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Cost-effectiveness of screening for colorectal cancer with once-only flexible sigmoidoscopy and faecal occult blood test

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Abstract

On the basis of a randomized controlled trial we estimate the cost per life-year gained for six different strategies for colorectal cancer screening. Individuals in the age group 50 to 64 years were randomly selected for either flexible sigmoidoscopy or a combination of flexible sigmoidoscopy and a faecal occult blood test. A comprehensive dataset was collected from the trial to estimate costs and gained life-years. There are some indications that screening for colorectal cancer can be cost-effective, but the results are not statistically significant after this short follow-up period.

Keywords – screening; cost-effectiveness analysis; colorectal cancer; multinomial logit; probabilistic sensitivity analysis

JEL: I10, I18, C41, C52

1. Introduction

Colorectal cancer is one of the most frequent types of cancer in the Western World; in Norway it is the most prevalent. Screening or mass-examination of individuals without symptoms of cancer allows cancer to be diagnosed and treated at an asymptomatic stage. In addition, removal of polyps discovered during screening may prevent the development of future cancers. Since population screening is resource-demanding, a careful analysis of costs and health benefits needs to be undertaken to ensure that screening represents an efficient use of societal resources. In many European countries screening for colorectal cancer has already been introduced without proper evidence of its cost-effectiveness.

The aim of this paper is to study whether screening for colorectal cancer is socially beneficial. If screening enables us to diagnose cancers in the asymptomatic stage, the cancers are less severe and the probability of surviving will increase. Removal of polyps is expected to prevent the development of future cancers. Prevention of future cancers will both reduce the probability of developing colorectal cancer and the probability of dying from colorectal cancer. These two effects will increase the health benefit. Further, the conclusion depends on consequences of screening on resource allocation.

We develop a model to evaluate the cost-effectiveness of screening for colorectal cancer. The health benefit is measured as life-years gained and defined as the difference in life-expectancy for the screening group and the control group. Life expectancy depends on the probability of developing colorectal cancer, the probability of surviving from colorectal cancer and the probability of dying from causes other than colorectal cancer. These probabilities are estimated in the paper; screening is expected to reduce the two first probabilities. Total screening costs are analysed from a societal perspective and include costs such as direct program costs, treatment costs and production losses.

From such a cost-effectiveness model we can derive information about the cost of screening per life-year gained; the marginal cost per life-year gained, by including an additional test; and the effect on cost of screening including avoided treatment costs and production gains.

The analysis is based on a comprehensive dataset collected from a randomized trial in Norway (NORCCAP – Norwegian Colorectal Cancer Prevention). This is a once-only screening with flexible sigmoidoscopy or flexible sigmoidoscopy in combination with a faecal occult blood test (FOBT). The Norwegian trial, together with screenings in the UK (Atkin et al. 2002), Italy (Segnan et al. 2002) and the US (Weissfeld et al. 2005), are the first

randomized controlled trial of this type. The data set includes individual level data on trial costs, use of health care services, labour market participation, travel expenses, incidences of cancer with stage description, date of death, and socio-economic variables such as income, education, age, and gender.

No screening is chosen as the comparator in this analysis. The study is undertaken from a societal perspective on the basis of ‘intention to treat’. ‘Intention to treat’ means that the comparison is made between those who were invited to screening versus those who were not, regardless of whether they had a screening examination or not. Because non-participants to screening are selective, we would introduce bias by comparing those who actually had screening with the control group. By including only participants, we cannot be certain whether the findings stem from the intervention or the fact that there is selection bias with regard to participation. Findings from sub-groups, such as participants and non-participants, *along with* findings for the whole intervention group will provide important information about how the effects are distributed among the sub-groups.

Results from the cost-effectiveness analysis show that the cost per life-year gained depends on which categories of costs are considered. When direct program costs are included screening with a combination of flexible sigmoidoscopy and FOBT for the age group 55 to 59 years is the most cost-effective alternative, while when indirect program costs are included, a combination of flexible sigmoidoscopy and FOBT for the age group 60 to 64 years is preferable to other preventive health measures. Inclusion of treatment costs implies that screening with a combination of flexible sigmoidoscopy and FOBT for the age group 55 to 59 years increases the cost per life-year gained, and thus become the most cost-effective screening strategy. The sensitivity analysis indicates that our findings are not robust.

The paper is structured as follows: Section 2 describes the randomized control trial. Section 3 presents the structure of the model and how the expected life-years and life-years gained are estimated. The estimation of the transition probabilities used in the model is presented in Section 4, where Section 4.1 and 4.2 present the estimation of the transitions from well to colorectal cancer or death and the transition from colorectal cancer to death, respectively. In Section 5 we present the four categories of screening costs used in the analysis: direct and indirect programme costs, and direct and indirect programme consequences. Section 6 presents life expectancy and cost-effectiveness results based on the four different screening cost alternatives, and Section 7 contains the uncertainty analyses. In Section 8 the underlying assumptions on which the results are based are discussed and compared with the literature. Section 9 offers some conclusions.

2. Data

NORCCAP (Norwegian colorectal cancer prevention, see Bretthauer et al. (2002)), was a randomized controlled trial in the period 1999-2001. NORCCAP was implemented in two counties: Telemark (165,855 inhabitants in 2003) and Oslo (517,401 inhabitants in 2003). Each year from 1999 to 2001, approximately 7,000 individuals were invited to participate in NORCCAP (3,500 from each county). In 1999 and 2000 individuals between 55 and 64 years were invited, while individuals between 50 and 54 years were invited in 2001. After one reminder letter, the overall participation rate reached 65 percent for the whole period. The probability of participation depends on individual characteristics such as income, travel expenses, expected benefit from screening, and the use of health care services (Aas, 2004 and 2005).

The NORCCAP trial was a once-only screening, and the screening methods used were flexible sigmoidoscopy and FOBTs¹. Half of the intervention/screening group was offered flexible sigmoidoscopy and the other half flexible sigmoidoscopy in combination with FOBT. Flexible sigmoidoscopy enables the physician to observe the inside 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 polyps², which are early signs of cancer. The FOBT is self-administered and requires stool samples on three consecutive days. The samples are smeared onto cards containing chemically impregnated paper and forwarded to the laboratory at the time of screening participation.

Figure 1 describes the patient flow in NORCCAP. A participant fulfilling the inclusion criteria³ has to empty his⁴ bowels before undergoing the sigmoidoscopy. The sigmoidoscopy results can be either positive or negative, where a positive sigmoidoscopy is defined as having an adenoma < 10 mm and/or having a polyp ≥ 10 mm (it is more than 95 percent certain that such a polyp is an adenoma). Adenomas are growths that are benign, but some are known to have the potential, over time, to transform into cancer. If the individual was invited to a combination of flexible sigmoidoscopy and a FOBT, the FOBT is analysed *after* the sigmoidoscopy. An individual with a positive sigmoidoscopy is referred for a work-up colonoscopy, independent of the result of the FOBT, while the individual with a negative sigmoidoscopy is referred for a colonoscopy only if the FOBT is positive. Colonoscopy, like

¹ The FOBT used here is a FlexSureOBT®, an immunochemical test for human blood.

² Polyps are outgrowths in the colon. The larger they are, the more likely they are to develop into cancer in the future.

³ The exclusion criteria for NORCCAP included being treated for cancer and taking anticoagulants.

⁴ Both males and females participated in the screening, but we refer to the individual as he.

flexible sigmoidoscopy, enables the physician to observe the inside of the large intestine. Unlike flexible sigmoidoscopy, colonoscopy is an examination of the entire large intestine, both rectum and colon.

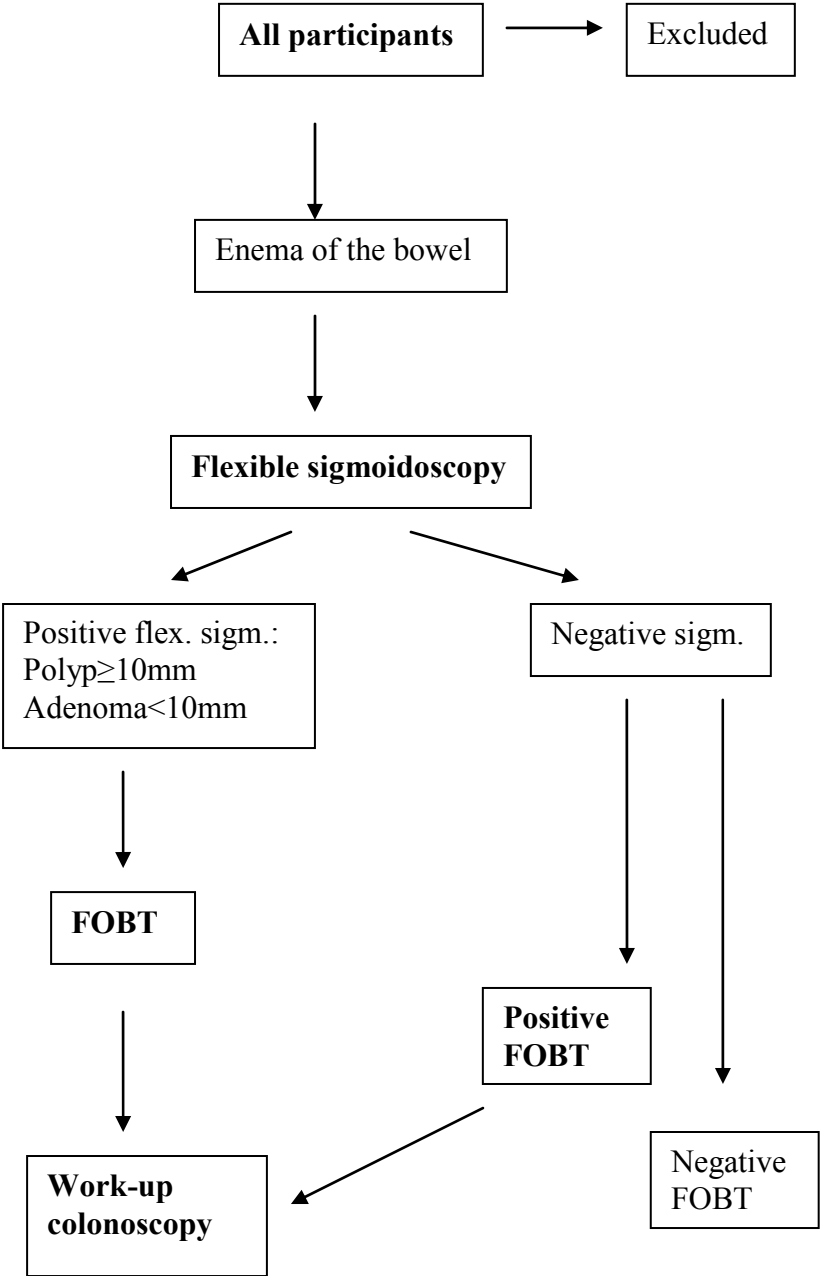


Figure 1: NORCCAP and patient flow for individuals undergoing flexible sigmoidoscopy alone or in combination with FOBT.

In NORCCAP the total screening group and control group were randomly drawn with regard to date of birth (see details in A1). The total screening group consists of all individuals invited to the screening, i.e., the participants, non-participants, the individuals excluded, and the individuals from whom the invitation letter was returned unopened. The criteria related to which cases to include in the sample are important in order to have comparable datasets. In the total screening group we have included all colorectal cancers and deaths from the start of the year in which they were invited. For individuals in the control group born in 1935 to 1945 we have included all colorectal cancers and deaths from the start of either 1999 or 2000, depending on the year in which they were included in the control group (see A1 for details). For individuals born in 1946 to 1950 we have included all colorectal cancers and deaths from the start of 2001. As a consequence the control group was reduced from 79,808 to 79,191. The total screening group originally consisted of 20,780 but was reduced to 20,559 because 86 individuals declined the data merger, 45 individual died and 131 developed colorectal cancer or died from it before the screening period.

In Table 1 the number of asymptomatic and symptomatic cancers, CRC deaths and deaths from causes other than CRC are reported according to age group and screening strategy. From the Table we see that there is a decline in colorectal cancer deaths for the two oldest age groups of 40 to 50 percent. The decline is largest for the groups offered a combination of flexible sigmoidoscopy and FOBT.

Table 1: Proportions of asymptomatic and symptomatic diagnosed colorectal cancers and deaths, both colorectal cancer and causes other than colorectal cancer according to screening group and age (numbers in parenthesis).

Age group	Screening group	Asymptomatic	Symptomatic	CRC deaths	Deaths (other causes)
50 to 54	Control (37,496)	-	0.0023 (86)	0.0005 (18)	0.0182 (685)
	FS (3,454)	0.0015 (5)	0.0009 (3)	0.0006 (2)	0.0182 (63)
	COMB (3,464)	0.0014 (5)	0.0023 (8)	0.0006 (2)	0.0159 (55)
55 to 59	Control (26,230)	-	0.0055 (144)	0.0021 (54)	0.0375 (984)
	FS (4,307)	0.0023 (10)	0.0030 (13)	0.0014 (6)	0.0345 (149)
	COMB (4,174)	0.0019 (8)	0.0041 (17)	0.0012 (5)	0.0314 (131)
60 to 64	Control (15,465)	-	0.0100 (155)	0.0031 (48)	0.0588 (909)
	FS (2,528)	0.0024 (6)	0.0095 (24)	0.0020 (5)	0.0570 (144)
	COMB (2,632)	0.0027 (7)	0.0084 (22)	0.0015 (4)	0.0517 (136)

The dataset includes information about age, gender, date and cause of death, number of social security recipients, and labour market status from Statistics Norway. Data on incidences, time of diagnosis, and cancer stage of advancement at the time of diagnosis are obtained from the Cancer Registry of Norway; Baseline findings are from NORCCAP (Gondal et al. 2003). Information on both inpatient and outpatient services are from the National Patient Register and the National Insurance Administration. The data are from 1999 to 2004.

3. Structure of the model

The expected benefits from screening for colorectal cancer using flexible sigmoidoscopy alone or in combination with FOBT are an increased probability of surviving cancer and a reduced number of future incident cancers. The first effect is a result of earlier detection of cancer since colorectal cancer often is diagnosed at a very late stage, which is negatively correlated with the survival probability. The second effect is a consequence of the removal of polyps from the colon, which otherwise could develop into cancer in the future. In this paper we apply the number of life-years gained as the effect measure.

