Exploring the Natural History of Esophageal Adenocarcinoma and Possibilities for Early Detection and Intervention

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Exploring the Natural History of Esophageal Adenocarcinoma and Possibilities for Early Detection and Intervention

Verkenning van het natuurlijk verloop van oesophagus adenocarcinoom en mogelijkheden voor vroege opsporing en interventie

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CHAPTER 1

General introduction

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1.1 ESOPHAGUS CANCER EPIDEMIOLOGY

Esophageal cancer is the eighth most common cancer in the world and because of its high fatality rate, ranks sixth among all cancers with respect to mortality (figure 1). The vast majority of esophageal cancers are either squamous cell carcinoma (SCC) or esophageal adenocarcinoma (EAC). Where the SCC develops the squamous cells of the esophagus, EAC develops from intestinal epithelium: Barrett's esophagus. In this condition the squamous cells of the distal esophagus are replaced by intestinal epithelium with goblet cells, and specialized intestinal metaplasia. As there are differences in origin of the two major subtypes of esophageal cancers, the subtypes also vary in cancer etiology and development. Moreover, the two types are differently distributed

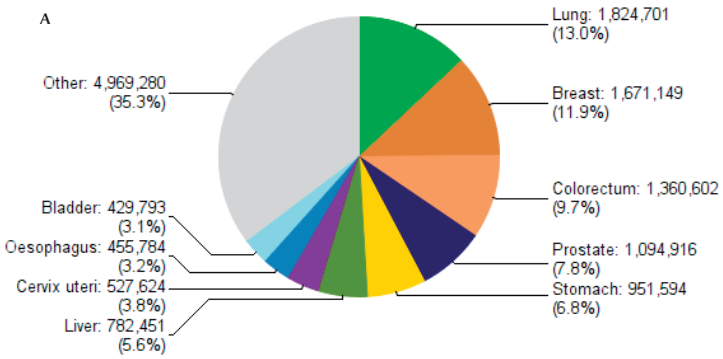

Figure 1a. Esophageal cancer incidence worldwide (2012). Source: GLOBOCAN 2012 (IARC – 23.2.2015)

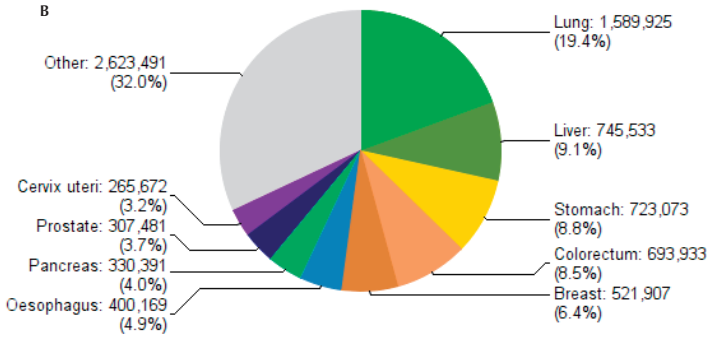

Figure 1b. Esophageal cancer mortality worldwide (2012). Source: GLOBOCAN 2012 (IARC – 23.2.2015)

globally. Where EAC is more common in western countries such as the United States and Europe, SCC is more prevalent in Asian and African countries.

Although the overall incidence of esophagus cancer is relatively low, there are some interesting changes in the patterns of secular incidence trends of both subtypes, shifting the dominant type from SCC to EAC since 1990 in western countries. While SCC incidence has been declining and recently nearing plateau in the United States and other parts of the Western world, EAC incidence has experienced an alarming increase over the past four decades. In many western countries incidence of EAC has increased more rapidly than any other malignancy, with average annual increases up to 8.2% for males during the past two or three decades.[1-7]

In the United States, the male EAC incidence rose from 0.9 per 100,000 population in 1975 to 6.5 per 100,000 population in 2009, whereas the female EAC increased from 0.2 to 0.9 per 100,000 population in the same period (figure 2). The discrepancy between EAC incidence rates in gender is large: in western countries the incidence of EAC in the male population is at least seven times higher than in the female population.[8]

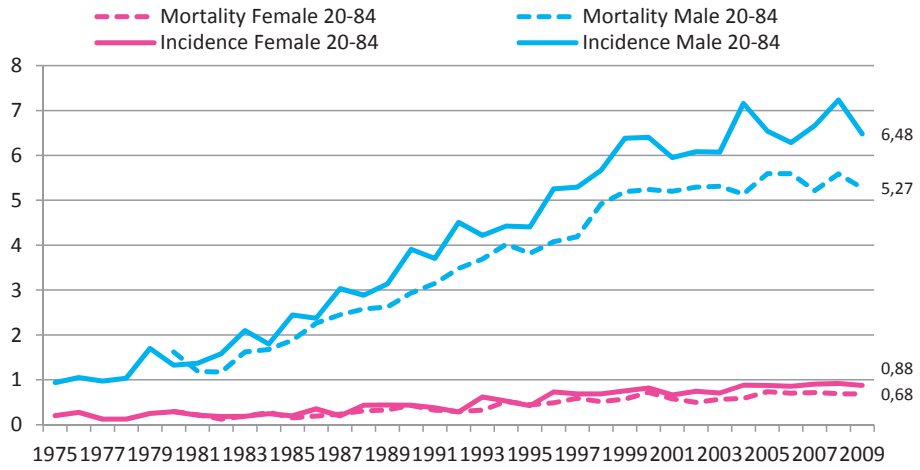

Figure 2. United States esophageal adenocarcinoma incidence and mortality per 100,000 United States standard population. Source: Surveillance, Epidemiology, and End Results (SEER) Program

In the Netherlands, 2400 esophageal cancers are diagnosed annually, of which 1800 are adenocarcinomas (~75%). The cumulative risk for EAC in the total Dutch population is 0.32% up to age 65, and 0.95% up to age 80.[9]

In line with the major increase in cancer incidence rates, mortality rates have also increased dramatically (figure 2). Approximately 60% of the diagnosed cancers patients is given palliative care due to incurable disease. The remaining 40% of the patients

can be treated by chemotherapy, chemo radiotherapy, surgery (complete resection), endoscopic resection, or a combination of these to enlarge probability of survival. Patients diagnosed at stage T1aN0M0 (early localized stage) are considered for endoscopic resection, and therefore have a considerably higher survival than patients diagnosed in a more advanced stage. Because of modest improvement in prognosis over time, the increase in EAC mortality is slightly less pronounced than in EAC incidence. However the 5-year survival rate remained low around 15%.[10]

The median and average age of EAC diagnosis is 68, and a 30% of the diagnosed patients is older than 75 at diagnosis.[11] In U.S. males, the highest incidence rates are seen at age group 80-84 (figure 3). The malignant stages of EAC diagnosis are classified in three stages: localized, regional and advanced. At localized diagnostic stage the cancer is only found in the esophagus. In regional stage the cancer has spread to lymph nodes or nearby tissues. When the cancer has spread to organs or lymph nodes away from the esophagus this is specified as advanced state.

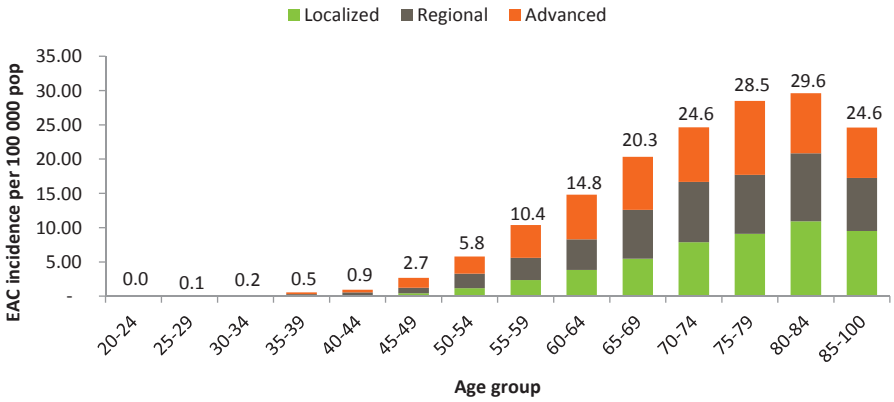

Figure 3. United States esophageal adenocarcinoma incidence rates per 100,000 males from 2000-2009 per age group. Source: Surveillance, Epidemiology, and End Results (SEER) Program

1.2 BARRETT'S ESOPHAGUS AND THE NATURAL HISTORY OF EAC

Barrett's esophagus (BE) is a condition in which the squamous epithelium of the distal esophagus is replaced by columnar epithelium containing goblet cells, which can be recognized during endoscopy by red coloration of the normally vale pink mucosa. BE is presumed to be a complication of gastro-esophageal reflux disease (GERD) and symptoms of GERD such as heartburn and/or acid regurgitation are associated with BE and EAC.[12, 13] BE can only be diagnosed by endoscopy, after which biopsies are taken for histologic confirmation.

The development from BE towards EAC is a stepwise process. BE starts off as non-dysplastic (ND) BE, but can progress towards higher grades of dysplasia (low-grade dysplasia LGD and high-grade dysplasia HGD) and eventually cancer. The risk for progression in BE is positively correlated to the grade of dysplasia found at endoscopy and biopsies. The majority of BE patients will have a low risk for progression towards EAC, since they are diagnosed without the presence of dysplasia. Table 1 shows the yearly risk for EAC and the combined risk for HGD and/or EAC in BE patients according to their initial dysplastic grade (ND, LGD or HGD) and for a total BE population. In meta-analyses, the annual risk for EAC development increases from 0.3%-0.6% annually in patients with ND BE to 6.6% annually in BE patients with HGD. Furthermore the meta-analyses show that the annual risk of progression to HGD and EAC in a total BE population can be three times larger than the annual risk of progression to EAC alone. Population-based studies generally show a lower risk of progression towards EAC, ranging between 0.12% and 0.14%.

Table 1. Risk for malignant development of esophageal adenocarcinoma in patients with varying dysplastic stages of Barrett's esophagus.

	Meta-analyses		Population-based studies
Dysplastic grade of BE	**individuals diagnosed with EAC risk (range)**	**individuals diagnosed with risk of developing EAC and/or HGD (range)**	**individuals diagnosed with EAC risk (range)**
Total	0.41-0.7%	0.9-1.2%	0.12-0.14%
No dysplasia (ND)	0.33-0.60%		
Low-grade dysplasia (LGD)	1.7%		
High-grade dysplasia (HGD)	6.6%		

EAC: Esophagus adenocarcinoma; ND: No dysplasia; LGD: Low-grade dysplasia; HGD: High grade dysplasia.
Source: de Jonge, et al[16] .

The-prevalence of BE in the total population is unknown. It is believed that there is a large proportion of silent BE present in the population. Recent estimations suspect a BE prevalence of 1-2% in the total adult population.[14] BE is most common in males, studies have shown a 2-4 times increased incidence rate for males compared with females.[15] Furthermore, BE diagnosis is more common at older ages as incidence rates rise linearly up to age 70 and decrease again after age 84.

The number of individuals diagnosed with BE in the general adult population and on average per endoscopy has been rising up to the early 2000s.[15, 17] After 2000 data from the U.K. and the Netherlands show a steady pattern in number of BE diagnoses up to 2012.[18] It remains controversial whether the rise in BE diagnosis is caused a higher risk

of developing BE, or is caused by alternative explanations. These explanations include the changed definition of BE around 1990, when short segment BE (BE length <= 3 cm) was also classified as BE. Also, a higher proportion of endoscopies are done because of GERD symptoms, enlarging the probability of finding BE in the tested population.

1.3 RISK FACTORS FOR BE AND EAC

Several determinants are associated with the development of EAC. In general, a combination of the BE incidence in the population and the cancer progression in these BE patients are responsible for the EAC incidence in the total population. Some risk factors only influence the development of precursor BE, other risk factors may only influence malignant development within BE patients and furthermore there are risk factors that influence both steps of the process (figure 4). For the first step, studies have shown that male gender, smoking, obesity, prolonged symptoms of GERD, hiatus hernia, and absence of infection with *Helicobacter pylori* (*H.Pylori*) are associated with BE development. For the second step (malignant progression within BE patients), male gender, longer segment length, presence of dysplasia, and absence of *H. Pylori* infection are significant risk factors. A protective effect is shown in patients with aspirin and statins medication.[19]

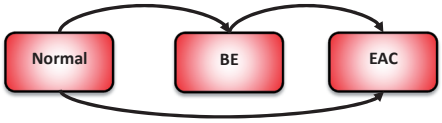

Figure 4. Graphical representation of the influence of risk factors on the development of esophageal adenocarcinoma.

1.4 EARLY DETECTION OF EAC

Detection and surveillance of BE

BE can be detected by endoscopy followed by histologic confirmation. Because there are no specific signs and symptoms exclusively indicating BE, most patients are diagnosed with BE by coincidence undergoing a gastro-endoscopy because of persistent reflux symptoms. Hence, BE is detected by endoscopy either by chance (during endoscopy for conditions unrelated to GERD) or by intention (during screening endoscopy for GERD symptoms). As for the latter, patients with GERD symptoms are first medically treated by the general practitioner. When these symptoms are persistent, the general

practitioner will refer the patient to the gastroenterologist for additional treatment, who will perform a gastro-endoscopy with biopsies. The patient will be sedated and the gastroenterologist will examine the esophagus with an endoscope, searching for abnormalities in the esophageal glands and extracting biopsies when irregularities are seen.

The development of EAC from BE is a stepwise process, and applying endoscopic surveillance gives the opportunity of early detection of malignant abnormalities in the esophagus. Currently around 92% of the diagnosed EAC is found at first endoscopy, that is, without an earlier confirmed BE diagnosis.[20] In contrast, only a small percentage of the patients diagnosed with BE (6-11%) will eventually develop EAC.[21, 22]

In the past years, the number of endoscopies has increased simultaneously with the number of diagnosed BE patients, resulting in a total number of 216 thousand gastrointestinal endoscopies in 2009 in the Netherlands.[23] In the Netherlands it is common practice to apply surveillance to diagnosed BE patients, based on international guidelines for surveillance intervals.[24] The surveillance recommendations for BE patients according to these international guidelines are dependent on the dysplastic grade found in the biopsies. U.S. and British guidelines recommend surveillance for BE patients without dysplasia every 3-5 year, and surveillance for BE patients with LGD every 6 months for the first year, and every year after the first year of diagnosis. Treatment or surveillance with a 3 month interval is recommended for BE patients with high grade dysplasia. The treatment of BE with HGD is described in the guidelines for esophageal carcinoma treatment.[25] The majority BE of patients will be found without dysplasia (85-90%), while fewer patients are diagnosed with lowgrade (8-15%) or highgrade (1-3%) dysplasia. Unfortunately, misclassification of dysplastic BE state is common due to sampling error when taking the biopsy specimens, and inter- and intra-observer variability when validating the histology by the pathologists. The prospect for every diagnosed BE patient is a lifetime of burdensome gastroscopies, while most of the diagnosed patients will never develop EAC and die due to other causes than EAC.[26]

Radiofrequency ablation

Endoscopic eradicative treatments (EET) can be used to eradicate the Barrett's segment including dysplasia and early EAC from the esophagus. Most commonly used eradicative treatment methods are endoscopic mucosal resection (EMR) and radio frequency ablation (RFA). It is not uncommon that both methods are used during the treatment process; treatment will start with endoscopic mucosal resection of nodular tissue and is followed by RFA to ablate the metaplastic cells. RFA involves the placement of a balloon catheter in the esophagus, through which radiofrequency energy is

delivered ablating the circumferential segment of the esophagus. Multiple treatments are needed to ablate the entire BE tissue and after 1-2 years the intestinal metaplasia or dysplasia is completely eradicated in most cases. Varying studies show high levels of eradication of both BE and dysplasia (>90%).[27] Recurrence of metaplasia and dysplasia is not uncommon, and post-treatment surveillance with additional focal RFA is often required to prevent malignant progression.

Evidence for effectiveness

There is evidence that BE patients with HGD have a lower risk of EAC development if they participate in an endoscopic surveillance program.[28, 29] Moreover, if the tumor is discovered in an earlier malignant state, more treatment possibilities are available and the average survival rate for these patients is higher than for patients with EAC discovered in an advanced state. Although surveillance provides these benefits, no randomized trials have investigated whether the mortality of patients with BE decreases when they join a surveillance program.[30] There is reasonable evidence that indicates that endoscopic treatment such as endoscopic eradication therapy, RFA, photodynamic therapy or EMR in BE patients with confirmed HGD is effective.[31] In conclusion, there is circumstantial evidence for the effectiveness of surveillance in BE patients, and once HGD is detected there is reasonable evidence that treatment of those patients is effective.

Cost effectiveness of surveillance and treatment

The cost effectiveness of BE surveillance and treatment is highly dependent on the risk of progression to EAC. Surveillance for patients with dysplasia is likely to be cost-effective, while the cost effectiveness of surveillance of patients without dysplasia is controversial.[32] Ablative treatments for HGD is cost-effective, however the efficacy of ablation largely influences the results. A recent Dutch study found that when assuming a willingness-to-pay threshold of €35000 per quality adjusted life years (QALY), surveillance - with EMR and RFA in case HGD dysplasia is found- is cost-effective with an interval of 5 years for patients with ND BE and 3 years for BE patients with LGD.[33] These surveillance intervals are less frequent than recommended guidelines and common practice in the Netherlands.

1.5 MICROSIMULATION OF EAC

Mathematical modeling is a powerful methodology which can be used to estimate the consequences of health care decisions. In esophageal cancer, models are currently being used to calculate the effects and costs of management interventions for screen-

ing, surveillance and treatment. In addition to economic evaluations applications of disease modeling include projections of future incidence and gaining insights to the natural history of the disease by systematically integrating available data.

In collaboration with the University of Washington, the Erasmus/UW-EAC model is developed as part of the Cancer Intervention and Surveillance Modeling Network (CISNET). CISNET is a National Cancer Institute (NCI) funded consortium where mathematical and computational modelers work together closely to address current emerging questions concerning cancer intervention and surveillance. Using a comparative modeling approach, limitations such as uncertainty in disease-specific natural history parameters and effectiveness of screening and surveillance are investigated. The Erasmus/UW-EAC model was established in 2011, and is part of a framework of MISCAN (Microsimulation Screening Analysis)models for cancer screening analysis: breast, colon, prostate, lung and cervix.

A detailed description of the Erasmus/UW-EAC model and the data sources that informed the quantification of the model can be found in the model appendix and in previous publications.[34, 35] In brief, the model first simulates the life histories of a large population of individuals from birth to death. After this, the natural history of the disease is modeled according to current knowledge on BE incidence and malignant progression. Depending on age, sex and baseline individual risk BE may develop in an individual, which over time may progress to LGD and HGD. In a minority of patients malignant cells can arise from HGD, transforming to localized EAC that can progress

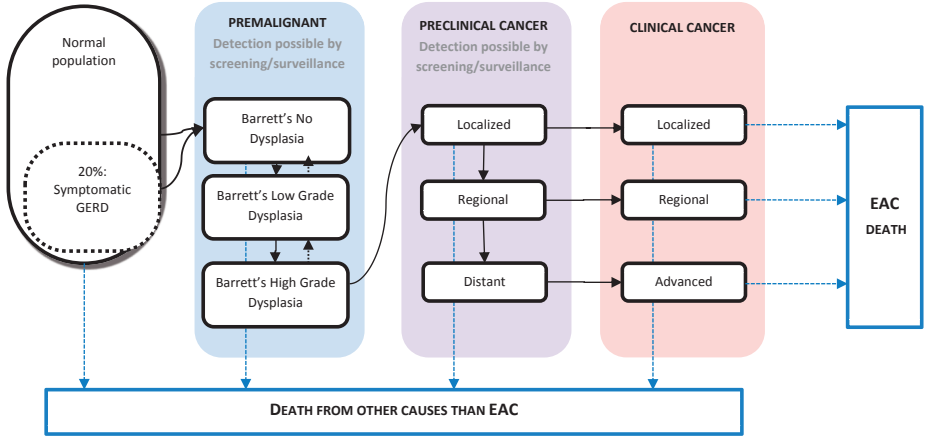

Figure 5. Graphical representation of the Erasmus/UW-EAC model.

sequentially into regional and advanced EAC. In every preclinical cancer stage there is a probability of the cancer being diagnosed due to the development of symptoms. The cure rate and survival after diagnosis depend on the stage of the cancer. Patients may die of other causes at any moment during their lifetime (figure 5).

1.6 RESEARCH QUESTIONS AND OUTLINE OF THIS THESIS

The overarching goal of this thesis is to gain insight into the unknowns of the natural history of EAC, and to predict the impact of these unknowns to inform decision making concerning the early detection and treatment of EAC. The work in this thesis is divided into two parts. In part one we focus on the natural history of EAC and explore the trends in EAC incidence and mortality and drivers of those trends. Part two explores trends in EAC control. As new treatments are emerging, we studied the effects of new treatments and interventions. The research questions and hypothesis of the studies subscribed in the chapters are as follow:

Part I: Natural history and secular trends of esophageal adenocarcinoma

- Research question 1: Can changes in lifestyle trends explain EAC incidence trends? (Chapter 2)
- Research question 2: What is the estimated future EAC incidence and mortality? (Chapter 3)
- Research question 3: Can we reconcile published data and accurately estimate the EAC incidence in BE using simulation modeling? (Chapter 4)

Part II: Possibilities for early detection of and intervention

- Research question 4: What is the current knowledge on possibilities for earlier detection for EAC and the benefits of early detection on the burden of EAC in the population? (Chapter 5)
- Research question 5: What is the influence of uncertainty in the risk of EAC development in patients with BE on the expected effectiveness and efficiency of hypothetical screening and treatment interventions? (Chapter 6)
- Research question 6: What is the long-term impact of endoscopic eradicative treatment on population EAC incidence and mortality? (Chapter 7)

Chapter 8 concludes this thesis with summarized answers of the research questions, further discussion of these answers and the direction for future research. In the model appendix we have described the MISCAN-EAC model and the alternations of the model used in the studies.

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PART I

NATURAL HISTORY AND SECULAR TRENDS OF ESOPHAGEAL ADENOCARCINOMA INCIDENCE AND MORTALITY

CHAPTER 2

Comparing trends in esophageal adenocarcinoma incidence and lifestyle factors between the United States, Spain and the Netherlands

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ABSTRACT

Background*:* The incidence of esophageal adenocarcinoma (EAC) in the western world has been rapidly increasing. The trends in obesity and other lifestyle-associated factors have been hypothesized to be important drivers of this increase. We tested this hypothesis by comparing changes in these factors with changes in EAC incidence over time between three western countries.

Methods*:* Data on EAC incidence trends were abstracted from the SEER-9 registry (1975-2009) for the U.S., from multiple cancer registries (1980-2004) in Spain, and from Eindhoven Cancer Registry (ECR) in the Netherlands (1974-2010). In addition we collected trend data on obesity, smoking and alcohol consumption. The trend data were analyzed using log-linear regression.

Results: In 1980 the EAC incidence was similar among the 3 countries ([0.46-0.63] per 100,000). EAC incidence increased in all, with the largest increase observed in the Netherlands, followed by U.S. and Spain (Estimated Annual Percentage of Change = 9.7%, 7.4%, 4.3% respectively). However, this pattern was not observed in lifestyle factors associated with EAC. With regards to obesity, U.S. clearly has had the highest prevalence rates both in the past and in the present. For alcohol, the highest consumption rates are seen in Spain. Smoking showed a reverse trend compared to EAC among all three countries in the last 20 years.

Conclusion: International trends in EAC incidence do not match corresponding trends in lifestyle-associated factors including obesity. Our findings suggest that factors other than obesity must be the important drivers for the increase in EAC incidence.

INTRODUCTION

Esophageal cancer is the eight most common cancer in the world and because of its high fatality rate, ranks sixth among all cancers with respect to mortality[1]. The cases can be divided into two major histological types, squamous cell carcinoma (SCC) and esophageal adenocarcinoma (EAC). In countries where incidence rates of EAC have been examined, there has been a sharp increase in cancer incidence over the last few decades[2-10], whereas rates of SCC have remained relatively stable. In many western countries[3, 5, 6, 10-13] incidence of EAC has increased more rapidly than any other malignancy, with average annual increases up to 8.2% for males during the past two or three decades.

EAC is assumed to develop from Barrett's Esophagus (BE).[14-16] BE is presumed to be a complication of gastro-esophageal-reflux disease (GERD) and symptoms of GERD such as heartburn and/or acid regurgitation are associated with EAC.[17, 18] Two lifestyle-associated factors believed to be associated with the development of EAC are obesity and smoking.[19, 20] Alcohol consumption has no clear association with the development of EAC.[21, 22] The most well-established factor is obesity, and the obesity epidemic is believed to be an important driver of the rise in EAC. If this were true; however, it would be expected that trends in obesity and other lifestyle-associated risk factors would match trends in EAC incidence. In this study, we tested this hypothesis by comparing changes in lifestyle-associated factors with changes in EAC incidence over time between the U.S., Spain and the Netherlands.

MATERIAL AND METHODS

Incidence

We used the Surveillance, Epidemiology, and End Results database (SEER)-9 to abstract the U.S. EAC incidence data from 1975 to 2009 for white males and females (C15, ICD-O: 8140-8149, 8160-8231, 8250-8499, 8501-8574, 8576). SEER-9 has information on all diagnosed malignancies among residents of the nine original SEER geographic areas, representing approximately 10% of the population of the U.S. From 1975 to 2009 a total of 13225 EAC cases were registered for white race, both sexes. Spanish data were obtained from 13 population-based cancer registries in Spain from 1980 to 2004 for the incidence of adenocarcinoma in the esophagus (C15, ICD-O: 8140-8570).[3] The 13 registries cover approximately 26% of the total Spanish population and have collected data for at least 10 consecutive years of the study period. From 1980 to 2004 a total of 1503 cases of EAC were registered for both sexes. Incidence data for the Netherlands were obtained from the Eindhoven Cancer Registry (ECR), which collects data on all

newly diagnosed malignancies in the South of the Netherlands, covering 13% of the Dutch population. From 1974 to 2010, 1680 EAC cases were registered for both sexes (C15, ICD-O codes similar to U.S.).

