General Introduction

Epidemiology of colorectal cancer

Colorectal cancer (CRC) is a major health problem, with more than 1.8 million new cases and 881,000 deaths estimated worldwide in 2018.[1] CRC is most common in developed countries, where the highest incidence rates are observed in parts of Europe (e.g. Slovenia, Slovakia, Hungary, The Netherlands, and Norway), Australia, New Zealand, Northern America, and Eastern Asia (e.g. Japan and the Republic of Korea).[1, 2] In contrast, most of the regions of Africa and Southern Asia tend to have low CRC incidence rates (**Figure 1.1**).

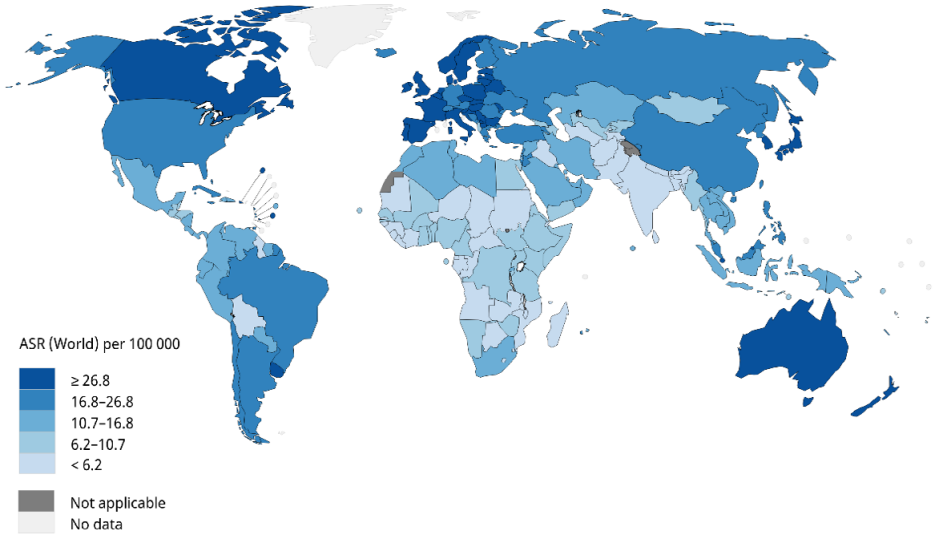

Figure 1.1. Worldwide age-standardized colorectal cancer incidence per 100,000 person-years (both sexes and all ages) estimated in 2018. Data source: GLOBOCAN 2018 Graph production: IARC (http://gco.iarc.fr/today) World Health Organization.[1]

The main risk factors for CRC are low physical activity, smoking, obesity, diabetes, red meat, processed meat, and alcohol consumption.[3] Those factors can be considered as indicators of the Western diet/lifestyle and are more prevalent in high developed countries.[4] As a consequence, CRC is the second leading cause of cancer deaths in these areas.[1, 2] CRC incidence rates increase also with age, especially above age 50 years.[2] Overall, approximately 4.2% of individuals in US will be diagnosed with CRC at some point during their lifetime according to the Surveillance, Epidemiology, and End Results (SEER) data (2014-2016).[5] At young age, CRC is very rare and mainly caused by specific hereditary disorders such as familial adenomatous polyposis and hereditary non-polyposis CRC (Lynch Syndrome, LS).[6] The lifetime risk of CRC of an individual with LS is approximately 50-80%.[6] Among individuals with family history of CRC, the risk of developing CRC is at least 2 times higher than in those who have no relatives affected by CRC.[7, 8] Furthermore, recent studies have shown also that individuals with Cystic Fibrosis (CF) and Childhood Cancer Survivors (CCS) are

at high risk of developing CRC at young age (<50 years).[9-13] Among the individuals with CF, the deficiency of the cystic fibrosis transmembrane conductance regulator (CFTR) has been identified as one of the potential driver of CRC.[14] It is associated with profound changes in mucus release and expression of mucin proteins, which may contribute in the pathogenesis of CRC.[15, 16] CRC risk among individuals with CF was found up to 30-fold greater compared to the general population and varies depending of previous lung transplantation.[11, 17] In CCS, radiation exposure (i.e. abdominal or pelvic radiation therapy) is an important risk factor for a secondary gastrointestinal cancer. An higher incidence of CRC was also observed among CCS that were previously treated with procarbazine chemotherapy.[12, 18] Compared to the general population, CCS may have a CRC risk up to 16-fold increased depending of primary cancer treatment or diagnosis.[10, 12, 19]

