among patients aged 85 years or older than among younger patients. The age gradient was steeper in England than in other countries. For instance, between patients aged 75–84 years and those aged 85 years or older, the absolute difference in the proportion of patients who received resectional surgery for stage III rectal tumours was 29·6% in England, 20·9% in Sweden, and 12·8% in Denmark. We found no age gradient in the proportion of patients treated for rectal cancer in Norway, except for patients with stage IV cancer.

To assess the validity of our findings and check whether the age differences in the likelihood of patients receiving resectional surgery were driven by differences in the management of patients diagnosed at aged 90 years or older, we repeated the analyses with exclusion of this patient group. The patterns we observed persisted in this reanalysis (appendix pp 3, 6–7).

Overall, Sweden had the highest survival for colon and rectal cancer and the highest proportion of patients receiving resectional surgery, compared with those of the other countries (although outcomes in Norway were generally similar, or better in specific strata, to those in Sweden). To highlight any groups of patients who might be at a disadvantage in the likelihood of receiving resectional surgery compared with patients in other countries, we applied the coefficients for Sweden to data from the other three countries and interpreted it as the probability of a patient receiving resectional surgery if they had been treated as in Sweden, given their observed age, sex, and disease stage. The number of events per parameter was above the recommended threshold of ten in all categories,[31] at 100 events per parameter for our most complex model in the category with fewest events (stage IV rectal cancer).

In this hypothetical scenario, changes in the proportion of patients with stage I colon or rectal cancer receiving resectional surgery would be minor (figure 3). In England, Denmark, and Norway there would be a higher proportion treated among patients with stage II and III colon and rectal cancer, if treated as in Sweden. Overall, the largest improvements in the proportion of patients receiving resectional surgery would be seen in patients with stage II (from 78·9% to 90·7%) or III (from 70·3% to 88·2%) rectal cancer in England. The proportion of patients receiving resectional surgery for stage IV colon cancer in Denmark and England would increase (from 39·1% to 51·1% in Denmark and from 40·0% to 49·8% in England)—whereas in Norway, the proportion would decrease (from 55·6% to 49·9%) if patients had been

treated as in Sweden. The hypothetical decrease in the proportion of stage IV patients receiving surgery in Norway would be even larger for rectal cancer (from 47·4% to 28·8%).

Patients with missing disease stage were slightly older than the mean age for each country and cancer type (range 75·3–77·3 years for colon cancer and 74·5–75·4 years for rectal cancer). The proportion of patients with colon cancer without known disease stage who had evidence of having resectional surgery was lower than that of any known stage category in each country and higher in England than in the other three countries (table 3). The proportion of patients with rectal cancer without known disease stage who had evidence of having resectional surgery was higher in Sweden than in the other three countries. Survival of patients with colorectal cancer without known disease stage was higher in Sweden than in Denmark, England, and Norway. Additionally, survival of these patients was higher than that of patients with known stage III disease and lower than that of patients with known stage IV disease, in all four countries (table 2).

Discussion

In this study, to understand the mechanisms underlying international differences in cancer outcomes, we compared the characteristics of patients diagnosed with colorectal adenocarcinoma in Denmark, England, Norway, and Sweden. We provide updated figures of up to 3-year net survival in these countries, and our results support previous findings of lower survival for patients in England and, to a lesser degree, in Denmark, than in Sweden or Norway.[2–5] Our results also support findings that Denmark seems to be closing the survival gap with Sweden and Norway, particularly for rectal cancer.[4,6,24] In the stage-specific analyses, we noted no significant differences between countries in survival for patients diagnosed with early stage (I or II) colorectal adenocarcinomas, but wider international survival differences in patients with more advanced disease stages (III or IV). Additional information on treatment, available from specialised colorectal cancer registries, helped us to understand these survival differences better.

Cancer survival is largely determined by receipt of potentially curative treatment, which, in the case of colorectal cancer, is primarily surgery. Treatment options mainly depend on disease stage and the underlying health status of patients, which is determined by their comorbidities, frailty, and age.

Clinical guidelines for cancer treatment aim to standardise and assure adequate cancer care for a population. The amount of detail in the national clinical guidelines regarding colorectal cancer management varied, with recommendations from England being generally less specific than guidelines from Denmark, Norway, and Sweden.[14,15,32,33] Nonetheless, indications for surgery were largely consistent between these countries, especially for rectal tumours. Treatment guidelines for colon cancer in Denmark, Norway, and Sweden explicitly recommend the removal of the part of the bowel that contains the tumour and its mesentery (and en-bloc resection, if the visceral fascia is compromised because of ingrowth of the tumour into neighbouring organs).[13,14,32] By contrast, English guidelines recognise mesorectal excision as the standard surgery for most rectal tumours but do not explicitly recommend the corresponding procedure (dissection in the embryological plane) for colon tumours.[15]

None of the guidelines for the countries in our study mentions age as an exclusion criterion for receiving surgical treatment. However, we found stark differences between countries in the proportion of patients aged 75 years or older who received resectional surgery. Older patients (aged 75 years or older with stage II–IV rectal cancer or stage IV colon cancer and aged 85 years or older for the other stages of rectal and colon cancer) in England had a lower probability of receiving resectional surgery than patients of a similar age with similar disease extension in the other three countries, and a lower probability than younger patients in England. Countries with better survival—Norway and Sweden—had a higher proportion of older patients receiving resectional surgery than that in England for most stages of disease. England had the steepest negative age gradient in the proportion of patients receiving resectional surgery and had a survival deficit in comparison with the other three countries, particularly for rectal cancer. These patterns persisted even after we excluded patients aged 90 years or older from the analyses. Conversely, we noted a higher proportion of patients younger than 85 years who were diagnosed with stage I or II tumours who had evidence of resectional surgery in England than in the other three countries. Of the countries studied, only England had a colorectal cancer screening programme with national coverage during the study period.[34] The diagnosis and treatment of asymptomatic disease through screening might explain the high proportion of patients surgically treated for early stage disease in the eligible age group in England. In the other countries in our study, screening was not implemented at national level during the study period[34] and could not have affected the disease stage distribution or population-based survival.

Although less aggressive treatment for older patients might sometimes be justified because of comorbidity or frailty, concerns have been raised that some of the disparities in age-related cancer care in England arise because of clinical decision making on the basis of chronological age.[35] A 2011 report[36] showed lower resection rates in older patients with cancer in England during 2004–06 than those of younger patients, with less than 2% of patients aged 80 years or older having a major resection surgery for six of 13 cancers examined.

Although an increase in the proportion of patients receiving resectional surgery does not necessarily translate into better short-term survival because aggressive treatment might be associated with high short-term

mortality, our findings suggest that international differences in survival are, at least in part, determined by differences in patient selection practices for surgical treatment. Choices in management of older patients with colorectal cancer might greatly affect population-based survival because the mean age at diagnosis is about 70 years.[37]

Patients in countries with a greater proportion of patients treated with surgery and better short-term survival might also have more access to laparoscopic surgery or better postoperative care than in the other countries. Although there is conflicting evidence about the long-term benefit of a laparoscopic versus an open surgical approach for rectal cancer,[38,39] laparoscopic surgery is associated with lower perioperative mortality and fewer complications than open surgery.[40,41] In Denmark, the increasing use of laparoscopic surgery for colorectal cancer has been associated with a reduction in perioperative mortality rates.[42] Differences between countries in the use of this approach might explain some of the differences in the proportion of patients receiving surgical treatment and, potentially, in survival. However, we were not able to account for this information in our analysis because not all datasets had sufficiently complete data for this question.

Our study has some limitations. We were able to do this international comparison of detailed clinical characteristics and outcomes for patients with colorectal cancer because of the existence of specialised colorectal cancer registries. These include core variables that have previously been examined for comparability and validated—in these and other European colorectal cancer registries.[43] However, some residual data quality issues might affect the comparability of results. Our analyses accounted for age, sex, and disease stage, but comparable information on comorbidities—an important determinant of treatment—was not available in all countries. Furthermore, comorbidity measures might not reveal a patient's overall health status. Performance status scales, which are commonly used to assess patients' general condition (such as their degree of independence) and eligibility for specific treatments,[44] might not be ideal for older patients with cancer, especially those with multiple comorbidities.[45] Although comprehensive geriatric assessment scales have been proposed and validated,[45] they are rarely used, documented, or routinely collected.[46] Nevertheless, at the population level, the burden of cardiovascular disease—the most common contraindication for surgery—is similar in the four countries included in our study.[47] Population-based all-cause mortality and life expectancy in older ages are also similar in these four countries (appendix p 4), supporting the validity of the findings in our study.

The overall proportion of patients with unknown disease stage is notably higher in England than in Denmark, Norway, and Sweden. The reasons for stage information to be missing are likely to differ according to how high or low the proportion of unknown stage is and, therefore, probably differ between countries. Patients with unknown disease stage had a lower probability of receiving resectional surgery than patients with known stage, and had similar survival to that of patients with advanced disease stages. Therefore, our complete-case analysis might overestimate stage-specific survival and the proportion of patients receiving resectional surgery in England, and provides a conservative estimate of the disparities between England and the other three countries in our study.

In Denmark, 9·3% of patients were not registered in the Danish Colorectal Cancer Group database and thus, their treatment status remained undetermined. By contrast with the Danish National Cancer Registry, the Danish Colorectal Cancer Group database only includes adults with a first-time diagnosis of colorectal adenocarcinoma treated in Danish public hospitals who were in contact with a surgical department.[19] Therefore, we calculated a potential range of the proportion of patients that might have had resectional surgery and estimated upper and lower limits of the probable distribution of resectional surgery in Denmark. Because of the Danish Colorectal Cancer Group database's exclusion criteria and the stage distribution of patients without a Danish Colorectal Cancer Group database record, it is probable that a substantial number of these patients did not undergo resectional surgery. Assuming that none of these patients received resectional surgery, the proportion of patients with rectal cancer who received resectional surgery was still higher in Denmark than in England and similar to that in Sweden for most combinations of age and disease stage. Nevertheless, these missing data might have masked some age and stage trends in the likelihood of patients undergoing resectional surgery, especially for colon cancer.

We were not able to ascertain treatment intent, residual disease status, venous invasion status, or postoperative complications in patients who received resectional surgery. We expect that the prognosis of patients who underwent resectional surgery but had residual disease or any postoperative complication was poorer than those without residual disease. Systematic differences in the distribution of such patients between these four countries, or differences in their perioperative management, might affect the between-country comparability of these results. Furthermore, patients with non-resectable tumours in better-performing countries might be more likely to be offered other treatment (such as treatment to prolong life or make tumours amenable to resection) than patients in worse-performing countries. For example, clinical guidelines in Norway and Sweden describe the importance of neo-adjuvant or conversion treatment of metastatic tumours to render them resectable,[13,14] whereas guidelines in England prioritise symptom control and state that initial systemic treatment followed by surgery should be considered only if both primary and metastatic

tumours are judged to be resectable.[15] Moreover, in countries that frequently use neo-adjuvant therapy with delayed surgery for rectal cancer, the resulting down-staging could cause an underestimation of the differences in stage-specific survival when these countries are compared with settings where neo-adjuvant treatment is more variable or followed by immediate surgery.

The completeness and granularity of the data collected by the colorectal cancer registries regarding chemotherapy and radiotherapy varied greatly during the study period—from complete registration of radiotherapy protocols in Norway and Sweden to a high proportion of missing information in England. These inconsistencies meant that including radiotherapy and chemotherapy in our analyses was not possible (appendix p 5). Adjuvant chemotherapy is associated with improved outcomes in stage III colon cancer and is used universally, but for stage II colon cancer and rectal cancer (in general) its value and therefore its use have been more variable.[48–50] Neo-adjuvant radiotherapy decreases recurrence rates, but evidence for its effect on survival is conflicting and so use also varies within countries[16,51] and between countries.[17] The use of targeted therapy in combination with chemotherapy might help to make tumours amenable to resection in some patients with metastatic or locally advanced disease,[52] but no survival benefit has been shown for this combination.[53] For patients with metastatic disease treated with non-curative intent, optimal use of systemic therapy contributes to longer survival.[52,54] Variability between countries in the use of these additional therapies, and other differences in oncological care beyond surgery, might also contribute to the observed differences in survival.

Despite the limitations of the data included in our study, we have identified important international differences in the distribution of resectional surgery by age and disease stage. The main data quality issue (the higher proportion of patients with unknown disease stage in England) is likely to have led to a conservative estimate of the differences found in stage-specific survival outcomes in England compared with those of other countries. We noted that differences in survival between patients with colorectal cancer treated in England, Denmark, Norway, and Sweden tended to increase with time after diagnosis, and it is possible that these differences between countries would widen with longer follow-up.

Changes in practice during and after the study period are likely to affect future trends. Over the past two or three decades, colorectal cancer outcomes have improved in all the countries compared in our study.[3,24,55] The centralisation and specialisation of colorectal cancer surgery have been suggested as important drivers of this improvement.[4] A 2012 Cochrane review[56] found a clear association between operative mortality and 5-year survival with hospital and surgeon caseload and specialisation. Specialisation of surgeons has led to more widespread and aggressive treatment of metastatic disease, with increased use of chemotherapy and resection of metastases. However, it is likely that centralisation and specialisation vary between the four countries in our study, and these changes in practice are also likely to affect patient survival differently in these countries.[4,6]

Expedited referral routes were initiated in England and Denmark in the 2000s, in response to low cancer survival related to system delays.[57,58] Similar rapid referral routes were introduced in Norway and Sweden in 2016, following the Danish experience. Although diagnostic delays are important factors in cancer care, the effect of these referral routes on cancer survival remains uncertain.

In Denmark, a nationwide screening programme with a monitoring database was introduced in 2014.[59] The Norwegian Directorate of Health is planning to introduce a national colorectal cancer screening programme in Norway in 2019, offering a faecal immunochemical test or colonoscopy to individuals when they turn 55 years.[60] Similarly, a national colorectal cancer screening programme is due to be implemented in Sweden in 2019, following regional screening programmes.[61] In England, a one-off screening test with flexible sigmoidoscopy for people aged 55 years is being rolled out.[62] With increases in diagnosis and treatment of asymptomatic disease, it is likely that survival and the proportion of patients treated for early stage disease will increase in the future.

Since 2013, surgeon-specific outcomes have been reported annually as quality measures in England.[63] It is hoped that this increase in accountability will lead to improvements in patient care. However, these changes might also affect patient selection for surgery. The major reorganisation of the NHS in 2013,[64] alongside substantial resource constraints in the NHS[65] in the past decade, has had a potentially negative effect on cancer services. For instance, the 62-day treatment waiting time target—the aim that a patient should wait no more than 2 months from the date that the hospital receives an urgent referral for suspected cancer to the start of their treatment—has been missed for several quarters running, showing that services are unable to meet the demands placed on them.[66] Given the ongoing financial pressures and austerity in the UK and the NHS, the future trends in survival for patients with cancer in England are uncertain.

Our findings have important policy implications, suggesting that the colorectal cancer survival deficit in England as compared with Denmark, Norway, and Sweden can be attributed partly to shortfalls in provision of surgical treatment. We showed that older patients in England, in particular, were less likely to receive resectional surgery than patients with similar characteristics in the other countries in our study. We posit that increases in the proportion of patients receiving resectional surgery might translate into better longer-term outcomes in England, provided that adequate postoperative care is also available.

Improving the capture of information on patients with colorectal cancer in specialised clinical registries,

including data from individuals who are not eligible for surgery, would allow a more complete population-based comparison of colorectal cancer outcomes. Complete and comparable data on comorbidities, frailty, and additional therapies are required to improve understanding of international differences and inequalities in cancer outcomes.

Contributors

SW, BR, MPC, and SBM designed the study. SBM did the literature review. CDG, MM, and MPC prepared the data protocol and data call. JC and LHI (Denmark), SBM and CDG (England), EAS and MGG (Norway), and KL and BG (Sweden) prepared national datasets according to the protocol. SBM developed and applied algorithms to derive and harmonise clinical variables. All authors contributed to the data harmonisation and variable definition process. CM and CDG prepared the survival model selection algorithm. SBM did the data analyses, and prepared the first draft of the manuscript, tables, and figures. SW and BR supervised the study. All authors had access to results at the data preparation and analysis stages, contributed to the interpretation of the results, revised and critically reviewed the manuscript, and approved the submitted version. SBM, CDG, SW, BR, and MPC had access to all the data in the study and take responsibility for its integrity and the accuracy of the analyses.

Declaration of interests

BR reports grants from the UK Department of Health, outside the submitted work. All other authors declare no competing interests.

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Supplementary appendix

This appendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

Supplement to: Majano SB, Di Girolamo C, Rachet B, et al. Surgical treatment and survival from colorectal cancer in Denmark, England, Norway, and Sweden: a population-based study. *Lancet Oncol* 2018; published online Dec 10. http://dx.doi.org/10.1016/S1470-2045(18)30646-6.

Data received according to data specification	Colon tumours											
	Denmark			England			Norway			Sweden		
	Records	Patients	Percentage	Records	Patients	Percentage	Records	Patients	Percentage	Records	Patients	Percentage
	8,856	**8,815**	**100.00**	**71,292**	**71,292**	**100.00**	**9,006**	**8,668**	**100.00**	**12,168**	**11,790**	**100.00**
Ineligible morphology*	206	204	2.31	1,359	1,359	1.91	241	222	2.56	0	0	0.00
Ineligible topography**	0	0	0.00	0	0	0.00	0	0	0.00	0	0	0.00
Aged < 18 years	0	0	0.00	4	4	0.01	0	0	0.00	0	0	0.00
Aged 100+ years	2	2	0.02	0	0	0.00	2	2	0.02	1	1	0.01
Total ineligible	**208**	**206**	**2.34**	**1,363**	**1,363**	**100.00**	**243**	**224**	**2.58**	**1**	**1**	**0.01**
Total eligible	**8,648**	**8,609**	**100.00**	**69,929**	**69,929**	**100.00**	**8,763**	**8,444**	**100.00**	**12,167**	**11,789**	**100.00**
Age-site mismatch	0	0	0.00	0	0	0.00	0	0	0.00	0	0	0.00
Age-site-morphology mismatch	3	3	0.03	3	3	0.00	1	1	0.01	1	1	0.01
Invalid dates	3	3	0.03	0	0	0.00	5	5	0.06	2	2	0.02
Death certificate only	36	36	0.42	0	0	0.00	99	99	1.17	0	0	0.00
Duplicate registration***	0	0	0.00	0	0	0.00	0	0	0.00	0	0	0.00
Synchronous tumour***	0	0	0.00	0	0	0.00	4	2	0.02	193	95	0.81
Multiple primary same site***	77	38	0.44	0	0	0.00	607	290	3.43	539	259	2.20
Total exclusions	**81**	**42**	**0.49**	**3**	**3**	**0.00**	**424**	**105**	**1.24**	**381**	**3**	**0.03**
Included in analysis	**8,567**	**8,567**		**69,926**	**69,926**		**8,339**	**8,339**		**11,786**	**11,786**	

*: Specific non-adenocarcinoma ICD-O-3 morphological codes; **: Topographical codes C21.X (anal tumours). ***: Total exclusions do not include patients in this row because one record is kept for each.

Appendix Table 1. Data quality control (ineligible and excluded records) by country - Colon cancer diagnoses 2010-2012.

Data received according to data specification	Rectal tumours											
	Denmark			England			Norway			Sweden		
	Records	Patients	Percentage	Records	Patients	Percentage	Records	Patients	Percentage	Records	Patients	Percentage
	4,476	**4,474**	**100.00**	**28,650**	**28,650**	**100.00**	**3,453**	**3,438**	**100.00**	**5,832**	**5,800**	**100.00**
Ineligible morphology*	72	70	1.56	948	948	3.31	291	288	8.38	0	0	0.00
Ineligible topography**	0	0	0.00	103	103	0.36	17	17	0.49	0	0	0.00
Aged < 18 years	1	1	0.02	0	0	0.00	0	0	0.00	1	1	0.02
Aged 100+ years	1	1	0.02	0	0	0.00	1	1	0.03	1	1	0.02
Total ineligible	**74**	**72**	**1.61**	**1,051**	**1,051**	**100.00**	**309**	**306**	**8.90**	**2**	**2**	**0.03**
Total eligible	**4,402**	**4,402**	**100.00**	**27,599**	**27,599**	**100**	**3,144**	**3,132**	**100.00**	**5,830**	**5,798**	**100.00**
Age-site mismatch	0	0	0.00	0	0	0.00	0	0	0.00	1	1	0.02
Age-site-morphology mismatch	0	0	0.00	0	0	0.00	0	0	0.00	0	0	0.00
Invalid dates	7	7	0.16	0	0	0.00	4	4	0.13	0	0	0.00
Death certificate only	4	4	0.09	0	0	0.00	17	17	0.54	0	0	0.00
Duplicate registration***	0	0	0.00	0	0	0.00	0	0	0.00	0	0	0.00
Synchronous tumour***	0	0	0.00	0	0	0.00	2	1	0.03	56	28	0.48
Multiple primary same site***	0	0	0.00	0	0	0.00	22	11	0.35	8	4	0.07
Total exclusions	**11**	**11**	**0.25**	**0**	**0**	**0.00**	**33**	**21**	**0.67**	**33**	**1**	**0.02**
Included in analysis	**4,391**	**4,391**		**27,599**	**27,599**		**3,111**	**3,111**		**5,797**	**5,797**	

*: Specific non-adenocarcinoma ICD-O-3 morphological codes; **: Topographical codes C21.X (anal tumours). ***: Total exclusions do not include patients in this row because one record is kept for each.

Appendix Table 2. Data quality control (ineligible and excluded records) by country - Rectal cancer diagnoses 2010-2012.

		Colon tumours				Rectal tumours			
		Denmark	**England**	**Norway**	**Sweden**	**Denmark**	**England**	**Norway**	**Sweden**
		n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Age									
	15-54	463 (70.2)	4,237 (74.3)	495 (75.5)	712 (82.5)	371 (77.1)	2,065 (66.4)	248 (71.7)	465 (74.3)
	55-64	1,091 (73.7)	8,956 (75.7)	990 (73.6)	1,442 (80.3)	705 (75.4)	4,083 (68.8)	499 (73.5)	860 (78.0)
	65-74	2,077 (73.1)	15,554 (76.2)	1,844 (75.5)	2,999 (82.1)	1,072 (71.4)	5,733 (68.6)	664 (70.2)	1,439 (75.7)
	75-84	1,818 (70.8)	14,855 (67.6)	1,974 (73.9)	3,255 (83.3)	698 (63.1)	3,962 (54.4)	510 (63.0)	1,090 (69.0)
	84-99	468 (62.8)	3,386 (48.3)	553 (62.2)	915 (77.2)	118 (44.5)	593 (28.9)	124 (52.3)	208 (47.4)
Sex									
	Male	2,875 (70.7)	25,362 (70.0)	2,869 (72.1)	4,614 (80.5)	1,837 (69.6)	10,772 (62.1)	1,232 (68.2)	2,410 (71.5)
	Female	3,042 (72.0)	21,626 (70.5)	2,987 (74.3)	4,709 (83.0)	1,127 (68.3)	5,664 (60.2)	813 (67.2)	1,652 (72.6)
Stage at diagnosis									
	I	741 (89.7)	6,860 (93.9)	816 (86.3)	1,299 (91.0)	739 (93.5)	5,058 (90.6)	599 (85.9)	1,106 (90.5)
	II	2,463 (93.0)	16,040 (94.4)	2,115 (88.3)	3,434 (97.3)	922 (90.2)	3,927 (80.0)	551 (84.8)	1,134 (91.4)
	III	1,816 (90.9)	15,280 (91.0)	1,637 (88.0)	3,184 (95.8)	892 (85.4)	5,269 (71.2)	534 (84.1)	1,344 (88.3)
	IV	870 (39.7)	6,185 (41.0)	1,139 (56.9)	1,334 (51.2)	305 (33.3)	1,287 (26.3)	328 (48.2)	376 (29.6)
	Unknown	27 (4.3)	2,623 (24.4)	149 (18.7)	72 (13.9)	106 (20.5)	895 (22.6)	33 (9.3)	102 (26.1)
Total		5,917 (71.3)	46,988 (70.2)	5,856 (73.2)	9,323 (81.7)	2,964 (69.1)	16,436 (61.5)	2,045 (67.8)	4,062 (71.9)

Resectional surgery: Surgery removing the primary tumour, within nine months of diagnosis, excluding diagnostic, and palliative procedures.

Appendix Table 3. Proportion of surgically-treated patients below age 90 years by age, sex and stage at diagnosis, colorectal adenocarcinoma diagnoses, 2010-2012.

	Life expectancy in years			
Age	**Denmark**	**England**	**Norway**	**Sweden**
Females				
70	15.8	16.3	16.8	16.8
75	12.3	12.7	13.0	13.0
80	9.2	9.5	9.6	9.6
85	6.6	6.7	6.8	6.8
90	4.4	4.5	4.4	4.4
Males				
70	13.3	14.0	14.0	14.3
75	10.2	10.7	10.6	10.9
80	7.5	7.9	7.7	7.9
85	5.3	5.6	5.4	5.5
90	3.6	3.8	3.6	3.6

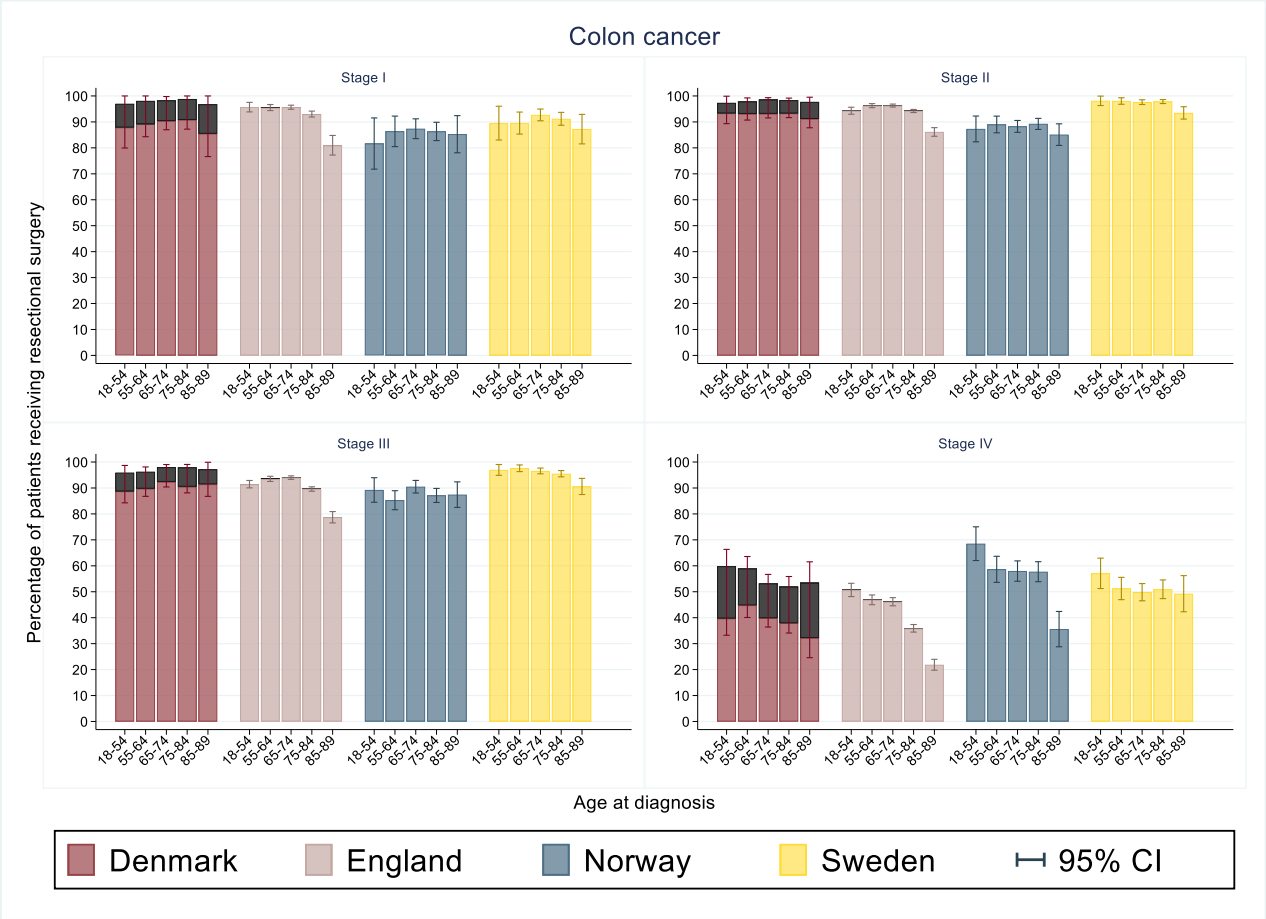
Based on population-based life tables produced by the London School of Hygiene & Tropical Medicine.[1]

Appendix Table 4. Life expectancy in people aged 70+ years in the general population, 2010.