Obesity

Obesity was defined as a body mass index of 30 kg/m2 or more. Available data on obesity may be measured (the weight and height of a person are directly measured by trained observers) or self reported (gathered through questionnaire surveys). Although self reported obesity data can be biased, leading to lower obesity prevalence than measured obesity data[23-28] we chose to use self reported data because these were abstracted from larger national surveys instead of measured obesity data gathered by smaller local studies in Spain and the Netherlands. Self reported obesity data obtained by national surveys are available for the U.S. (NHIS, 1997-2009 all races)[29], Spain (NHS, 1987-2009)[15, 30], and the Netherlands (CBS, 1981-2009).[31] We abstracted these data from the Organization for Economic Co-operation and Development database.[32] To obtain estimates for self reported obesity data in the U.S. before 1997, we developed a linear regression model using data abstracted from the NHANES[33] national survey, which has obtained measured obesity data in the U.S. since 1961. A linear regression model was fitted to data from the overlapping time horizon (1997-2009) and the model was used to estimate self reported obesity prior to 1997 (self reported obesity prevalence = 0.75 * measured obesity prevalence).

Smoking

Smoking prevalence was defined as the prevalence of adult smokers (daily and occasional) in the population. U.S. data was abstracted from NHANES (1965-2010, all races).[34] Before 1992 only daily smokers were registered, but since 1992 these data also include occasional smokers. Spanish smoking prevalence was derived from the various national and European health surveys (1978-2009)[15, 30, 32, 34] where current smoking was defined as daily and occasional, over age 16. Because there were no data available before 1978 we used the estimated prevalence for daily smokers from 1945-1975.[35] For the Netherlands the smoking prevalence was abstracted from STIVORO (1958-2010), reporting daily and occasional smokers over age 15.[36]

Alcohol

We defined alcohol use as the recorded adult (15+) annual alcohol consumption per capita by country. The data for the three countries were obtained from the World Health Organization (WHO) data repository (1962-2009).[37]

Statistical Analysis

Annual EAC incidence rates were calculated per 100,000 person-years, and were age-standardized to the European standard population (ESP).[38] Temporal trends were assessed using joinpoint regression, for which the joinpoint regression program (version 3.5.2) from the Surveillance Research Program of the U.S. National Cancer Institute was used.

Joinpoint regression analysis finds the best-fit line through trend data, and tests whether a set of multi-segmented lines is a significantly better fit than a single line. The intersections of lines are called joinpoints with each joinpoint denoting a statistically significant (P=.05) change in trend. Each line segment between two joinpoints can be characterized with the estimated annual percentage of change (EAPC), reflecting a change in trend data at a constant percentage of the rate of the previous year within the time horizon of the line segment. The joinpoint regression analysis fits a series of joined straight lines on a log scale to the trends using y=ax+b, where y=ln(rate of trend data), x=calendar year and a= slope coefficient. The EACP is calculated from the equation: *(EAPC= 100 * (e^a -1))*.[39, 40]

The average annual percentage of change (AAPC) was used to analyze differences in the slopes of the time trends of time horizons we compared, which was the longest available time horizon for which trend data were available in all three countries. The AAPC was computed as a weighted average of the slope coefficients of the joinpoint regression line with the weights equal to the length of each line segment on the time interval *(*$AAPC = \left(e^{\frac{\sum w_i a_i}{w_i}}\right)$*, a_i= slope coefficient for each line segment i, w_i=number of years in time horizon of line segment i)*.

The difference between two AAPCs was obtained by using the approximate 95% confidence interval (CI) with the estimated difference of *AAPC(1) – AAPC(2)*.

RESULTS

Incidence

In 1980, the first year of commonly available data, EAC incidence was comparable in the three countries (US 0.63/100,000, Netherlands 0.55/100,000, Spain 0.46/100,000 (figure 1). In subsequent years, however, both the U.S. and the Netherlands reported a greater increase in incidence than Spain. The incidence in the Netherlands was comparable to the U.S. incidence until 1998; thereafter, EAC incidence in the Netherlands exceeded the U.S. incidence. For the complete period 1975-2009, the rate at which EAC incidence increased was significantly greater in Netherlands (AAPC=9.6, 95% CI [8.1-11.2]) than in the U.S. (AAPC=6.1, 95%CI[5.4-6.8]). When comparing the somewhat shorter overlapping period between data from Spain and the U.S. of 1980-2004, the increase in EAC is significantly greater in the U.S. (AAPC=7.4, 95%CI [6.5-8.2]) than in Spain (AAPC=4.3, 95%CI[3.1-5.5]) (table 1).

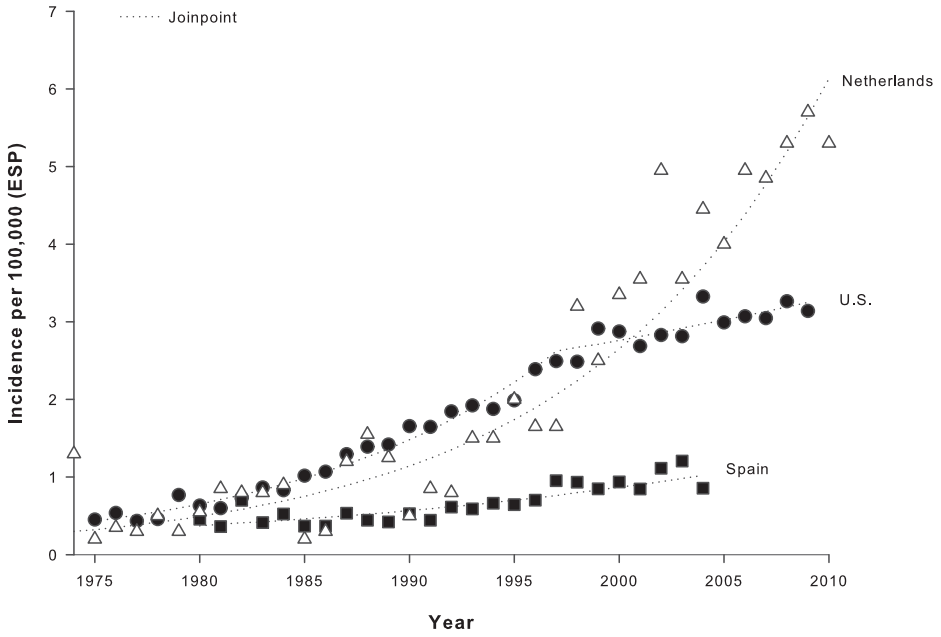


Figure 1 Esophageal Adenocarcinoma incidence (male and female)

Figure 1. EAC incidence rate trends over time for U.S., Spain and the Netherlands

Obesity

The obesity trends for the three countries demonstrate a different sequence than the EAC incidence trends (figure 2A). From 1987 on, the U.S. has had the highest obesity prevalence (15.0%), followed by Spain (6.8%) and the Netherlands (5.3%); this order is preserved throughout the entire observation period. In the last year of observation (2009) the obesity prevalence had increased to 27.7%, 16.0% and 11.8% for respectively the U.S., Spain and the Netherlands.

Smoking

In 1965, the first year of commonly available data, smoking prevalence was highest in the Netherlands (58.7%), followed by the U.S. (41.9%) and Spain (21.6%). This sequencing was altered when the Spanish smoking prevalence increased from 1965 to a peak in 1985, exceeding that of the Netherlands and U.S. (figure 2B). Both U.S. and the Netherlands had decreasing smoking prevalence (table 2) through the whole observation period. In the final year of commonly available data (2009) the smoking prevalence was highest in Spain (29.9%) followed by the Netherlands (28.0%) and the U.S. (20.6%).

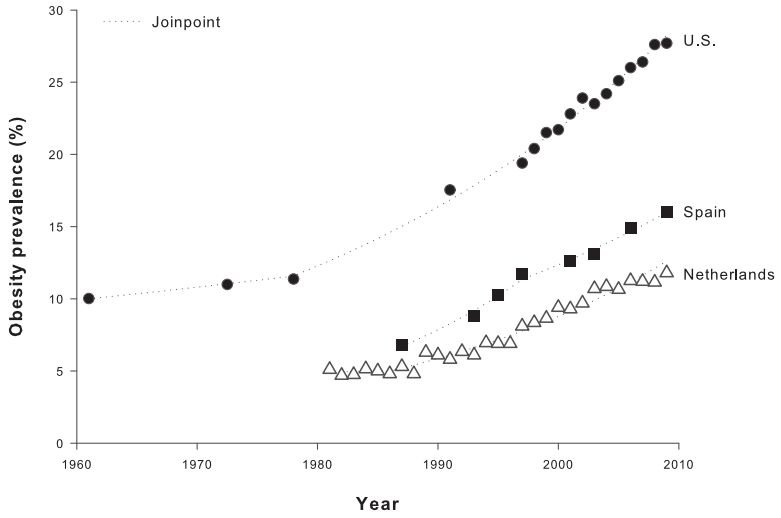
Table 1. Estimated Annual Percentages of Change (EAPC) of EAC incidence rate, obesity and smoking prevalence, and alcohol consumption with joinpoint log-regression analysis for U.S., Spain and the Netherlands.

							Joinpoint analysis: total available period							
	Joinpoint analysis: overlapping periods						Trend 1		Trend 2		Trend 3		Trend 4	
EAC Incidence	**Years**	**IR startyear**	**IR endyear**	**AAPC**		**CI**	**Years**	**EAPC**	**Years**	**EAPC**				
U.S.	1980-2004	0.63	3.32	7.4*	6.5	8.2	1975-1997	8.5*	1997-2009	1.8*				
Spain	1980-2004	0.46	0.86	4.3*	3.1	5.5	1980-2004	4.3*						
Netherlands	1980-2004	0.55	4.45	9.7*	6.8	12.7	1974-2010	8.8*						
Obesity prevalence	*Years*	*PR startyear*	*PR endyear*	*AAPC*		*CI*	*Years*	*EAPC*	*Years*	*EAPC*				
U.S.	1987-2009	15.01	27.70	2.8*	2.6	3	1961-1978	0.9*	1978-2009	2.9*				
Spain	1987-2009	6.80	16.00	4.0*	3.3	4.7	1987-1997	5.4*	1997-2009	2.9*				
Netherlands	1987-2009	5.30	11.80	4.1*	3.7	4.5	1981-1986	0.2	1986-2009	4.1*				
Smoking prevalence	*Years*	*PR startyear*	*PR endyear*	*AAPC*		*CI*	*Years*	*EAPC*	*Years*	*EAPC*	*Years*	*EAPC*	*Years*	*EAPC*
U.S.A.	1965-2009	41.90	20.60	-1.6*	-2.0	-1.2	1961-2010	-1.7*						
Spain	1965-2009	21.55	29.87	-0.0	-0.5	0.4	1945-1985	1.5*	1985-2009	-1.3*				
Netherlands	1965-2009	58.70	28.00	-2.0*	-2.3	-1.6	1958-1970	-0.0	1970-1989	-2.9*	1989-1996	0.5	1996-2010	-2.0*
Alcohol consumption	*Years*	*ANC startyear*	*ANC endyear*	*AAPC*		*CI*	*Years*	*EAPC*	*Years*	*EAPC*	*Years*	*EAPC*	*Years*	*EAPC*
U.S.A.	1962-2009	7.99	8.67	0.2*	0.1	0.3	1962-1971	2.3*	1971-1982	0.6*	1982-1996	-1.9*	1996-2009	0.7*
Spain	1962-2009	14.64	11.37	-0.4	-0.8	0.1	1962-1972	1.8*	1972-1993	-3.3*	1993-2005	-1.5*	2005-2009	4.4*
Netherlands	1962-2009	4.29	9.20	1.7*	1.3	2	1962-1975	7.9*	1975-1979	0.5	1979-1988	-1.7*	1988-2009	-0.4*

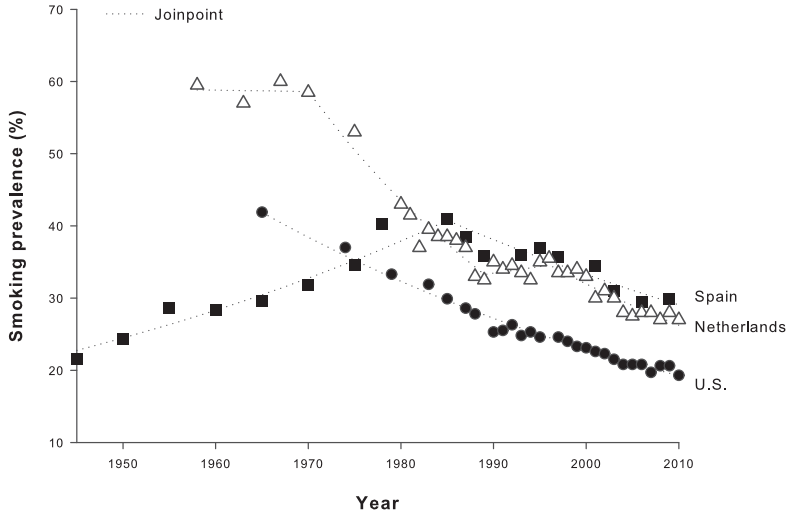
IR = Incidence rate, PR = prevalence, ANC=Annual liter consumption per capita, EAPC= Estimated Annual Percentage of Change, AAPC=Average Annual Percentage of Change, CI=95% Confidence Interval

***Significant different from zero, 96% CI**

A. Obesity prevalence



B. Smoking prevalence



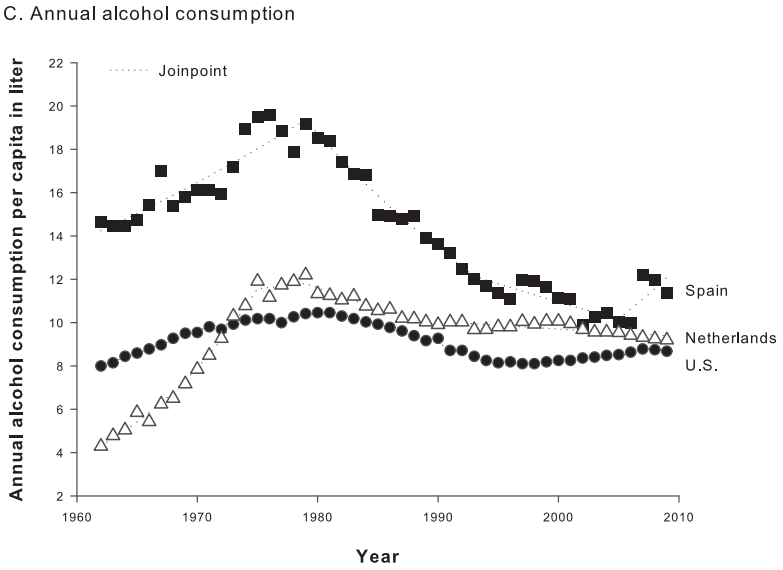


Figure 2. Lifestyle factor trends over time for U.S., Spain and the Netherlands
A) Obesity prevalence
B) Smoking prevalence
C) Annual alcohol consumption

Alcohol

In 1962 the highest annual alcohol consumption per capita was in Spain (14.6 ltr), followed by the U.S. (8.0 ltr) and the Netherlands (4.3 ltr) (table 1). Spain continued to have the highest alcohol consumption per capita during the observation time frame, although after a peak in 1976 consumption decreased to a consumption level comparable to the Netherlands in 2005 (figure 2C). The Netherlands have exceeded the U.S. trend since 1973. In 2009, the alcohol consumption was highest in Spain (11.4 ltr) followed by the Netherlands (9.2 ltr) and the U.S. (8.7 ltr).

Trends by sex

There is a large difference in the EAC incidence rates between males and females. Female EAC incidence in the Netherlands is greater than the U.S. through the entire observation period, while the male EAC incidence in the Netherlands exceeds the U.S after 2003. In both males and females, the lowest rates are seen in Spain.

Identical country-sequencing is found in the obesity trends for males and females. The differences between male and female obesity prevalence are similar among the Netherlands and U.S., with the uniform feature of higher female obesity prevalence. In Spain male obesity has exceeded female obesity since 2006.

For smoking prevalence, the U.S. and the Netherlands show similar trends for males and females, both having decreased since 1967, with males having a higher smoking prevalence than females. In Spain male smoking prevalence peaked in the 70s, when the female prevalence was still negligible, whereas female prevalence peaked after the 90s.

For the alcohol consumption per capita no sex-specific data are available, although we assume that alcohol consumption is higher in men than in women.[41] In the supplementary files sex-specific tables and figures for EAC incidence, obesity and smoking prevalence are shown.

Table 2. Comparisons of Average Annual Percentages Change in EAC incidence, obesity, smoking and alcohol consumption for U.S., Spain and the Netherlands.

Trend	Years	Countries	AAPC(1)			AAPC(2)	AAPC(1)-AAPC(2)	CI	
EAC Incidence	1975-2009	U.S.	6.1*	-	Netherlands	9.6*	-3.5*	-4.9	-1.6
	1980-2004	U.S.	7.4*	-	Spain	4.3*	-3.1*	1.4	4.5
	1980-2004	Spain	4.3*	-	Netherlands	9.7*	-5.4*	-7.9	-2.3
Obesity prevalence	1981-2009	U.S.	2.8*	-	Netherlands	3.4*	-0.6	-1.5	0.4
	1987-2009	U.S.	2.8*	-	Spain	4.0*	-1.2*	-2.1	-0.2
	1987-2009	Spain	4.0*	-	Netherlands	4.1*	-0.1	-0.4	0.3
Smoking prevalence	1965-2009	U.S.	-1.6*	-	Netherlands	-2.0*	0.4	-0.7	1.4
	1965-2009	U.S.	-1.6*	-	Spain	-0.1	-1.5*	-2.8	-0.8
	1965-2009	Spain	-0.1	-	Netherlands	-2.0*	1.9*	1.3	3.1
Alcohol consumption	1962-2009	U.S.	0.2*	-	Netherlands	1.7*	-1.5*	-2.1	-0.8
	1962-2009	U.S.	0.2*	-	Spain	-0.4	0.6	-0.4	1.5
	1962-2009	Spain	-0.4	-	Netherlands	1.7*	-2.1*	-3.1	-0.9

AAPC = Average Annual Percentage of Change, CI = Confidence Interval
*Significant different from zero, 95% CI

DISCUSSION

EAC incidence in the U.S., Spain and the Netherlands show large differences in both absolute rates and time trends; however, all trends have increased over time. Time trends for obesity, smoking and alcohol in these countries, however, do not correlate with EAC incidence trends. These findings suggest that even if obesity were to provide a mechanism supporting the development of EAC, alternative factors must be the underlying drivers for the increasing incidence of EAC.

We analyzed time trends for different lifestyle-associated factors. Although obesity is increasing in all three countries, the differences in absolute prevalence and prevalence

changes over time between countries do not match the EAC incidence trend, as would be expected if obesity were the most significant risk factor. Moreover, a comparison between Spain and the U.S. reveals a reverse relationship; while the increase in EAC incidence is greater in the U.S. than Spain, the obesity increase in Spain is greater than in the U.S. Moreover, the Netherlands has a greater increase in EAC incidence than the U.S., but there was no difference in the AAPCs of obesity between the Netherlands and the U.S (1981-2009). Regarding smoking, a prior pooled analysis revealed an odds ratio (OR) of 1.96 for ever smokers versus never smokers.[20] However, the expected lag between exposure and cancer would be no more than 50 years; therefore, the absence of an observed decrease in EAC incidence suggests smoking is not an important risk factor. Finally, the trends do not support alcohol to be a risk factor for EAC (table 3).

Table 3. Hypotheses of the relationship between lifestyle factors and EAC incidence.

Hypotheses:	Absolute rates	Change in rates
Obesity is a driver of the increase in EAC	Does not support: the country-sequencing of EAC incidence and obesity prevalence differ.	Supports: the EAC incidence and obesity prevalence is increasing in all countries.
		Does not support: Spain has a lower increase than U.S. in EAC incidence* (1980-2004), but a greater increase in obesity prevalence* (1987-2009). Furthermore, the Netherlands have a greater increase in EAC incidence than U.S. * (1975-2009), but a similar increase in obesity prevalence (1981-2009).
Smoking is a driver of the increase in EAC	Supports: the country-sequencing of EAC incidence and smoking prevalence may correlate, but only with a lag time > 50 years.	Does not support: Prevalence of smoking is decreasing in all countries.
Alcohol is a driver of the increase in EAC	Does not support: the country-sequencing of alcohol consumption does not correlate with EAC incidence.	Does not support: alcohol consumption is decreasing, while EAC incidence is increasing in all countries.

* significant, 95% CI

When interpreting the time trends several alternative explanations for the increasing EAC incidence may be postulated. First, the time trends might reflect changes in diagnostics. With the refinement of various diagnostic modalities and the increased use of endoscopy among patients with GERD symptoms or Barrett's esophagus, increased diagnosis might be a reason for the observed increased incidence of EAC. Since there has been a concomitant increase in EAC mortality it is unlikely that changes in diagnostics are a major influence on EAC incidence. Second, a reclassification of tumors could result in an observed increase in EAC incidence. However, changes in reclassification of tumors would be expected to show corresponding reductions in tumors adjacent

to the esophagus, which have not been observed. Gastric cardia incidence has remained stable in all of the examined countries for the last two decades. In addition, we observed a steady rise of EAC incidence, instead of a discrete change that would represent reclassification influences. Finally, although the trends imply that obesity, smoking and alcohol are not the primary cause for the rise in EAC incidence, it is possible that the effect of these risk factors could be masked by an unknown protective factor with differential prevalence across the countries.

If the incidence of EAC is increasing, yet not caused by obesity or smoking alternative explanations must be sought. Chronic *Helicobacter pylori (H. pylori)* infection has been hypothesized to protect against GERD and BE due to induction of atrophic gastritis and hypochlorhydria.[42] Advances in sanitation and the widespread use of antibiotics have been postulated to contribute to the decline in *H. pylori* infection, especially in western countries. Therefore, it is conceivable that the increase in EAC incidence in western countries may be in part caused by the decline in *H. pylori* colonization rates.[43, 44] Because of the paucity on *H. pylori* infection trend data across the countries we were not able to include this factor in our study.

We chose to include the U.S., Spain and the Netherlands in our study because while the incidence rates of EAC are increasing in all countries, the rate of change differs, and the trends in lifestyle-associated factors vary greatly. Although several prior studies have compared EAC incidence between multiple countries[2, 5, 10, 45, 46] only one examined trends in risk factors.[10] Our study is unique because we have simultaneously compared EAC incidence rates between three countries and the trends in lifestyle-associated factors hypothesized to cause EAC, which is also the strength of this study. If we would have analyzed the trends for each country individually our conclusions might have been different. Looking only at the U.S., we may have supported the hypothesis that obesity and smoking are drivers for the EAC trend since obesity has the steepest slope in the lifestyle factor trend data. For the Netherlands we would have concluded that smoking might be the driving lifestyle factor because the obesity increase starts increasing relatively late in time. For Spain the conclusion would be that smoking and alcohol consumption would have no influence on EAC increase at all, and obesity is the only supporting lifestyle factor. However, by examining all countries simultaneously, it appears that smoking and obesity cannot be the main drivers because their trends are inconsistent among the three countries.

While the inclusion of multiple countries is a strength of this study, analyzing time trends between countries also has limitations. First, definitions of predictors and outcomes can be dissimilar between various data sources. For example, morphology

codes for EAC incidence differed slightly between Spain and the other countries. Using the Spanish morphology codes in the U.S. would result in an increase of 0.33% in total EAC cases from 1975-2009. Additionally, EAC incidence trends in the US were based on whites only for comparability with rates in Spain and the Netherlands. However, long-term data for obesity were available for the total population only. Given the comparability of trends between blacks and whites and the fact that whites constitute a large majority of the population, we do not expect this to substantially influence our results. Second, there were variations in ages, collection methods and inclusion criteria between the three countries. However, we do not believe this variation influenced our results significantly since we examined trend data that were highly correlated over ages, collection methods and inclusion criteria. Third, the available time horizons of the data were dissimilar between countries for lifestyle-associated factors and EAC incidence trends. However, the overlapping periods were sufficient for testing our hypothesis whether these factors could be main drivers for the increasing EAC incidence. Furthermore, the level of detail available for the risk factors we studied was limited. We were unable to identify the quantity of smoking by country and sex, and the composition of cigarettes for each country. The distribution of alcohol consumption in the population, and the type of alcohol consumption would reflect more specific trends. The consumption of wine has been significantly larger in Spain than the two other countries, while the consumption of beer was modestly largest in the Netherlands up to 2006. These differences, as well as differences in quantity of smoking may influence the risk for EAC incidence. Fourth, results of ecological analysis at the population level may not reflect associations at the individual level. Furthermore, interactions between the lifestyle factors and development of EAC cannot be analyzed in this study design. Fifth, differences in healthcare practices and adoption of new practices between the three countries could not be specified and implemented in our analysis. Finally, it is possible that the time period was insufficient to observe the impact of lifestyle factors on EAC incidence. If smoking and obesity are associated with the development of BE, the impact of these factors on EAC may require a long lag time.

