Summary

Colorectal cancer (CRC) is a major health problem. Globally, 1.8 million new cases and 881,000 deaths are estimated every year. The main risk factors for CRC are low physical activity, smoking, obesity, diabetes, red meat, processed meat, and alcohol consumption. Those factors can be considered as indicators of the Western diet/lifestyle and are more prevalent in high developed countries. CRC incidence rates increase also with age, especially above age 50 years. 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). 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).

The burden of CRC can be reduced with CRC screening. Although CRC screening has been recommended by several health organizations and medical associations worldwide, it has not been implemented homogenously across countries. There are two main ways to provide CRC screening at population level: via opportunistic screening or via organized screening. In Europe, existing organized programs differ in terms of target ages, screening interval, and primary tests. In contrast, screening is mainly opportunistic in US and individuals are free to choose between screening tests. Several countries are facing organizational and financial barriers that limit the uptake of their CRC screening programme and its beneficial impacts. Decision-making in the field of CRC screening is complex with many parameters that can influence the effectiveness of a screening programme. Using microsimulation models can be useful for quantifying future outcomes and costs of screening, planning resources and identifying optimal policies to reduce CRC incidence and mortality. However, many of the current models are proprietary, limiting the capacity of policymakers to freely inform their decisions using models.

In the first part of this thesis, four studies were reported to describe the steps that are required to standardize the structure of a microsimulation model and make it the core of an online, open, and user-friendly model application (for European policymakers). These steps included: i) assessing effectiveness of CRC screening in different screening settings; ii) validating the model structure and its assumptions; 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.

In **Chapter 2**, we performed a systematic review to assess how mortality effects of CRC screening varied across European regions and screening settings. Six databases were searched for relevant studies investigating the effect of various screening tests. We identified 18 relevant studies published with European data. The results of this review, which has been published in a 2020 issue of the *European Journal of Cancer*, showed that the estimated effectiveness of gFOBT and FS screening appeared similar across different European regions. Compared to no screening, individuals invited to gFOBT screening had 8% to 16% lower CRC mortality than non-invited individuals. Among those invited to FS screening, CRC

mortality reductions varied from 21% to 30%. FIT screening might reduce up to 41% of CRC mortality, whereas colonoscopy screening might lead to a CRC mortality reduction of 88%. However, evidence for the effectiveness of FIT and colonoscopy screening was limited.

In **Chapter 3**, the structure of the Microsimulation Screening Analysis-Colon (MISCAN-Colon) model was tested. In its development, MISCAN-Colon was calibrated using CRC incidence data, scientific evidence from autopsy studies (adenoma prevalence and multiplicity), expert opinions, and the results of FS trial (UKFSS trial). We performed an external and predictive validation study using the results of another European screening trial (NORCCAP). The NORCCAP trial is a randomized controlled trial that assessed the effectiveness of flexible-sigmoidoscopy screening (with follow-up time comparable to the UKKFSS trial). We found that MISCAN-Colon predictions were highly consistent to the NORCCAP trial results, suggesting that the MISCAN-Colon structure allows for accurate predictions of CRC incidence and mortality reduction through FS screening.

Although the MISCAN-Colon model structure has been externally validated, it does not imply that the assumptions of the model are valid considering different populations or different screening settings. CRC incidence rates varied remarkably across countries (especially in Europe). Several factors may be behind those variations (genetics, lifestyle, and socioeconomics). However, it is unclear how these factors impact the natural history of disease and may impact on the reliability of the MISCAN-Colon core assumptions. In **Chapter 4**, this uncertainty was assessed. We developed three new versions of the MISCAN-Colon model for quite diverse European countries (Italy, Finland, and Slovenia) and screening settings (gFOBT, FIT, and FS) varying only a minimum set of country-specific parameters. We specifically tested the assumption that differences in CRC across European countries can solely be related by differences in adenoma prevalence and not progression from adenoma to CRC. We derived a standardized process for validating the models. These regional model versions were validated against the best available evidence for the effectiveness of screening from the corresponding region (identified in **Chapter 2**): the Screening for COlon REctum (SCORE) trial and the Florentine fecal immunochemical test (FIT) screening study for Italy; the Norwegian Colorectal Cancer Prevention (NORCCAP) trial and the guaiac fecal occult blood test (gFOBT) Finnish population-based study for Finland. When published evidence was not available (Slovenia), the regional model was validated using cancer registry data. We found that the MISCAN-Colon model versions accurately estimated CRC stage distributions, incidence, mortality rates, and mortality reduction due to screening in Europe. Moreover, our findings provide an important implication. The natural history of CRC may not vary substantially across Europe, increasing the reliability in the MISCAN-Colon structure and assumptions.

Those results can also allow a further standardization of the model as provided in **Chapter 5**. An open, user-friendly, and online tool based on MISCAN models for breast, cervical and colorectal cancer was developed (also known as the "EU-TOPIA evaluation

tool"). It was presented to 120 researchers and policymakers from 26 European countries during three workshops organized by the EU-TOPIA project (Malmö in September 2018; Turin in April 2019; and Brussels in January 2020). The overall goal of this project was to share knowledge, create professional networks, and assist all European countries in monitoring, evaluating, and improving their cancer screening programmes. The CRC version of the "EU-TOPIA evaluation tool" was derived with the results of this thesis (**Chapters 2**, **3**, and **4)**. It allows European researchers and policymakers to quantify future outcome of CRC screening in their countries, providing several model results, such as the number of predicted cancer cases, cancer-specific deaths, screening tests, positive tests, diagnostic follow-up tests, surveillance tests, complications, and screen-detected cancers per calendar year (2018-2050) and/or age group (40-50, 50-74, or 75-100).