Below we present a modelling framework for analysing the effect of screening on life expectancy. Several types of probabilities form the foundation of the model. The probabilities are presented in Table 2 where three types are of specific interest; the probability of developing colorectal cancer; the probability of dying from colorectal cancer, and; the probability of dying from causes other than colorectal cancer. If screening reduces the two first probabilities, life-expectancy will increase. The model consists of a number of mutually exclusive states, black and grey ovals, as displayed in Figure 2. The individual will always be in one and only one of the states at a given moment in time. During one cycle the individual can move from one state to another or remain in the same state. A set of transition probabilities describes the movement between the different states. Figure 2 presents the model applied to the estimation of costs and life-years gained for individuals invited to flexible sigmoidoscopy. In this model a cycle is one calendar year. The main states in the model are well, sick (defined as either having asymptomatic or symptomatic colorectal cancer), and dead. The white ovals represent intermediate states of screening procedures, which the patient may enter and leave during one cycle. Grey and black ovals are states in which the individuals can stay for at least one full cycle.

Table 2: The probability applied in the model with definitions.*

Probability	Definition
$q_{12}(X)$	The transition probability at age X in screening group g of being well and dying from causes other than colorectal cancer.
$q_{13}(X)$	The transition probability at age X in screening group g of being well and diagnosed with a symptomatic colorectal cancer.
$q_{32}^A(v; X)$	The transition probability at age X of dying during treatment of an asymptomatic diagnosed colorectal cancer, where v refers to year after diagnosis.
$q_{32}^S(v; X)$	The transition probability at age X of dying during treatment of a symptomatic diagnosed colorectal cancer, where v refers to year after diagnosis.
a	The probability of participating in screening group g .
h	The probability of having a work-up colonoscopy in screening group g .
c	The probability of being diagnosed with an asymptomatic colorectal cancer in screening group g .
k	The probability in screening group, g of being recommended to take a follow-up colonoscopy t years after the screening.
m	The probability in screening group g of having a valid FOBT.
p	The probability in screening group g of being well at the start

* The estimates are reported in Appendix A2, A3 and A4.

An individual invited to screening has a probability a of participating in the screening and $(1-a)$ of not participating (for various reasons). All non-participants are assumed to be well. When participants are examined by flexible sigmoidoscopy, a proportion of them, h , are referred further to a work-up colonoscopy, while $(1-h)$ are defined as well. For individuals referred to a colonoscopy, the probability of having asymptomatic cancer is equal to c . As asymptomatic cancers are only diagnosed at the screening, the probability that an individual referred to colonoscopy is well is defined as $(1-c)$. Let p be the probability of being diagnosed with an asymptomatic cancer, then $(1-p)$ is the probability of being well at the start.

Let $t = 1, 2, \dots, 36$, refer to the cycle (or year), superscripts S and A refer to whether the cancer are symptomatic and asymptomatic and the states be enumerated as follows: well is state one, death is state two and colorectal cancer is state three. The transition probability of being well at age X and diagnosed with symptomatic colorectal cancer is $q_{13}(X)$ and the transition probability at age X of being well and dying of causes other than colorectal cancer is $q_{12}(X)$. Let $v = 1, 2, 3$ and 4 refer to duration (years) from diagnosis, then the probabilities of dying during treatment of asymptomatic cancer is equal to $q_{32}^A(v; X)$ and the probability of dying during treatment of symptomatic cancer is equal to $q_{32}^S(v; X)$. The details about the transition probabilities are presented in the next section.

A proportion of the individuals participating in the screening were recommended for follow-up colonoscopies after the screening (k). Some individuals were recommended to do the follow-up colonoscopy five years after the screening, while others ten years after the screening, thus the probability depends on time. The proportions of recommended follow-up colonoscopy for each cycle is calculated based on data from the trial, see A4. These follow-ups are included as intermediate states for an individual who is well. The probability that an individual at the follow-up colonoscopy will be diagnosed with colorectal cancer is defined as $q_{13}(X)$, and is assumed to be equal to the probability in the general population. If the individual does not have colorectal cancer at a follow-up colonoscopy, the individual is included in the state of well $[1 - q_{13}(X)]$.

Based on findings in Aas (2007) it is assumed that the total duration of treatments on average last for four years. Then, the probabilities of becoming well after four years of treatment for an asymptomatic diagnosed and a symptomatic diagnosed cancer are given by

$$\prod_{v=1}^4 (1 - q_{32}^A(v; X)) \quad (1)$$

$$\prod_{v=1}^4 (1 - q_{32}^S(v; X)) \quad (2)$$

All the probabilities used in the model are presented with definitions in Table 2. The estimates are reported in Appendix A2 and A4. The participation probability is equal to the probability of having a flexible sigmoidoscopy and is lower for the youngest age group. The number of work-up colonoscopies increases with age, which would be expected since the number of polyps in the colon is higher for the age groups 55 to 59 and 60 to 64 years. In the model, where a combination of flexible sigmoidoscopy and FOBT is evaluated we need to include the probability of having a valid test. A valid test is defined as a test in which it is feasible to examine one, two, or three of the stool samples. As the FOBT only is a supplement to flexible sigmoidoscopy, we have not included false positive estimates and have not modelled the effect of only FOBT on life expectancy or costs.

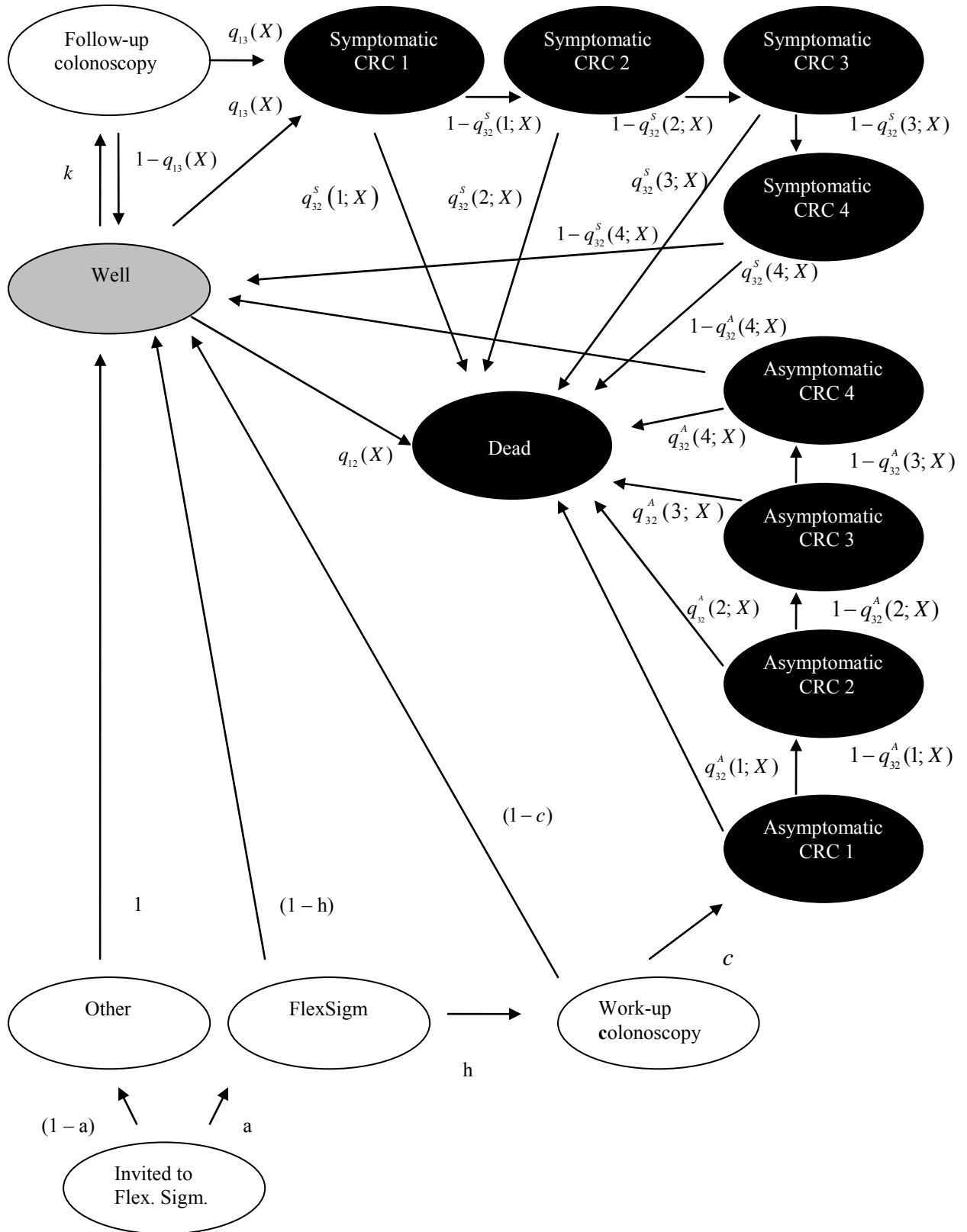


Figure 2: Screening by flexible sigmoidoscopy where black and grey ovals represent states in which patients remain for at least a full 1-year cycle. The white ovals represent intermediate states of screening procedures which patients may enter and leave during a cycle. The arrows represent transition between various states.

Based on the model introduced above, we can simulate life expectancy for the different screening strategies and the control group. Let the nine screening groups be represented by $g = FS5054, FS5559, FS6064, COMB5054, COMB5559, COMB6064, C5054, C5559$ and $C6064$, where $g = 1, 2, \dots, 9$, respectively and $L^g(t)$ be the surviving probability at time t for screening group g . Since time of death is distributed over the cycle, we include half-cycle correction, which reduce the health benefit (survival probability) to the half in the first and the last cycle. Total life expectancy LE for screening group g is then given by

$$LE^g = 0.5[L^g(1) + L^g(T)] \sum_{t=2}^{T-1} L^g(t).$$

The probability of surviving $t = 1$ for screening group g at age X_t is given by:

$$\begin{aligned} L^g(1) = & 0.5\{(1-p)[1-q_{12}(X_1)-q_{13}(X_1)] \\ & + (1-p)q_{13}(X_1)[1-q_{32}^S(1; X_1)] \\ & + p[1-q_{32}^A(1; X_1)]\} \end{aligned} \quad (3)$$

The first line of (3) is the probability of remaining in the state well during cycle one, i.e. not dying from causes other than colorectal cancer and not being diagnosed with colorectal cancer. The second line is the probability of surviving the first year of treatment for symptomatic cancer, while the last line represents the probability of surviving the first year of treatment for asymptomatic cancer. The probability of surviving until the start of cycle three is given by

$$\begin{aligned} L^g(2) = & (1-p)[1-q_{12}(X_1)-q_{13}(X_1)][1-q_{12}(X_2)-q_{13}(X_2)] \\ & + (1-p)q_{13}(X_1)[1-q_{32}^S(1; X_1)][1-q_{32}^S(2; X_2)] \\ & + (1-p)[1-q_{12}(X_1)-q_{13}(X_1)](1+k_2)q_{13}(X_2)[1-q_{32}^S(1; X_2)] \\ & + p[1-q_{32}^A(1; X_1)][1-q_{32}^A(2; X_2)] \end{aligned} \quad (4)$$

Equation (4) contains of four parts: The first line in is the probability of remaining in the state well through cycle two, i.e. not dying from other causes than colorectal cancer or being diagnosed with symptomatic cancer in cycle two. Further, the second line is the probability of surviving until the third year of treatment for a symptomatic cancer diagnosed in cycle one. Line three is the probability of surviving until the second year of treatment of a symptomatic

cancer diagnosed in cycle two. The last line is the probability of being diagnosed with an asymptomatic colorectal cancer in cycle one and surviving until the third year of treatment.

$$\begin{aligned}
L^s(3) = & (1-p) \prod_{t=1}^3 [1 - q_{12}(X_t) - q_{13}(X_t)] \\
& + (1-p) q_{13}(X_1) [1 - q_{32}^s(1; X_1)] [1 - q_{32}^s(2; X_2)] [1 - q_{32}^s(3; X_3)] \\
& + (1-p) [1 - q_{12}(X_1) - q_{13}(X_1)] q_{13}(X_2) [1 - q_{32}^s(1; X_2)] [1 - q_{32}^s(2; X_3)] \\
& + (1-p) \prod_{t=1}^2 [1 - q_{12}(X_t) - q_{13}(X_t)] q_{13}(X_3) [1 - q_{32}^s(1; X_3)] \\
& + p [1 - q_{32}^A(1; X_1)] [1 - q_{32}^A(2; X_2)] [1 - q_{32}^A(3; X_3)]
\end{aligned} \tag{5}$$

where (5) is the probability of surviving until cycle 4. Let $T = 36$ and r be the discount rate, then life-years gained (LYG) for screening group 1 is given by

$$LYG^1 = (1+r)^{-(t-1)} \{LE^s - LE^7\} \tag{6}$$

4. Transition probabilities

4.1 Transition from well to colorectal cancer or to death from causes other than colorectal cancer

In this Section we estimate the transitions from well to colorectal cancer (q_{13}) and from well to death (q_{12}). We have data on colorectal cancer diagnosis and deaths from 1999 to 2004 for which number of years of observation ranges from a maximum of six (for individuals invited in 1999) to a minimum of four (for individuals invited in 2001). The variation in age ranges from 50 to 69 years.

Because groups were limited we have simplified the estimation by assuming that observations for an individual are independent over time. This implies that an individual surviving six years is counted as six different individuals all being well, while an individual surviving until dying after four years is counted as three well individuals and one dying. If there are unobserved individual-specific factors that are correlated over time, the transition over years will not be independent and accordingly the estimates of the model parameters will be biased. This potential bias is however not expected to have an impact on the comparison between the screening group and the control group because there is no reason to believe that the correlation over time will be affected of screening.

