The effect of screening on treatment cost:

The case of colorectal cancer

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Abstract

This paper presents a medical cost function developed for a screening programme. The medical cost function is a function of advancement both directly and indirectly through survival. We discuss how the medical cost function is affected by screening through a shift in the distribution of cancers according to advancement. We show that screening reduces the treatment cost for cancers diagnosed at the screening, even though the medical cost function not unambiguously increases with stage of advancement. This is the first step in a cost-effectiveness analysis, and even though the results are favourable to the introduction of screening for colorectal cancer as a preventive health measure, total screening costs and health benefits must be evaluated to arrive at a recommendation.

Keywords: treatment cost, stage of advancement, screening, probabilistic sensitivity analysis, bootstrap method.

JEL: I10, I12, C41, H42

1. Introduction

Analyses of health care interventions are now regarded as providing fundamental information for government decisions about resource allocation. Since resources are scarce, such decisions should be based on a thorough analysis of all the consequences of the intervention concerned.

The aim of the present analysis is to investigate the relation between screening and colorectal treatment cost (CRTC). The CRTC function depends on two main factors: stage of advancement of the cancer and survival time. The stage of advancement affects the CRTC function both directly and indirectly, directly by the relation between the intensity of colorectal treatment and the stage of advancement, while indirectly by the relation between the stage of advancement and survival. The CRTC function is affected by increased survival as more treatment can be offered. The CRTC function is a positive function of advancement when the direct effect of stage of advancement on the CRTC function is positive and greater than the effect of advancement through survival.

Screening results in early detection of asymptomatic cancers, i.e. cancers that on average are less advanced than cancers diagnosed as a result of symptoms. Thus screening implies a shift in the distribution of cancers towards less advanced cancers. If the CRTC function is a positive function of advancement, screening will result in a reduction in the CRTC function. It is possible to compare CRTC for asymptomatic cancers and symptomatic cancers without including stage of advancement. By including stage of advancement we contribute to the explanation of the difference in CRTC for asymptomatic and symptomatic cancers.

We estimate CRTC as a function of advancement, building on the work of Etzioni et al. (2001). We assume that the individual never fully recovers from colorectal cancer, which means that the expected CRTC depends on the length of time the individual survives after the cancer diagnosis. Since we are not able to follow all individuals from the time of diagnosis until death and have different observation periods for each individual, the dataset is censored by the exit possibilities: death and the end of the dataset. To estimate expected CRTC, survival is used to adjust for censoring in the dataset. Independent of the stage of advancement, the survival probability is assumed to depend on individual characteristics of the patient, such as age and education.

In Etzioni et al. (2001), Bleeker et al. (2001), Ramsey et al. (2002), Ramsey et al. (2003) and Brown et al. (2002), the survival distribution is analysed by the Kaplan-Meier

estimator (Kaplan and Meier, 1958). We estimate a parametric survival function in which all relevant individual characteristics are included simultaneously. In order to study the hypothesis that screening results in a reduction in CRTC function, we base the analysis on a randomized controlled trial (RCT).

Based on the principle 'intention to treat', we compare with the control group the expected CRTC for all individuals invited to the screening, rather than only the expected CRTC for those actually participating in the screening. The invited group (total screening group) is divided into three subgroups on the basis of their participation status and time of diagnosis: 1) asymptomatic participants, 2) symptomatic participants and 3) non-participants. A RCT is not needed to compare expected CRTC for asymptomatic participants with expected CRTC in the control group. But with the RCT it is possible derive useful information by comparing expected CRTC in the total screening group and for different subgroups with expected CRTC in the control group, which yields results that not are analysed in Etzioni et al. (2001), Bleeker et al. (2001), Ramsey et al. (2002), Ramsey et al. (2003) and Brown et al. (2002). For instance, if the expected CRTC in the control group is higher than the expected CRTC for asymptomatic participants and lower than expected CRTC for non-participants, the findings could be explained by selection bias with regard to participation and not the fact that screening reduces stage of advancement.

If the expected CRTC for an asymptomatic participant is lower than that for an individual in the control group, the potential cost savings of increasing participation will be considerable. If the expected CRTC is higher for a non-participant than for an individual in the control group, the potential cost savings of increasing participation will be even greater. The variation in the estimated expected CRTC due to differences in survival time is also captured in this analysis, but the expected CRTC may also vary as a result of, for instance, different practices between hospitals, uncertain cost estimates or the age of the patient. To give a realistic picture of the uncertainty of expected CRTC estimates we use both probabilistic sensitivity analysis (PSA) and the bootstrap method for calculating 95 percent confidence intervals. Brown et al. (2002) use bootstrapping, but to our knowledge no one has used PSA and compared it with the bootstrap method in the estimation of treatment cost.

The results show that the expected CRTC increases with the stage of advancement of colorectal cancer and that screening reduces future treatment costs. Hence, the results of this first step in the cost-effectiveness analysis are favourable to the introduction of screening for colorectal cancer as a preventive health measure. The reduction in future treatment costs is not supported by the PSA, since the confidence interval is large. The confidence interval

calculated by the bootstrap method is narrower than that calculated by the PSA and does not invalidate the conclusion that screening is favourable to a reduction in the CRTC.

The paper is structured as follows. Section 2 is a description of screening and the treatment of colorectal cancer, and Section 3 presents the statistical methods used. Section 4 is a report of the data: 4.1 presents the data in the survival analysis and 4.2 the treatment cost data. Section 5 presents the results of the survival analysis and Section 6 the estimated CRTC and the uncertainty analyses. The sensitivity analysis is presented in Section 7 while we in Section 8 discuss the underlying assumptions on which the results are based.

2. The colorectal treatment cost function

The expected benefits from screening for colorectal cancer are a higher probability of not dying from the cancer and a lower risk of developing the cancer. The first benefit results from detection of the cancer at an early stage, since colorectal cancer is often diagnosed at a very late stage, which is negatively correlated with the survival probability. The second effect is linked to the removal of polyps, which could develop into cancer, from the colon.

Let us assume that an individual with colorectal cancer is treated according to standard procedures. Then we can define the CRTC-function for an individual as

$$CRTC = c[A, T(A, \theta); \tau] \tag{1}$$

where A is a continuous variable that describes the advancement of the disease, T is time alive from the time of diagnosis, and θ is a vector of factors that affects the time the individual remains alive after the diagnosis, such as age, gender and education, while τ is a vector of factors that affects the CRTC, such as differences in treatment procedures across hospitals. From (1) we see that advancement enters the CRTC function both directly and indirectly through the survival function. From equation (1) the change in CRTC with an increase in advancement is given by

$$CRTC_A^{'} = c_A^{'} + c_T^{'} T_A^{'} \tag{2}$$

where $c_A^{'}$ refers to the derivative of cost with respect to advancement, $c_T^{'}$ denotes the derivative of cost with respect to survival time from diagnosis and $T_A^{'}$ is the derivative of survival time from diagnosis with respect to advancement.

The above description of the various treatment procedures shows that the amount of treatment given to an individual increases with advancement. Given this relation we expect the *CRTC* function to increase in accordance with advancement, i.e. $c_A^{'} > 0$ since we expect treating the less advanced cancers are less costly than more advanced cancers. But treatment for colorectal cancers can last for several years and as the survival prognosis is poorer for more advanced cancers, fewer resources may be spent on patients with poorer prognosis than on those with better prognosis because they receive less intensive treatment. If this is so, it is no longer given that *CRTC* is an unambiguous positive function in advancement.

Since treatment lasts for several years *CRTC* increases with the time the individual remains alive after a cancer diagnosis (survival), i.e. $c_T^{'} > 0$. The surviving time is further closely related to advancement: the probability of dying is much smaller for an individual diagnosed with a less advanced cancer than for one with a more advanced one, i.e. $T_A^{'} < 0$.

The second part of the right hand side of equation (2) is negative, i.e. the sign of equation (2) is uncertain. In order to provide evidence for increasing CRTC with regard to advancement, the direct effect of an increase in advancement has to be positive, $c_A^{'} > 0$. This condition is necessary, but not sufficient. In addition, the direct effect has to be greater than the indirect effect as a consequence of longer survival time (in absolute value), hence

$$c_A^{'} > | c_T^{'} T_A^{'} | . \tag{3}$$

Screening is expected to result in a decline in advancement A. If (3) holds, we would expect that CRTC for an asymptomatic participant in screening is smaller than the CRTC in the control group.