	Colon tumours				Rectal tumours			
	Denmark	**England**	**Norway**	**Sweden**	**Denmark**	**England**	**Norway**	**Sweden**
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Stage I								
Radiotherapy	2 (0.2)	132 (1.8)	2 (0.2)	2 (0.1)	218 (27.5)	1,934 (34.1)	260 (36.9)	613 (49.2)
Chemotherapy	36 (4.3)	137 (1.8)	12 (1.2)	21 (1.4)	207 (26.1)	649 (11.4)	162 (23.0)	118 (9.5)
Stage II								
Radiotherapy	21 (0.8)	389 (2.2)	19 (0.8)	23 (0.6)	282 (27.3)	2,414 (48.1)	344 (52.2)	817 (64.6)
Chemotherapy	527 (19.4)	2,798 (16.0)	115 (4.6)	417 (11.4)	371 (35.9)	1,369 (27.3)	241 (36.6)	266 (21.0)
Stage III								
Radiotherapy	20 (1.0)	662 (3.8)	19 (1.0)	11 (0.3)	303 (28.5)	4,084 (54.3)	305 (47.3)	991 (63.9)
Chemotherapy	1,254 (61.6)	8,143 (47.2)	827 (42.8)	1,774 (51.6)	720 (67.8)	3,488 (46.4)	233 (36.1)	741 (47.8)
Stage IV								
Radiotherapy	81 (3.6)	564 (3.6)	54 (2.6)	14 (0.5)	217 (23.2)	1,776 (35.3)	286 (40.9)	390 (30.1)
Chemotherapy	1,361 (60.3)	6,426 (41.0)	672 (32.3)	298 (11.2)	624 (66.7)	2,516 (50.1)	271 (38.8)	205 (15.8)
Missing stage								
Radiotherapy	10 (1.4)	350 (2.9)	15 (1.7)	4 (0.7)	162 (28.5)	1,091 (25.0)	126 (31.3)	124 (28.1)
Chemotherapy	94 (13.2)	1,136 (9.5)	28 (3.2)	15 (2.6)	138 (24.3)	462 (10.6)	24 (6.0)	74 (16.8)

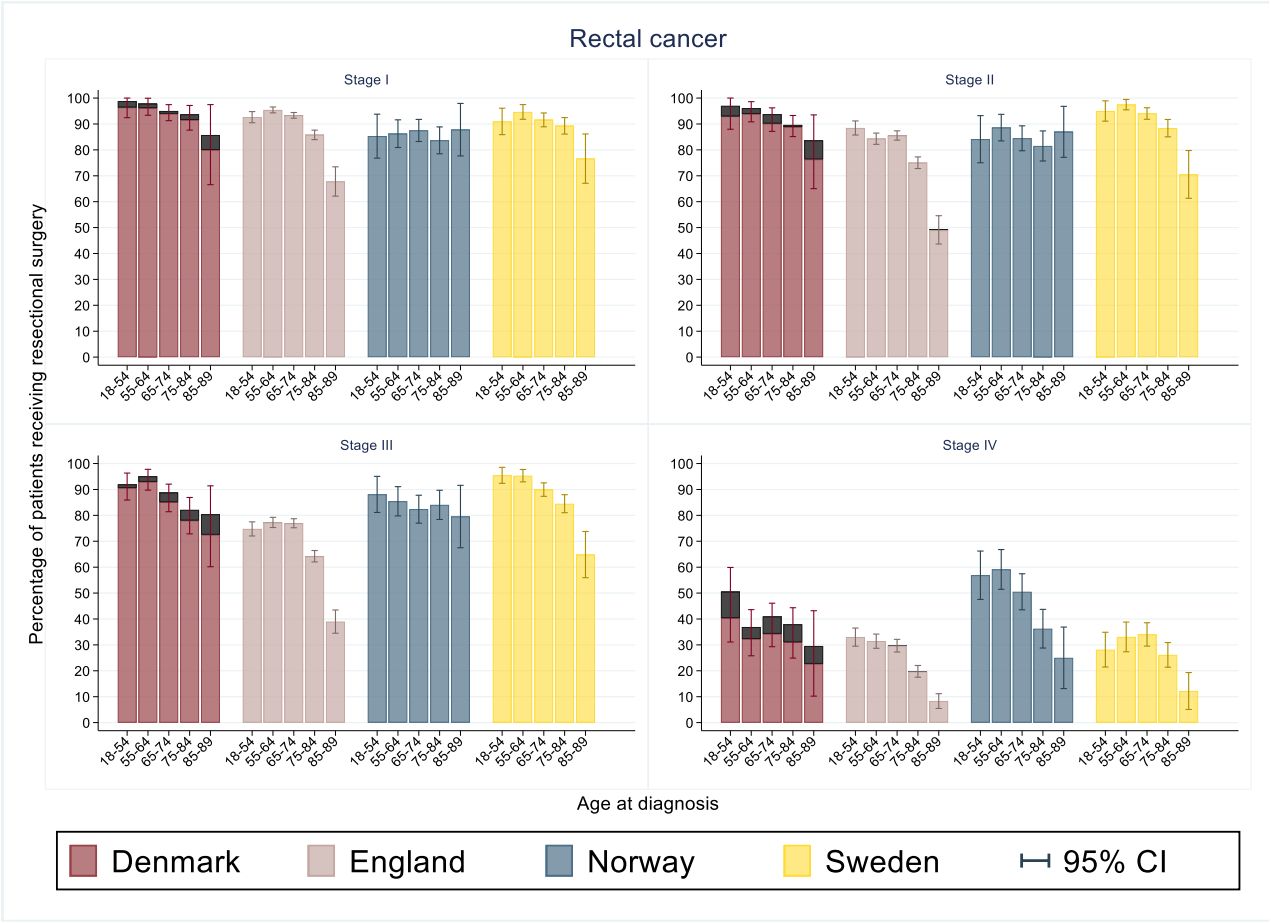
Notes: Missing data on chemotherapy (all countries), and radiotherapy (Denmark and England) mean that the figures presented are not fully comparable. Cautious interpretation is advised.

Appendix Table 5. Proportion of patients with evidence of receiving radiotherapy and chemotherapy by stage, colorectal adenocarcinoma diagnoses 2010-2012.



Appendix Figure 1a: Proportion of patients younger than 90 years with evidence of receiving resectional surgery for colon adenocarcinoma, by stage at diagnosis and age group, diagnoses 2010-2012.

To be compared with Figure 2a; Resectional surgery: Surgery removing the primary tumour, within nine months of diagnosis, excluding diagnostic and palliative procedures. For Norway and Sweden, we had information on surgical status for all patients. Information on surgery was missing for some patients in Denmark and for a tiny proportion of patients in England. The dark shaded areas at the top of the bars for Denmark and (less visible) for England represent the proportion of patients with unknown surgical status, by stage and age-group. The overall height of the bars represents the proportion we would observe if all of the patients with missing treatment data had received surgery.



Appendix Figure 1b: Proportion of patients younger than 90 years with evidence of receiving resectional surgery for rectal adenocarcinoma, by stage at diagnosis and age group, diagnoses 2010-2012.

To be compared with Figure 2b; Resectional surgery: Surgery removing the primary tumour, within nine months of diagnosis, excluding diagnostic and palliative procedures. For Norway and Sweden, we had information on surgical status for all patients. Information on surgery was missing for some patients in Denmark and for a tiny proportion of patients in England. The dark shaded areas at the top of the bars for Denmark and (less visible) for England represent the proportion of patients with unknown surgical status, by stage and age-group. The overall height of the bars represents the proportion we would observe if all of the patients with missing treatment data had received surgery.

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3.3 Exploring the role of comorbidity in explaining differences in stage-specific treatment of rectal cancer between Denmark and England

3.3.1 Background

The work presented in the previous section showed that in comparison with Norway and Sweden, England still lags behind in colon and rectal cancer survival, overall and in the stage-specific analysis. In contrast, CRC survival in Denmark is close to that of Norway and Sweden, especially for rectal cancer. This finding is consistent with another recent international comparison of cancer survival.[156] We also show that the proportion of patients receiving resectional surgery for colorectal cancer was lower in England than in the other countries, especially in the older age groups and/or with stage IV disease. In the paper, we argue that the suboptimal management of older patients in England could help explain international differences in cancer survival.[128] A plausible alternative explanation of this finding is that older cancer patients in England have a higher degree of concomitant chronic conditions than patients of similar age and disease extension in the other countries, so the higher risk of perioperative mortality and morbidity affects negatively their eligibility for surgery.[83,157] This is unlikely to be the case in the general population of these countries because life expectancy is highly comparable in the older age groups.[158] The prevalence of comorbidity in cancer patients may, however, differ from the one in the general population, as some chronic conditions may share risk factors with the cancer in question; for instance, obesity is a risk factor for both ischaemic heart disease and colorectal cancer.[159]

To account for the effect of comorbidity in determining receipt of treatment, in this follow-up analysis, I examined the distribution of resectional surgery by stage, age and comorbidity level in patients with non-metastatic rectal cancer in Denmark and England, for which we had information on comorbidity, addressing objective 3 of this research degree project. I focus on patients with non-metastatic disease because these tumours should be amenable to surgical resection, in the absence of other contraindications for surgery.

3.3.2 Materials and methods

Data sources and variable definitions

Patients with non-metastatic (stage I-III) rectal adenocarcinoma diagnosed during 2010-2012 in Denmark and England were included in the analysis. Information on patients diagnosed in Denmark was obtained from National Cancer Registry records linked to the Danish Colorectal Cancer Group (DCCG.dk) database. Information on patients diagnosed in England was obtained from National Cancer Registry records linked to the National Bowel Cancer Audit (NBOCA) data, and to the Hospital Episode Statistics (HES) database.

'Resectional surgery' was defined as the procedure to remove the primary tumour, regardless of the intent and outcome of the surgery, performed within nine months of diagnosis. Procedures to derive TNM stage and resectional surgery were described previously.[126,128]

For Danish patients, diagnoses recorded up to 10 years before their cancer contributed to the Charlson Comorbidity Index (CCI), derived by Danish Colorectal Cancer Group Database (DCCG.dk) staff; for English patients, CCI was calculated using diagnoses recorded in secondary care records (Hospital Episode Statistics, HES) up to 9 years before the cancer diagnosis, using an algorithm previously described.[124] For all patients, diagnoses made in the 3 months previous to the cancer diagnosis were excluded. Individual chronic conditions included in the CCI and their associated scores are listed in Table 3.1. For analyses, the CCI was then categorised into 3 levels: no record of comorbidity (CCI 0), mild comorbidity (CCI 1-2), and moderate to severe comorbidity (CCI 3 and above).

Individual diagnoses	CCI score
Myocardial infarction	1
Congestive heart failure	1
Peripheral vascular disease	1
Cerebrovascular disease	1
Dementia	1
Chronic pulmonary disease	1
Rheumatic disease	1
Peptic ulcer disease	1
Mild liver disease	1
Diabetes without chronic complication	1
Diabetes with chronic complication	2
Hemiplegia or paraplegia	2
Renal disease	2
Previous malignancy	2
Moderate or severe liver disease	3
Metastatic solid tumour	6
AIDS/HIV	6

Table 3.1: Chronic conditions included in the Charlson Comorbidity Index (CCI)

Statistical analyses

First, I compared the proportion of patients with rectal adenocarcinoma receiving resectional surgery by age and disease stage by country, focusing on patients without record of comorbidity. I then carried out a sensitivity analysis to examine whether the age gradient could be explained by misclassification of the comorbidity status in an important proportion

of patients in England. If this were the case, a share of patients in England did not undergo surgery because they had comorbidity that contraindicated it, but they were incorrectly classified as having no comorbidity due to lack of this information in secondary care records. The sensitivity analysis entailed randomly changing the comorbidity status of approximately half of patients in England without record of resectional surgery, and no comorbidity. This was done by assigning each relevant patient a value of a uniformly distributed random variable (with values between 0 and 1), and changing the comorbidity status of the lowest half. Effectively, these patients were excluded from the sub-analysis focusing on those without comorbidity, increasing the proportion of patients treated in England. The procedure was performed 1000 times. Results from individual iterations were averaged to obtain the proportion treated, and were also used to obtain standard errors and 95% confidence intervals.

Finally, I used a multivariate logistic regression model to predict the probability of receiving resectional surgery by country, age, sex, stage and comorbidity status. The initial model included the main effects of country, age, sex, stage, and comorbidity level and all potential interactions. Main effects were kept a priori in the final model, plus relevant interactions based on the likelihood ratio test. The non-linear effect of age was modelled using restricted cubic spline variables. After predicting the probability of receiving potentially curative surgery, I compared the instantaneous rate of change in (or, the first derivative of) the probability of receiving resectional surgery by age between the countries for each combination of sex, stage and comorbidity level.

3.3.3 Results

Proportion of patients without comorbidity undergoing resectional surgery

Comorbidity information was available for 97.2% (out of 2,887) and 99.9% (out of 18,208) of eligible patients in Denmark and England, respectively. Patients without a DCCG.dk record in Denmark (2.8%), and those with neither NBOCA nor HES record in England (0.1%) were classified as having no record of comorbidity. In Denmark, 31.4% of patients with non-metastatic rectal adenocarcinoma had a record of comorbidity, while in England, 22.3% of such patients had a record of comorbidity. In both countries, the prevalence of comorbidity increased with age (from 9.3% in the 18-55 age group to 43.0% in the 85+ in Denmark; and from 8.2% in the 18-55 age group to 34.4% in the 85+ in England).

As in our previous paper,[128] the proportion of patients receiving resectional surgery for rectal adenocarcinoma decreased with increasing age in both countries, and the age decline was substantially steeper in England than in Denmark at each stage of disease (Figure 3.1). There

was no significant difference in the proportion of patients treated for stage I disease (Figure 3.1), though it tended to be lower in England in patients aged 85 years or older. The proportion of patients receiving resectional surgery for stage II and III rectal cancer was substantially lower in England than in Denmark in those aged 75 years or older without a record of comorbidity.

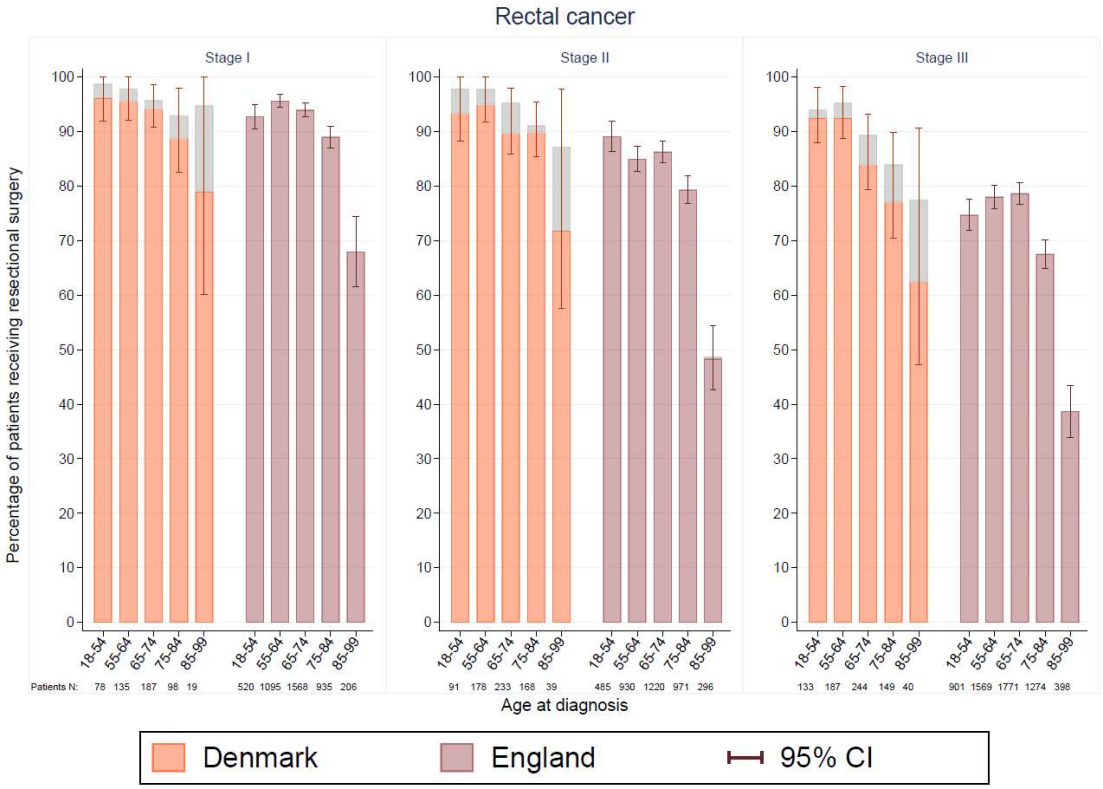

Figure 3.1: Percentage of patients with evidence of resectional surgery for rectal cancer, 2010-2012, excluding patients with comorbidity

Error bars are 95% CI. Resectional surgery: surgery to remove the primary tumour within 9 months of diagnosis, excluding diagnostic and palliative procedures. Light grey areas represent the proportion of patients with unknown surgical status by stage and age group; overall height of the bars shows the proportion of patients that would receive surgery if all patients with missing treatment data had surgical treatment.

The proportion of patients with neither evidence of comorbidity nor of resectional surgery was substantially larger in England (14.7%, or 2,677 patients) than in Denmark (7.4%, or 214 patients), as was the overall prevalence of comorbidity (reported above). Because of the lower prevalence of comorbidity in England, I carried out a sensitivity analysis to assess whether potential misclassification of the comorbidity status of patients without surgery in England could explain why the proportion of older patients surgically treated was lower in England than in Denmark. Of patients diagnosed in Denmark, 1970 (68.5%) were included in the sensitivity analysis. The exact number English patients included varied slightly between the 1000 iterations of the sub-analysis, and ranged between 12,597 (69.2%) and 12,782 (70.2%), with an average of 12,686 (69.7%) patients.

The proportion of patients surgically treated in England increased in comparison with the results including patients with no record of comorbidity (irrespective of their treatment status), in all combinations of stage and age group, due to the exclusion of an important proportion of English patients with neither evidence of comorbidity nor of surgery (Figure 3.2). After this additional exclusion, the proportion treated for patients aged younger than 85 years was similar between the countries. In contrast, the pattern of a lower proportion of older patients receiving resectional surgery in England was still obvious in stage II and III rectal cancer patients, though less marked than in the previous analysis.

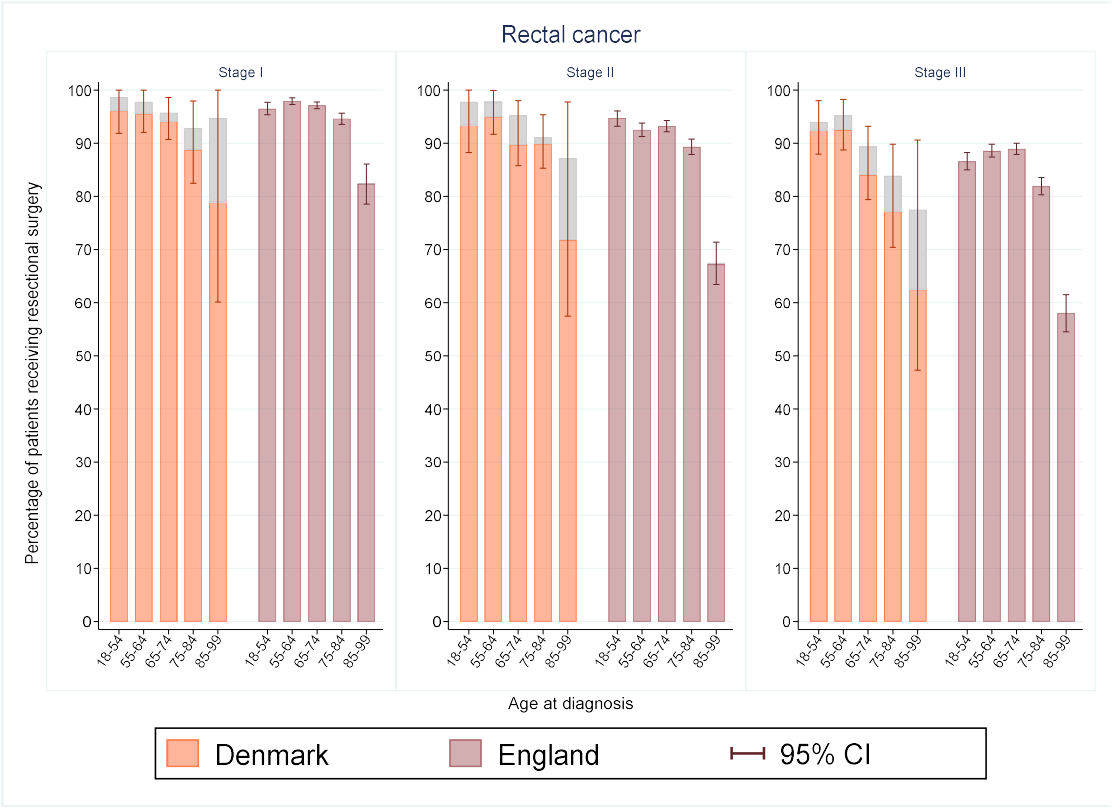

Figure 3.2: Percentage of patients with evidence of resectional surgery for rectal cancer, 2010-2012, excluding those with comorbidity and approximately half of patients in England without surgery and without comorbidity

Error bars are 95% CI. Resectional surgery: surgery to remove the primary tumour within 9 months of diagnosis, excluding diagnostic and palliative procedures. Light grey areas represent the proportion of patients with unknown surgical status by stage and age group; overall height of the bars shows the proportion of patients that would receive surgery if all patients with missing treatment data had surgical treatment.

Probability of receiving resectional surgery by age and comorbidity

The final logistic regression model to predict receipt of resectional surgery included the effects of country, stage, comorbidity level, three restricted cubic spline variables for age, and all relevant interactions. The effect of age on the probability of having resectional surgery varied by country, stage, comorbidity level, and sex. Similarly, the effect of

comorbidity on the outcome varied by country, stage, age, and sex. The effect of stage also varied by country and by comorbidity status and age.

Figures 3.3a and 3.3b show the predicted probability of receiving treatment by age in each strata of stage and comorbidity level in Denmark and England for women and men, respectively. Because 'sex' was one of the variables included in the logistic regression models, the predictions from these models are presented by sex, even if the results are largely comparable between women and men. In both countries the probability of receiving treatment decreased in older ages, usually after 70 years of age. In each combination of stage, comorbidity level and sex, the predicted probability of receiving resectional surgery was consistently lower in England than in Denmark. The probability of receiving surgery tended to be similar between the countries for younger patients, for whom there was more uncertainty around the estimates than for older patients, thus wider 95% confidence intervals. In general, the difference in the probability of receiving resectional surgery between Denmark and England increased with increasing stage, comorbidity level, and age.

In patients with stage I disease without comorbidity, the probability of receiving treatment was similar between the countries. In stage I patients with comorbidity, the predicted probability of treatment was lower in England than in Denmark at each age of diagnosis; and it tended to be larger with increasing age and level of comorbidity. For instance, the predicted probability of receiving resectional surgery in men aged 60 years, without comorbidity, and stage I rectal cancer was 96.5% (95% confidence interval 95.0-97.5) in Denmark and 94.9% (93.9-95.7) in England; while at age 85 years the predicted probability of resectional surgery was 82.8% (77.5-87.1) in Denmark and 79.8% (77.0-82.4) in England. In men with stage I disease and CCI score 1-2, the predicted probability of receiving surgery at age 60 was 97.8% (96.4-98.6) in Denmark and 94.4% (92.7-95.7) in England; in the same subgroup, the predicted probability of receiving surgery at age 85 years was 85.5% (79.7-89.8) in Denmark and 73.2% (68.8-77.1) in England.

In patients with stage II disease, the probability of receiving surgery was lower in England than in Denmark in each level of comorbidity, and significantly so (judged by the lack of overlap of 95% confidence intervals) from around age 50 years and older. The predicted probability of receiving surgery in women without comorbidity and with stage II disease at age 60 years was 94.0% (92.1-95.4) in Denmark and 87.0% (85.1-88.6) in England; while at age 85, it was 79.3% (74.9-83.1) in Denmark and 66.3% (63.1-69.3) in England. In women with stage II disease and CCI score 1-2, the probability of receiving surgery at age 60 years

was 95.0% (92.6-96.6) in Denmark and 82.2% (78.0-85.7) in England; and at age 85, it was 78.1% (71.5-83.5) in Denmark and 50.9% (45.7-56.0) in England.

Patients with stage III disease in Denmark were also more likely to receive resectional surgery than those in England at all ages, and significantly so for patients aged 50 years and older. For instance, the predicted probability of receiving surgery in women without comorbidity and with stage III disease at age 60 years was 90.2% (87.9-92.2) in Denmark and 79.4% (77.4-81.2) in England; at age 85, it was 69.0% (64.2-73.4) in Denmark and 52.6% (49.6-55.6) in England. In women with stage III disease and CCI score 1-2, the probability of receiving surgery at age 60 years was 92.0% (88.7-94.3) in Denmark and 72.9% (68.5-76.9) in England; and at age 85, it was 67.8% (60.3-74.4) in Denmark and 37.2% (32.8-41.8) in England. The trends were similar between women and men.

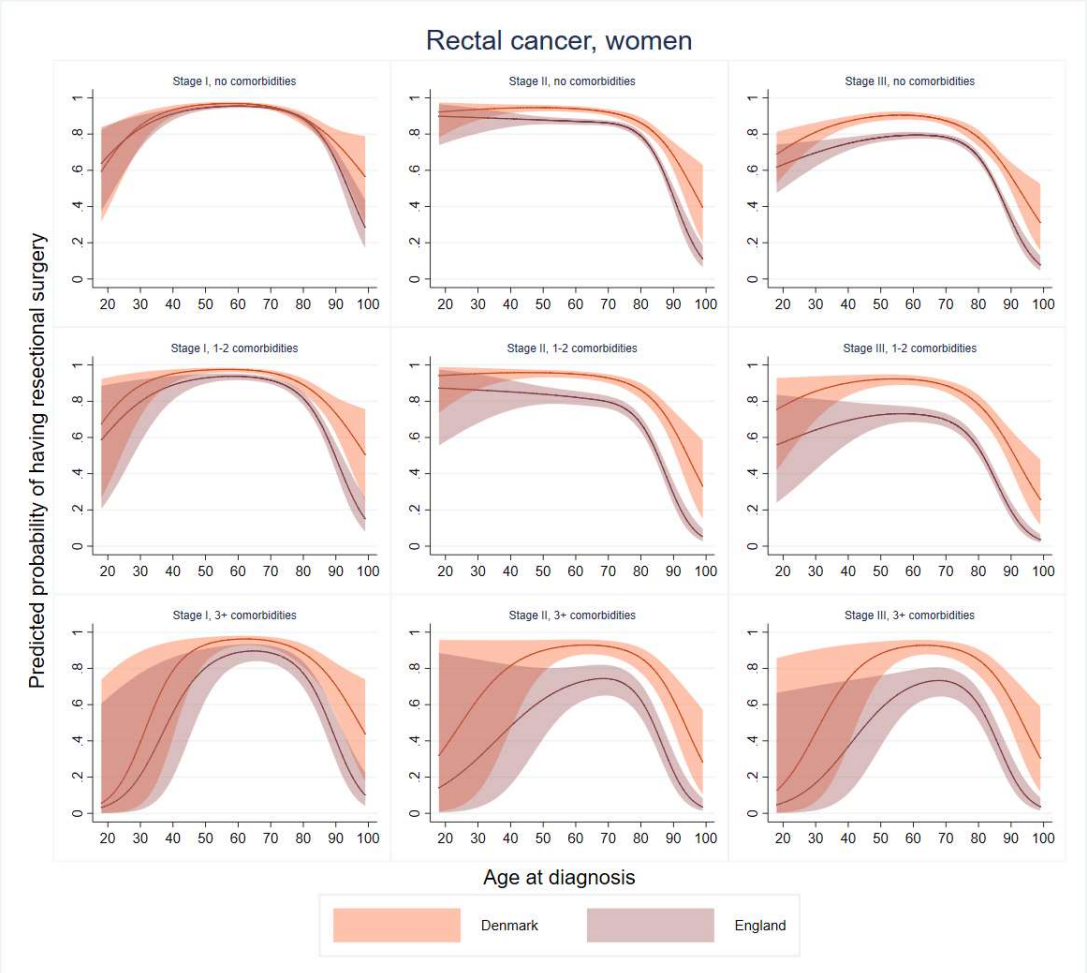

Figure 3.3a: Predicted probability of receiving radical surgery by age, comorbidity, and country in women diagnosed with rectal cancer, 2010-2012

Predicted from a logistic regression model including country, three restricted cubic spline variables for age, stage, comorbidity level, sex, and relevant interactions between these factors. Resectional surgery was defined as surgery to remove the primary tumour within 9 months of diagnosis, excluding diagnostic and palliative procedures. Categories of comorbidity represent levels of the Charlson Comorbidity Index score. Area around prediction lines represent 95% confidence intervals.

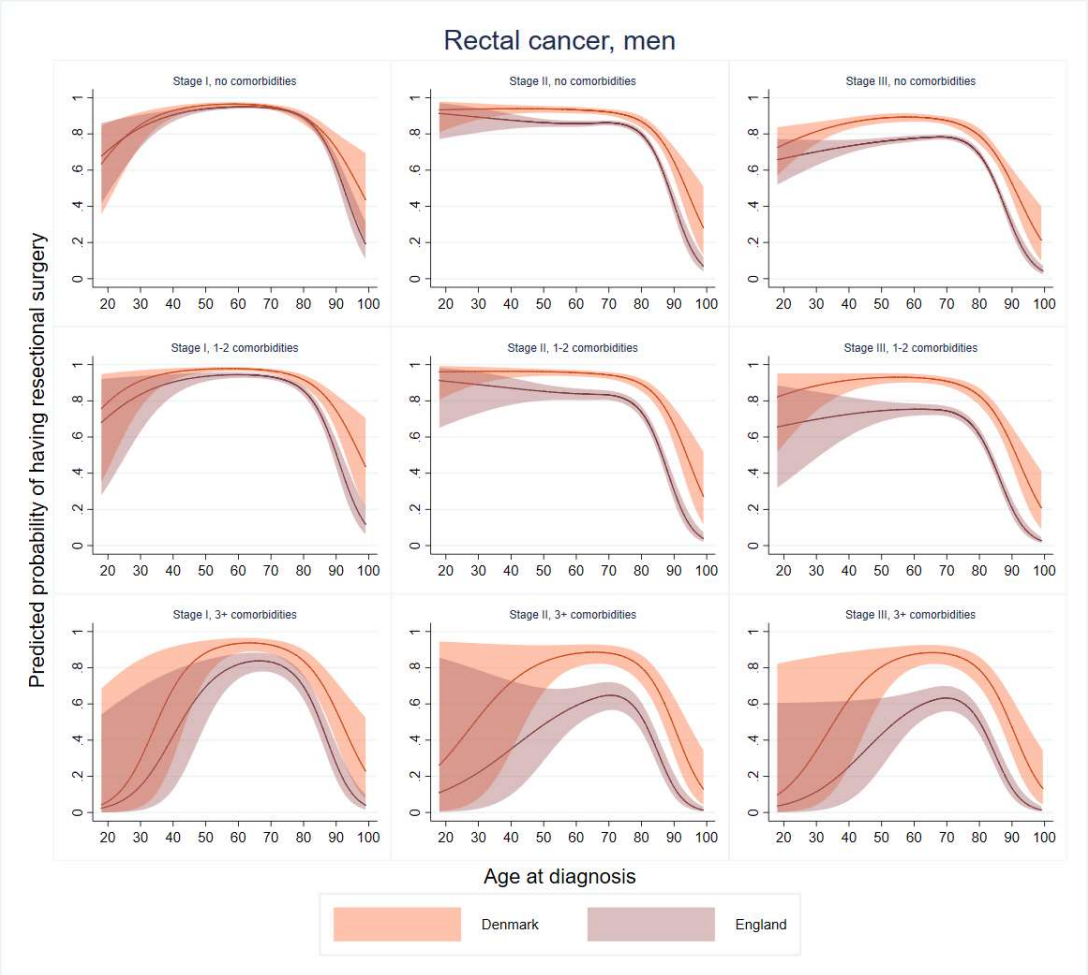

Figure 3.3b: Predicted probability of receiving resectional surgery by age and country in men diagnosed with rectal cancer, 2010-2012

Predicted from a logistic regression model including country, three restricted cubic spline variables for age, stage, comorbidity level, sex, and relevant interactions between these factors. Resectional surgery was defined as surgery to remove the primary tumour within 9 months of diagnosis, excluding diagnostic and palliative procedures. Categories of comorbidity represent levels of the Charlson Comorbidity Index score. Area around prediction lines represent 95% confidence intervals.