In conclusion, international trends in lifestyle-associated factors most commonly implicated in EAC development, including obesity, are discordant with the trends in EAC incidence. This analysis suggests that other important drivers for the increase in EAC incidence in the three observed countries must be present.

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SUPPLEMENTARY INFORMATION

This section includes the sex-specific tables and figures for EAC incidence, obesity and smoking prevalence. Female EAC incidence in the Netherlands is greater than the U.S. through the entire observation period, while the male EAC incidence in the Netherlands exceeds the U.S after 2003 (figure S1, S2). In both males and females, the lowest rates are seen in Spain.

Identical country-sequencing is found in the obesity trends for males and females. The differences between male and female obesity prevalence are similar among the Netherlands and U.S., with the uniform feature of higher female obesity prevalence. In Spain male obesity has exceeded female obesity since 2006 (figure S3,S4).

For smoking prevalence, the U.S. and the Netherlands show similar trends for males and females, both having decreased since 1967, with males having a higher smoking prevalence than females. In Spain male smoking prevalence peaked in the 70s, when the female prevalence was still negligible, whereas female prevalence peaked after the 90s (figure S5,S6). The sex-specific estimated annual percentages of change (EAPC) for the EAC incidence rate, obesity and smoking prevalence and joinpoint log-regression analyses for U.S., Spain and the Netherlands are shown in Table S1 and S2.

Table S1. Male Estimated Annual Percentages of Change (EAPC) of EAC incidence rate, obesity and smoking prevalence with joinpoint log-regression analysis for U.S.A., Spain and the Netherlands.

							Joinpoint analysis											
	Log-regression over total overlapping period						Trend 1		Trend 2		Trend 3		Trend 4		Trend 5		Trend 6	
EAC Incidence	**Years**	**IR startyear**	**IR endyear**	**AAPC**	**CI**		**Years**	**EAPC**	**Years**	**EAPC**								
U.S.A.	1980-2004	1.10	6.35	7.4*	6.4	8.4	1975-1996	9.0*	1996-2009	1.8*								
Spain	1980-2004	0.74	1.58	4.4*	3.3	5.6	1980-2004	4.4*										
Netherlands	1980-2004	0.80	7.60	10.8*	6.8	15	1974-2010	9.1*										
Obesity prevalence	*Years*	*PR startyear*	*PR endyear*	*AAPC*	*CI*		*Years*	*EAPC*	*Years*	*EAPC*								
U.S.A.	1987-2009	13.97	28.20	3.2*	3	3.5	1961-1978	1.2*	1978-2009	3.4*								
Spain	1987-2009	6.40	17.30	4.4*	3.8	5.5	1987-2009	4.4*										
Netherlands	1987-2009	4.20	11.20	4.8*	4.2	5.3	1981-2009	4.5*										
Smoking prevalence	*Years*	*PR startyear*	*PR endyear*	*AAPC*	*CI*		*Years*	*EAPC*	*Years*	*EAPC*	*Years*	*EAPC*	*Years*	*EAPC*	*Years*	*EAPC*	*Years*	*EAPC*
U.S.A.	1965-2009	51.20	23.20	-1.9*	-2	-1.7	1965-1990	-2.3*	1990-2010	-1.3*								
Spain	1965-2009	55.70	35.34	-1.4*	-2.1	-0.8	1945-1978	1.1*	1978-2009	-2.2*								
Netherlands	1965-2009	80.17	30.00	-2.3*	-3.6	-0.9	1958-1975	-1.6*	1975-1982	-6.2	1982-1985	0.5	1985-1988	-5.3	1988-1996	0.3	1996-2010	-2.1*

IR = Incidence rate, PR = prevalence, ANC=Annual liter consumption per capita, EAPC = Estimated Annual Percentage of Change, AAPC=Average Annual Percentage of Change, CI=95% Confidence Interval

*Significant different from zero, 96% CI

Table S2. Female Estimated Annual Percentages of Change (EAPC) of EAC incidence rate, obesity and smoking prevalence, with joinpoint log-regression analysis for U.S.A., Spain and the Netherlands.

						Joinpoint analysis									
	Log-regression over total overlapping period					Trend 1		Trend 2		Trend 3		Trend 4		Trend 5	
EAC Incidence	**Years**	**IR startyear**	**IR endyear**	**AAPC**	**CI**	**Years**	**EAPC**								
U.S.A.	1980-2004	0.22	0.77	6.6*	5.6 7.7	1975-2009	6.0*								
Spain	1980-2004	0.18	0.14	3.9*	0.6 7.3	1980-2004	3.9*								
Netherlands	1980-2004	0.30	1.30	7.5*	5.1 9.9	1974-2010	6.2*								
Obesity prevalence	*Years*	*PR*	*PR endyear*	*AAPC*	*CI*	*Years*	*EAPC*	*Years*	*EAPC*	*Years*	*EAPC*				
U.S.A.	1987-2009	15.32	27.30	2.7*	2.4 2.9	1961-1978	0.6	1978-2009	2.7*						
Spain	1987-2009	7.30	14.70	3.4*	2.3 4.5	1987-2009	3.4*								
Netherlands	1987-2009	6.40	12.40	3.6*	3.1 4.1	1981-1994	1.7*	1994-1998	8.1	1998-2009	2.4*				
Smoking prevalence	*Years*	*PR startyear*	*PR endyear*	*AAPC*	*CI*	*Years*	*EAPC*	*Years*	*EAPC*	*Years*	*EAPC*	*Years*	*EAPC*	*Years*	*EAPC*
U.S.A.	1965-2009	33.70	18.10	-1.4*	-1.8 -1	1965-1983	-0.7*	1983-1990	-3.0*	1990-1999	-1.0*	1999-2005	-3.0*	2005-2010	-0.5
Spain	1965-2009	3.60	24.59	4.3*	3.4 5.3	1945-1985	9.2*	1985-2009	0.1						
Netherlands	1965-2009	36.40	26.00	-0.9*	-1.7 0	1958-1970	3.5*	1970-1989	-1.9*	1989-1999	0	199-2005	-3.7*	2005-2010	1.2

IR = Incidence rate, PR = prevalence, ANC=Annual liter consumption per capita, EAPC = Estimated Annual Percentage of Change, AAPC=Average Annual Percentage of Change, CI=95% Confidence Interval

*Significant different from zero, 96% CI

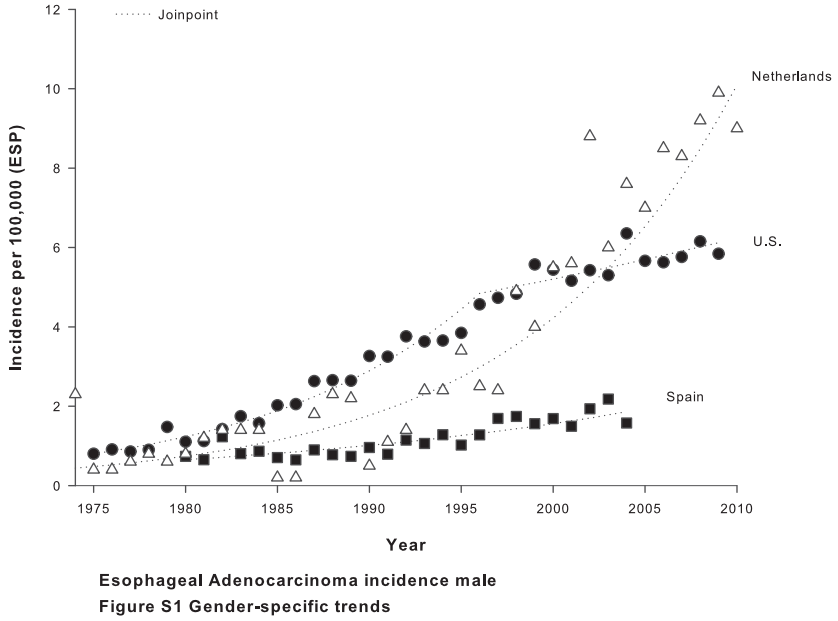

Figure S1. Male EAC incidence rate trends over time for U.S., Spain and the Netherlands

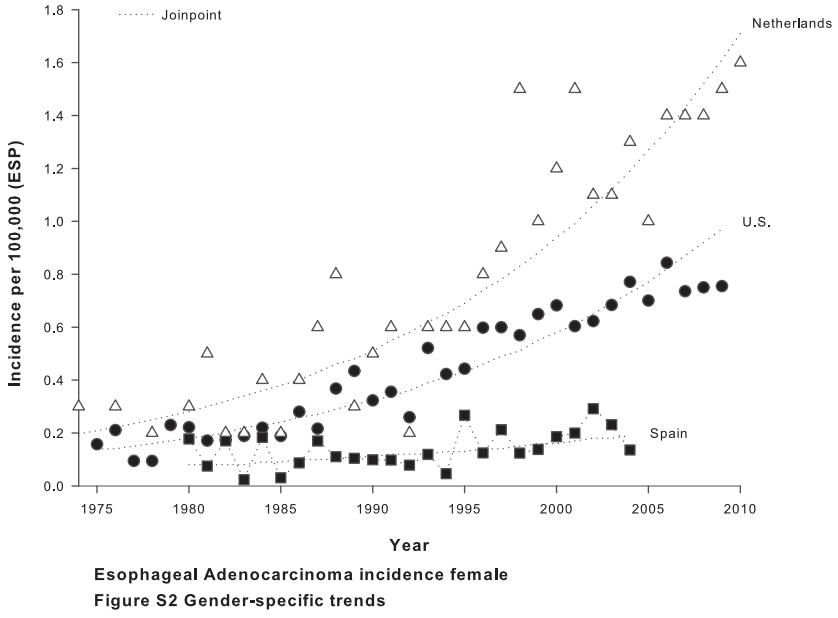

Figure S2. Female EAC incidence rate trends over time for U.S., Spain and the Netherlands

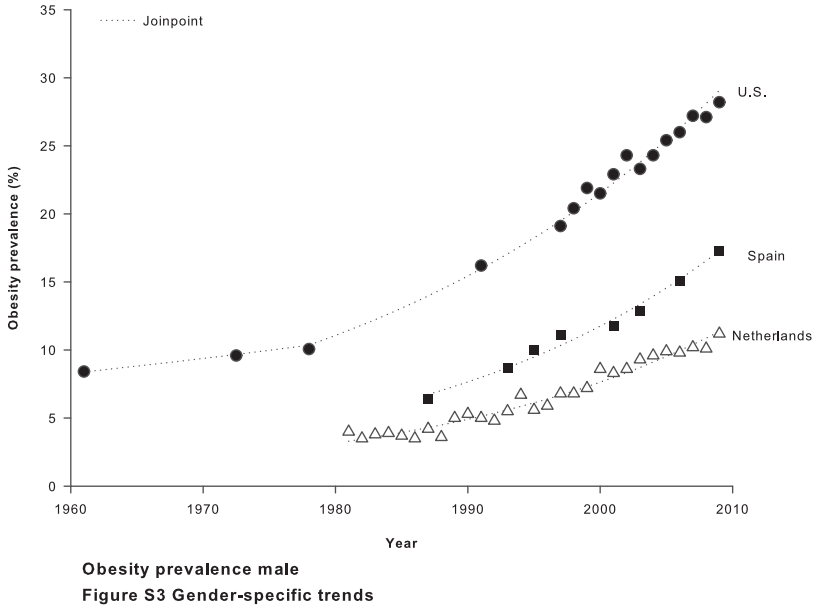

Figure S3. Male Obesity prevalence trends over time for U.S., Spain and the Netherlands

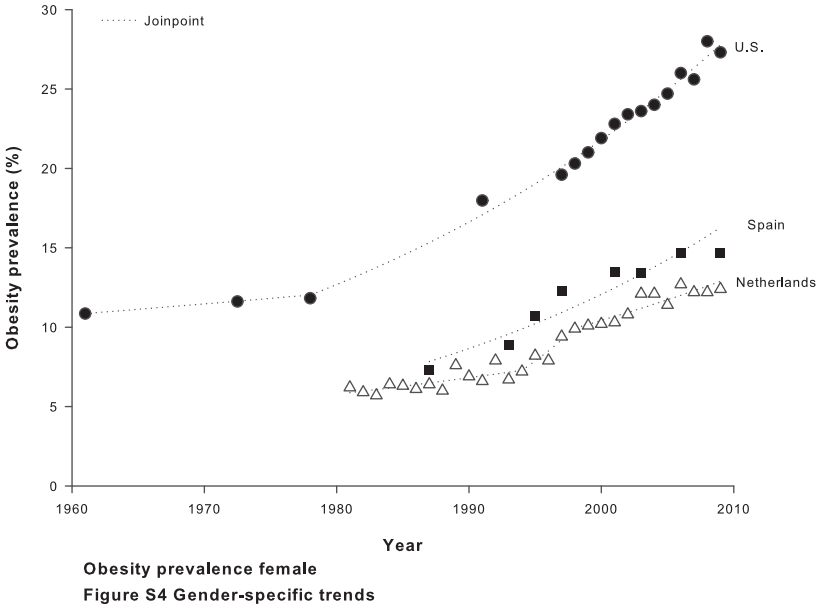

Figure S4. Female Obesity prevalence trends over time for U.S., Spain and the Netherlands

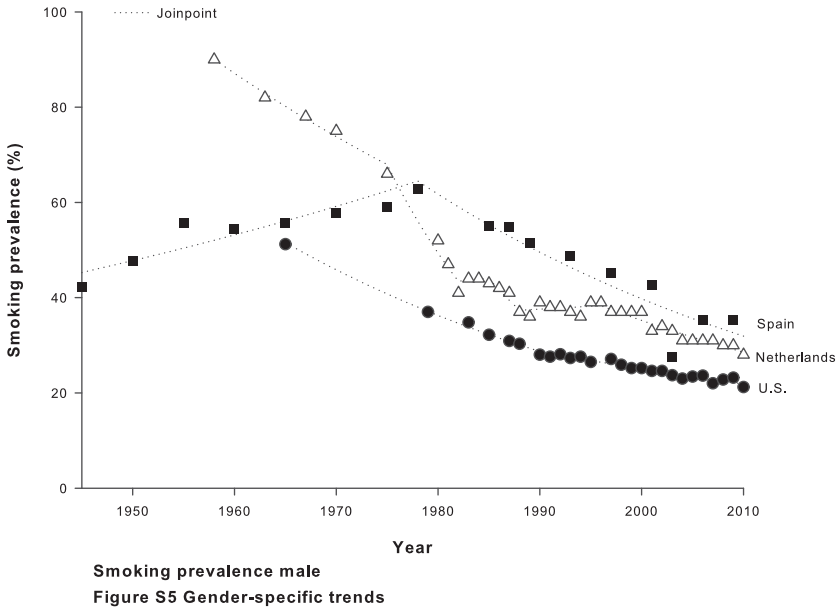

Figure S5. Male Smoking prevalence trends over time for U.S., Spain and the Netherlands

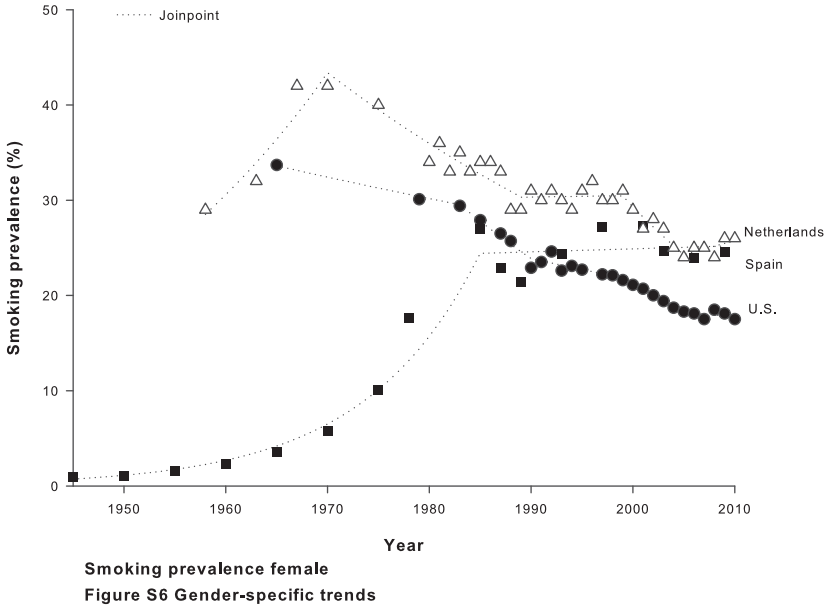

Figure S6. Female Smoking prevalence trends over time for U.S., Spain and the Netherlands

CHAPTER 3

Exploring the recent trend in esophageal adenocarcinoma incidence and mortality using comparative simulation modeling

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ABSTRACT

Background: The incidence of esophageal adenocarcinoma (EAC) has increased five-fold in the United States since 1975. The aim of our study was to estimate future U.S. EAC incidence and mortality and to shed light on the potential drivers in the disease process that are conduits for the dramatic increase in EAC incidence.

Methods: A consortium of three research groups calibrated independent mathematical models to clinical and epidemiologic data including EAC incidence from the Surveillance, Epidemiology, and End Results (SEER 9) registry from 1975–2010. We then used a comparative modeling approach to project EAC incidence and mortality to year 2030.

Results: Importantly, all three models identified birth cohort trends affecting cancer progression as a major driver of the observed increases in EAC incidence and mortality. All models predict that incidence and mortality rates will continue to increase until 2030 but with a plateauing trend for recent male cohorts. The predicted ranges of incidence and mortality rates (cases per 100,000 person years) in 2030 are 8.4-10.1 and 5.4-7.4 respectively for males, and 1.3-1.8 and 0.9-1.2 for females. Estimates of cumulative cause-specific EAC deaths among both sexes for years 2011-2030 range between 142,300 and 186,298, almost double the number of deaths in the past 20 years.

Conclusions: Through comparative modeling, the projected increases in EAC cases and deaths represent a critical public health concern that warrants attention from cancer control planners to prepare potential interventions.

Impact: Quantifying this burden of disease will aid health policy makers to plan appropriate cancer control measures.

INTRODUCTION

The vast majority of esophageal cancers are either squamous cell carcinoma (SCC) or adenocarcinoma (EAC). While esophageal SCC incidence has been declining in the U.S. and other parts of the western world, EAC incidence has experienced an alarming five-fold increase over the past four decades.[1] There is no consensus regarding the causes of this increase in EAC incidence, although an increasing prevalence of gastroesophageal reflux disease (GERD) related to increases in abdominal obesity[2] and wider eradication of Helicobacter pylori infection[3, 4] have been suggested, among others. GERD is a risk factor for Barrett's esophagus (BE), a pre-dysplastic condition associated with progression to EAC.[5] Current EAC prevention efforts have focused on endoscopic screening for BE, although the benefit and effectiveness are uncertain.[6, 7] Recent analyses of historical trends in EAC incidence and mortality in the U.S. suggest that EAC incidence continues to rise, although the EAC incidence rate may be beginning to plateau in recent years.[8, 9] Projections of future EAC incidence and mortality would provide important data for health policy makers as they track cancer trends and plan appropriate cancer control policy. In this analysis, we utilized independent mathematical models in a comparative modeling approach to make future EAC incidence and mortality projections.

Mathematical modeling is a powerful methodology which can be used to make projections by systematically integrating available data. Despite its potential, one common criticism of modeling is that independent modeling efforts often yield disparate results. These differences can primarily be attributed to differing model inputs and model structures, and often a lack of transparency in model assumptions, all impeding wider acceptance of simulation modeling results. The Cancer Intervention and Surveillance Modeling Network (CISNET) is a National Cancer Institute (NCI) funded consortium of mathematical and computational modelers who work closely together to address many of these limitations using a comparative modeling approach. Comparative modeling is a powerful method to improve each of the participating models by providing an environment where experts in modeling methodology, cancer control and clinical management can easily and openly collaborate. This context allows for an iterative process where common calibration targets are shared but other aspects of the individual models are free to differ. After each model is calibrated and applied independently, the prediction targets are shared and analyzed cooperatively, providing a transparent setting for iterative improvement of the models, and enhancing our understanding of the natural history of a particular type of cancer. After model development and refinement, CISNET researchers can then use their models to evaluate the impact of potential interventions on trends in cancer incidence and mortality, helping to optimize cancer control strategies. CISNET models have been utilized by the U.S.

Preventive Services Task Force (USPSTF) for breast[10] and colorectal cancer screening guidelines[11], in formulating draft recommendations for lung cancer screening[12], and by the Centers for Medicare and Medicaid Services (CMS) to compare the effectiveness of CRC screening strategies.[13, 14]

The CISNET consortium focuses on five cancer sites: breast, colorectal, lung, prostate, and esophagus. The esophagus group is comprised of four academic institutions that have developed three independent models of EAC. Our three independent models were calibrated to historic EAC incidence and mortality rates between the years 1975-2010 for all males and all females from the Surveillance, Epidemiology and End Results (SEER 9) database.[15] After calibration, we compared the calibration results from the three models to reinforce each model's validity against the available data. Afterward, the models were used to generate independent projections of EAC incidence and mortality to the year 2030. We also outputted the BE prevalence, progression rates to detected cancer in patients with BE, and average EAC sojourn time (time interval between preclinical EAC and clinically detected EAC); all are important underlying factors that may be subject to secular trends related to period and/or birth cohort. In modeling these trends we had developed a better understanding of the observed increases in EAC incidence and mortality.

MATERIALS AND METHODS

The Models

We analyzed EAC incidence and mortality rates by using three mathematical models that were developed independently by participants in the NCI's CISNET consortium: the Multiscale Esophageal AdenoCarcinoma (MSEAC) Model from the Fred Hutchinson Cancer Research Center (Seattle, WA) - FHCRC model, the Esophageal Adeno-Carcinoma Model (EACMo) from the Massachusetts General Hospital (Boston, MA) - MGH model, and University of Washington (Seattle, WA) and the Microsimulation Screening Analysis model from Erasmus University Medical Center (Rotterdam, The Netherlands) - UW-MISCAN-Esophagus model(Erasmus/UW-EAC model). The major features of the models are also summarized in the appendix. Each model computes the life histories of a population of hypothetical individuals from birth (UW-MISCAN and FHCRC) or age 20 (MGH) to death and has a natural history component that tracks the progression of esophageal disease or precursor states preceding adenocarcinoma. All three models include the following health states: healthy, GERD symptoms, BE without dysplasia, BE with dysplasia, preclinical cancer, clinically diagnosed cancer, and death. The UW-MISCAN and MGH models further categorize dysplasia in BE into low-grade dysplasia (LGD) and high-grade dysplasia (HGD).

The primary differences between these models are in the modeling methodology. The FHCRC model is a biological model based on the paradigm of initiation, promotion, and progression where carcinogenesis arises from the accumulation of mutations and clonal expansion of partially altered cells on the pathway to malignancy (appendix figure A1). The FHCRC model also combines likelihood and multiscale spatial simulation methods to represent health states as observation or detection processes built into a detailed tissue- and cell-level model of carcinogenesis.[16, 17] It also includes random transitions from normal esophageal tissue to BE that occur with a rate which reflects the prevalence of GERD in the general population.[18, 19] The mathematical construct of the model yields a numerical hazard function, which predicts the age-specific incidence of EAC and therefore was used for parameter estimation. In contrast, the MGH and UW-MISCAN models are empirically-based simulations of natural histories. The MGH model is a Markov state transition simulation model which simulates a cohort of hypothetical individuals and does not allow for disease regression (appendix figure A4).[2, 20, 21] The UW-MISCAN model is a microsimulation model using a discrete event formalism which simulates individuals one at a time and also allows for disease regression in the health states prior to cancer (appendix figure A7).

Although the three models differ substantially in their modeling structure, they all generate predictions of incidence and mortality as a function of age and stage of EAC diagnosis.

Modeling of EAC Trends

Mathematical models can be utilized to investigate the impact of shifting risk factor patterns on the population burden of cancer. Other CISNET cancer groups have modeled known risk factors, such as the Lung group that used historical smoking data to investigate the total number of lives saved between 1975 and 2000 as a result of the implementation of tobacco control policies.[22] Since EAC incidence has experienced a dramatic increase, it is imperative that our modeling incorporates the mechanism(s) that effectively shed light on the potential causes of this increase. The three CISNET groups opted to capture this increase using a generalization of the traditional age-period-cohort (APC) formalism[23-25] in which age, period and cohort trends are applied to rates within the natural history model. The FHCRC group used likelihood methods to evaluate period and cohort trends affecting specific cell kinetic rates, including trends on BE incidence. The MGH and UW-MISCAN groups varied the transition rates between health states in the models which depend on age, calendar year and birth year of the cohort. The traditional Age-Period-Cohort (APC) models are log-linear models which simultaneously analyze the age, period, and cohort effects in data from registries such as the SEER 9 Program. By replacing the age effects in the traditional APC approach with functionally constrained parametric models, we finesse a well-known

'linear-trend' non-identifiability problem[26-28] allowing us to explore both period and cohort effects jointly. These effects were estimated together with the age dependent parameters (UW-MISCAN) or after the age dependent parameters were established (MGH). For FHCRC, the period and cohort effects were calibrated jointly with estimation of the cell kinetic parameters and mutation rates in the EAC hazard function. For the details of modeling EAC trends in each model, see the model appendix and corresponding Figures A2,3,5,6,and 8.