Natural history of colorectal cancer

CRC includes all the cancers that occur in the rectum, sigmoid colon, descending colon, transverse colon, ascending colon, or cecum. Most of those cancers develop from benign precursor lesions (adenomas) through the adenoma-carcinoma sequence.[20, 21] A minority of CRCs are believed to develop through an alternative pathway (i.e. from sessile serrated polyps).[22] Conventional adenomas may have a tubular, tubulovillous, or villous histology. Some of those may grow in size and, when high-grade dysplasia occur, become malignant.[21] CRC may be diagnosed in different stages considering information on tumor extension, size, affected lymph nodes, and affected distant organs (metastasis) (**Table 1.1.**).[23] Survival after a CRC diagnosis depends of stage at diagnosis, with poor prognosis reported when CRC is diagnosed at advanced stage.[5]

Table 1.1. Colorectal cancer stages according to the American Joint Committee on Cancer

Stage	TNM*	Description
0	Tis, N0, M0	Tumor remains 'in situ', i.e. intraepithelial or invading the lamina propria
I	T1-2, N0, M0	Tumor invades the submucosa (a) or muscularis propria
II	T3-4, N0, M0	Tumor invades the subserosa or pericolorectal tissues, or other organs and structures
III	T1-4, N1, M0	Tumor affects 1-3 regional lymph nodes or 4 or more
IV	T1-4, N0-2, M1	Tumor affects distant organs

Source: the American Joint Committee on Cancer in their 5th edition Manual for Cancer Staging,[23] which for colorectal cancer is closely related to alternative classifications such as TMN[24] and Dukes' staging.[25] *In TNM classification, T reflects the invasiveness of the primary tumor, N the number of lymph nodes affected, and M the metastasis to distant organs.

Despite that 30-50% of people will develop at least one adenoma throughout their lifetime, few of those adenomas actually progress and become clinical CRC. The average duration from an adenoma onset to CRC incidence was estimated to be approximately 20 years, with the last

2-4 years in a preclinical CRC latent phase.[26] In order to reduce the burden of CRC, several public health policies can be implemented. Policies that aim to change habits and CRC associated lifestyles factors are classified as primary prevention. However, given the long pre-clinical screen detectable phase, CRC is well suited to benefit from policies belonging to the second prevention, such as screening interventions.[27] In this thesis, we will focus on screening, where adenomas may be early detected and removed before progressing into CRC.

Colorectal cancer screening

Screening can be defined as a strategy that can detect an unrecognized disease among individuals without symptoms. In case of CRC, screening aims to detect CRC in earlier stage with more favorable prognosis or to prevent CRC incidence by removing precursor lesions. As CRC is characterized by a long pre-clinical screen-detectable phase,[26] screening has been proven to be an effective policy in reducing the burden of CRC.[28-34] However, screening can also result in serious complications, overdiagnosis, or overtreatment of CRCs (that would be never diagnosed without screening). There are several tests available for CRC screening (**Table 1.2.**). These tests can be categorized in three main groups: stool, endoscopy, and imaging tests.

Table 1.2. Colorectal cancer screening tests.

Screening test	Test characteristics	Available evidence
Stool tests		
guaiac fecal occult blood test (gFOBT)	Target: *blood in the stool*; Samples: *two from three consecutive bowel movements each;* Result type: *Qualitative.*	CRC mortality reduction ranging from 11% to 32%[32, 33, 35, 36]
Fecal immunochemical test (FIT)	Target: *blood in the stool;* Samples*: one from one bowel movement;* Result type: *Quantitative (positivity cut-off).*	36% CRC mortality reduction[37]
Stool DNA test	Target: *blood in the stool or DNA mutations;* Samples: *one from one bowel movement;* Result type: *Quantitative (positivity cut-off).*	Higher sensitivity compared to FIT[38]
Endoscopy		
Flexible sigmoidoscopy (FS)	Visual inspection of the left colon and rectum. Adenomas can be detected and removed.	CRC mortality reduction ranging from 21% to 30%.[28, 34, 39]
Colonoscopy	Visual inspection of whole colon and rectum. Adenomas can be detected and removed.	No mortality data available yet.
Imaging		
Computed tomography (CT) colonography	Three-dimensional images of the colorectum. The presence of CRC or adenomas can be detected.	No mortality data available yet. Higher participation, but lower detection rates compared to colonoscopy.[40]