Let j refer to the state to which the individual can transfer, $j = 2$ and 3 . The transitions are independent of time and duration, but change with age, X , and intervention group, $g=FS5054, FS5559, FS6064, COMB5054, COMB5559, COMB6064, C5054, C5559$ and $C6064$. The probability for individual i to transform from well to CRC or death is assumed to be given by the multinomial logit model:

$$q_{ilj}(X) = \frac{e^{\sum_g \beta_{0j} g_i + X_i \beta_{1j}}}{1 + e^{\sum_g \beta_{02} g_i + X_i \beta_{12}} + e^{\sum_g \beta_{03} g_i + X_i \beta_{13}}} \quad (7)$$

where $i = 1, 2, \dots, N$, $j=2$ and 3 , $\beta_{02}, \beta_{03}, \beta_{12}$ and β_{13} are parameters to be estimated by the model. Let $Y_{ilj} = 1$ if individual i goes from state 1 to state j . From this we can derive the log likelihood function⁵

$$\text{LogL} = \sum_{i=1}^N \sum_{j=2}^3 Y_{ilj} \log q_{ilj}(X) \quad (8)$$

The parameters in (8) are estimated by the maximum likelihood method⁶. The results from the estimation are reported in Table 3 and presented according to age groups. The transition from well to both death and colorectal cancer increases with age.

For all age groups in Table 3, the control group for a specific age group is the reference group and the parameter estimates are only reported for the screening strategies within the relevant age group. For the age group 60 to 64 years, there are no significant differences between the control and the two intervention groups with regard to the effect on death and colorectal cancer. For the age group 55 to 59 years a combination of flexible sigmoidoscopy and FOBT has a significant negative effect on death, while only flexible sigmoidoscopy has a significant negative effect on the probability of developing colorectal cancer. In the age group 50 to 54 years the only significant effect is the negative effect on the probability of developing colorectal cancer for the individuals invited to only flexible sigmoidoscopy.

⁵ For further details on multinomial logit, see Green (2002)

⁶ Estimated with STATA release 8.

Table 3: Parameters estimates of the multinomial logit model (SD in parenthesis). No. of observations is 687604

Transition from well (I) to:	Variable	60 to 64 years	55 to 59 years	50 to 54 years
Death (j=2)	Age	0.00033 (0.00003)***	0.00033 (0.00003)***	0.00033 (0.00003)***
	Screening group			
	C5054	-	-	Ref.
	FS5054	-	-	0.00003(0.0005)
	COMB5054	-	-	-0.00052(0.0005)
	C5559	-	Ref.	-
	FS5559	-	-0.00032 (0.0003)	-
	COMB5559	-	-0.0007 (0.0003)**	-
	C6064	Ref.	-	-
	FS6064	-0.00013 (0.00036)	-	-
	COMB6064	-0.00054 (0.00034)	-	-
Colorectal cancer (j=3)	Age	0.00004 (0.00001)***	0.00004 (0.00001)***	0.00004 (0.00001)***
	Screening group			
	C5054	-	-	Ref.
	FS5054	-	-	-0.00036 (0.0001)***
	COMB5054	-	-	0.00001(0.00021)
	C5559	-	Ref.	-
	FS5559	-	-0.00026 (0.0001)***	-
	COMB5559	-	-0.00015(0.0001)	-
	C6064	Ref.	-	-
	FS6064	-0.00009 (0.00011)	-	-
	COMB6064	-0.00002 (0.00012)	-	-

*** Significant at 1 percent level, ** Significant at 5 percent level, * Significant at 10 percent level

The estimated coefficients are used to predict the transition probabilities for the age groups 50 to 67. The predicted probabilities are then used to simulate the surviving probabilities for the first six cycles. However, as the variation in age is limited, we used information from the Cancer Registry of Norway and Statistics Norway to predict the transitions from cycle 7. From cycle 7, it is assumed that for a given age the transitions are equal for the screening groups and the control group. Hence, due to insufficient information, we do not include the effect of screening on the probability of developing colorectal cancer in the future. The transitions are reported in Appendix, A3.

4.2 Transition from colorectal cancer to death

In this Section we estimate the transitions from colorectal cancer to death $q_{32}^A(v; X)$ and $q_{32}^S(v; X)$ the first four years after diagnosis. We have data on colorectal cancer diagnosis and deaths from 1999 to 2004 for which number of years of observation ranges from a

maximum of six (for individuals invited in 1999) to a minimum of four (for individuals invited in 2001). The variation in age ranges from 50 to 69 years. In Aas (2007) it is shown that the transition from colorectal cancer to death is independent of duration within the age group 50 to 69, thus the probability of dying during treatment of asymptomatic and symptomatic cancer are $q_{32}^A(X)$ and $q_{32}^S(X)$, respectively. From Aas (2007) we know that treatment costs for colorectal cancer are approximately zero five years after diagnosis. Based on this, we assume that all individuals, except those dying during treatment, are treated for colorectal cancer within four years of diagnosis. The transitions are assumed to depend on age at the time of diagnosis, X , and whether the cancer is diagnosed due to symptoms or not⁷. The transition probability for individual i diagnosed with an asymptomatic and symptomatic cancer to die one out of four years of treatment of colorectal cancer is then estimated by the logit models:

$$q_{32}^A(X) = 1 - \left(\frac{1}{1 + e^{X_i \beta_{Aj}}} \right)^{1/4} \quad (9)$$

$$q_{32}^S(X) = 1 - \left(\frac{1}{1 + e^{X_i \beta_{Aj}}} \right)^{1/4} \quad (10)$$

To estimate the probability in (9) we use data for 41 asymptomatic cancers out of which two died within four years of treatment. To estimate (10) we use 471 symptomatic cancers out of which 159 died during four years of treatment. We use the maximum likelihood method⁸. The results are presented in Table 4. We see that age do not have any significant effect on the probability of dying, thus the probability of dying during four years of treatment is independent of both age and duration. The probability of dying is then constant over the four years. For asymptomatic diagnosed cancer $q_{32}^A(X) = 0.012$ and for symptomatic cancer $q_{32}^S(X) = 0.097$. The transitions are reported in A3. The predicted probabilities are used to simulate the conditional probability of being well at the start of cycle t and surviving until cycle $t+1$ for the six first cycles.

⁷ The transition is in Aas (2007) shown to depend on variables like education and Dukes stages, but these factors are not included here since they are not needed in the estimation of life-expectancy.

⁸ Estimated with STATA release 8.

Table 4: Parameter estimates from the logit model (SD in parenthesis). No of observation are 513 out of which 41 is asymptomatic.

Screening group	Variable	Coefficients
Asymptomatic diagnosed cancer		
	Age	- 0.0058 (0.009)
Symptomatic diagnosed cancer		
	Age	- 0.0033 (0.005)

*** significant at a 1 per cent level, ** significant at a 5 per cent level, * significant at a 10 per cent level

Technically, the model can predict transition for all cycles, but as we know that increasing age is expected to reduce survival and survival is also expected to depend on the duration (Cancer Registry of Norway, 2003), we do not use the result in Table 4 to predict beyond cycle six. From cycle 7 we supplement with data from the Cancer Registry of Norway and Statistics Norway (Statistics Norway, 2004). From cycle seven, the deaths during treatment of symptomatic colorectal cancer include only colorectal cancer as cause of death. From the Cancer Registry of Norway we know that the probability of dying depends on time from diagnosis, about 58 percent of the deaths occur within the first year and 20, 13, and 9 percent during the second, third, and fourth years, respectively (the transitions used are reported in A3).

5. Screening costs

We divided the costs into four categories, which allow us to analyse how inclusion of different cost estimates affect the cost per life-year gained. It also facilitates comparison with relevant literature because previous analyses on cost-effectiveness of colorectal cancer screening include various cost estimates.

The first category encompasses the direct program costs and includes the opportunity cost of all resources used to carry out the screening (Table 5). The cost of invitations to screening and reminder letters is a rough estimate that includes stamps, envelopes, and letters. Reimbursement from the National Insurance Administration is used to estimate the cost of diagnostic sigmoidoscopy and therapeutic colonoscopy. 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 to reflect the true cost. The price of Laxabon® for bowel cleansing before a colonoscopy is the market price the individual has to pay at the pharmacy.

Table 5: Direct program costs, unit price, and source of information (prices from 2003)

Screening costs	Unit cost (Euro)	Source
Invitation letter	2	Expert opinion
Reminder	2	Expert opinion
Diagnostic sigmoidoscopy	180	The National Insurance Administration
Therapeutic colonoscopy (inclusive polypectomy and biopsy)	225	The National Insurance Administration
Laxabon® - bowel cleansing	8.75	Market price
FOBT test in the letter	3	Expert opinion
FOBT examination	5	Expert opinion

The indirect program cost is the second cost category and includes the individual's travel expenses to the screening and, if required, to the colonoscopy (if he had a high or low risk adenoma). From Aas (2004, 2005) we know that average travel expenses for those participating were 9 Euro. Furthermore, the indirect program costs also contain production losses resulting from travel time to the screening examination and/or to the colonoscopy and the time used on the sigmoidoscopy and/or the colonoscopy examination. On average, the time travelling to the screening centre for a flexible sigmoidoscopy screening examination or colonoscopy is 1 hour and 15 minutes, see Aas (2005). Preparation at the centre and sigmoidoscopy takes about 45 minutes so the total screening time (travelling and sigmoidoscopy) is two hours. Since the colonoscopy requires bowel preparation before the examination⁹ and the examination itself is more extensive than a flexible sigmoidoscopy, it is assumed that total colonoscopy time (travelling and colonoscopy) is one day. Because there is almost no unemployment in Norway, we use the human capital approach to estimate the opportunity cost of the production loss. The production losses depend on the age of the individual because the proportion working declines with age. From Aas (2004, 2005) we know that the proportion working in the age groups 50 to 54 years, 55 to 59 years, and 60 to 64 years is 0.82, 0.81 and 0.62, respectively. Production loss per day is calculated on the basis of gross income reported for individuals responding to the survey used in Aas (2004, 2005).

From Table 6 we see that the production loss declines with age, which can be explained by an increasing proportion working part time in the older age groups. We have assumed the opportunity cost for individuals not working is equal to zero.

⁹ The bowel cleansing has to start at 4 pm on the day before the colonoscopy.

Table 6: Indirect program costs, unit price and source of information (2003)

Screening costs	Cost (Euro)	Source
Travel expenses	9	Aas (2004, 2005)
Production loss per day		
50 to 54	311	Aas (2004, 2005)
55 to 59	306	Aas (2004, 2005)
60 to 64	288	Aas (2004, 2005)

The third category is direct program consequences. There are two direct program consequences with regard to treatment cost of colorectal cancer. The first effect is reduced future treatment cost resulting from reduction in future incidence of colorectal cancer and the second effect reflects the fact that screening allows diagnosis of asymptomatic cancers, which are less expensive to treat¹⁰. In Table 7 treatment cost is presented for symptomatic and asymptomatic cancers and includes surgery, chemotherapy, and follow-up colonoscopies (radiotherapy is not included). The treatment follows certain standard procedures (Norwegian Gastrointestinal Cancer Group, 1999), but there is room for individual variation. The treatment costs are estimated on the basis of information about inpatient stays and outpatient consultations from the National Patient Register and the National Insurance Administration. We use hospital reimbursement as the basis for estimating treatment costs. The hospitals have “activity-based financing” 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. DRGs describe a hospital's case-mix. In Norway there are approximately 500 different DRGs. Each DRG¹¹ 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 reimbursements from the National Insurance Administration by a factor of 1.5 so that they reflect the true cost. We use the DRG weights for 2003 for all years since there have been no major changes in the treatment for colorectal cancer.

To estimate the treatment cost we use all registered care directly related to the treatment of colorectal cancer from our database¹². The data stems from the National Patient

¹⁰ Details will be published a forthcoming paper by Aas, 2007. The effect of screening on treatment cost – the case of colorectal cancer.

¹¹ The unit price of a DRG is equal to Euro 3,706 in 2003.

¹² For details on the estimation of the estimation of treatment costs, see Aas (2007).

Register with the appropriate fees, DRGs, and DRG weights. Treatment costs are estimated for asymptomatic cancers and symptomatic cancers. The estimation is done in several steps: first, calculating treatment cost per registration; second, estimating total treatment costs per month for the stage by adding the treatment cost per registration for each month for all individuals in the stage; third, estimating the average treatment costs per month for the stage by dividing total treatment cost per month for that stage by the sum of individuals diagnosed with cancer at that stage *and* alive in that specific month; fourth, adjusting the average treatment cost per month for estimated survival per month according to Dukes stage; and finally, adding together the average treatment cost per month over the whole period to arrive at the expected colorectal cancer treatment cost for either a Dukes stage or a participation group.

On average, the treatment period lasts for four years after diagnosis, see Aas (2007). In the model we assume that recurrences are indirectly captured in the treatment cost. The treatment of symptomatic cancers costs about 9,000 Euro more than asymptomatic cancers.

Table 7: Treatment cost for colorectal cancer according to date of diagnosis and year from diagnosis

Category	First	Second	Third	Fourth	Total
Symptomatic cancers	18,880	4,718	2,734	1,908	28,240
Asymptomatic cancers	16,416	2,058	493	196	19,163

In addition to treatment costs, the direct consequences also include costs related to future recommended follow-up colonoscopies. The recommendation for the majority of colorectal cancer patients is to have a five-year follow-up colonoscopy, but for some patients an earlier follow-up plus an additional colonoscopy up to ten years after screening are recommended. The last follow-up is in cycle 11. We use the costs per colonoscopy in Table 6. Probabilities are reported in Appendix A4.

Finally, the fourth category of costs is the indirect program consequences. This includes travel expenses and production loss resulting from future recommended colonoscopies and production gain due to early detection or reduced severity. If the screening prevents future incidences, this could also result in production gains. We use the estimates of travel expenses and production loss reported in Table 6 and the probabilities in Appendix A4 to calculate production loss for future recommended colonoscopies.

Table 8: Descriptive statistics on the number of days of sick leave according to age group and time of diagnosis (asymptomatic and symptomatic)

Age group	Diagnosis	Mean	N	Std. dev
50-54	Symptomatic	262.06	34	145.9
	Asymptomatic	199.83	6	199.6
55-59	Symptomatic	294.32	34	177.8
	Asymptomatic	281.92	13	119.3
60-64	Symptomatic	235.26	53	148.7
	Asymptomatic	255.67	9	114.8
Total	Symptomatic	259.39	121	157.3
	Asymptomatic	255.89	28	136.5

To estimate production gains we test whether or not there are differences in the number of days of sick leave after a cancer diagnosis between asymptomatic diagnosed cancers and symptomatic cancers. We use information from Statistics Norway about a number of social security recipients, labour market status, and number of days of sick leave to estimate the production gain. In Table 8 the number of days of sick leave is reported for individuals working at the time of diagnosis according to age group and whether the cancer was diagnosed at an asymptomatic or symptomatic stage. While there is almost no difference in number of days of sick leave according to symptomatic or asymptomatic stage for the two oldest age groups, there is a difference for individuals in the age group 50 to 54 years. This indicates that early diagnosis results in some production gains for the youngest age group. However, because the standard deviation is large, the difference is not statistically significant and we have therefore not included production gains in the model.