Common Calibration Targets

All three CISNET models were calibrated to EAC incidence rates from the Surveillance, Epidemiology, and End Results (SEER 9) program data for all men and all women aged 20-84 years in the United States from 1975–2010. Following the method in one of our previous analyses[8], the cancer incidence rates are comprised of cancers defined/identified by the International Classification of Diseases for Oncology, third edition (ICD-O-3) histology codes 8140- 8141, 8143- 8145, 8190- 8231, 8260-8263, 8310, 8401, 8480-8490, 8550-8551, 8570-8574, and 8576. Standard mortality statistics are not available for EAC because death certificates do not include the histology of the cancer. However, incidence-based mortality (IB mortality) data in SEER utilize cancer registry information to link characteristics of the incident cancer (e.g. stage, histology) to individual death certificates.[29] The incidence and mortality rates generated by the models are also stratified by the SEER historic stages: localized (confined to primary site), regional (spread to regional lymph nodes), distant (cancer metastasized), and unknown (unstaged).[30] The MGH group opted to calibrate to IB mortality rates along with the EAC incidence from SEER. The UW-MISCAN group used SEER stage-specific EAC survival data stratified by calendar groups, while the FHCRC group used SEER specific survival rates stratified by gender and age groups, as model inputs to calculate the mortality rates. For the UW-MISCAN and FHCRC groups, the IB mortality rates from SEER are used to validate their mortality outputs. All three models also use U.S. census data and projections for past (from 1975 onwards) and future (up to 2030) population size.[31]

Model Outputs

The primary endpoints or model outputs for this study were the projections of overall EAC incidence and mortality rates up to calendar year 2030. SEER incidence and mortality rates corresponding to the years 1975 to 2010 were organized by birth cohorts and used as model calibration targets. We also calculated the cumulative EAC deaths from 2011 to 2030, using national population projections from the United States Census Bureau[31], to quantify the burden of disease on society. Other predictions included the average time between developing preclinical cancer and cancer diagnosis (EAC

sojourn time) and the annual rate of patients diagnosed with BE (without dysplasia or with LGD) progressing to clinically diagnosed EAC, to be compared with rates in the literature. These progression rates were calculated for age-at-diagnosis with BE at age 60 and with five years of follow-up time. The cancer progression rate measures the percentage of BE patients who advance to EAC. While the MGH and FHCRC models calculated the cancer progression rate as a prediction mainly based on fitting EAC incidence patterns, the UW-MISCAN model included calibration to progression rates of BE patients with age-at-diagnosis at age 65 and average 5 year follow-up, averaged between calendar years 1990-2005 (0.18% for males, 0.08% for females). However, the estimated cancer progression rates from UW-MISCAN for the other values of age-at-diagnosis with BE are model predictions. Additional intermediate outputs included the prevalence of GERD and BE adjusted to the 2000 U.S. population. GERD and BE are the two important precursor states of EAC. The existing literature reports a wide range of estimates on the prevalence of these two precursor states. As part of the comparative modeling method, we independently integrated the available evidence to produce estimates. The approaches to estimating these prevalence values among the three models are described in the appendix.

RESULTS

Calibration and Projections of Incidence and Mortality Rates

All three CISNET models were calibrated to individual birth-cohort incidence data from SEER. The EAC incidence and mortality rates for each cohort were aggregated to generate age-adjusted rates for the general population (age-adjusted to the 2000 U.S. Standard Population). The EAC incidence rates by calendar year until year 2010 for each birth cohort from the three independent models appeared to fit SEER 9 data well and appeared reasonably consistent with each other (appendix figure A9).

The male incidence rates by age until year 2030 for each birth cohort with projections from each model are shown in Figures 1a-1c. All three models project that the EAC incidence will continue to increase. For later birth cohorts, incidence results show that the incremental differences between birth cohorts has decreased, indicating a deceleration of the birth cohort effect. For females, the projected incidence rates from all models also showed increasing incidence rates by advancing birth cohorts (appendix figure A10). However, the trend in the incremental differences between birth cohorts was not as clear, likely due to the relatively low incidence rates for females with greater statistical variance of the estimated parameters resulting in model predictions with greater uncertainty. After aggregating the projections for all cohorts, the total EAC incidence and mortality rates between ages 20-84 (age-adjusted to the 2000 U.S.

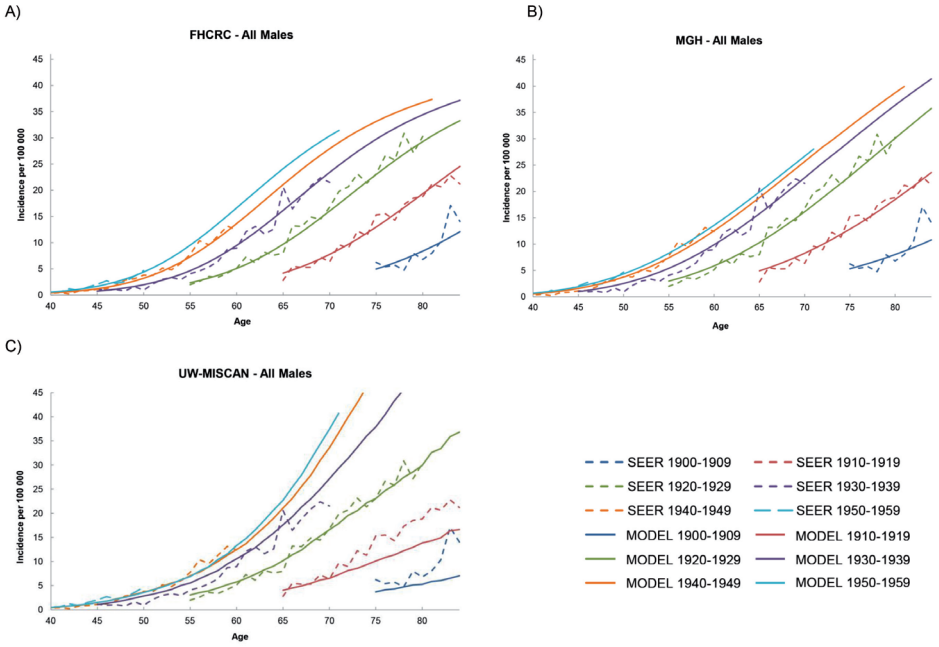

Figure 1. The EAC incidence rates by 10 year birth cohorts for all males. The cohort born in 1959 would be 71 years old in calendar year 2030. (A) FHCRC – All Males (B) MGH – All Males (C) UW-MISCAN – All Males.

population) were calculated and are shown in Figures 2a-2d. Despite the differences in approach and mathematical formalism between the three models, all three models yielded small variations in their model fits to SEER and projections to 2030 for total EAC incidence and mortality rates. The three models all projected an increase in EAC incidence and mortality until 2030. The ranges of incidence and mortality rates for all males in 2030 predicted by three models are 8.4-10.1 and 5.4-7.4 cases per 100,000 person years, respectively. These translate to a 7-10 and 7-8 fold increase in the EAC incidence and mortality rates, respectively, from 1975 to 2030. For all females, the future incidence and mortality rates in 2030 are estimated to be 1.3-1.8 and 0.9-1.2 cases per 100,000 person years, respectively. From 1975 to 2030, the increases in incidence and mortality rates for females will increase by 8-9 and 9-10 times. A closer look at the incidence rate stratified by stage-at-diagnosis revealed that the localized EAC incidence rates exhibited the slowest increases, followed by regional and finally, distant (figures 3a-3c).

To quantify the impact on public health, we calculated the number of cumulative EAC cancer deaths estimated using our predicted mortality rates and population projections from the U.S. Census Bureau, summarized in Table 1. The estimated cu-

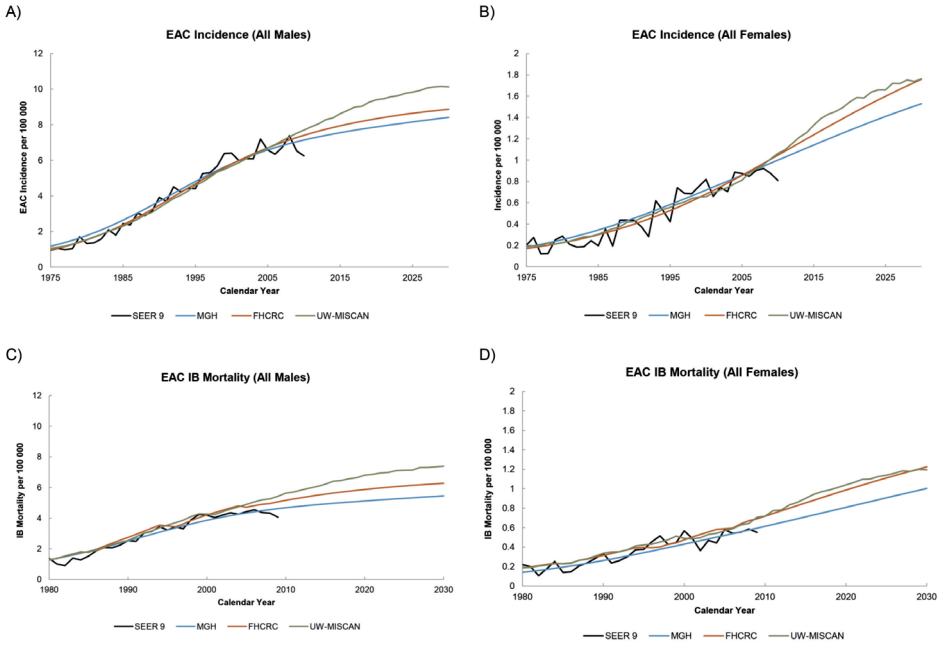

Figure 2. The SEER and projected EAC incidence rates for both males and females are shown in (A) and (B). The black line is the SEER data and the colored lines are predictions from the three simulation models. The incidence based mortality rates are shown in (C) and (D).

mulative cause-specific EAC deaths from males and females in the years 2011-2030 will be between 142,300 and 186,298 cases. Compared to the EAC deaths in the years 1991-2010, the predicted number of cumulative cases will approximately double. In order to separate out the effect of changes in demographic composition, we repeated the calculation using the 2000 U.S. Standard Population. Our results indicate that the cumulative EAC deaths in the years 2011-2030 will be 1.6 times more than those in the previous two decades.

Progression Rate and Prevalence of Precancerous States

The rates of BE patients progressing to clinical EAC are shown in Figures 4a-4b. The results are shown for patients born between year 1915 to 1970 (these patients will be at age 60 between year 1975 and 2030) who were diagnosed with non-dysplastic BE or LGD at age 60 with five years of follow-up time. All three models suggested a strong birth cohort effect on the progression rates with increasing progression rates in younger birth cohorts until the cohorts born in 1940, followed by a leveling off in the cohorts born after 1940. For males born after 1940, the ranges of progression rates are 0.10-0.20% per person year. However, the three models predict that in contrast to males, progression rates for females have not yet leveled off.

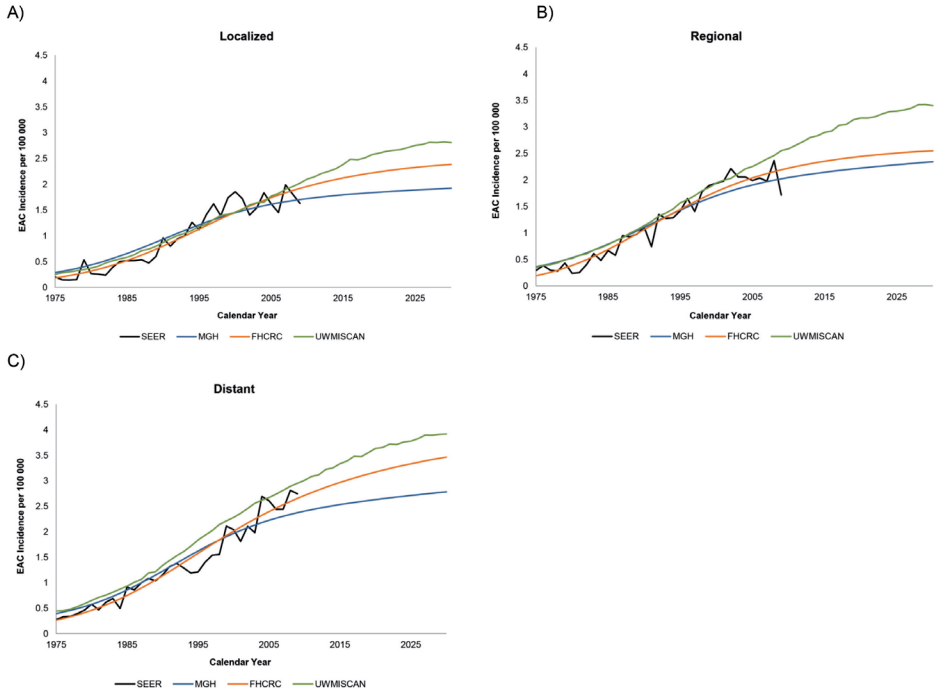

Figure 3. The SEER and projected EAC incidence rates for all males stratified by stage at diagnosis are shown below. (A) Localized (B) Regional (C) Distant.

Table 1. Cumulative EAC Deaths over Time

Future Cumulative EAC Deaths:	Group	1991-2010	2011-2030
Males	MGH	72,884	122,525
	FHCRC	81,069	140,000
	UW-MISCAN	83,118	160,750
Females	MGH	9,110	19,775
	FHCRC	10,397	24,736
	UW-MISCAN	10,489	25,548
Total	MGH	81,994	142,300
	FHCRC	91,466	164,736
	UW-MISCAN	93,607	186,298

EAC = esophageal adenocarcinoma

The top two rows of the table display the predicted numbers of cumulative EAC deaths; the 1st and 2nd rows are numbers for males and females respectively. The bottom row of the table shows the male and female numbers combined.

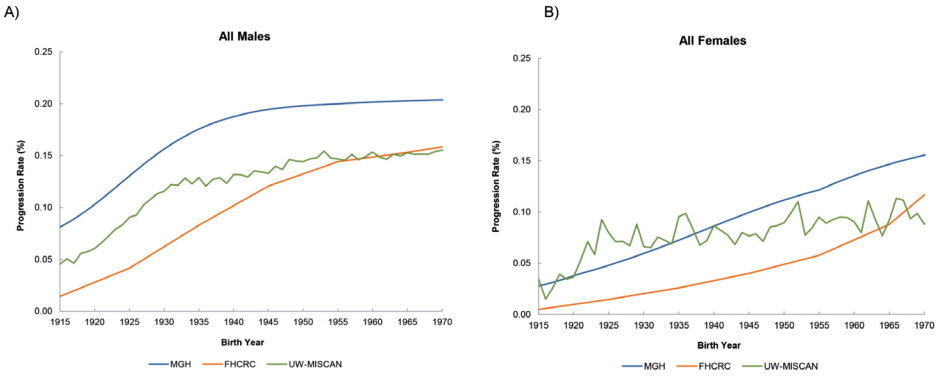

Figure 4. Progression rates by birth year are shown below. The progression rates were calculated for age-at-diagnosis with BE at age 60 with five years of follow-up time. (A) All Males (B) All Females.

Figures 5a-5d show the prevalence of GERD symptoms and BE for males and females generated by the three CISNET modeling groups. The three groups have varying estimates for GERD prevalence, but overall showed similar trends. The outputs of GERD prevalence from three models remain relatively constant over time. For BE prevalence, the FHCRC model predicted no change with calendar year, while BE prevalence predictions from MGH and UW-MISCAN have increased over the past years.

EAC Sojourn Time

The EAC sojourn time is a useful concept to understand the nature of disease progression and detection. However, it is difficult to measure in clinical settings since it depends on unobservable events in the disease process (for example the appearance of preclinical cancer). The capacity of the models to predict this important time scale can be a strength and will help us to examine the impact of screening and specific interventions. Figures 6a-6b show the EAC sojourn time as estimated from the three models; these estimates show considerable differences in spite of model calibration using the same SEER 9 data. The EAC sojourn time estimate from the UW-MISCAN group is relatively constant over birth cohorts. Meanwhile, the EAC sojourn time predicted by the MGH model shows an increase with advancing birth years. The FHCRC model predicted that the EAC sojourn time decreases with birth year. The average male sojourn times are 10.2, 7.1, and 4.9 years for FHCRC, MGH, and UW-MISCAN, respectively. For females, the average sojourn times are 13.3, 9.0, and 4.5 years for FHCRC, MGH, and UW-MISCAN, respectively. The variation between this secondary prediction from the three groups can thus be attributed to fundamental differences in model structure and model-specific constraints used to facilitate model calibration.

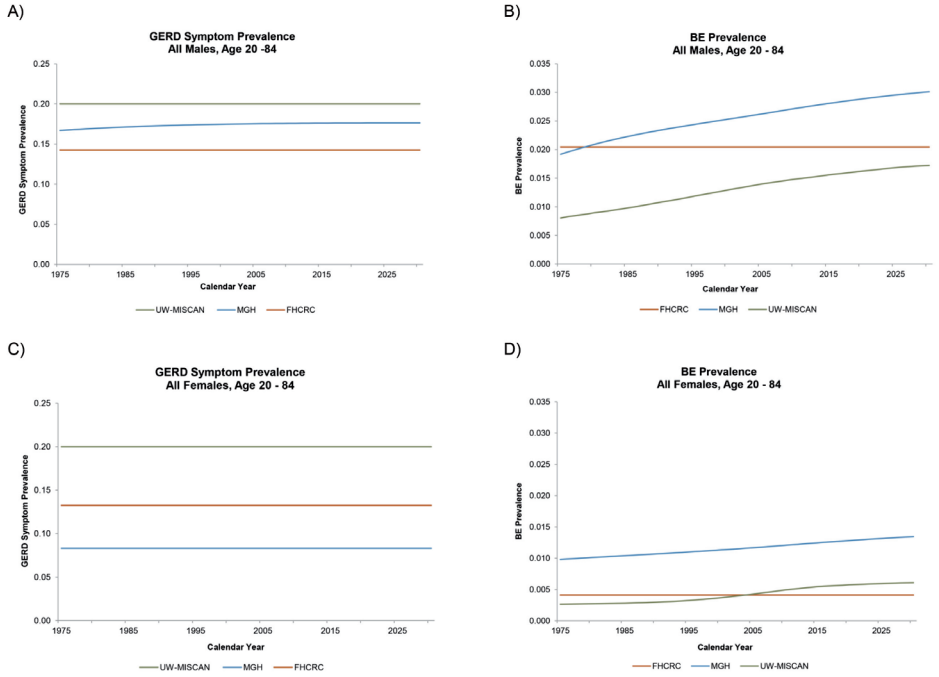

Figure 5. The estimated GERD symptom and BE prevalence of all males (top row) and all females (bottom row) in the US. (A) GERD Symptom Prevalence, All Males (B) BE Prevalence, All Males (C) GERD Symptom Prevalence, All Females (D) BE Prevalence, All Females.

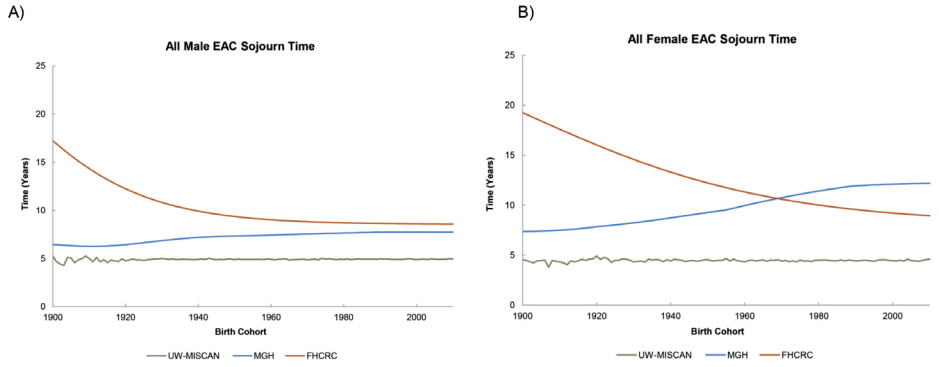

Figure 6. The EAC sojourn times (time between preclinical cancer and cancer diagnosis) for males and females are shown below. (A) All Male EAC Sojourn Time (B) All Female EAC Sojourn Time.

DISCUSSION

Three independent mathematical models were calibrated to U.S. SEER 9 data, specifically the EAC incidence and IB mortality rates from 1975 to 2010. The models were then used to generate incidence and mortality projections until the year 2030. Although the models differ considerably in structure and design, from biologically-based modeling at the cellular level to empirically-based simulations of natural histories, the models' projections (excluding sojourn time estimates) are consistent with one another. Furthermore, all three models identify modification of cancer progression rates (modeled as a birth cohort effect) as an important driver of the observed temporal trends for EAC incidence and mortality. We believe that comparative modeling greatly benefits from an interdisciplinary, collaborative approach to cancer risk prediction, increasing the credibility of model projections and deepening our understanding of EAC epidemiology and natural history. We conclude that EAC incidence and mortality rates will likely continue to increase until 2030 although the rate of the increase appears to weaken with advancing birth cohorts. For the period from 2011 to the year 2030 we estimate that there will be between 142,300 and 186,298 cumulative EAC deaths in the U.S. which is about double the number of EAC deaths that occurred between 1991 and 2010.

Several studies have reported the progression rates of patients with non-dysplastic BE to EAC. Hvid-Jensen et al. reported one of the lower rates of progression, 0.12% per person year to EAC among patients with non-dysplastic BE and LGD.[32] A meta-analysis by Desai et al. reported a progression rate of 0.33% per person year from BE to EAC when only higher quality, more recent studies were included.[33] A frequently cited progression rate of 0.5% per person year was reported from a meta-analysis that attempted to adjust, using a funnel plot, for publication bias.[34] These reported progression rates range between 0.1% and 0.5% per person year and are consistent with our model estimates for younger cohorts.

The reporting of EAC sojourn time is rare in the literature. Previously, the MGH group had estimated that the range of sojourn times was between 4 to 9 years[35], which is in agreement with current results from both the MGH and UW-MISCAN groups. These sojourn time estimates are also consistent with a study which suggested the time from endoscopically detectable esophageal cancer to clinical symptoms as on average 4-5 years.[36] The variability of EAC sojourn time estimates from three models can be attributed to the differences in the modeling approaches between research groups and inclusion or exclusion of additional calibration targets in addition to SEER 9 data. The three groups used different mathematical frameworks to model the disease pro-

gression of EAC. The UW-MISCAN model is a microsimulation model using discrete event formalism, the MGH model is a Markov transition state model, and the FHCRC group has developed a multiscale model that includes multistage clonal expansion processes and detailed spatio-temporal simulations of BE screening outcomes. Additional differences included disease pathways that were unique to each group's model. For example, the UW-MISCAN model allows disease regressions prior to patients developing preclinical EAC while the MGH model does not allow for such regressions. In contrast, the FHCRC model explicitly incorporates cell death and differentiation and thus allows for clonal extinction of precursor lesions including preclinical cancer. The longer FHCRC estimates are likely a consequence of defining preclinical cancers as clonal lesions of any size, including smaller and earlier malignancies such as intramucosal carcinoma that may be difficult to detect endoscopically.

Our study has several limitations. First, although there are some known risk factors associated with EAC, none seem dominant. We opted to model the trend in EAC incidence and mortality by varying the transition rates between health states (MGH and UW-MISCAN) and the biological parameters (FHCRC) using a generalization of the age-period-cohort (APC) formalism. Thus, varying the transition rates as a proxy for changing risk factor trends did not allow us to investigate the etiology of EAC or to develop a cancer prevention and control policy to reduce the risk of developing EAC. However, the identification of cancer progression as an important driver of EAC trends may provide a focus for future investigation and possible interventions. We have developed a computational framework which allows us to update the analysis as additional clinical evidence on the key risk factor(s) and their impact on EAC emerges. Second, all of our models depict the biological progression following a specific sequence: healthy, absence or presence of GERD symptoms, BE without dysplasia, BE with dysplasia, preclinical cancer, and detected cancer. Although this is the commonly accepted paradigm for EAC carcinogenesis, all EACs may not follow this prescribed sequence or alternative pathways may exist within this paradigm adding heterogeneity which the models do not capture.[37, 38]

Despite the limitations, our study has several strengths. We present incidence and mortality projections to 2030 using comparative modeling to investigate EAC trends in multiple birth cohorts. By modeling multiple cohorts separately, our models comprehensively capture incidence and mortality rates with changing age structures as different birth cohorts age. Our comparative modeling approach compares and contrasts the results from independently developed simulation and likelihood-based models using common calibration targets. The approach to resolve differences in model outputs is one of the benefits of comparative modeling, which has been used in other

CISNET comparative modeling analyses. When differences are found, it provides the opportunity to pinpoint the source, which could be a result of error(s) in the model(s), or a consequence of fundamental lapses in knowledge surrounding the natural history of the disease. This approach provides a check for model validity but also the opportunity to identify and discuss gaps in knowledge. This iterative and in many aspects integrative process is perhaps the major strength of comparative modeling and the CISNET consortium, where preliminary model results can be discussed in an open and non-threatening environment conducive to model enhancements that improve risk predictions and therefore credibility.

A statistical analysis on EAC incidence between years 1973-2006 reported that the overall incidence may be plateauing in recent years.[9] A subsequent analysis which included three additional years of incidence data found that the EAC incidence rate continues to increase, although at a decelerating rate.[8] Our projections using three comprehensive computational cancer models also suggest that the incidence and mortality rates of EAC will continue to increase; however, the rate of increase appears to be slowing down for the younger male cohorts. In summary, we used a comparative modeling approach to examine U.S. population trends in EAC. The specific causes of the historical increase in EAC incidence and mortality remain unclear. However, our joint modeling of potential drivers behind the increasing incidence and mortality trends implicates an enhanced BE-to-EAC progression as significant factor (figures 4a-4b), in addition to trends that may be driving up the prevalence of BE in the U.S. population as predicted by the MGH and UW-MISCAN models (Figures 5a-5d). The future projected increase in cumulative EAC deaths and incidence reflect a significant concern and burden to society. Our findings highlight the importance of public health and cancer control planning with potential interventions to curtail the projected EAC morbidity and mortality.

