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Diverging Trends in Colorectal Cancer Morbidity and Mortality. Earlier Diagnosis Comes at a Price

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In developed countries, time trends in the incidence of colorectal cancer differ markedly from trends in mortality. This study sought to explain simultaneously changes in both colorectal cancer incidence and mortality. Data on first admissions, interventions and outcome from the national hospital registry over the period 1978–1989 and data on mortality from *Statistics Netherlands* over the same period were analysed by age-period models and subsequently entered in a Markov chain model, simulating disease history from first admission to death. Over the period 1978–1989, age adjusted numbers of first admissions and interventions increased by 37% and 32%, respectively, while mortality declined by 8%. For every 100 patients admitted between 1987 and 1989, 13 more will survive compared with 1978–1980. Of these, 3 will be saved by improving results of primary treatment but the other 10 will survive their diagnosis for the subsequent 10 years. Although progress in treatment has been made, therapeutic improvement can account only for the smaller part of the divergence between morbidity and mortality. Increased diagnostic activity, raising incidence and lowering mortality simultaneously, is the most likely cause of the unexplained divergence.

Key words: colorectal neoplasms, epidemiology, The Netherlands, prognosis, screening, prevention and control, computer simulation models

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INTRODUCTION

Cancer registers in many developed countries detect increasing incidences of cancers unrelated to smoking, and commonly attribute these increases to changing environmental hazards [1, 2]. However, in the same countries, trends in cancer mortality differ strikingly from trends in incidence; as a rule, mortality has been decreasing while incidence has been increasing [3, 4]. This divergence between incidence and mortality can be explained by improved therapy and/or decreasing lethality [1, 2]. Advances have been made in specific therapies, such as the dramatic improvements of treatment in juvenile cancers, and the more modest gains realised by adjuvant chemotherapy in advanced breast and colorectal cancer [5, 6]. However, unspectacular but effective non-specific changes have probably contributed even more to lowered cancer lethality, because they apply to the majority of solid tumours, and such changes include better preparation of the surgical patients, safer procedures and anaesthesia, improved control of infections, more effective reanimation, etc.

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An alternative hypothesis explaining this divergence is increased case detection. By lowering diagnostic thresholds, lesions with less invasive potential are added, increasing incidence and improving prognosis at the same time [7]. If this is the case, it implies that part of the observed morbidity increase is iatrogenic and perhaps preventable. To shed light on the likelihood of either explanation, we have examined the incidence, mortality and survival from colorectal cancer in The Netherlands.

Colorectal cancer is the second most frequent cancer among men and women in The Netherlands, showing an incidence increase relative to mortality (Figure 1).

In The Netherlands, mass screening for colorectal cancer is not recommended. The Dutch policy makers feel that the unavoidable increase in morbidity and costs, induced by the many false positives (faecal occult blood testing) and/or by more demanding diagnostic procedures (sigmoido- or colonoscopy) are not justified by the still uncertain decrease in mortality [8, 9]. However, individual physicians may feel otherwise, and are free to act accordingly. Long before mass screening for breast cancer was introduced in The Netherlands, the regional cancer registry showed increasing numbers of small tumours, witnessing earlier diagnosis [10]. Contrary to breast cancer, we do not possess accurate data on colorectal cancer stages at primary diagnosis in The Netherlands. Such information would be much harder to