Let C^g be total screening costs for screening group g over all cycles. The incremental screening costs (ΔC) for screening group 1 is then given by

$$\Delta C^1 = (1+r)^{-(t-1)} [C^1 - C^7] \quad (11)$$

6. Results

In this analysis we simulate cost per life-year gained for six alternative strategies¹³. There are three age groups (50-54, 55-59, 60-64 years) and two screening interventions,

¹³ We use TreeAge Pro 2005 in the estimation of the model.

flexible sigmoidoscopy alone or in a combination with FOBT. We discount both costs and effects and apply a discount rate equal to four percent, which is according to Norwegian guidelines from The Norwegian Ministry of Finance (2005). Based on equation (6) and (11), cost per life-year gained for (CE^s) for screening group 1 will then be given by

$$CE^1 = \frac{\Delta C^1}{LYG^1} \quad (12)$$

In Table 9 the estimated life expectancy (LE^s) in years is reported for all six strategies and the control groups based on the principle of ‘intention to treat’. The expected life-years gained (LYG) are also reported. The largest gain in life expectancy is in the age group 60 to 64 years, for an individual invited to both flexible sigmoidoscopy and FOBT; the age group 55 to 59 years invited to a combination of flexible sigmoidoscopy and FOBT has the second largest gain. From the findings in Tables 1 and 3, we would expect that largest increase in life-years would be for individuals in the age groups 55 to 59 years or 60 to 64 years. The probability of dying during treatment of an asymptomatic diagnosed cancer is 5 percent each year (compared with 11.5 percent for a symptomatic diagnosed cancer). There is a large difference in life-years gained between screening with only flexible sigmoidoscopy and the combination of flexible sigmoidoscopy and FOBT. The results are driven by the difference in the probability of dying from causes other than colorectal cancer. As the samples in the different screening groups are small with regard to death, the difference can occur by chance. If, however, there is a positive relationship between the probability of dying during treatment of colorectal cancer and deaths from causes other than colorectal cancer (for instance from pneumonia), early detection may also reduce the probability of dying from other causes during the first years after the screening.

Initially, 2,632 individuals in the age group 60 to 64 years were invited to a combination of flexible sigmoidoscopy and FOBT. Given the increase in life expectancy shown in Table 9, a total number of 237 life-years are gained¹⁴. From Statistics Norway we find average life expectancy for an individual 62 years of age to be approximately 20 years; thus, approximately 12 individuals could live until the age 82¹⁵. As the number of life-years gained is zero for the age group 50 to 54 with only flexible sigmoidoscopy, reporting cost-effectiveness is not meaningful.

¹⁴ $2,632 * 0.09 = 237$ life-years gained.

¹⁵ $237/20 = 12$

Table 9 also presents the results from the cost-effectiveness analyses presented. There are four different estimations representing different cost categories. In three out of four alternatives, screening the age group 55 to 59 years with a combination of flexible sigmoidoscopy and FOBT is the most cost-effective alternative.

When only direct program costs are considered, the cost per life-year gained is Euro 1,633¹⁶. The second most cost-effective alternative is screening the age group 60 to 64 years with a combination of the two tests, closely followed by the age group 55 to 59 years examined only with flexible sigmoidoscopy. Inclusion of indirect program costs increases the cost per life-year gained to Euro 2,156, but it also changes the most cost-effective alternative to the age groups 60 to 64 years with both flexible sigmoidoscopy and FOBT. The change in the most cost-effective alternative can be explained by a higher proportion working in the age group 55 to 59 years. The difference in cost-effectiveness between the second and third most cost-effective alternatives increases since a larger proportion is working in the younger age groups.

Taking direct program consequences into consideration increases the costs per life-year gained for all screening strategies, and changes the ranking of the most cost-effective alternative. Inclusion of direct program consequences implies a reduction in cost per life-year gained for both screening strategies in the age group 55 to 59, while for the other age groups it implies an increase in cost per life-year gained. This changes the ranking of the strategies as the inclusion of treatment costs implies that the most cost-effective alternative changes to the age group 55 to 59 years with a combination of the two tests. The age group 60 to 64 years with a combination of the two tests has the second lowest cost per life-year gained. The increase in cost per life-year gained in the age group 55 to 59 years is smaller than the increase in cost per life-year gained in the age group 60 to 64 years, which can be explained by different proportions of asymptomatic diagnosed cancers. In the age group 60 to 64 years, the asymptomatic cancers constitute of a smaller proportion of the total number of diagnosed cancers than in the younger age groups (see Table 1). Direct program consequences include costs resulting from future follow-up colonoscopy. These costs will, for all alternatives, increase the cost per life-year gained and do not change the ranking of the strategies.

¹⁶ $147/0.09=1,633$

Table 9: Life-years, screening costs and costs per life-year gained according to screening strategy and groups of screening costs (monetary units in Euro)

Strategy	Effect		Cost alt. 1*		Cost alt. 2**		Cost alt. 3***		Cost alt. 4****	
	LE	LYG	Cost	CE	Cost	CE	Cost	CE	Cost	CE
C5054	16.74	-	0		0		724		724	
FS5054	16.74	0.00	137	-	189	-	1,025	-	1,034	-
COMB5054	16.76	0.02	119	5,950	172	8,600	1,005	14,050	1,013	14,450
C5559	15.37	-	0		0		948		948	
FS5559	15.41	0.04	151	3,775	208	5,200	1,155	5,175	1,169	5,525
COMB5559	15.46	0.09	147	1,633	203	2,255	1,165	2,411	1,177	2,544
C6064	13.83	-	0		0		1,040		1,040	
FS6064	13.84	0.01	153	15,300	194	19,400	1,271	23,100	1,285	24,500
COMB6064	13.92	0.09	151	1,678	194	2,156	1,259	2,433	1,271	2,567

* Cost alternative 1 includes the direct program costs

** Cost alternative 2 includes the direct and indirect program costs

*** Cost alternative 3 includes the direct and indirect program costs and direct program consequences

**** Cost alternative 4 includes the direct and indirect program costs and direct and indirect program consequences

A reduction in future incidences implies a further reduction in the cost per life-year gained. Access to additional data can help determine whether or not the screening method will prevent future incidence of cancer.

The last cost alternative consists of the indirect programme costs. These costs are related to travel expenses, the use of Laxabon® for bowel cleansing, and production loss due to time used on future recommended follow-up colonoscopies. The age group 55 to 59 years screened with a combination of flexible sigmoidoscopy and FOBT is also the most cost-effective alternative in this cost alternative.

In Table 10 the incremental cost-effectiveness ratio (ICER) based on cost alternative 4 in Table 9 is reported. The ICER is defined as the incremental cost per incremental effect. Because screening is a once-only event, all screening strategies are mutually exclusive and must be compared. The screening strategies are reported in ascending order according to cost, where costs reported are the difference in cost between a screening group and the control group. The incremental cost is the increase in cost between screening strategies¹⁷. Life-years gained (LYG) (also reported in Table 9) and incremental LYG¹⁸ are reported in columns four and five, respectively. The ICER is reported in column six¹⁹ and we see that the ICER for the age group 55 to 59 years with a combination of flexible sigmoidoscopy and FOBT is Euro 160. All the other screening strategies are dominated because the incremental cost is positive and the incremental effect is either zero or negative.

¹⁷ The incremental cost for COMB5559 is equal to 229 – 221 = 8

¹⁸ The incremental effect for COMB5559 is equal to 0.09 – 0.04 = 0.05

¹⁹ The incremental effect for COMB5559 is equal to 8/0.05 = 160

Table 10: The incremental cost-effectiveness ratio according to screening strategy. Monetary units in Euro.

Strategy	ΔC^*	Incremental cost	LYG	Incremental LYG	ICER
FS5559	221		0.04		
COMB5559	229	8	0.09	0.05	160
COMB6064	231	2	0.09	0.00	(Dominated)
FS6064	240	9	0.01	-0.08	(Dominated)
COMB5054	289	49	0.02	-0.07	(Dominated)
FS5054	310	21	0.00	-0.09	(Dominated)

*Cost alternative 4 includes the direct and indirect program costs and direct and indirect program consequences

7. Sensitivity analysis

The estimation of life-years gained and costs in the model consists of several factors. Some of these factors are uncertain. In this section we want to test whether the inclusion of uncertainty changes the findings from Section 6, and give an indication of which type of uncertainty tends to most affect the findings.

Two types of sensitivity analysis are included in this paper. First, we use deterministic sensitivity analysis to see how one factor at a time influences cost-effectiveness. Second, we include a probabilistic sensitivity analysis (PSA), which is a parametric method, as we make assumptions about the distribution. Both the U.S. panel on cost-effectiveness analysis (Gold et al. (1996)) and the National Institute of Clinical Excellence (NICE) in the UK (2006) 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.

In Table 11 the results from the deterministic sensitivity analysis are presented. All of the alternatives are based on the fourth cost alternative (all costs included) from Table 9 in Section 6. In alternative 1 we have increased the value in the fee-for-service for sigmoidoscopy and colonoscopy to account for uncertainty in the estimate of the true marginal cost. Alternative 1 includes the cost per life-year gained by assuming a doubling of the fee-for-service (Samdata somatikk, 2004). The cost per life-year gained is increased for all strategies, but the ranking remains unchanged.

The simulation of treatment costs is based on stage of advancement. Because treatment costs increase with stage of advancement, the treatment costs for asymptomatic

cancers is lower than for symptomatic cancers²⁰. Stage of advancement is measured in groups and not on a continuous scale, thus there will be variations in costs within each group and our predictions will be the expected costs of recommended treatment. In addition, 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 predictions are based on fees and DRGs. These are average predictions and in some situations do not reflect the true treatment cost for a particular patient. For example, the same type of treatment according to the DRG for two individuals of 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 diseases concurrent to the treatment for colorectal cancer may also result in variations in treatment costs. Alternative 2 in Table 10 shows the cost-effectiveness based on the assumption that the treatment costs for asymptomatic cancers is equal to the treatment costs for symptomatic cancers. This assumption increases the cost per life-year gained for all screening strategies, for the most cost-effective alternative by about Euro 5,500.

Table 11: The effect on costs per life-year gained of changing the value of some of the factors used in the model according to screening strategy (monetary units in Euro).

Strategy	Alt 1		Alt 2		Alt 3		Alt 4	
	ΔC	CE	ΔC	CE	ΔC	CE	LE	CE
C5054	724		724		724		28.79	
FS5054	1,078	-	1,773	-	1,031	-	28.78	-
COMB5054	1,051	16,350	1,749	51,250	1,010	14,300	28.80	31,000
C5559	948		948		948		25.23	
FS5559	1,218	6,750	1,862	22,850	1,167	5,475	25.29	3,683
COMB5559	1,223	3,056	1,714	8,511	1,175	2,522	25.38	1,527
C6064	1,040		1,040		1,040		21.41	
FS6064	1,335	29,500	1,874	83,400	1,291	25,100	21.43	12,250
COMB6064	1,331	3,233	1,866	9,178	1,277	2,633	21.60	1,215

Alt 1: The cost of sigmoidoscopy and colonoscopy is 240 Euro and 300 Euro, respectively.

Alt 2: Equal treatment costs for asymptomatic and symptomatic diagnosed cancers

Alt 3: Production loss per individual estimated to be equal to 225 Euro for all three age groups

Alt 4: No discounting of health benefits

The third alternative includes a different prediction of the production loss resulting from time required for the screening and the colonoscopy. The estimates used in the simulation of total screening costs are based on Aas (2004, 2005), however, not all participants answered the questionnaire so the estimates could be biased. We therefore include

²⁰ For details, see Aas (2007).

an estimate from another Norwegian study (Hem, 2000) where the average wage per day is equal to Euro 225. From Table 11 we see that this change implies a very small to change the cost-effectiveness.

Although the recommended procedure is to discount both costs and health effects at the same rate (NICE, 2006 and Drummond et al., 2005), there are arguments for not discounting health benefits at all or for doing so using a lower discount rate than for costs (see Drummond et al., 2005). We have included an alternative where the health benefits are not discounted in order to see the magnitude of the effect of discounting on the health benefits. Comparing the findings in Table 11 with the life-expectancy in Table 9, we see that life-expectancy for most alternatives will increase by eight to twelve life years, and that all cost-effectiveness ratios decline. The ranking is unchanged.

In Section 4 we concluded that estimates of the differences in number of days of sick leave are too uncertain to be included in the model. Still, there were some indications in Table 8 that there were potential production gains in the age group 50 to 54 years. We have therefore tried to estimate the difference in number of days of sick leave that would be needed to change the ranking of the cost-effectiveness in Table 9. In order for the age group 50 to 54 years with both flexible sigmoidoscopy and FOBT to be ranked as the most cost-effective strategy, the difference in number of days of sick leave would have to be 505 days.

From the deterministic sensitivity analysis we see that there are changes in the cost-effectiveness levels and the rankings, but the changes are relatively small. Thus, any decisive change in the cost-effectiveness must stem from uncertainty in the estimates of the transition probabilities.

In the probabilistic sensitivity analysis we include the uncertainty in the cost of sigmoidoscopy and colonoscopy, variation in the treatment costs, together with uncertainty in the transition probabilities. The cost of sigmoidoscopy and colonoscopy are assumed to be uniformly distributed with variation from 1.5 to 2 times higher than the fee for service reimbursement from the National Insurance Administration (Samdata somatikk, 2004).

With regard to the distribution of the treatment costs, we use findings from the bootstrap in Aas (2007). Bootstrapping is a method for assigning measures of accuracy to statistical estimates, in the present case the treatment cost estimates. We use bootstrapping to estimate the standard error (see Efron and Tibshirani 1993) of the treatment cost shown in Table 7. The bootstrap standard error is estimated by using the original samples. A bootstrap sample (equal to n) of treatment cost in year 1 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 treatment cost in year 1) from each bootstrap sample and calculate the standard deviation. Mean and 95 percent confidence intervals are presented in Table 12 according to asymptomatic or symptomatic diagnosed cancer and year from diagnosis. The confidence interval is overlapping for the two first years. Because colorectal cancer treatment cost only has positive values, we use gamma distributions to represent uncertainty (Spiegelhalter et al., 2004). To estimate the coefficients in the gamma distribution, we use calculated mean and variance from the bootstrap. The assumptions used in the PSA are presented in Appendix A5.