In the theoretical presentation it was assumed that advancement is a continuous variable. Colorectal cancers are often presented in stages according to advancement, where the stages are defined according to some discrete factors. The continuous factors like the size of the tumour will be included as the variation within each stage. In this paper we apply the Dukes staging system, which is one of the most frequently used. In this system there are four stages of advancement, in ascending order:

Dukes A: Cancer localised within the bowel wall

Dukes B: Cancer which penetrates the bowel

Dukes C: Cancer which has spread to lymph nodes

Dukes D: Cancer with distant metastasis

The mix of discrete and continuous factors, complicates the discussion, because a shift in the distribution towards less advanced cancer will affect the distribution of cancers both between and within Dukes stages. Shifts between stages will occur when for example screening implies that the category Dukes B after screening includes cancers that without screening would have been categorised in more advanced stages or that some cancers categorised as Dukes B without screening, with screening will be categorised as Dukes A. Shifts within stages occurs when the most advanced Dukes B cancers are categorised as less advanced Dukes B due to screening. The effect of screening on the distribution of Dukes C cancers would be similar to Dukes B. For Dukes A there is a possibility that there will be an accumulation of cancers in the least advanced part of Dukes A. At the same time, more advanced cancers will be categorised as Dukes A as a result of screening and belong to the more advanced part of Dukes A. In addition, as a result of screening, some carcinoma "in situ" will be diagnosed and treated. Carcinoma "in situ" is a group of abnormal cells that remain in the tissue in which they first formed. These abnormal cells may become cancer and spread into nearby normal tissue. Some of these would never become symptomatic and thus unnecessary treatment is offered. Carcinoma "in situ" cancers could be expected to shift the distribution within the Dukes A towards less advanced cancers. The shift for Dukes D cancers will unambiguously be towards less advanced cancers as cancers are entering in the upper part of the distribution.

A shift in the distribution of cancers according to advancement will change the CRTC for each Dukes stage if and only if the distribution of cancers according to advancement within each Dukes stage is affected by screening.

From equation (1) we see that CRTC depends on survival time, which is a function of not only advancement and screening, but also of individual characteristics. High age is generally assumed to reduce survival probability (see Fenn et al. 1996), so that, given the same diagnosis, an individual of 65 has a smaller probability of surviving than an individual who is only 55. Since women on average live longer than men (Statistics Norway 2003), we expect that a woman will have a higher probability of surviving than a man. Other factors also

play a role here. Education level is expected to reduce the probability of dying, see Kravdal (2000). Survival after a diagnosis of colorectal cancer varies between counties in Norway; for example Oslo County has a lower survival rate than Telemark County (the Cancer Register 2003). Life expectancy in Norway is higher than most other countries (Statistics Norway 2003). As this study contains individuals in the age group 50 to 64 years, most of the immigrants are first generation. Hence, we would expect survival to be higher for individuals born in Norway.

3. Empirical specification

In our model we assume that an individual diagnosed with cancer never fully recovers. This is a simplification of a more dynamic approach and will be discussed in concluding remarks. As the individual is assumed to never fully recover, he has to be followed up until death. Our assessment of the full treatment cost is based on this assumption. It is not possible to follow individuals for such a long period in clinical trials, which means that the data are censored, with two exit possibilities: death and end of dataset.

The purpose of this study is to estimate differences in the cumulative CRTC of treating individuals in the total screening group or screening sub-groups and the control group. Building on the work of Etzioni et al. (2001), we define the expected CRTC for each screening group as:

$$E^D = \sum\nolimits_t [1 - F^D(t)] E_t^D \qquad t = 0, \ldots, S \tag{4}$$

where D refers to the total screening group or screening sub-groups and the control group, t denotes months after diagnosis, where $t = 0$ denotes the month of diagnosis, $F^D(t)$ is the cumulative distribution of T, $1 - F^D(t)$ is the probability of surviving to month t, and E_t^D is the average CRTC incurred in month t among all cases surviving to this time. E_t^D includes the CRTC both for individuals surviving through month t and for those dying in month t. The survival function is here used to estimate expected CRTC per month, thus the expected CRTC for a specific month is weighted by the probability of being alive in that specific month. Hence, the cost of a specific inpatient service is weighted less 20 months from diagnosis than 5 months from diagnosis. Thus (4) expresses the expected CRTC. Survival can be modelled in several ways, where a proportional hazard model and an accelerated failure time model are

two alternatives. In a proportional hazard model the coefficients relates to a proportional change in the hazard rate and not survival. Like Fenn et al. (1996) we apply an accelerated failure time model since in this model it is easier to infer directly the response of survival time to the independent variables. The regression coefficients relate proportionate changes in survival time to a marginal change in a given regressor, with all other characteristics held fixed. Let *T* denote survival time and let *x* be a vector of explanatory variables. Assume that

$$\ln(T) = x\beta_D + z \tag{5}$$

where β_D is a vector of parameters and z is an error term[1]. Like Fenn et al. (1996) we assume furthermore that $z = \sigma u$, where $\sigma > 0$ is a scale parameter and u is a "standardized" random term with cumulative distribution equal to the Weibull distribution

$$P^D(u \le y) = 1 - \exp(-e^y) \tag{6}$$

From (5) and (6) we get

$$\begin{aligned} P^D(T \ge t) &= P^D(\ln T \ge \ln t) \\ &= P^D(x\beta_D + \sigma u \ge \ln t) \\ &= P^D(u \ge \frac{1}{\sigma}\ln t - \frac{1}{\sigma}x\beta_D) \\ &= \exp(-\exp(\frac{1}{\sigma}\ln t - \frac{1}{\sigma}x\beta_D) \\ &= \exp(-t^{1/\sigma}e^{-x\beta_D/\sigma}) \end{aligned} \tag{7}$$

Let $p = 1/\sigma$. Then the corresponding survival function is given by

$$P^D(T > t) = 1 - F^D(t \mid x, p) = \exp(-t^p e^{-x\beta_D p}) \tag{8}$$

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[1] From (5) we can find the expected survival time $E(T) = \Gamma(1 + \frac{1}{p})e^{x\beta_D}$, where the $\Gamma(.)$ is the gamma function and equal to a constant. The log is then given as $\log E(T) = x\beta_D + \log\Gamma(1 + \frac{1}{p})$.

where p represent duration dependency, which can be constant (corresponding to $p=1$), negative (corresponding to $p<1$) and positive (corresponding to $p>1$). A positive duration dependency, implies that the probability of surviving increases over time, i.e. an individual who has survived for five years has a higher probability to survive to the next period than an individual who has survived only two years. When p is one, the Weibull distribution is reduced to the exponential distribution. The hazard function is defined as the conditional probability of dying in the next instant of time given that the individual survived to time *t*, and is from (8) given by[2]

$$h^D(t \mid x, p) = pt^{p-1}\exp(-\beta_D xp) \tag{9}$$

Our dataset contains censored spells, since we do not follow up all the individuals until they die. For those still alive at the end of the observation period, we only know that the duration was at least t_j. Consequently, the contribution to the likelihood of this observation is the value of the survival function, i.e. the probability that a duration of survival is longer than t_j. Let $d_j = 1$ if the *j*th spell is uncensored, $d_j = 0$ if censored. If the sample consists of *n* independent spells, the log likelihood function for screening group *D* is then given by[3]

$$L^D(\beta_D, \sigma) = \sum_{i=1}^{n} d_i \ln f^D(t_i \mid \beta_D, \sigma) + \sum_{i=1}^{n}(1-d_i)[1-F^D(t_i \mid \beta_D, \sigma)] \tag{10}$$

Estimating (10) for asymptomatic participants, total screening group and the control group would capture the effect of screening on the distribution of cancers both between and within Dukes stages. In this paper we are not able to estimate (10) because of a limited numbers of observation. It is therefore impossible to estimate separate survival functions for asymptomatic participants, total screening group and the control group; thus, we need to simplify. One alternative is to estimate a survival function for all individuals and let survival depend on Dukes stages, screening groups and control group and an interaction between

[2] The density function is the slope of the survival function in (8) and defined as:
$f^D(t \mid x, p) = \lim_{\Delta t \to 0} \frac{\Pr(t \le T \le t + \Delta t \mid D)}{\Delta t} = -\frac{\partial F^D}{\partial t}$ and the relation between the hazard function, the density function and survival function is defined as $f^D(t \mid x, p) = h^D(t \mid x, p)[1 - F^D(t \mid x, p)]$

[3] See Green (2002)

Dukes stage and group. Such an approach could reveal whether screening adds an extra effect to Dukes stages on survival, i.e. if screening shifts the distribution within stages. This estimation is also impossible because of data limitations. Two options have been considered: Estimating the survival function based on a pooled data sample, i.e. both screened and unscreened individuals, and estimating the survival function separately for the control group. We choose the latter first of all we then know that the results in the control group will be consistent. If we use the pooled data, results in both the control group and the screening groups can be biased. But this simplification implies that screening does not affect the distribution of cancers within each Dukes stage. Based on this assumption, the log likelihood function is

$$L(\beta,\sigma) = \sum_{i=1}^{n} d_i \ln f(t_i \mid \beta,\sigma) + \sum_{i=1}^{n} (1-d_i)[1-F(t_i \mid \beta,\sigma)] \tag{11}$$

4. Data

The basis for our study is NORCCAP (the Norwegian Colorectal Cancer Prevention, see Bretthauer et al. (2002)), which was carried out in Norway in the period 1999-2001.