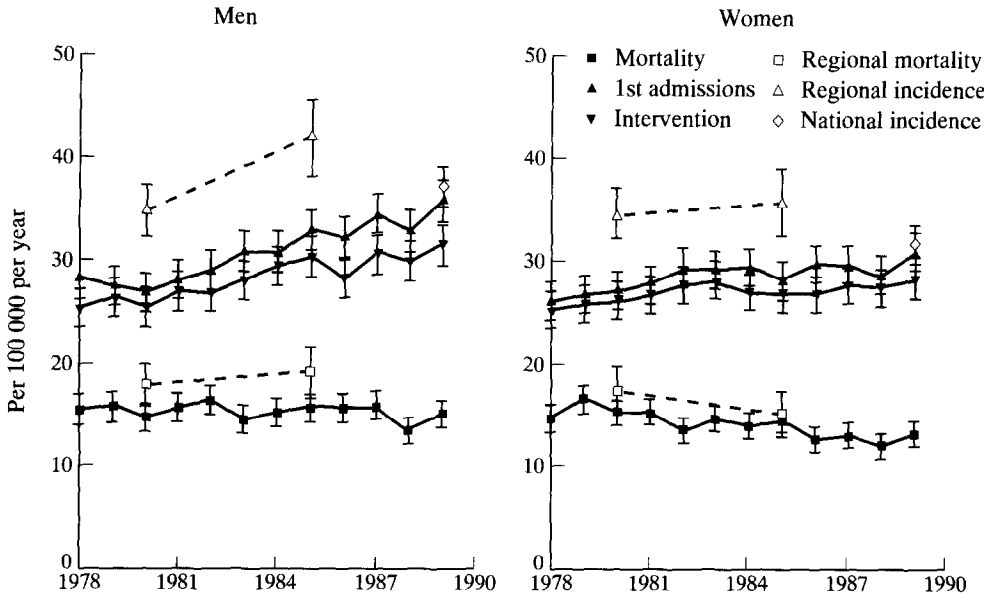

Figure 1. Solid lines and symbols show the age standardised rates (30–64 years) of first admissions, major interventions and deaths within The Netherlands. Broken lines and open symbols show the cancer incidence and mortality from the Southeastern Netherlands (1978–1987) and the national cancer incidence (1989) [14]. The error bars show 95% confidence limits (see text).

interpret in any case because staging in colorectal cancer is more dependent on modern diagnostic imaging. This may give rise to stage migration: previously missed invasion of deeper tissues may be diagnosed by more modern diagnostic imaging, such as magnetic resonance imaging (MRI), causing an artefactual migration from milder to more severe disease stages [11].

This paper presents the trends in first admissions for colorectal cancer as primary diagnosis, major interventions during these first admissions to the hospital and mortality over the period 1978–1989 in The Netherlands. The change in prognosis needed to explain the divergence between incidence and mortality is quantified, and we conclude that it is unlikely that improved therapy can explain the improving prognosis.

PATIENTS AND METHODS

Numbers of deaths from colon and rectum cancer (International Classification of Diseases, 9th revision, Nos 153 and 154) by calendar year (1978–1989), 5 year age group (30–64) and sex were obtained from *Statistics Netherlands* [12]. Person years at risk were approximated by the midyear population of an age and sex group in a calendar year. Summary estimates over age were calculated by using direct standardisation, using the European Standard Population as weights; standard errors were calculated from the formula:

$$\left(\sum_a \frac{w_a^2 O_a}{N_a^2}\right)^{1/2}$$

where O represents the numbers, N the midyear population, w the weights and a the 5 year age groups between 30 and 64 years [13]. Colon and rectum cancer were taken together in one group to avoid possible changes in codification [3]. Nationwide data on colorectal cancer incidence have been available since 1989 [14]. The regional cancer register in the Southeastern Netherlands (SE-N) has published cancer incidences since 1975, but the population covered is relatively small (1 million) and, in the period of interest (1978–1989), the colorectal cancer mortality in SE-N was significantly higher than in the rest of The Netherlands (see Figure 1 and Table 1) [15, 16].