Table 12: Mean and 95 percent confidence intervals for mean treatment costs for asymptomatic and symptomatic diagnosed cancers according to year from diagnosis. Numbers in Euro.

Year	Asymptomatic		Symptomatic	
	Mean	95 percent CI	Mean	95 percent CI
1	16,416	(13,638 – 20,127)	18,880	(17,614 – 20,461)
2	2,058	(923 – 4,161)	4,718	(3,509 – 6,385)
3	493	(238 – 1,091)	2,734	(1,608 – 4,692)
4	196	(91 – 463)	1,908	(582 – 6,837)

We include uncertainty in the transition probabilities by letting the transition probabilities for each stage vary by ten percent, and let the variation be represented by a uniform distribution. For each stage, the estimated coefficients represent by a minimum and a maximum value. We then use a Monte Carlo simulation to estimate the uncertainty in the parameters by selecting values from the distributions. Monte Carlo simulation in TreeAge recalculates the model repeatedly as a form of (deterministic) sensitivity analysis. We assume that the parameters are independent. The results from the PSA analysis are presented in Table 13.

The first column in Table 13 presents the mean life-years for all groups. The second column reports the 95 percent confidential interval for life-years for the six screening groups. All confidence intervals are overlapping with the mean life-years for the corresponding control group. For instance, the mean life-years in the age group 55 to 59 years are 15.36 for the control group. The 95 percent confidential interval for the mean life-years for the age group 55 to 59 years with only flexible sigmoidoscopy and the combination of the two tests are 15.14 to 15.70 and 15.17 to 15.74, respectively. The third column presents the mean costs from the PSA analysis, while the fourth column reports the 95 percent confidence interval for

the screening costs for the six screening groups. For all screening strategies, the costs are significantly higher than the control group. The results from the PSA imply that the results are statistically non-significant for all screening groups, both with respect to costs and life-expectancy.

Table 13: Mean and 95 percent confidential interval from PSA of screening cost and life-year according to screening strategy. Numbers in Euro.

Strategy	Mean life-years	95 percent CI	Mean costs	95 percent CI
C5054	16.74	-	724	
FS5054	16.74	(16.52 – 16.96)	1,032	(940 – 1,132)
COMB5054	16.75	(16.52 – 16.95)	1,011	(896 – 1,145)
C5559	15.36		948	
FS5559	15.42	(15.14 – 15.70)	1,167	(1,070 – 1,271)
COMB5559	15.46	(15.17 – 15.74)	1,180	(1,054 – 1,317)
C6064	13.83		1,040	
FS6064	13.84	(13.53 – 14.19)	1,284	(1,175 – 1,402)
COMB6064	13.92	(13.61 – 14.26)	1,269	(1,147 – 1,404)

8. Discussion

As pointed out in the introduction, NORCCAP is one of four RCTs that evaluate once-only flexible sigmoidoscopy, but several cohort studies have also been conducted. Frazier et al. (2000) find that the cost per life-year gained for a once-only flexible sigmoidoscopy at the age of 55 is \$ 1,200. Leshno et al. (2003) find that the cost per life-year gained is about \$ 1,237 for a combination of annual FOBT and flexible sigmoidoscopy every fifth year when only those participants with high-risk polyps are referred to a follow-up colonoscopy. If the criterion for a follow-up colonoscopy is changed to any adenomatous polyp regardless of size or histology, the cost per life-year gained is \$ 2,486. Sonnenberg et al (2000) find that the cost per life-year gained is \$ 74,032 for a combination of annual FOBT and flexible sigmoidoscopy every fifth year. All of these studies include direct program costs and consequences, but not indirect program costs and consequences.

We know from RCT that FOBT significantly reduces cancer mortality (Mandel et al., 1993, Hardcastle et al., 1996, Kronborg et al., 1996 and 2004). The reduction is between 16 and 20 percent. Gyrd-Hansen et al. (1998) find that the cost per life-year gained is Euro

2,277²¹ when screening individuals 65 to 74 years every second year. This estimate does not include treatment costs, which would be expected to reduce the cost per life-year gained. Whynes et al. (1998) finds that the cost per QALY gained is between Euro 2,164 and Euro 8,977 depending on time horizon in the analysis and the costs included²².

In this study, cost-effectiveness analysis is applied to estimate costs per life-year gained. Estimating the health effect in life-years gained implies that every year the individual is not dead counts equally. It is a simple measure to capture, but it only includes the effect of screening on mortality and not the gain from screening on morbidity. Drummond et al. (2005) present some situations where it is preferable to use quality adjusted life-years (QALY). For example, when the expected health effects include both mortality and morbidity, and when it is relevant to make comparisons with other programs using QALYs as a health measure. A QALY represents a measure for which improvement in quality of life and not perfect health is the main outcome. In this study, the model counts a year not dead as one year, while if we had included QALYs in the analysis, a year under treatment would not be counted as one year. Introducing QALYs as the health measure will have an uncertain effect on the cost-effectiveness because it will affect the health outcome in several ways: first, participation in screening will imply a reduction in quality of life, as participation could heighten anxiety. Second, during treatment for colorectal cancer the quality of life will be reduced. An asymptomatic cancer is less severe; hence, quality of life should be expected to be higher for individuals diagnosed with asymptomatic cancer than with a symptomatic cancer. Finally, screening with flexible sigmoidoscopy and colonoscopy is expected to reduce the prevalence of colorectal cancer. The first effect will increase the cost per QALY, the second and third effects will reduce the cost per QALY. The total effect is therefore uncertain. We know from a cost-effectiveness analysis of a follow-up program of colorectal treatment, that the QALY of Dukes B and Dukes C are measured to 0.83, see Norum and Olsen (1997). As QALYs are often used in economic evaluations, using life-years gained makes it difficult to compare different strategies or different health programs; thus, further research should also include an estimate with QALYs.

Two types of biases can occur in an evaluation of cost per life-year gained of a screening program: length bias and lead-time bias. Length bias occurs because screen-detected cancers are prone to be less aggressive cancers. An aggressive cancer has a short asymptomatic period, defined as the period in which the cancer can be diagnosed with a

²¹ The costs are in 1993 DKK and Euro 1 = DKK 7.466

²² The costs are in £ 1995-96 and Euro 1 = £ 0.633

screening test. Therefore, most aggressive cancers are diagnosed due to symptoms. The less aggressive cancers are over-represented in the screening cohort because they have a longer asymptomatic period and are more likely to be present (detectable) at any particular point in time (time of the screening examination). As the probability of cure and survival is higher for a patient with less aggressive cancer than for patients with more aggressive cancers, screening may not have an effect on survival. Lead-time bias occurs when screening falsely prolongs survival. Through screening, the cancer is diagnosed earlier than when diagnosed due to symptoms, but the outcome in terms of date of death remains unchanged by screening intervention. Thus, the individual will gain no additional life-years. 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.

Lead time bias can only influence the findings in this model because of potential bias in the estimation of the transition from treatment of asymptomatic diagnosed colorectal cancer to death. In the estimation of survival we normalise all the dates of diagnosis to zero, i.e. survival is measured as the time alive from the time of diagnosis. Thus we can not be sure whether increased survival is due to earlier diagnosis or true prolonged survival. To adjust for this potential bias, we have run the model with the assumption that the transition from treatment of asymptomatic diagnosed colorectal cancer to death is the same as for symptomatic diagnosed cancers. Life-years gained changes by definition for all age groups, but with two decimals the change can only be seen in the age group 50 to 54 years with a reduction of 0.01 for both screening groups. This indicates that lead time bias is not a serious problem in this cost-effectiveness analysis.

A multinomial logit is used to estimate the transition from well to colorectal cancer or death. If observations for the same individual are not independent over periods, the estimated transition will be biased. For example, if the probability of staying well depends on individual characteristics the observations will not be independent. We tried to estimate a model that took into account that the observations may not be independent, but are not included because finding proper starting values in the maximum likelihood estimations was problematic. Future research should focus on this problem in order to further improve the modelling.

Whether false positives are a problem in this analysis depends on the definition of false positive. If false positive is defined as undergoing treatment of colorectal cancer without having colorectal cancer, there are no false positives. But, if false positive is defined as the proportion of the individuals referred to a work-up colonoscopy that never would have developed colorectal cancer, false positives do exist in this analysis. In the NORCCAP study

the criteria for a work-up colonoscopy was a positive flexible sigmoidoscopy and/or a positive FOBT. A positive sigmoidoscopy is defined as having an adenoma ≤ 10 mm and/or having a polyp ≥ 10 mm (it is more than 95 percent certain that such a polyp is an adenoma). As only a proportion of these adenomas and polyps develop into cancer in the future, many are examined with colonoscopy without any personal benefit. How to define the inclusion criteria for a work-up colonoscopy requires that the proportion of false positives is balanced with the proportion of false negatives. If the number of individuals referred to work-up colonoscopy is reduced the number of false positives will decline, while the number of false negatives will increase.

As a consequence of reducing the incidence of colorectal cancer and postponing deaths, individuals will, on average, live longer. There are several changes in resource allocation that are not included in the analyses, such as increased use and need of: nursing homes, home nursing care and help services, terminal care, and visits to a general practitioner. There has been a discussion in the literature about whether or not these costs should be included in the cost-effectiveness analysis, see Garber and Phelps (1997), Meltzer (1997), Weinstein et al. (1997) and Johannesson and Meltzer (1998). Obtaining estimates of these costs is difficult because of the lack of available data. Including these future costs will increase the cost per life-year gained in all health care interventions, thus inclusion of future costs in screening for colorectal cancer will not necessarily entail that screening becomes less preferable compared with other interventions. On the other hand, these future costs will have a greater impact on the cost per life-year gained for the age group 60 to 64 than for the age group 55 to 59 years and 50 to 54 years due to discounting. Future costs in the last years of life will, for instance, be discounted for 10 more years in the age group 50 to 54 years than in the age group 60 to 64 and thus weigh relatively less in the cost per life-years gained.

9. Concluding remarks

The results of this study indicate that screening for colorectal cancer by means of FOBT combined with flexible sigmoidoscopy is cost-effective for the age groups 55 to 59 years and 60 to 64 years depending on which screening costs are included in the model. When the screening costs include direct program costs, screening the age group 55 to 59 years is the most cost-effective, while when indirect direct program costs are included screening the age group 60 to 64 years with a combination of flexible sigmoidoscopy and FOBT is most cost-

effective. Inclusion of treatment costs implies that screening with a combination of flexible sigmoidoscopy and FOBT in the age group 55 to 59 years is most cost-effective.

As the differences in the transition probabilities and costs are non-significant, the cost-effectiveness analyses are not robust. If the robustness improves with the availability of additional data, the insurer would have a stronger argument for introducing screening to the age group 55 to 59 years in the general population. In the model any differences between the screening groups and the control group with regard to the probability of developing colorectal cancer are only included for the six first cycles. Thus the effect of screening on future probability of developing colorectal cancer is not included. Additional data will continually update this transition from well to colorectal cancer and any effect of screening on the probability of developing cancer will gradually be included.

To improve our understanding of the consequences of once-only screening for colorectal cancer with flexible sigmoidoscopy and FOBT, there should be more research on the dynamics in the transitions between different states. Access to more data can give us the information needed. Further, there is much information to be obtained from the different subsamples, e.g. participants, non-participants, and those excluded. If the probability of developing cancer among non-participants is higher than in the control group, the insurer has an argument for trying to increase participation in screening.

References

- Aas, E., 2004. Hvem er det som møter frem til screening? Økonomisk Forum. 2004:7, 34 – 44.
- Aas, E., 2005. Pecuniary compensation increases the participation rate in screening for colorectal cancer. HERO-report.
- Aas, E., 2007. The effect of screening on treatment costs – the case of colorectal cancer. Unpublished paper.
- Atkin, W.S., Cook, C.F., Cuzick, J., Edwards, R., Northover, J.M.A., Wardle, J., 2002. Single flexible sigmoidoscopy screening to prevent colorectal cancer: baseline findings of UK multicentre randomised trial. *Lancet* (359). 1291 – 1298.
- Bretthauer, M., Gondal, G., Larsen, I.K., Carlsen, E., Eide, T.J., Grotmol, T., Skovlund, E., Tveit, K.M., Vatn, M.H., Hoff, G., 2002. Design, Organization and Management of a Controlled Population Screening Study for Detection of Colorectal Neoplasia. *Scandinavian Journal of Gastroenterology* 5. 569 – 573.
- Cancer Registry of Norway, 2003, “Cancer in Norway 2003, (www.kreftregisteret.no/forekomst%202003/Kreft_i_Norge2003)
- Drummond, M.F., Sculpher, M.J., Torrance, G.W., O’Brian, B.J., Stoddardt, G.L., 2005. *Methods for the Economic evaluation of Health Care Programmes*. Oxford University Press. New York.
- Efron, B., Tibshirami, R.J, 1993. *An introduction to the Bootstrap*. Chapman & Hall.
- Fenn, P., McGuire, A., Backhouse, A.Jones, D., 1996. Modelling programme costs in economic evaluation. *Journal of Health Economics* (15), 115 – 125.
- Frazier, A.L., Colditz, G.A., Fuchs, C.S., Kuntz, K.M., 2000. Cost-Effectiveness of Screening for Colorectal Cancer in the General Population. *JAMA* (15), 1954 – 1961.
- Garber, A.M., Phelps, C.E., 1997. Economic foundation of cost-effectiveness analysis. *Journal of Health Economics* (16), 1 – 31.
- Gold, M.R., Siegel, J.E., Russell, L.B., Weinstein, M.C., 1996. *Cost-effectiveness in Health and Medicine*. Oxford University Press. New York.
- Gondal, G., Grotmol, T., Hofstad, B., Bretthauer, M., Eide, T.J., Hoff, G., 2003. The Norwegian Colorectal Cancer Prevention (NORCCAP) Screening Study – Baseline Findings and Implementation for Clinical Work-up in Age Groups 50 – 64 Years. *Scandinavian Journal of Gastroenterology* (6). 635 – 642.
- Greene, W., 2002. *Econometric analysis*. Fifth edition. Prentice-Hall Inc.