The choice of design for NORCCAP was influenced by a pilot study; see Hoff et al. (1985). NORCCAP was implemented in two counties: Telemark (165,855 inhabitants in 2003), where the pilot study had been carried out, and Oslo (517,401 inhabitants in 2003). Oslo represents a typical urban area, while Telemark has both urban and rural areas. NORCCAP was a once-only screening, using the screening methods flexible sigmoidoscopy and faecal occult blood tests.[4] Half of the total screening group was offered flexible sigmoidoscopy and the other half a combination of flexible sigmoidoscopy and faecal occult blood tests. Flexible sigmoidoscopy enables the physician to examine the interior of the large intestine from the rectum through the distal part of the colon (about 50 cm of the total colon), called the sigmoid colon. This procedure makes it possible to look for adenomas,[5] and the presence of adenomas denotes an increased risk of developing colorectal cancer. The faecal occult blood test is self-administered and requires stool samples on three consecutive days. The samples are smeared onto chemically impregnated cards and sent to the laboratory at the

[4] The faecal occult blood test used here is a FlexSureOBT®, an immunochemical test for human blood.
[5] Adenomas are outgrowths in the colon. The larger they are, the more likely they are to develop into cancer.

time of screening participation. The NORCCAP exclusion criteria included being treated for cancer and taking anticoagulants.

Every year from 1999 to 2001, 7,000 individuals were invited (3,500 from each county) to participate in NORCCAP. During 1999 and 2000, individuals between 55 and 64 were invited, and in 2001 individuals between 50 and 54 were invited. The participation rate for the whole period was 65 percent.

The dataset consists of all individuals invited to the screening (20,780) and a control group (79,808). The control group consists of all the remaining individuals in the same age-group from the two counties. The dataset includes information about age, gender, education, county of residence, time and cause of death, and other demographic variables obtained from Statistics Norway. From the Cancer Registry of Norway we obtained data on incidence, time of diagnosis and stage of advancement at the time of diagnosis. From the National Patient Register we obtained information on inpatient and outpatient services at the hospitals in Telemark and Oslo. The total observation period is from 1999 to 2003, i.e. $S=60$ in equation (4).

Table 1: Proportions of cancers distributed according to stage of advancement in screening subgroups and control group. Number of observations 292.

	Participants		**Non-participants**	**Control group**
Variable	**Asymptomatic**	**Symptomatic**		
Dukes A	0.513	0.038	0.000	0.065
Dukes B	0.205	0.538	0.417	0.287
Dukes C	0.256	0.346	0.500	0.533
Dukes D	0.026	0.077	0.083	0.115

In the period 1999 to 2003, 450 individuals in the dataset were diagnosed with colorectal cancer, and it was possible to classify 292 by the Dukes staging system. Table 1 shows the proportion of cancers according to screening subgroup and stage of advancement. About 75 percent of cancers detected at screening were either Dukes A or Dukes B. For symptomatic participants the proportion of Dukes B is higher than in the control group, while the proportion for all stages among non-participants and the control group is fairly similar.

Table 2: Number of cancers from 1999 to 2003 according to screening subgroups and stage of advancement. Total numbers of cancers in the subgroups are reported in brackets.

Group		During screening			After screening	
	Dukes	**1999**	**2000**	**2001**	**2002**	**2003**
Asymptomatic participants (39)						
	A	5	11	4		
	B	3	2	3		
	C	2	7	1		
	D	0	1	0		
Symptomatic participants (26)						
	A	0	0	0	1	0
	B	1	5	0	6	2
	C	0	1	1	4	3
	D	0	1	1	0	0
Non-participants (12)						
	A	0	0	0	0	0
	B	0	1	3	1	0
	C	2	0	1	2	1
	D	0	0	1	0	0
Total screening group (77)						
	A	5	11	4	1	0
	B	4	8	6	7	2
	C	4	8	3	6	4
	D	0	2	2	0	0
Controls (215)						
	A	2	3	3	5	1
	B	5	14	16	14	9
	C	6	26	33	30	24
	D	1	6	7	5	5
Total screening group and controls (292)						
	A	7	14	7	6	1
	B	9	22	22	21	11
	C	10	34	36	36	28
	D	1	8	9	5	5

In Table 2 we show the number of cancers from 1999 to 2003 according to screening group and stage of advancement. Since the screening was carried out from 1999 to 2001, no cancers are recorded among asymptomatic participants in 2002 and 2003. The number of cancers among symptomatic participants is, as expected, lower in the screening period (1999 to 2001) compared with the period after the screening period: 10 and 16 cancers, respectively. We expect cancers among non-participants to be diagnosed later in the observation period than cancers among asymptomatic participants, but this is not confirmed by our study, since eight cancers are diagnosed during the screening period and only four afterwards. This may be due to the small size of the sample. The number of cancers in the total screening group is the sum of the cancers in the three screening subgroups.

To estimate expected CRTC we use two different samples. When we analyse expected CRTC as a function of Dukes stages we include all cancers, i.e. that number of observations are 292. When we compare expected CRTC in the total screening group or screening sub-groups with the control group, we use another sample. To ensure comparable expected CRTC accumulated, we include cancers diagnosed within the same period. Thus the cancers diagnosed from 1999 to 2001 are included since this is the period in which the screening was carried out. The cancers diagnosed after the screening, 2002 and 2003, are therefore excluded from the sample, which then is reduced to 179 observations.

4.1 Survival

Out of 215 individuals diagnosed with cancer during the period 1999 to 2003, 59 died during the period. In the analysis we have included all deaths occurring during treatment for colorectal cancer. In Table 3 we show the number of cancers, number of total deaths and proportion of cancers and total deaths for each stage of advancement. The proportion of cancers or total deaths is arrived at by dividing the number of cancers diagnosed at a particular stage of advancement by the total number of cancers diagnosed or the total number of deaths, respectively. Over 50 percent of all the cancers are diagnosed at the Dukes C stage. Most of the total deaths occur in the Dukes C and Dukes D groups. Dukes D has the highest proportion of deaths. The total proportion of deaths is 0.274 (59/215).

Table 3: Numbers of cancers, proportion of cancers, numbers of deaths and proportions of deaths according to stage of advancement. M=215.

Stage of advancement	**No of cancers**	**Proportion of cancers**	**No of deaths**	**Proportion of deaths**
Dukes A	14	0.065	3	0.051
Dukes B	58	0.270	3	0.051
Dukes C	119	0.553	36	0.610
Dukes D	24	0.112	17	0.288
Total	215	1.000	59	1.000

In the control group the mean age at the time of diagnosis tends to be slightly higher for the individuals that are alive compared to the mean age for those who are dead, 59.6 and 58.7, respectively. Table 4 shows the proportion dead according to the socio-economic variables used in the analysis. The numbers indicate that there is almost no difference in

survival status for gender. There are some differences in proportion dead, and the proportion is higher for individuals: living in Oslo, born in a country other than Norway and having a low level of education.

Table 4: Descriptive statistics for discrete variables according to survival status. M = 215.

Variable	Category	Dead
Gender		
	Male	0.27
	Female	0.28
County		
	Oslo	0.30
	Telemark	0.20
Native country		
	Norway	0.26
	Other country	0.36
Education (years)		
	Low (0-10)	0.35
	Intermediate (11-14)	0.27
	High and very high (15+)	0.21

4.2 Treatment cost

The intensity of the treatment is closely related to the advancement of the cancer. The treatment follows certain standard procedures (Norsk Gastrointestinal Cancer Gruppe, 1999), but there is room for individual variation. Colorectal cancer refers to cancer of the colon or the rectum. Unless the localisation is specified, our use of the term "treatment" covers both types. Surgery is the most common treatment for colorectal cancer. If the cancer is limited to a polyp, the patient can undergo a simple polypectomy (removal of the polyp), or a local excision, in which a small amount of surrounding tissue is also removed. If the tumour has invaded the bowel wall or surrounding tissues, a partial resection (removal of the cancer and a portion of the bowel) is necessary, together with removal of local lymph nodes to determine whether the cancer has spread to this area. In cases where it is not possible to reconnect the two parts of the colon, a colostomy (an opening in the abdominal wall to allow the passage of stools) is performed. Even though in a majority of patients the whole tumour seems to have been removed by surgery, the cancer recurs in as many as 40 percent of these patients, and chemotherapy is also given to reduce the risk. There is some controversy about whether patients with Dukes B disease should receive chemotherapy. The patients in this group who are considered to be at higher risk of recurrence are given chemotherapy for six to eight months, and the remainder are followed up closely, generally without receiving

chemotherapy. Patients who present with Dukes C cancer are typically treated for 12 months. With regard to radiation therapy, there are differences between colon and rectal cancer. Colon cancer is not usually treated with radiation therapy, although this may be an option if the cancer has invaded another organ or adhered to the abdominal wall. Radiation therapy is an option for all stages of rectal cancer, but its use increases with the stage of advancement. At follow-up all patients are checked for recurrence. Follow-up usually entails physical examinations and colonoscopies.