Therefore, we used primarily national hospital register data as a proxy for incidence. In addition to administrative data, the hospital register records the diagnosis at discharge (primary and secondary), the result at discharge (alive or dead), all major interventions, and whether it is a first admisison for the considered cancer or not. We considered first admissions with colorectal cancer as primary diagnosis (International Classification of Diseases, 9th revision, Nos 153 and 154), and major interventions during first admission as partial or total colectomy, rectum amputation or enterostomy [17]. Comparing the (national) incidence for 1989 with the first admissions of the hospital register, we decided to limit the analysis up to the age of 64 years. The hospital register became increasingly incomplete in the higher age groups, but for the younger age groups the incidence corresponded closely with the first admissions (see Figure 1 and Table 1). It has been shown before that more than 97% of all patients under 65 years with colorectal cancer are treated in The Netherlands [18]. Therefore, the nationwide hospital register of The Netherlands is an acceptable proxy of colorectal cancer incidence, if limited to the young and middle aged patients (30–64 years old).

Period trends in intervention, first admission and mortality rates have been estimated by loglinear regression analysis [19]. The observed rates are related to age group, sex and calendar year as follows:

$$E_{a,s} = N_{a,s} e^{(\alpha_{a,s} + \beta_{a,s} x)}$$

where E is the expected number (of deaths, first admissions or interventions) and N the midyear population; a denotes 5 year age groups from 30 to 64 years of age, s sex and x is the calendar year. β is the slope of the regression line of the logarithm of the rates of every age and sex group versus calendar year, and represents the trend of age- and sex-specific rates over time.

Table 1. Age standardised incidence and mortality per 100 000 per year and their standard errors (SE), by sex, period and source. The cancer register figures from the period 1978–1987 are from the Southeastern region only; those from 1989 are the first available national data (see text)

Men (30–64 years of age)

	Cancer register			Hospital register		
	Incidence (SE)	Mortality (SE)	Ratio (SE)	First admission (SE)	Mortality (SE)	Ratio (SE)
1978–1982	34.9 (1.3)*	17.9 (1.0)*	1.95 (0.14)*	28.2 (0.3)	14.9 (0.2)	1.90 (0.03)
1983–1987	42.0 (1.9)*	19.2 (1.3)*	2.19 (0.18)*	33.9 (0.4)	15.3 (0.3)	2.21 (0.05)
1989	37.3 (1.0)	15.1 (0.6)	2.47 (0.12)	35.9 (1.0)	15.1 (0.6)	2.38 (0.12)

Women (30–64 years of age)

	Cancer register			Hospital register		
	Incidence (SE)	Mortality (SE)	Ratio (SE)	First admission (SE)	Mortality (SE)	Ratio (SE)
1978–1982	34.7 (1.3)*	17.6 (1.1)*	1.98 (0.15)*	27.8 (0.3)	14.4 (0.2)	1.93 (0.03)
1983–1987	35.8 (1.7)*	15.2 (1.1)*	2.35 (0.21)*	30.2 (0.4)	14.2 (0.3)	2.14 (0.05)
1989	31.8 (0.9)	13.2 (0.6)	2.41 (0.12)	31.2 (0.8)	13.2 (0.9)	2.36 (0.17)

* From the Southeastern region; all other data are national.

Summary estimates over age are calculated by specifying only sex as an explanatory β variable.

The disease history is modelled by a Markov type state transition model (see Figure 2). The model assumes three groups of patients after definite diagnosis: a fraction which dies during first admission termed CFR (case fatality rate); a fraction which leaves hospital "cured" and a fraction which will die of the disease at some later time, provided they do not die from other causes (termed "not cured"). The probability of dying from colorectal cancer for the not cured is lognormally distributed over time, characterised by a geometric mean (identical to the median survival time) and variance (see Appendix) [20]. Consequently, the model accommodates changes in four components of prognosis: the probability of surviving primary treatment, the probability of being cured and, if not cured, the median survival time and variance before dying from colorectal cancer. The CFR, defined as the fraction that dies in hospital within 2 months of primary diagnosis, is known from the hospital register. The fraction which is cured approximates the fraction surviving 10 years after hospital discharge (corrected for death from other causes): the risk of dying more than 10 years after diagnosis of colorectal cancer equals the risk of death of the reference population [21]. All patients, the cured and the not cured, run twice the risk of the reference population for a second primary colorectal cancer [22]. All persons, healthy, cured and not cured, run a risk of dying from all other causes, determined by Dutch life tables corrected for colorectal cancer death [12].