- Gyrd-Hansen, D., Søgaaard, J., Kronborg, O., 1998. Colorectal cancer screening: Efficiency and effectiveness. *Health Economics* (7), 9 – 20.
- Hardcastle J.D., Chamberlain, J.O., Robinson, M.H.E., Moss, S.M., Amar, S.S., Balfour, T.W., et al., 1996. Randomised controlled trial of faecal occult blood screening for colorectal cancer. *Lancet* (348), 1472-7.
- Hem, K.G., 2000. Økonomiske konsekvenser av sykefravær (Economic consequences of sick leave). STFT78 A00508. SINTEF Unimed.
- Johannesson, M., Meltzer, D., 1998. Some reflections on cost-effectiveness analysis. *Health Economics* (7), 1 – 7.
- Kronborg, O., Fenger, C., Olsen, J., Jørgensen, O.D., Sødergaard, O., 1996. Randomized study of screening for colorectal cancer with faecal occult-blood test. *Lancet* (348). 1467 – 1471.
- Kronborg, O., Jørgensen, O.D., Fenger, C., Rasmussen, M., 2004. Randomized study of biennial screening for with faecal occult blood test: results after nine screening rounds. *Scand Journal of Gastroenterol* (39). 846-51.
- Leshno, M, Halpern, Z., Arber, N., 2003. Cost-Effectiveness of Colorectal Cancer Screening in the Average Risk Population. *Health Care Management Science* (6), 165-174.
- Mandel, J.S., Bond, J.H., Church, T.R., Snover, D.C., Bradley, G.M., Schuman, L.M., et al, 1993. Reducing mortality from colorectal cancer by screening for fecal occult blood. Minnesota Colon Cancer Control Study. *New England Journal of Medicine* 19, 1365-71.
- Meltzer, D, 1997. Accounting for future costs in medical cost-effectiveness analysis. *Journal of Health Economics*. 16, 33 – 64.
- National Institute for Health and Clinical Excellence (NICE), 2006, “The guidelines Manual”, London: National Institute for Health and Clinical Excellence. Available from www.nice.org.uk
- Norsk Gastrointestinal Cancer Gruppe (NGICG), 1999. Kolorektalcancer og analcancer. En veiledning for leger. PDC Tangen a.s. Aurskog. <http://www.ngicg.no/gronnbok/gronnbok.htm>.
- Norum, J, JA Olsen, 1997. A cost-effectiveness approach to the Norwegian follow-up programme in colorectal cancer. *Annals of Oncology*. 8, 1081 – 1087.
- Samdata somatikk, 2004. Sammenligningsdata for den somatiske spesialisthelsetjenesten 2003. SINTEF Helse rapport 1/04.

- Segnan, N., Senore, C., Andreoni, B., Aste, H., Bonelli, L., Crosta, C., et al., 2002. Baseline finding of the Italian multicenter randomised controlled trial of ‘Once-Only sigmoidoscopy’ SCORE. *Journal of National Cancer institute* (94), 1763 – 1772.
- Sonnenberg, A, F. Delcò, J.M. Inadomi. “Cost-Effectiveness of Colonoscopy in Screening for Colorectal Cancer,” *Annals of Internal Medicine*, 2000; 8, 573-584.
- Spiegelhalter D.J, Abrams, K.R., Myles, J.P., 2004. *Bayesian Approaches to Clinical Trials and Health-Care Evaluation*. John Wiley & Sons Ltd. England.
- STATA release 8, 2003. *Users guides*. A Stata Press Publication. Texas.
- Statistics Norway, 2004. *Dødsårsaksregisteret (Population statistics, deaths)*.
<http://www.ssb.no/emner/02/02/10/dode/>
- The Norwegian Ministry of Finance, 2005. *Veileder i samfunnsøkonomiske analyser (Guidelines in economic evaluation)*.
http://odin.dep.no/filarkiv/258190/Veileder_samf.ok.analyser_2005.pdf.
- TreeAge pro, 2005. *Users manual*. TreeAge Software inc.
- Weinstein, M.C., Manning, W.G., 1997. Theoretical issues in cost-effectiveness analysis. *Journal of Health Economics* (16), 121 – 128.
- Weissfeld, J.L., Schoen, R.E., Pinsky P.E., Bresalier R.S., Church, T., Yurgalevitch S., Austin, J.H., Prorok, P.C., Gohagen, J.K., 2002. Flexible sigmoidoscopy in the PLCO cancer screening trial: results from the baseline screening examination of a randomized trial. *Journal of National Cancer Institute* (13), 568 – 573.
- Whynes, D., Neilson, A.R., Walker, A.R., Hardcastle, J.D., 1998. “Faecal occult blood screening for colorectal cancer: Is it cost-effective? *Health Economics* (7), 21 – 29.

Appendix:

A1. The sample

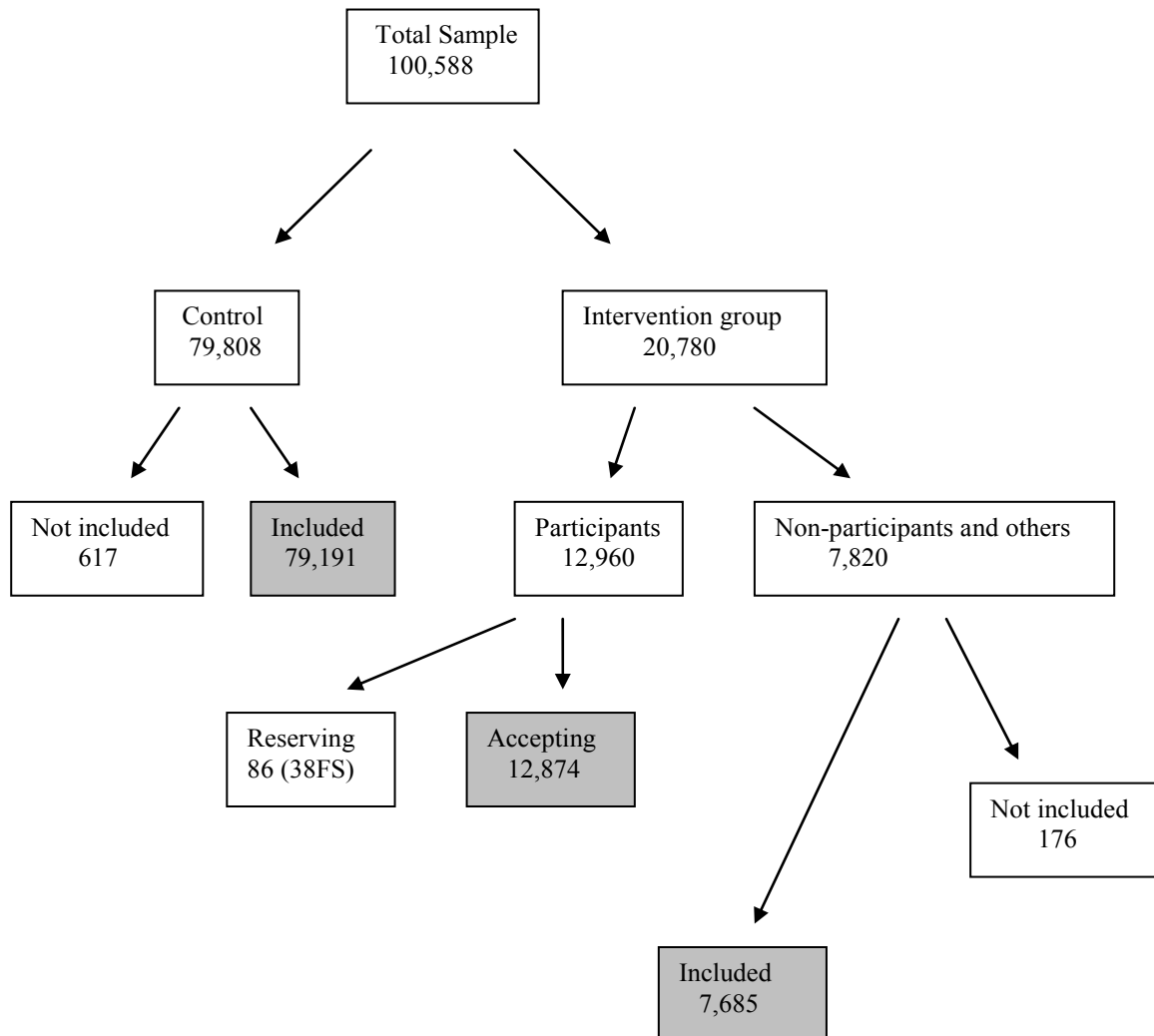


Figure A1: Number of individuals in the study according to participation status and groups included in the analysis.

Telemark:

1999:

Intervention (half of the cohort): 1935, 1936, 1938, 1940, 1942, 1944

Control (half of the cohort): 1935, 1936, 1938, 1940, 1942, 1944

2000:

Intervention (half of the cohort): 1937, 1939, 1941, 1943, 1945

Control (half of the cohort): 1937, 1939, 1941, 1943, 1945

2001:

Intervention (half of the cohort): 1946, 1947, 1948, 1949, 1950

Control (half of the cohort): 1946, 1947, 1948, 1949, 1950

Oslo:

1999:

Intervention (1/6 of the cohort): 1935, 1936, 1938, 1940, 1942, 1944

Control (5/6 of the cohort): 1935, 1936, 1938, 1940, 1942, 1944

2000:

Intervention (1/6 of the cohort): 1937, 1939, 1941, 1943, 1945

Control (5/6 of the cohort): 1937, 1939, 1941, 1943, 1945

2001:

Intervention (1/6 of the cohort): 1946, 1947, 1948, 1949, 1950

Control (5/6 of the cohort): 1946, 1947, 1948, 1949, 1950

Further assumptions:

CRC and deaths are included from the year the individuals either were invited to screening or were assumed to be part of the control group. For the age cohorts 1935, 1936, 1938, 1940, 1942 and 1944 we include all cancers and deaths from 01.01.99 for both intervention and control group; for the age cohorts 1937, 1939, 1941, 1943 and 1945, we include cancers and deaths from 01.01.00 for both intervention and control group; and for the age cohorts 1946, 1947, 1948, 1949 and 1950, we include cancers and deaths from 01.01.01 for both intervention and control group.

A2. Fractions applied in the model

Table A1: Fractions applied in the model according to screening strategy and age group²³.

Probability	FS5054	COMB5054	FS5559	COMB5559	FS6064	COMB6064
<i>a</i>	0.59	0.57	0.66	0.62	0.66	0.63
<i>h</i>	0.09	0.08	0.12	0.11	0.13	0.12
<i>c</i>	0.00162	0.0013	0.00246	0.0202	0.00237	0.00263
<i>m</i>	0	0.51	0	0.51	0	0.51

²³ FS refers to flexible sigmoidoscopy and COMB refers to the combination of flexible sigmoidoscopy and FOBT

A3. Descriptive statistics

Table A2: The estimated transition from well to death from causes other than colorectal cancer applied in the model according screening strategy, age group and stage.

Stage	50 to 54 years			55 to 59 years			60 to 64 years		
	C	FS	COMB	C	FS	COMB	C	FS	COMB
0	0.00205	0.00207	0.00180	0.0047	0.0044	0.0039	0.0072	0.0070	0.0063
1	0.00222	0.00224	0.00195	0.0051	0.0047	0.0042	0.0078	0.0075	0.0068
2	0.00241	0.00242	0.00211	0.0055	0.0051	0.0046	0.0084	0.0082	0.0073
3	0.00260	0.00262	0.00228	0.0060	0.0055	0.0050	0.0091	0.0088	0.0079
4	0.00282	0.00284	0.00247	0.0065	0.0060	0.0054	0.0099	0.0096	0.0086
5	0.00305	0.00307	0.00267	0.0070	0.0065	0.0058	0.0107	0.0103	0.0093
6	0.00576	0.00576	0.00576	0.0079	0.0079	0.0079	0.0136	0.0136	0.0136
7	0.00585	0.00585	0.00585	0.0101	0.0101	0.0101	0.0157	0.0157	0.0157
8	0.00706	0.00706	0.00706	0.0105	0.0105	0.0105	0.0172	0.0172	0.0172
9	0.00697	0.00697	0.00697	0.0122	0.0122	0.0122	0.0192	0.0192	0.0192
10	0.00706	0.00706	0.00706	0.0128	0.0128	0.0128	0.0212	0.0212	0.0212
11	0.00793	0.00793	0.00793	0.0136	0.0136	0.0136	0.0230	0.0230	0.0230
12	0.01007	0.01007	0.01007	0.0157	0.0157	0.0157	0.0261	0.0261	0.0261
13	0.01045	0.01045	0.01045	0.0172	0.0172	0.0172	0.0285	0.0285	0.0285
14	0.01220	0.01220	0.01220	0.0192	0.0192	0.0192	0.0330	0.0330	0.0330
15	0.01282	0.01282	0.01282	0.0212	0.0212	0.0212	0.0365	0.0365	0.0365
16	0.01356	0.01356	0.01356	0.0230	0.0230	0.0230	0.0394	0.0394	0.0394
17	0.01574	0.01574	0.01574	0.0261	0.0261	0.0261	0.0453	0.0453	0.0453
18	0.01716	0.01668	0.01668	0.0285	0.0285	0.0285	0.0555	0.0555	0.0555
19	0.01924	0.01876	0.01876	0.0330	0.0330	0.0330	0.0622	0.0622	0.0622
20	0.02119	0.02119	0.02119	0.0365	0.0365	0.0365	0.0679	0.0679	0.0679
21	0.02298	0.02298	0.02298	0.0394	0.0394	0.0394	0.0722	0.0722	0.0722
22	0.02611	0.02611	0.02611	0.0453	0.0453	0.0453	0.0863	0.0863	0.0863
23	0.02855	0.02779	0.02779	0.0555	0.0555	0.0555	0.0917	0.0917	0.0917
24	0.03299	0.03223	0.03223	0.0622	0.0622	0.0622	0.1033	0.1033	0.1033
25	0.03648	0.03648	0.03648	0.0679	0.0679	0.0679	0.1144	0.1144	0.1144
26	0.03942	0.03942	0.03942	0.0722	0.0722	0.0722	0.1342	0.1342	0.1342
27	0.04528	0.04528	0.04528	0.0863	0.0863	0.0863	0.1487	0.1487	0.1487
28	0.05547	0.05499	0.05499	0.0917	0.0917	0.0917	0.1609	0.1609	0.1609
29	0.06218	0.06170	0.06170	0.1033	0.1033	0.1033	0.1795	0.1795	0.1795
30	0.06791	0.06791	0.06791	0.1144	0.1144	0.1144	0.2031	0.2031	0.1605
31	0.07217	0.07217	0.07217	0.1342	0.1342	0.1342	0.2122	0.2122	0.1791
32	0.08630	0.08630	0.08630	0.1487	0.1487	0.1487	0.2404	0.2404	0.2031
33	0.09169	0.09001	0.09001	0.1609	0.1609	0.1609	0.2504	0.2504	0.2122
34	0.10335	0.10167	0.10167	0.1795	0.1795	0.1795	0.2854	0.2854	0.2404
35	0.11441	0.11441	0.11441	0.2031	0.2031	0.2031	0.3204	0.3204	0.2504
36	0.13418	0.13418	0.13418	0.2122	0.2122	0.2122	0.2854	0.2854	0.2854

Table A3: The estimated transition from well to colorectal cancer applied in the model according to screening strategy, age group and stage.