In both countries, the probability of receiving resectional surgery decreased with increasing age, however, this decline started at an earlier age, and at a faster rate in England than in Denmark. To explore this further, I compared the first derivative of the probability, or, the rate of change in the probability with a very small increment in age. This rate of change is positive when the probability increases with age and negative when the probability of surgery is decreasing with age. Results for each strata of stage, comorbidity level are presented in Figure 3.4a and 3.4b for women and men, respectively (as per the predictions in Figures 3.3a and 3.3b).

In general, in both countries, the rate of change in the probability of receiving resectional surgery was positive (increasing probability with increasing age) until around age 65 years, after which it became negative (decreasing probability with increasing age), in each strata of

stage and comorbidity level. However, in each strata, the rate of decrease in the probability of receiving resectional surgery with age appeared steeper in England than in Denmark. To evaluate this, I compared the age at which the rate started to decrease considerably (arbitrarily defined as the point at which the probability of receiving treatment decreased by more than 2% with a very small increase in age, by approximately one third of a day, or 1/1000 year). This rate of change in the probability of treatment was observed in all strata in both countries, and systematically occurred at an earlier age in England than in Denmark. For instance, in men with stage II rectal cancer and no comorbidity, the probability of receiving resectional surgery decreased by more than 2% from age 81 years in England and from 85 years in Denmark. In both countries the rate of change in the probability remained negative in older ages, though the rate of decrease was less marked (closer to zero) in oldest ages, as the predicted probabilities reached a plateau.

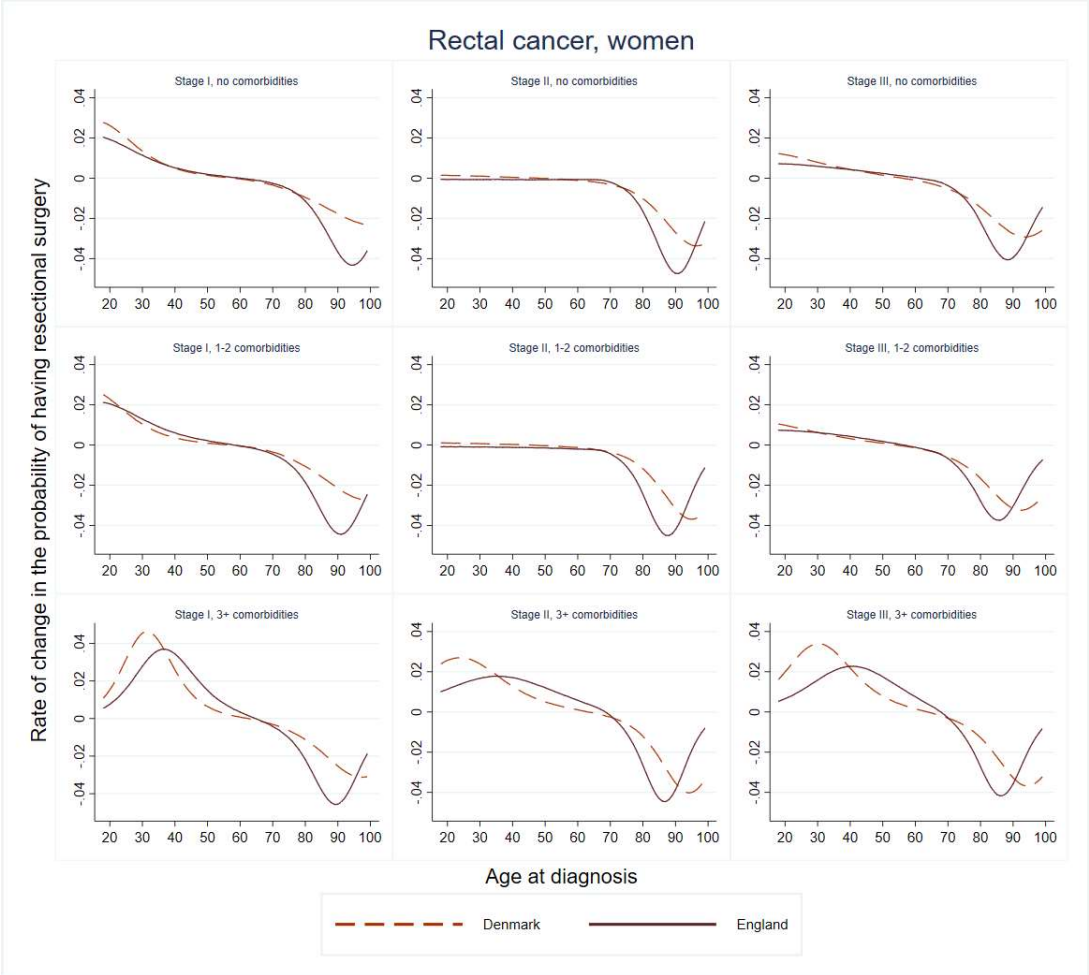

Figure 3.4a: Instantaneous rate of change in the probability of receiving resectional surgery in women diagnosed with rectal cancer, 2010-2012

Instantaneous rate of change was defined as the change in the probability of receiving resectional surgery with a very small increase in age of approximately one third of a day, or 1/1000 year. A positive value represents an increase in the probability, and vice versa. An increasing but negative rate (increase towards 0) represents a decrease in the probability at a slower rate than at the previous age. Predicted from a logistic regression model including country, three restricted cubic spline variables for age, stage, comorbidity level, sex, and relevant interactions between these factors. Resectional surgery defined as surgery to remove the primary tumour within 9 months of diagnosis, excluding diagnostic and palliative procedures.

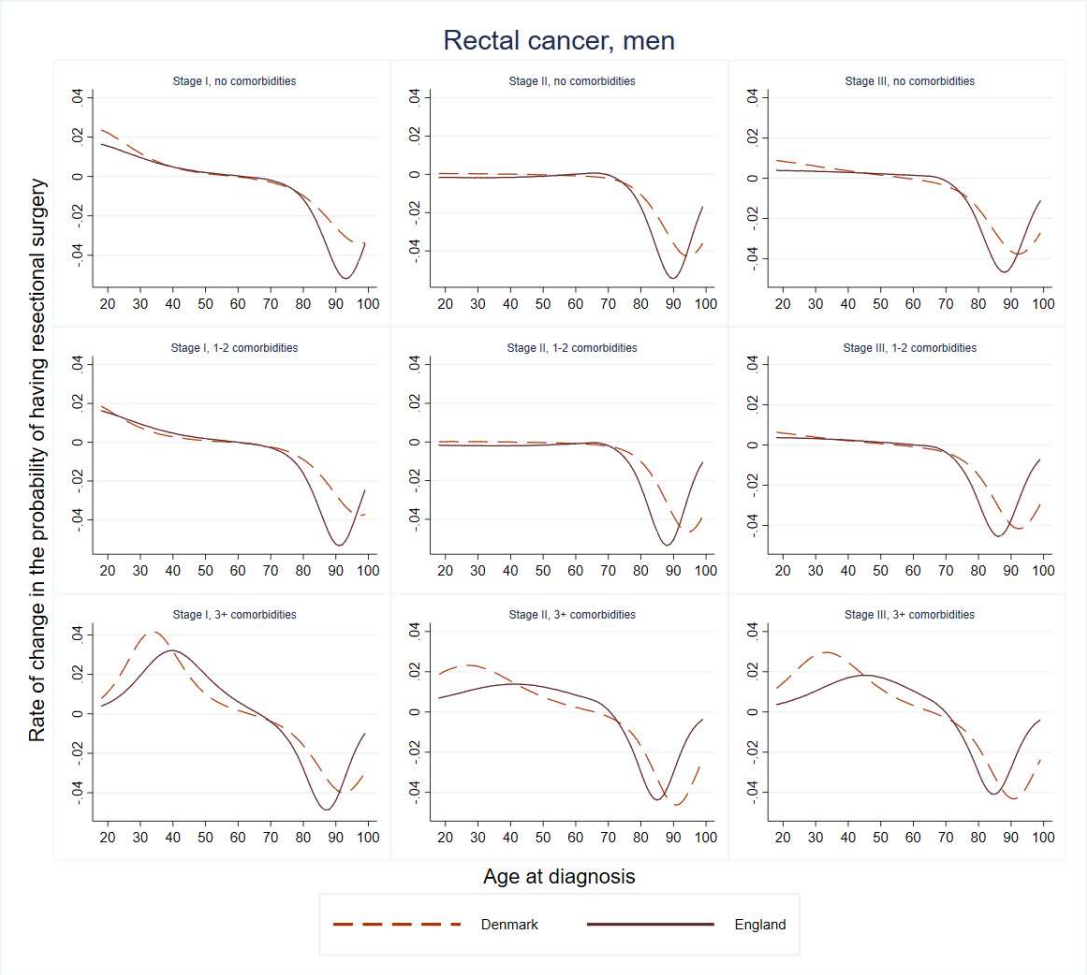

Figure 3.4b: Instantaneous rate of change in the probability of receiving resectional surgery in men diagnosed with rectal cancer, 2010-2012

Instantaneous rate of change was defined as the change in the probability of receiving resectional surgery with a very small increase in age of approximately one third of a day, or 1/1000 year. A positive value represents an increase in the probability, and vice versa. An increasing but negative rate (increase towards 0) represents a decrease in the probability at a slower rate than the previous age. Predicted from a logistic regression model including country, three restricted cubic spline variables for age, stage, comorbidity level, sex, and relevant interactions between these factors. Resectional surgery defined as surgery to remove the primary tumour within 9 months of diagnosis, excluding diagnostic and palliative procedures.

3.3.4 Discussion

After accounting for comorbidity, patients in England, especially older ones, were less likely to undergo resectional surgery for non-metastatic rectal cancer than patients with similar disease stage and age in Denmark. The difference in the probability of receiving potentially curative surgical treatment between the countries increased with increasing comorbidity level, disease stage and age. These findings suggest that although comorbidity is an important determinant of treatment, it does not fully explain the differences in the proportion of patients surgically treated for rectal adenocarcinoma between Denmark and England.

Comorbidity is an important determinant of cancer outcomes through different mechanisms. Patients who have frequent contact with the healthcare system to control their chronic condition(s) may be monitored more closely and have their cancer diagnosed at an earlier stage than patients with no regular contact with healthcare.[160,161] In contrast, certain chronic conditions, such as diabetes, renal disease, and dementia, may hinder early cancer diagnosis by masking some of its associated symptoms.[160,162] Furthermore, serious concomitant chronic conditions may contraindicate procedures to diagnose, stage and treat cancer. Several studies have found that comorbidity affects cancer outcomes, potentially in relation to lower probability or receiving potentially curative treatment.[59,83,124,160]

As expected, in the analysis, comorbidity, age, and stage at diagnosis were important determinants of receiving resectional surgery for rectal cancer in Denmark and in England, however, the magnitude of the effect of these factors varied between the countries, shown by the significant interactions (judged using the likelihood ratio test) between these factors (comorbidity, age and stage) and the variable 'country'. For each stage and age, the predicted probability of receiving treatment in Denmark between patients with no record of comorbidity and those with a low CCI score (1-2) was similar. In contrast, the predicted probability of receiving surgery for patients in England was substantially lower in patients with low CCI score (1-2) than those without comorbidity, even in patients with stage I disease. The decline in the probability of receiving surgery with increasing comorbidity in England was especially pronounced for older patients.

There have not been many population-based studies examining the role of comorbidity in explaining cancer treatment and survival, because this information is not traditionally collected in national cancer registration, and potentially because of comparability issues. A recent ICBP study examined the role of comorbidity in explaining differences in lung cancer survival between nine jurisdictions in Australia, Canada, Norway and the UK using national cancer registry data linked to secondary care records. They compared three measures of comorbidity (Charlson, Elixhauser, and the total number of in-patient days), focusing on the first six diagnostic codes made in the 4-36 months previous to the cancer diagnosis. Overall, they found these comorbidity measures to have good "face validity" ("degree to which the indicators evaluated the construct of comorbidity they purported to measure"),[163] however, they had little predictive validity in 1-year survival models. They judged the reliability of the indices ("the extent to which the indices measured a stable phenomenon across populations"),[163] by comparing age-standardised prevalence rates of the indexed conditions, which they found to vary substantially between jurisdictions. Researchers concluded that

they were not able to quantify the level of comparability of these indices between jurisdictions due to differences in coding practices, and called for further efforts in standardising data collection practices.[163] Although it is not entirely clear which comorbidity measure is ideal for international comparisons of population-based cancer outcomes, the CCI is a frequently used measure in epidemiological research, as it can be feasibly and reliably derived from secondary care records.[83,124,163]

The Charlson Comorbidity Index was proposed in 1987 as a method to predict mortality risk in longitudinal studies.[61] The CCI scores common chronic conditions based on their associated age-standardised relative risks of death at one year (obtained from a cohort of hospitalised patients in 1984 in the US); the scores are then added to obtain a composite index.[61] The CCI has the major advantage of being easily applicable to routinely collected, administrative hospital data, thus it is frequently used because of its simplicity and reproducibility.[124,164] However, the simplicity of the CCI is also a source of criticism because its additive nature assumes that there is no synergy or interactions between the different chronic conditions included. Another critique of the CCI is that some of the conditions included have improved prognosis since the index was developed. A particular concern is that HIV/AIDS is given the same score (6) as a metastatic solid tumour, although the prognosis of treated HIV is much better than what it was in the 1980s, and better than most metastatic solid tumours.

In a 2010 study, researchers adapted the CCI to the largest longitudinal primary care database, the UK-based General Practice Research Database (GPRD; nowadays called Clinical Practice Research Datalink, CPRD) to examine its relationship with mortality. They found a significant association between the derived CCI and 5-year mortality, and concluded that the CCI was a good discriminator of mortality.[165] Authors argued that the issue of HIV having better prognosis was unlikely to affect their results because of the low prevalence of the disease in the data (8 HIV cases in a sample of over 145,000 individual patient records).[165] Their findings are consistent with another study comparing the performance of the CCI between English primary and secondary care records (from CPRD and HES, respectively), which found that with either source of information, the CCI had 'excellent performance' in predicting mortality at one and five years of follow-up.[166] In a different discussion on the weight of HIV for the CCI, researchers argued that inaccurate results are more likely in populations with a high prevalence of HIV/AIDS, and suggested the HIV weight for the CCI should be reassessed in such cases.[167] In the CRC population included in this analysis, there were 3 HIV cases in England (out of 18,208 patients, and out of 45 with a CCI ≥6). The

corresponding figure for Denmark is not available as I had access to the composite CCI score rather than to individual diagnoses, but judging by the proportion of patients with a CCI ≥6 (29 out of 2,887), it is sensible to conclude that HIV prevalence in this population was also very low. Therefore, despite the known issue with the weight of HIV/AIDS, it is likely that the CCI is a valid discriminator of mortality risk in the study population.

Alternative measures of disease severity may be better predictors of mortality than the CCI. For instance, the Acute Physiology and Chronic Health Evaluation (APACHE) II, generally used in critical care, is a better discriminator of in-hospital mortality than the CCI, as it uses twelve physiological measurements (including arterial pH, heart and respiratory rate, serum sodium and potassium, among others), rather than individual chronic diagnoses.[164] The additional resources needed to derive physiology-based scores, however, prevent its use in population-based research,[164] making the CCI the best, and frequently the only, measure of comorbidity available for research.

The prevalence of comorbidity was lower in England than in Denmark overall and in each age group, and under-ascertainment of diagnoses from secondary care records cannot be excluded. To minimise the issue of comparability of different degrees of comorbidity, and of potential under-ascertainment of comorbidity diagnoses, the first part of the analysis was restricted to patients with no evidence of comorbidity. Then, I carried out a sensitivity analysis for misclassification of the comorbidity status in patients in England who did not receive surgery. The findings were robust even to the quite extreme scenario I used in the sensitivity analysis, suggesting that there is indeed a difference in the proportion treated, after accounting for comorbidity differences. Furthermore, the higher prevalence of comorbidity (including some conditions which are affected by similar risk factors as colorectal cancer) is consistent with the higher incidence of colorectal cancer in Denmark than in England and the UK.

Norway and Sweden were also included in our *Lancet Oncology* paper (Section 3.2), but I was not able to include them in the analysis adjusting for comorbidity because comorbidity information was not available in their respective specialised registries without additional linkage to secondary care records (impossible within the timeframe of this study). Nonetheless, the comparison between Denmark and England is particularly relevant. Historically, both countries have had poorer cancer outcomes than Norway and Sweden.[3] Recent reports have shown that cancer survival in Denmark is now closer to that in Norway and Sweden; whereas cancer survival in England, though improved, still lags behind.[1,156] The paper presented in Section 3.2 included both colon and rectal cancer patients, however

these subsequent analyses by comorbidity status did not include colon cancer patients because of the high proportion of patients without a DCCG.dk record and therefore with missing information on comorbidity and surgical status (more than twice as many as rectal cancer patients). This missing information would have added substantial uncertainty around the estimates, precluding a fair comparison of treatment status by age, stage and comorbidity.

In England, surgical specialties have periodically reported outcomes for individual consultants and hospitals since 2013. The clinical outcome publications include case numbers and 90-day mortality for patients undergoing elective colorectal cancer surgery by surgeon and hospital. Additional surgical outcomes are reported in specific annual reports, for instance, unplanned 30-day readmissions in the 2016 report, and positive circumferential rectal resection margin rate in the 2018 report. None of these measures/targets, however, monitor that patients eligible for potentially curative treatment are actually receiving it. Moreover, there is some debate on whether the publication of surgeon-specific outcomes encourages risk-adverse behaviour from surgeons, even while they may facilitate informed decision-making for patients.[168] A recent examination at the potential issue of "gaming of clinical data" found no evidence of decrease in the overall proportion undergoing bowel resection, nor in the 90-day mortality rates (adjusted for patient characteristics) after the public reporting of surgeon-specific outcomes.[168] Results were not shown by substrata of patients, and although the overall figures remain constant, it is possible that high-risk patients (e.g. older, and with multiple morbidity) may be affected by risk-adverse behaviour prompted by such reporting. Concerns exist about the challenging task of correctly identifying poor performance at surgeon level when the numbers of specific procedures per surgeon are low, and so would be the statistical power to detect outliers; hence, the lack of evidence of poor performance would not necessarily indicate good performance.[169] Others have pointed out how the (over-)emphasis on the role of individual surgeons on patient outcomes disregards the importance of the complex interaction between several factors, including the organisational culture,[170] perioperative care, support from other health professionals, and the communication between them.[171,172]

Wider health system factors may be particularly important for older cancer patients: even with best intentions, clinicians may be reluctant to indicate aggressive treatment to patients if adequate postoperative care and social support are unavailable.

Anastomotic leakage, the most severe complication following colorectal resectional surgery, is associated with high morbidity and mortality.[173-175] Reported risk factors include malignant

disease, emergency surgery, high ASA score, and old age, among others.[176] Prevention of this complication is somewhat elusive, but its early detection is key to minimise its negative consequences.[174,175] Close follow-up in the immediate postoperative period is thus essential to detect anastomotic leakage in the pre-clinical phase, for instance by observation of changes in the drainage fluid, biochemical parameters of systemic reactions (such as C-reactive protein) and by prompt access to radiographic tests.[174,176,177] A close follow-up in the postoperative period is also key to ensure hemodynamic stability, and to avoid medical complications following abdominal surgery.[178]

A national, population-based study of postoperative mortality after colorectal cancer surgery in England found a decrease in postoperative mortality from 6.8% to 5.8% between 1998 and 2006 (5.8% after elective surgery, and 14.9% after emergency surgery during the whole study period), and significant variation between NHS hospitals, after accounting for different patient and tumour characteristics.[179] A single-centre study of postoperative mortality in patients undergoing emergency laparotomy in Bath found that patients admitted to critical care and high dependency units had lower short-term mortality than those sent to the standard post-anaesthesia unit.[180] The study authors note that there was no lack of critical care beds in their institution during the study period, and that the decision on postoperative care was made solely on clinical grounds (though often based on incomplete patient history).[180] In England, however, the (lack of) availability of critical care beds for non-cardiac surgery has been highlighted as a problem affecting surgical outcomes.[181-183] A 2011 investigation on short-term mortality in patients aged 75 years and older after colon cancer surgery in England found wide variation in adjusted 30-day mortality between NHS Trusts.[184] They reported increased odds of early mortality with increasing age (after adjusting for comorbidity, sex and surgical approach); and decreased odds of early mortality with the laparoscopic approach.[184] Although authors did not investigative the effect of postoperative care directly, they argued that institutional differences in the use of intensive care and geriatric services could be behind the differences in early mortality between Trusts.[184] A 2006 study using data from the Intensive Care National Audit & Research Centre database in the UK found that less than 15% of 'high risk' surgical patients (mainly older, with coexisting chronic conditions) had been admitted to intensive care units following surgery, and accounted for 80% of the deaths, though represented only 12.5% of the surgical population.[183]

In recognition of unsatisfactory levels of care after emergency surgical admissions, the Emergency Laparotomy Network and audit (NELA) was established in 2010 in England.[178] In

its first report, authors acknowledged that surgical mortality is influenced by the hospital's ability to recognise and manage complications, and that this likely to be better done in a critical care unit than in a standard ward.[178] Authors also found that when requested, a critical care bed was available most of the times, however, the rate of referral appeared "inappropriately low", given the high postoperative mortality.[178]

Postoperative mortality in Denmark has been reported to be higher than in Norway and Sweden, and more similar to that in England.[185] Between 2001 and 2011 Denmark saw an important decrease in postoperative mortality following elective colorectal cancer surgery from 7.3% to 2.8%[186] (a larger decrease than the one reported for England between 1998 and 2006).[179] The laparoscopic surgical approach has been associated with the reduction in mortality following colon cancer surgery (it was used in over 65% of colon cancer surgery in 2015).[186,187] A study of CRC diagnoses in Denmark during 2001-2004 found a wide variation in 30-day postoperative mortality (3.5-44.1%), with the odds of death 4.6 times higher in emergency patients, and 5.8 times higher in patients with high ASA score; authors argued that the hospitals' ability to manage these patients were behind the institutional variation in postoperative mortality.[188] A 2014 study found that mortality following an emergency surgery remained high (18.5%).[189] A failure to recognise complications early, and inadequate level of care (admission to standard ward followed or not by critical care unit admission) were found as determinants of postoperative mortality.[189] A more recent analysis of postoperative mortality in Denmark (2005-2015) reported further decreases in 90-day postoperative mortality during the study period (from 31% to 24%).[190] Proposed explanations of reductions in postoperative mortality following CRC surgery in Denmark include improvements in the organisational structures (such as centralisation of surgery in specialised centres), perioperative optimisation and use of laparoscopic surgery.[71,186]

A 2010 review of the global burden critical illness in adults reported a lower number of ICU beds per 100,000 population in the UK (3.5) than any of the other European countries included (such as Sweden, 8.7; Spain, 8.2; and Germany, 24.6), and lower than other developed countries such as Australia (8.0) and Canada (13.5).[191] After non-cardiac surgery, patients are generally admitted to a standard post-anaesthesia unit, then transferred to critical care units if complications develop.[189,192] However, access to critical care may well vary (within and) between countries. In England, there is extreme variation in the planned used of critical care following colorectal surgery (from 0 to 97% of patients undergoing colorectal surgery after an emergency admission) between CCGs.[193] Access to ICU following colorectal cancer surgery in the English NHS varies by institution (personal communication

with colorectal surgeon Michael Machesney). Furthermore, access to critical care beds for colorectal cancer patients may depend not only on the number of beds available but also on the overall number of patients undergoing non-cardiac surgery at a given institution. In Denmark, on the other hand, specialised centres in which elective colorectal cancer surgery is performed generally have access to ICU when deemed necessary (personal communication with colorectal surgeon Professor Lene H. Iversen).

It is possible the unavailability of adequate postoperative care for older colorectal cancer patients is more of a problem in England than in the Scandinavian countries, and that this may help explain why older patients in England, and those with comorbidities are less likely to receive resectional surgery than those in Scandinavian countries.

It is also possible that, although clinical guidelines generally recommend surgery, older patients receive other treatment modalities instead of surgery (chemotherapy and/or radiotherapy, and palliative care) to avoid operative risk and minimise complications, especially in those with multimorbidity. The data on chemotherapy and radiotherapy was not sufficiently complete in all the datasets to allow a fair comparison between countries.[128] More recently, there have been efforts to improve the registering of those data in the specialised CRC registries, and/or dedicated datasets for these treatment modalities, like the Radiotherapy Dataset[194] and the Systemic Anti-Cancer Therapy Dataset[195] in England. Future research should exploit these additional data sources to explore further this issue and compare stage-specific outcomes across age groups by treatment modality.

Along with health system factors, negative perceptions of ageing influence patients' health behaviour, their expectations of care, and potentially, the clinical decision-making. So-called 'therapeutic nihilism', where clinicians and/or patients believe that treatment is of little value, may be more prevalent when evaluating older cancer patients, whose life expectancy is (often wrongly) considered to be short.[196] Negative perceptions of old age are likely perpetuated by the findings of poor operative outcomes in older patients (partly, a result of inadequate postoperative care), thus potentially creating a vicious cycle that results in older patients not receiving surgery, and having poor cancer outcomes.

Provided that adequate postoperative care is available, cancer outcomes may be improved by increasing access to – and the proportion of patients receiving – potentially curative treatment, which for many cancers including colorectal tumours, is surgery. In England, improved patient outcomes though improved access to surgery has already been documented for lung cancer.[197] Analyses of the National Lung Cancer Audit data have shown

a wide variation (by socioeconomic status, geographic location and age) in resection rates and lung cancer survival in England.[198,199]

Potential explanations of the age inequalities in cancer management in England, such as frailty, the availability and use of adequate perioperative care, and attitudinal factors deserve closer examination. Recent data streams such as clinical audits and patient-reported outcomes offer the possibility to explore some of these issues further.

3.4 Study implications and link to Chapter 4

Surgery is the cornerstone of colorectal cancer management both for curative and palliative purposes. There are however differences in the proportion of patients receiving resectional surgery in each stage of disease, with a sharp decline in the proportion treated with increasing age in England, the country with poorest colorectal cancer survival in comparison with Denmark, Norway and Sweden. The sharp decline in the proportion of patients receiving resectional surgery with increasing age was not as marked in the comparator countries. So, why are older cancer patients in England less likely to receive resectional surgery than those in Denmark, Norway and Sweden? Despite some differences in clinical guidelines, indications for surgery are highly comparable between the countries, and in none of these is chronological age a contraindication for surgical treatment. A plausible explanation of the differences found is varying levels of comorbidity, and its associated risk of perioperative mortality, between the countries. However, the differences in the proportion of patients treated (between Denmark and England) were still evident even after excluding patients with comorbidity. Residual confounding due to misclassification of comorbidity status is possible, however, after a sensitivity analysis for misclassification of comorbidity, the difference in the proportion treated in the older age groups was still evident. Furthermore, the predicted probability of receiving resectional surgery in England was lower than in Denmark at comparable levels of comorbidity, especially in the older ages. The findings suggest that, although important, comorbidity alone does not explain the deficit in the proportion treated in England in comparison with Denmark. Differences in the postoperative care may explain some of the differences in the management of colorectal cancer in older patients.

Further research should look into the role of additional treatment modalities in explaining the lower proportion of older patients in England receiving resectional surgery. Although chemotherapy and/or radiotherapy are generally indicated along with rather than instead of surgery, it is possible that these treatments are being indicated to replace surgery in order to minimise complications and mortality risk. Additional datasets from England would

provide more detailed information on radiotherapy (National Radiotherapy Dataset, RTDS)[194] and on chemotherapy (Systemic Anti-Cancer Therapy Dataset, SACT).[195]

Potential follow-up work should include closer examination and comparison of postoperative care, early mortality, postoperative complications and failure to rescue, by different characteristics including age, comorbidity, and urgency of admission. Such comparison may shed light into understanding whether and how perioperative care may be improved to improve cancer outcomes.

The findings presented in this chapter justify closer examination of the age disparities in cancer management within England because the underlying causes of under-management of cancer in older patients are not obvious. Comorbidity and its associated risk of perioperative mortality and complications may be a mechanism by which older patients are less likely to have optimal management than their younger counterparts in England, and elsewhere. Moreover, older cancer patients and those with multimorbidity are more likely to be diagnosed following an emergency admission. Colorectal cancer patients who present to secondary care as emergencies (because of bowel obstruction, bleeding, and/or perforation, for instance) have worse outcomes than patients diagnosed through elective routes. They are frequently in a poor acute health status, which may impede them to undergo optimal investigation and treatment. The following chapter focuses on exploring these factors – comorbidity and the diagnostic route – and their contribution as mechanisms behind the age difference in the likelihood of having an incomplete diagnostic investigation and potentially curative surgery for colorectal cancer in England, after accounting for differences by sex and socioeconomic status.

Chapter 4: Exploring health status and emergency presentation as mechanisms behind the age inequalities in colorectal cancer management in England

4.1 Introduction

In Chapter 3 of this thesis, I showed that the age differences in the receipt of surgical treatment were not as evident in Denmark, Norway and Sweden, as they were in England, and that these differences were unlikely to be explained by differences in the prevalence of comorbidity, at least between Denmark and England. I argued that these differences in management may explain partly the "survival gap" between England and the Scandinavian countries.

In this chapter, I explore in more detail the age differences in the probability of receiving adequate management of colorectal cancer within England. According to current clinical guidelines, diagnostic and staging investigations should be offered to all colorectal cancer patients, unless procedures are contraindicated by 'major comorbidity'.[41] If true, the age differential in the completeness of staging investigation should be mostly explained by age differences in prevalence of comorbidity. Major comorbidity may contraindicate surgical treatment due to increased perioperative risk. The diagnostic route may also influence cancer care and outcomes. Patients diagnosed with cancer through an emergency admission usually have a poor acute health status at diagnosis, and are less likely to be fully investigated and treated. [37,38]

In the work presented in this chapter, I use causal mediation analysis to examine and disentangle some of the underlying mechanisms underpinning age differences in the management of colorectal cancer patients in England. The paper presented in the next section (4.2) examines age inequalities in the completeness of diagnostic and staging investigation, and the extent to which these age differences are explained by comorbidity and the diagnostic route (emergency presentation or not). The following section (4.3) focuses on the age inequalities in the receipt of potentially curative surgery for stage I-III colorectal cancer, and the role of comorbidity, the diagnostic route, and the investigation in explaining these differences.

4.2 Age variation in the completeness of diagnostic and staging investigation for colorectal cancer

This section addresses objective 4 of this research degree project, which is to examine the effect of age on receiving a complete diagnostic and staging investigation for colorectal cancer and to explore how this relationship is mediated by comorbidity and the diagnostic route in England. The research for this section has been reported in the paper entitled "Exploring age variation in colorectal cancer diagnostic and staging investigation in England using mediation analysis", which was submitted for peer-review to the *European Journal of Epidemiology* in March 2019.