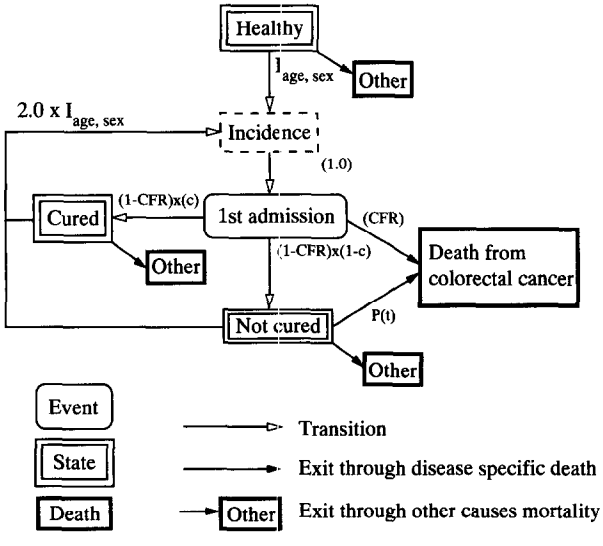

Figure 2. The Markov model of colorectal cancer. Incidence is determined by age and sex. Persons may die in hospital (CFR), or may be cured (c). If not, they face a time-dependent probability of cancer death P(t) (see Appendix). All patients run a risk of dying from other causes and a higher risk of a second primary tumour.

The survival distribution is first estimated by an iterative non-linear least squares regression, weighted for the numbers of death, based on survival figures from the Norwegian and SE-N cancer registry [23, 24]. Then, by using incidence and survival, the model determines expected mortality: the model starts from observed incidence and calculates expected numbers of death, given a stated survival and cure rate. Combinations of cure rates and survival periods will lead to age-specific estimates of mortality, which may or may not be different from observed estimates (see Appendix). Numerous pairs of cure rates and survival periods have been tested. The variance between calculated and observed numbers of deaths is tested by assuming a Poisson distribution of the probability of death (see Appendix) [25]. If the calculated numbers differ significantly from the observed ($P < 0.05$), that specific pair of cure rate and survival period is rejected as unlikely.

RESULTS

For both sexes, rates of first admissions increased over the period 1978–1989, while mortality remained stable or declined (Figure 1). The cancer incidence and mortality of the Southeastern Netherlands showed the same trend, although the incidence mortality ratios were somewhat higher (Table 1). The cancer incidence of 1989 corresponded closely with the first admission rates of the hospital register of the same year (Figure 1).

Table 2 shows the annual changes by age and sex, estimated by the loglinear age-period models. Over this relatively short period, first admission rates increased by 39.9% (Males) and 20.4% (Females), rates of major interventions after primary diagnosis increased by 32.6% (Males) and 14.0% (Females), but mortality nearly remained stable for men (+ 2.2%) and declined substantially among women (− 15.3%). Hence, clinical incidence increased by more than 35% relative to mortality, and the incidence of major interventions increased by 30%. The standard errors (SE) in Table 1 show that this increase in clinical incidence compared with mortality is highly significant. Major intervention rates during primary admission increased 5% less steeply than first admission rates: this difference is statistically not significant, but probably indicates a shift from major surgery towards more non-invasive colonoscopic treatment for early lesions.

The CFR in these age groups declined quite strongly: from 5.6% (SE 0.5) for men and 5.9% (SE 0.5) for women in 1978–1980 to 2.5% (SE 0.3) and 2.4% (SE 0.3), respectively. However, as shown in Table 1, this decline in lethality can only explain the smaller part of the observed difference between the morbidity and mortality trend: late mortality, excluding deaths during first admission, increased by 9.2% among men and decreased among women (−9.5%).