The guaiac fecal occult blood test (gFOBT), the fecal immunochemical test (FIT), and the stool DNA test fall in the first group (stool tests), aiming to detect blood in the stool (or DNA mutations in the case of the stool DNA test). These three tests differ by their detection target (gFOBT: any blood; FIT: human haemoglobin; stool DNA: human blood and mutated DNA from neoplastic cells), number of required samples (gFOBT: two from three consecutive bowel movements each; FIT and stool DNA: one from one bowel movement), and type of result (gFOBT: qualitative; FIT, and stool DNA: quantitative, allowing variation in the positivity cut-off). For all of those tests, individuals – after a positive result – are referred to a full endoscopy examination (i.e. colonoscopy). The effectiveness of gFOBT has been demonstrated in randomized controlled trials (RCTs), with an observed reduction in CRC mortality ranging from 11% to 32%.[32, 33, 35, 36] Up to 36% of CRC mortality could be reduced using FIT screening at population level.[37] However, published evidence on effectiveness of FIT screening is limited and not from conventional RCTs. Ongoing studies comparing gFOBT and FIT have shown that, at similar positivity rates, FIT detects more advanced neoplasia than gFOBT.[41-45] Thus, it is reasonable to expect that FIT screening is generally more effective than gFOBT screening. The effectiveness of stool DNA testing has not been demonstrated by RCTs. However, a study compared FIT and stool DNA test, reporting a lower specificity and a higher sensitivity for detecting adenomas and CRC for stool DNA screening.[38]

Endoscopy screening includes all the procedures that involve a visual inspection of the colorectum using a flexible tube equipped with a fiber optic camera. CRC screening can be performed with a colonoscopy (complete investigation of the colorectum) or with a flexible-sigmoidoscopy (FS; inspection of the rectum up to the end of the transverse colon). Both procedures have a high sensitivity, allowing to detect and remove adenomas and CRC. However, individuals with a positive FS result are usually referred to undergo colonoscopy for a complete inspection of the colorectum. Both procedures require a bowel preparation and can cause serious complications. However, colonoscopy is associated with substantially higher complication risks and more burdensome bowel preparation than FS. Several RCTs have demonstrated the effectiveness of one-time sigmoidoscopy screening, showing a reduction in CRC mortality ranging from 21% to 30%.[28, 34, 39] Two RCTs are currently ongoing investigating the effectiveness of colonoscopy, but results on CRC mortality are not expected to be available before 2021.[46, 47] Since colonoscopy inspects a larger part of the colorectum compared to FS (and shares identical screening principles), it may be reasonable to expect colonoscopy to be more effective than FS given equal screening intensity.

Computed tomography (CT) colonography is an imaging. It involves two CT scans that allows the construction of two-dimensional and three-dimensional images of the colorectum. Those images can be used to detect the presence of CRC or adenomas. However, the effectiveness of this technique has not been demonstrated and results on CRC mortality are lacking. A clinical study has shown that CT colonography might be associated with higher

screening participation than colonoscopy, but lower advanced adenoma and CRC detection rates.[40] Moreover, CT colonography requires a burdensome bowel preparation comparable to colonoscopy.

Colorectal cancer screening at population level

CRC screening has been recommended by several health organizations and medical associations worldwide.[48-50] There are two main ways to provide CRC screening at population level: via opportunistic screening or via organized screening. In the opportunistic approach, there is not a recommended best test option and no screening invitations are sent. It is up to general practitioners to discuss with their patients whether or not to participate in CRC screening (and with which test). Organized or programmatic approach is also referred as population-based screening. Population-based screening programmes are publicly funded and the recommended screening tests are usually free of change. Those programmes are implemented to ensure active invitation of the entire target population at regular intervals. Several countries implemented CRC screening in the past decades. Given the focus of this thesis, we will focus on the most relevant screening settings implemented in Europe (mainly population-based) and the United States (US, opportunistic). At population level, CRC screening is generally focused on the general population (individuals at average CRC risk). However, specific CRC screening guidelines were also proposed in the past decades for groups of individuals at increased CRC risk, such as those with family history of CRC, LS, CF, or CCS.[51-54]