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Student ID Number	376763	**Title**	Ms
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Surname/Family Name	Benitez Majano		
Thesis Title	Exploring age inequalities in the management and survival of colorectal cancer patients		
Primary Supervisor	Dr Sarah Walters		

If the Research Paper has previously been published please complete Section B, if not please move to Section C.

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SECTION D – Multi-authored work

For multi-authored work, give full details of your role in the research included in the paper and in the preparation of the paper. (Attach a further sheet if necessary)	I am the lead author of this paper. I co-planned the study with my supervisors, prepared the data for analyses, carried out analyses under supervision of SV, BR and SW, and prepared the draft of the paper. Co-authors provided feedback and input on the data preparation, analyses, interpretation and on the paper drafts.

SECTION E

Student Signature	
Date	25th February 2019

Supervisor Signature	
Date	

Title

Exploring age variation in colorectal cancer diagnostic and staging investigation in England using mediation analysis

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Abstract

Background

Older cancer patients often have fewer staging investigations and inferior treatment compared to younger patients. This suboptimal cancer management is commonly attributed to the increased likelihood of an emergency presentation, and to comorbidity, which is more prevalent in older patients and may contraindicate some medical interventions. We aim to quantify how far the age disparities in completeness of diagnostic and staging investigations for colorectal cancer (CRC) are explained by patients' health status and their diagnostic route (emergency or not).

Methods

We obtained information on colon and rectal cancer patients diagnosed in England during 2010-2012 from population-based cancer registry records. Staging investigations and comorbidities in the six years before the cancer diagnosis were derived from the National Bowel Cancer Audit and Hospital Episodes Statistics datasets. A counterfactual-based mediation analysis, allowing for multiple mediators, was used to quantify the proportion of the age effect on staging investigations mediated by health status or diagnosis route. A novel sensitivity analysis technique for multiple mediators was developed to assess the robustness of the findings against unmeasured confounding.

Results

Around half of patients had complete staging investigations. For colon cancer, there was a J-shaped association with patients aged 60-69 years being the least likely to have an incomplete DSI. The risk of an incomplete DSI in rectal cancer patients increased linearly with age. The age-investigation association was barely mediated by health status, but was partly mediated by being diagnosed through an emergency route. Overall, an important proportion of the age differential was not mediated by these factors, particularly in older patients. These findings were robust to strong degrees of unmeasured confounding of the relationship between the diagnostic route and having complete staging investigations.

Discussion

Colorectal cancer patients' health status and diagnostic route did not fully explain the age differential in the completeness of staging investigations, contradicting prevailing beliefs. Findings suggest the important role of decision-making based on chronological age in investigation completeness. Age-related inequalities in cancer management seem to occur as early as at the diagnostic and staging investigations phases. Clearer recommendations should be included in the clinical guidelines for the management of older cancer patients.

Background

Cancer is an important contributor to disease burden in older people [1]. It is estimated that by 2030, 76% of cancers in men and 70% in women will occur in people over the age of 65 years [2]. Nonetheless, older cancer patients are known to have fewer diagnostic and staging procedures, less evidence-based treatment, and worse cancer outcomes than younger patients [1].

Colorectal cancer (CRC) is generally diagnosed through referral from primary care, screening, or after an emergency admission. In England, a cancer-specific referral route (two-week wait route, TWW) was introduced in the 2000s to hasten referral for suspected cancer to secondary care and avoid delays in diagnosis [3]. The National Bowel Screening Programme, rolled-out in 2006, offered biennial faecal occult blood testing (FOBT) to people aged 60-69 years, and was extended up to age 74 years in 2009 [4, 5]. Despite its national coverage, uptake is reportedly low [6]. Patients diagnosed through emergency admissions (about a third and a sixth of colon and rectal cancer patient populations, respectively) frequently have poorer health at the time of diagnosis, are less likely to receive potentially curative treatment, and generally have poorer survival than patients diagnosed through other routes [7, 8, 9].

Once in secondary care, patients are investigated to exclude or confirm a CRC diagnosis, usually with colonoscopy or flexible sigmoidoscopy [10]. If the CRC diagnosis is confirmed, patients undergo further investigations to determine the extent of disease, described by TNM (tumour/node/metastases) stage, and to plan for optimal management. TNM stage is a combination of clinical stage, determined by physical examination and imaging procedures, and pathological stage of the primary tumour and regional lymph nodes, usually established during (generally therapeutic) surgery. Figure 1 summarises the patient pathway to CRC diagnosis and staging.

Suboptimal cancer management and poorer outcomes in older cancer patients are often presumed to relate to their comorbidity and/or frailty ('biological age'), and how this affects their options for effective treatment and their recovery from it [11, 12]. There are concerns, however, that the age differential in patient care and outcomes may be partly due to clinical decision-making based primarily on chronological age [13].

A complete investigation is essential for determining optimal treatment. According to current English clinical guidelines, diagnostic and staging investigations should be offered to all CRC patients, unless procedures are contraindicated, usually by 'major comorbidity' [10]. If this is true, the age differential in the completeness of staging investigation should be mostly explained by differences in comorbidity, and potentially, the diagnostic route (emergency or non-emergency), between age groups. Disentangling these underlying mechanisms is crucial to improve cancer management and outcomes.

In this study we aim to examine the mechanisms behind age differences in the completeness of diagnostic and staging investigations in England, and to explore the role of patients' health status and route to diagnosis using counterfactual-based mediation analysis.

Materials and methods

Data sources and variables

All colorectal cancer patients aged 15-99 years diagnosed in England during 2010-2012 and recorded in the national cancer registry were included. Individual tumour records were linked to the National Bowel Cancer Audit (NBOCA) data [14], Hospital Episodes Statistics (HES) [15], and the Routes to Diagnosis monitoring dataset (RtD) for additional clinical information [8]. A binary variable was used to classify patients as having been diagnosed through an emergency presentation (EP) or not. Age was categorised into six groups: 15-49, 50-59, 60-69, 70-79, 80-89 and 90-99 years. We used the 60-69 age category as the reference for analysis, as this would include people eligible for CRC screening.

We developed an algorithm to obtain information on *diagnostic and staging investigations* (DSI) performed within three months of the cancer diagnosis from NBOCA and HES records. The HES dataset contains information on in-patient, out-patient, and Accident & Emergency (A&E) diagnoses, and medical procedures performed within the English National Health Service (NHS). It uses the OPCS Classification of Interventions and Procedures 4.7 [16], an NHS Fundamental Information Standard for the classification of interventions and procedures performed in NHS hospitals in England. Codes for DSI procedures were identified. In cases of multiple codes for the same procedure in a single patient,

priority was given to those considered more precise (for instance 'Diagnostic endoscopic examination of lower bowel and biopsy of lesion of lower bowel using fibreoptic sigmoidoscope' was preferred to 'Unspecified endoscopic examination of lower bowel using fibreoptic sigmoidoscope'), and those performed closest to the cancer diagnosis date. Information on procedures was summarised into several categories: chest tomography, abdominal tomography, pelvic tomography, pelvic magnetic resonance imaging, colonoscopy, and CT colonography [10]. Information derived from HES was then complemented with data from NBOCA. This information was summarised into a binary indicator showing whether or not a 'complete' staging investigation was conducted, following definitions from NICE guidelines for CRC management [10]. For colon cancers, 'complete' was defined as having a colonoscopy or barium enema or CT colonograph, and CT scans of chest, abdomen and pelvis. Pelvic MRI was added to the definition for rectal tumours.

Information on TNM stage at diagnosis was derived from NBOCA and National Cancer Registry records using an algorithm previously described [17]. Information on comorbidity was extracted from HES records using an algorithm developed by Maringe *et al* [18]. Chronic conditions diagnosed or treated within the secondary care setting up to six years before and up to the date of the CRC diagnosis were included. Individual conditions included ischaemic heart disease, heart failure, stroke, peripheral vascular disease, peptic ulcer, chronic kidney disease, chronic obstructive pulmonary disease, chronic liver disease, diabetes mellitus, dementia, para/hemiplegia, human immunodeficiency virus infection, obesity and previous cancer. The information was used to derive the Charlson Comorbidity Index (CCI) [19]. Information on metastatic disease (stage IV) and comorbidity were summarised into a binary variable '*health status'* (good: no comorbidity, non-metastatic CRC; poor: Any comorbidity and/or metastatic CRC).

Socioeconomic status of patients at the time of the CRC diagnosis was represented by the income domain of the Index of Multiple Deprivation of the Lower Layer Super Output Area (LSOA) of residence, categorised into five categories of deprivation according to the quintiles of the national distribution of the LSOA-level deprivation scores.

Statistical analysis

Mediation analysis was used to examine and disentangle the underlying mechanisms of the relationship between age (X) and the completeness of diagnostic and staging investigations (Y). It consists of splitting the total effect of the main exposure on the outcome into direct (not mediated) and indirect (mediated) effects through one or several mediating variables (mediators).

Health status and EP are considered as potential mediators of the effect of age on having an incomplete DSI, with health status also potentially mediating the relationship between age and EP. The causal diagram of Figure 2 shows the assumed causal relationships between relevant factors.

We used causal mediation analysis to decompose total effects into indirect and direct effects in the presence of interactions and non-linearities [20], which are common in complex scenarios like this one. Direct and indirect effects were defined as average contrasts between the outcomes of the study participants in different age groups under different hypothetical interventions on the mediator(s), as explained below.

In the counterfactual-based mediation analysis below, we decompose the average difference in DSI between study participants in a given age group and participants with the same distribution of sex and deprivation in the reference age group (60-69). We refer to this as a total effect (TE), and decompose it into a direct and indirect effect. We define the direct effect (DE) of age on the outcome as the average risk difference of seeing the outcome between a given age group and the reference (60-69) if, for all patients, the health status and emergency presentation status were set at a fixed subject-specific level, randomly drawn from the distribution of these variables for reference patients of the same sex and deprivation status.

The indirect effect (IE) of age on the outcome is defined as the change in risk of seeing the outcome in the given age group if, for all patients in that group, the distribution of health status and emergency presentation status are shifted from how it is in reference patients to how it is from patients of the same gender and deprivation status in the considered age group.

We further decompose the IE into "path-specific" effects through each of the mediators (health status - Ma, and EP - Mb). The path-specific effect via health status represents the effect that may arise when age influences health status, which may then in turn affect the outcome (either directly, or by influencing EP). It is denoted IEa. The path-specific effect via Mb represents the effect that may arise when age directly influences the risk of emergency presentation (and not mediated via health status), which may then in turn affect the outcome. It will be denoted IEb. These effects, which add up to the IE, were estimated along with the DE using a parametric g-computation procedure, as described by Daniel *et al* [21]. To do this, we first modelled each of the mediators and the outcome using multivariate logistic regression:

- Health status was modelled as a function of age, deprivation quintile, sex and any interaction(s) that were significant at the 10% level.
- EP status was modelled as a function of health status, age, deprivation quintile, sex and any interaction(s) that were significant at the 10% level.
- Completeness of diagnostic and staging investigation was modelled as a function of emergency presentation status, health status, age, deprivation quintile, sex and any interaction(s) that were significant at the 10% level.

Using the resulting models, we simulated the outcomes for each one of the hypothetical scenarios compared in the definitions of the IE, DE and TE, as well as the definitions of the path-specific effects, in temporal order. For instance, to estimate IEb, we used the above models to simulate for each subject what the health status, emergency presentation status and outcome would be if that subject had a particular age different from the reference level (age 60-69). We next simulated for each subject what the emergency presentation status would be if that subject's age were at the reference level, but their health status was as simulated before. We then simulated what the outcome would be for that subject if they had the particular age (different from the reference level), the health status that was previously simulated, and the emergency presentation status that was newly simulated. The average contrast between these two simulated outcomes for each subject then represents IEb. Standard error and confidence intervals were estimated using 10,000 non-parametric bootstrap samples. Results from iterations were averaged to obtain point estimates.

Like all mediation analyses, the above estimation procedure relies on untestable assumptions. These are unavoidable because we conceptualise the effect on an outcome of shifting the distributions of health status and emergency presentation, and these effects may be confounded [20].

In particular, the assumptions that we invoked, are:

- Positivity: each health status and emergency presentation status can be observed at every level of the confounders. This is required to avoid having subgroups of the study population where everyone has the same health status or emergency presentation status, in which case the data carry no information about the effects of mediator on outcome [22].
- No interference: A patient's DSI status is not affected by the health status or emergency presentation status of other patients.
- An additional assumption of no unmeasured confounding between mediators and outcome ($U_{m\text{-}y}$), shown in the causal diagram of Figure 2, is needed to identify the partitioned (or path-specific) effects.

Missing data on health status and emergency presentation status were handled using single stochastic imputation with chained equations, and compared against results from the complete-case analysis. A single imputation was sufficient, since the imputation procedure was also evaluated as part of the bootstrap procedure. Imputation models for health status and EP included the variables and interactions in the prediction models listed earlier, plus the outcome (DSI status) and the Nelson-Aalen estimator of the cumulative hazard rate function, evaluated at the observed event time. All analyses were carried out using Stata version 15 [23].

Sensitivity analysis for unmeasured confounding

The assumption of no unmeasured confounding ($U_{m\text{-}y}$) between the mediator(s) and the outcome may well be violated [24]: $U_{m\text{-}y}$ may induce bias in the estimate of the DE since adjusting for the mediator

then introduces a spurious association between age and $U_{m\text{-}y}$ (and thus also the outcome) and results in what is called collider bias.

In view of this, we developed a novel sensitivity analysis technique that can be used in combination with the g-computation strategy, even with multiple mediators. We used it to test the robustness of the findings against unmeasured confounding of the relationship between the mediator(s) and the outcome.

We focus the sensitivity analysis on the relationship between the second mediator (EP) and the outcome, because we expect stronger confounding of the association between the cancer diagnostic route and investigations than between patients' health status and the cancer investigations. Nevertheless, this technique can be extended to multiple mediators. In our analysis, we expect there is unmeasured confounding by one or several quality measures of cancer services in secondary care (U), which may determine both the diagnostic route (EP) and having a complete investigation (Y). For instance, hospitals without sufficient resources to meet demand may be incapable of offering adequate and timely staging investigations to diagnosed CRC patients; and may also be unable to offer timely outpatient appointments for suspected cancer, leading to more diagnoses being initiated through emergency admissions.

The sensitivity analysis invokes three unknown sensitivity parameters that express the strength of the association between U and the relevant mediator (parameters λ_0 and λ_1), and between U and Y (parameter β). Assuming different strengths of associations between U, M and Y, we compared the findings with the original ones assuming no unmeasured confounding.

The hypothetical variable U may be a vector of quality measures of secondary care, with higher U meaning better quality of care. Without loss of generality, we let U have mean zero. We moreover let U have variance of 1, conditional on X (age group), Mb (emergency presentation), and C (deprivation group, sex, and health status), in order to fix the scale (and thereby the meaning of the sensitivity parameters). We further assume that U is independent of X and C.

We performed the analyses under different scenarios, with varying strengths of association between U and Mb (parameters λ_0 and λ_1), and between U and Y (parameter β), where:

- β represents the strength of association between U and the outcome, on the log-odds ratio scale.
- λ_0 represents the risk difference of U between non-emergency presenters (Mb=0) and emergency presenters (Mb=1) in the reference age group (60-69 years).
- $\lambda_0 + \lambda_1$ represents the difference in the probability in being treated in a hospital with good quality of care between non-emergency and emergency presenters, in the other age categories.

We foresee that a larger probability of being treated in a 'good' hospital (U) is associated with a lower probability of having an incomplete investigation (Y). On the β scale, that means that we would expect β to be lower than 0, which would correspond to an odds ratio for the association between U and outcome below 1. In other words, we would expect patients in 'good' hospitals to be less likely to have incomplete investigations. The further away β is from 0, the stronger the association between U and Y. A β value of 0 implies that U is not associated with Y and that there is hence no unmeasured confounding.

Because they are defined on the risk difference scale, both λ_0 and $\lambda_0 + \lambda_1$ lie between -1 and 1, though it is unlikely that they would take these extreme values. Following the same logic as for β, λ_0 and $\lambda_0 + \lambda_1$ are likely positive, as we can assume that non-emergency presenters are more likely to be managed in 'good quality' hospitals than emergency presenters. Given that likely positive direction of association, the most extreme difference would be that non-emergency presenters are all managed in 'good' hospitals while all emergency presenters are managed in 'bad' hospitals in the unexposed, that is $\lambda_0=1$.

We would expect λ_0 to be somewhat larger than $\lambda_0 + \lambda_1$, assuming that the main exposure (age) might, although not necessarily, have played a larger role in the latter. A λ_1 value of zero would mean that the risk difference of U between non-emergency presenters and emergency presenters was the same in all age groups.

In summary, some combinations of the sensitivity parameters that would reflect a very strong confounding effect of U on the association between Mb and Y are:

- β = -0.5: People treated in a good quality hospital had a 39.9% smaller odds of having an incomplete DSI than people treated in a bad quality hospital.
- λ_0 = 0.5: Non-emergency presenters are 50% more likely to be managed in a 'good' hospital than emergency presenters, in the unexposed.
- λ_1 = -0.1: Non-emergency presenters are 40% more likely to be managed in 'good' hospital than emergency presenters, in the exposed ($\lambda_0 + \lambda_1$).

Results

Descriptive results

There were 64,509 colon cancer patients and 35,433 rectal cancer patients diagnosed in England during 2010-2012. Mean age at diagnosis was slightly lower in rectal cancer patients (70.0 vs 72.2 years in colon cancer patients). Approximately 47.5% of colon and 37.3% of rectal cancers were diagnosed in women (Table 1).

There was a known diagnosis route for 93.5% of colon and 92.8% of rectal cancer patients. The most frequent diagnosis route for colon cancer was EP (27.9%), followed by the two-week wait pathway (TWW, 23.5%). For rectal cancer, the most frequent route to diagnosis was TWW (36.1%), followed by standard General Practitioner (GP) referral (25.4%). 9.5% of colon and 10.1% of rectal cancer patients were diagnosed through screening. After imputation of missing values of health status and EP status the distribution of these variables was comparable to that in the complete-case sample (Table 1).

Stage at diagnosis was known for 67.8% of colon and 71.7% of rectal cancer patients. Among patients with known stage, 32.9% of colon cancer and 26.5% of rectal cancer patients had evidence of metastatic disease (TNM stage IV).

39.4% of colon and 31.2% of rectal cancer patients had evidence of at least one of the chronic conditions indexed in the Charlson comorbidity index in the six years prior to their CRC diagnosis. Approximately 53.1% of colon and 44.5% rectal cancer patients had evidence of either a pre-existing chronic condition and/or metastatic disease at the time of diagnosis, which we classified as having a 'poor' health status.

Around a third (37.0%) of colon cancer patients and half (52.1%) of rectal cancer patients had what we defined as an incomplete DSI. The proportion of patients with an incomplete investigation increased with age: patients in the oldest age group (90-99 years) had a higher proportion of incomplete DSI (62.1% for colon and 81.3% for rectal cancer) than patients aged 60-69 years (31.6% for colon and 48.0% for rectal cancer). Colon cancer patients in the youngest age group (15-49) were more likely to have an incomplete DSI than patients aged 60-69 years (45.0% vs 31.6%). This J-shaped relationship between the main exposure and the outcome was not seen in rectal cancer (Table 2).

The proportion of patients with an incomplete DSI was higher in patients with 'poor health status': 38.7% and 55.7% of colon and rectal cancer, respectively, in comparison with 21.2% and 35.3% of colon and rectal cancer patients without evidence of comorbidity or metastatic disease.

Patients who were diagnosed through an EP were more likely to have an incomplete DSI (54.4% of colon and 73.9% of rectal cancer patients) than those diagnosed through other routes (21.2% of colon and 35.3% of rectal cancer patients). Those with unknown route to diagnosis were the most likely to have an incomplete investigation (71.9% of colon and 83.8% of rectal cancer patients).

Mediation analysis

Colon Cancer

The total effect (TE) measured the risk difference (RD) of having an incomplete DSI between each age group and the baseline (60-69 years). For colon cancer, there was a J-shaped association with patients aged 60-69 years being the least likely to have an incomplete DSI (Table 3, Figure 3a). Patients in the youngest age group (15-49 years) had 8% additional risk of incomplete DSI, while the oldest (90-99 years) had 20% additional risk of incomplete DSI.

Separating the TE into mediated and non-mediated effects, the first mediator, health status, explained very little of the age differential, and tended to be protective of the outcome (negative IE mediated by health status) consistently in all age groups (RD ranged between -0.001 in the 15-49 to -0.008 in the 90-90 age group).

In all age groups, the second mediator, emergency presentation, mediated an important part of the age differences in the completeness of DSI: in absolute terms a harmful effect of EP was similar among all age groups (RD range: 0.031 in the 90-99 to 0.050 in the 15-49 age group), but the proportion mediated varied between them, with the smallest proportion mediated being in the oldest age group.

The effect of age that was not mediated by either of these two mechanisms (DE) varied considerably by age group: it was somewhat protective in the age groups adjacent to the reference category (RD: -0.011 in the 50-59; and -0.028 in the 70-79 age group) but harmful in the youngest (RD: 0.033) and particularly in the oldest (RD: 0.173). Patients in the oldest age group had 17.3% additional risk of having an incomplete DSI that was not explained by their health or EP status.

In terms of proportions, emergency presentation seemed to explain most of the age variation in the outcome - in all age groups except for the oldest, for which the RD remained largely unexplained by either health status or EP.

Rectal Cancer

The risk of an incomplete DSI in rectal cancer patients increased with age. In comparison with those aged 60-69 years, rectal cancer patients in the 15-49, 50-59 and 70-79 age categories had lower risk of having an incomplete DSI (TE range -0.028 -0.022) (Table 3, Figure 3b). Patients in the oldest age groups had considerably higher risk of the outcome (TE 0.053 in the 80-89; and 0.241 in the 90-99 age group).

The first mediator, health status, did not explain much of the age differential, and tended to be protective of the outcome in all age groups (range -0.011 -0.003). Similarly, the mediated effect by emergency presentation in the completeness of DSI was relatively small, though harmful, in all age groups (RD range: 0.004-0.010).

The DE, or effect of age that was not mediated by either of these two mechanisms, was protective in patients aged 15-59 and 70-79 in comparison with patients aged 60-69 years; but was harmful in the 80-89 (RD 0.052) and 90-99 (RD 0.248) age groups. In other words, patients in the oldest age group had an additional 24.8% risk of having an incomplete investigation in comparison with patients aged 60-69 years that was not explained by differences in health status, and emergency presentation. Most of the TE of age was therefore not mediated in the older age groups.

Results of the sensitivity analysis

Results from the sensitivity analysis show that the stronger the association between U (quality of hospital) and the outcome, and between U and Mb (emergency presentation), the higher the proportion of the TE that is explained by Mb, while the non-mediated effects move away from being harmful, in all age groups. However, the changes were insufficient for Mb to explain all the age differences in having an incomplete DSI, or to change the general interpretation of the original results, especially in the oldest and in the youngest age categories. The total and partitioned effects remained largely consistent with the original results (Figure 3).

Discussion

Age is associated with the completeness of diagnostic and staging investigations of CRC patients: we found a J-shaped association between age and the risk of an incomplete DSI in colon cancer patients, and a consistently increasing risk of an incomplete DSI with age for rectal cancer. Both older colon and rectal cancer patients (80+ years) have the highest risk of having incomplete investigations. We used mediation analysis to examine health status and emergency presentation as mechanisms to explain this age differential in DSI.

Health status (a combination of the effect pre-existing chronic conditions and metastatic CRC disease at the time of diagnosis) did not explain the age differences in investigations. For colon cancer, emergency presentation explained most of the age differences in DSI, except among the oldest age

group (90-99 years). The higher risk of incomplete DSI in rectal cancer patients aged 80 years and older (compared to those aged 60-69) remained largely unexplained by differences in health status and emergency presentation. Our findings suggest that suboptimal management of older cancer patients begins in the diagnostic and staging investigation stage.

Less intensive cancer management in older patients may be reasonable in some cases, however, there are concerns in England that age-related disparities in cancer care and outcomes partly arise because of clinical decision-making based primarily on chronological age rather than also considering biological age [13, 25, 26, 27, 28]. A recent study of non-small cell lung cancer patients in England found a dramatic decrease in the probability of receiving major surgery after age 75 years, even in patients with early stage disease and no reported comorbidity [29]. Another study found that chronologic age was an important determinant of clinical decision-making in a patient-scenario exercise, even if clinicians did not explicitly recognise it as such [26]. In a recent international comparison, older CRC patients in England were less likely to receive potentially curative surgery than patients with a similar extent of disease and age in Denmark, Norway and Sweden [30]. Life expectancy at 65 and 85 years are similar between these countries [31], so it is unlikely that comorbidity explains the international differences in receipt of treatment.

Suboptimal management of older patients has been extensively described for different chronic conditions including cancer [10, 12, 32, 33]. The higher prevalence of comorbidity in older age increases the likelihood of adverse events, which can outweigh the potential benefits of cancer-directed treatment as recommended by clinical guidelines [11, 33]. Additionally, older patients may be disadvantaged by contemporary health research, policy, and clinical guidelines which largely focus on single illnesses [34]. Specialised services allow the development and delivery of improved treatments of individual conditions, but may not be as beneficial for older patients who often have more complex clinical profiles. Despite the need for scientific evidence to justify clinical interventions in older cancer patients, they are generally excluded from clinical trials, and are underrepresented in research [1, 32, 35]. This is usually justified by the variable levels of comorbidity in older patients, which may compromise the generalisability of the findings. However, clinicians lack sufficiently detailed guidance to provide adequate cancer care to the elderly, and may tend as a result to err on the side of caution when deciding whether to recommend invasive tests and procedures. Similarly, patients and carers may benefit from more information about the implications of undergoing or refusing clinical interventions. Despite the uncertainty around cancer management in older patients, ‘old age’ is not a contraindication for investigation and treatment according to clinical guidelines [10].

A recent study found that the probability of dying within 90 days of a colon cancer diagnosis increased with age, even in patients with early stage disease and without comorbidity [36, 37]. Postoperative mortality also increases with age, and is higher in patients with comorbidity and in those who undergo emergency procedures [38]. Differences in early mortality may explain some of the age differences in DSI completeness: some patients, likely older, may have died before being fully investigated. Other patients, however, may have died early as a consequence of suboptimal management. Conscious of this potential reverse-causality, we reran the analyses in a subsample of patients who survived at least 90 days after diagnosis. Selecting patients who survived at least 90 days likely causes an underestimation of the true age differences, as some patients who were excluded may have died early as a result of suboptimal management in relation to age. However, although the risk differences in the older age groups decreased in comparison with the original results, especially for colon cancer, the finding that age differences in the completeness of CRC investigations were not fully explained by comorbidity and the diagnostic route remained valid (Web-Appendix Figure 2). Thus the differences in early mortality are unlikely to explain the findings.

Our finding of suboptimal management in the pre-treatment stage is important because without a complete investigation, a fully informed decision about treatment options simply cannot be made.

Study limitations

To our knowledge, this is the first time that information on diagnostic investigations has been derived from multiple data sources and used to assess the adequacy or completeness of those investigations based on current clinical guidelines in England. Until recently, such detailed clinical information was not routinely collected, and despite best efforts, it may still be incomplete.

HES contains information on medical procedures for administrative and financial purposes. Expensive procedures and/or those that are performed during a hospital admission are more likely to be included than less expensive diagnostic tests done in outpatient settings [personal communication: Sean McPhail, Public Health England]. Investigations performed in the private health sector are generally missing from HES. Since we are not able to differentiate people who underwent investigations but have missing information, from patients who did not undergo those procedures, our results may suffer from misclassification bias. However, we believe that purely administrative determinants of missing data are likely to affect all age groups alike. Missing information on diagnostic procedures performed in the private sector, is likely to be more prevalent in younger patients of working age, and/or patients of higher socioeconomic level, implying that a misclassification would only serve to underestimate the extent to which DSI is incomplete in older patients.

Similarly, we relied on secondary care health records for obtaining information on comorbidity. It is possible that some patients with no record of comorbidity, actually had undiagnosed and/or unmanaged chronic conditions. Furthermore, our comorbidity measure may well lack diagnoses made and managed solely in primary care. Such misclassification, if present, may particularly affect patients with certain characteristics (e.g. more deprived, or institutionalised), who may also tend to be older. The vast majority of patients (99.3%), however, had a secondary care record, therefore, we believe that major comorbidities would have been recorded if present. If managed exclusively in primary care, these conditions are unlikely to be major comorbidities that would contraindicate the staging procedures explored in this analysis.

Additional clinical information would have helped to characterise the overall health status of CRC patients. For instance, performance status scales are generally used in clinical settings to assess the degree of independence of cancer patients, and help determine eligibility for specific treatments [39, 40]. Some authors argue, however, that these scales are not ideal for older cancer patients, especially those with multiple comorbidities [41].Older patients have higher prevalence of cognitive impairment, depression, decreased mobility and may also lack social support [34, 42]. Although comprehensive geriatric assessment tools have been proposed and validated [41, 43], these are not commonly used in practice. Moreover, indicators of frailty (increased vulnerability resulting from decreased reserves from multiple physiologic systems [44]), such as cognitive impairment, malnutrition, and decreased mobility are rarely documented formally for older cancer patients [1].

Our measure of health status combined information on comorbidity with information on metastatic CRC to provide a richer measure than comorbidity alone. Nevertheless, this measure may still not capture the full extent to which frailty affects the clinical decision-making process. We tried several regroupings of the comorbidity information (e.g. cardiovascular risk, disability-related, minor/major comorbidity, CCI score categories), yet, none was an important predictor of the outcome in our data. Future research on the topic of age inequalities in cancer management would certainly benefit from improved measures of frailty in older patients, and documentation of those measures in electronic health records. A better understanding of the role of social support as a determinant of cancer management and outcomes would also potentially be useful to develop targeted interventions.

Another limitation of this study is the missing information on the mediators, especially on stage information used for the health status variable. Additionally, we lacked information to characterise the healthcare provider and other health system factors that may impact the mediator(s) and outcome. We carried out imputation of missing information, and a sensitivity analysis for unmeasured confounding to address these issues. These techniques, however, come with assumptions and thus our findings would have been stronger had the relevant data been available.

We have used counterfactual-based causal inference methods to examine age differences in CRC management. We have however refrained from calling the direct effect of age 'causal' because age is a "non-manipulable exposure" [45, 46]. We recognise that it is not a person's age per se that is a causal determinant of their cancer management. The direct effect of age represents the inequality that would remain if the distribution of health status and EP were equal between age groups. It reflects the effect of other factors strongly associated with age (for instance, social isolation and attitudes towards old age) that cause age inequalities, and which may – and should – be subject to intervention.