Stage	50 to 54 years			55 to 59 years			60 to 64 years		
	C	FS	COMB	C	FS	COMB	C	FS	COMB
0	0.00027	0.00028	0.00027	0.00071	0.00039	0.00047	0.00125	0.00119	0.00105
1	0.00029	0.00030	0.00029	0.00075	0.00042	0.00050	0.00133	0.00128	0.00112
2	0.00031	0.00032	0.00031	0.00081	0.00044	0.00054	0.00142	0.00136	0.00120
3	0.00033	0.00034	0.00033	0.00086	0.00047	0.00057	0.00152	0.00146	0.00128
4	0.00035	0.00036	0.00035	0.00092	0.00051	0.00061	0.00162	0.00156	0.00137
5	0.00037	0.00039	0.00038	0.00098	0.00054	0.00065	0.00173	0.00166	0.00146
6	0.00089	0.00089	0.00089	0.00140	0.00140	0.00126	0.00227	0.00227	0.00227
7	0.00140	0.00140	0.00140	0.00227	0.00227	0.00204	0.00313	0.00313	0.00313
8	0.00140	0.00140	0.00140	0.00227	0.00227	0.00204	0.00313	0.00313	0.00313
9	0.00140	0.00140	0.00140	0.00227	0.00227	0.00204	0.00313	0.00313	0.00313
10	0.00140	0.00140	0.00140	0.00227	0.00227	0.00204	0.00313	0.00313	0.00313
11	0.00140	0.00140	0.00140	0.00227	0.00227	0.00204	0.00313	0.00313	0.00313
12	0.00227	0.00227	0.00227	0.00313	0.00313	0.00282	0.00413	0.00413	0.00413
13	0.00227	0.00227	0.00227	0.00313	0.00313	0.00282	0.00413	0.00413	0.00413
14	0.00227	0.00227	0.00227	0.00313	0.00313	0.00282	0.00413	0.00413	0.00413
15	0.00227	0.00227	0.00227	0.00313	0.00313	0.00282	0.00413	0.00413	0.00413
16	0.00227	0.00227	0.00227	0.00313	0.00313	0.00282	0.00413	0.00413	0.00413
17	0.00313	0.00313	0.00313	0.00413	0.00413	0.00372	0.00476	0.00476	0.00476
18	0.00313	0.00313	0.00313	0.00413	0.00413	0.00372	0.00476	0.00476	0.00476
19	0.00313	0.00313	0.00313	0.00413	0.00413	0.00372	0.00476	0.00476	0.00476
20	0.00313	0.00313	0.00313	0.00413	0.00413	0.00372	0.00476	0.00476	0.00476
21	0.00313	0.00313	0.00313	0.00413	0.00413	0.00372	0.00476	0.00476	0.00476
22	0.00413	0.00413	0.00413	0.00476	0.00476	0.00428	0.00464	0.00464	0.00464
23	0.00413	0.00413	0.00413	0.00476	0.00476	0.00428	0.00464	0.00464	0.00464
24	0.00413	0.00413	0.00413	0.00476	0.00476	0.00428	0.00464	0.00464	0.00464
25	0.00413	0.00413	0.00413	0.00476	0.00476	0.00428	0.00464	0.00464	0.00464
26	0.00413	0.00413	0.00413	0.00476	0.00476	0.00428	0.00464	0.00464	0.00464
27	0.00476	0.00476	0.00476	0.00464	0.00464	0.00418	0.00464	0.00464	0.00464
28	0.00476	0.00476	0.00476	0.00464	0.00464	0.00418	0.00464	0.00464	0.00464
29	0.00476	0.00476	0.00476	0.00464	0.00464	0.00418	0.00464	0.00464	0.00464
30	0.00476	0.00476	0.00476	0.00464	0.00464	0.00418	0.00464	0.00464	0.00464
31	0.00476	0.00476	0.00476	0.00464	0.00464	0.00418	0.00464	0.00464	0.00464
32	0.00464	0.00464	0.00464	0.00464	0.00464	0.00418	0.00464	0.00464	0.00464
33	0.00464	0.00464	0.00464	0.00464	0.00464	0.00418	0.00464	0.00464	0.00464
34	0.00464	0.00464	0.00464	0.00464	0.00464	0.00418	0.00464	0.00464	0.00464
35	0.00464	0.00464	0.00464	0.00464	0.00464	0.00418	0.00464	0.00464	0.00464
36	0.00464	0.00464	0.00464	0.00464	0.00464	0.00418	0.00464	0.00464	0.00464

Table A4: The estimated transition from colorectal cancer to death for symptomatic diagnosed cancers applied in the model according to time from diagnosis, age group and stage.

Stage	Symptomatic diagnosed cancers											
	Year 1			Year 2			Year 3			Year 4		
	5054	5559	6064	5054	5559	6064	5054	5559	6064	5054	5559	6064
0	0.123	0.123	0.123	0.123	0.123	0.123	0.123	0.123	0.123	0.123	0.123	0.123
1	0.123	0.123	0.123	0.123	0.123	0.123	0.123	0.123	0.123	0.123	0.123	0.123
2	0.123	0.123	0.123	0.123	0.123	0.123	0.123	0.123	0.123	0.123	0.123	0.123
3	0.123	0.123	0.123	0.123	0.123	0.123	0.123	0.123	0.123	0.123	0.123	0.123
4	0.123	0.123	0.123	0.123	0.123	0.123	0.123	0.123	0.123	0.123	0.123	0.123
5	0.123	0.123	0.123	0.123	0.123	0.123	0.123	0.123	0.123	0.123	0.123	0.123
6	0.227	0.227	0.227	0.078	0.078	0.078	0.051	0.051	0.051	0.035	0.035	0.035
7	0.227	0.227	0.227	0.078	0.078	0.078	0.051	0.051	0.051	0.035	0.035	0.035
8	0.227	0.227	0.199	0.078	0.078	0.069	0.051	0.051	0.045	0.035	0.035	0.031
9	0.227	0.227	0.199	0.078	0.078	0.069	0.051	0.051	0.045	0.035	0.035	0.031
10	0.227	0.227	0.199	0.078	0.078	0.069	0.051	0.051	0.045	0.035	0.035	0.031
11	0.227	0.227	0.209	0.078	0.078	0.072	0.051	0.051	0.047	0.035	0.035	0.032
12	0.227	0.227	0.209	0.078	0.078	0.072	0.051	0.051	0.047	0.035	0.035	0.032
13	0.227	0.199	0.347	0.078	0.069	0.120	0.051	0.045	0.078	0.035	0.031	0.054
14	0.227	0.199	0.347	0.078	0.069	0.120	0.051	0.045	0.078	0.035	0.031	0.054
15	0.227	0.199	0.35	0.078	0.069	0.121	0.051	0.045	0.078	0.035	0.031	0.054
16	0.227	0.209	0.35	0.078	0.072	0.121	0.051	0.047	0.078	0.035	0.032	0.054
17	0.227	0.209	0.345	0.078	0.072	0.119	0.051	0.047	0.077	0.035	0.032	0.054
18	0.199	0.347	0.345	0.069	0.120	0.119	0.045	0.078	0.077	0.031	0.054	0.054
19	0.199	0.347	0.345	0.069	0.120	0.119	0.045	0.078	0.077	0.031	0.054	0.054
20	0.199	0.35	0.345	0.069	0.121	0.119	0.045	0.078	0.077	0.031	0.054	0.054
21	0.209	0.35	0.345	0.072	0.121	0.119	0.047	0.078	0.077	0.032	0.054	0.054
22	0.209	0.345	0.343	0.072	0.119	0.118	0.047	0.077	0.077	0.032	0.054	0.053
23	0.347	0.345	0.36	0.120	0.119	0.124	0.078	0.077	0.081	0.054	0.054	0.056
24	0.347	0.345	0.373	0.120	0.119	0.129	0.078	0.077	0.084	0.054	0.054	0.058
25	0.35	0.345	0.373	0.121	0.119	0.129	0.078	0.077	0.084	0.054	0.054	0.058
26	0.35	0.345	0.373	0.121	0.119	0.129	0.078	0.077	0.084	0.054	0.054	0.058
27	0.345	0.343	0.373	0.119	0.118	0.129	0.077	0.077	0.084	0.054	0.053	0.058
28	0.345	0.36	0.373	0.119	0.124	0.129	0.077	0.081	0.084	0.054	0.056	0.058
29	0.345	0.373	0.373	0.119	0.129	0.129	0.077	0.084	0.084	0.054	0.058	0.058
30	0.345	0.373	0.352	0.119	0.129	0.121	0.077	0.084	0.079	0.054	0.058	0.055
31	0.345	0.373	0.352	0.119	0.129	0.121	0.077	0.084	0.079	0.054	0.058	0.055
32	0.343	0.373	0.352	0.118	0.129	0.121	0.077	0.084	0.079	0.053	0.058	0.055
33	0.36	0.373	0.352	0.124	0.129	0.121	0.081	0.084	0.079	0.056	0.058	0.055
34	0.373	0.373	0.352	0.129	0.129	0.121	0.084	0.084	0.079	0.058	0.058	0.055
35	0.373	0.352	0.352	0.129	0.121	0.121	0.084	0.079	0.079	0.058	0.055	0.055
36	0.373	0.352	0.352	0.129	0.121	0.121	0.084	0.079	0.079	0.058	0.055	0.055

A4. Follow-up colonoscopy

Table A5: Proportion of follow-up colonoscopy applied in the model according to screening strategy, age group and stage.

Stage	50 to 54 years		55 to 59 years		60 to 64 years	
	FS	COMB	FS	COMB	FS	COMB
0	0	0.0003	0.0002	0.0003	0.0004	0.0004
1	0.0005	0.0022	0.003	0.003	0.0028	0.0034
2	0.0027	0.0011	0.002	0.0018	0.0008	0.0008
3	0.0043	0.0052	0.0205	0.0154	0.0261	0.0226
4	0.0049	0.0036	0.0306	0.0288	0.0352	0.0283
5	0.0281	0.0263	0.0064	0.0048	0.0028	0.0023
6	0	0.0011	0.001	0	0	0
7	0.0011	0	0.0007	0	0.0004	0.0008
8	0.0019	0.0005	0.0042	0.0035	0.0036	0.006
9	0.0019	0.0016	0.0057	0.0053	0.0032	0.0034
10	0.0005	0.0027	0.0005	0.001	0	0.0004
11	0	0	0	0.005	0	0
12	0	0	0	0	0	0

A5. Assumptions in the sensitivity analysis

Based on Figure A1 to A8, we assume that treatment costs are gamma distributed with α and λ can be estimated from the following two definitions:

$$\text{Mean} = \alpha/\lambda$$

$$\text{Variance} = \alpha/\lambda^2$$

Table A6: Assumptions in the probabilistic sensitivity analysis ranking the four years of treatment. Mean and variance are reported in NOK.

Year	Mean	St.dev.	α	λ
Symptomatic				
1	18,880	785	578.00	0.0306
2	4,718	735	41.05	0.0087
3	2,734	721	14.49	0.0053
4	1,908	1,361	1.91	0.0010
Asymptomatic				
1	16,416	1,610	103.00	0.0063
2	2,058	765	7.27	0.0035
3	493	194	6.46	0.0131
4	196	82	5.71	0.0291

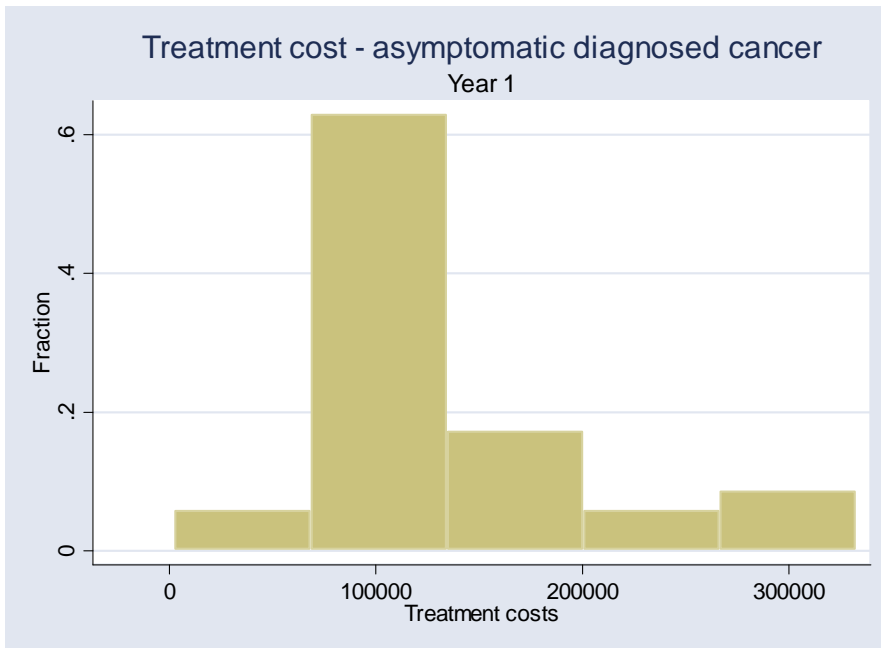


Figure A1: Treatment cost for asymptomatic diagnosed cancers during the first year after time of diagnosis. Numbers in NOK.