Europe

In 2003, the European Council recommended the implementation of organized CRC screening for men and women aged 50-74 years in all European countries.[55] The recommendation was to use gFOBT screening because effectiveness of FIT, FS, or colonoscopy screening had not been demonstrated at that time. In 2012, new evidence-based European guidelines for quality assurance in CRC screening were released, proposing that FIT, FS, and colonoscopy could be considered reasonable alternatives to gFOBT screening.[56] In Europe, existing organized programs differ in terms of target ages, screening interval, and primary test (**Table 1.3.**).[57-61] In Finland, biennial guaiac FOBT (gFOBT) screening is offered to men and women aged 60-69 years,[62] and in the Netherlands, Belgium, Denmark, Estonia, France, Spain, Slovenia, Ireland, Malta, Monaco, Montenegro, Serbia, Sweden, and Hungary biennial FIT screening is offered in various positivity cut-offs and age ranges (within ages 50 and 75 years). CRC screening also varies within the countries, for instance, in Italy. There, 112 regional CRC screening programs were gradually implemented during 2003-2012, some offering FIT and some offering flexible sigmoidoscopy (FS).[63] Furthermore, several countries that implemented gFOBT screening are currently switching to FIT (i.e. Finland, and part of UK). Other countries, such as Germany, Greece, and Czech Republic, implemented an

opportunistic screening programme offering colonoscopy screening. Where a stool test is used a primary test, organized screening programme generally invite individuals in the target population through mail: some countries invite individuals to collect their stool test from GPs or pharmacies; others directly send the kit test with the invitation letter (i.e. The Netherlands).

Table 1.3. Colorectal cancer screening programmes in Europe

Country	Type of programme	Screening Test	Screening Interval	Target age
Austria[59]	Opportunistic; PB in one region	Colonoscopy FIT	1	40-80
Belgium[59]	PB	FIT	2	56–74 (Flemish Region) 50–74 (Wallonia Brussels)
Bosnia and Herzegovina[60]	Opportunistic	FIT	nd	≥50
Croatia[59]	PB	gFOBT	2	50-74
Cyprus[59]	PB (pilot)	FIT	2	50-69
Czech Republic[59]	PB	FIT Colonoscopy	1 (FIT, 50–54) 2 (FIT, 55–70) 10 Colonoscopy	50–70 (FIT) ≥ 55 (Colonoscopy)
Denmark[59]	PB	FIT	2	50-74
Estonia[59]	PB	FIT	2	60-69
Finland[59]	PB	gFOBT	2	60-69
France[59]	PB	FIT	2	50-74
Georgia[60]	PB (pilot)	gFOBT	2	50-69
Germany[59]	Opportunistic	FIT Colonoscopy	1 (FIT, 50–54) 2 (FIT, 55–70) 10 Colonoscopy	50–54 (FIT) ≥ 55 (Colonoscopy)
Greece[59]	Opportunistic	gFOBT Colonoscopy	2 (gFOBT) 5 Colonoscopy	50-70
Hungary[59]	PB	FIT	2	50-70
Ireland[59]	PB	FIT	2	60-69
Italy[59]	PB	FIT FS (Piedmont)	2 (FIT) Once (FS)	50-70 58 or 60
Latvia[59]	Opportunistic	gFOBT	1	>50
Luxembourg[59]	PB	FIT Colonoscopy	2 (FIT) 10 Colonoscopy	55-74
Malta[59]	PB	FIT	2	55-66
Monaco[60]	PB	FIT	2	50-80
Montenegro[61]	PB	FIT	2	57-66
Netherlands[59]	PB	FIT	2	55-75
Norway	PB (pilot)	FIT FS	2 (FIT) Once (FS)	55-64

Table 1.3. Colorectal cancer screening programmes in Europe (*continued*)

Country	Type of programme	Screening Test	Screening Interval	Target age
Poland[59]	PB	Colonoscopy	Once	55-64
Portugal[59]	PB	FIT	2	50-70
San Marino[60]	PB	FIT	2	50-75
Serbia[60, 61]	PB	FIT	2	50-74
Slovenia[59]	PB	FIT	2	50-74
Spain[59]	PB	FIT	2	50-69
Sweden[59]	PB	FIT	2	60-69
Switzerland[58]	Opportunistic; PB in one canton	FIT Colonoscopy	2 (FIT) 10 Colonoscopy	50-69
UK[59]	PB	gFOBT FIT FS (England)	2 (gFOBT/ FIT) Once (FS)	55–74 (England) 60–74 (Northern Ireland) 50–74 (Scotland) 60–74 (Wales)

PB, Population-based; and nd, data not available; FIT, faecal immunochemical test; FS, flexible sigmoidoscopy; gFOBT, guaiac faecal occult blood test.