The aim is to measure the opportunity cost of treating colorectal cancer by means of information from the National Patient Register and the National Insurance Administration. The costs of outpatient and inpatient services are calculated from the reimbursement system. The cost of outpatient services is covered by fee for service, activity-based financing and block grants, and that of inpatient services by activity-based financing and block grants. The activity-based financing is based on diagnosis-related groups (DRG). The DRG system classifies hospital services into groups that are medically related and homogeneous with regard to use of resources. DRG is a way of describing the hospital's case-mix. In Norway there are about 500 different DRGs. Each DRG is given a weight that reflects the treatment cost. For outpatient services the fee for service only partly covers the true cost. On the basis of a Norwegian study (Samdata somatikk, 2004) we have adjusted all the fees from the National Insurance Administration by a factor of 1.5 so that they better reflect the true cost. During the observation period the DRG weights have changed in spite of no major changes in the treatment for colorectal cancer. The unit price for DRG has also changed[6], but we apply the DRG weight and unit price for 2003 for all observation years[7]. Whether fee for service, DRG weights and unit price reflect the opportunity cost will be discussed in more detail in the concluding remarks. Some of the patients were treated for other diseases during the observation period, but we include only costs that are directly related to the treatment of colorectal cancer[8]. We therefore disregard any relation between the treatment of colorectal cancer and other diseases. A proportion of the individuals having adenomas at the screening were recommended to undertake a follow-up colonoscopy. As the focus in this paper is on expected CRTC for individuals diagnosed with colorectal cancer, other costs as a consequence of screening are not included here. Such costs will be included in an economic evaluation of the screening trial, see Aas (2007).

[6] Changes in the unit price for DRG can be explained by for instance changes in efficiency and input prices.
[7] One DRG was in 2003 equal to EUR 3706
[8] The outpatient and inpatient services, together with the fees or DRGs and DRG weights, are shown in Appendix A1.

Table 5: Descriptive statistics for selected outpatient and inpatient services. Mean number of treatments according to stage of advancement at diagnosis. Number of observations 292.

Service		Dukes A	Dukes B	Dukes C	Dukes D
Outpatient					
	Therapeutic colonoscopy	0.17	0.29	0.14	0.07
	Diagnostic colonoscopy	0.51	0.93	0.57	0.25
	Therapeutic sigmoidoscopy	0.17	0.01	0.03	0.00
	Diagnostic sigmoidoscopy	0.03	0.09	0.11	0.05
Outpatient					
	Chemotherapy – unspecified	0.43	1.71	8.65	6.5
	Chemotherapy – group 1	0	0.12	0.89	1.36
	Chemotherapy – group 2	0	0	0.01	0.11
Inpatient					
	Rectum resection with additional diagnosis or complications	0.23	0.09	0.22	0.21
	Rectum resection without additional diagnosis or complications	0.17	0.21	0.13	0
	Major surgery of the large intestine with additional diagnosis or complications	0.14	0.28	0.39	0.54
	Major surgery of the large intestine without additional diagnosis or complications	0.26	0.34	0.20	0.04
	Malignant disease in the gastrointestinal organs with additional diagnosis or complications	0.03	0.13	0.39	0.68
	Malignant disease in the gastrointestinal organs without additional diagnosis or complications	0.03	0.07	0.24	0.18

Table 5 shows the most frequently used outpatient and inpatient services. The table illustrates variations in treatment for the different stages of advancement, and shows the average number of registrations per individual at each stage, i.e. the total number of registrations divided by the number of individuals diagnosed at each stage. There is no obvious relation between the proportion of patients who have undergone colonoscopy and stage of advancement. On the other hand there is a clear correlation between cancer stage and chemotherapy. An individual with Dukes B receives on average 1.83 chemotherapy treatments, an individual with Dukes C on average 9.55 treatments and an individual with Dukes D on average 7.97. An individual with Dukes C or Dukes D also tends to need more

advanced surgery; 0.39 of the individuals with Dukes C and 0.54 of those with Dukes D had undergone extended surgery on the colon, with complications.

5. Results of the survival analysis

To estimate expected CRTC, we first estimate the survival function, *1-F(t)*, in equation (8) by estimating the log likelihood in (11)[9]. The coefficients from the estimation are presented in Table 6[10]. The positive signs indicate a higher probability of survival. Two different specifications of the model are presented in the table in order to show the stability of the results.

We find that the probability of surviving declines with the stage of advancement of the cancer at diagnosis, as can be seen from the positive coefficients for Dukes A, B and C. The probability of surviving increases with the education level, since an individual with a low level of education is less likely to recover than an individual with long education. In general, recovery is supposed to depend on the waiting time from diagnosis to start of treatment, the treatment itself, and the individual's general health status, spirit of determination and ability to make use of his knowledge about cancer. The level of education could be an indicator of how much the individual is able to influence these factors. For example, he can influence the time from diagnosis to the start of treatment by choosing a hospital with a short waiting time. Recovery is also likely to depend on the individual's ability to make use of his knowledge about treatment to adopt behaviour that enhances the treatment.

There are no significant differences in survival with regard to age, county of residence, native country or gender. The coefficients in both models are of a fairly similar magnitude and alter little when variables are excluded. The parameter p represents the duration dependency, which in the estimation is not different from one (at a five percent level); hence the distribution of T is exponential in x, the duration dependency is constant and the hazard function in (9) is constant. Given mean value of the covariates, we estimate the hazard function in (9) to be 5.1 per thousand.

The survival function is estimated and presented in Figure 1. The Figure shows that survival falls from 1 to about 0.62. Since only 59 out of 215 died during the period, the survival function will not end at zero. In order to illustrate our results better, we calculated the

[9] The estimations were done by the use of STATA 8

[10] During the estimation we tried several distributions like Cox, generalized gamma and log-normal, but all estimation resulted in the same findings.

hazard function for two different sub-samples by using the estimated coefficients and equation (9).

Table 6: Regressors of survival function. M = 215. (SD in parenthesis)

Variable		**Model 1**	**Model 2**
Constant		2.548 (1.568)	2.701 (0.280)***
Dukes stage			
(ref. Dukes D)	A	1.499 (0.548)***	1.553 (0.527)***
	B	2.804 (0.575)***	2.846 (0.579)***
	C	1.127 (0.267)***	1.099 (0.264)***
Age by diagnosis		0.002 (0.025)	
County			
(ref. Oslo)	Telemark	0.097 (0.300)	
Native country			
(ref. Norway)	Not Norway	-0.296 (0.313)	
Gender			
(ref. male)	Female	0.133 (0.230)	
Education			
(ref. low)	Intermediate (11–14)	0.337 (0.263)	0.364 (0.310)
	Long (15 +)	0.669 (0.321)**	0.641 (0.280)***
P		1.235 (0.134)*	1.224 (0.132)*
LR chi² (*p value*)		53.46 (0.000)	52.16 (0.000)

*** significant at a 1 percent level, ** significant at a 5 percent level, * significant at a 10 percent level

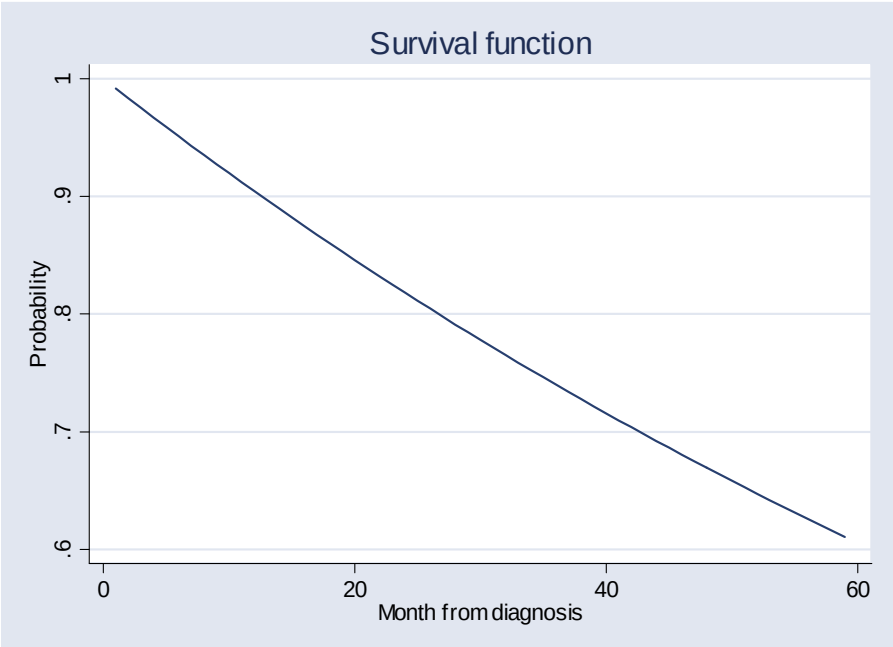

Figure 1: The survival function. M=215.