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CHAPTER 4

An accurate cancer incidence in Barrett's esophagus: a best estimate using published data and modeling

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ABSTRACT:

Background & Aims: Published estimates for the rate of progression from Barrett's esophagus (BE) to esophageal adenocarcinoma (EAC) vary. We used simulation modeling to reconcile published data and more accurately estimate the incidence of EAC among people with BE.

Methods: We calibrated the ERASMUS/UW model for EAC to match the 0.18% annual rate of progression from population-based studies. This model was then used to simulate the design of prospective studies, introducing more endoscopic surveillance. We used the model to predict rates of progression for both types of studies and for different periods of follow up, and compared the predicted rates with published data.

Results: For the first 5 y of follow up, the model reproduced the 0.19% average annual rate of progression observed in population-based studies; the same disease model predicted a 0.36% annual rate of progression in studies with a prospective design (0.41% reported in published articles). After 20 y these rates each increased to 0.63%–0.65% annually, corresponding with a 9.1%–9.5% cumulative cancer incidence. Between these periods, the difference between the progression rates of both study designs decreased from 91% to 5%.

Conclusions: In the first 5 y after diagnosis, the rate of progression from BE to EAC is likely to more closely approximate the lower estimates reported from population-based studies than the higher estimates reported from prospective studies, in which EAC is detected by surveillance. Clinicians should use this information to explain to patients their short-term and long-term risk if no action is taken, and then discuss the risks and benefits of surveillance.

INTRODUCTION

In the last four decades, esophageal adenocarcinoma (EAC) has become an important cancer in terms of incidence and mortality due to a spectacular rise in incidence in the western world. The discrepancy between EAC incidence rates by gender is large: the incidence of EAC in men is at least 7-fold that in women and this difference is consistently seen in all western countries. Barrett's esophagus (BE) is the precursor of EAC and its estimated prevalence in the total population ranges between 1.6-6.8%, depending on study.[1]

Given its relevance for clinical management of BE, many have studied the progression rate from BE to EAC. Usually, one calculated the annual progression rate by dividing the number of EAC cases observed in a specified BE cohort by the number of person-years of follow up in the specified cohort. The resulting estimates for the annual progression rate from BE to EAC vary widely in literature within a range of [0.07%, 3.6%], whereas the annual progression rates from BE to HGD/EAC are 1.5-2.5 fold higher.[2-4] Apart from selection bias, publication bias, study size, and cohort characteristics, which all contribute to the difficulty of comparing these estimates, there are important differences in study design. Earlier, a plausible annual progression was estimated at between 0.41% and 0.5% based on meta-analyses that were restricted to prospective studies.[2, 4, 5] However, several large recently published population-based studies suggest that the progression rate is actually much lower (~0.18%).[6-8] The length of follow up in both designs is regularly between five to seven years.

The uncertainty in the progression rate from BE to EAC is a major driver of the controversy in the management of Barrett's esophagus because the (cost-) effectiveness of surveillance and treatment crucially depends on the incidence and progression rate of cancer in BE.[9] Identifying the true risk of progression to cancer would greatly improve the decision making process. In this study, we hypothesize that the difference in estimates of progression rates between prospective and population-based studies could be explained by the practice of endoscopic surveillance performed in prospective studies, resulting in earlier detection of preclinical cancers. The aim of this study was to provide a more accurate estimate for the clinical cancer incidence in BE by reconciling published data.

MATERIAL AND METHODS

This section includes the description of the methods used in our study. We firstly describe the features of the microsimulation model after which we discuss which

characteristics are applied to the model in order to reproduce the population-based study design. Next, we discuss how the model is calibrated using the characteristics of the population-based design which is followed by a description of the model simulations including the characteristics of the simulated population and the differences between the two designs. We conclude with an overview of the evaluation outcomes and sensitivity analysis.

The ERASMUS/UW-Esophageal adenocarcinoma (EAC) model

The ERASMUS/UW-EAC model was developed as part of a collaboration between the Erasmus Medical Center (Rotterdam, the Netherlands) and the University of Washington (Seattle, U.S.A.). The model was previously used in a comparative modeling study to explore the future trends of EAC incidence and in a study to evaluate the influence of the uncertainty in progression rates on hypothetical screening and treatment interventions.[9, 10]

A more detailed description of the model with the quantification of inputs and calibration targets is given in the appendix. In brief, the model simulates the life histories of a large population of individuals from birth to death. Part of the population has symptomatic gastro-esophageal reflux disease (GERD). People may develop non-dysplastic (ND) BE (disease onset) depending on age and the presence of GERD symptoms (6-times increased risk compared to no GERD symptoms). Once BE has developed, low-grade dysplasia (LGD) may develop in BE which in time may progress to high-grade dysplasia (HGD). Furthermore, there is also a probability that HGD will regress towards LGD, and LGD towards ND BE. In HGD malignant cells can arise, transforming to localized EAC that can progress sequentially into regional and distant EAC. In every preclinical cancer stage there is a probability of the cancer being diagnosed due to the development of symptoms versus remaining asymptomatic and progressing undiagnosed into the next cancer stage (figure 1). Once a cancer is diagnosed, individuals may die from it, depending on its stage and age. As a competing risk, persons may die of other causes at any moment during their lifetime.

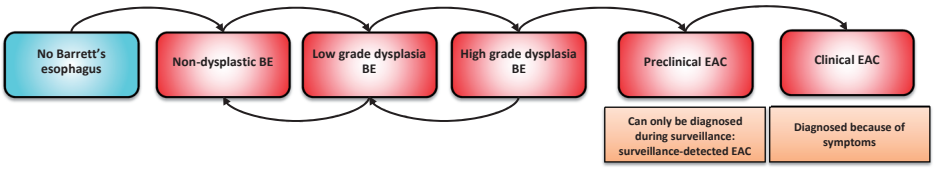

Figure 1. Graphical representation of the Erasmus/UW Model

Reproducing population-based design

We adjusted the model in order to reproduce the characteristics of the population-based study design by implementing realistic surveillance and diagnostic inaccuracy as observed in population-based studies. BE with or without LGD was detected at index endoscopy. The occurrence of subsequent surveillance was based on two population-based studies reporting percent of the study population having surveillance6, 8 and the surveillance intervals as observed in Jonge et al.[8] In this study 38% of the patients with only BE and 52% of those with also LGD received surveillance, with an initial surveillance interval of 2.0 and 1.4 years for ND and LGD patients respectively. These surveillance intervals are different than the current recommended endoscopic surveillance intervals (which are 3.0 (ND) and 1.0 (LGD) years) but are more consistent with the interval recommendations before 2011. Because there were no adherence data on repeat surveillance endoscopy from population-based studies, we used El Serag et al, reporting that 54% of the cohort follows recommended surveillance practice while 46% of the cohort adhered only to the first surveillance endoscopy.[11] In line with this study we assumed that after each endoscopy the adherence to the next endoscopy will diminish with similar rates. For all surveillance intervals after the initial interval, we used the recommended intervals for all following endoscopies (every 3 year, annually and every 3 months for respectively ND, LGD and HGD patients).

The assumed diagnostic inaccuracy for BE specimens was based on data gathered from literature (figure 2).[12] In practice some degree of misdiagnosis of the dysplastic grade is very common because interpretation and grading of biopsies specimens is subjective. In addition there is sampling error, defined as dysplastic or malignant tissue that is missed when obtaining the biopsy.

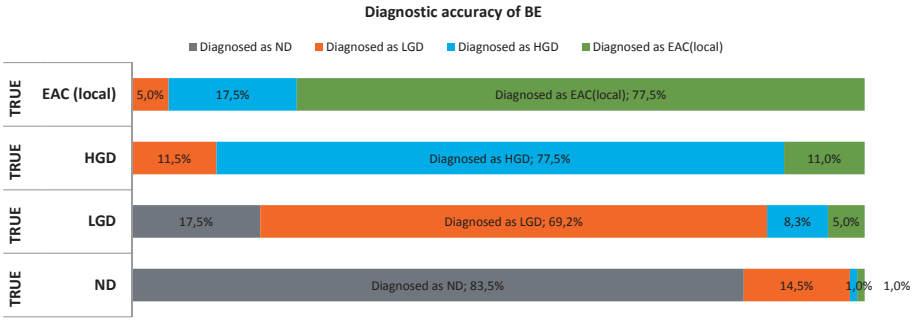

Figure 2. Diagnostic inaccuracy of endoscopic surveillance in the main analysis of our model

Calibration of the model

The model was calibrated to the 2000-2009 incidence data from SEER, the proportion of LGD and HGD in the BE population and the average sojourn time of preclinical (asymptomatic) EAC before becoming clinical (symptomatic) EAC. The model was calibrated to fit the BE to EAC weighted annual progression rate for males in recently published population based studies (~0.18% annually).[6-8]

Population simulated

Since the average age of diagnosis of BE is 60-65 in most studies we have chosen to consider individuals within our simulated cohort with BE at age 65 and follow them until EAC incidence, death by other causes or end of follow up. Furthermore, because most studies excluded HGD at baseline in their reports of surveillance and cancer incidence, we have included only diagnosed non-dysplastic (ND) and low-grade dysplastic (LGD) BE. However, this includes HGD and EAC patients underdiagnosed as ND and LGD.

Simulation of cohort and design

We subsequently used the calibrated model to simulate the population according to three scenarios: 1) without surveillance, 2) population-based study design and 3) prospective cohort design. The only difference between the three scenarios is the intensity of surveillance applied after the initial endoscopy. In the scenario without surveillance, none of the included BE patients received any surveillance. For the population-based study design, as for the calibration, 38% of the BE ND patients and 52% of LGD patients received initial surveillance, while in the prospective design 100% of BE ND and LGD patients received initial surveillance. Repeat surveillance and diagnostic inaccuracy are assumed to be similar in the two designs and as stated above (see Reproducing population-based design).

Outcomes

We evaluated two primary outcomes: annual progression rate to EAC diagnosis and annual progression rate to HGD detection or EAC diagnosis combined. In line with published studies we removed the cancers that were detected within the first six months of follow up. We distinguished clinical EAC and surveillance-detected EAC. We define clinical EAC as a cancer being diagnosed by symptoms, whereas surveillance-detected EAC is a cancer diagnosed during surveillance endoscopy.

In the first outcome (EAC cases only), when HGD is detected at surveillance, there is no treatment but there is an increase in frequency of the surveillance by shortening the interval to 3 months (individual is still considered in follow up). Only if the

patient develops EAC he/she is considered an endpoint and included as a case in the progression rate calculation. For the second outcome (HGD and EAC cases combined) , when HGD is detected by surveillance, this is included as a case and considered as an endpoint (individual no longer considered in the follow up), corresponding with the situation where HGD is treated. The annual progression rate was defined by the number of diagnosed cases divided by the number of person-years in follow up. We included only the true-positive diagnosed EAC in the final outcomes, assuming that over-diagnosed or false positive EAC cases would have been recognized as such during the further staging process and therefore were also not counted in the studies. We calculated the annual progression rate without any influence of surveillance (clinical progression rate). Additionally, for both designs and varying lengths of follow up the annual progression rate and the cumulative cancer incidence were calculated. The key outcome of our study is the difference in percentages between the predicted rates of both study designs for varying follow up lengths. This difference was calculated by dividing the difference in predicted rates between the two designs by the predicted rate of the population-based design.

Sensitivity analysis

Next to the progression rate throughout the disease to EAC, which has been addressed to by calibration as the central issue to our analysis, we addressed in the sensitivity analyses other uncertain assumptions that would influence EAC incidence during follow up: 1) the intensity of surveillance during follow up, 2) overdiagnosis of BE at baseline in the population based design , and 3) the duration of surveillance over time.

Perfect surveillance scenario

Since the frequency of surveillance incurs large uncertainty, we explored the impact of the most extreme difference in surveillance between the two study types. In this scenario we assumed no surveillance (0%) for the population-based study design, and 100% surveillance (every 3 year, annually and every 3 months for respectively ND, LGD and HGD patients) for all individuals over the total follow up period for the prospective design.

False-positive BE scenario

We have looked at the validity of BE diagnosis within population-based studies. For population-based studies with large registries one may raise the question how often a coded BE registration is correctly defined. We have alternatively assumed that within the population-based design only 61.9% of the registered BE cases has true BE in accordance with the findings of Corley et al.[13], and that the other 38.1% are false-positive

diagnosed individuals which should not contribute to the denominator when calculating the progression rate.

Halting surveillance scenario

We looked at the impact of diminishing surveillance over time. Because of comorbidity, there is a higher probability that patients may not be fit for endoscopy at older age. In practice it is therefore not uncommon that surveillance is halted for older patients. In this sensitivity analysis, we stopped offering surveillance after a 10 year period, at age 75.

RESULTS

The calibration to the population-based study, including realistic surveillance, resulted in an annual progression rate of 0.19% for BE (ND+LGD) to EAC with a 5 year follow up. Without surveillance, the annual progression rate to clinical EAC (clinical progression rate) would only have been 0.07%. The same disease model predicted an annual progression rate to EAC for the prospective design of 0.36% after a five year follow up, 91% higher than in the population based design (figure 3). These estimates were close to the published estimates of 0.41% annual progression rate with a 128% difference between designs. Figure 4 shows that the number of EAC diagnosed by surveillance declined over time in both designs, due to the assumed diminishing number of surveillance endoscopies in both designs. Whereas in the first five years of follow up the proportion of surveillance detected cancers was 82% and 98% of the total cancer diagnosis for the population-based and prospective design respectively, this proportion declined to 26% and 62% for years 15-20 of follow up. The earlier diagnosis of cancer caused by surveillance is mainly relevant on the short term. After 20 years the model predicted that 9.1%-9.5% of the BE (ND+LGD) population would have developed EAC, with a difference between the designs of only 5% (table 1).

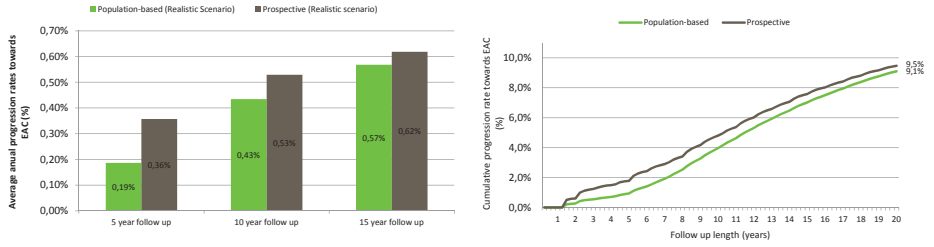

Figure 3. Cancer incidence rates for different lengths of follow up in the realistic scenario: A) average annual progression rates toward EAC and B) cumulative cancer incidence towards EAC

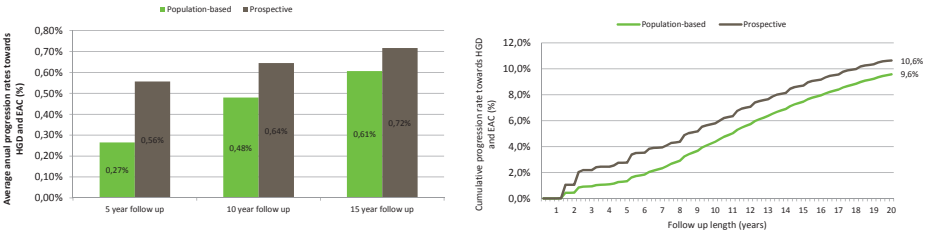

Figure 4. High-grade dysplasia and cancer incidence rates for different lengths of follow up in the realistic scenario: A) average annual progression rates toward HGD and EAC and B) cumulative cancer incidence towards HGD and EAC

Table 1. Simulation results of the population-based design and prospective design for the realistic scenario. The table shows the average annual progression rate and the cumulative cancer incidence rates for both i) EAC diagnosis and ii) HGD and EAC diagnosis for follow up lengths of 5,10,15 and 20 years. In addition, the average number of person-years is shown for each scenario.

Annual progression rate						
	EAC			HGD and EAC		
Follow up length	Population-based	Prospective	Difference	Population-based	Prospective	Difference
5 year follow up	0.19%	0.36%	92%	*0.27%*	*0.56%*	110%
10 year follow up	0.43%	0.53%	22%	*0.48%*	*0.64%*	34%
15 year follow up	0.57%	0.62%	9%	*0.61%*	*0.72%*	18%
20 year follow up	0.63%	0.65%	5%	*0.66%*	*0.74%*	13%
Cumulative progression rate						
	EAC			HGD and EAC		
	Population-based	Prospective		Population-based	Prospective	Difference
5 year follow up	0.9%	1.8%	91%	1.3%	2.8%	108%
10 year follow up	4.0%	4.8%	21%	4.4%	5.8%	33%
15 year follow up	7.0%	7.6%	8%	7.5%	8.7%	17%
20 year follow up	9.1%	9.5%	4%	9.6%	10.6%	11%
Average number of person-years per BE patient						
	EAC			HGD and EAC		
	Population-based	Prospective		Population-based	Prospective	
5 year follow up	5.0	5.0		5.0	4.9	
10 year follow up	9.2	9.1		9.0	8.6	
15 year follow up	12.4	12.3		12.0	11.3	
20 year follow up	14.6	14.5		14.0	13.0	

BE: Barrett's esophagus; EAC: Esophageal adenocarcinoma

A similar pattern was seen when evaluating the progression rate to HGD and EAC combined. Simulated progression rates were approximately 1.5 times higher than for EAC alone and the difference between the population-based and prospective design decreased from 110% (0.27% versus 0.56%) after a five year follow up to 13% (0.66% versus 0.74%) after 20 years. After 20 years, the model predicted a cumulative incidence of 9.6%-10.6% to HGD and EAC (figure 5).

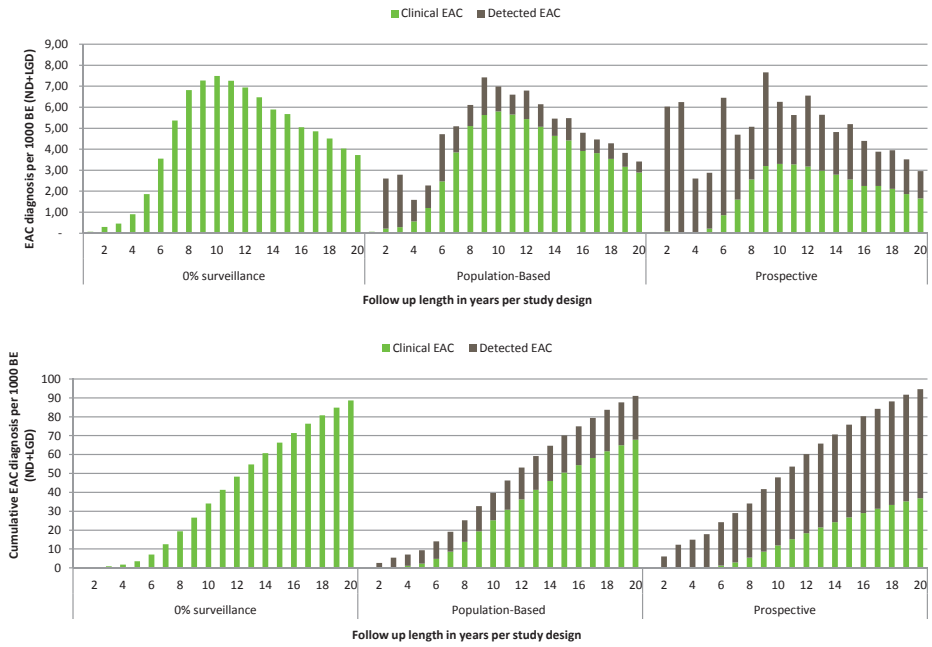

Figure 5.
A) Cancer incidence rates per 1000 BE patients for 20 years of follow up in the population-based design without any surveillance (perfect surveillance scenario), in the population-based and prospective design for the realistic scenario.
B) Cumulative cancer incidence rates per 1000 BE patients for 20 years of follow up in the population-based design without any surveillance (perfect surveillance scenario), in the population-based and prospective design for the realistic scenario.

Sensitivity analysis

Perfect surveillance scenario

Assuming no surveillance in the population-based study design and 100% surveillance in the prospective cohort design, resulted in considerably larger differences in a 5-year average annual progression rates (0.07% and 0.50% in the population-based and prospective design respectively, see figure 6a). This shows how sensitive the simulated progression rates are to intensity of surveillance. Without surveillance, 8.9% of the BE

patients will develop EAC within 20 years. An additional 1.1% of the patients will be detected with EAC because of surveillance (figure 6b).

False-positive BE scenario

If we assumed that only 61.9% of the registered BE cases had true BE in the population-based design, and that the other 38.1% are false-positive diagnosed individuals, the progression rates in the population-based design increased with 30%. The observed progression rate of 0.18% actually only occurs in the 61.9% of the population with BE. In other words, the progression rate in BE patients is in reality 0.24% after 5 years of follow up (figure 6c). Calibrating the model to this rate would results in estimated 0.10% clinical progression rate without surveillance. Our results only show the effect of the false-positive BE on the population-based studies, which means that the results for the prospective cohort design are identical to the base case scenario. The inclusion of

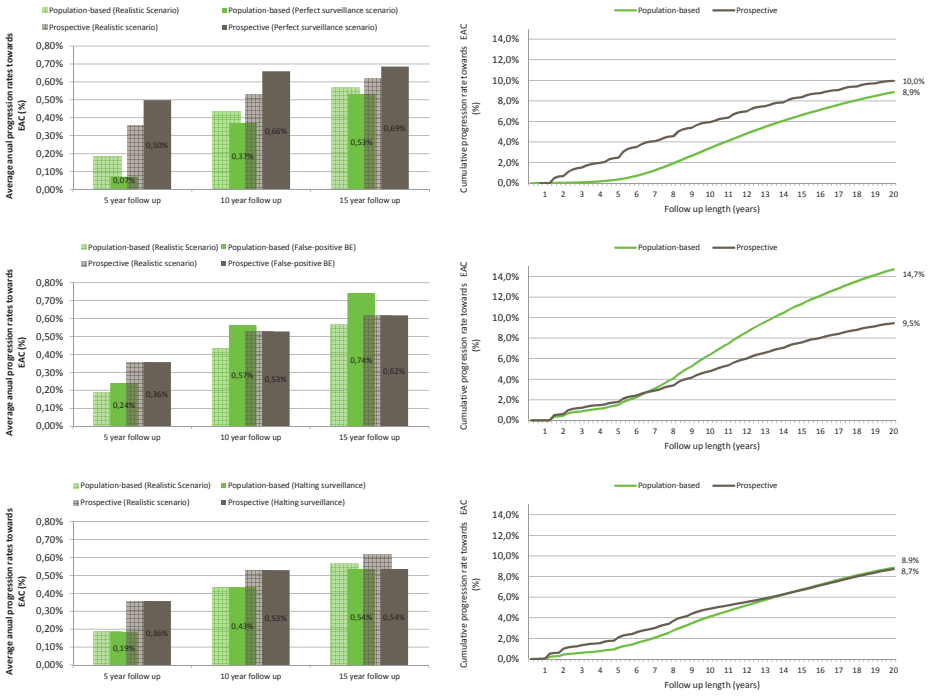

Figure 6. Cancer incidence rates for different lengths of follow up in the sensitivity analysis:
Perfect surveillance scenario A) average annual progression rates toward EAC and B) cumulative cancer incidence towards EAC
False-positive BE scenario C) average annual progression rates toward EAC and D) cumulative cancer incidence towards EAC
Halting surveillance scenario E) average annual progression rates toward EAC and F) cumulative cancer incidence towards EAC

false-positive BE patients in the population-based studies has a large influence on the estimated progression rate.

Halting surveillance scenario

Halting surveillance after a 10-year period of follow-up, only affects long term outcome since surveillance assumptions are identical to the base case for the first 10 years. After 20 years of follow up, the cancer incidence was 8.7% and 8.9% in the population-based and the prospective study design. Compared to our main analysis (with a cancer incidence of 9.1%-9.5% after 20 years) fewer cancers were detected in the long-term. Halting surveillance could therefore be a favorable option since the cancers that are not diagnosed by screening because of the halted surveillance are also not diagnosed because of symptoms. Overdiagnosis because of early surveillance-detected EAC is minimized when halting surveillance (figure 6f).

DISCUSSION

The underlying value for progression to EAC, the clinical progression rate, according to our model was estimated at 0.07%/year. This was in a 60-year old with BE (ND or LGD) with 5 year follow-up and including realistic diagnostic inaccuracy. This annual rate increased to 0.37% when evaluated after a 10 year follow up. The 0.19% and 0.36% annual progression rates after 5 years estimated in a population-based and prospective design respectively converged to a 9.1% and 9.5% cumulative cancer incidence after 20 years. The relative differences between progression rates of the two designs decreased from 91% and 21% after 5 and 10 years, to 9% and eventually 5% after 15 and 20 years of follow up. Results including HGD show that in the long run at least 0.5% of the population-based cohort and 1.1% of the prospective cohort will be over diagnosed with HGD that would not have progressed to cancer even if not detected and treated. The differences between progression rates of the two designs diminish at a slower rate when evaluating both HGD and EAC instead of only EAC.