The United States

In the US, screening was introduced more than three decades ago.[64] However, it is not organized. CRC screening is mainly opportunistic and individuals are free to choose between screening tests. CRC screening recommendations differ in the US. The US Preventive Services Task Force suggests CRC screening among individuals aged from 50 to 75 years: annually with gFOBT, FIT, or stool DNA testing (or 3-yearly for stool DNA, as suggested by the manufacturer); every 5 years with FS or CT colonography; or every 10 years with colonoscopy.[49] The American Cancer Society (ACS) recommends that adults aged 45 years or older undergo regular CRC screening (up to age 75 years): annually with FIT, high sensitive gFOBT; every 3 years for stool DNA testing; every 5 years with FS or CT colonography; or every 10 years with colonoscopy.[50] Medicare – the national social insurance program for individuals aged 65 years or older – covers CRC screening: using gFOBT, sigmoidoscopy, and barium enema since 1998; colonoscopy since 2001; FIT since 2003, and stool DNA testing since 2014. However, Medicare beneficiaries without a supplementary insurance must face out-of-pocket spending when a polyp is detected and removed during a colonoscopy examination. The reason behind this extra spending is attributable to nature of the intervention. Medicare classifies colonoscopy as a diagnostic examination rather than preventive and, therefore, it is subject to 20 percent coinsurance (out-of-pocket spending).[65] The same is also applied when colonoscopy is performed after a positive stool test, regardless of the outcome.

Screening recommendations for high risk groups

Individuals at higher risk of developing CRC have specific recommendations.[51-54] Those are specifically tailored for each high-risk group. In the US, individuals with a family history of CRC are recommended to undergo colonoscopy screening every 5 years starting at age 45 years.[53] Individuals with Lynch syndrome should undergo colonoscopy every 1–2 years starting at age 20–25 years.[54] The US Children Oncology Group have recently suggested that CCS who were treated with abdominal or pelvic radiation therapy should undergo colonoscopy screening every 5 years from age 30 years.[52] Finally, the US CF Foundation and the Cystic Fibrosis CRC Screening Task Force, using the findings of a modelling decision analysis (included in this thesis),[66] recommend that individuals with CF should be screened with colonoscopy every 5 years starting from age 40 years.[51] However, organ transplant recipients with CF should initiate colonoscopy screening at age 30 years.[51] In Europe, specific recommendations vary depending on the country. For instance, in the Netherlands, individuals with a first degree relative diagnosed with CRC before age 50 are recommended to be screened with colonoscopy every 6 years starting at age 45 years. Nevertheless, at present, there are no specific recommendations for the CF population and CCS in Europe.

Screening evaluation and microsimulation modeling

Overall, the differences among organized screening programmes are the results of different processes in decision-making and in evaluating available scientific evidence. Although CRC screening is generally associated with a reduction in CRC mortality (**Table 1.2**), there is still uncertainty about which screening strategy is the best for specific conditions (i.e. country-specific CRC risks, population screening preferences, or limited country-level resources). Screening is also associated with harms, such as colonoscopy complications and overtreatment. Policy-makers, before implementing a screening programme, should therefore have enough scientific evidence supporting effectiveness screening and proving that benefits overcome the potential harms and justify the resources required for the screening. RCTs are the most robust source of that knowledge and indispensable for evaluating efficacy of screening (including the benefits-harms ratio). Some RCTs have been also used to pilot the implementation of population-based screening programmes, monitoring screening benefits, harms, and costs at population level.[62]

The need of modeling

Although RCTs are important and useful sources of scientific evidence, they have critical limitations. First, RCTs are time consuming and expensive. This explains why effectiveness of some CRC screening tests has not been demonstrated by RCTs (i.e. FIT and colonoscopy screening). Moreover, high risk groups, such as individuals with CF or CCS, are generally small populations. The time necessary to enroll enough individuals in an RCTs and the associated costs (for those populations) will be even higher compared to those needed for