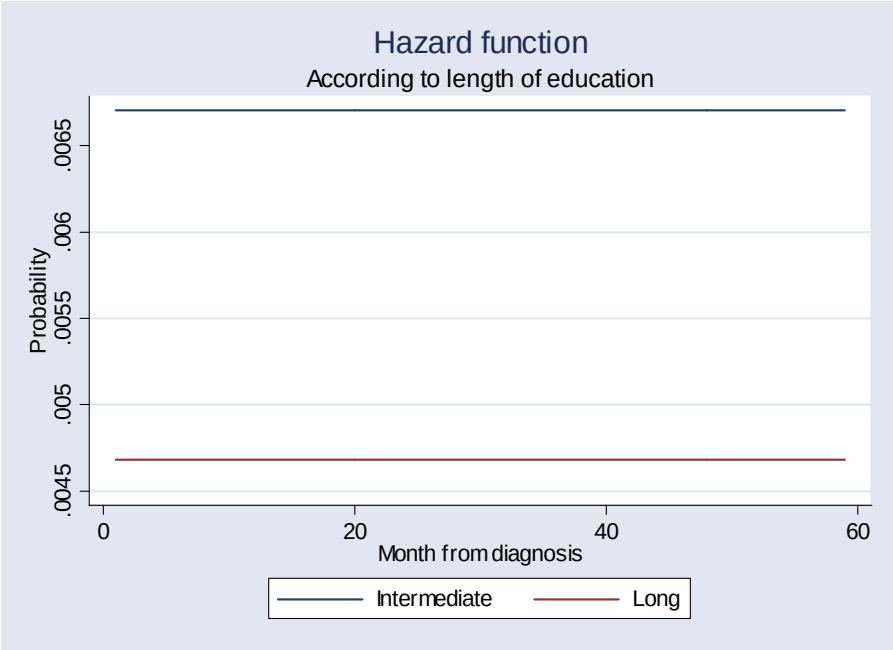

Figure 2: The hazard rate for the two levels of education. M=215.

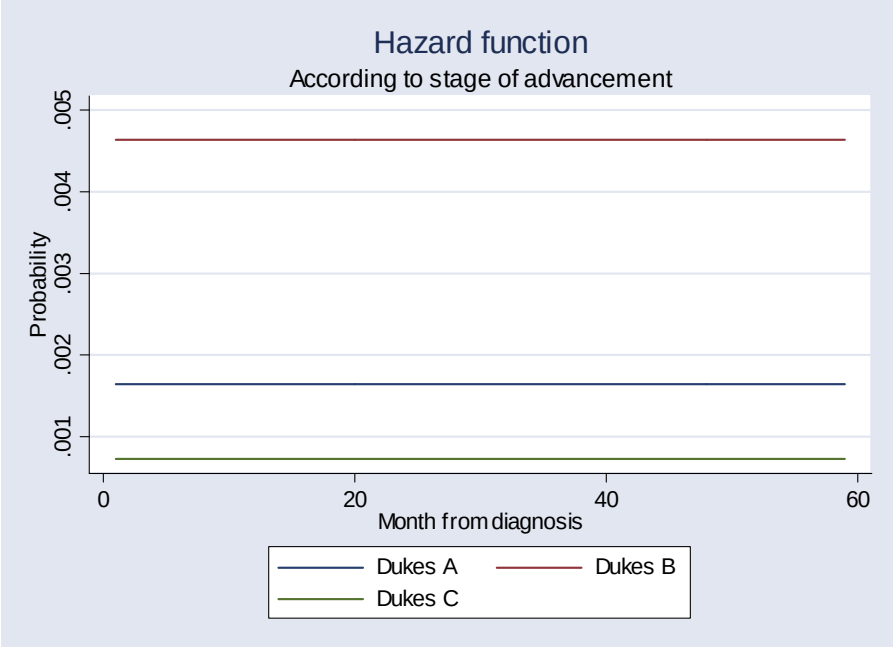

Figure 3: The hazard rate according to stage of advancement. M=215.

The calculations are presented in Figure 2 and Figure 3. In Figure 2 the estimated hazard function according to the two levels of education included in the analysis, intermediate and long, is presented. The figure illustrates the differences in prognosis for the two different levels. The hazard function for long education is lower than for intermediate education, i.e.

the probability of dying in the next instant of time given that the individual is alive at time *t* is higher for an individual diagnosed with intermediate education at any point in time after the cancer diagnosis. After 60 months from diagnosis an individual with long education has about 8 percent higher probability of surviving than an individual with intermediate education.

In Figure 3 we present the hazard function accord to stage of advancement. The hazard function for Dukes C is higher than both Dukes A and Dukes B, i.e. the probability of dying in the next instant of time given that the individual is alive at time *t* is higher for an individual diagnosed with Dukes C at any point in time after the cancer diagnosis. After 60 months from diagnosis an individual with Dukes A has about 14.5 percent higher probability of surviving than an individual with Dukes C.

6. Colorectal treatment cost

In order to say something about the overall gain from screening, we have to compare expected CRTC for the asymptomatic participant with that for the control group. The differences in expected CRTC between these two groups are shown in Table 7.

To estimate the expected CRTC we use all the registrations directly related to the treatment of colorectal cancer from the National Patient Register with the appropriate fees, DRGs and DRG weights. The estimation is done in several steps: first, calculating treatment cost per registration; second, estimating total CRTC per month by adding up the treatment cost per registration for each month for all individuals in the stage; thirdly, estimating average CRTC per month by dividing total CRTC per month by the sum of individuals diagnosed with cancer *and* alive in that specific month; fourthly, estimating the expected CRTC per month by adjusting average CRTC per month for survival according to Dukes stages; fifthly, the costs are discounted at four percent rate; and finally, adding together the expected CRTC per month over the whole period to arrive at the expected CRTC for the screening groups and the control group. Predicted survival for each month according to stage of advancement is presented in Appendix A2.

The expected CRTC for a colorectal cancer diagnosed among asymptomatic participants is EUR 17,201 while that for a colorectal cancer in the control group is EUR 23,568. In addition, the table shows that the expected CRTC for the total screening group is lower than the expected CRTC for the control group[11]. The expected CRTC for a colorectal

[11] The CRTC in the total screening group is not equal to the average of the cost for the three screening subgroups since the number of cancers within each group is not the same.

cancer for asymptomatic participants is EUR 6,367 higher than the expected CRTC in the control group. In this study we have only included colorectal cancer diagnosed in the period 1999 to 2001. In this period 68 percent of all diagnosed cancers were asymptomatic, thus the expected CRTC for the total screening group is affected. Including several years will reduce the proportion of asymptomatic cancers and thus we will expect that the expected CRTC for the total screening group will increase and the difference between the total screening group and the control group decline.

Table 7: Expected CRTC adjusted for survival according to screening groups and control group. Number of observations 179. Numbers in Euro (EUR 1 = NOK 8)

	Colorectal treatment cost		
Group	**Outpatient**	**Inpatient**	**Total**
Participation			
CRC at screening	3,840	13,361	17,201
CRC after screening	4,667	13,355	18,022
Non participation	9,295	16,224	25,519
Total screening	4,767	13,770	18,537
Control	6,743	16,825	23,568

To explain the results in Table 7 we present the expected CRTC for each stage of advancement according to screening group in Table 8. Table 8 shows that expected CRTC increases from Dukes A to Dukes C, but declines for Dukes D for the total screening group and the control group. The fall in CRTC from Dukes C to Dukes D can be explained by lower survival in this group. The decline in CRTC for Dukes D is smaller than the increase in CRTC from Dukes B to Dukes C. For asymptomatic participants there is only one observation on the expected CRTC for Dukes D, thus it is hard to draw conclusions about the rise in expected CRTC from Dukes C to Dukes D. In the control group expected CRTC for a Dukes A is approximately EUR 14,532, while expected CRTC for Dukes C is EUR 26,855. The largest increase in expected CRTC is from Dukes B to Dukes C, which is accounted for by the fact that the largest increase in outpatient services occurs between these two stages. We know that a patient with Dukes B receives less chemotherapy than a patient with Dukes C. The increase in expected CRTC for inpatient services is likely to be related to the need for more extensive and complicated surgery for a patient with Dukes C or Dukes D than for a patient with Dukes A or Dukes B.

From Table 8 expected CRTC for each Dukes stage is also presented according to screening groups and control group. In this paper we have assumed that the survival according to Dukes stages is not affected by screening, thus we assume that the distribution of cancers within each Dukes stage is the same as without screening. Even though the same survival function has been applied to estimate expected CRTC in the screening groups and the control group, the expected CRTC in the screening groups could be different from the expected CRTC in the control group and reflect a different distribution of cancers within each Dukes stage. If the expected CRTC in the screening groups is the same as the expected CRTC in the control group, it could reflect a similar distribution of cancers within each Dukes stage, but not necessarily, because screening could have an effect on survival. If screening does not have an effect on survival, equal expected CRTC in the screening groups and the control group implies that the distribution within each Dukes stage is unchanged. But, if survival has an effect on survival, the distribution of cancers within each Dukes stage could be different even though expected CRTC in the screening groups and the control group are equal. When expected CRTC in the screening groups and the control group are different in Table 8, we can conclude that screening has an effect on the distribution of cancers within each Dukes stage. The effect on expected CRTC of screening on survival comes in addition. The effect of screening on survival within each Dukes stage is uncertain. If screening increases survival within a Dukes stage, the expected CRTC reported in Table 8 for the screening groups are too low, while if screening reduces survival the expected CRTC are too high. The interpretation of different expected CRTC between the screening groups and the control group depends on the distribution of expected CRTC within each Dukes stage.