We believe this is the first study in which the difference between observed progression rates is explained using population-based modeling. Our results suggest that the gap between the published progression rates from population based studies and prospective studies can be largely explained by differences in study design, more specifically by the differences in the surveillance intensity. Performing endoscopic surveillance in individuals with BE leads to earlier detection of cancers and thus to a higher observed cumulative EAC incidence if follow up time is not very long (e.g., 20 years). In the situation without surveillance, a proportion of these cancers (those not

over-diagnosed) would have developed symptoms that lead to clinical cancer diagnosis later on. However, given closure of the study e.g. after five years, some of these cancers would not have been observed yet without surveillance. In our simulations, significant differences between the study designs mainly impacted the progression rates when the follow up length is less than 10 years, which is mainly explained by our assumption of diminishing surveillance over time. Thus, the true average annual incidence of clinically apparent EAC in BE over the long-term is approximately 0.64%/year, but much lower when observed only over 5 years (approximately 0.2%/year). Much of the later cancers may represent over-diagnosis of pseudo-disease as the risk of competing causes of death increase as the patient ages making the diagnosis of the cancer at those later time points less relevant to all-cause mortality.

Our study is limited by uncertainties. We have assumed the same surveillance intervals and diagnostic inaccuracy for EAC in those undergoing surveillance for both designs. Possibly, however, the diagnostic accuracy higher within prospective studies because these trials are performed by more expert endoscopists using better-established biopsy and pathologist grading protocols than e.g. in average population-wide practice. Next, the more exact frequency and intensity of surveillance was uncertain in both types of studies. We have based our base case assumptions on the few studies describing surveillance quantitatively. In order to evaluate the impact of our surveillance assumptions we have simulated varying scenarios in the sensitivity analysis in which surveillance is altered. These analyses showed that when assuming perfect adherence to the protocol for all study participants in the prospective design, the 5-years progression rate was 0.50% annually instead of 0.36% with the base case less perfect surveillance compliance assumptions. This reflects the influence of the surveillance protocol on the predicted progression rate, indicating that the published progression rates for prospective studies will be highly influenced by surveillance protocol on short term. Thirdly, we did not account for HGD treatment when calibrating the model on the BE to EAC progression rate. The reason is that the studies we used for the calibration were performed prior to the uptake of endoscopic therapy for dysplastic but non-cancerous BE. If published progression estimates in prospective cohort studies show persistently lower progression rates than previously assumed (~0.50%), we aim to research the effect of this treatment intervention in future. Finally, there were only a limited number of population-based studies available to provide us with information concerning the progression rate, and each study is subject to their own limitations. These limitations magnifies the uncertainty about the size of the difference between the study designs.

The published estimates for annual progression rates for about 5 years of follow up differed 128% between population-based and prospective studies (0.18% and 0.41%

respectively). The model-predicted progression rates of our model compared very well in absolute level and resulted in a difference of 91%. Hence, more than two-third of the difference between published estimates for the short time progression rate to EAC was explained by our estimated differences in study design. The remaining unexplained difference could easily be caused by uncertainties in surveillance intensity and diagnostic accuracy assumptions. Especially the impact of uncertainties concerning surveillance is large, as we showed in our sensitivity analysis: the most extreme estimated gap between designs by varying the surveillance intensity (0.07% versus 0.50% for no surveillance versus complete surveillance for all) was considerably larger than the observed gap between designs (0.18% and 0.41%).

Previous research examined whether publication bias, the selective reporting of studies featuring positive or extreme results, may have caused the wide range of progression rate published, and in particular resulted in overestimation of cancer risk in literature.4 The researchers found that reported cancer risk was strongly negatively associated with the size of the study, which could be explained by publication bias. Our study shows that this association may not be caused so much by study size but rather by study design, as large studies are more likely to be population based and characterized by low endoscopic surveillance.

Our findings have several implications for practice. First of all when the progression rate is inferred from a study, the surveillance practiced in the study should be carefully accounted for as well as the follow up length. For example, calibrating a model to the rates observed in the cohort studies without including surveillance, will overestimate progression rates and lead to cost-effectiveness analyses that corroborate too intensive surveillance recommendations. Modelers must make the distinction between the progression rate to clinical cancer in the situation without surveillance, and progression rate with surveillance, including surveillance detected pre-clinical cancers. For (calibration to) the former, it is recommended that models use the lower end of the published estimates, approximating the clinical progression rate in order to prevent overestimation of cancer incidence without surveillance and thereby provide more valid cost-effectiveness calculations of surveillance and treatment. Next, especially towards patients but also between professionals, the so called clinical progression rate is the only definition which is unambiguous and relevant for risk interpretation: it is not influenced by surveillance. Even the direction of this influence can vary, depending on the intensiveness of the surveillance, combined with the aggressiveness of associated pre-cancer treatment (eradication of dysplasia could decrease the observed EAC progression rate) and the frequency of over-diagnosis (detection of clinically insignificant disease would increase observed progression rates). The clinical progression rate is

also simple: it only includes the clinical diagnosed cancers that will develop in a situation without interventions before clinical symptoms develop. The clinical progression rate is best approximated by the published population-based studies.

Although population-based studies best approximates the true clinical progression rate, this does not mean that there is no use for the rates from prospective cohort studies. These studies can provide us with valuable information on the impact of surveillance practice on cancer incidence, that clinicians can use to inform their patients on the risks (cancer diagnosis at earlier age with the possibility of over-diagnosis) and benefits (less invasive treatment and improvement of prognosis) of surveillance. Prospective cohort studies offer the possibility to estimate duration and significance of screen detectable disease and the sensitivity of surveillance for these precursors. This typically could be done by modeling, by simultaneous calibration to studies with little and with much surveillance. To this end, a good description of the interventions and of surveillance versus symptom detected cancers by length of follow up in empirical studies is mandatory.

In conclusion, the published differences between the lower progression rates reported from population-based studies and the higher progression rates observed in prospective studies can be explained by detection bias from endoscopic surveillance in the prospective studies. For a short time frame, the clinical progression rate from BE to EAC, reflecting the individual risk, is likely to be closer to the estimations in the population-based studies than prospective studies because less surveillance was performed in the former studies. Clinicians informing their BE-patients about their cancer risk can best use this clinical progression rate, which is not influenced by surveillance detected cancers.

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PART II

POSSIBILITIES FOR EARLY DETECTION AND INTERVENTION

CHAPTER 5

Possibilities for early detection of esophageal adenocarcinoma: a systematic review

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Submitted

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ABSTRACT

Objectives: The incidence of esophageal adenocarcinoma (EAC) has been rising in the Western world for the past few decades. The prognosis for diagnosed EAC patients is poor and although new treatment methods are emerging, only 15% of the diagnosed EAC patients survive after 5 years. The aim of this study was to systematically review the current knowledge on the possibilities for early detection of EAC and the benefits of early detection with regard to the burden of EAC in the population.

Methods: We performed a systematic literature search for articles published between 2002 and 2013 (Medline, PubMed). We summarized evidence on possibilities of early detection of EAC based on predictive signs, symptoms and risk factors; decreasing doctor/ patient delay; screening and surveillance for EAC and its precursor lesion Barrett's esophagus (BE); risk factors for progression to EAC in BE patients under surveillance, and whether early detection of EAC led to improved prognosis.

Results: We included 49 papers in our study. Risk factors for (precursors of) EAC were male gender, waist-to hip ratio, gastro-esophageal reflux symptoms and genetic factors. However, early detection on the basis of (a combination of) these risk factors in the general population did not lead to earlier detection of EAC. Scarce evidence indicates that patient- and doctor delay did not negatively impact survival of EAC. Observational studies show that patients diagnosed in a surveillance program for BE had a better survival than those diagnosed outside such a program. However, whether surveillance for BE will lead to health benefits, in terms of mortality reduction, was not investigated. Modeling studies suggest that surveillance for BE can be effective in patients with dysplasia, while cost-effectiveness improves by stratification of patients based on risk factors for carcinogenesis. Esophagitis, nodularity, BE segment length, dysplasia, and detecting aneuploidy/ tetraploidy or methylation in biopsies from BE are predictors for malignant progression.

Conclusion: Early detection of EAC on a population level by means of screening is not yet shown to be successful as signs, symptoms and risk factors identified for EAC in the general population are also associated with other diseases and not exclusively predictive for EAC. There is no definite evidence, but only strong suggestions that early detection of EAC in a high-risk population, such as BE patients is effective by means of surveillance. In order to improve cost-effectiveness, surveillance should be optimized by improving risk stratification in this population. New diagnostic modalities are emerging including genetic- and epigenetic markers that might provide higher predictive values for progressive BE, providing new opportunities for early detection on both population level and high-risk populations.

INTRODUCTION

Esophagus cancer can be divided into two subgroups: esophageal adenocarcinoma (EAC) and squamous cell carcinoma (SCC). In countries where incidence rates of EAC have been examined, there has been a sharp increase in cancer incidence over the past few decades[1-9], whereas rates of SCC have remained relatively stable. In many Western countries[2, 4, 5, 9-12] the incidence of EAC has increased more rapidly than any other malignancy. Although new techniques for treatment of EAC are emerging, survival of patients diagnosed with EAC has remained poor because most cases are diagnosed at an advanced stage of malignancy, resulting in a 5-year survival rate of less than 15%.[13] The main precursor of EAC is Barrett's esophagus (BE), which can only be diagnosed by endoscopy and biopsy taking for histologic confirmation. Currently ~92%[14] of diagnosed EAC is found at first endoscopy, that is, without an earlier confirmed BE diagnosis. Furthermore, only a small percentage of BE diagnosed patients (6-11%[15, 16]) eventually develops EAC. In order to decrease the burden of this disease in the population, it is essential to know if early detection of EAC is possible, and how large the potential health gain is of diagnosing this disease in an earlier phase of malignancy.

There are different aspects of early detection, which are included in the conceptual framework of potential health gains (figure 1). The first aspect pertains to the question whether early detection is possible by earlier recognition of specific signs, symptoms and risk factors. For this, we will investigate which of these factors are associated with BE and EAC development. The second aspect concerns the question whether doctor- and/or patient delay occur. Problems with swallowing are among the first indications of EAC. A delayed diagnosis can be caused by patient's unawareness of signs, symptoms and high risk factors, delaying the time between symptoms and visiting a doctor. Furthermore, it can be speculated that if patients and doctors would have a higher awareness of determinants and associated factors of EAC, EAC might be earlier detected because indications for EAC have been timely identified. The time between a doctor's visit and reference towards specific medical care can also cause a delay in diagnosis. A third aspect to consider is screening and surveillance. Screening involves the detection of a cancer or it's precursor in order to treat the patient in an early phase and prevent the silent development towards a malignant cancer or progression into an advanced/late tumor stage. Examples of currently used population-wide screening include breast, cervix an colorectal cancer.[17] With surveillance a population known to be at higher than average risk is regularly being examined. Currently, early detection of EAC is possible by diagnosing the precursor BE with upper endoscopy after which regular surveillance or treatment according to dysplastic grade is generally advised. An emerging question is whether determinants for malignant high-grade dysplasia (HGD)

and EAC in BE can be identified to optimize surveillance for patients with high risk. The potential health gains from screening and surveillance for EAC in terms of mortality reduction are required to provide evidence for valid decision making considering both costs and benefits for screening and surveillance methods.

In this study we aimed at summarizing the current evidence on whether early detection of EAC and its precursors is possible based on i. signs, symptoms and risk factors, ii. decreasing doctor- and/or patient diagnostic delay, iii. screening for and surveillance of BE and iv. risk stratification within BE patients.

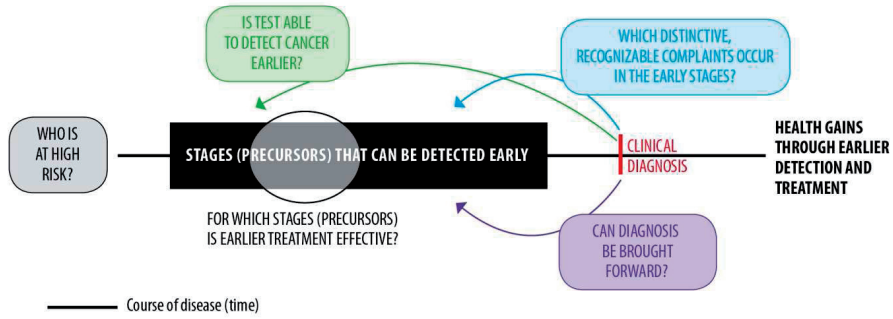

Figure 1 .Conceptual framework of potential health gains.

METHODS

Table 1 shows the research questions that cover the various aspects of early detection possibilities for EAC and its precursors. For each of the research questions, we performed a systematic literature search in Medline (Pubmed), to identify studies published since 2002 up to January 24th 2013, without restrictions to language of publication, using a combination of MESH terms (supplementary files S1). References from selected articles were searched for additional relevant literature.

Criteria for inclusion and exclusion

After retrieving the citations from the database, articles were selected for eligibility by 2 authors, first by screening the title and abstract, then after full text reading. Each search had common eligibility criteria for the inclusion of populations, the disease cases (EAC as primary disease, BE), the language of the study and the study types (reviews, RCT, cohort studies, case control and expert opinion). Additional criteria were stated according to the subject of the research question (supplementary information). Only empirical data studies, either observational or randomized controlled, with sample

Table 1. Research questions and searches in our systematic review.

Research questions	Questions for search strategy
1. For which signs, symptoms and risk factors should we increase awareness to enable the early detection of EAC?	a. Are there signs and symptoms that are predictive of an early phase of EAC? b. Which methods can be used to identify these signs and symptoms?
2. Is early detection of EAC possible by decreasing doctor/ and patient delay?*	a. Can the prospective at EAC diagnosis deteriorate by doctor/patient delay? b. Which factors are of importance?
3. Is early detection of EAC possible by screening for BE or surveillance of BE, and what are the estimated health benefits of early detection?	a. Does EAC have a detectable preclinical phase? b. Which systematic detection (screening or surveillance) methods are available? c. What are the test characteristics of these methods? d. Does systematic detection of EAC lead to less EAC mortality? e. Is systematic detection of EAC cost-effective?
4. Can we identify risk factors for HGD and EAC development in BE?	

* To increase the number of citations the start date of this search was set to 1990 instead of 2002. BE: Barrett's esophagus; EAC: Esophageal adenocarcinoma.

sizes larger than 100 and systematic reviews were included. Finally, studies had to be validated as 'valid and applicable', for which assessment forms of EBRO and Cochrane were used.[18] All studies were assessed as valid and applicable for inclusion.

Data extraction

Information from each study was extracted from the selected articles by 3 authors. The variables compiled from the studies varied by research question. For the first research question concerning signs, symptoms and risk factors, risk factor for BE and/or EAC s and odds ratios were extracted. These variables were also extracted for the research question concerning risk factors for BE (research question 4). For the second research question concerning doctor and patient delay the delay in diagnosis and outcome on survival were extracted. Screening strategy, detection rate, sensitivity, Quality adjusted lifeyears (QALY), EAC incidence and deaths and costs were retrieved for the different articles found for research question 3.

RESULTS

In total 1376 articles were retrieved from searching databases. After exclusion of duplicates and screening of title and abstract 197 titles were included for full text screening.

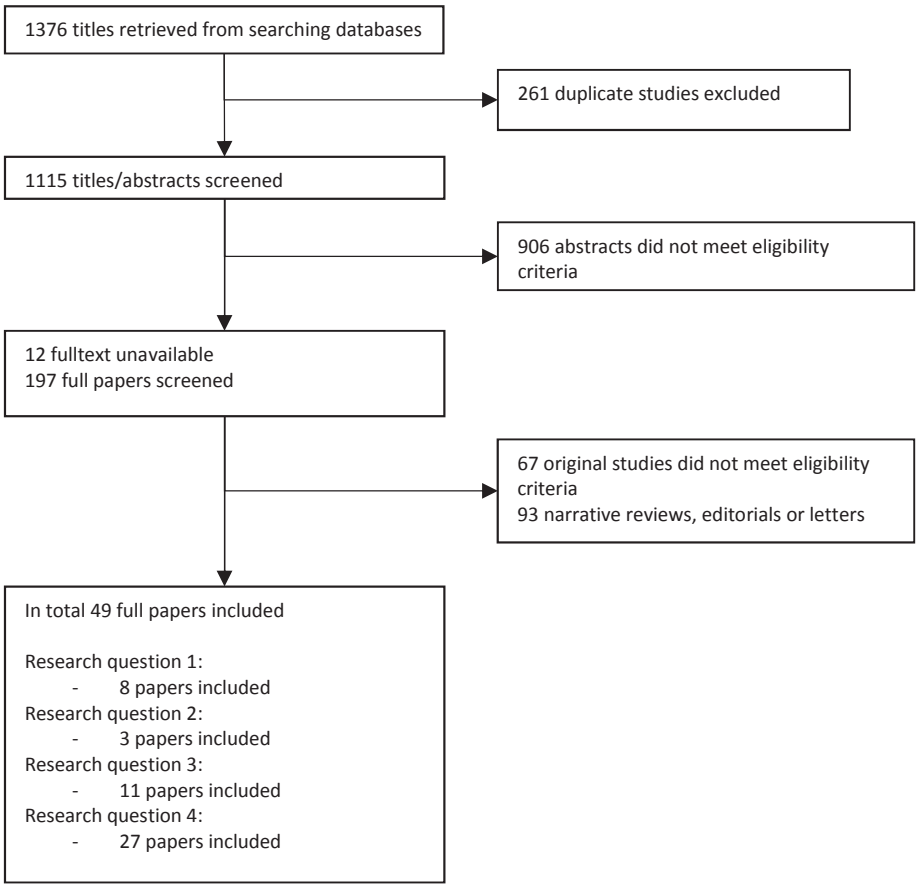

Figure 2. Inclusion overview references.

Eventually 49 articles were included (figure 2). Eight papers referred to signs, symptoms and risk factors of EAC, 3 to diagnostic delay, 11 to screening, surveillance and health gains, and 27 to risk stratification in BE patients.

1. For which signs, symptoms and risk factors should we increase awareness to enable the early detection of esophageal adenocarcinoma?

We stratified the predictive value of signs, symptoms and risk factors by the outcomes EAC, BE and malignant potential (with BE and/or EAC combined to one outcome measure).

Esophageal adenocarcinoma

We found a number of risk factors, which were significantly associated with EAC development in the general population. The highest associations were found for daily symptoms of gastro-esophageal reflux disease (GERD), more than 20 years of GERD symptoms, more than 30 packyears of smoking, and family history (Table 2a).

Despite the presence of multiple risk factors, the predictive value of these risk factors was low. One prospective cohort study[27] followed a large population from general practices. An algorithm was developed based on symptoms and risk factors (age, smoking status, dysphagia, hematemesis, abdominal pain, loss of appetite, weight loss and anemia) to predict a high risk for gastro-esophageal cancer (gastric

Table 2. Signs, symptoms and risk factors for the development of EAC, BE and malignant potential in the general population.

Table 2a	Reference group	Outcome	OR 95% CI	Study
Frequency of GERD symptoms				
Daily GERD symptoms	*Less than daily or no GERD symptoms*	EAC	7.40 (4.94-11.10)	Rubenstein, et al.[19]
Weekly GERD symptoms	*Less than weekly or no GERD symptoms*	EAC	4.92 (3.90-6.22)	Rubenstein, et al.[19]
Duration of GERD symptoms				
>20 year GERD symptoms	*No symptoms*	EAC	5.41(2.45-11.90)	Rubenstein, et al.[19]
<10-15 year GERD symptoms	*No symptoms*	EAC	3.05(1.51-6.08)	Rubenstein, et al.[19]
Demographic factors				
Male gender	*GERD population*	EAC	1.74 (1.10-2.75)	Chak, et al.[20]
Age	*GERD population*	EAC	1.05 (1.02-1.09)	Chak, et al.[20]
Lifestyle factors				
Alcohol	*GERD population*	EAC	1.72 (1.09-2.69)	Chak, et al.[20]
Obese (10 years ago)	*GERD population*	EAC	3.32 (1.37-8.05)	Chak, et al.[20]
Smoking*	*Asymptomatic population*	EAC	1.75 (1.29-2.38)	Pandeya, et al.[21]
Smoking*	*Asymptomatic & symptomatic GERD*	EAC	3.44 (1.30-9.08)	Casson, et al.[22]
Smoking* duration (per 10 years)	*Asymptomatic population*	EAC	1.20 (1.06-1.36)	Pandeya, et al.[21]
Smoking*: pack years (> 30)	*Asymptomatic & symptomatic GERD*	EAC	6.11 (2.2-17.32)	Casson, et al.[22]
Smoking*: time since quit smoking(per 10 year)	*Asymptomatic population*	EAC	0.82 (0.71-0.94)	Pandeya, et al.[21]
Genetic factors				
Family history (BE/EAC/EGJA)			12.23 (3.34-44.76)	Chak, et al.[20]

Table 2b	Study population	Outcome	OR 95% CI	Study
Demographic factors				
Male gender	*GERD*	SSBE	2.7 (1.6 – 4.5)	Edelstein, et al.[23]
	GERD	LSBE	3.9 (1.9 – 8.1)	Edelstein, et al.[23]
Age	*GERD*	SSBE	1.4 (1.1 – 1.6)	Edelstein, et al.[23]
	GERD	LSBE	1.5 (1.2 – 1.9)	Edelstein, et al.[23]
Lifestyle factors				
Increased waist-hip ratio[1]	*GERD*	SSBE	1.9 (1.0 – 3.5)	Edelstein, et al.[23]
	GERD	LSBE	4.1 (1.5 – 11.4)	Edelstein, et al.[23]
Genetic factors				
IL-1 Ra + 2018 genotype 2/2, ≥copy of allel 2 -in IL-1β 511	*Esophagitis*	BE ND	9.5 (1.19-75.93)	Gough, et al.[24]
IL-1 Ra +2018 genotype 2/2	*Esophagitis*	BE ND	3.04 (0.81-11.47)	Gough, et al.[24]
IL-10 1082 genotype 2/2	*Esophagitis*	BE ND	1.84 (1.04-3.28)	Gough, et al.[24]
Genetic polymorphism:				Casson, et al.[25]
Active GSTM1 in smokers			7.9 (1.14-54.76)	
Active GSTT1 in smokers			3.2 (1.23-8.35)	

and esophageal cancer) in the next two years. Varying thresholds high risk groups (in terms of proportion of individuals with the highest risk) were used and validated in a separate validation cohort to determine the predictive value of the algorithm. Using a threshold of 10 % of the individuals with the highest risk, the positive predicted value of the algorithm was only 1.2%.

Barrett's esophagus

For BE, the strongest associations were found with the cytokines interleukins (IL) showing odds ratios between 1.84 and 9.5 for varying types. An increased waist to hip ratio and male gender showed a moderately increased risk of BE. All risk factors showed a higher association with long segment BE than with short segment BE (Table 2b).

Malignant potential

Studies did not distinguish between BE and adenocarcinoma patients, but analyzed the risk factors for the common outcome. BE and EAC showed a strong correlation with the presence of cytokine interleukins and male gender. A moderate correlation was seen for other risk factors (race, age, PPI and hiatus hernia) (Table 2c). The crude ratio in Nason et al.[22] was not adjusted for confounding factors.

Table 2c	Study population	Outcome	OR 95% CI	Note	Study
Demographic factors					
Male gender	*Asymptomatic & symptomatic GERD*	BE and EAC	6.56 (3.46-12.44)	Crude[2]	Nason, et al.[26]
Caucasian	*Asymptomatic & symptomatic GERD*	BE and EAC	3.36 (1.03-10.95)	Crude	Nason, et al.[26]
Age	*Asymptomatic & symptomatic GERD*	BE and EAC	1.03 (1.02-1.05)	Crude	Nason, et al.[26]
Clinical factors					
Proton pomp inhibitors (PPI)	*Asymptomatic & symptomatic GERD*	BE and EAC	2.41 (1.55-3.72)	Crude	Nason, et al.[26]
Hiatus hernia	*Asymptomatic & symptomatic GERD*	BE and EAC	3.36 (2.36-5.57)	Crude	Nason, et al.[26]
Genetic factors					
IL-1 Ra + 2018 genotype 2/2, ≥copy of allel 2 -in IL-1β 511	*Esophagitis*	BE LGD HGD and EAC	6.29 (0.75-52.89)		Gough, et al.[24]
	Esophagitis	BE and EAC	7.89 (1.03-60.30)		Gough, et al.[24]
IL-1 Ra +2018 genotype 2/2	*Esophagitis*	BE LGDHGD and EAC	3.7 (1.02-13.61)		Gough, et al.[24]
	Esophagitis	BE and EAC	3.4 (0.99-11.56)		Gough, et al.[24]
IL-10 1082 genotype 2/2	*Esophagitis*	BE LGDHGD and EAC	2.05 (1.15-3.62)		Gough, et al.[24]
	Esophagitis	BE and EAC	1.94(1.16-3.25)		Gough, et al.[24]

* For smoking-related risk factors, the odds ratio was calculated for smokers compared with never-smokers.[1] definition elevated waist - hip ratio : ≥ 0.9 Men , Women ≥ 0.8.[2] Crude ratio: is not adjusted for confounding factors in this study, therefore, the OR can be higher or lower than it actually is. OR: odds ratio; EGJA: Esophago-gastric junctional adenocarcinoma; EAC: Esophagus adenocarcinoma; GST: glutathione S-transferees GERD : Gastro esophageal Reflux Disease ; SSBE : Short Segment BE , LSBE : Long segment BE; BE : Barrett esophagus; ND: No dysplasia; LGD: Low-grade dysplasia, HGD: High-grade dysplasia

Table 3. Characteristics of the studies found for doctor/patient delay.

Study	Median duration	Outcome
Grotenhuis, et al.[28]	T1: 13 weeks T2: 20 weeks	5-yr survival: T1, ≤3 vs > 3months 24.0% vs 29.3% (p=0.10); T2-T1, <5wks 24.7%, 5-8wks 21.7%, >8wks 32.3% (p=0.12)
Martin, et al.[29]	T1: 17.1 weeks	T1: Diagnosis in stadium I and II vs III and IV 7 weeks vs 21 weeks (p=0.02)
Rothwell, et al.[30]	T2: 15 weeks	T2: Not significant on survival

EAC, esophageal adenocarcinoma, T1, 1[e] symptoms-diagnosis cancer; T2, 1[e] symptoms -treatment.