RCTs carried out enrolling average risk individuals. Second, RCTs generally have a limited follow-up time, limiting the determination of lifetime health effects and costs (needed for evaluating cost-effectiveness of screening). Furthermore, RCTs may be carried out with different settings and effectiveness of screening might differ accordingly. For instance, effectiveness of FS has been investigated in several RCTs in Europe,[28, 30, 34] differing for screening participation (58-81%), sample size, age at screening (from 50-55 to 64 years), and enrolment procedure. However, when a population-based screening programme was implemented with FS, participation rates were not greater than 40%.[67] Finally, a RCT cannot evaluate every single combination of screening test, starting age, stopping age, interval, CRC risk, life expectancy, and country-level resources. Hence, RCTs alone are not able to answer questions regarding how screening should differ in different context or settings. Decision models can be a useful tool to extrapolate information from RCTs and investigate screening in specific problem conditions (i.e. different CRC risk, life expectancy, costs, or population preferences).

MISCAN-Colon

The Microsimulation Screening Analysis-Colon (MISCAN-Colon) model is a well-established microsimulation model that was developed by the department of Public Health of Erasmus MC, Erasmus University Medical Center, Rotterdam.[68] Its general structure is reported in **Figure 1.2**. Briefly, MISCAN-Colon simulates the life history of several individuals from birth to death (with screening and without screening). In each simulated individual, zero, one, or more adenomas may occur, which may progress in size, and develop into a (preclinical) cancer. Survival after a cancer diagnosis is modelled according to age, stage, and localization of the cancer at diagnosis. Screening may alter the simulated life histories, detecting cancer at an earlier stage or removing precancerous lesions. Furthermore, screening might result in overdiagnosis, overtreatment, in serious complication, or – in rare cases – in a premature death (fatal complication). The model quantifies the effectiveness and costs of screening comparing all life histories with screening with the corresponding life histories without screening.

Several studies included in this thesis were performed using the MISCAN-Colon model. For more detailed information about the model, its structure, and underlying assumptions, we refer to the **Model Appendix** included at the end of this thesis.

Sharing the access to MISCAN-Colon model

As mentioned before, microsimulation models have been proved to be useful tools in providing support for CRC screening decisions.[66, 69, 70] However, many of the current models (including MISCAN-Colon) are proprietary, limiting the capacity of policymakers to freely inform their decisions using models.[71] Considering these difficulties, the EU-TOPIA project (EU-Framework Programme, Horizon 2020 – 634753) has decided to standardize the