Conclusions

Our study shows that clinical decision-making for colorectal cancer patients in England is affected by their age at diagnosis, even though chronological age does not contraindicate investigation or treatment interventions according to current clinical guidelines. The suboptimal management of older CRC patients in England starts before treatment options become clear, during the diagnostic and staging phases.

These age differences in the likelihood of having incomplete diagnostic and staging investigations were not explained by comorbidity, and only partially by the diagnostic route, contradicting prevailing beliefs. The role of other potential mechanisms which may help or hinder the undertaking of these investigations, such as frailty and social support, should be examined further.

Having a full investigation is essential for having optimal treatment and for improving cancer outcomes. Although clinical guidelines and health policy do not exclude older patients, targeted efforts that specifically address their needs are needed to improve evidence-based management and cancer outcomes of this group.

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Tables

	Colon		Rectum	
	N (%)	After imputation	N (%)	After imputation
Age group				
15-49	3,432 (5.3)		2,148 (6.1)	
50-59	5,828 (9.0)		4,722 (13.3)	
60-69	15,913 (24.7)		10,066 (28.4)	
70-79	20,352 (31.5)		10,494 (29.6)	
80-89	16,200 (25.1)		6,912 (19.5)	
90-99	2,784 (4.3)		1,091 (3.1)	
Female	30,649 (47.5)		13,198 (37.2)	
Stage at diagnosis				
I	5,391 (12.3)		5,725 (22.5)	
II	12,374 (28.3)		5,328 (21.0)	
III	11,594 (26.5)		7,623 (30.0)	
IV	14,384 (32.9)		6,728 (26.5)	
[Unknown]	20,766 (32.2)		10,029 (28.3)	
Comorbidity	25,389 (39.4)		11,065 (31.2)	
Health status*				
0	18,313 (34.8)	22,920 (35.5)	13,216 (45.6)	16,214 (45.8)
1	34,260 (65.2)	41,589 (64.5)	15,761 (54.4)	19,219 (54.2)
[Unknown]	11,936 (18.5)		6,456 (18.2)	
Route to diagnosis				
Non Emergency routes	42,332 (65.6)	44,990 (69.7)	28,554 (80.6)	30,722 (86.7)
Screening	6,145 (10.2)		3,566 (10.8)	
Two-week-wait	15,174 (25.2)		12,772 (38.9)	
Standard GP	14,060 (23.3)		9,015 (27.4)	
Other	6,953 (11.5)		3,201 (9.7)	
Emergency presentation	17,964 (29.8)	19,519 (30.3)	4,320 (13.1)	4,711 (13.3)
[Unknown]	4,213 (6.5)		2,559 (7.2)	
Staging investigation				
Incomplete	23,848 (37.0)		18,444 (52.1)	
Total	64,509 (100.0)		35,433 (100.0)	

Table 1: Characteristics of colon and rectal cancer patients, England 2010-2012

Notes: *: Health status is 0 when there was no record of comorbidity or metastatic disease, 1 when there was record of comorbidity and/or metastatic disease, and Unknown when there was no record of comorbidity and unknown stage. GP: General practitioner.

	No DSI⁺ N (%)	After imputation	N (%)	After imputation
Age group				
15-49	1,546 (45.0)		1,037 (48.3)	
50-59	2,070 (35.5)		2,247 (47.6)	
60-69	5,024 (31.6)		4,827 (48.0)	
70-79	6,637 (32.6)		5,221 (49.8)	
80-89	6,841 (42.2)		4,225 (61.1)	
90-99	1,730 (62.1)		887 (81.3)	
Stage at diagnosis				
I	1,050 (19.5)		2,067 (36.1)	
II	2,695 (21.8)		2,051 (38.5)	
III	2,757 (23.8)		2,791 (36.6)	
IV	5,628 (39.1)		3,660 (54.4)	
[Unknown]	11,718 (56.4)		7,875 (78.5)	
Comorbidity				
No	13,921 (35.6)		12,083 (49.6)	
Yes	9,927 (39.1)		6,361 (57.5)	
Health status*				
0	3,878 (21.2)	5,964 (26.0)	4,665 (35.3)	6,756 (41.7)
1	13,262 (38.7)	17,884 (43.0)	8,780 (55.7)	11,688 (60.8)
[Unknown]	6,708 (56.2)		4,999 (77.4)	
Emergency diagnosis status				
0	11,046 (26.1)	12,781 (28.4)	13,108 (45.9)	14,893 (48.5)
1	9,771 (54.4)	11,067 (56.7)	3,191 (73.9)	3,551 (75.4)
[Unknown]	3,031 (71.9)		2,145 (83.8)	
All patients	23,848 (37.0)		18,444 (52.1)	

Table 2: Distribution of the outcome, incomplete diagnostic and staging investigation, by cancer by age group, stage, comorbidity and emergency presentation status

Notes: *: Health status is 0 when there was no record of comorbidity or metastatic disease, 1 when there was record of comorbidity and/or metastatic disease, and Unknown when there was no record of comorbidity and unknown stage.

	Colon			
	TE	DE	IEa	IEb
Age group				
15-49	0.082 (0.063 0.101)	0.033 (0.014 0.053)	-0.001 (-0.003 0.001)	0.050 (0.048 0.052)
50-59	0.027 (0.012 0.043)	-0.011 (-0.026 0.003)	-0.001 (-0.003 0.001)	0.040 (0.038 0.041)
60-69		(Reference)		
70-79	0.016 (0.005 0.027)	-0.028 (-0.037 -0.020)	-0.003 (-0.004 -0.001)	0.047 (0.045 0.049)
80-89	0.065 (0.054 0.077)	0.026 (0.016 0.036)	-0.005 (-0.007 -0.002)	0.044 (0.042 0.047)
90-99	0.196 (0.173 0.218)	0.173 (0.149 0.198)	-0.008 (-0.012 -0.004)	0.031 (0.027 0.035)
	Rectum			
	TE	DE	IEa	IEb
Age group				
15-49	-0.028 (-0.053 -0.004)	-0.030 (-0.055 -0.004)	-0.004 (-0.008 -0.001)	0.006 (0.003 0.009)
50-59	-0.029 (-0.047 -0.011)	-0.036 (-0.054 -0.018)	-0.003 (-0.006 -0.001)	0.010 (0.008 0.013)
60-69		(Reference)		
70-79	-0.022 (-0.037 -0.008)	-0.027 (-0.041 -0.012)	-0.005 (-0.008 -0.002)	0.009 (0.007 0.012)
80-89	0.053 (0.036 0.071)	0.052 (0.035 0.069)	-0.007 (-0.011 -0.003)	0.009 (0.005 0.013)
90-99	0.241 (0.203 0.280)	0.248 (0.209 0.286)	-0.011 (-0.017 -0.005)	0.004 (-0.002 0.010)

Table 3: Risk difference of having an incomplete staging investigation by age group in comparison with patients aged 60-69 years. Colon and rectal cancer diagnoses, England, 2010-2012

Notes: TE: Total effects; DE: Direct Effects (not mediated); IEa: Indirect effects mediated through health status; IEb: Indirect effects mediated through emergency presentation; Positive numbers indicate higher risk of having an incomplete staging investigation in comparison with the reference age group (60-69 years) and vice versa.

Figures

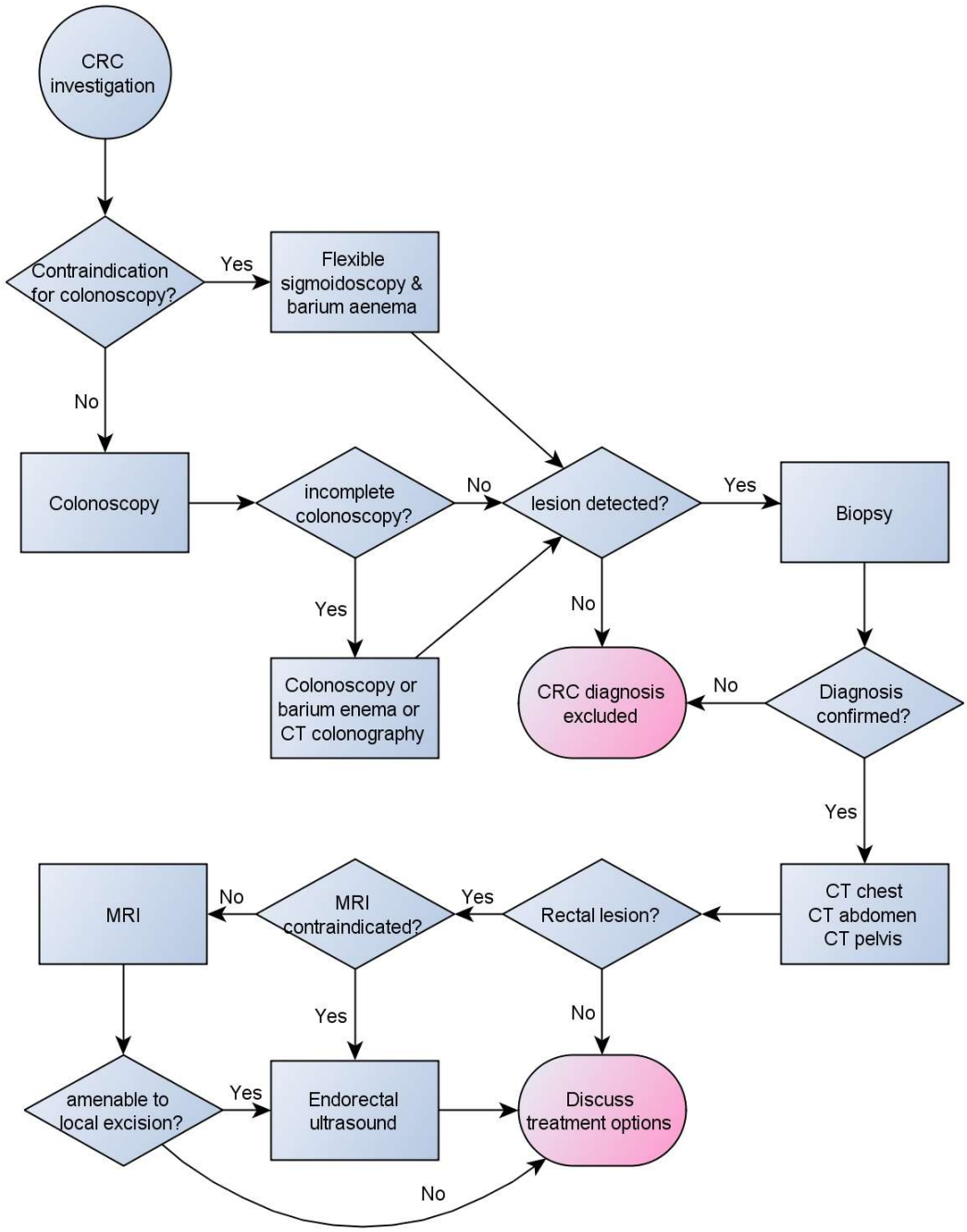


Figure 1: Pathways to diagnosis and staging investigation (DSI) of colorectal tumours (used to defined 'complete DSI' in this study)

Notes: CRC: Colorectal cancer; CT: Computerised tomography; MRI: Magnetic resonance imaging.

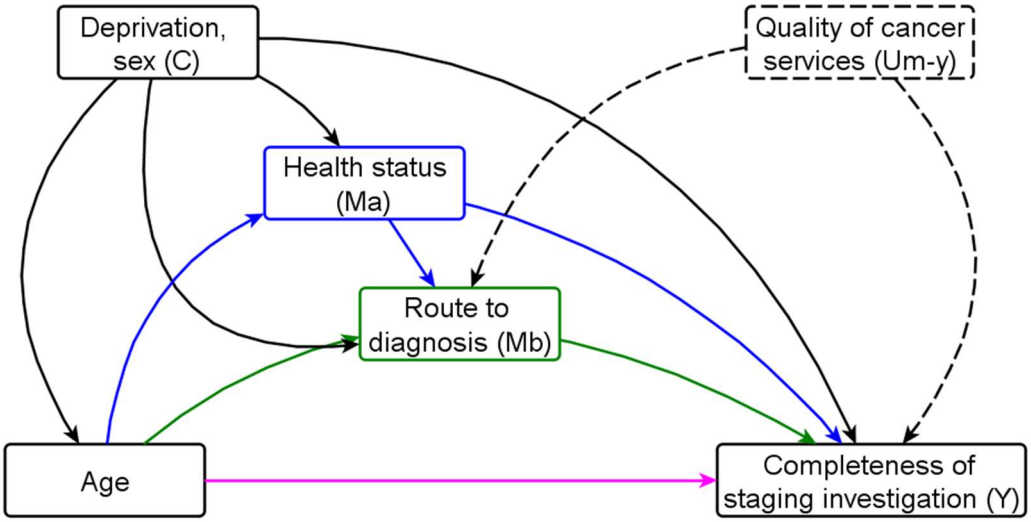


Figure 2: Hypothesised causal relations between age at presentation and different characteristics of colon and rectal cancer patients

Note: X: main exposure, age at presentation; C: measured confounders; Ma: First mediator; Mb: Second mediator; Y: outcome; Um-y: Unmeasured confounding of the relationship between the second mediator and the outcome; Solid line: measured. Dashed line: Unmeasured. Black arrows: confounding. Blue arrows: pathway through the first mediator. Green arrows: pathway through the second mediator.

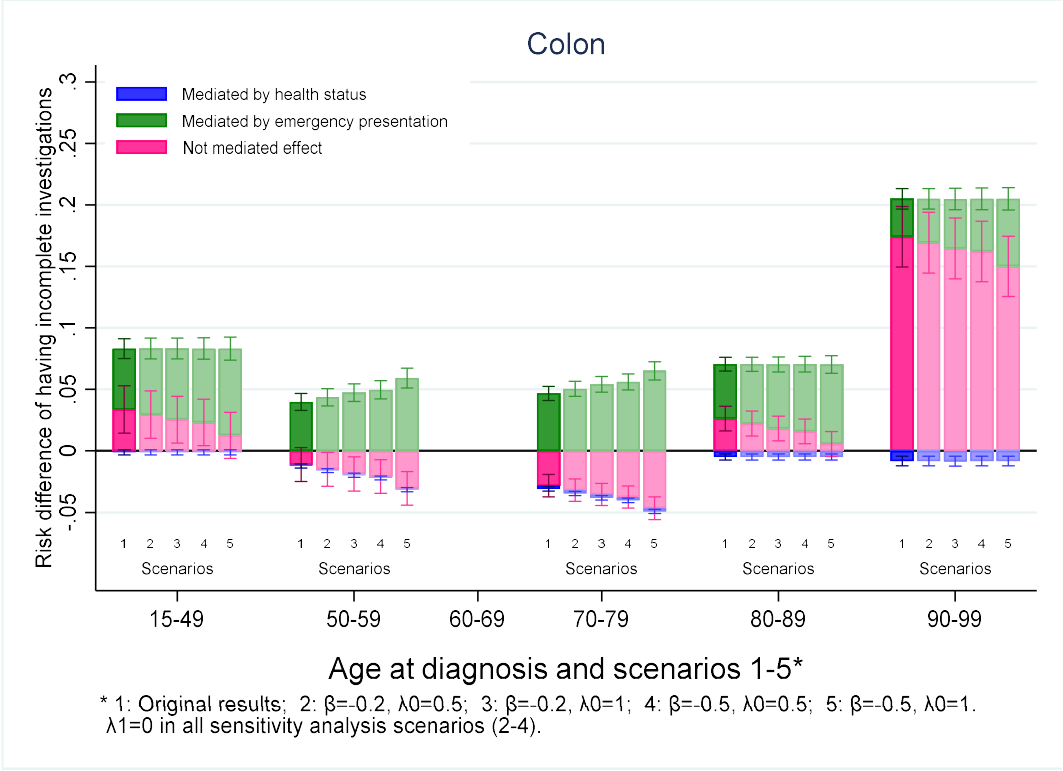


Figure 3a: Differences in the risk of having an incomplete diagnostic and staging investigation (DSI) for colon cancer, in comparison with patients aged 60-60 years.

Results from original mediation analysis (scenario 1), and sensitivity scenarios (scenarios 2-5, lighter colours) for unmeasured confounding of the relationship between emergency presentation and the DSI.

Sensitivity parameters: Scenario 2: β=-0.2, λ0=0.5; Scenario 3: β=-0.2, λ_0=1; Scenario 4: β=-0.5, λ0=0.5; Scenario 5: β=-0.5, λ_0=1. λ_1=0 in all sensitivity analysis scenarios (2-4).

Interpretation: β = -0.5: people treated in a good quality hospital had a 39.9% smaller odds of having an incomplete DSI than people treated in a bad quality hospital; λ_0 = 0.5: Emergency presenters are 50% more likely to be managed in a good hospital in comparison with emergency presenters, in the unexposed; λ_1 = 0: Emergency presenters are 50% more likely to be managed in a good hospital in comparison with emergency presenters, in the exposed ($\lambda_0 + \lambda_1$).

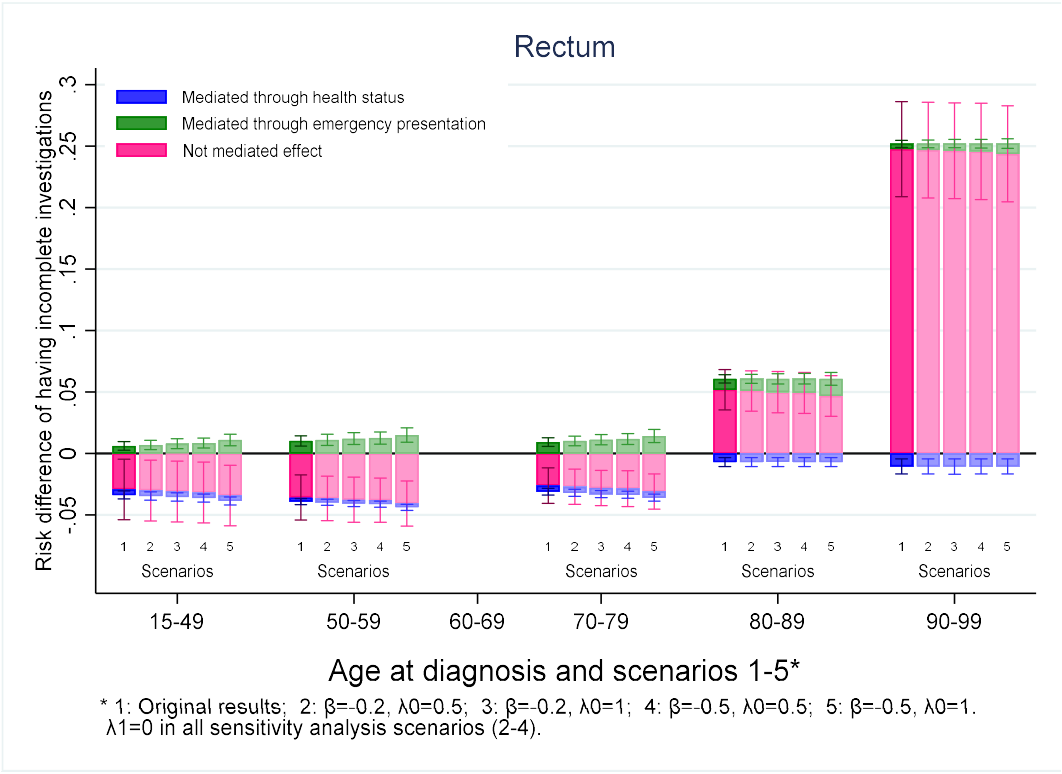
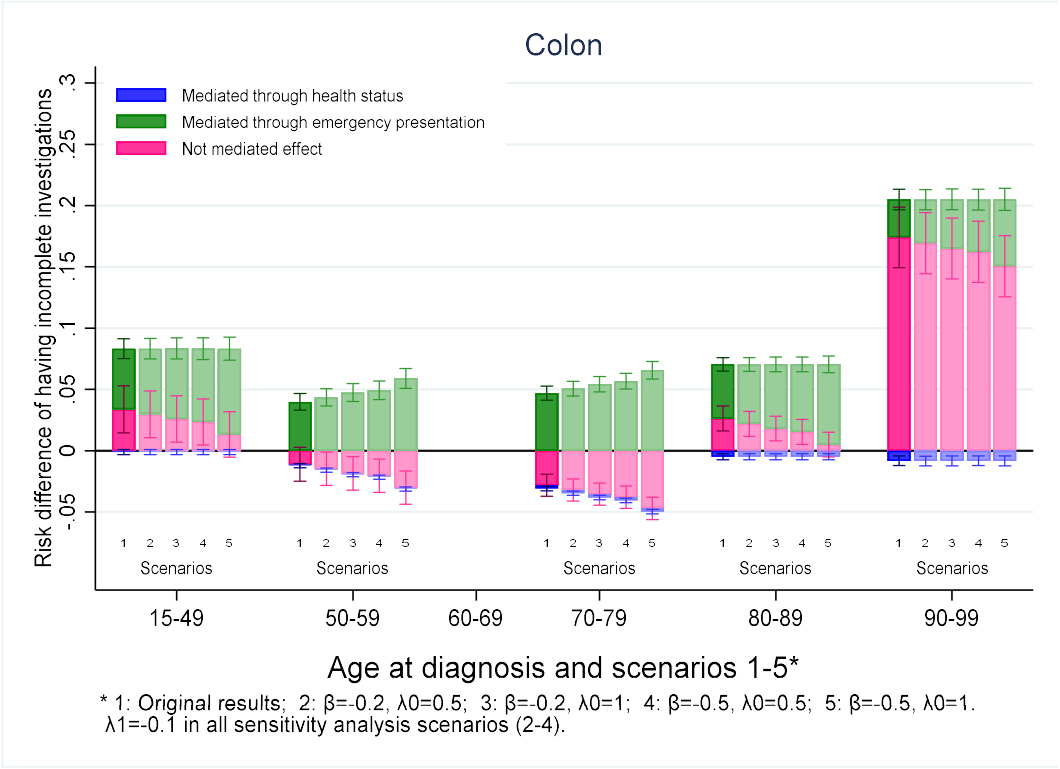


Figure 3b: Differences in the risk of having an incomplete diagnostic and staging investigation (DSI) for rectal cancer, in comparison with patients aged 60-60 years.

Results from original mediation analysis (scenario 1), and sensitivity scenarios (scenarios 2-5, lighter colours) for unmeasured confounding of the relationship between emergency presentation and the DSI.

Sensitivity parameters: Scenario 2: β=-0.2, λ_0=0.5; Scenario 3: β=-0.2, λ_0=1; Scenario 4: β=-0.5, λ_0=0.5; Scenario 5: β=-0.5, λ_0=1. λ_1=0 in all sensitivity analysis scenarios (2-4).

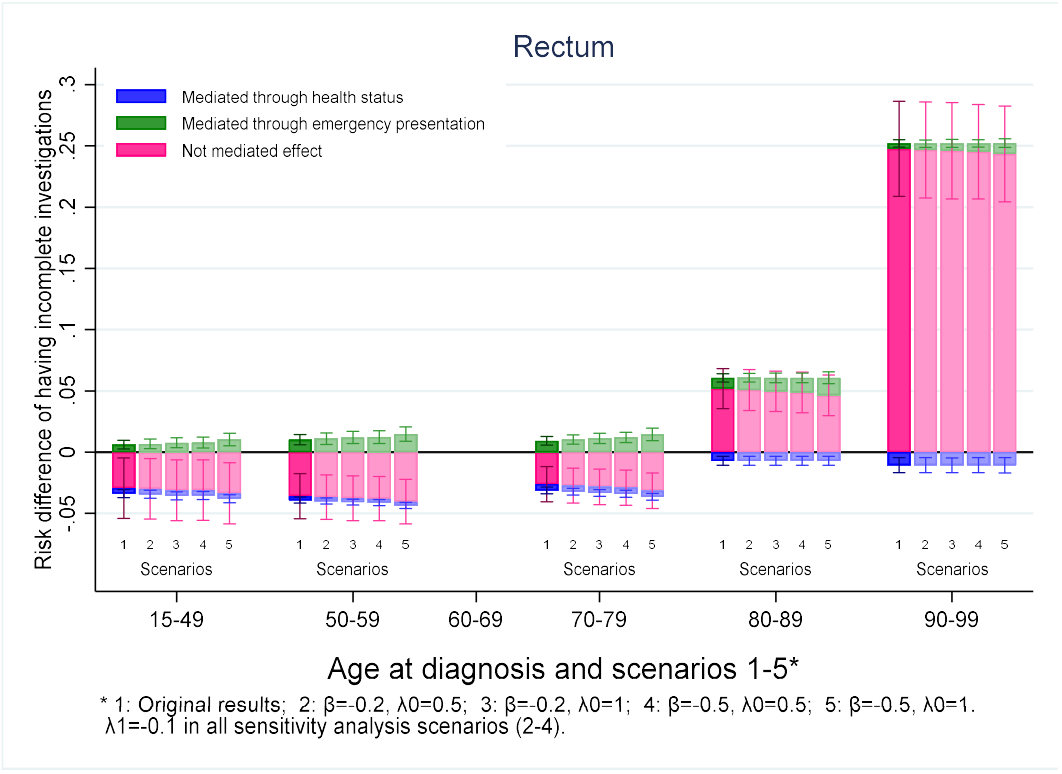
Interpretation: β = -0.5: people treated in a good quality hospital had a 39.9% smaller odds of having an incomplete DSI than people treated in a bad quality hospital; λ_0 = 0.5: Emergency presenters are 50% more likely to be managed in a good hospital in comparison with emergency presenters, in the unexposed; λ_1 = 0: Emergency presenters are 50% more likely to be managed in a good hospital in comparison with emergency presenters, in the exposed ($\lambda_0 + \lambda_1$).



Appendix Figure 1a: Differences in the risk of having an incomplete diagnostic and staging investigation (DSI) for colon cancer, in comparison with patients aged 60-60 years. Results from mediation analysis, colon cancer (Λ1= -0.1)

Notes: Sensitivity parameters: Scenario 2: β=-0.2, λ0=0.5; Scenario 3: β=-0.2, λ_0=1; Scenario 4: β=-0.5, λ0=0.5; Scenario 5: β=-0.5, λ_0=1. λ_1=0 in all sensitivity analysis scenarios (2-4).

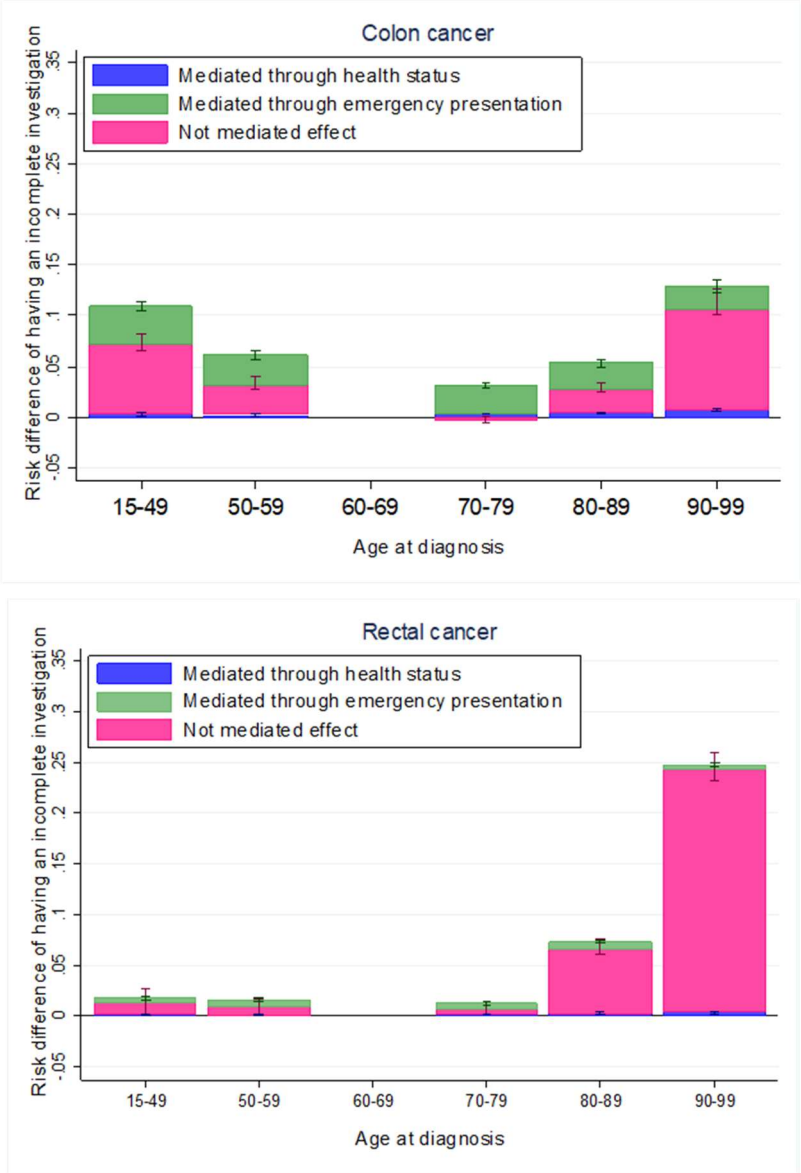
Interpretation: β = -0.5: people treated in a good quality hospital had a 39.9% smaller odds of having an incomplete DSI than people treated in a bad quality hospital; λ_0 = 0.5: Emergency presenters are 50% more likely to be managed in a good hospital in comparison with emergency presenters, in the unexposed; λ_1 = 0: Emergency presenters are 50% more likely to be managed in a good hospital in comparison with emergency presenters, in the exposed ($\lambda_0 + \lambda_1$).



Appendix Figure 1b: Differences in the risk of having an incomplete diagnostic and staging investigation (DSI) for rectal cancer, in comparison with patients aged 60-60 years. Results from mediation analysis, rectal cancer (Λ1= -0.1)

Notes: Sensitivity parameters: Scenario 2: β=-0.2, λ0=0.5; Scenario 3: β=-0.2, λ_0=1; Scenario 4: β=-0.5, λ0=0.5; Scenario 5: β=-0.5, λ_0=1. λ_1=0 in all sensitivity analysis scenarios (2-4).

Interpretation: β = -0.5: people treated in a good quality hospital had a 39.9% smaller odds of having an incomplete DSI than people treated in a bad quality hospital; λ_0 = 0.5: Emergency presenters are 50% more likely to be managed in a good hospital in comparison with emergency presenters, in the unexposed; λ_1 = 0: Emergency presenters are 50% more likely to be managed in a good hospital in comparison with emergency presenters, in the exposed ($\lambda_0 + \lambda_1$).



Appendix Figure 2: Differences in the risk of having an incomplete diagnostic and staging investigation (DSI) for colon (a) and rectal (b) cancer, in comparison with patients aged 60-60 years, excluding patients who died within 90 days from diagnosis.