Table 3 shows relative survival rates which fit closely the observed incidence and mortality rates of two 3 year periods at the beginning and at the end of the study period. Alongside these simulated relative survival rates are the figures from Scandinavian and Dutch cancer registries originally used for estimation of the survival distribution. The simulated (fitted) survival rates are slightly lower than the observed. This can be expected if the hospital register misses a few very early lesions with good prognosis, curable by non-invasive procedures (see Discussion).

The relative survival expected for 1987–1989 predicts that cure rates (equal to the 10 year relative survival rate after hospital discharge) have increased by 11.8%, given a constant median survival time: from 41.8% (range 38.8–44.5) in 1978–1980 to 53.6% (range 51.2–55.1) in 1987–1989. In other words, for every 100 patients (< 65 years old) admitted in 1978–1980, 6 died in hospital and 55 in the subsequent years; 9 years later less than 3 died in hospital and 45 will die in subsequent years. 13 extra patients survived a colorectal cancer diagnosis, 3 thanks to lowered hospital mortality.

Figure 3 shows areas of all pairs of cure rates and median survival time which fit the observed incidence and mortality within 95% confidence limits (see Appendix). As median survival increases, the corresponding cure rate has to decrease to fit the given mortality. Indeed, two processes can explain any change in mortality rates, given incidence: death from colorectal cancer can be cancelled (hence, persons are cured; arrow a in Figure 3) or postponed (hence, median survival is increased; arrow b in Figure 3). Obviously, both processes can also take place at the same time (arrow c in Figure 3). For example, the incidence and mortality data of 1978–1980 can be explained by a median survival of 1.5 years and a cure rate of 0.44 or by a median

Table 2. Annual change of admissions, major interventions and deaths by age and sex over the period 1978–1989; *"late deaths" refers to all patients dying after surviving primary diagnosis and treatment, and corrects for changes in operative lethality*

Men; % annual change (standard errors in parentheses)				
Age group	First admissions	Interventions	All deaths	Late deaths
30–34	0.0 (1.9)	−2.2 (2.2)	−5.5 (3.1)	−4.7 (3.2)
35–39	0.2 (1.5)	−0.4 (1.7)	−3.1 (2.3)	−2.4 (2.4)
40–44	5.9 (1.5)	4.2 (1.2)	0.5 (1.7)	0.7 (1.8)
45–49	3.1 (0.9)	2.4 (0.9)	−0.8 (1.3)	−0.4 (1.4)
50–54	3.3 (0.7)	2.4 (0.7)	1.2 (1.0)	1.9 (1.0)
55–59	3.4 (0.6)	3.0 (0.6)	0.0 (0.8)	−0.5 (1.1)
60–64	2.8 (0.5)	2.6 (0.5)	0.7 (0.6)	1.3 (0.7)
30–64	3.1 (0.3)	2.6 (0.3)	0.2 (0.4)	0.8 (0.4)
Women; % annual change (standard errors in parentheses)				
Age group	First admissions	Interventions	All deaths	Late deaths
30–34	2.6 (2.1)	3.2 (2.4)	−0.3 (3.7)	−0.6 (3.8)
35–39	−0.2 (1.6)	1.4 (4.2)	−2.2 (2.5)	−1.8 (2.6)
40–44	0.1 (1.2)	−0.1 (1.2)	−2.6 (1.8)	−2.4 (1.8)
45–49	2.2 (0.9)	1.0 (1.0)	−1.9 (1.4)	−0.9 (1.4)
50–54	2.0 (0.7)	1.1 (0.7)	−1.3 (1.0)	−0.5 (1.1)
55–59	1.1 (0.6)	1.0 (0.6)	−1.5 (0.8)	−1.1 (0.8)
60–64	2.2 (0.5)	1.6 (0.5)	−1.4 (0.7)	−0.7 (0.7)
30–64	1.7 (0.3)	1.2 (0.3)	−1.5 (0.4)	−0.9 (0.4)