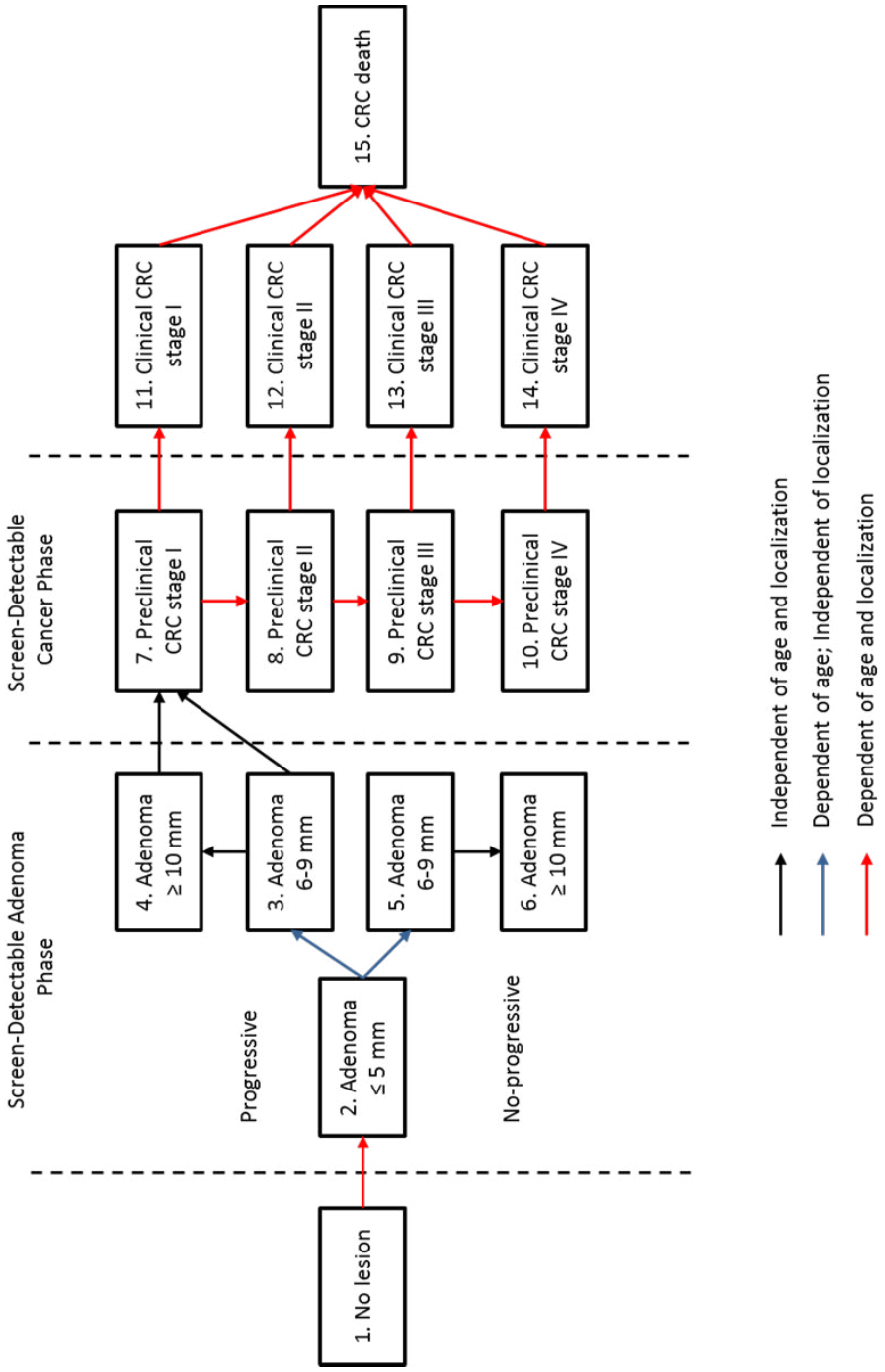

Figure 1.2. Model structure with adenoma-carcinoma sequence for progressive adenomas and non-progressive adenoma sequence

structure of MISCAN-Colon and use it for developing a user-friendly online tool (the CRC version of the EU-TOPIA evaluation tool).[72] So, each European policymaker may be able to directly upload country-specific data and use those to adjust the MISCAN-Colon model simulating future costs, harms, and benefits of CRC screening in his or her country.

The EU-TOPIA project

The overall aim of the project is to improve health outcomes and equity of breast, cervical and colorectal cancer screening programmes across Europe, accounting for demographical, medical, political, economic, and cultural differences between and within European countries. The EU-TOPIA evaluation tool (based on MISCAN-Colon and developed in this thesis) is one of the key components of the project.[72] The results of that specific version of the evaluation tool are designed to guide CRC screening decision-making throughout a health policy cycle (**Figure 1.3**).

Within this cycle, European policymakers (or researchers who are tasked to investigate possible ways to improve health outcomes in their population) are assisted and guided by the EU-TOPIA research team to:

i) monitor the current effectiveness of screening in their country using a monitoring tool (determining key benchmarks and quality indicators to quantify equity, benefits, and harms);
ii) estimate and evaluate future harms and benefits of the screening (with the EU-TOPIA evaluation tool);
iii) identify country-specific barriers or inequities that are limiting potential benefits of screening throughout a specific barrier tool (the EU-TOPIA evaluation tool is also used to quantify the additional benefits of removing those barriers);
iv) design feasible road-maps for removing the barrier and achieve those additional benefits (taking in account country-specific capacity limits in resources or legislations).

Research questions and outline of the thesis

The aim of this thesis is to first describe the steps that are required to standardize the structure of a microsimulation model (as MISCAN-Colon) and make it as the core of an online user-friendly model application. Briefly, these steps include: i) assessing effectiveness of CRC screening in different screening settings (**Chapter 2**); ii) validating the model structure and its assumptions (**Chapters 3-4**); and iii) building an online user-friendly platform that allow users to easily upload country-specific data, adjust a model, and simulate future outcomes of CRC screening in their countries (**Chapter 5**).