The second part of this thesis consists of three studies that illustrate how the MISCAN-Colon model can be used to inform policymaking in the US. There, individuals are free to choose between screening tests, which are reimbursed by health insurances and/or the Centers for Medicare and Medicaid Services (CMS). However, because of a loophole in legislation, Medicare/Medicaid beneficiaries face a 20% coinsurance for a diagnostic colonoscopy, or if polyps are detected and removed at screening colonoscopy. In **Chapter 6**, the MISCAN-Colon model estimated that 36% of screening colonoscopies performed in the US were subject to this coinsurance requirement. Waiving the coinsurance would increase the total lifetime costs for CMS, from US$2.675 million per 1000 65-year-olds to US$2.726 million (+ US $51,000; +1.9%). We also estimated that waiving this coinsurance would be cost-effective if it increased the screening rate from 60.0 percent to 60.6 percent in Medicare beneficiaries (US $50,000 willingness-to-pay threshold). It is important also to mention that the waiver would primarily affect the out-of-pocket costs of Medicare beneficiaries from low socioeconomic status background, who more often lack Medigap and supplemental insurance.

The second study of this part of the thesis (**Chapter 7**) was a decision analysis formally requested by the CF Foundation. Individuals with CF have shown to be at higher risk of developing CRC compared to the average risk population. However, no CRC screening recommendations were indicated in the CF population. We adjusted the existing MISCAN-Colon microsimulation model to reflect increased CRC risk and lower life-expectancy in patients with CF. We quantified benefits and costs of 76 different screening scenarios separately for individuals who never received an organ transplant and patients who had received an organ transplant. MISCAN-Colon estimated up to 19.1 CRC deaths in absence of screening per 1,000 30-year old individuals with CF who have not had a transplant. Up to 79% of the premature deaths for CRC (15.1 per 1,000) may be averted recommending colonoscopy screening from age 40 years with a screening interval of 5 years (at acceptable cost of US $84,000 per life-year gained from screening). Optimal screening may start earlier in those who underwent organ transplant (from age 35 years, cost of US $71,000 per life-

year gained), depending on the patient's age at time of transplantation. This study was used by the Cystic Fibrosis CRC Screening Task Force in determining their CF CRC screening consensus recommendations and published in a 2018 issue of *Gastroenterology* (Journal of the American Gastroenterological Association).

In contrast to individuals with CF, recommendations for earlier initiation of CRC screening already existed for CCS. The US Children Oncologic Group (COG) recommend colonoscopy screening every 5 years from age 30 years for those previously treated with radiation therapy (recommendations released in 2018). However, other expert groups argue that available evidence is insufficient to base those recommendations. In **Chapter 8**, the existing MISCAN-Colon microsimulation model was adjusted, using data from the Childhood Cancer Survivors Study and Pediatric Oncologic Group Ontario, to reflect the increased CRC risk and lower life-expectancy in CCS. We evaluated 91 different screening strategies. Screening with colonoscopy from age 35 to 65 years every 10 years was optimal for CCS treated with radiation therapy, averting 82.3% of CRC deaths compared to no screening (97 colonoscopies needed per CRC death prevented) at acceptable costs ($92,000 per life-year gained by screening). The results of our study, published in a 2019 issue of the *Journal of National Cancer Institute*, shows that the current US COG recommendations are not likely to be the most cost-effective. Under most clinically plausible scenarios, commencing screening at age 35 would be the most cost-effective approach, supporting indirectly the previous recommendations released by the US COG in 2013, in which they recommended colonoscopy screening from age 35 years with a screening interval of 5 years for CCS treated with radiation therapy at dosages greater or equal than 30 Gray.

Based on the results presented in this thesis we conclude that:

- Effectiveness of gFOBT screening does not vary substantially, across quite diverse European regions and populations (Chapter 2).
- FS screening was evaluated only in RCTs in Europe and its effectiveness appeared similar across different European regions (Chapter 2).
- The MISCAN-Colon was able to replicate CRC incidence and mortality outcomes of the NORCCAP trial (Chapter 3).
- The natural history of CRC (specifically the assumptions on progression rates from adenoma to CRC) might be assumed similar across quite diverse European populations and countries (Chapter 4).
- The MISCAN-Colon model is a reliable tool for informing decisions in CRC screening (Chapters 3 and 4).
- A standardized, open, and user-friendly version of the MISCAN-Colon model can be designed and provided for European policymakers and researchers (the EU-TOPIA evaluation tool; Chapter 5).

- In the US, waiving Medicare coinsurance payments for diagnostic and primary therapeutic colonoscopy is cost-effective, and may contribute to reducing CRC health disparities (Chapter 6).
- Considering the high risk of developing CRC, individuals with CF can benefit from an early initiation of CRC screening, especially those that underwent a transplantation. Moreover, CRC screening in this population is cost-effective (Chapter 7).
- In CCS, colonoscopy screening is cost-effective among those treated with abdominopelvic radiation therapy (≥ 30 Gray; Chapter 8).

Furthermore, our findings support the following recommendations:

- Validated microsimulation models may be useful tools for informing decisions in CRC screening.
- Medicare coinsurance payments should preferably be waived. This policy is expected to have favorable balance of health and cost impact.
- Individuals with CF should consider colonoscopy screening from age 40 years and repeat screening every 5 years.
- Individuals with CF that underwent an organ transplant should commence colonoscopy screening at age 30 or 35, depending on the age at transplantation.
- CCS treated with radiation therapy (≥ 30 Gray) should commence colonoscopy screening at age 35 years as indicated by the previous COG guidelines (released in 2013).