4.3 Age variation in the receipt of potentially curative surgery for colorectal cancer in England

4.3.1 Background

Older patients are less likely to receive optimal care, and frequently have poorer health outcomes than younger patients. This pattern has been described for several chronic conditions, including cardiovascular disease and cancer.[12,200] The age gap in patient care appears to be particularly true for conditions that require surgical interventions, such as hip replacement for osteoarthritis, coronary artery bypass graft surgery for coronary heart disease, and bowel excision for colorectal cancer, even if these conditions are most prevalent in later life. Although the suboptimal management of chronic conditions in older patients is an important issue in other countries, it seems to be particularly critical in England.[13] Increasing evidence indicates that in England, older colorectal cancer patients are less likely to receive surgical management than younger patients.[201,202] It is essential to understand what factors give rise to inequalities in cancer care in order to design and implement targeted interventions to improve cancer outcomes.

In our paper in section 4.2, we showed that within England, older colorectal cancer patients were less likely to have a complete diagnostic and staging investigation than younger patients. Exploring the underlying mechanisms, it seemed that the difference in the proportion of patients who were diagnosed through an emergency presentation between age groups partly explained the age difference in investigations, especially for colon cancer. However, differences in the prevalence of comorbidity did not explain the difference in the completeness of diagnostic and staging investigation between patients aged 60-69 years and those 70 years and older. In older patients, most of the age difference in investigation remained 'non-mediated' by these factors.

Moving forward in the cancer patient management pathway, in this section, I explore the age differences in the likelihood of having resectional surgery for non-metastatic colon and rectal cancer in England, addressing objective 5 of this research degree project. I focus on non-metastatic disease because according to clinical guidelines, stage I-III colorectal tumours should be amenable to surgical resection, provided there are no contraindications for surgery. I use causal mediation analysis to examine how much comorbidity, the diagnostic route, and having a complete investigation explain the difference in the likelihood of having the primary tumour removed between age groups, after controlling for deprivation and sex differences.

4.3.2 Materials and methods

Data sources and variable definitions

Patients aged 15-99 years and diagnosed with non-metastatic colon and rectal adenocarcinoma in England during 2010-2012 were included. Patients with metastatic disease (TNM stage IV; 21.2% of all diagnoses), those with unknown stage (30.2% of all diagnoses) were excluded from this analysis, to ensure that all patients included were eligible for resectional surgery based on the extension of the disease (in other words, they were 'at risk' of having the outcome). As in the analyses presented in Section 4.2, individual tumour records from the National Cancer Registry were linked to the National Bowel Cancer Audit (NBOCA) data, Hospital Episodes Statistics (HES), and the Routes to Diagnosis monitoring dataset (RtD).

The exposure of interest was age, which was categorised into six groups: 15-49, 50-59, 60-69, 70-79, 80-89 and 90-99 years. The 60-69 age category was used as the baseline for analysis.

Information on comorbidity was derived from HES, as described using the algorithm developed by Maringe *et al*.[124] A binary indicator was used to flag the presence of any major comorbidity, including one or more of the following diagnoses: heart failure, cerebrovascular disease, chronic obstructive pulmonary disease, dementia, severe renal disease, severe liver disease, hemi/paraplegia, human immunodeficiency virus infection, and morbid obesity.

A binary variable was used to classify patients as having been diagnosed through an emergency presentation (EP) or not, using information from the RtD dataset.

Binary indicators for the completeness of diagnostic and staging investigation, and for resectional surgery status were derived from HES and NBOCA data using the algorithms described in Chapter 2.

Deprivation quintile of patients at the time of the CRC diagnosis was represented by the income domain of the Index of Multiple Deprivation of the Lower Layer Super Output Area (LSOA) of residence at the time of diagnosis.

Statistical Analyses

As in the analysis presented in the paper in Section 4.2, counterfactual-based mediation analysis was used to decompose the effect of age on the outcome, which is the likelihood of not receiving resectional surgery for stage I-III colorectal cancer. I chose to present the outcome in its negative form (not having surgery), so the direction of the associations are

comparable with the results presented in Section 4.2, where the outcome was having an incomplete diagnostic and staging investigation.

These analyses are a sequential progression of those presented in Section 4.2, which examined the effect of age (main exposure), health status (first mediator) and emergency presentation status (second mediator) on having a complete diagnostic and staging investigation (outcome). The present analysis focuses on the effect of age on having resectional surgery (outcome), using the investigation status as a third mediator, following comorbidity and emergency presentation. Figure 4.1 shows the directed acyclic graph with the causal assumptions made in this analysis.

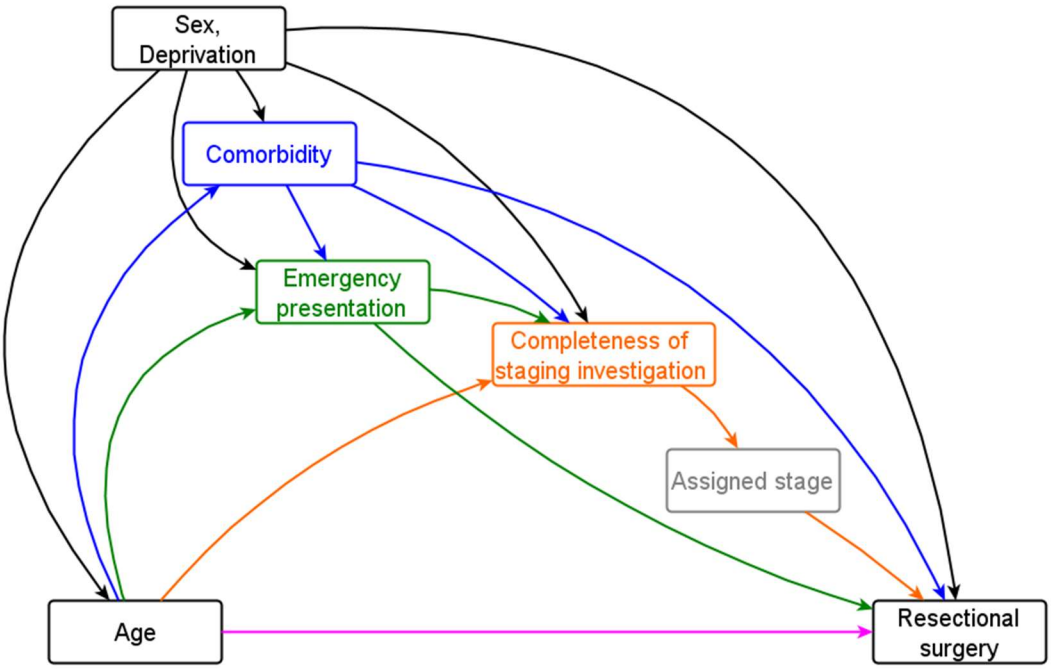


Figure 4.1: Assumed causal relationships between the relevant variables

The **pink** arrow represents the direct effect of age on the outcome (likelihood of not undergoing resectional surgery for colorectal cancer). The **blue** pathway represents the effect of age on the outcome that is mediated through comorbidity. The **green** pathway represents the effect of age on the outcome that is mediated by the diagnostic route, that is, being diagnosed following an emergency presentation. The **orange** pathway represents the effect of age on the outcome that is mediated through having a complete diagnostic and staging investigation. Because the mediators are ordered sequentially, a part of the effect of 'upstream' mediators is mediated by 'downstream 'mediator(s).

I denominate as the 'total effect (TE) of age' the average difference in the outcome (not having resectional surgery) between patients in a given age group and patients in the reference category (age 60-69 years), with the same distribution of deprivation and gender. The TE is decomposed into 'mediated' (or direct) and 'non-mediated' (indirect effects).

In a single mediator setting, the direct effect (DE) expresses the effect of the exposure on an outcome, comparing two counterfactual scenarios with different levels of the exposure

variable, while fixing the level of the mediator (in both scenarios) to a specific value drawn from the distribution of that variable in the unexposed, given the covariates, [203] or

$$DE = E [Y(1, M(0) – Y(0, M(0))]$$

Applied to this research question, the direct effect of age on the outcome (not having resectional surgery) is the average risk difference of seeing the outcome between a given age group and the reference (60-69) if, for all patients, their comorbidity status, emergency presentation status (EP), and the diagnostic and staging investigation status (DSI) were set at a fixed level, randomly drawn from the distribution of these variables for patients in the reference age group, of the same gender and deprivation status.

In a single mediator setting, the indirect effect (IE) captures the average change in the outcome that would be seen if, for all patients, different levels of the mediator are contrasted (a specific level, randomly drawn from the distribution of this variable in the exposed *versus* another specific level, randomly drawn from the distribution of this variable in the unexposed, given the confounders), while fixing the main exposure to the reference level, or:

$$IE = E [Y (1, M(1)) – Y(1, M(0))]$$

Applied to the research question, the IE is the average risk difference in the outcome that would be seen contrasting two counterfactual scenarios in which all patients are in the reference age category (60-69 years), with contrasting levels of the mediators (comorbidity, EP, and DSI): the first being a fixed level, randomly drawn from the distribution of these variables for a given age category, and the second one being a fixed level, randomly drawn from the distribution of these variables for the reference age category, of the same gender and deprivation status.

The IE are further decomposed into “path-specific” effects through each of the mediators (comorbidity status [Ma], EP [Mb] and DSI [Mc]). The path-specific effect via health status represents the effect that may arise when age influences comorbidity status, which may then in turn affect the outcome (either directly, or by influencing EP and DSI). It will be denoted IEa. The path-specific effect via Mb represents the effect that may arise when age influences the risk of being diagnosed through an emergency presentation (but not mediated by comorbidity), which may then in turn affect the outcome. It will be denoted IEb. Finally, the path-specific effect via Mc represents the effect that may arise when age directly influences the risk of having an incomplete diagnostic and staging investigation (not mediated through comorbidity and/or EP), which may then in turn affect the outcome. These effects (Ma, Mb,

and Mc), which add up to the IE, as well as the DE, were estimated using a parametric g-computation procedure.[148] The first step in g-computation is to model each of the mediators and the outcome, in this case using multivariate logistic regression:

- Comorbidity status was modelled as a function of age, deprivation quintile, sex and any interaction(s) that were significant (at 10% level).
- EP status was modelled as a function of comorbidity status, age, deprivation quintile, sex and any significant interaction(s).
- Completeness of diagnostic and staging investigation was modelled as a function of emergency presentation status, comorbidity status, age, deprivation quintile, sex and any significant interaction(s).
- Resectional surgery status was modelled as a function of diagnostic and staging investigation status, emergency presentation status, comorbidity status, age, deprivation quintile, sex and any significant interaction(s).

The resulting models were then used to simulate the outcomes for each one of the hypothetical scenarios compared in the definitions of the IE, DE and TE, as well as the definitions of the path-specific effects, in temporal order. As in the previous analyses, standard error and confidence intervals were estimated using 10,000 non-parametric bootstrap samples. Results from iterations were averaged to obtain point estimates.

4.3.3 Results

Descriptive analysis

Out of the 64,509 colon cancer patients and 35,433 rectal cancer patients diagnosed during 2010-2012 in England, 28,971 and 18,336 had non-metastatic adenocarcinoma, respectively. Mean age at diagnosis was slightly lower in rectal (69.4 years) than in colon cancer patients (72.0 years) (Table 4.1).

The proportion of patients with stage I disease was lower in patients with colon cancer (18.1%) than in those with rectal cancer (30.6%).

There was a known diagnosis route for 97.8% of colon and 97.1% of rectal cancer patients. The most frequent diagnosis route was the two-week wait in both colon (28.8% of those with known route) and rectal (42.2%) cancer patients. Emergency presentation was the diagnostic route for 21.3% of colon and 7.3% of rectal cancer patients with a known route. After imputation of missing values of EP status, its distribution was comparable to that in the complete-case sample (Table 4.1).

Approximately 37.8% of colon and 29.2% of rectal cancer patients had evidence of at least one of the chronic conditions indexed in the CCI in the six years prior to their CRC diagnosis. The prevalence of comorbidity increased with age, from 11.7% in patients aged 15-50 years to 44.0% in those aged 90 years and older.

Around a fifth (21.5%) of colon cancer patients and a third (36.6%) of rectal cancer patients had what we defined as an incomplete DSI. The proportion of patients with an incomplete investigation increased with age: patients in the oldest age group (90-99 years) had a higher proportion of incomplete DSI (34.9% for colon and 44.5% for rectal cancer) than patients aged 60-69 years (17.9% for colon and 33.9% for rectal cancer). Colon cancer patients in the youngest age group (15-49) were more likely to have an incomplete DSI than patients aged 60-69 years (21.2% vs 17.9%). For rectal cancer, the proportion of patients with an incomplete DSI increased with increasing age.

Around a third (37.0%) of colon and half (52.1%) of rectal cancer patients with non-metastatic disease did not have evidence of undergoing resectional surgery. The oldest age group (90-99 years) had the highest proportion of patients not undergoing resectional surgery (62.1% and 81.3% of colon and rectal cancer, respectively). Colon cancer patients in the 60-69 age group and rectal cancer patients in the 50-59 age group were the most likely to undergo resectional surgery (68.4% and 52.0%, respectively).

The proportion of patients without evidence of undergoing resectional surgery was higher for patients with later stage at diagnosis. It was also higher in patients diagnosed after an emergency presentation (54.4% of colon and 73.9% of rectal cancer patients) than in patients diagnosed through other routes (26.1% of colon and 45.9% of rectal cancer patients). The proportion of patients not undergoing surgery was slightly higher in patients with comorbidity than in those without evidence of comorbidity. Among patients with an unknown route to diagnosis, 71.9% of colon and 83.8% of rectal cancer patients had no evidence of undergoing resectional surgery.

	Colon		Rectum	
	N (%)	After imputation	N (%)	After imputation
Age group				
15-49	1,295 (4.5)		1,045 (5.7)	
50-59	2,573 (8.9)		2,477 (13.5)	
60-69	7,621 (26.3)		5,611 (30.6)	
70-79	9,879 (34.1)		5,684 (31.0)	
80-89	6,784 (23.4)		3,185 (17.4)	
90-99	819 (2.8)		334 (1.8)	
Female	13,659 (47.1)		6,530 (35.6)	
Stage at diagnosis				
I	5,246 (18.1)		5,616 (30.6)	
II	12,256 (42.3)		5,261 (28.7)	
III	11,469 (39.6)		7,459 (40.7)	
Comorbidity	10,937 (37.8)		5,353 (29.2)	
Route to diagnosis				
Non Emergency routes	22,279 (78.7)	24,192 (78.9)	16,500 (92.7)	18,551 (92.6)
Screening	3,830 (13.5)		2,420 (13.6)	
Two-week-wait	8,165 (28.8)		7,514 (42.2)	
Standard GP	6,918 (24.4)		4,939 (27.7)	
Other	3,366 (11.9)		1,627 (9.1)	
Emergency presentation	6,042 (21.3)	6,479 (21.1)	1,304 (7.3)	1,485 (7.4)
[Unknown]	650 (2.2)		532 (2.9)	
Diagnostic and staging investigation				
Incomplete	6,240 (21.5)		18,336 (36.6)	
Resectional surgery				
No surgery	2,164 (7.5)		3,554 (19.4)	
Total	28,971 (100.0)		18,336 (100.0)	

Table 4.1: Characteristics of patients diagnosed with non-metastatic colon and rectal cancer in England, 2010-2012

Resectional surgery defined as surgical procedure to remove primary tumour and surrounding tissues, excluding diagnostic and palliative non-resectional procedures.

	Colon			Rectum		
	N (%) not treated*	N (%) not treated* after imputation	Total of patients per category	N (%) not treated*	N (%) not treated* after imputation	Total of patients per category
Age group						
15-49	55 (4.2)		1,295	168 (16.1)		1,045
50-59	115 (4.5)		2,573	343 (13.8)		2,477
60-69	234 (3.1)		7,621	698 (12.4)		5,611
70-79	532 (5.4)		9,879	959 (16.9)		5,684
80-89	915 (13.5)		6,784	1,152 (36.2)		3,185
90-99	313 (38.2)		819	234 (70.1)		334
Stage at diagnosis						
I	323 (6.2)		5,246	491 (8.7)		5,616
II	748 (6.1)		12,256	1,042 (19.8)		5,261
III	1,093 (9.5)		11,469	2,021 (27.1)		7,459
Comorbidity						
No	1,042 (5.8)		18,034	2,109 (16.2)		12,983
Yes	1,122 (10.3)		10,937	1,445 (27.0)		5,353
Emergency presentation (EP) status						
Non- EP	1,295 (5.8)	1,530 (6.3)	22,279	2,855 (17.3)	3,370 (18.2)	16,500
EP	688 (11.4)	791 (12.2)	6,042	527 (40.4)	655 (44.1)	1,304
[Unknown]	181 (27.8)		650	172 (32.3)		532
Diagnostic and staging investigation status						
Complete	1,326 (5.8)		22,731	2,049 (17.6)		11,624
Incomplete	838 (13.4)		6,240	1,505 (22.4)		6,712
All patients	2,164 (7.5)		28,971	3,554 (19.4)		18,336

Table 4.2: Absence of resectional surgery: Number and proportion of patients with no evidence of resectional surgery for colon and rectal cancer by age group, stage, comorbidity and emergency presentation status. England, 2010-2012

Resectional surgery defined as surgical procedure to remove primary tumour and surrounding tissues, excluding diagnostic and palliative non-resectional procedures. *: Not treated: number and percentage of patients with no evidence of undergoing resectional surgery.

Mediation analysis

In the logistic regression model for the outcome, the main exposure (age) and the three mediators were significantly predictive of the outcome. However, none of the mediators explained the age differences in treatment receipt (Figure 4.2 and Table 4.3). This means that the difference in the prevalence of these factors in oldest and youngest age groups – in comparison with the reference age category (60-69) – do not explain the difference between age groups in the likelihood of undergoing resectional surgery.

Patients diagnosed with colon cancer at age 90-99 years had 28.6% (22.6-34.6) additional risk of not undergoing resectional surgery compared with those aged 60-69 years, and most of this additional risk was not mediated by any of the three mechanisms explored. Patients

aged 80-89 had 9.9% (7.1-11.5) additional risk of not undergoing surgery. The risk in the younger age categories (59 years and younger and 70-79 years) was not significantly different to that of the reference category, 60-69 years.

Patients diagnosed with rectal cancer at age 90-99 years had 53.2% (48.3-58.0) additional risk of not undergoing resectional surgery than those aged 60-69 years, and most of it was not mediated by any of the three mechanisms explored. Patients aged 80-89 had 18.7% (16.0-21.5) additional risk of not undergoing surgery. The risk in the youngest age category (1549 years) was slightly higher (2.8%, 0.7-4.9) than in the reference category. Patients aged 70-79 years had the same risk of the outcome as in the reference category.

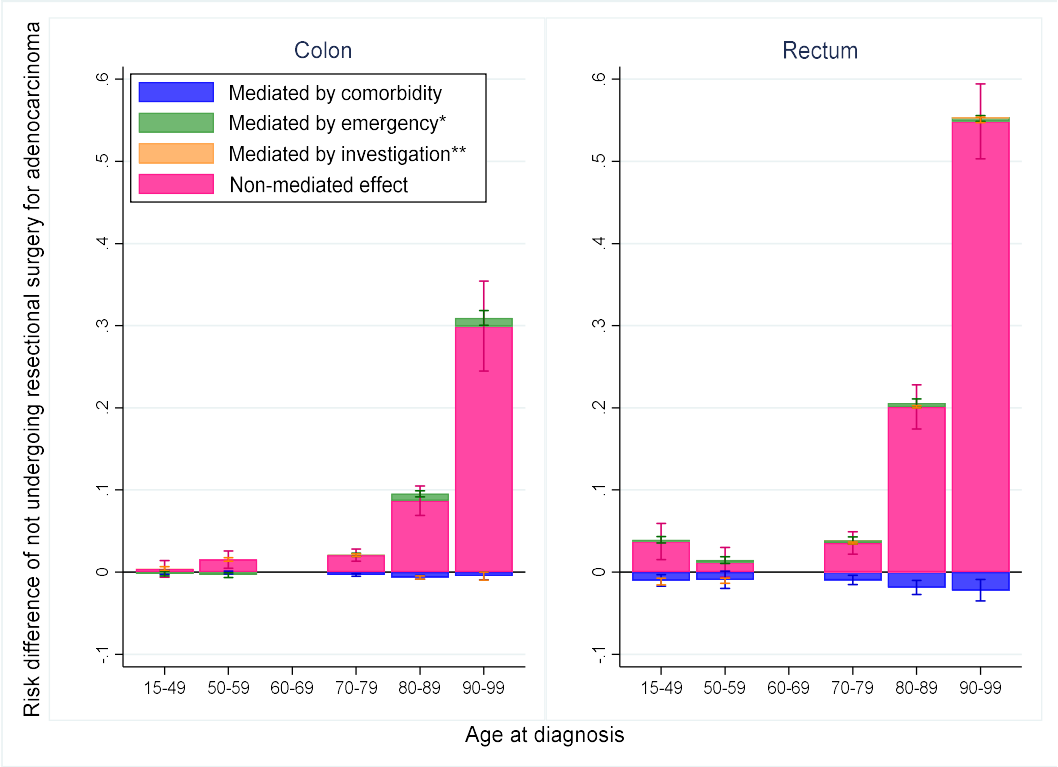


Figure 4.2: Risk difference in having resectional surgery for colon and rectal adenocarcinoma in comparison with patients diagnosed at age 60-69 years, England, 2010-2012

Non-mediated effects or direct effect of age; *: being diagnosed through an emergency presentation; **: having an incomplete diagnostic and staging investigation.

	Colon				
Age group	Total effect	Direct effect	Indirect effect a	Indirect effect b	Indirect effect c
15-49	0.002 (-0.009 0.012)	0.006 (-0.006 0.017)	-0.004 (-0.008 0.000)	-0.001 (-0.005 0.002)	0.001 (-0.003 0.006)
50-59	0.009 (-0.001 0.020)	0.017 (0.004 0.030)	-0.004 (-0.012 0.004)	-0.004 (-0.007 0.000)	0.000 (-0.003 0.004)
60-69			(Reference)		
70-79	0.017 (0.008 0.025)	0.022 (0.013 0.031)	-0.006 (-0.010 -0.003)	0.001 (-0.001 0.004)	0.000 (-0.002 0.003)
80-89	0.093 (0.071 0.115)	0.094 (0.074 0.114)	-0.012 (-0.018 -0.007)	0.012 (0.006 0.018)	-0.001 (-0.003 0.001)
90-99	0.286 (0.226 0.346)	0.289 (0.231 0.347)	-0.015 (-0.025 -0.004)	0.012 (0.001 0.023)	-0.001 (-0.007 0.006)
	Rectum				
Age group	Total effect	Direct effect	Indirect effect a	Indirect effect b	Indirect effect c
15-49	0.028 (0.007 0.049)	0.037 (0.015 0.059)	-0.010 (-0.017 -0.003)	0.002 (-0.002 0.006)	-0.002 (-0.006 0.003)
50-59	0.004 (-0.011 0.019)	0.012 (-0.006 0.030)	-0.009 (-0.020 0.001)	0.003 (-0.001 0.007)	-0.001 (-0.004 0.002)
60-69			(Reference)		
70-79	0.029 (0.015 0.044)	0.035 (0.022 0.049)	-0.010 (-0.015 -0.004)	0.003 (-0.001 0.008)	0.000 (-0.001 0.001)
80-89	0.187 (0.160 0.215)	0.201 (0.174 0.228)	-0.019 (-0.027 -0.010)	0.005 (-0.001 0.010)	0.000 (-0.001 0.002)
90-99	0.532 (0.483 0.580)	0.549 (0.503 0.594)	-0.022 (-0.035 -0.009)	0.003 (0.000 0.007)	0.002 (-0.002 0.005)

Table 4.3: Risk difference of not undergoing resectional surgery by age group in comparison with patients aged 60-69 years. Colon and rectal non-metastatic adenocarcinoma diagnoses, England, 2010-2012

Total effect: total risk difference in comparison with that of reference groups (age 60-69 years); Direct effects: of age, or non-mediated effect; Indirect effect a: mediated through comorbidity; Indirect effect b: mediated through emergency presentation; Indirect effect c: mediated through diagnostic and staging investigation; Positive numbers indicate higher risk of not undergoing resectional surgery in comparison with the reference age group (60-69 years) and vice versa.

4.3.4 Discussion

This study shows that older patients are less likely to have surgical treatment for colorectal cancer, even in the subgroup of patients with non-metastatic disease. I examined the role of comorbidity, the diagnostic route (being diagnosed through an emergency presentation or not), and the completeness of staging investigation in explaining these age differences within England. Although these factors were important determinants of treatment receipt, they explained very little of the differences in the receipt of resectional surgery for non-metastatic colon and rectal adenocarcinoma between age groups.

These findings are consistent with those presented in Chapter 3. Comorbidity did not explain the differences in the probability of receiving resectional surgery for rectal cancer between Denmark and England; and it did not explain the age differences in the probability of receiving a full investigation, or resectional surgery within England. The findings are however somewhat contrasting to the ones presented in Section 4.2, with regards to the role of emergency presentation as a mediating factor. Emergency presentation seemed to be an important mechanism for the age differences in investigation but not for surgical treatment. There are two potential explanations of this finding. First, patients diagnosed through an EP may still receive some sort of resectional surgery, regardless of the investigation. This is plausible because in case of an acute event, such as an obstruction, surgery is still indicated, though the intent (curative or palliative) may be different than an elective procedure. Intent or outcome of the surgical procedure was not considered in the definition of treatment used in the analysis, so variation in the intent could not examined. Second, excluding patients with unknown stage and metastatic disease may have caused the exclusion of an important proportion of patients diagnosed through an emergency route and unlikely to have surgery because of their acute condition. Selecting patients for whom surgery should be indicated, as I have done, likely highlights the age differences that remain unexplained by biological factors such as comorbidity, advanced stage, and emergency presentation. The finding of age inequalities in cancer management in this selected group are important precisely because they point the attention away from these biological factors, and suggest that alternative explanations should be sought.

As in the studies presented previously in this thesis, it is possible that the measure of comorbidity used in this analysis does not capture fully the overall health status of patients at the time of diagnosis. I used a binary indicator to flag patients with ‘major conditions’ that

might have contraindicated surgery because of increased risk of postoperative mortality and complications, such as heart failure, cerebrovascular disease and dementia. A binary indicator, however, oversimplifies the wide spectrum of health status, thus potentially leading to residual confounding. I considered different categorisation of the comorbidity information that was available, including several categories of the Charlson Comorbidity Index with increasing severity, flags for conditions with potential disability associated, and/or markers for increased cardiovascular risk. None of these variables improved the prediction of the outcome in the logistic regression model, suggesting that the binary indicator used was not worse than the other ways of categorising the comorbidity information.

Another limitation of the indicator of health status used is that it may not fully capture 'frailty', or the increased vulnerability resulting from decreased reserves from multiple physiologic systems.[79] Frailty is likely considered in the decision to treat because it is associated with poor outcomes. However, the concept of frailty as a clinical syndrome is fairly new;[80] and although several operational definitions have been proposed,[81,82] none is widely used in practice to assess frailty objectively. The working definition of frailty is therefore likely to vary. Improving the assessment of the health status of patients (including frailty), and its monitoring through clinical audit and registration, would allow a better understanding of the operative risks of patients, and better monitoring and comparison of cancer outcomes.

The age disparities in the likelihood of receiving resectional surgery (as well as having a full investigation) were larger for rectal than for colon cancer. The colon and rectum have different location, blood supply, venous drainage, and thus treatment.[19] Because its location is closer to the anal canal and sphincter, a permanent stoma is more frequently required after rectal cancer surgery than after colon cancer surgery. A permanent stoma has implications for patient lifestyle and quality of life,[204] and may be more difficult to manage for patients who are less independent and/or lack social support. A recent study of social support in surgically treated CRC patients found poorer health-related quality of life outcomes in those who reported low levels of social support.[205] The prospect of life-changing consequences following surgery may be preventing older patients from receiving surgery, potentially more so for rectal cancer patients than for colon cancer patients.

In comparison with colon cancer surgery, rectal cancer surgery is more frequently followed by surgical complications, such as anastomotic leakage.[19,175] Although surgical complications are less frequent in colon cancer patients, they are reported to be more likely to die from

them, than rectal cancer patients.[206] Medical postoperative complications, such as pneumonia and cardiovascular events, are more frequent in colon cancer patients – who are older on average – than in rectal cancer patients.[19,175] Several studies have found that increasing age is an independent predictor of short-term mortality and postoperative medical complications.[206-208] Iversen and colleagues found that postoperative medical complications, but not surgical ones, were a strong predictor of short-term mortality following emergency surgery for colon cancer.[207] Marusch and colleagues found that pneumonia and cardiovascular complications resulted in a high postoperative morbidity and mortality in older colorectal cancer patients.[208] Arguably, it is difficult to differentiate surgical from medical complications, as these may arise from interrelated events. However, all this evidence highlights the importance of close observation for surgical and non-surgical complications in the postoperative period, especially in older patients and those at higher risk of complications, to improve surgical outcomes.

In general, the anticipated risk of operative mortality influences the decision to offer surgical treatment, and it might be a particularly important consideration in older patients. Multimorbidity, frailty and disability are known risk factors for postoperative mortality, but are not the only determinants. As discussed in the previous chapter, perioperative care is also an important determinant of cancer outcomes. In comparison to other European countries, the availability of critical beds per hospital population is lower in England.[191] Furthermore, access to high-dependency and intensive care varies between hospitals, especially for patients undergoing non-cardiac surgery. It is possible that limited access to adequate postoperative care is affecting the prospects of older patients getting surgical treatment, because they are more likely to develop postoperative complications, and need admission to ICU for organ support.[209]

Given the limited health resources, it is probable that chronological age is being used in England as a criterion to ration and prioritise the allocation of health resources (such as intensive care beds) consequently affecting older patients' prospects of undergoing aggressive cancer treatment. Rationing of resources means denying potentially beneficial medical care to a particular group of patients in order to conserve and use those resources for a different type of patients.[210] Rationing of health resources based on age is not explicit policy in the UK, however, it may occur.[211] There are arguments for and against it. Some people think it is fair to give priority to younger patients over older ones for scarce potentially life-saving resources, because the old have already lived more years, whereas the young

should have the same opportunity to live as many years.[211,212] The counterargument to this is that all lives are equally valuable, regardless of age, sex, race, and any other characteristic.[213,214] Resource rationing may happen at the micro level (at individual level), macro level (by health authorities or institutions), and even at societal level.[215] Age-based rationing is obvious in screening programmes, for instance, where the age eligibility criterion is justified based on targeting the population at highest risk. Age-based rationing at the individual level in the clinical setting is more difficult to assess because the clinical judgement is supposed to involve a comprehensive assessment of the patient's needs.[215] In 1998, Kapp argued that age-based rationing of medical treatment (dialysis, access to coronary care and cancer treatment) in the UK had been justified "under the linguistic guise of medical "indications"".[210] In the current context, these claims may no longer apply to the same extent, as several measures have been introduced to avoid age discrimination since then.[216,217] However, clinicians will inevitably need to make decisions at the individual level, and it is arguably unfair that they bear the responsibility to deny resources to some patients when resources are constrained.