In Table 8 we see that expected CRTC for asymptomatic participants are different for all Dukes stages from the expected CRTC for the control group, thus it seems like screening affects the distribution of cancers within Dukes stages. For Dukes A the expected CRTC is lower for asymptomatic participants than the expected CRTC in the control group. The finding indicates that a Dukes A cancer for asymptomatic participants requires, on average, less intensive treatment than a Dukes A in the control group, thus the distribution of cancers within Dukes A has shifted towards less advanced cancers. Carcinomas “in situ” may partly explain the difference in advancement. If survival is estimated separately for the screening groups and the control group, the difference in expected CRTC for asymptomatic participants and control group could be affected. If survival for Dukes A is higher for asymptomatic participants, the expected CRTC for asymptomatic participants would increase and approach the expected CRTC for the control group.

The expected CRTC for Dukes B is also lower for asymptomatic participants than for the control group, thus there are indications that screening affects the distribution of advancement within Dukes B towards less advanced cancers. A shift to less advanced cancers within Dukes B would be expected to increase survival for asymptomatic participants. Thus, the expected CRTC for Dukes B would increase if survival is adjusted for screening groups. The distribution within Dukes C for asymptomatic participants is shifted towards more advanced cancers, as the expected CRTC is higher for the asymptomatic participants than in the control group. If screening has a negative effect on survival within Dukes C for asymptomatic participants, the expected CRTC would decline if screening is included in the estimation of survival. For Dukes D it is expected that screening shifts the distribution towards less advanced cancers. This could imply more extensive treatment, as more treatment alternatives are possible, which can explain the finding in Table 8. The result is uncertain as it is based on only one observation. At the same time, the unambiguous reduction in advancement within the stage will imply an increase in survival. Thus the inclusion of the effect of screening on survival would therefore imply that the difference in expected CRTC between asymptomatic participants and the control group will increase.

Table 8: Expected CRTC adjusted for survival according to stage of advancement and selected screening groups. N=292. Figures in euros (EUR 1 =NOK 8)

Advancement	**Screening group**	**Colorectal treatment cost**		
		Outpatient	**Inpatient**	**Total**
Dukes A	Asymptomatic participants	1,037	10,593	11,630
	Total screening group	1,004	10,064	11,068
	Control group	517	14,015	14,532
Dukes B	Asymptomatic participants	501	12,622	13,123
	Total screening group	2,727	13,296	16,023
	Control group	2,109	13,857	15,966
Dukes C	Asymptomatic participants	10,285	18,254	28,539
	Total screening group	8,891	15,653	24,544
	Control group	9,564	17,291	26,855
Dukes D	Asymptomatic participants	16,627	22,959	39,586
	Total screening group	3,950	14,941	18,891
	Control group	8,083	15,318	23,401

7. Sensitivity analysis

In the statistical model we assumed that treatment cost depends on the time the individual remains alive after the time of diagnosis. Since it is likely that costs vary within each stage of advancement, our expected CRTC estimates are uncertain. Even though there are guidelines for the treatment of colorectal cancer, health personnel at one hospital or within one hospital may have different views on the amount or type of treatment, like chemotherapy, necessary for a specific patient. The cost estimates are based on fees and DRGs. These are average estimates and in some situations do not reflect the true treatment cost for a particular patient. For instance, the same type of treatment according to the DRG of two individuals with different ages may call for a different use of resources. If the older individual recovers more slowly he will need a longer stay in hospital than the younger individual, a difference that is not necessarily reflected in the DRG. Complications due to treatment of other disease concurrent to treatment for colorectal cancer may also result in variations in treatment costs. From Table 8 there are also indications that the expected CRTC within each Dukes stage are affected by screening.

We use two different methods to account for the uncertainty in the expected CRTC estimates; probabilistic sensitivity analysis (PSA) and bootstrapping[12]. The PSA is a parametric method, as we make assumptions about the distribution, while the bootstrap method is nonparametric. We present the results of both methods, since our conclusions are affected by the choice of method. Both the US panel on cost-effectiveness analysis (Gold et al., 1996) and the National Institute of Clinical Excellence (NICE) in the UK (2004), have suggested using PSA to deal with uncertainty in cost-effectiveness models because a well-conducted PSA will provide a more realistic representation of variations in the model results. All uncertainty in the parameters is included simultaneously in a PSA. The uncertainty in a specific parameter is represented by a distribution. Because CRTC only has positive values, we use gamma distributions to represent uncertainty (Spiegelhalter et al., 2004). We then use a Monte Carlo simulation to estimate the uncertainty in the parameters by selecting values from the distributions. Inferences from the cost estimates in the model are summarized in Appendix A3, and Table A5 and A6. The parameters are estimated by using the distribution of CRTC estimates for all individuals within each group (according to stage of advancement or total screening group and control group). From these distributions we derive the mean and variance, which we use in the estimation of the parameters. Monte Carlo simulation in

[12] One-way sensitivity analysis and Tornado diagrams are alternative sensitivity analyses, but are not included as uncertainty is not directly related to specific variables for in-patient services.

TreeAge recalculates the model repeatedly as a form of (deterministic) sensitivity analysis. We assume that the parameters are independent.

Bootstrapping is a method for assigning measures of accuracy to statistical estimates, in the present case the expected CRTC estimates. We use bootstrapping to estimate the standard error (see Efron and Thibshirani 1993) of the expected CRTC as shown in Tables 7 and 8. The bootstrap standard error is estimated by using the original samples. A bootstrap sample of CRTC for Dukes C (n = 144) is obtained by random sampling *n* times, with replacement, from the original sample, which means that some of the observations will be sampled once, others several times and some not at all. The method generates a large number of bootstrap samples, each of size *n.* We reapply the estimator (for instance the CRTC for Dukes C) from each bootstrap sample and calculate the standard deviation.

The results of the Monte Carlo simulation and bootstrapping are shown in Table 9. As a consequence of the broad distribution of CRTC estimates within asymptomatic participants, the total screening and the control group and within each stage of advancement (shown in Appendix A3), the width of the gamma distributions in the PSA is large, and the 95 percent confidence intervals therefore overlap. However, we also show the proportion of recalculations that rank the expected CRTC for a specific group in the simulation. The confidence intervals of the asymptomatic participants and the control group overlap, but in about 69 percent of the simulations the control group is ranked with the highest expected CRTC. In about 83 percent of the simulations either Dukes C or Dukes D is ranked with the highest CRTC despite the fact that the confidence intervals are wide. The 95 percent confidence intervals with the bootstrap method are smaller. Due to random sampling with replacement, extreme values (both high and low) are given less weight than in the PSA, where the extreme values are included in the estimation of variance. Table 9 shows that according to the bootstrap method the expected CRTC for the asymptomatic participants is lower than expected CRTC in the control group, while the expected CRTC for the total screening group slightly overlap the confidence interval for the control group. These findings show that there is a reduction in the CRTC function. The expected CRTC for Dukes A is significantly different from the CRTC for Dukes C and Dukes D. The CRTC for Dukes C is significantly higher than the CRTC for Dukes A and Dukes B, but not significantly different from the CRTC for Dukes D.

Table 9: Expected CRTC and PSA with 95% confidence intervals, and proportions of recalculations where the Dukes stage is ranked with the highest CRTC according to the PSA and bootstrap method, with 95% confidence intervals. Figures represent cost in Euros.

Category	CRTC	PSA	Proportion of highest ranking	Bootstrap
Asymptomatic participants	17,736	(4,629 – 38,832)	0.312	(13,779 – 20,953)
Total screening group	18,492	(4,744 – 42,902)		(15,435 – 21,669)
Control group	24,006	(6,917 – 62,906)	0.688	(21,194 – 26,568)
Dukes A	11,779	(2,406 – 28,712)	0.046	(9,741 – 15,595)
Dukes B	15,470	(3,735 – 36,505)	0.126	(13,844 – 18,226)
Dukes C	26,656	(7,249 – 70,678)	0.454	(23,653 – 29,150)
Dukes D	23,282	(6,917 – 59,588)	0.374	(18,377 – 26,538)

8. Concluding remarks

In this paper we have examined whether screening results in a reduction in the treatment cost for colorectal cancer, because such a reduction would be an incentive for the insurer to invest in screening. Since the purpose of screening is to reduce the proportion of advanced cancers, a reduction in the treatment cost can be expected to occur if colorectal cancer treatment cost is an increasing function of the advancement of the cancer. Colorectal cancer treatment cost is estimated as a function of advancement and adjusted for survival. Our findings show that the colorectal cancer treatment cost not unambiguously increase with advancement at the time of diagnosis. Still, we find that the expected colorectal treatment cost for asymptomatic participants are lower than that for the control group. This finding is favourable with regard to investing in screening, but total screening costs and health effects need to be evaluated before a conclusion on investing in screening can be drawn.

We know that colorectal cancer treatment cost estimates are uncertain. The probabilistic sensitivity analysis gives overlapping 95 percent confidence intervals for the four stages of advancement of the cancer and between the asymptomatic participants, total screening group and the control group. Despite these wide intervals, about 69 percent of the simulations ranked the control group as having a higher cost than the asymptomatic participants. In about 83 percent of the simulations the two most advanced stages were ranked as having the highest colorectal treatment cost. The PSA is a parametric method which assumes that the variation in treatment cost between individuals can be represented by a specific distribution. This is a strong assumption; we therefore also used the bootstrap method, which is a non-parametric method. The 95 percent confidence intervals with the bootstrap method are narrower, and there are significant differences in relation to the PSA in

the colorectal treatment cost between the asymptomatic participants and the control group. In addition there are differenced in the treatment cost between the two least advanced cancer stages and the two most advanced.