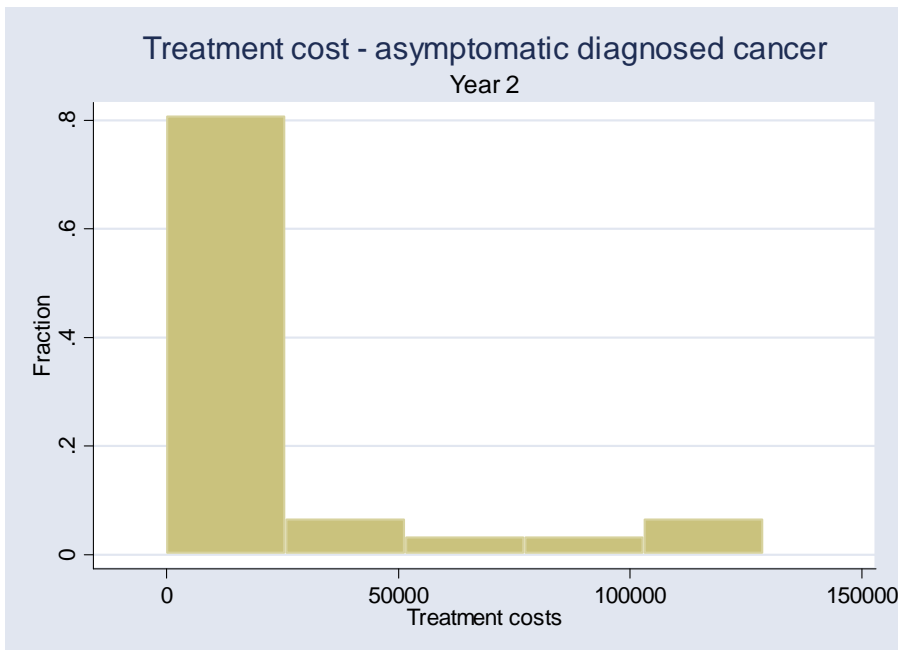


Figure A2: Treatment cost for asymptomatic diagnosed cancers during the second year after time of diagnosis. Numbers in NOK.

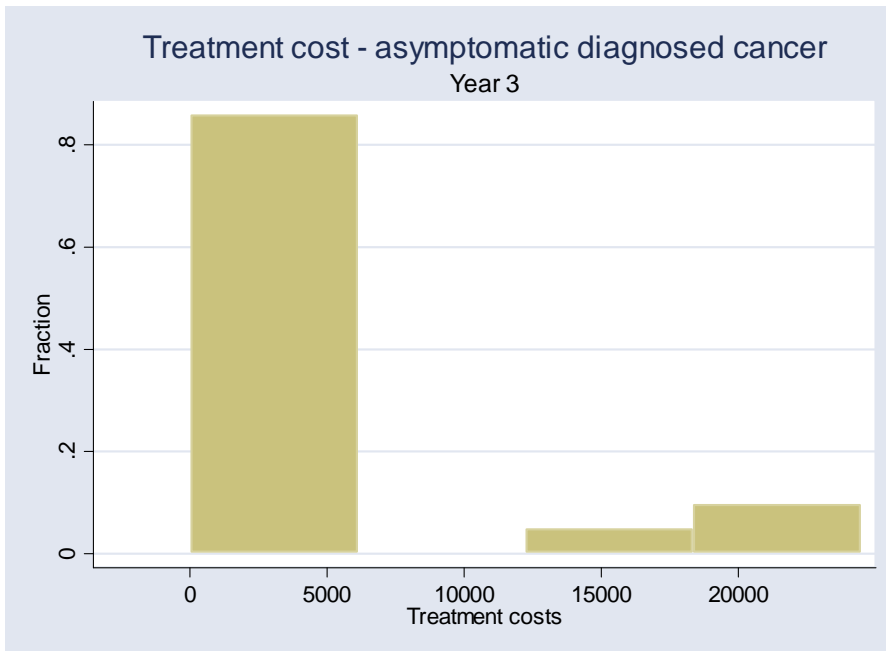


Figure A3: Treatment cost for asymptomatic diagnosed cancers during the third year after time of diagnosis. Numbers in NOK.

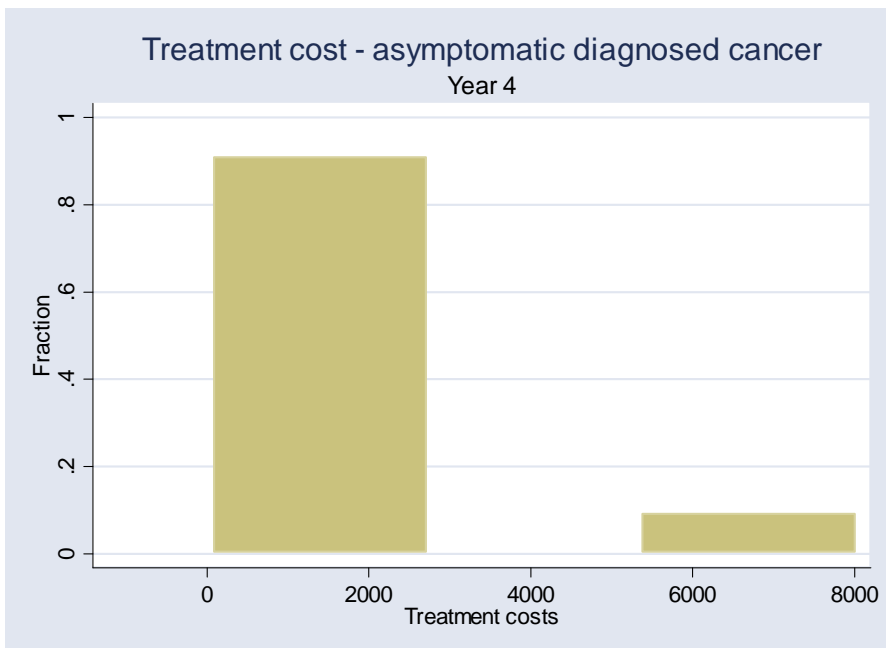


Figure A4: Treatment cost for asymptomatic diagnosed cancers during the fourth year after time of diagnosis. Numbers in NOK.

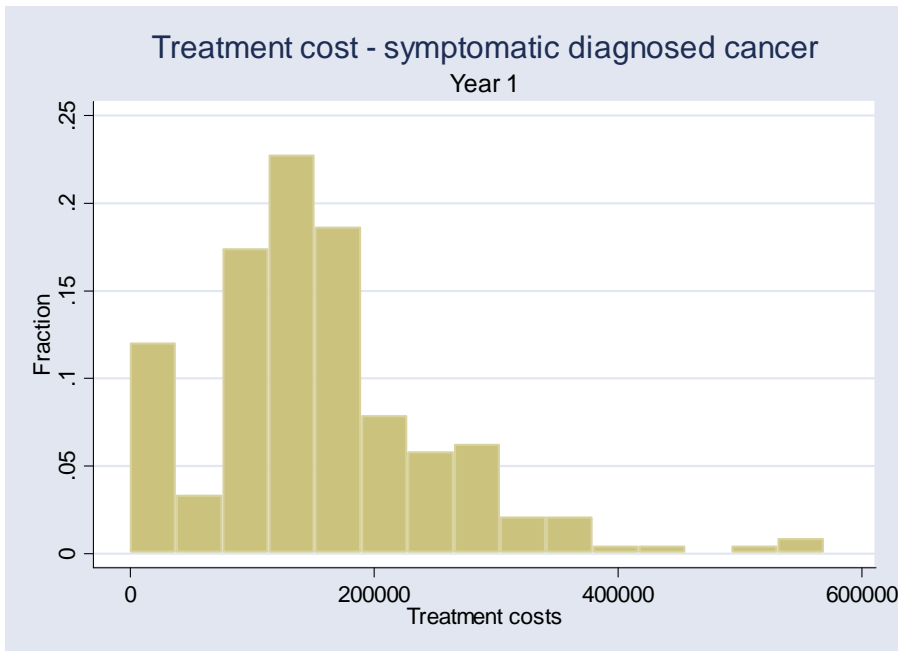


Figure A5: Treatment cost for symptomatic diagnosed cancers during the first year after time of diagnosis. Numbers in NOK.

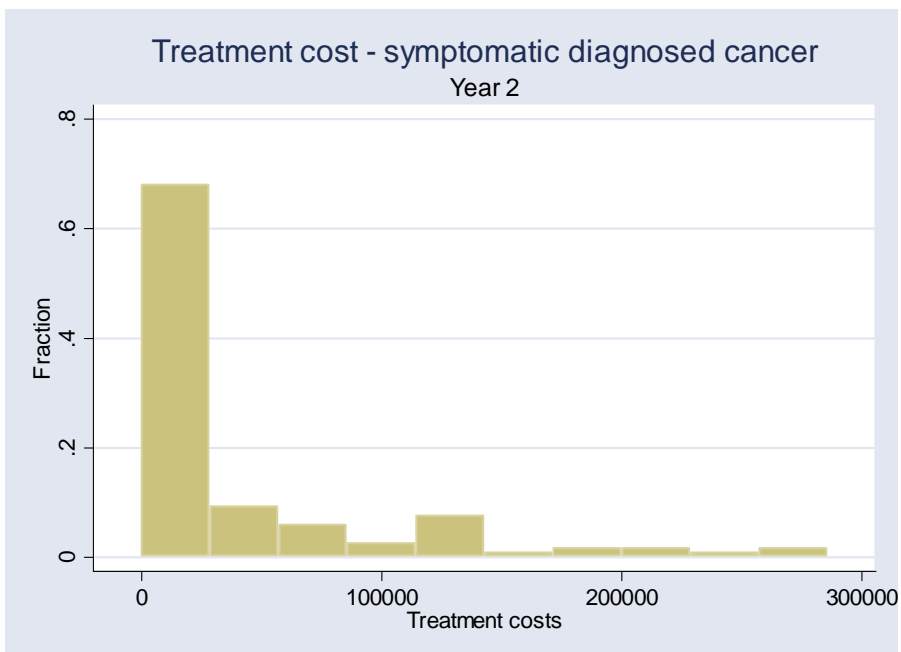


Figure A6: Treatment cost for symptomatic diagnosed cancers during the second year after time of diagnosis. Numbers in NOK.

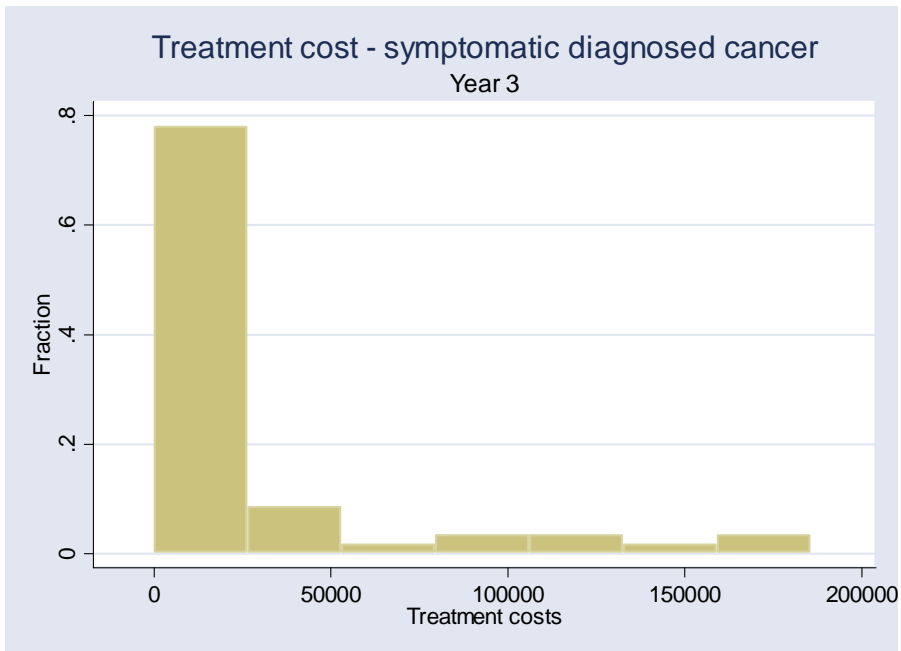


Figure A7: Treatment cost for symptomatic diagnosed cancers during the third year after time of diagnosis. Numbers in NOK.

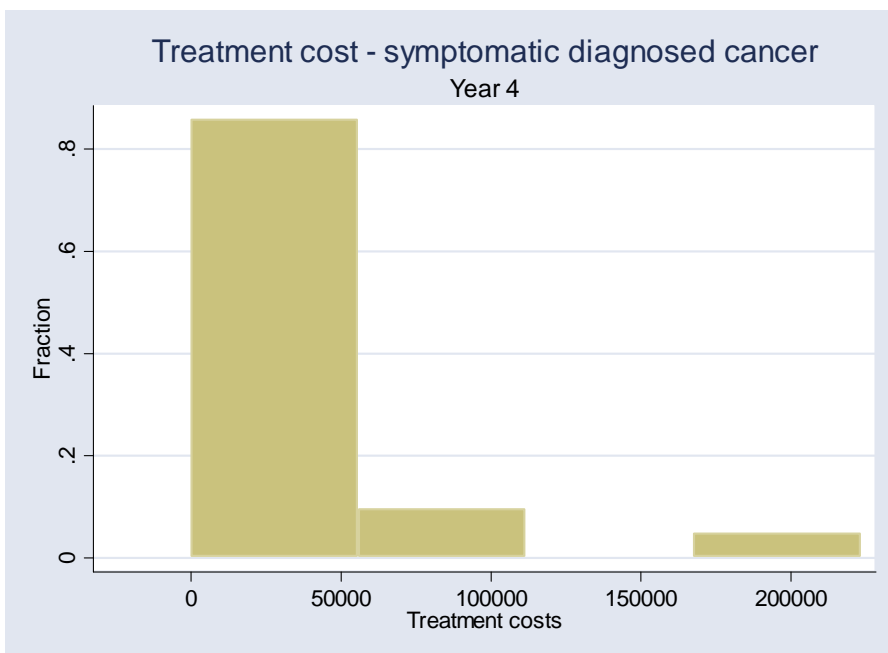


Figure A8: Treatment cost for symptomatic diagnosed cancers during the fourth year after time of diagnosis. Numbers in NOK.