In conclusion, to improve cancer outcomes, the finding of poorer surgical outcomes in older colorectal cancer patients should not justify them not receiving surgery, but rather encourage further efforts to improve patient safety in the perioperative period. Several measures to optimise patients' condition preoperatively (such as incentive spirometer and chlorhexidine for oral care),[206,218] to evaluate their surgical risk, and to plan their postoperative care[68,69,77,78] have been proposed in order to avoid or minimise postoperative complications, and to predict the risk of complications preoperatively. Without taking sides pro/against age-based rationing of health resources (which will come in Chapter 5), it is clear that any such decision needs to follow a wider discussion and agreement at a societal level, so that expectations are clear, as well as the responsibility and accountability for such decisions.

Chapter 5: Discussion

5.1 Contributions of this work

In this study, I examined the impact of increasing age on the likelihood of having optimal management of colorectal cancer, and its role in explaining international differences in cancer survival. To do this, first, I carried out an international comparison of CRC management and survival between Denmark, England, Norway and Sweden. I found that that for each disease stage, age-standardised net survival up to three years after a colon or rectal cancer diagnosis was poorer in England than in Norway, Sweden, and Denmark (rectal cancer only). In all countries, survival of patients with missing stage was between that of patients with stage III and stage IV disease. The proportion of patients with missing stage was substantially larger in England than in the other countries, suggesting an underestimation of the differences found in the stage-specific analysis. The pattern of Denmark substantially reducing the survival deficit in comparison with Norway and Sweden over time, while England showed a smaller survival improvement, is consistent with another recent population-based survival comparison from the CONCORD programme.[156]

The findings from the first International Cancer Benchmarking Partnership (ICBP) study had shown that, during 1995-2007, the survival deficit in the UK and Denmark was particularly large for colorectal cancer patients aged 65 years and older.[3] Authors suggested that the survival trends were consistent with later diagnoses or differences in treatment. Subsequent ICBP analyses focusing on CRC found that an adverse stage distribution was contributing to the lower survival in Denmark; while the UK jurisdictions included had considerably lower stage-specific survival, suggesting unequal access to optimal treatment.[5] This ICBP study did not include all CRC patients diagnosed in the UK because at the time stage data was not widely available. The availability of stage data has improved considerably since then, and even more when applying the algorithm to derive stage from different data sources described in Chapter 2.[126] As a result, I was able to conduct a more recent population-based comparison of CRC stage-specific survival using national data for Denmark, England, Norway and Sweden. The finding of lower stage-specific survival in England presented in Chapter 3 of this thesis is consistent with that reported in the ICBP 2013 publication.[5]

To explore the role of cancer management in explaining the international differences in survival, I compared between Denmark, England, Norway and Sweden, the proportion of patients receiving resectional surgery for each stage of disease in different age groups (and

separately for colon and rectal tumours). Older patients in England were less likely to receive resectional surgery than patients of similar age and extension of disease in Denmark, Norway and Sweden. In patients younger than 75 years, comparing the distribution of resectional surgery receipt for each stage and age group between the countries, the proportion treated was generally comparable between the countries, and higher in England than in the other countries for stage I disease. In patients aged 75 years and older, the proportion treated was systematically lower in England than in the other countries, for each disease stage. In patients with rectal cancer, there was an age gradient (decrease in the proportion treated by age) in Denmark, England and Sweden, which was particularly pronounced in England; while in colon cancer patients, a clear age gradient in the proportion treated was only evident in England of the four countries compared. The patterns in treatment receipt by stage in the older age group mirror the survival findings, in that Norway and Sweden had both the highest survival and highest proportion of older patients treated, and England had the lowest survival and lowest proportion of older patients treated, of the countries compared. To my knowledge, this is the first international population-based comparison of CRC treatment receipt by stage and age between these countries.

To account for the role of comorbidity in explaining the international differences in the proportion of patients receiving resectional surgery and in survival, I then carried out sub-analyses of the proportion of patients treated for non-metastatic rectal adenocarcinoma in Denmark and England – the countries for which comorbidity information was readily available. The lower proportion of patients treated in the older age groups in England (in comparison with Denmark) was evident at different levels of comorbidity, with the exception of patients with stage I disease and no record of comorbidity. After adjusting for comorbidity, the probability of receiving resectional surgery for CRC was still lower in England than in Denmark, and the between-country difference in the probability to be treated tended to increase with increasing age, stage and level of comorbidity. The findings indicate that although comorbidity helps determines treatment eligibility, it does not fully explain the between-country differences in the proportion treated in the older age groups, at least between Denmark and England.

To date, few studies have examined the role of potentially curative treatment in explaining population-based survival, as this information is rarely collected in population-based national cancer registries. The European Registration of Cancer Care (EURECCA) initiative of the European Society of Surgical Oncology (ESSO) and European Cancer Organisation (ECCO),

a multidisciplinary platform aiming to improve the quality of cancer care, has produced several publications focusing on colorectal cancer comparing clinical audit data, clinical practice and cancer outcomes across Europe.[42,120] Recently, a EURECCA study examined treatment and survival of patients diagnosed with rectal cancer at age 80 years and older in Belgium, Denmark, The Netherlands, Norway and Sweden in 2001-2010.[219] In patients with non-metastatic disease they found a higher proportion of patients undergoing surgery in Denmark (92.4% of those registered in the DDCG database) and Sweden (92.0%) than in Norway (77.3%), and higher cancer survival in Sweden than in the other countries. In those with stage IV disease, the proportion of patients undergoing surgery was higher in Norway (40.6%) than in Sweden (34.0%) and Denmark (22.2%), and 5-year survival was similar between the countries.[219] They also report wide differences in the use of radiotherapy and chemotherapy. Their results on the proportion treated are comparable to those reported in Chapter 3, but because their focus was on patients aged 80 and older, they did not report fluctuations in the proportion treated by age group; and they did not include England in their analyses. Nonetheless, there has been increasing evidence that older cancer patients in England are less likely to receive treatment than patients of similar age in other countries, and compared with younger patients in England. A EURECCA Breast Cancer Group study examined the variation in treatment and survival of patients diagnosed with non-metastatic breast cancer at age 70 years and older in Belgium, England, Ireland, The Netherlands and Poland during 2000-2013. The proportion of patients without evidence of surgery (breast-conserving or mastectomy) in England was lower than in the other countries for stage I and II, and second lowest (after Ireland) for stage III disease.[220] Survival was also lowest in England for each stage of disease.[220] Another recent population-based study of patients diagnosed with non-small cell lung cancer in England during 2009-2012 found that the predicted probability of receiving surgery decreased sharply after age 65 years, even in patients with stage I-II disease, good performance status and no evidence of comorbidity.[199]

Several studies have found that comorbidity affects cancer outcomes, potentially in relation to lower probability of treatment with curative intent. However, until recently, there have not been many international population-based studies examining the role of comorbidity in explaining cancer treatment and survival, because this information is not routinely collected in national cancer registration. In the recent ICBP study examining the role of comorbidity in explaining differences in lung cancer survival between nine jurisdictions in Australia, Canada, Norway and the UK, authors concluded that they were not able to quantify the level of

comparability of these indices between jurisdictions due to differences in coding practices, and called for further efforts in standardising data collection practices.[163] There is therefore no accepted standard for measuring comorbidity for international comparisons of population-based cancer survival. Still, the Charlson Comorbidity Index is frequently used as a measure of comorbidity in epidemiological research because can be feasibly and reliably derived from secondary care records.[124]

To explore in more detail the age differences in CRC management within England, I assessed some of the potential underlying mechanisms behind the age differences in CRC management using mediation analysis methods. I started by examining the initial phase of cancer management, the diagnostic and staging investigation. I found that the proportion of patients receiving a full diagnostic and staging investigation for CRC was lower in patients aged 80 years and older than in younger patients. The diagnostic route partly explained some of the age differences, however, patients' health status did not significantly explain the age differences. The results were robust to a sensitivity analysis for unmeasured confounding of the relationship between the diagnostic route and the likelihood of having an incomplete investigation. I then explored the role of having a major comorbidity (diagnosis of heart failure, cerebrovascular disease, dementia, diabetes with organ damage, severe renal or hepatic disease, or hemi/paraplegia) emergency presentation, and having a full investigation as sequential mechanisms that may explain the age differences in the likelihood of receiving resectional surgery for CRC in England. The results of this analysis are consistent with the previous ones (looking at the age differences in investigations), in that most of the age differences in the outcome remained 'not mediated' or unexplained by these mechanisms.

The findings presented in this thesis add to the increasing evidence showing that older colon and rectal cancer patients in England are less likely to receive optimal treatment than younger patients, even after accounting for differences in known 'risk factors' for under-management, namely, disease stage, comorbidity, and the diagnostic route (emergency or not).[201,202,221] An analysis of data from rectal cancer patients diagnosed in England during 2009-2014 found a substantial difference in the proportion of patients undergoing major resection, from 66.5% in patients younger than 70 years, to 31.7% in those aged 80 years and older.[201] They also reported significant variation in resection rates in patients 80 years and older between NHS Trusts, after adjusting for sex, deprivation, year of diagnosis, Charlson comorbidity score, disease stage and diagnostic route.[201] An analysis of regional data from the Northern and Yorkshire cancer registry including information on patients

diagnosed with colon cancer during 1999-2010 found that patients aged 60-69, 70-79, and 80 years and older were significantly less likely to receive surgery and adjuvant chemotherapy than those younger than 60 years, after adjusting for sex, deprivation, stage, and period of diagnosis.[202] Another cohort study looking at patterns of cancer care by age group in patients who died during 2005-2011 (and had their cancer registered in the Northern and Yorkshire cancer registry) found that patients aged 18-69 years had the highest likelihood of receiving chemotherapy, radiotherapy or surgery (68.7, 64.5 and 37.3%, respectively), while the aged 80 years and older had the lowest probability of receiving each type of treatment (27.1, 57.6, and 33.6%, respectively).[221] Colorectal cancer was one of the cancer types included, among others, indicating that the issue of under-management of cancer in older patients is wider, and not specific to CRC.

In the analyses presented in Chapter 4, I did not only 'control for' other potential explanatory factors of the differences in management by age group (comorbidity, the diagnostic route, and stage in the analysis examining surgical treatment), but also quantified the extent to which they explained the age differences. To do this, I used innovative analytic methods from the counterfactual-based causal inference framework, causal mediation analysis. To date, few studies have used causal mediation to understand inequalities in cancer outcomes. Valeri and colleagues used causal mediation analysis to examine the role of stage in explaining race differences in colorectal cancer survival in the US.[222] Similarly, Li and colleagues used causal mediation methods to examine how much of the socioeconomic inequalities in breast cancer survival in Northern England were explained by disease stage and treatment.[223] Both studies found that stage at diagnosis explained some of the racial and socioeconomic differences (respectively) in survival. To my knowledge, there have not been any published studies focusing on examining the underlying mechanisms behind age inequalities in cancer management and outcomes.

All the findings presented in this thesis consistently indicate that there are age inequalities in the management of colorectal cancer patients in England in comparison with older patients in other countries (who also consistently perform better than England in terms of cancer survival), and in comparison with younger patients in England. These differences in cancer management are not fully explained by differences in biological factors such as disease stage or comorbidity, as it is frequently assumed. In the next section, I will explore other potential explanations of the age inequalities in cancer management.

5.2 On data harmonisation and comparability of results

Several steps were taken to ensure the comparability of outcomes between specific groups of patients included in the analyses. The inclusion criteria and variable definitions were based on the standard and widely used classifications, such as the third edition of the International Classification of Diseases for Oncology topographical and morphological codes and the Union for International Cancer Control TNM Classification of Malignant Tumours, adhered to by the four colorectal cancer registries contributing with data for the analyses. Despite the use of the same standard classification systems, registration practices may vary. For instance, registries may use different editions of the same classifications leading to inconsistent definitions.

Section 2.3 covered variable definitions and presented different algorithms to derive clinical information. As discussed in Section 2.3.2, the 'non-restrictive' strategy to derive stage information addresses the main challenge in cancer registries using different editions of the TNM Classification: the handling of information on distant metastases.

I collaborated with clinicians and registry staff in the four countries to ensure the inclusion criteria and definitions used in the analyses were as harmonised as possible. For instance, the Swedish ColoRectal Cancer Registry collects information on colon and rectal adenocarcinomas, and no other types of tumours (based on ICD-O-3 morphology codes). The other national colorectal cancer registries (in Denmark, Norway and England) do not have such eligibility criterion based on tumour morphology. Therefore, for the international comparison of treatment and survival of CRC between these countries, tumours of specific morphology other than adenocarcinoma were excluded from the analysis.

Similarly, the definition of 'resectional surgery' took into account (only) information that was available in all relevant data sources. For example, reliable information on residual disease after removal of the primary tumour (and on the surgical intent) was not available in all datasets, therefore this information was not taken into account, even when available. Similarly, the time window for eligible surgical procedures was up to nine months after diagnosis took into account that some patients may have received neoadjuvant therapy with delayed surgery,[134] and allowing additional time to account for delays between diagnosis and start of treatment.

Despite best efforts, some differences in practices cannot be fully accounted for in the data preparation and harmonisation process. For instance, the handling of death certificate

initiated cancer diagnoses is known to vary between registries. This process entails tracing back additional clinical information from death certificates in a routine basis (if additional information is found, the case is classed as death certificate initiated, or DCI; if no additional information is found, the case is classified as death certificate only, or DCO). The proportion of DCO cases is frequently used to judge completeness of registry data (with a high proportion of DCOs indicating under-ascertainment of cases).[224] DCO cases are generally excluded from survival analysis,[225] including the survival analyses presented in this thesis. Both DCOs and DCIs have an important effect on the survival estimates. By definition DCO cases have 0 survival time, as they are diagnosed at the event time, and similarly, DCIs will likely have a short survival time. In Sweden, however, because of legal reasons, registries do not accept registration from death certificates.[226] The underreporting of cases to the Swedish Cancer Register is however relatively small. A quality study using a 1998 sample estimated that the underreporting was 3.7%, with substantial variation between cancer sites (from "low to modest" for breast and digestive tumours to "substantial" for leukaemia and lymphoma).[227] This may result in an overestimation of survival, especially short-term. A 2019 study examined whether different registry practices between ICBP jurisdictions, such as the handling of death certificate cases and using different hierarchical rules for the incidence date, could have a potential effect on survival estimates. The study found that after tracing back DCI cases in Sweden and standardising incidence dates, 1-year survival from colorectal cancer decreased by around 3% in Norway and Sweden. These 1-year survival estimates, however, were still higher in Norway and Sweden than in England by around 5% at one year. It is thus unlikely that these differences in registration practice will explain all the differences in survival, especially in the longer term.

Incidence rates of colorectal cancer vary between the countries, as reported in Section 1.2. Of the countries included in this thesis, CRC incidence is reportedly highest in Norway, followed by Denmark, and lowest in Sweden. It is unclear the extent to which these are true differences in incidence (and risk factors), or partly a reflection of differences in case-ascertainment and/or coding. The lack of cancer registration from death certificates in Sweden may partly explain the lower incidence of CRC, however it is unlikely to completely explain the difference (for instance between 42.6 diagnoses per 100,000 in men in Norway in comparison with 32.2 diagnoses per 100,000 in men in Sweden). The proportion of DCO cases are around 1.0% in Norway, a country with diagnostic activity, cancer outcomes, and long-standing cancer registries comparable to those in Sweden. Thus, it is improbable that

the proportion of (unregistered) DCOs would be much higher in Sweden than in Norway. Another possibility is that countries with higher incidence of CRC are over-ascertaining cases, such as the registration of *in situ* tumours (carcinoma confined within the basement membrane of the bowel epithelium).[228] Specialised CRC registries include only invasive tumours, however, there might be some inter-observer variability in the pathologic assessment of tumour tissue, especially of polyps and whether they are classified carcinoma *in situ* or intramucosal carcinoma (Tis in TNM classification of malignant tumours),[43] or invasive adenocarcinoma (invading submucosa, T1 and higher in TNM classification of malignant tumours).[43,228] If present, this inter-observer variability may affect the comparability of the results for the earliest stage category, and potentially more so in countries with relatively high proportion of diagnoses with asymptomatic disease.

The four countries included in the analyses have 100% public health coverage. However, health financing and the role of the private health sector in providing services and reporting activities somewhat varies between the countries. Government compulsory and contributory schemes finance most of the health spending in the UK (83% of total health spending), Denmark, Norway and Sweden (84% of total health spending in each country) (2011 data).[229] Private health financing includes out-of-pocket payments and different types of private health insurance complementing (cost-sharing after basic coverage), supplementing (adding further services) or replacing (provider faster access or wider choice of providers) public health services.[230] Household out-of-pocket payments make a smaller proportion of health expenditure in the UK (10%) than in Denmark, Norway and Sweden (around 15%), while voluntary healthcare payment schemes make up a higher proportion of healthcare spending in the UK (around 8%) than in Denmark (2%), Norway and Sweden (<1%).[229] The proportion of the population covered by private health insurance is however larger in Denmark (24% in 2011, mainly complementary and supplementary services) than in the UK (10.9% in 2011, mainly duplicate services).[229] Reportedly, 98-99% of hospital activity in England is funded by the NHS.[231,232] In England, NHS care providers are required to submit data to the National Cancer Registration Analysis System (NCRAS), including NHS-funded activities carried out in the private sector (and presumably privately-funded activity carried out in the NHS).[232] Though private hospitals in England may voluntarily submit data to the registry, it is likely that diagnoses and/or procedures made entirely in the private sector are not fully captured in population-based datasets. Similarly, in Denmark, the DCCG.dk registers procedures carried out in public hospitals. The analyses presented in Section 3 account for

the uncertainty about the surgical status of patients not registered in the DCCG.dk. However, the under-ascertainment of cancer activity in the private sector may bias the results, especially in the demographic groups with relatively high use of private insurance services: least-deprived and those of working age.

Previous research has found that most of the international differences in survival are found in the first year at diagnosis,[233] and that differences decrease when conditioning five-year survival to surviving the first year after diagnosis.[3,233] Conditioning 5-year survival to surviving the first year ('five-year conditional survival') may reduce the bias due to differences in registration practices, and also account for differences in late presentation when examining survival for all stages combined. Møller and colleagues examined the EUROCARE-4 findings from a UK perspective, comparing survival estimates between European countries and the European average. Overall, one-year survival estimates for England were below the European average, while conditional five-year survival was just above the European average.[233] Still, five-year conditional survival for colorectal cancer patients in England was lower than those in Norway and Sweden, and higher than in Denmark.[233] Stage-specific survival estimates, which account for the differences in late presentation and delayed diagnosis, were still lower in England than in Norway and Sweden in a previous international study.[3] These findings are consistent to those presented in Section 3 of this thesis, except that CRC survival in Denmark is now closer to that in Norway and Sweden.[128]

The survival analyses presented in this thesis are also stage-specific. Survival estimates are presented for the longest possible follow-up time in the available data, three-years after diagnosis, for which differences in registration have lower impact than for shorter follow-up. The under-ascertainment of cases and potential misclassification of surgical status in relation to the use of private health services will systematically affect more affluent patients and those of working age. Any comparison of treatment receipt between younger and older patients (and between deprived and affluent patients) will possibly underestimate the proportion treated in the younger (and affluent) group, thus underestimating the age (and socioeconomic) inequalities.

5.3 Explaining the age inequalities in health outcomes

There is a considerable amount of evidence that older patients with treatable conditions are not always receiving optimal care. Suboptimal management of older patients is not an issue specific to (colorectal) cancer. Inadequate management of older patients has been

extensively reported for other conditions such as cardiovascular disease, mental health conditions, and hip replacement for osteoarthritis, to name a few.[12,200,234-236] Similarly, under-management of older patients has been examined in other geographic settings, though mainly in developed countries.[92,237-239]

There is debate as to whether the age differential in the management of chronic conditions is due to "age-differentiated behaviour" (justifiable reasons for under-treating older patients) or due to age discrimination resulting from ageism (unjustifiable on biological grounds).[102,104] Distinguishing age-differentiated behaviour from age discrimination in the provision of health may be particularly challenging because clinical decision-making involves a comprehensive assessment of patients' needs, and it is difficult to disentangle the influence of chronological age from the other factors considered for that decision.

There are several ways of exploring the effect of discrimination on health inequalities. Because discrimination is not easy to measure, the most common way to examine it at a population level is 'indirectly' through a comparison of outcomes between age groups, while adjusting for the effect other risk factors (usually the biological and sociodemographic determinants of the outcome).[240] Any residual difference in outcomes would then suggest that discrimination is a possible explanation, assuming that there is no unmeasured confounding. The analyses presented in this thesis have followed this indirect approach to explore age inequalities in CRC management. The findings of this work consistently show that after accounting for the biological determinants (stage, comorbidity and the diagnostic route), there are still residual differences the outcome (CRC management) by age group. The finding of age inequalities in CRC management after adjusting for biological factors is consistent with other recent studies.[201,202,221] Age discrimination needs to be considered as a potential contributor to the remaining age differences in cancer management.

The assumption of no unmeasured confounding (which indicate discrimination) is however a strong one. It could be argued against the evidence here presented that residual confounding due to frailty might explain the under-management of cancer in older patients, and their adverse health outcomes. Comorbidity, frailty, and disability are interrelated, but increasingly recognised as different processes.[79,80] Frailty represents a state of vulnerability and limited capacity to tolerate and respond to stressors because of limited reserves and function of different physiologic systems. Although this formal definition is generally accepted, there is no standard way to diagnose frailty and measure its associated risk of adverse health outcomes in practice.[80] As a result, although informative for clinical decision-

making, frailty in practice is likely (at least partly) a subjective interpretation of the expected tolerance of patients to disease and intervention(s), and therefore, possibly informed by other factors including attitudes, beliefs, and the wider context. For instance, a clinician may be less likely to treat a frail patient, if that patient were also lacking social support or a good environment in which to recover from the intervention. The clinician making such decision would most probably be doing it in good faith. However, the result is still that the patient is not receiving optimal treatment.

Ageist attitudes and age discrimination might negatively affect health outcomes at the individual level. There is however the issue with measuring discrimination at the individual level that it requires the individual to recognise that they are being discriminated against.[240] To recognise age discrimination directly in a clinical setting, therefore, it would require older patients or their carers to know how other, younger, patients would be treated. Age discrimination is thus likely to be under-recognised and under-reported. With this in consideration, it is not surprising that, evidence on the (direct) effect of age discrimination on health outcomes tends to focus on the effect of self-perception of ageing on mental health outcomes or health behaviour.[240] For instance, studies have shown that patient 'preferences' on treatment may be adversely influenced by negative views of ageing held by themselves and their carers.[102] Patients with negative self-perception of ageing may have harmful health behaviours and may have low expectations of their care.[241] Some studies have examined the effect of self-perception of ageing on more objective health outcomes, such as cardiovascular events and longevity, and found that people with negative perceptions of ageing had more acute cardiovascular events and shorter life span than those with positive views of age.[242,243] Arguably, negative perceptions of ageing could be partly a consequence of personal experiences of poor health.

The traditional biomedical and lifestyle frameworks used in epidemiological research favour measuring exposures and risk factors (biological, chemical or physical; and health behaviours, respectively) at the individual level to understand disease distribution in the population.[244] Within these epidemiological frameworks, measuring exposure to 'discrimination' and its effect on health outcomes is problematic. The study of health inequalities and social determinants of health can benefit from 'alternative' theoretical frameworks to guide epidemiological questions and analysis of inequalities.[240] One of these alternatives is the ecosocial theoretical framework of disease distribution, first proposed by Nancy Krieger in 1994. This theoretical framework pays particular attention to the ecologic

and societal context, during the life course and historically, in which social inequalities arise, and how people express biologically (or 'embody')[245] their experience through this context, thus creating population trends in health and disease.[107,240,244] Taking from this theory, we can scrutinise in more detail the wider context to appreciate whether age discrimination is a plausible explanation of the age inequalities in health outcomes.

Age discrimination is reportedly the most frequent type of discrimination,[246] however, it has remained relatively under-studied.[214,240] Empirical evidence of direct age discrimination in the clinical setting exists. For instance, studies have shown that clinicians are more reluctant to share diagnoses and prognoses with older patients, and that they spend less contact time with older than with younger patients.[247-249] An analysis of the English Cancer Patient Experience Survey (CPES) found that older patients tended to be more satisfied with their care than younger patients; however, they were also less likely to report being given written information about their test that was easy to understand, and information about side effects.[250] Older patients were also less likely to be given the name of the cancer nurse specialist in charge of their care, and less likely to be asked to participate in research.[250] These findings are similar to previous NHS inpatient surveys, and suggest that patient satisfaction, as it is based on personal expectations, is not an ideal indicator of age discrimination.[251] Moreover, the findings of these surveys suggest that older patients could benefit from better support to navigate the health care system.

The proportion of people with limiting long standing illness or disability increases with age.[252] Access to adequate social support is thus particularly important for the older population to enable them to function independently. Independent living refers to having control and choice over the support that one needs, rather than living alone and doing everything for oneself.[85,253] Social care includes a wide range of non-medical services for people with different types and levels of needs because of physical or learning disabilities, mental health needs, among others. In England, publicly funded social care services are provided by local authorities after assessment of needs and financial means (income and assets).[254] As in other countries, services for people aged 65 years and older are delivered through a generic service for older people, while younger adults use particular services according to their particular needs.[85] This age difference in the organisation and delivery of the services suggests that there are different (and lower) standards and expectations for the care of older people.[85] It has been reported that older people and those with mental health needs are likely to underestimate their needs, probably in relation to having low expectations of care, or denial

of their needs.[255] Conversely, people with physical, sensory or learning disabilities tend to over-assess their needs; potentially in relation to a longer history of advocacy, campaigning, and awareness of their rights.[255] A study of social care services in Norway (interviewing municipality managers in charge of allocation of social care services) found a tendency for preferential treatment of younger patients, possibly in relation to higher levels of expectations, advocacy and rights consciousness.[256] In a setting of limited resources (availability of staff more than financial constraints in the Norwegian context), informants tended to prioritise the need of the young for getting ready to go to work or school, suggesting that the ambition of independence was not there for older patients.[256]

The majority of social care in the UK is provided informally by family and social network or paid for privately.[254] The expectation is that social care is an out-of-pocket expense for those who can afford it, and that public services are reserved for those with financial need (and is generally co-funded). However, austerity measures have meant that public spending on social care and social protection in the UK has fallen consistently in real terms and as a percentage of gross domestic product since 2009-2010,[254,257] putting additional pressure on the services already under strain. It is likely that these cuts disproportionately affect older people, who in general have more complex needs, but lower expectations and advocacy for their rights, in comparison to other vulnerable groups. Given the current situation of social care services in the UK, it is unlikely that older people with care needs (even those who meet the financial need criteria) are being adequately supported to have choices in their social care. Furthermore, gaps in the provision of social care is associated with frequent use of acute health services.[258-261] The fact that social care services in England (and the UK) are structurally disconnected from the healthcare system makes it particularly difficult for people who need to navigate both systems. Similarly, it makes it difficult for clinicians to assess the likely long-term effects of treatment on patients' lives, and adequately plan their care.

Comorbidity, frailty and disability are associated with a higher risk of complications and mortality following surgery. These factors are generally perceived as "biological" determinants of surgical treatment eligibility and receipt, especially in older people. However, the influence that these factors have on health outcomes is not deterministic, but largely influenced by the wider context. The availability of an adequate level of postoperative care is equally (if not more) important for short-term outcomes. It is likely that CRC patients in England do not have comparable access to intensive care after surgery as patients in other

countries do (See Section 3.3.4). The elevated risk of postoperative mortality in relation to inadequate postoperative care disproportionally affects the prospect of older patients receiving surgery, because they are more likely to need intensive care (because of multimorbidity or emergency surgery). Moreover, it is plausible that given the limited resources, younger patients are prioritised for treatment and post-operative care over older patients. Similarly, prioritisation of limited resources favouring younger over older patients is likely to be the case for publicly funded social care services. Disability is a potential endpoint of different types of chronic conditions and/or frailty, and is also determined by the physical environment, social expectations and availability of social support. It is therefore possible that age, comorbidity, (perceptions of) frailty and disability have a heavier weight in the clinical decision-making process in England than in the Scandinavian countries. The limited availability of adequate postoperative care and social care in England may help explain the lower proportion of older patients receiving surgical treatment for CRC in England, in comparison with Denmark, Norway and Sweden.

Another frequently mentioned determinant of treatment receipt is "patient choice". It is often believed that older patients tend to prefer less-aggressive treatment options than younger patients. This belief has been challenged, and there is now a good amount of evidence supporting the notion that most older cancer patients want to have optimal treatment of their cancer.[102,262] Moreover, "preferences" are likely influenced by the amount of practical support patients require and have available at home, as well as the travel time to treatment centres.[263,264] The CPES findings of older patients being the least likely to be given information about their treatment, and about secondary effects of treatment suggests that the treatment choice (even if it were a true choice) is less likely to be an informed one in older patients.[250] Furthermore, the expectations of care are informed by personal (or close) experience with the healthcare system, which until recently had limited focus on the needs of older patients.