The estimates of the survival function show that the probability of surviving declines with stage of advancement and increases with the level of education. Estimates derived from the Weibull model show that the duration dependency is not different from one; hence the hazard rate is constant.

From the estimation of Equation (11) we find that the survival after 5 years is 0.75, 0.85, 0.55 and 0.13 for Dukes' A to D respectively (see A2 for details). Tveit et al. (1996) find survival to vary from 0.80 – 0.90 (for Dukes' A and B) to less than 0.05 for Dukes D. This indicates that survival is overestimated in our models for all groups, but especially for Dukes' D. There are at least two explanations for this overestimation. Firstly, only about 7 percent of the cancers are diagnosed in 1999 (first year of observations) and have a five years duration. This may cause uncertainty in the estimation of survival. Secondly, only 292 out of 450 cancers are categorised according to the Dukes staging system. If the cancers used in the analysis not represent the distribution of cancers, the expected colorectal treatment cost will be biased and expected colorectal treatment cost and survival could be affected. If advanced cancers within each stage are underrepresented in the sample, it would imply that survival is overestimated. A decline in survival will imply a reduction in the expected colorectal treatment cost. If the reduction in the expected colorectal treatment cost is lager for Dukes D than for the other Dukes categories, the conclusion in Section 6 can change. But, a larger proportion of advanced cancers also implies more intensive treatment and increased expected colorectal treatment cost. The total effect of the bias on expected colorectal treatment cost for each Dukes stage is therefore uncertain.

If the 215 cancers in the control group with stage description do not represent the distribution of cancers between stages, the expected colorectal treatment cost could be affected. In Tveit et al. (1996) the distribution of cancers according to Dukes stages is reported to be: Dukes A – 10 percent, Dukes B – percent, Dukes C – 35 percent and Dukes D – 25 percent. From the distribution of cancers in Table 1, the data set used in this paper includes too few Dukes A and Dukes D, too many Dukes C, and the same proportion of Dukes B. Given the estimated expected colorectal treatment cost for each Dukes stage in Table 8, the expected colorectal treatment cost for the control group would decline if we had applied a distribution of cancers according to Tveit et al. (1996).

In Table 2 the number of cancers is recorded according to stage of advancement and screening groups. The number of cancers among non-participants is 12 with stage description, which is about 30 percent of all cancers diagnosed among non-participants during the period. In the control group about 60 percent of all cancers could be categorised in the Dukes stage system. According to the discussion above, including all cases could change the expected colorectal treatment cost. In future research it would be interesting to analyse if expected colorectal treatment cost for non-participants changes when all cancers are included.

We know from the discussion in Section 6 that screening seems to affect the distribution of cancers within each Dukes stage, although a firm conclusion is not possible because not all relevant data are collected. The first choice of analysis would be to estimate expected colorectal treatment cost separately for the screening groups and the control group based on equation (10). Then it would be possible to determine whether Dukes stages have a different effect on survival for asymptomatic participants and for the control group. If there are differences, the expected colorectal treatment cost could be adjusted for survival for the specific screening group. The expected colorectal treatment cost would then capture changes in the distribution of cancers within Dukes stages that both change the intensity of treatment and survival. We would then have the best estimate on expected colorectal treatment cost.

In this paper we base the survival analysis on data from the control group in NORCCAP. Even though this group consists of approximately 80 000 persons, the sample is still small. To reduce the uncertainty, estimation of survival in the control group could have been based on register data from the Cancer Registry of Norway. Using register data would not solve the problem with categorising the cancers according to the Dukes staging system. In order to solve the last problem, applying another staging system should be considered in future research. Data on colorectal cancer treatment cost is based on data from the National Patient Register and NORCCAP because general permission was not given to merge data from the National Patient Register with other registers.

We assume in the model that the individual never fully recovers from colorectal cancer and has to be followed up until death in order to get the full treatment cost. Since the observation period is five years, 1999 to 2003, and only 59 out of 215 died during this period, the expected colorectal cancer treatment cost can be higher. It is possible to estimate expected colorectal cancer treatment cost beyond the observation period. Together with estimates of future colorectal cancer treatment cost per month we can use the survival model to predict future survival probability. We believe that prediction is unnecessary as most recurrences appear within four to five years after the diagnosis. In table 10 the expected colorectal cancer

treatment cost per year is reported. The expected colorectal cancer treatment cost is at the highest in the first year and drop to zero or almost zero the fifth year.

Table 10: Expected colorectal cancer treatment cost according to stage of advancement and year from diagnosis. Figures present costs in Euro. M=179.

Category	Year 1	Year 2	Year 3	Year 4	Year 5
Dukes A	12,211	607	1,818	162	128
Dukes B	14,435	2,159	1,106	622	38
Dukes C	22,510	5,782	2,948	3,160	0
Dukes D	20,994	3,257	298	7	0

The purpose of screening is to detect, treat and prevent cancer earlier in the cancer progression than would normally occur with symptomatic diagnosis and thus achieve a lead-time to prolong life expectancy. Lead-time bias occurs when screening falsely prolongs survival. Then the individual gains no additional life-years as the time for diagnosis has only been moved forward. The patient's awareness of having cancer and level of anxiety will be extended causing a reduction in quality of life. In this analysis, lead time bias with regard to survival is not relevant here as survival is based on data for the control group. But, if the survival function is estimated for each screening group, the result could be affected by lead time bias.

The effect of lead-time on treatment intensity is captured in the analysis. Lead-time implies that all cancers are less severe at the time of diagnosis. Some of these cancers may need less intensive treatment as asymptomatic and not symptomatic. For instance it could be that the asymptomatic diagnosed cancers do not qualify for chemotherapy. In this situation the expected colorectal cancer treatment cost will be reduced. But, early diagnosis could also imply more intensive treatment, because the cancers are severe and thus qualify for more intensive treatment, for instance surgical procedures or more extensive chemotherapy. More extensive treatment will increase expected colorectal cancer treatment cost. If lead-time is most likely to increase expected colorectal treatment costs, the expected colorectal cancer treatment costs according to Dukes stages should be adjusted downwards. From Table 8 we see that there is a tendency for lead-time to imply a reduction for Dukes A and Dukes B, while it implies an increase for Dukes C and Dukes D.

The data from the National Patient Register do not contain information about radiation therapy, which is mainly used in the treatment of rectal cancer. We do not believe that this lack of data changes the conclusion that screening reduces colorectal cancer treatment cost, since the amount of radiation therapy increases with severity. The lack of data will only result in underestimation of colorectal cancer cost.

The aim of the present study was to measure the opportunity cost of treating colorectal cancer. The opportunity cost of an input can be measured by the value of its best alternative use. In this study we use DRG-cost and fee for service as measures for opportunity cost, thus the question is whether these measures reflect the true opportunity cost. Both DRG-cost and fee for service are cost estimates of the resource use in the treatment of colorectal cancer, of which labour is the main resource. An increase in the number of treatments of colorectal cancer results in increased input of labour. If there is no unemployment, the increase in labour will be labour that already is employed. Since the gross wage rate can be interpreted as a minimum estimate of the employer's willingness to pay for the labour, the wage rate is interpreted as a minimum estimate of the opportunity cost. If the opportunity cost is higher than the estimates we use in our study, the differences in the colorectal cancer treatment cost according to stage of advancement will be greater. Hence the absolute value of the reduction in colorectal cancer treatment cost from screening will also be greater.

This paper presents the first step of a cost-effectiveness analysis of a once-only screening for colorectal cancer, based on a randomized controlled trial (RCT). The present RCT provides us with a useful instrument for analysing whether screening influence the cost of treating the disease in question, which in this study is colorectal cancer. Treatment of cancer is usually extensive and costly; thus interventions that could reduce future costs are of great interest for the government as insurer. However, the CRTC is only one factor in the total cost function. The total cost function (Meltzer, 1997, Garber and Phelps, 1997, Weinstein, M.C. and W.G. Manning, 1997 and Johannesson and Meltzer, 1998) also includes costs related to the screening, production loss and future treatment costs. Two cost components are relevant with regard to this paper: As a consequence of screening, some individuals with adenomas receive a recommendation for a follow-up colonoscopy. Follow-up colonoscopies will increase the cost consequences of introducing screening, but not the expected colorectal cancer treatment costs. Further, in this analysis, cancers "in situ" result in a lower expected colorectal cancer treatment cost for Dukes A cancers. In a cost-effectiveness analysis detection of cancers "in situ" will imply an increased probability of being diagnosed with colorectal cancer. Hence, total costs will increase due to unnecessary treatment. The total cost function will be calculated as part of the larger analysis of the cost-effectiveness of screening.

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Appendix

A1: Out-patent fees, DRG codes and DRG weights

Table A1: Outpatient services with fee codes, fees (EUR 1 =NOK 7.91).