Table 3. Published relative survival rates in % from Scandinavian countries [23, 26, 27] *and The Southeastern Netherlands (SE-N)* [24] *are compared with the simulated relative survival, which fits best observed first admission and mortality rates from the periods mentioned*

	Observed					Simulated	
	Finland	Norway	Sweden	Sweden	SE-N	The Netherlands	
Time after diagnosis	1953–1974	1972–1975	1970–1974	1975–1979	1975–1985	1978–1980	1987–1989
2 months	NA	NA	88.6	90.6	NA	94.2	97.5
1 year	54.2	67.1	70.5	71.7	NA	68.0	74.3
3 years	NA	47.8	NA	NA	NA	48.2	58.8
5 years	31.1	42.7	45.0	46.8	46.5	42.6	54.6
10 years	30.2	NA	41.9	NA	42.2	39.4	52.3

NA, not available in published figures.

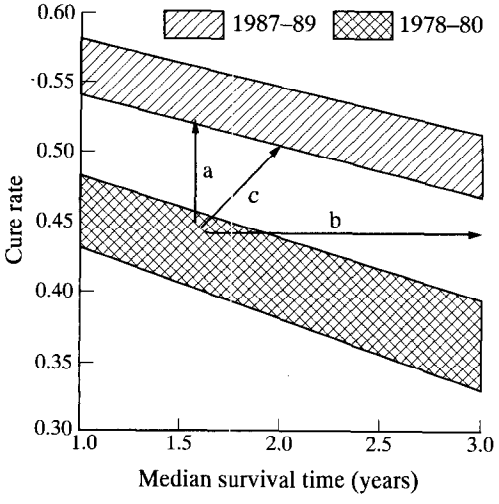

Figure 3. Two way sensitivity analysis. The two areas contain all pairs of cure rate and median survival of the not cured which will fit the given incidence and mortality rates of 1978–1980 and 1987–1989 within 95% confidence limits. The arrows indicate three hypothetical explanations for the difference between the two periods: increase of numbers which are cured (a), increase of survival of the not cured (b), or a combination of both (c).

survival of 3 years and a cure rate of 0.37. The incidence and mortality figures of 1987–1989 can be explained by a median survival of 1.5 years and a cure rate of 0.54 or a median survival of 3 years and a cure rate of 0.50. Figure 3 shows also that the model is much less sensitive to changes in assumptions about the median survival time than cure rate. To fit the same combinations of incidence and mortality, cure rates have to decrease by an average of 4.2% (a relative decrease of 10%) when median survival increases within 1 year (a relative increase of more than 50%). This is a consequence of the fact that more than 80% of those who will eventually die of colorectal cancer will do so within 3 years of their diagnosis. Consequently, prolonged survival in the absence of cure cannot explain much of the widening gap between incidence and mortality; cure rates must have improved considerably. The most plausible explanation for the increasing cure rates is increasing case detection. Earlier diagnosis probably improves the effectiveness of treatment [9] and certainly increases the numbers of benign lesions.

DISCUSSION

The first question to be addressed concerns the validity of the data. We found increasing clinical incidence and decreasing mortality. For the considered age groups, colorectal cancer mortality trends are generally valid [3]. Artefactual trends may be caused by higher diagnostic efficacy in more recent periods; fewer fatal cancers are missed and more patients with widespread cancer have the site of primary origin of their cancer determined. However, these changes in diagnostic practice will increase, not lower disease-specific mortality.