2. Is early detection of esophageal adenocarcinoma possible by decreasing doctor- and patient delay?

Little has been published about doctor- and patient delay in EAC and even the three studies found did not distinguish between the two esophageal cancer subtypes. The estimated median time from initial symptoms to final diagnosis (T1) ranged between 13-17 weeks. The estimates of the median duration of the entire process, from initial symptoms to treatment (T2), ranged between 15-20 weeks. The effect of delay on the survival rate was investigated only in one prospective study.[28] No significant effect of patient delay on 5-year survival was found (Table 3).

3. Is early detection of esophageal adenocarcinoma possible by screening for Barrett's esophagus or surveillance of Barrett's esophagus, and what are the estimated health benefits of early detection?

Screening modalities

The three studies identified for the diagnostic accuracy of screening modalities included alternatives for the conventional endoscopy. Ramirez et al. evaluated the diagnostic accuracy of string capsule endoscopy in 100 reflux patients who were referred for endoscopy. The other studies evaluated the diagnostic performance of the cytosponge, among 504 patients with a prescription of acid suppressants from their GP (Kadri et al.[34]) and among 47 BE patients and 99 healthy controls (Lao-Sireix et al.[33]). In all these studies the sensitivity and specificity of the alternative modalities was high compared to histological biopsies (Table 4). The positive predictive value of the cytosponge was low in the study with a low BE prevalence in the population (PPV: 26.8% BE prevalence 3%) compared to the studies with a higher prevalence of BE (PPV: 69% and 78% with BE prevalence 34% and 32%).

Table 4. Screening modalities.

Study	Diagnostic modality	Reference modality	Diagnostic outcome (BE/EAC)	Sensitivity/ Specificity	Positive predictive value (PPV)	Prevalence of BE in sample population
Ramirez, et al.[31]	String capsule endoscopy	Histologic diagnosis of BE	BE	93.5%, 78.7%	69%	34%
Lao-Sirieix, et al.[32]	Cytosponge using marker TFF3	Histologic diagnosis of BE	BE	78%, 94%	78%	32%
Kadri, et al.[33]	Cytosponge using marker TFF3	Histologic diagnosis of BE	BE	73.3%, 93.8%	26.8%	3%

BE: Barrett's Esophagus

Table 5. Health gains of early detection.

Study	Study design	Cohort	Comparison	Outcome definition	Outcome
Roberts, et al.[34]	Prospective cohort	HGD/EAC patients diagnosed within a surveillance program	HGD/EAC patients diagnosed on index endoscopy	5-year survival rates	50% vs 2.7%
Cooper, et al.[35]	Retrospective population-based	HGD/EAC patients diagnosed with a prior a) endoscopic surveillance b) GERD diagnosis c) BE diagnosis	HGD/EAC patients diagnosed on index endoscopy	Hazard ratio of survival	a: 0.9 b: 0.45 c: 0.66

Health gaens of early detection

We found two cohort studies, both presenting positive results for the health benefits of early detection in BE patients.[34, 35] The large prospective cohort study[34] investigated health gains of early detection due to surveillance of BE patients, and showed higher 5-year survival rates (50% vs. 2.7%) for HGD/EAC patients that were found within a surveillance program, compared to HGD/EAC patients that were found on index endoscopy (Table 5). We should consider the possibility that the results of these studies are influenced by lead and length time bias. Early detection by surveillance advances the time of diagnosis compared to controls (lead time) and results in the preferential diagnosis of low-risk cancers (length time). To avoid these biases, investigators in randomized trials of cancer screening and surveillance should compare mortality rates from the disease in question in the whole population randomized to screening and surveillance with those in the whole control population, instead of comparing survival rates of disease cases. In addition, the time origin is taken as the point of randomization, not the point of diagnosis. This was not the case in the presented studies. Roberts et al.[34] chose a 5-year survival, as opposed to a shorter time interval, as the primary endpoint in an attempt to lessen the effects of lead time bias. Cooper et al.[35] studied the health gains by early detection due to screening (previously known GERD or BE diagnosis) and due to surveillance (BE patient under endoscopic surveillance) compared to HGD/EAC patients diagnosed on index endoscopy. The investigators aknowledge the posibility of lead time bias as potential explanation for the observerd protetcive effects in their discussion.

Cost-effectiveness of early detection

Of the six cost-effectiveness studies, four evaluated surveillance scenario's using conventional endoscopy[36-39]; two of these applied screening in males with gastro-esophageal reflux disease (GERD), one study applied screening in males undergoing colonoscopy and one study applied surveillance in males with BE. The two other studies evaluated other modalities than conventional endoscopy (Table 6). Compared to a situation without screening, conventional endoscopy led to more QALY's, but also

Table 6. Results of cost-effectiveness of early detection by modeling studies.

Study	Population	Screening method	Surveillance method	Notes	QALYS	Costs per patient	ICER/QALY
Conventional diagnostic modality: standard endoscopy							
Rubenstein, et al.[36]	50-year old Caucasian GERD males	a) No screening b) One-time endoscopy	a) No surveillance b) ND every 3 year, LGD every 6 mo, HGD every 3 mo		a) 16.466 b) 16.637	a) $104 b) $2443	a) - b) $13 721*
Gupta, et al.[39]	50-year old male undergoing colonoscopy screening	a) No screening b) One-time endoscopy c) One-time endoscopy d) One-time endoscopy	a) No surveillance b) No surveillance c) ND every 3 year, LGD every year, HGD every 3 mo d) ND every 3 year, LGD every year, HGD every 3 mo	c)Part follows surveillance guidelines, part of HGD/mucosal EAC patients receives EET d) Everyone followed surveillance guidelines, all HGD/mucosal EAC patients receive ET	a) 18.0789 b) 18.0828 c) 18.0839 d) 18.0849	a) $479.90 b) $933.40 c) $960.70 d) $957.00	a) - b) $115 664* c) $95,559* d) $79 882*
Inadomi, et al.[37]	50-year old GERD males	a) No screening b) One-time endoscopy c) One-time endoscopy	a) No surveillance b) ND no surveillance, LGD every 6 mo, HGD every 3 mo c) ND surveillance every 5 year, LGD every 6 mo, HGD every 3 mo	c) ND surveillance are multiple scenario's, in this table we show the results of 5 year interval	a) 16.466 b) 16.624 c) 16.624	a) $104 b) $1748 c) $2053	a) - b) $10 440** c) $12 336*
Sonnenberg, et al.[38]	60-year old male BE patients		a) No surveillance b) All BE every 2 years		-	a) $7829 b) $12257	a) – b) $16 965* / UALY

Table 6. Results of cost-effectiveness of early detection by modeling studies. (continued)

Study	Population	Screening method	Surveillance method	Notes	QALYS	Costs per patient	ICER/QALY
Alternative diagnostic modalities							
Benaglia, et al.[40]	50-year old GERD males	a) No screening b) One-time endoscopy c) One-time cytosponge	a) No surveillance b) ND every 3 year, LGD every 6 mo, HGD ET c) ND every 3 year, LGD every 6 mo, HGD ET		a) 17.964 b) 17.977 c) 17.979	a) $132 b) $431 c) $373	a) – b) $22 167* c) $15 724*
Nietert, et al.[41]	50-year old GERD males	a) No screening b) One-time conventional endoscopy c) One-time ultrathin endoscopy	a) No surveillance b) ND,LGD every 2 year, HGD esophagectomy c) ND,LGD every 2 year, HGD esophagectomy		a) 19.3266 b) 19.3329 c) 19.3366	a) $11 785 b) $12 332 c) $12 119	a) – b) $86 833* c) $55 764*

* compared to no screening and no surveillance

**surveillance of only dysplastic BE patients compared to no screening and no surveillance

ICER: incremental cost-effectiveness ratio, QALY: Quality adjusted life year, UALY: Unadjusted life years, ND: non-dysplastic BE, LGD: low-grade dysplasia, HGD: high-grade dysplasia, ET: endotherapy

to higher costs. Gupta et al.[39] shows us that an improved adherence of guidelines in terms of adhering to the recommended surveillance intervals in combination with a higher proportion of HGD patients treated with endotherapy (ET) can reduce costs compared to less adherence and a lower proportion of HGD patients treated with ET. Inadomi et al.[37] shows that the surveillance of patients without dysplastic BE does not improve the QALYs gained compared to only applying surveillance in patients with dysplastic BE. Furthermore, this study shows that it is more cost-effective to apply surveillance only in dysplastic BE patients, compared to applying surveillance in all BE patients (non-dysplastic and dysplastic). Results suggest that the ultra-thin endoscopy and cytosponge are more cost effective than standard endoscopy for screening and surveillance, as both with the use of one of these diagnostic modalities lead to more QALYs gained and lower costs (Table 6).

4. Can we identify risk factors for high-grade dysplasia and esophageal adenocarcinoma development in Barrett's esophagus?

The results are shown for demographic, lifestyle and clinical factors, and genetic and molecular factors.

Demographic, lifestyle, and clinical factors

Looking at prospective cohort studies with more than 700 patients, nodularity and dysplasia are predictive for progression to high-grade dysplasia and EAC (Table 7). Length of the BE segment, esophagitis and length of hiatal hernia have a weaker association with progression to malignancy. Factors for which varying or inadequate results were

Table 7. Summary of the predictive value of demographic and clinical factors of progression to esophageal adenocarcinoma in Barrett 's esophagus patients.

Factor	Outcome	Predictive value (95% BI)	Study
Clinical factors			
Nodularity	Progression to HGD/EAC	RR: 7.70 (2.63-21.98) *	Rugge, et al.[43]
	Progression to HGD/EAC	RR: 2.0 (0.6 – 6.6)	Sikkema, et al.[44]
Low-grade dysplasia	Progression to HGD/EAC	RR: 3.74 (1.22-11.43)	Rugge, et al.[43]
	Progression to HGD/EAC	RR: 9.7 (4.4-21.5)	Sikkema, et al.[44]
Specialized intestinal metaplasia	Progression to HGD/EAC	HR: 3.54 (2.09-6.00)	Bhat, et al.[45]
Length of BE segment	Progression to HGD/EAC	RR: 1.16 (1.03-1.30)	Rugge, et al.[43]
	Progression to HGD/EAC	RR: 1.11 (1.01 – 1.2)	Sikkema, et al.[44]
Esophagitis	Progression to HGD/EAC	RR: 3.5 (1.3 – 9.5)	Sikkema, et al.[44]

^ Specialized Intestinal Metaplasia . In most of the countries (the Netherlands, U.S.) is to find SIM , however, a prerequisite for the diagnosis of Barrett 's esophagus, in the UK , this is not the case * nodularity/ulcer HGD: high-grade dysplasia; EAC: esophageal adenocarcinoma; RR: Relative risk, OR: Odds ratio Table contains only prospective cohort studies with a cohort >=700 patients with a significant association.

reported are male gender, age, obesity, smoking and reflux symptoms. The results of smaller studies and other designs were mainly in line with the large prospective cohort studies (significant associations with nodularity, dysplasia status, esophagitis and length of BE segment). Results for other associations were often varying between studies. In general high associations were additionally found for the presence of a hiatal hernia and lower associations for long duration of GERD symptoms and BMI. Varying results were also found for gender, age, shorter durations of GERD symptoms, smoking, race, alcohol use, NSAIDS, PPI use and *H. Pylori* status.

Table 8. Summary of the predictive value of genetic and epigenetic factors for progression to esophageal adenocarcinoma in Barrett 's esophagus patients.

Factor	Outcome	Predictive value (95% CI)	Study
Genetics		OR (else different defined)	
DNA content abnormalities			
Aneuploidy	Progression to EAC	5.9 (3.1-11)	Rabinovitch, et al.[46]
tetraploidy/increased 4N	Progression to EAC	1.36 (1.26-1.47)	Chao et al.[58]
	Progression to EAC	4N >6%: 12 (6.2-22), >15%: 10 (4.1-27), 6-15%: 12 (6.2-24)	Rabinovitch, et al.[46]
high diploid S-phase	Progression to EAC	1.16 (1.01-1.32)	Chao et al.[58]
	Progression to EAC	S phase>5.5 vs <=5.5%: 2.3(1.2-4.4)	Rabinovitch, et al.[46]
Tumor suppressor loci			
P53 LOH	Progression to HGD/EAC	17p (p53) LOH; 3.6 (1.3-10)	Reid, et al.[47]
Leukocyte telomere length	Progression to EAC	HR 2.39-4.66 (shortest vs longest length quartile	Risques, et al.[48]
Epigenetics			
Methylation			
p16, RUNX3, HPP1, NELL1, TAC1, SST, AKAP12, and CDH13	Progression to HGD/EAC	Specificity (95% CI) at sensitivity 0.90. 0.523 – 0.567 (range for all models)	Jin, et al.[42]

HGD: high-grade dysplasia; EAC: esophageal adenocarcinoma; RR: Relative risk, OR: Odds ratio

Genetic and molecular factors

Table 8 shows that the strongest association with malignant development in BE re found with detection of aneuploidy and tetraploidy with increased 4N. Methylation of a combination of genes has a high specificity for the prediction for progression towards EAC.[42]

DISCUSSION

We systematically compiled the current available knowledge on the possibility of early detection of EAC according to four different aspects: early detection on the basis of signs, symptoms and risk factors, early detection by prevention of patient- and doctor delay, and early detection by means of screening and/or surveillance of BE. We included 49 of the 1115 identified papers in our review.

Although we found that frequent and a long duration of GERD symptoms are positively associated with the development of BE and/or EAC in the population, together with smoking (more than 30 pack years), family history, increased waist-to-hip ratio and male gender, the possibilities of early detection of EAC by signs, symptoms and risk factors are limited. A prediction model to early detect EAC in the general population of Hippisley-Cox and Coupland[27] including many of the risk factors of this review, had a positive predictive value for the actual diagnosis of EAC of only 1.2%. By using such a model, a large part of the population will be falsely suspected of having EAC, resulting in unnecessary diagnostic testing. For genetic factors we found that several cytokines interleukins and genetic polymorphisms are predictive for malignant development. Possibilities for early detection by evaluating genetic factors for BE and/or EAC in the general population is not yet feasible on a large scale. The costs of population screening would currently be too high. Benefits from population screening are only possible when genetic factors can be identified that are strong predictors of EAC.

Secondly, we studied the role of patient- and doctor delay, which is however not well-studied. The time interval between first symptoms and treatment did not seem to affect EAC survival. However, this finding was based on only one study. Based on the current evidence available on patient- and doctor delay no final conclusions concerning the impact of delay on survival can be made.

The third research question focused on the possibilities of early detection of (precursors of) EAC by screening, and the attainable health benefits of such early detection. String capsule endoscopy and cytosponge have recently been introduced and seem promising alternative diagnostic modalities for detecting BE for the golden standard conventional endoscopy followed by histological confirmation. The sensitivity and specificity of these tests seem comparable or even higher than conventional endoscopy and moreover, these alternative diagnostic modalities are far less burdensome for the patient. However, there is no evidence yet that early detection of EAC by means of screening for BE in the general population, based on these modalities, can lead to early detection of EAC and health benefits. Furthermore, these studies are often due to length and lead time bias. Early detection of EAC by means of surveillance of BE seems to lead to health benefits, in terms of mortality reduction and higher quality of life, as shown in the included cohort studies. A prior diagnosis of BE and adherence to

a surveillance program were found to significantly improve the probability of survival, which reflects a combination of more options of safer and less-invasive treatment methods because EAC may be found at an earlier stage, and a larger absolute proportion of EAC cases detected in earlier, less fatal stages. However, none of these studies were designed as a randomized controlled trial, resulting in no definitive evidence for health benefits.

The cost effectiveness of screening and surveillance was only assessed in modeling studies. Surveillance in dysplastic patients was more cost effective than surveillance in ND BE patients. This is in line with a published review concerning the cost-effectiveness of surveillance in ND BE patients, in which the authors concluded that surveillance is unlikely to be cost- effective49. Modeling studies are subject to uncertainty in parameter assumptions, for which progression towards EAC within BE had the largest impact on the attainable health benefits. When assuming a high progression rate towards malignancy in the model, a large number of cancers will develop resulting in a higher effectiveness of screening and surveillance scenarios. In summary, surveillance for BE seems to be effective in terms of increasing the health benefits of patients found due to early detection, however cost-effectiveness of surveillance is controversial and highly dependent on risk of EAC which has a high level of uncertainty.

Finally we studied the determinants for malignant progression in BE patients. There are indications that a number of demographic and clinical factors may contribute to the prediction of progression to HGD / EAC in BE patients, such as esophagitis, dysplasia, nodularity, and possible length of BE segment. In addition preliminary research indicates that a number of molecular biomarkers in biopsies from BE, i.e. DNA content abnormalities, p53 loss of heterozygosity (LOH) and leukocyte telomere length have a high predictive value for progression. In addition aneuploidy, tetraploidy and methylation are predictors for neoplastic progression in BE.

This unique review comprises an extensive overview of the current available knowledge on early detection of EAC. The study had a broad perspective to cover all possible aspects of early detection for EAC. However, the study has some limitations. First, we conducted the searches only in Medline and did not include other medical literature databases. Secondly, we only included references from the past 10 years, to obtain the most recent studies. Although we have worked with a small time frame for our literature search, the explosive amount of research on BE and EAC performed in the last decades provided us with sufficient information on the various topics. The only exception was research question 2, for which only a limited number of studies was found in the initial search and we therefore included references from 1990 forwards.

Over the past years a number of systematic reviews were performed concerning early detection of EAC. Most reviews focussed on one of the four aspects studied in our review, such as risk factors for BE and/or EAC, incidence of EAC in BE and prevalence of BE. One of these reviews (2010) found that age, gender, and length of BE segment, dysplasia and nodularity are risk factors for progression in BE with a high level of evidence, which coincide with the results from our review.[50] However, none of the currently known clinical and endoscopic criteria have sufficient predictive power to identify the group of BE patients that will progress towards EAC. Furthermore these reviews generally conclude that although some biomarkers have shown predictive ability with increased odds for BE progression, significant work needs to be done before a comprehensive and clinically useful BE prediction model can be developed. Difficulties in research for predictors are the small number of patients progressing to HGD or EAC, the fact that the outcomes have a high probability of sampling error since they depend on mucosal tissue sampling, and specifically, for biomarker research there is variation in the methods used between laboratories and lack of standardization.

Another review (2011) investigated genetic and epigenetic risk factors for EAC. The authors concluded that there is increasing understanding in the mechanisms underlying the progression of BE to EAC.[51] Although no study has completed all five phases (necessary to provide definitive evidence of health benefits for the patients), these studies have led to the identification of promising biomarkers such as DNA content abnormalities, p53 LOH and leukocyte telemore length. They also conclude that it is likely that the best model for predicting clinical outcome in BE patients will involve a combination panel of biomarkers as well as demographic and environmental exposures.

In conclusion, a complete overview of the current knowledge on all early detection possibilities of EAC is now available. The early detection of EAC on a population level by means of screening is not yet successful; signs, symptoms and risk factors in the general population are not exclusively predictive for EAC and screening is highly burdensome for individuals and costly to apply to the general population. New modalities are emerging including genetic- and epigenetic markers that might provide higher predictive values for BE and progressive BE in the general population. There is no definitive evidence, but only a strong suggestions that early detection of EAC by means of surveillance in a high risk population, e.g. BE patients, is effective. In order to improve cost effectiveness surveillance should be optimized by improving risk stratification in this population.

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Table S1. Search strategies and eligibility criteria.

	Research question 1: For which signs, symptoms and risk factors should we increase awareness to enable the early detection of EAC?	Research question 2: Is early detection of EAC possible by decreasing doctor/ and patient delay?	Research question 3: Is early detection of EAC possible by screening for BE or surveillance of BE, and what are the estimated health benefits of early detection?
	• Are there signs and symptoms that are predictive of an early phase of EAC? • Which methods can be used to identify these signs and symptoms?	• Can the prospective at EAC diagnosis deteriorate by doctor/patient delay? • Which factors are of importance?	Search a: • Does EAC have a detectable preclinical phase?
	(Risk factors [Mesh] OR Signs and symptoms [Mesh] OR (suspect* [ti/ab] OR suspic* [ti/ab])) AND ((“Esophageal Neoplasms”[Mesh] OR (Barrett Esophagus[mesh] OR Esopha* [ti/ab]) AND (neoplasms[MESH] OR cancer*[ti/ab] OR tumor[ti/ab] OR tumors[ti/ab] OR tumou*[ti/ab] OR neoplas*[ti/ab] OR carcinoma* [ti/ab]))) AND (“Population Surveillance”[Mesh] OR surveil*[tw] OR mass screening [tw] OR screen*[tw] OR (early[tw] AND detection[tw])) AND (eng[la] OR dutch [la] OR French[lang] OR German[lang] OR Italian[lang] OR Spanish[lang] OR Portuguese[lang]) AND 2002:5000[dp]	(“Delayed Diagnosis”[Mesh] OR “Referral and Consultation”[Mesh] OR ((“patients”[MeSH] OR “patients”[All Fields] OR “patient”[All Fields]) AND ((delay[All Fields] OR late[All Fields]) AND detection[All Fields]))) AND ((“Esophageal Neoplasms”[Mesh] OR (Barrett Esophagus[mesh] OR Esopha* [ti/ab]) AND (neoplasms[MESH] OR cancer*[ti/ab] OR tumor[ti/ab] OR tumors[ti/ab] OR tumou*[ti/ab] OR neoplas*[ti/ab] OR carcinoma* [ti/ab]))) AND (eng[la] OR dutch [la] OR French[lang] OR German[lang] OR Italian[lang] OR Spanish[lang] OR Portuguese[lang]) AND 1990:5000[dp]	Search b: • Which systematic detection (screening or surveillance) methods are available? Search c: • What are the test characteristics of these methods? Search d/e: • Does systematic detection of EAC lead to less EAC mortality? • Is systematic detection of EAC cost-effective?
	• 252 hits	• 76 hits	Search a (Asymptomatic Diseases [Mesh] OR Presymptomatic Disease [Mesh] OR Neoplasm Staging [mesh]) AND ((“Esophageal Neoplasms”[Mesh] OR (Barrett Esophagus[mesh] OR Esopha* [ti/ab]) AND (neoplasms[MESH] OR cancer*[ti/ab] OR tumor[ti/ab] OR tumors[ti/ab] OR tumou*[ti/ab] OR neoplas*[ti/ab] OR carcinoma* [ti/ab]))) AND (“Population Surveillance”[Mesh] OR surveil*[tw] OR mass screening [tw] OR screen*[tw] OR (early[tw] AND detection[tw])) AND (eng[la] OR dutch [la] OR French[lang] OR German[lang] OR Italian[lang] OR Spanish[lang] OR Portuguese[lang]) AND 2002:5000[dp] • 139 hits

Search b

(Diagnostic molecular pathologies [Mesh] OR Molecular Diagnostic Techniques [Mesh] OR Diagnostic Techniques, Endocrine [Mesh] OR Diagnostic Tests, Routine [Mesh] OR Diagnostic Self Evaluation [Mesh] OR Biomarker [ti/ab] OR Diagnostic Techniques and Procedures [Mesh]) AND (("Esophageal Neoplasms"[Mesh] OR (Barrett Esophagus[mesh] OR Esopha* [ti/ab]) AND (neoplasms[MESH] OR cancer*[ti/ab] OR tumor[ti/ab] OR tumors[ti/ab] OR tumou*[ti/ab] OR neoplas*[ti/ab] OR carcinoma* [ti/ab]))) AND ("Population Surveillance"[Mesh] OR surveil*[tw] OR mass screening [tw] OR screen*[tw] OR (early[tw] AND detection[tw])) AND (eng[la] OR dutch [la] OR French[lang] OR German[lang] OR Italian[lang] OR Spanish[lang] OR Portuguese[lang]) AND 2002:5000[dp] NOT (animals[mesh] NOT humans[mesh])

- 766 hits

Search c

Diagnostic Techniques and Procedures [Mesh] AND sensitivity and specificity [Mesh] AND (("Esophageal Neoplasms"[Mesh] OR (Barrett Esophagus[mesh] OR Esopha* [ti/ab]) AND (neoplasms[MESH] OR cancer*[ti/ab] OR tumor[ti/ab] OR tumors[ti/ab] OR tumou*[ti/ab] OR neoplas*[ti/ab] OR carcinoma* [ti/ab])) AND ("Population Surveillance"[Mesh] OR surveil*[tw] OR mass screening [tw] OR screen*[tw] OR (early[tw] AND detection[tw]))) AND (eng[la] OR dutch [la] OR French[lang] OR German[lang] OR Italian[lang] OR Spanish[lang] OR Portuguese[lang]) AND 2002:5000[dp] NOT (animals[mesh] NOT humans[mesh])

- 134 hits

Search d/e:

("Mortality"[Mesh] OR Cost-Benefit Analysis [MESH]) AND "Early Detection of Cancer"[Mesh] AND (("Esophageal Neoplasms"[Mesh] OR (Barrett Esophagus[mesh] OR Esopha* [ti/ab]) AND (neoplasms[MESH] OR cancer*[ti/ab] OR tumor[ti/ab] OR tumors[ti/ab] OR tumou*[ti/ab] OR neoplas*[ti/ab] OR carcinoma* [ti/ab]))) AND (eng[la] OR dutch [la] OR French[lang] OR German[lang] OR Italian[lang] OR Spanish[lang] OR Portuguese[lang]) AND 2002:5000[dp]

- 9 hits

Inclusion criteria	- signs and symptoms - predictive factors - high risk groups	- delayed presentation of patient - delayed referral - delayed diagnosis	- screening, early detection - early diagnostic screening tests - biomarkers - imaging
Exclusion criteria studies focusing on	- screening, not focused on high risk groups - etiology	- systematic screening , diagnostics tests - complications due to diagnostic tests	

Common Criteria

Inclusion criteria

- EAC, Primary cancer, BE-EAC

population

- general population
- clinical population

type studies

- review
- randomized controlled
- case-control
- cohort study
- expert opinion

language

English, Dutch, German, French, Spanish, Italian, Portuguese

Exclusion criteria

other cancer types/diseases-
EAC as comorbidity factor at other diseases, comorbidity for EAC

studies focusing on

- treatment or guidelines for treatment
- prognostic factors for disease progression and survival
- epidemiology

population:

- children(< 18 year), animals

type study:

- case reports
- laboratory experiments (in vitro, in vivo studies)

language:

- other than inclusion criteria

Table S2. Study characteristics included in the review.
Table S2a. Characteristics of the studies found for signs, symptoms and risk factors of esophageal adenocarcinoma

Author(reference)	Country	Study design	Sample size	BE cases	EAC cases	BE and/or EAC	Section
Casson, et al.	Canada	Case-control study	307	125	56	-	EAC
Chak, et al.	U.S.	Observational study	375	-	110	-	EAC
Hippisley-Cox, et al.	U.K.	Prospective cohort study	1 238 971	-	2527[1]	-	EAC
Rubenstein, et al.	Sweden, U.S., Ireland & North Ireland, Australia	Meta-analysis	5855	-	1189	-	EAC
Gough, et al.	U.K.	Case-control study	456	-	-	203	BE/EAC
Edelstein, et al.	U.S.	Case-control study	605	197	-	-	BE/EAC
Nason, et al.	U.S.	Case-control study	769	-		122[2]	BE/EAC
Pandeya, et al.	Australia	Case-control study	1875	-	367	-	BE/EAC

BE: Barrett's esophagus; EAC: Esophageal adenocarcinoma
[1]cases include patients with gastro-esophageal cancer
[2]cases are patients with BE and/or EAC

Table S2b. Characteristics of the studies found for doctor/patient delay.