Fee code		Procedure	Fee (EUR)
		INTERNAL MEDICINE AND SUBSPECIALTIES	
A01		Simple examination	8
A02		Complete examination	28
		Gastroenterology	
	A10a	Ultrasound examination	56
	A10b	Simple secretion and absorbtion examinations	56
	A11a	Esophagus manometry	90
	A11b	Diagnostic gastroduodenoscopy	90
	A11c	Diagnostic sigmoideoscopy	90
	A11d	Therapeutic gastroduodenoscopy	90
	A12a	Therapeutic colonoscopy	152
	A12b	24 hours PH-monitoring of esophagus	152
	A12c	Extensive absorption and secretion examination by means of radioactive isotop	152
	A12d	Diagnostic colonoscopy	152
	A12e	Therapeutic sigmoideoscopy	152
	A12f	ERCP with radiographic guidance	152
	A12g	Endoscopic ultrasound examination with flexible endoscope, incl. videotaping	152
		Surgical specialities	
B01		Simple examination	8
B02		Complete examination	28
		General surgery	
	B03a	Removal of mammary tumor, skin tumour, lymph nodes, etc.	56
	B03b	Removal of deep foreign objects	56
	B03c	Simple wound treatment	56
	B03d	Incision and drainage of abscess	56
	B03e	Anoskopy with string ligature of haemorrhoids	56
	B04a	Extensive wound treatment	90

		Oncology	
H01		Simple examination	8
H02		Complete examination	28
	H03a	Punction cytology for representative sampling	56
	H03b	Removal of acsites	56
	H03c	Removal of hydrothorax	56
	H03d	Telephonic counselling of non-hospital doctors about oncology treatment at home or in another institution	56
	H04a	Blood or plasma transfusion incl. necessary tests, blood typing and test of crossmatch	90
	H04b	Socio-medical evaluation by means of psychiatrist, social worker or ergotherapeut	90
	H04c	Psychosocial evaluation, palliative measures and follow-up of patients in collaboration with interdisciplinary team associated with oncology department	90
	H04d	Oncologic therapy in the patient's home or other locations outside the hospital.	90
	H05a	Intravenous infusion of particularly toxic cytostatics	0
	H05b	Intravesical chemotherapy	0
	H05c	External radiation, per area	83
	H05d	Treatment of pain by means of anaesthesiologist, oncologist or nurse	83
	H06a	Interstitial radiation therapy	152
	H06b	Sociomedical evaluation and treatment of cancer patients	152
	H06e	Lengthy consultation (> 1 hour)	152
	H06c	Photodynamic therapy of skin cancer, per lesion	106
	H06f	Close up radiation of benign lesions, per area	2

Table A2: Outpatient services, DRG codes and DRG weights

DRG code	Procedure	DRG weight
410 A	Chemotherapy, unspecified	0.18
410 B	Chemotherapy, group 1	0.32

Table A3: Inpatient services, DRG codes and DRG weights (ac: additional diagnosis or complication)

DRG code	Procedure	DRG weight
78	Pulmonary embolism, air embolism, fatty embolism	1.52
89	Pneumonia and pleuritis age 18+ with ac	1.53
128	Deep thrombophlebitis	0.9
146	Rectum resection with ac	4
147	Rectum resection without ac	3.08
148	Major surgery of the colon with ac	4.29
149	Major surgery of the colon without ac	2.54
152	Minor operation on the small intestine or colon with ac	2
153	Minor operation on the small intestine or colon without ac	1.34
157	Minor intestinal surgery and surgery on anus and colostomy with ac	1.18
158	Minor intestinal surgery and surgery on anus and colostomy without ac	0.58
170	Surgery of gastrointestinal organs ITAD with ac	2.85
171	Surgery of gastrointestinal organs ITAD without ac	1.38
172	Malignant disease of the gastrointestinal organs with ac	1.24
173	Malignant disease of the gastrointestinal organs without ac	0.9
416	Sepsicaemia with diseases of main diagnosis group 18, age 18+	1.81
418	Postoperative & posttraumatic infections related to main diagnosis group 18	0.83
420	Fever without known cause, age 18+	0.8
462A	Rehabilitation, complex	0.12
462B	Rehabilitation, standard	0.12
462C	Rehabilitation, other	0.71

A2. Predicted survival for each month

Table A4: Predicted survival according to stage of advancement. Number of observations 215.

Month	Dukes A	Dukes B	Dukes C	Dukes D
1	1.0000	1.0000	1.0000	1.0000
2	0.9952	0.9973	0.9900	0.9660
3	0.9904	0.9946	0.9801	0.9332
4	0.9857	0.9919	0.9703	0.9014
5	0.9809	0.9892	0.9606	0.8708
6	0.9762	0.9866	0.9510	0.8412
7	0.9715	0.9839	0.9415	0.8126
8	0.9669	0.9813	0.9321	0.7849
9	0.9622	0.9786	0.9227	0.7583
10	0.9576	0.9760	0.9135	0.7325
11	0.9530	0.9733	0.9044	0.7076
12	0.9484	0.9707	0.8953	0.6835
13	0.9439	0.9681	0.8864	0.6603
14	0.9394	0.9655	0.8775	0.6378
15	0.9349	0.9629	0.8687	0.6161
16	0.9304	0.9603	0.8601	0.5952
17	0.9259	0.9577	0.8515	0.5750
18	0.9215	0.9551	0.8429	0.5554
19	0.9170	0.9525	0.8345	0.5365
20	0.9126	0.9499	0.8262	0.5183
21	0.9083	0.9474	0.8179	0.5007
22	0.9039	0.9448	0.8097	0.4836
23	0.8996	0.9423	0.8016	0.4672
24	0.8952	0.9397	0.7936	0.4513
25	0.8909	0.9372	0.7857	0.4360
26	0.8867	0.9346	0.7778	0.4211
27	0.8824	0.9321	0.7700	0.4068
28	0.8782	0.9296	0.7623	0.3930
29	0.8740	0.9271	0.7547	0.3796
30	0.8698	0.9246	0.7472	0.3667
31	0.8656	0.9221	0.7397	0.3543
32	0.8614	0.9196	0.7323	0.3422
33	0.8573	0.9171	0.7250	0.3306
34	0.8532	0.9146	0.7177	0.3193
35	0.8491	0.9122	0.7106	0.3085
36	0.8450	0.9097	0.7034	0.2980
37	0.8410	0.9073	0.6964	0.2879
38	0.8369	0.9048	0.6894	0.2781
39	0.8329	0.9024	0.6826	0.2686
40	0.8289	0.8999	0.6757	0.2595
41	0.8249	0.8975	0.6690	0.2507
42	0.8210	0.8951	0.6623	0.2421
43	0.8170	0.8927	0.6557	0.2339
44	0.8131	0.8902	0.6491	0.2260
45	0.8092	0.8878	0.6426	0.2183
46	0.8053	0.8854	0.6362	0.2108
47	0.8015	0.8831	0.6298	0.2037
48	0.7976	0.8807	0.6235	0.1968
49	0.7938	0.8783	0.6173	0.1901
50	0.7900	0.8759	0.6111	0.1836
51	0.7862	0.8736	0.6050	0.1774
52	0.7824	0.8712	0.5990	0.1713
53	0.7786	0.8688	0.5930	0.1655
54	0.7749	0.8665	0.5870	0.1599

55	0.7712	0.8642	0.5812	0.1544
56	0.7675	0.8618	0.5754	0.1492
57	0.7638	0.8595	0.5696	0.1441
58	0.7601	0.8572	0.5639	0.1392
59	0.7565	0.8549	0.5583	0.1345
60	0.7529	0.8526	0.5527	0.1299

A3. Assumptions in the probabilistic sensitivity analysis

α and λ can be estimated from the gamma distribution using the following two definitions:

$\alpha = \text{mean}^2/\text{variance}$

$\lambda = \text{mean}/\text{variance}$

Table A5: Assumptions in the probabilistic sensitivity analysis ranking the four stages of advancement. Mean and variance are reported in NOK. Number of observations 292.

Dukes	Treatment costs:	Mean	Variance
Dukes A			
	Outpatient	4,139	$(2{,}506)^2$
	Inpatient	112,117	$(87{,}184)^2$
Dukes B			
	Outpatient	16,686	$(46{,}132)^2$
	Inpatient	110,855	$(58{,}587)^2$
Dukes C			
	Outpatient	76,509	$(105{,}975)^2$
	Inpatient	138,324	$(71{,}936)^2$
Dukes D			
	Outpatient	64,663	$(91{,}579)^2$
	Inpatient	122,540	$(58{,}988)^2$

Table A6: Assumptions in the probabilistic sensitivity analysis ranking the screening group and the control group. Mean and variance are reported in NOK. Number of observations 179.

Dukes	Treatment costs:	Mean	Variance
Asymptomatic participants	**Outpatient**	30,723	$(58{,}418)^2$
	Inpatient	106,894	$(53{,}675)^2$
Total screening group	**Outpatient**	38,135	$(68{,}830)^2$
	Inpatient	110,156	$(53{,}856)^2$
Control			
	Outpatient	53,940	$(90{,}887)^2$
	Inpatient	134,596	$(63{,}197)^2$