Subsequently, this thesis aims to demonstrate how models can be used to help policymakers in their decisions about CRC screening regarding populations at different risk of CRC (**Chapters 6-8**).

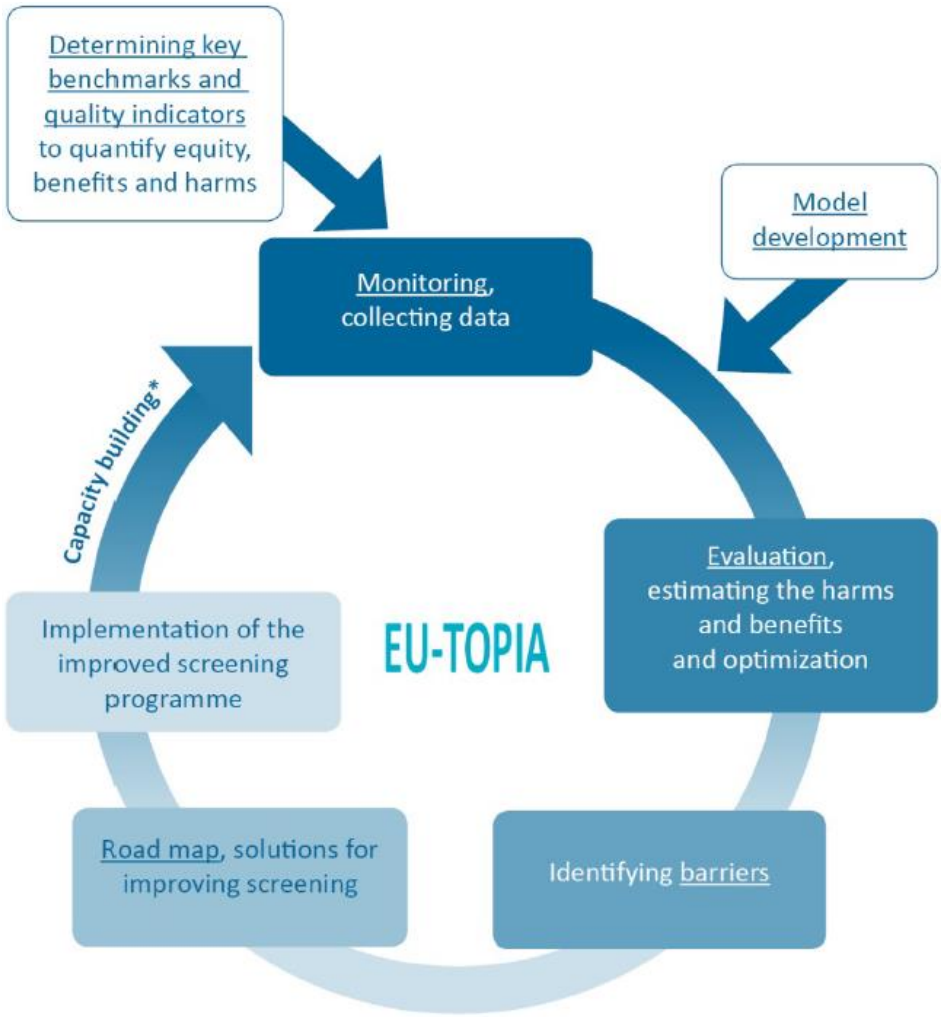

Figure 1.3. Steps of the EU-TOPIA project based on the health policy cycle.

More specifically, we addressed the following questions:

- What is the effectiveness of CRC screening in Europe? How does reduction in CRC mortality due to screening vary according to screening settings and European regions? (**Chapter 2**)
- What is the reliability of MISCAN-Colon model parameters? How valid are the results of the MISCAN-Colon model? (**Chapter 3**)
- Is the reliability of the MISCAN-Colon model parameters affected by a different country population or screening setting? (**Chapter 4**)
- How can models be used to inform policy decisions regarding CRC screening in Europe? (**Chapter 5**)

- What is the impact of waiving Medicare coinsurance for screening colonoscopy in US? Can it be cost-effective? (**Chapter 6**)
- Given the higher risk of developing CRC among individuals with CF, is early CRC screening cost-effective? What is the optimal screening strategy in this population in US? (**Chapter 7**)
- What is the optimal age to start colonoscopy screening among CCS in US? (**Chapter 8**)

Chapter 9 includes a general discussion of the studies described in this thesis.