Incidence data are collected from the hospital register, which is not constructed for epidemiological purposes. Less than 3% of young and middle aged patients with a primary diagnosis of colorectal cancer will not be treated, thus hospitalisation rates for incident colorectal cancer are nearly complete [18]. If anything, patients with early lesions curable by non-invasive colonoscopic procedures tend to be treated more often in outpatient clinics, which will cause an artefactual decreasing trend of admission instead of increasing. Only substantial changes in codification practices of both admissions for colorectal cancer and of major interventions might have biased trend estimates; we cannot exclude *a priori* such changes, but they seem unlikely for such a short period and for a disease such as colorectal cancer. Finally, the Dutch hospital register shows the same trends as those observed in the regional cancer register in the Southeastern Netherlands (Table 1 and Figure 1); similar analyses will yield similar results. Regional differences do exist, but nevertheless are small. The Netherlands are small, with a homogeneous population.

Our analysis might be weakened by the cross-sectional nature of the incidence and mortality data, biasing our assessment of (longitudinal) changes in prognosis. However, the effects of therapy are period-, not cohort-dependent and most deaths from colorectal cancer occur within 3 years of primary diagnosis (Table 3). The most recent mortality figures (1990–1992) suggest a sharpening decrease, particularly among men [12]. This would be inconsistent with the hypothesis that death is only postponed, not cancelled; such postponed deaths would cause a "catch-up" increase of mortality.

Increasing incidence and decreasing mortality of colorectal cancer can only be explained by a substantial improvement in prognosis. We have quantified the expected increase in survival needed: cure rates, defined as 10 year survival after hospital discharge, have to increase by 12% between 1978–1980 and

1987–1989, from 42 to 54%. The simulated survival distribution for the beginning of the period (1978–1980) was similar to the observed figures of cancer registries. The mortality soon after primary diagnosis decreased, as has been observed elsewhere [26, 28]. This can be attributed, at least partly, to increases in therapeutic efficacy, safer intervention procedures and better postoperative care [28]. However, as shown in Table 2, this change can only explain the smaller part of the observed divergence between morbidity and mortality. Recent advances have been made in the adjuvant treatment of advanced colorectal cancer, but such treatments were rarely applied before 1990 in The Netherlands [5, 6, 29]. We did not find any other indication of advances in treatment which might have benefited more than a small subgroup (such as patients with solitary hepatic metastases), except for the short-term results of surgery. Consequently, the statement that the divergence between incidence and mortality trends has been caused by improved therapy and decreasing lethality is not well supported.

If we exclude less likely alternative hypotheses, such as decreasing malignancy of colorectal cancer in humans, the most probable explanation of the improving prognosis remains increased case detection. Earlier diagnosis deals with both incidence and mortality simultaneously:

1. Earlier diagnosis may account for decreasing lethality. While this remains a matter for debate, there is now at least some evidence that earlier diagnosis improves long term prognosis [9].
2. Earlier diagnosis will increase incidence by shifting diagnosis towards an earlier age. In screening theory this is called lead time [7, 30]. Obviously, lead time alone would not cause an incidence increase: a tumour which is diagnosed at the earlier age, $(a - t)$, will not be diagnosed again at age (a). But, in period $(a - t)$, patients run a risk of dying of other causes and colorectal cancer incidence increases sharply with age. The steeper the incidence increases with age, the more lead time will increase observed incidence rates, by moving diagnosis to younger ages. For colorectal cancer, shifting the whole age-specific incidence curve of 1978–1980 by 1 year towards a younger age causes an increase of the age standardised incidence by 12.5%.

However, advancing diagnosis by 1 year in the natural disease progression will cause a shift of incidence by age which is always more than 1 year. This is caused by "length time bias"—the slower tumours grow, the likelier they are to be detected by earlier diagnosis [7, 30]. How much incidence will increase, given earlier diagnosis, depends again on the relation of incidence with age and of the time distribution of the "silent" period that tumours would have passed unnoticed previously, but are detected now. This distribution is unknown, but will reflect the variability of disease progression. A high variability implies many slowly growing tumours and a high potential to boost observed incidence. Such high variability seems likely; unsuspected macroscopic colorectal cancer during necropsy varies between 1 and 1.7% in occidental countries, representing nearly 20% of all incident colorectal cancers [31, 32]. Without early detection, many of those 'slow growers' will remain unnoticed because the person will have died before, from other causes.