The 2001 Department of Health's National Service Framework for Older People was the first national strategy and action plan to improve health and social care services for older people in the UK. It recognised that services were not always meeting older people's needs by "allowing organisational structures to become a barrier to proper assessment of need and access to care, and because best evidence-based practice is not in place across important clinical areas".[216] Tellingly, this strategy document also acknowledged that in the NHS, the 'one-size-fits-all' post-war approach to health services had survived too long, and that the

financial commitment to older people in public services – around 40% of NHS budget, and 50% of social services budget in 1998-1999 – had not translated into an institutional and cultural focus on their needs.[216] Several initiatives were set out, like the commitment to review the eligibility criteria for social care services to avoid age discrimination, the introduction of specialised stroke units in general hospitals, planned increments in intermediate care services to promote rehabilitation and avoid unplanned hospital admissions, among others.[216]

After the introduction of the National Service Framework for Older People, the UK Department of Health reportedly carried out a series of audits of NHS policy to identify those which were explicitly ageist.[251] Several years later, in the context of the Equality Bill 2009 (later Equality Act 2010), which outlawed age discrimination in the provision of goods and services, and the related European legislation promoting non-discrimination and equal opportunities irrespective of religion or belief, disability, age or sexual orientation in the European Union (COM(2008) 426), the Department of Health commissioned a series of reviews of the evidence of ageism and age discrimination in several public services (primary and secondary care, and social services) in the UK. The review of ageism in secondary care found that instances of explicit policy-based age discrimination within the NHS were likely rare. It however found substantial evidence of indirect discrimination and ageist attitudes among NHS staff.[251] Among the evidence presented in the review, is a University of Kent study on staff perceptions of ageist attitudes in the clinical setting, which reported that 32 out of 57 respondents had "sometimes or often" witnessed older patients not being referred to specialist services when needed.[265] The review also covers a 2003 survey to all staff of Wirral Hospital NHS Trust, which found that 13 out of 100 participant doctors replied 'No' to the question "Should older people have equal access to health care when compared with younger people?" as opposed to 5/100 trained nurses and 6/100 hospital managers.[251,266] Often, the reasoning included the important role of life expectancy in clinical decision-making. After listing many accounts of under-investigation and under-treatment in cancer care, stroke and cardiology, the authors recognise that the evidence is so strong and widespread that, even taking into account polypharmacy and comorbidity, they "must conclude that ageist attitudes are having an effect on overall investigation and treatment levels".[251] The authors also conclude that anecdotal indications of indirect age discrimination are widespread and rightly wonder "How many anecdotes does it take to constitute evidence?".[251]

Ageism and age discrimination in health and social care is much wider than one-to-one interactions. Global health policy and public health have been accused of being institutionally ageist for using and promoting the use of metrics such as potential years of life lost (YLL), disability-adjusted life years (DALY) and premature mortality (deaths occurring between ages 15 to 70 years) for setting global health targets.[213,214] YLLs and DALYs measure the burden of mortality according to the number of years between age at death and an arbitrary threshold around 70 years, after which death is given a null value. Though the meaning is not intended to be that life after the threshold is worthless, it sends a clear message about where priorities in global health 'should' be, and that treating older patients is likely of little value. The justifications for using these metrics (and this line of thought) include the "fair innings argument" which is the idea that there is a certain lifespan that can be reasonably expected for every member of a population, and that it is unfair if people cannot achieve that.[267] This injustice would legitimate, using this argument, giving priority to a younger patient over an older one if only one of them could receive a certain treatment because of scarce resources, all other things being equal. The other justification is an economic one, based on the grounds of younger people (in working age) being more productive and contributing more to society than older people.[213] In a provocative comment on the Journal of Medical of Ethics in 1994, AB Shaw (from the Bradford Royal Infirmary, West Yorkshire) argues that the case for ageism is moral (and economic) because health is a limited resource.[268] Though intuitive, these arguments contradict the United Nations universal value of equal rights, the principle of health as a human right for all, and the NHS principle of providing a "universal service for all based on clinical need, not ability to pay".[216] They perpetuate stereotypes of older people being frail and dependent,[214] when many people keep making substantial contributions to society in later life, and ignore that people in retirement have already made their societal contribution.[213]

In the context of austerity after the 2008 economic recession, 'efficiency savings' have been a priority in the NHS.[269-271] The push for savings has seen calls by NHS leading figures to keep "high-cost patients out of hospital",[272] and for community-based management of frail patients, likely older and/or with multimorbidity.[273,274] Several geriatricians have recommended improving hospital services to meet older patients' needs, rather than denying hospital management to those who most need it.[274-276] The focus of recent health policy on enabling and supporting people to take responsibility for their health not only overlooks the effect of the wider context on "patient choice",[277] but is also unhelpful for

older people with complex needs who are not having sufficient options for their care. A recent commitment to provide additional funding for the NHS, the NHS Long Term Plan published in early 2019, has acknowledged the need to "support people to age well", and to help more people live independently for longer at home.[278] The much-expected government plan (Green Paper) for social care funding and reform is however yet to be published, and it is currently not clear how the proposals to improve long-term care of older people will be delivered.[279-281]

The context of austerity makes the argument of rationing of resources based on age particularly relevant, and potentially palatable, despite the increasing political disposition to assert the right to health and social care of older people in England and the UK. Several opinion pieces by respected scholars and health professionals were published in scientific journals – mainly in the 1900s – arguing in favour of age discrimination and age-based rationing of resources on economic grounds and the "fair innings" argument.[268,282] The counterargument is, in my view, irrefutable. Age discrimination is unethical, and should be unacceptable in a society holding the principles of justice, equality and solidarity.[283,284] It would surely be considered inappropriate in the current societal context to propose a resource-rationing measure explicitly based on and discriminating against any of the other characteristics protected characteristics by the Equality Act 2010, such as gender, race, religion, or sexual orientation. Somehow, we as a society remain largely insensitive to the needs and rights of older people. A part of the problem seems to be that age discrimination is often covert.

Priorities in global health in general have remained focussed on diseases of the young, overlooking the needs of older people, and the increasing burden of non-communicable diseases.[9] The global health priorities on non-communicable diseases remain on primary prevention rather than treatment,[285] even if a large part of the potential to decrease the disease burden will likely come from secondary and tertiary prevention in older patients.[9] Recently, it was recognised that the original UN Millennium Development Goals, established after the Millennium Summit of the UN in 2000, were largely disconnected from the needs of the ageing population.[286] The 2002 Madrid International Plan of Action on Ageing (MIPAA) was subsequently signed by UN members, agreeing for the first time to "link questions of ageing to other frameworks for social and economic development and human rights". The document affirms older persons' entitlement to full access to health care and services, and the needs of these services to include the necessary personnel training and facilities to meet

the needs of older people.[287] It sets out a series of actions and objectives to address issues in relation to health promotion and well-being throughout life, universal and equal access to health-care services, HIV in older life, and training of care providers and health professionals to work with older persons.[287] The MIPAA has been recognised as a step in the right direction for equal treatment of older persons.[288,289] It was however criticised for failing to recognise the bias against older people in health metrics such as DALYs.[214] More recently, the World Health Organization's global strategy and action plan on ageing and health built on the MIPAA aligning the ageing agenda with the Sustainable Development Goals.[289] It was adopted by UN Member States in 2016, highlighting the need for multidimensional action to address the needs of the older population. The strategy introduced the concept of Healthy Ageing as wider than the absence of disease, and recognises that combatting ageism is "a fundamental step in fostering Healthy Ageing".[290] The timing and focus of the new WHO strategy 'campaigns' to challenge ageism[289] are telling. Ageism and age discrimination continues to be a pervasive issue.

Negative attitudes to older age are widespread in society. Contemporary demographic changes mean that an increasing proportion of the population is in the older age bands. As a society, we are aware of the economic burden from the high costs for health and social care of older people, and the high costs of pensions.[291] In the media, older people are often portrayed in a negative light, reflecting and shaping societal values.[292] Moreover, older people living with cancer may be subject to double stigmatisation because of their age, and because of their cancer diagnosis.[293] People with cancers associated with lifestyle risk factors (such as smoking and lung cancer; diet, physical inactivity and colorectal cancer) may be particularly stigmatised as it is perceived the cancer is a consequence of their lifestyle choices.[96] Age discrimination may also synergise with discrimination based on other characteristics, such as gender and race.

It is clear that evidence of a causal relationship between age discrimination and health outcomes will not come from a single study, nonetheless, considering the findings of this thesis in the wider context provides a better idea of the magnitude of the issue of age inequalities, and the potential determinants. Age discrimination is a widespread issue. Political commitments to address it, such as outlawing it and asserting the rights of older people is a step in the right direction, but they are not enough. Ageist attitudes and age discrimination are deeply rooted in society in general, and are magnified in the delivery of health and social care, especially in settings of limited resources. As with other types of

discrimination, acknowledging it exists, recognising it when it happens and its detrimental effects on individual and population health is necessary to tackle it.

In view of the wider context, it is not only plausible but also likely that age discrimination has a role in explaining the age differences in colorectal cancer management found in the studies presented in this thesis, as well as 'biological' factors, such as comorbidity, frailty and disability. The interaction between attitudinal and biological factors is however complex, and greatly affected by the wider context. Healthcare services are generally arranged to manage single conditions, and largely overlook the complex needs frequently experienced by older patients.[98] Additionally, financial cuts in health and social care are likely to translate into less adequate care that disproportionally affects older people. These wider factors are reflected in older people's poorer health and larger dependence, 'confirming' perceptions of older people being frail and dependent, and validating age discrimination in healthcare, which in turn affect health outcomes. It is likely that this vicious cycle is reinforced by the current austerity context in England, more so than in the Scandinavian countries, resulting in comparatively worse health outcomes. Figure 5.1 summarises the proposed vicious cycle between contextual, biological and attitudinal factors behind the finding of under-management of older CRC patients in England.

5.2.1 Breaking the cycle

Specialisation of care has allowed improvements in cancer outcomes, and it has contributed to the large focus of contemporary research and policy into developing and implementing unidisciplinary interventions.[98] Isolated, unidisciplinary health services are however not helpful for older people with complex needs and may lead to inadequate care and unnecessary polypharmacy.[294] In England, health services are currently disconnected from long-term and social care services, making it problematic to plan and secure adequate care, and return to independence after a hospital discharge.

The WHO's 2015 World Report on Ageing and Health suggests the implementation of an older-person-centred and integrated care approach to meet the complex needs of older people. Older-person-centred care focuses on the individual, their experience, needs, and preferences in their context as a part of a family and a community.[294] An important feature of integrated care is that it ensures that services are well coordinated around patients' needs.[295]

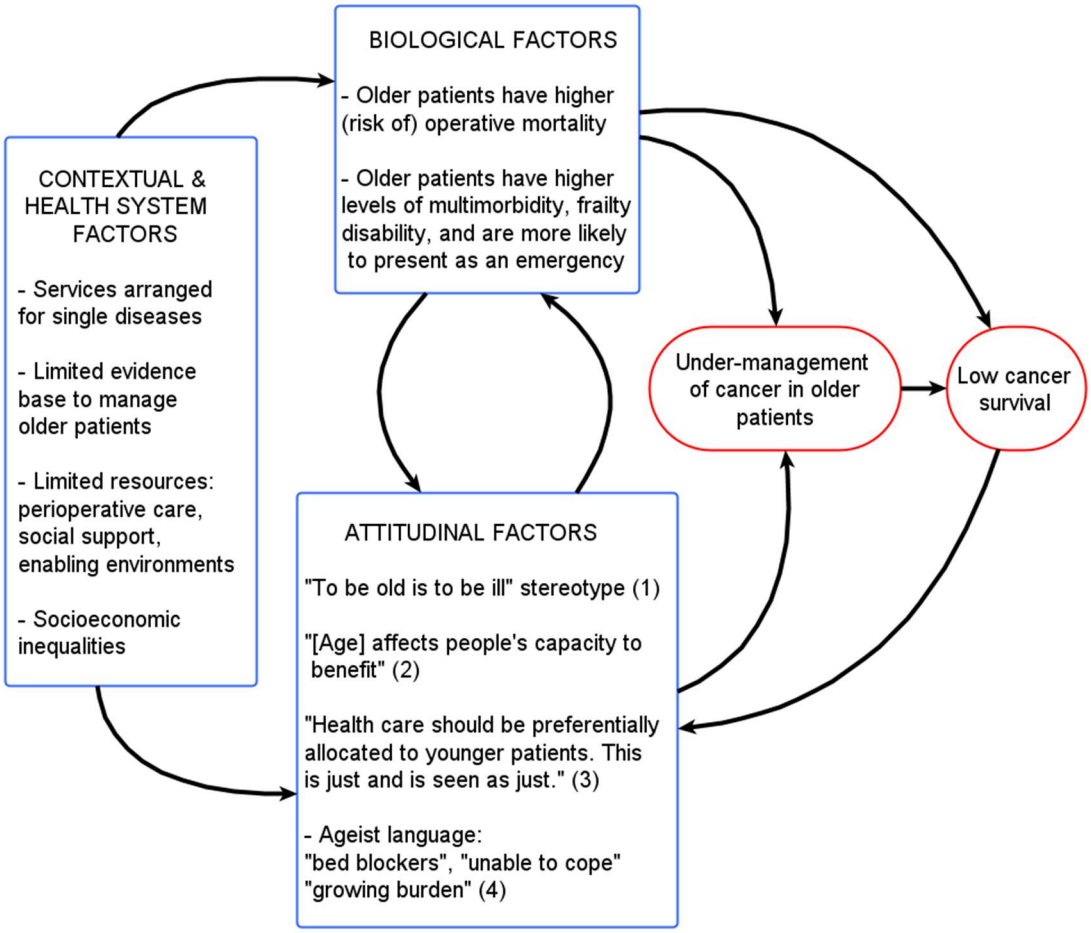


Figure 5.1: Relationship between biological, attitudinal and contextual factors that determine under-management of cancer in older patients and other cancer outcomes.

Notes: (1) from Schroyen et al, 2015.[92] (2) is a quote from Williams (1997) opinion piece.[282] (3) is a quote from Shaw (1994) opinion piece.[268] (4) examples of ageist language in clinical settings, from Oliver (2012) opinion piece.[292]

One of the first models of integrated care was established in Quebec, Canada in the late 1900s. The Program of Research to Integrate the Services for the Maintenance of Autonomy (PRISMA) aimed to address the problem of discontinuity of care for older people with multiple chronic conditions.[296] It involved coordination of services with shared information services, shared responsibility for patients, a single assessment tool (including ADL IADL, communication and mental abilities), and a single entry point for patients, who received individualised service plans. The services ranged from primary care, outpatient specialised care, emergency, inpatient, rehabilitation, personal care, home support, and pharmacy among others. The coordination was done through a 'case manager' (mostly social workers or nurses) who were in charge of managing all the services needed and communicates with the primary care physician, who was in charge of the medical management. Case managers were notified of any emergency admissions; and in the case of hospital admissions, the case manager helped with the discharge plan, to ensure that the needed community support was

available. Reassessment plans was performed based on needs. After four years, comparisons with the normal care system showed a significant reduction in the incidence and prevalence of functional decline, reduced number of emergency visits, and improved client satisfaction and empowerment. There was no significant change in cost, indicating that benefits were achieved without additional costs.[296] Several of the PRISMA components were then implemented at the provincial level.

Coordinated person-centred care is increasingly recognised as a particularly useful approach in the management of patients with complex needs. In England, The National Collaborative for Integrated Care and Support was established in 2013 aiming to promote a culture of cooperation and collaboration between different care sectors.[295] Recently, there have been initiatives to improve the integration and coordination of services. The Better Care Fund was introduced in 2016 providing financial support for local authorities and NHS organisations to plan and deliver services jointly.[297] New care models are being implemented in 'vanguard' sites, which can be later adapted in other local areas, including integrated primary and acute care, enhanced health at care homes, and multidisciplinary community health.[298] If successful, some of these initiatives could be scaled-up to a national scale to avoid further inequalities.

In cancer care, the role of the Clinical Nurse Specialist in cancer care (CNS) is to coordinate services and personalise the cancer care pathway to support patients and their carers.[299] The benefit of CNS for cancer patient outcomes has already been recognised, as well as potential detrimental effect of gaps in access.[300-302] It is likely that the needs of an older patient with cancer go beyond the "cancer pathway" which usually ends at discharge. For their care to be integrated, it needs to consider long-term care needs. The principles of care integration and coordination could be applied further to serve older patients (diagnosed with cancer or in general), as to consider in a holistic manner the treatment options, management of comorbidities, post-operative care, needs at home after discharge, follow-up and reintegration to normal life.

Aligning social with primary and secondary health services to serve the needs of older people requires a clear understanding of the environment in which people live, to appreciate their specific barriers and opportunities to improve their health and well-being. Furthermore, integration and coordination of requires adequate funding for both social and health care. It remains to be seen whether the awaited government plan for funding and reform social care services stimulates the integration of long-term care and health care.

The WHO's global strategy and action plan on ageing and health recognises that one of the most important barriers to effective policy on healthy ageing are the common negative attitudes and assumptions about older people.[290] Ageist views influence policy, research, and practice. A key to combat age discrimination is to recognise ageing as a normal and valued part of life, and older adults as appreciated members of society. Legislation, communication and education (especially of health and social care workforce) are key to identify (especially covert) ageism and tackle it.

More could be done to engage older patients in interventions to promote early diagnosis and optimal management of cancer. An ICBP study found that although symptoms awareness was not lower in the UK and Denmark than in Australia, Canada, Norway and Sweden, perceived barriers to symptomatic presentation, such as worries about wasting the doctor's time were higher in the UK than in the other countries.[303] The study also found that in comparison with the other countries, there was lower awareness of the increasing risk of cancer with age in UK participants.[303] A subsequent ICBP study looking into attitudes towards cancer in the UK found that participants aged 70 years and older were slightly less positive about the value of early diagnosis for increasing the chances of survival and of the prospect of cure after a cancer diagnosis than those aged 50-59 years, after accounting for differences in marital status, sex, education, ethnicity, UK region, self-rated health and cancer experience.[304] Increasing awareness and improving the general attitude towards cancer in old age, and towards the value of early detection and treatment of cancer in older patients and their carers may help improve cancer outcomes in this group. Nonetheless, other studies have found that cancer awareness and recognition of cancer symptoms does not necessarily result in seeking medical help.[305,306] Similarly, prompt help-seeking does not, on its own, lead to better cancer outcomes. A recent study showed that women were more likely to be diagnosed with colon cancer after an emergency presentation than men, despite being more frequent help seekers, probably because women more frequently present with low-risk or unspecific symptoms.[305] The authors argue that innovations in diagnostic strategies are needed [alongside cancer awareness and prompt help-seeking] to improve early diagnosis and prevent emergency presentations.[305]

Cancer screening programmes explicitly exclude older patients, with upper age limits at 74 years (extended recently from 69) for colorectal and breast cancer, and 64 years for cervical cancer. A study on ageism in the NHS qualified the age limits of screening programmes as one of the "most explicit forms of age discrimination in the NHS".[251] A review of the evidence

for colorectal cancer screening in older people concluded that there is actually little evidence on screening for older people, as none of the studies reviewed examined the benefits and limitations of screening in people aged 70 years and older, and few gave recommendations for upper age limits.[306] Several other national screening programmes offer screening to all people over 50 years of age, without an upper age limit.[306] It is likely that screening in older patients can play an important role not only in early detection but in improving the likelihood of receiving optimal treatment.

From the research perspective, much can be done to increase the evidence base of the effect of different interventions, such as screening and different treatment modalities on cancer outcomes in older patients. Research is needed to establish the benefit of screening in older patients, to inform or support any age limit or even the lack of one. With regards to treatment, there have been some recent efforts towards improving the evidence base for cancer treatment in older patients. The Medical Research Council (MRC)-funded FOCUS (Fluorouracil, Oxaliplatin, CPT11 (irinotecan): Use and Sequencing) trial on chemotherapy for advanced CRC had no upper age limits for inclusion with the intention of including more older patients, however median age was still 64 years (mainly because concerns about adverse effects in older patients). The subsequent FOCUS2 specifically targeted older patients with advanced CRC, who were eligible for surgery, but for whom the oncologist deemed full-dose regiments to be unsuitable.[307] It was the first large trial to recruit frail, older patients with advanced CRC. Although there was no difference in the outcome (progression-free survival) between the treatment arms (four arms of single or combined chemotherapy agents), the trial was ground-breaking in that it showed that older, frail patients can participate in clinical trials for cancer treatment.[307,308] In 2017, the US National Institutes of Health introduced a policy and guideline to promote the inclusion of individuals across the life span as participants in research supported by them.[309] Such push from funders should foster the expectation to include older patients in research, and for different stakeholders (clinicians, patients and researchers) to demand the improvement of the evidence base for managing older patients. Observational research can also be beneficial to understand and monitor health outcomes in older patients. Qualitative work is additionally needed to understand how the wider context and attitudinal factors affect health outcomes, and how to tackle them.

It is clear that a multidisciplinary approach is needed to improve cancer outcomes in older patients, involving policy-makers, clinicians, researchers, patients and their carers, and the

general public. More could be done to actively assert and defend older people's entitlement to full access to health and social care, as well as to recognise and tackle age discrimination. Policy-makers should recognise the potential dangers of using health metrics that give lower value to health outcomes of older people. The lack of evidence to manage older patients in the clinical setting should be a motivation to create and increase that evidence base, instead of a justification for suboptimal care. Better communication and integration between health and social support services would certainly contribute to better serve older patients with complex needs.

5.4 On methods to study health inequalities

Randomised controlled trials (RCTs) are widely considered the gold-standard for establishing causal relationships.[310,311] RCTs generally focus on a super-selected proportion of patients with a given condition (generally the ideal candidates for treatment, with no comorbidity), and are often criticised for their lack of external validity or real-world meaning. Population-based research, on the other hand, includes all the eligible population (usually defined geographically, and by a specific diagnosis), however, it generally lacks information on all potential confounders. Still, population-based observational studies are commonly used to understand the real-life burden of diseases, their implication on population health and health policy. Traditionally, epidemiological research uses observational data to test statistic associations between two factors (exposure and outcome). When this association is substantial, after taking into account potential confounders (generally by stratification, standardisation or regression modelling),[312] researchers usually make the case for the possibility of a causal link between the two factors, usually without the word "cause".

A great contribution to the study and understanding of causal inference and potential outcomes is attributed to Jerzy Neyman, who in 1923, used in the context of RCTs, potential outcome notation for the first time.[313] The application of potential outcomes and counterfactual thinking to observational settings (introduced by Donald Rubin,[314] and generalised by James Robins[315]) has arguably revolutionised the way we think about causal inference. The potential outcomes approach (where researchers ask what would have happened to the outcome, had the exposure been different) provides definitions and analytic methods that produce estimates, which under explicit assumptions, can be interpreted as causal effects.[316] The potential outcomes approach thus encourages 'interventional' thinking about the relationship between exposures and outcomes for

observational studies (or the 'randomised experiment paradigm'),[317] and urges researchers to clearly define exposures, outcomes, and potential well-defined intervention(s).[318]

Although the potential outcomes is not unanimously accepted, it stimulated an important debate in epidemiology about association and causation, especially in the observational setting. Traditionally, it is accepted that observational studies give evidence of associations, while the word causation is mostly avoided. Miguel Hernán (an influential proponent of causal inference methods) noted that although researchers often refrain from using the term "causal", and refer to estimates as associational, the goal of many observational studies is in fact causal.[319] This may apply to a big part of observational studies, however, the most valuable lesson from this framework is that it encourages an open and transparent discussion about the assumptions that are made to give estimates a causal interpretation.[316] Assumptions have always been there, but more as competence of statisticians than of epidemiologists.

The main quantitative findings presented in Chapters 3 and 4 of this dissertation fall within the biomedical and lifestyles frameworks of study of disease distributions. These analyses were greatly helped by the counterfactual-based causal inference thinking in several ways. It was particularly helpful for the analysis to represent visually the assumed causal relationships using DAGs. In this way, the assumed relationships that informed the quantitative analyses were explicit from the start. However, it is difficult, if not impossible, to summarise complex interactions between biological and social factors that influence health outcomes in a DAG, without it being an oversimplification of reality.[320] The discussion in Chapter 5 therefore takes from the ecosocial epidemiological framework to add additional context to the findings of age inequalities.

Another frequent criticism of causal methods is the limited value of their application to non-manipulable exposures, such as age or race.[321] The interventional approach to counterfactual-based causal inference, where a well-defined intervention is generally expected, is generally favoured because of its clarity, as it is relatively simple – for clinicians, epidemiologists and biostatisticians – to think of exposures as treatment arms in a randomised controlled trial, and of potential outcomes as results of potential interventions on the exposure. Results from such research potentially translatable into effective interventions. This approach, however, is not without its critics, because it arguably restricts the scope of epidemiological questions to those that may be subject to intervention,[322,323] when in reality there are many issues in population health, where an experimental approach

is simply not applicable. Social epidemiology and health disparity research focus on social determinants of health that are frequently non-manipulable because they cannot be modified (such as age or sex), or because they are complex social constructs (such as ethnicity and socioeconomic status) that are difficult to pinpoint. The fact that they are non-manipulable does not mean that such factors should not be considered as 'causes' of health outcomes – provided that by causation we mean the capacity of some variables to respond to changes in others.[322,324]

The interventional approach to assess causation is also criticised because a well-defined intervention is subject to what is humanly possible at one specific time.[322] A well-defined intervention can potentially be stretched to hypothetical interventions that are feasible, but probably not practical to tackle the issue in question.[323] Etiological causation (focusing on the reasons, as opposed to a potential intervention), on the other hand, may not lead researchers to feasible or practical interventions, but it can provide the justification to do something about the disparities in the outcome.[323]

Specific to causal mediation methods, there is a debate on whether the decomposition of effects is relevant for inference in population health. This is because the identification of natural (in)direct effects requires the use of 'composite cross-world counterfactuals' (combination of hypothetical scenarios that are not logically compatible, nor observable in real life for any individual, even in experimental settings), and thus their relevance for health policy and real-life interventions is unclear.[203,321] To address these limitations, instead of estimating 'natural' effects, I estimated 'interventional' effects, introduced by VanderWeele, Vansteelandt and Robins,[325] and adapted and extended by Vansteelandt and Daniel to the multiple mediator setting.[203] Interventional effects do not rely on cross-world counterfactuals and can be identified under weaker assumptions than natural effects.[203] Interventional effects differ from 'controlled effects' (preferred for public health questions)[321] in that in the counterfactuals used, for each subject, the mediators are set at some value randomly drawn from their distribution, given the confounders, rather than at a specific values.[326] Like controlled effects, interventional effects are considered to have more policy relevance than natural effects because they can inform specific interventions on the mediators (at population- and not necessarily at individual-level) to modify the outcome.[203]

Methods from the framework of causal inference using counterfactuals have enabled me to conduct a closer examination of the mechanisms behind the age inequalities in CRC management. The added value is that these methods allowed me to quantify the

contribution of specific mediators in the presence of statistical interactions, while being explicit about my assumptions. This complex analysis would not have been possible with traditional regression approaches to mediation analysis.[146,327] Clearly, an intervention on patients' age to reduce inequalities in cancer care is not feasible. However, it is possible to envisage potential intervention(s) would aim to reduce the prevalence of comorbidity or emergency presentations as means to reduce the age inequalities in CRC management. Given the findings, however, an intervention to reduce the prevalence of comorbidity – although potentially feasible and beneficial in several ways – would probably not result in reducing age inequalities in CRC management; and an intervention to reduce EP would probably have a substantial effect on the age differences in investigations, but a negligible one on reducing age inequalities in treatment receipt. I have, however, refrained from calling the effect of age 'causal' in the analysis presented in Chapter 4, because it is irrelevant for my research question about age inequalities in cancer management. Whatever the approach, the findings are consistent throughout the analyses: that older patients in England are not receiving optimal cancer care. The take-home message from the findings is not that chronological age *causes* or determines cancer management, but that there are other factors in relation to age, beyond comorbidity and the diagnostic route, that influence patients' likelihood of receiving optimal management. The findings highlight the need to explore other factors contributing to the age inequalities in cancer care and outcomes in order design targeted interventions to tackle them.

5.5 Potential extensions of this work

The work presented in this thesis could be extended in several ways. First, it would be useful to extend the application of the analyses of the age variation to other types of treatment for colorectal cancer (chemotherapy, radiotherapy with or without surgery). For the study period, information of chemotherapy and radiotherapy was not sufficiently complete or detailed in the English data sources, however newer databases, like the COloRECTal cancer data Repository (CORECT-R),[201] as well as the Radiotherapy Dataset[194] and the Systemic Anti-Cancer Therapy Dataset,[195] would allow a closer examination of additional therapies, as well as a more granular examination of the surgical treatment, and its variation by age.

An important barrier to effective cancer management in older patients is that the evidence base supporting treatment is limited, because they are generally excluded from clinical trials. Important questions regarding the effectiveness of standard treatment in older patients remain. An extension of this research could examine the potential benefit of surgery, as well

as other treatment strategies in prolonging survival. Research should also look into how different treatment strategies compare, and into whether the average treatment effect changes in different settings. Detailed population-based data offer a unique opportunity to perform such comparisons as long as the relevant (complex) analytic methods are applied.

The understanding of age inequalities in cancer management would benefit from a closer examination of the role of frailty in the clinical setting. First, it would be useful to compare the (variability of the) current operational definitions used in clinical settings, within England, and in comparison with other countries. Second, it would be interesting, in collaboration with clinicians, to find suitable measures (or proxies) of frailty from secondary care data sources, and to examine the predictive values of such measures for different patient outcomes (such as treatment receipt, complications, readmissions, morbidity, disability, quality of life, mortality and survival).

A closer examination of postoperative care and postoperative mortality by age and their geographic variation would be beneficial to understand variations in care and outcomes. The role of the diagnostic route (emergency or not), the timing of surgery, and the role of palliative procedures could inform practice and potentially allocation of resources.

Additional research on the influence of social support on cancer outcomes would improve the understanding of how to better support older cancer patients. For instance, because publicly-funded social services are delivered by local authorities (with geographically-defined target populations), it would be possible to conduct a natural experiment to assess the effect of one of the new care models recently introduced at a given local authority, and compare cancer outcomes with another local authority offering standard care. Similarly, proxy measures of social support (such as marital status, cohabitation) could be sought in secondary data sources, such as the Office for National Statistics' Longitudinal Study,[328] to compare cancer outcomes at different levels of social support.

From a qualitative perspective, it would be beneficial to extend the research into attitudes to ageing and older age held by clinicians, patients and the general public. An international comparison of attitudinal factors in the clinical settings would help clarify whether ageism is more of an issue in England than in other countries, and it would raise awareness of ageism in health care. Furthermore, it would be interesting to compare self-reported measures of discrimination (from patient-reported outcome measures) against measure of unconscious

bias or prejudice (and objective measure of discrimination)[240] in patients and healthcare staff.

The application of a similar research question and methodology to a different cancer site would be extremely beneficial. Although I have focused on the study of colorectal cancer, the issue of under-management of older patients is likely to happen (at least to a certain extent) for other cancer sites, as the wider context issues will certainly apply. In the case of no or lower age inequalities in the management of a different cancer, it could be informative to understanding how to tackle inequalities in CRC management.

5.6 Conclusion

In the work included in this thesis, I have used information on colorectal cancer patients from several national population-based data sources linked to national cancer registry records to examine age variations in colorectal cancer management. This work offers additional understanding on how age inequalities may come about, and potential opportunities to address them.

Older colorectal cancer patients in England are less likely to receive optimal management in comparison with patients of similar age in Denmark, Norway and Sweden, and in comparison with younger patients in England. The findings indicate that these differences in management are not fully explained by comorbidity, or stage at diagnosis (or the diagnostic route for the national comparison).

The finding of under-management of older patients is likely a reflection of complex interactions between biological, contextual, and attitudinal factors. Many older patients have complex needs, and the current organisation of health and social care services is likely unfit to serve those needs. Systemic change is required to address the needs of the ageing population, including better coordination and integration of services, better evidence base for improving the health of older patients, and continuous monitoring of health outcomes in this important and growing part of the population.

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