We conclude that the increase in incidence of colorectal cancer and the concomitant decrease in mortality cannot be caused by therapeutic improvements only. The most probable explanation of this divergence is increased cancer detection. This has important epidemiological and health policy implications:

(i) Increasing case-detection, which shifts cancer diagnosis to an earlier age both of the patient and the tumour, increases incidence (at least in age-dependent cancers) and decreases mortality simultaneously, biasing both as indicators of underlying cancer hazards. Time series of stage at primary diagnosis might confirm this; in the U.S.A., where incidence and mortality diverge similarly, more early lesions are detected, while rates of distant disease remain stable [33]. However, to evade stage migration bias, stages should be ascertained independently of modern imaging techniques.

(ii) No recommended screening policy, or even proof of benefit, was needed to increase case detection, and induce a parallel increase in major interventions. It is worrying that we do not know how much of the induced morbidity increase is truly rewarded by a mortality decrease.

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APPENDIX

Survival was modelled by using a discrete approximation of the lognormal distribution, with median survival μ, variance σ^2 and t_i the i-th month after diagnosis. The probability of surviving colorectal cancer until time $t_i P(S)_a$ is then given by:

$$P(S_a)_{t_i} = (1 - CFR_a)\left(c_a + (1 - c_a)\sum_{\tau = t_0}^{t_i}\left(\frac{1}{\tau\sqrt{2\pi\sigma}}\exp\frac{-(\log\tau - \mu)^2}{2\sigma^2}\right)\right)$$

The subscript a refers to two age groups (< 55 and 55–64 years); these age groups have been introduced because younger persons had a lower *CFR* and a higher cure rate, resulting in a better survival. *CFR* is the fraction of persons, first admitted for colorectal cancer, dying in hospital within 2 months, and c (for "cured") is the fraction of long-term (10 year) survivors. Models incorporating sex as a determinant for survival were not significantly better, and were ignored. c, μ and σ are estimated from observed survival figures, and then varied by the model (see further).

The presented cancer model is a subsector of a global public health model, modelling several diseases, and is implemented as a continuous time Markov chain, describing discrete sub-populations, cycling in 1 year steps. The continuous time specification allows multiple transitions in one time step [34]. To this aim, the parsimonious lognormal distribution, defined by two parameters, is translated into a sequence of exponential waiting time distributions, described by four parameters, simulating the lognormal survival distribution in the Markov model.

The subpopulation which survives mortality related to primary diagnosis and therapy but which is not "cured", enters a first stage. They will leave that stage with transition probability P and median duration $-\ln(0.5)/P$. After leaving this stage, parameter y distributes survivors over two subpopulations in two separate terminal stages, with transition probabilities q and r leading to death from colorectal cancer. For the purpose of this paper, these parameters have no direct practical meaning, except for simulating the lognormal survival distribution for a population of uncurable colorectal cancer patients.

The mean (and median) survival of incurable patients is changed by the model through P. The variables y, q and r are kept constant; changing these parameters has the same effect of prolonging the disease process. Random values between 0 and 1 are generated for the cure rate c and for the transition probability P, and the calculated number of colorectal cancer deaths are then compared to the observed numbers by the scaled deviance (log likelihood ratio statistic). Let $O_{a,s}$ be the observed number and $E_{a,s}$ the expected calculated by the model, with a reference to all 5 year age groups between 30 and 64 and s to sex, then the scaled deviance Δ [25] is calculated by

$$\Delta = 2\left[\sum_{a,s} O_{a,s} * \ln\left(\frac{O_{a,s}}{E_{a,s}}\right) - (O_{a,s} - E_{a,s})\right]$$

If the calculated numbers differ significantly ($P < 0.05$), the pair of c and P values is rejected as unlikely.