Author(reference)	Country	Study design	Sample size	Cancer type
Grotenhuis, et al.	*Netherlands*	*Prospective cohort study*	*491*	*esophagus cancer*
Martin, et al.	*U.K.*	*Retrospective (interview)*	*115*	*gastric cancer and esophagus cancer*
Rothwell, et al.	*Ireland*	*Retrospective (interview)*	*100*	*esophagus cancer*

Table S2c.Characteristics of the studies found for screening and health benefits of early detection.

Author(reference)	Country	Study design	Sample size	Section
Ramirez, et al.	U.S.	Diagnostic test	100	Screening modalities
Lao-Sirieix, et al.	U.K.	Diagnostic test	146	Screening modalities
Kadri, et al.	U.K.	Diagnostic test	504	Screening modalities
Rubenstein, et al.	U.S.	Modeling study	n.a.	Cost-effectiveness of early detection
Gupta, et al.	U.S.	Modeling study	n.a.	Cost-effectiveness of early detection
Inadomi, et al.	U.S.	Modeling study	n.a.	Cost-effectiveness of early detection
Sonnenberg, et al.	U.S.	Modeling study	n.a.	Cost-effectiveness of early detection
Nietert, et al.	U.S.	Modeling study	n.a.	Cost-effectiveness of early detection
Benaglia, et al.	U.K.	Modeling study	n.a.	Cost-effectiveness of early detection
Cooper, et al.	U.S.	Retrospective cohort	2754	Health gains of early detection
Roberts, et al.	U.K.	Prospective cohort	302	Health gains of early detection

n.a.: not applicable

Table S2d. Characteristics of the studies found concerning risk factors for esophageal adenocarcinoma development in Barrett's esophagus patients

Author(reference)	country	Study design	Sample size
Anandasabapathy, et al.	U.S.	Case-control study	109
Bird-Lieberman, et al.	U.K.	Case-control study	291
de Jonge, et al.	Netherlands	Case-control study	244
Gopal, et al.	U.S.	Case-control study	309
Rudolph, et al.	U.S.	Case-control study	396
Bhat, et al.	U.K.	Prospective cohort study	9334
Chao, et al.	U.S.	Prospective cohort study	276
Hage, et al.	Netherlands	Prospective cohort study	105
O'Connor, et al.	U.S.	Prospective cohort study	135
Rabinovitch, et al.	U.K.	Prospective cohort study	307
Reid, et al.	U.S.	Prospective cohort study	325
Risques, et al.	U.S.	Prospective cohort study	300
Rugge, et al.	Italy	Prospective cohort study	841
Sikkema, et al.	Netherlands	Prospective cohort study	713
Siahpush, et al.	U.S.	Prospective cohort study	344
Weston, et al.	U.S.	Prospective cohort study	324
von Rahden, et al.	Germany	Prospective cohort study	1438
Bani-Hani, et al.	U.K.	Retrospective cohort study	553
de Jonge, et al.	Netherlands	Retrospective cohort study	42207
Dulai, et al.	U.S.	Retrospective cohort study	575
Gatenby, et al.	U.K.	Retrospective cohort study	781
Gatenby, et al.	U.K.	Retrospective cohort study	612
Oberg, et al.	Sweden	Retrospective cohort study	147
Switzer-Taylor, et al.	New Zealand	Retrospective cohort study	212
Wong, et al.	U.S.	Retrospective cohort study	248
Hillman, et al.	Australia	229 retrospectively in 1996; 213 prospectively from that date	353
Jin, et al.	U.S.	Multicenter, double-blinded validation study	195

CHAPTER 6

The Impact of uncertainty in Barrett's esophagus progression rates on hypothetical screening and treatment decisions

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Medical Decision Making 2014 Oct 2

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ABSTRACT

Background: Estimates for the annual progression rate from Barrett's esophagus (BE) to esophageal adenocarcinoma (EAC) vary widely. In this explorative study, we quantified how this uncertainty impacts the estimates of effectiveness and efficiency of screening and treatment for EAC.

Design: We developed three versions of the Erasmus/UW-EAC model. The models differed with respect to the annual progression rate from BE to EAC (0.12% or 0.42%) and the possibility of spontaneous regression of dysplasia (yes or no). All versions of the model were calibrated to the observed Surveillance, Epidemiology, and End Results (SEER) esophageal cancer incidence rates from 1998 to 2009. To identify the impact of natural history we estimated the incidence and deaths prevented as well as numbers needed to screen (NNS) and treat (NNT) of a one-time perfect screening at age 65 that detected all prevalent BE cases, followed by a perfect treatment intervention.

Results: Assuming a perfect screening and treatment intervention for all BE patients, the maximum EAC mortality reduction (64%-66%) and the NNS per death prevented (470-510) were similar across the three model versions. However, three times more people needed to be treated to prevent one death (24 vs. 8) in the 0.12% regression model compared to the 0.42% progression model. Restricting treatment to those with dysplasia or only high-grade dysplasia (HGD) resulted in smaller differences in NNT (2-3 to prevent one EAC case) but wider variation in effectiveness (mortality reduction of 15%-24%).

Conclusion: The uncertainty in the natural history of the BE to EAC sequence influenced the estimates of effectiveness and efficiency of BE screening and treatment considerably. This uncertainty could seriously hamper decision making about implementing BE screening and treatment interventions.

INTRODUCTION

Over the past four decades, the incidence of esophageal adenocarcinoma (EAC) has rapidly increased. Barrett's esophagus (BE) is a precursor of EAC.[1] In BE, normal cells of the esophagus are replaced by intestinal metaplasia, which may progress to low-grade dysplasia (LGD), high-grade dysplasia (HGD) or adenocarcinoma.[2] Despite this concern, little is known about the prevalence of BE in the population and the time course of progression to EAC.

There are several unknown crucial characteristics of the epidemiology of BE to EAC sequence in the population that may have large influences on the estimates of effectiveness and efficiency of BE screening and treatment. First, estimates for the annual progression rate from BE to EAC vary widely in the literature within a range of 0.07%-3.6%.[3-5] Until recently, a progression rate of 0.42% annual progression was assumed most plausible.[6, 7] However, several large recently published population-based studies suggest that the progression rate is actually much lower (~0.12%).[8-10] Selection bias, publication bias, study size and differences in follow up years and cohort characteristics all contribute to the difficulty of comparing and validating these estimates. Secondly, there are large differences in the estimates of the prevalence of BE in the population (0.34%-25%).[11] Differences in BE definitions over time and between countries are an important bottleneck for obtaining consistent estimates. Thirdly, there are indications that BE with dysplasia might regress. Several studies have shown disappearance of dysplasia in BE surveillance cohorts.[6, 12] Regression has also been demonstrated in well-conducted studies with expert pathologists.[13] Disappearance perceived in subsequent biopsies could be the result misclassification because of subjective interpretation of LGD and HGD by pathologists or of sampling errors.

With the introduction of endoscopic mucosal resection and radiofrequency ablation, endoscopic therapy for BE with HGD is being increasingly viewed as first-line treatment.[14] However, the uncertainty in the natural history of EAC may have large influences on the expected effectiveness and efficiency of such interventions.

In this study we used micro simulation modeling to explore how uncertainty in the risk of EAC development in patients with BE impacts the expected effectiveness and efficiency of screening and treatment intervention.

METHODS

The Erasmus/UW-EAC model

The Erasmus/UW-EAC model was developed as part of the Cancer Intervention and Surveillance Modeling Network (CISNET). A detailed description can be found in the

model appendix. In brief, the model simulates the life histories of a large population of individuals from birth to death. Part of the population has symptomatic gastro-esophageal reflux disease (GERD) which is defined as weekly heartburn and/or acid regurgitation. These individuals are at increased risk to develop BE. However, BE can also develop in the absence of GERD symptoms (RR = 6.0 GERD to BE compared to non-GERD to BE, resulting from the assumption that 60% of the BE patients have symptomatic GERD 5). Depending on age, sex and baseline individual risk, low-grade dysplasia may develop from non-dysplastic (ND) BE, which may later progress to high-grade dysplasia. Although most individuals with BE will never develop cancer, malignant cells can arise from HGD, transforming to localized EAC which can progress sequentially into regional and distant EAC. In each cancer stage there is a probability of the cancer diagnosis due to the development of symptoms versus staying asymptomatic and progressing undetected into the next stage. Persons may die of other causes at any time during their lifetime (figure 1).

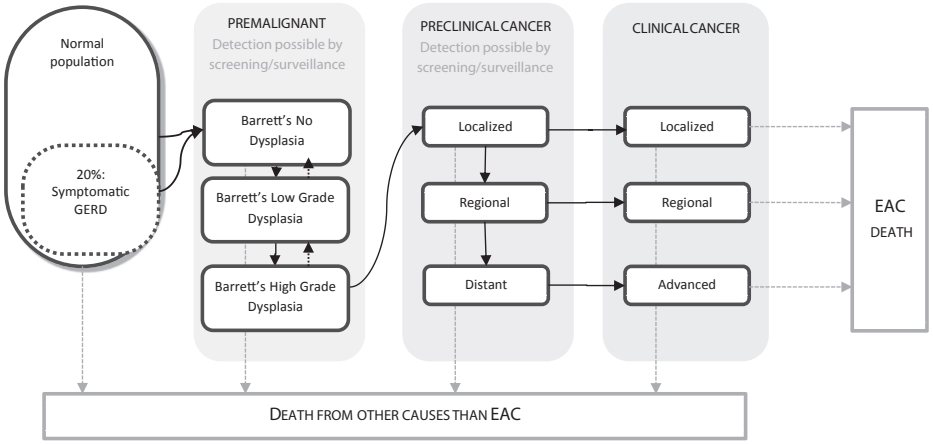

Figure 1. Graphical representation of the Erasmus/UW-EAC model

Model quantification

In order to quantify the effect of different natural history assumptions we developed three different model versions: low-progression model, high-progression model, and regression model. The natural history assumption on progression from BE to EAC is different in each model. Our low-progression model considers a low progression rate from BE (ND+LGD) at age 65 to EAC (0.12% annually within a five-year follow up), consistent with recently published studies.[15-17] The high-progression model considers a higher progression rate (0.42% annually), consistent with published reviews.[18-20] These two model structures include only progressive transitions. The regression model ad-

ditionally includes the possibility to regress from HGD to LGD and from LGD to no dysplasia and considers a low progression rate (0.12% annually from BE (ND+LGD) at age 65 to EAC within a five-year follow up). These main contrasts in model structures and the annual progression rate calibration target between the three models versions are shown in Table 1. In addition to the varying progression rates from BE to EAC, all models were calibrated to the age-specific esophageal cancer incidence as observed in the Surveillance, Epidemiology, and End Results (SEER) Program for 1998-2009 (without assuming secular trends), the amount of LGD and HGD in the 60-65 year old BE population and the estimated average sojourn time from undetected to detected EAC for the total EAC population. An overview of all calibration targets and the resulting natural history characteristics for each model version can be found in the model appendix. The BE prevalence was optimized in each model in order to match the EAC incidence while accounting for the differences in progression rates and model structure assumptions.

Table 1. Contrasting assumptions and calibration targets for three versions of the Erasmus/UW-EAC model.

	Low-progression model	High-progression model	Regression model
Contrast in Model structure	Only progression between states	Only progression between states	Regression in dysplasia states possible
Contrast in Calibration Target	0.12% annual progression rate BE to EAC	0.42% annual progression rate BE to EAC	0.12% annual progression rate BE to EAC

Perfect screening and perfect treatment intervention strategies

A hypothetical perfect screening and treatment intervention was introduced in the three alternative models. We modeled perfect screening and treatment interventions in order to study the effect of the alternative models independently from limitations in test performance and treatment outcomes. The cohort was assumed to be screened with a perfect test (i.e. sensitivity and specificity for BE and neoplasia of 100%, irrespective of symptomatic and non-symptomatic patients) at age 65. All preclinical cancers were detected and treated depending on the stage of EAC at the time of detection. After screening one of three perfect treatment strategies was applied for people with BE. Perfect treatment is defined as an intervention that ensures BE is effectively removed and EAC will not develop during the lifetime of the treated patient. All residual cases of EAC will therefore develop in patients without BE at the time of screening who developed BE and EAC within 15 years after that screening. In the first treatment strategy all BE patients with or without dysplasia were treated (BE treatment). The second treatment strategy provided no treatment for non-dysplastic BE patients, but only for LGD and HGD patients (dysplasia treatment). In the final treatment strategy only HGD patients receive treatment (HGD treatment).

Outcomes

We compared model variants on the outcomes of BE prevalence and EAC incidence by age group. The effectiveness of BE screening and treatment for all three treatment strategies was compared by the reduction in EAC incidence and EAC mortality. The efficiency of screening and treatment was examined by comparison of the number of screenings and treatments required, and number needed to screen and treat to prevent one EAC case of death. A sensitivity analysis was performed to compare the impact of hypothetical interventions in different age groups.

This study was funded by the National Cancer Institute.

RESULTS

The BE prevalence was highest in the model with regression [3.3% for age 60-65] followed by low progression [2.9% for age 60-65] and high progression [1.3% for age 60-65] (figure 2).

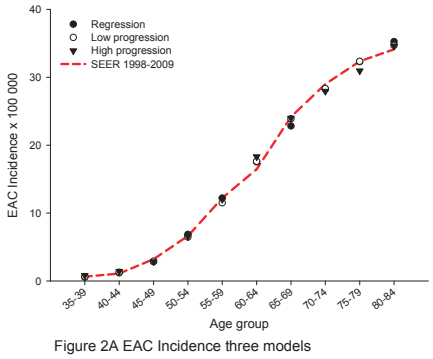

Figure 2A EAC Incidence three models

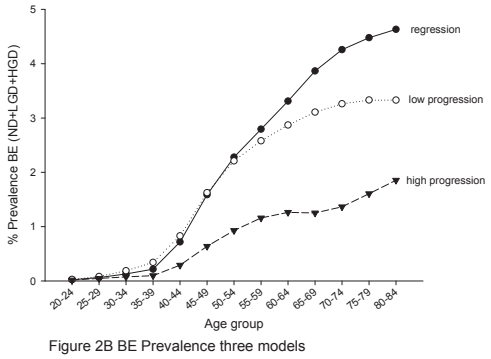

Figure 2B BE Prevalence three models

Figure 2A. EAC incidence for each alternative model compared to the background EAC incidence from SEER for each age group
Figure 2B. The BE prevalence for each alternative model for each age group

The differences in EAC incidence and mortality reduction from screening and treating all BE were negligible between the three models (table 2) but were more pronounced for dysplasia and HGD treatment. The maximum clinical incidence reduction was greatest in the strategy incorporating treatment of all patients with BE [58%-62%], followed by dysplasia treatment [26%-42%] and HGD treatment [4%-13%].

Differences in the EAC development in the untreated BE population directly reflect differences in the progression rates between the models. In case of treatment limited to dysplasia 7.5% of the ND BE developed into EAC in the high-progression model,

whereas in the low progression and the regression models less than 3.5% developed into EAC (figure 3).

Table 2. Effectiveness and efficiency, age 65-80.

	BE treatment		Dysplasia treatment		HGD treatment	
Incidence reduction						
low progression	62%		42%		13%	
high progression	58%		36%		4%	
regression	58%		26%		8%	
Mortality reduction						
low progression	66%		51%		24%	
high progression	64%		46%		15%	
regression	63%		36%		19%	
Screening efficiency	NNS/case	NNS/death	NNS/case	NNS/death	NNS/case	NNS/death
low progression	470	628	692	822	2,273	1,739
high progression	510	663	827	925	8,389	2,748
regression	503	667	1,139	1,171	3,842	2,274
Treatment efficiency	NNT/case	NNT/death	NNT/case	NNT/death	NNT/case	NNT/death
low progression	14.3	19.1	2.4	2.8	1.8	1.4
high progression	6.5	8.5	2.3	2.5	3.0	1.0
regression	18.3	24.3	5.2	5.3	2.3	1.3

Number needed to screen to prevent one case: NNS/case, Number needed to screen to prevent one death: NNS/death, Number needed to treat: NNT

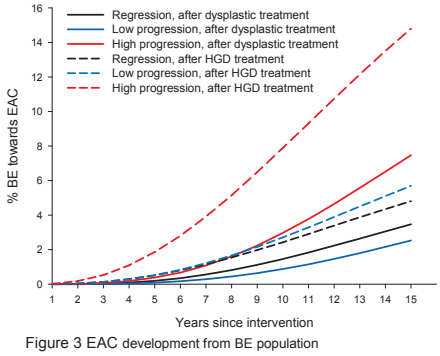

Figure 3 EAC development from BE population

Figure 3. EAC development in the untreated BE population in the three models after removal of the dysplasia treatment cases and HGD treatment cases

The number of treatments differ in each model because this is influenced by the variation in BE prevalence. As a consequence, the number of treatments required to treat all patients with BE is 3-fold higher in the regression model compared with the high-progression model, which requires the fewest number of treatments. Given this variation in number of treatments and the minor differences in effectiveness of screening and treatment, large differences are seen in the numbers needed to treat to prevent one EAC case (NNT/case) and numbers needed to treat to prevent one EAC death (NNT/death). The all-BE treatment strategy is most efficient in the high-progression model (NNT/death is 8.5), followed by the low-progression model (NNT/death is 19.1) and the regression model (NNT/death is 24.3) (figure 4). Almost no differences in the efficiency of HGD treatment are found between the three models.

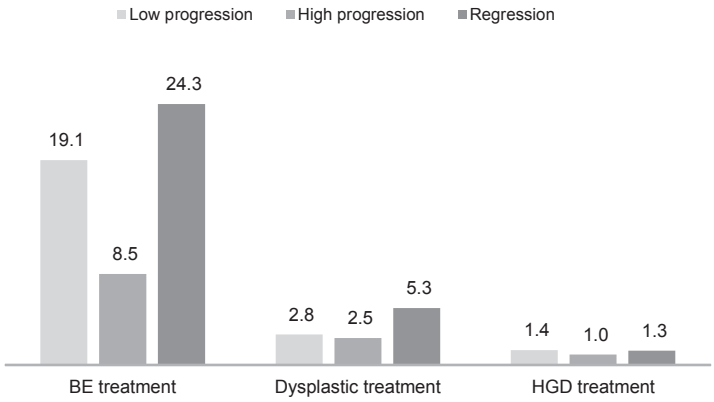

Figure 4. Representation of the number needed to treat to prevent one EAC death for each model in each treatment strategy

Additional sensitivity analyses were performed on the age of initial screening and treatment. In the case of treatment of all BE the incidence and mortality reductions were inversely associated with the initial age of screening; BE treatment in older age groups was less effective. Differences between the models in mortality reduction ranged from 5% to 34% for intervention age 75 compared to intervention age 55. The differences between the models in NNT/death ranged from 2.1- to 2.9- fold for the different intervention ages (supplementary files, table S1).

DISCUSSION

This study demonstrates that the current uncertainty surrounding BE progression is unlikely to lead to large differences in estimates of the effectiveness of BE screening and treatment in the strategy of treatment for all patients with BE. However, if treatment is restricted to BE patients with dysplasia, treatment effectiveness varies widely and is dependent on BE progression assumptions. Furthermore, the resources required to gain that effectiveness vary considerably when treating all BE: screening and treating of all BE requires up to 3 times more patients to be treated per death prevented in a situation with regression compared to a situation with high progression. Finally, the smaller number of patients treated when limiting therapy to patients with dysplasia results in smaller differences in the efficiency of treatment between the models when following the patients for a fifteen-year period.

BE prevalence differs considerably between the models (1%-3% at age 60-65). This difference is explained by differences in assumptions about BE progression. In case of low progression, a higher BE prevalence is needed compared with high progression, in order to calibrate to the same SEER-based cancer incidence. Because of this dependency the real progression rate parameter could be estimated if the real BE prevalence in the population would be known, and vice versa. Unfortunately, estimates for both parameters differ widely and estimates in all three models lie well within the plausible range published in the literature. Based on published data the estimated plausible range for BE prevalence is assumed to be within 1.6%-6.8%[21], which overlaps our simulation estimates. Our study shows that with a high BE prevalence there are more treatments required to obtain the same effectiveness of treatment in terms of cancer and death reduction.

Screening and treatment interventions for all BE patients or patients with dysplasia result in a larger reduction in EAC incidence than EAC mortality due to the risk of death from competing causes. When performing screening and limiting treatment to HGD patients just a small proportion of cancer incidence and deaths is reduced because of HGD treatment. Hence, a large proportion of death reduction from this strategy is due to early detection of malignancies at screening.

We focused on the potential effectiveness of treatment using simulation modeling of a hypothetical perfect intervention. We have used the approach that mirrors the maximal clinical incidence reduction (MCLIR); this theoretical approach identifies how and where differences in model structures manifest in their results.[22] Here the estimated incidence and mortality reductions correspond to the maximum possible clinical benefit in EAC incidence achievable by screening and treatment of BE lesions. We did

not implement a "real-life" intervention in our model because there is a paucity of data on treatment results of LGD and BE. Our point was merely to illustrate the impact of uncertainty in natural history on screening and treatment of BE in general. However, our study results can be generalized to (cost-) effectiveness of real-life interventions: the relative impact of the differences between model structures in this study can be directly translated to relative differences in effectiveness of real-life interventions.

Previous research found that both the progression rate from BE to EAC and the BE prevalence in the population were among the variables causing at least 10% variation in the incremental cost-effectiveness ratio[23], while our studies suggest that up to 70% variation in the effectiveness of treatment interventions may be due to differences in progression assumptions and BE prevalence. Two large cost-effectiveness studies on treatment of BE have been published.[24, 25] Both studies concluded cost-effective surveillance and treatment scenarios are present for treatment of HGD, but treatment of ND and LGD BE is far more expensive and not cost-effective. When comparing differences in NNT/death and NNS/death between our models with literature for other screening programs, we found that outcomes for efficiency of screening in terms of numbers needed to invite (NNI) are reported for breast cancer screening. A recent meta-analysis reported 1904 NNI/death, with a large 95% confidence interval between 929 and 6378 NNI/death.[26] Thus, the reported variation of NNI/death within the 95% confidence interval holds a 7-fold variation, while our results reported variation between models up to 3-fold for the NNT/death. Modeling studies reporting the influence of the uncertainty of input parameters and model structures on cancer screening also showed considerable differences for effectiveness of screening. The study that compared various models with different structures and input assumptions for the simulation of colonoscopy screening showed that the MCLIR after disease removal at age 65-80 varied from 51% to 90% between models , implying a difference of 80% in incidence reduction between models.[27] In our study the largest differences were seen in case of HGD treatment resulting in a difference of 230% in incidence reduction. A recent paper investigated the benefits and harms of computed tomography lung cancer screening strategies by five comparative simulation models. Differences in modeling results for the number of persons who were no longer dying of lung cancer varied between 177 and 863 per 100,000 individuals , which is a 5-fold difference in mortality reduction.[28] Our study showed a maximum of 1.6-fold difference between the mortality reduction of the models.

This study has three limitations that are noteworthy. First, for each model additional parameters apart from the BE incidence must be recalibrated. Therefore, some differences in model outcomes might be due to slightly different estimates in parameters such as preclinical sojourn times and the dysplastic proportion in the BE population.

When calibrating the high-progression model the model compensates by shortening the sojourn times. This resulted in a high percentage of dysplastic patients in the total BE population. Thus, it was not feasible to reach the main calibration target of a high progression in combination with a low proportion of LGD in BE (calibration target of 9%). Consequently optimization of the high-progression model resulted in a high proportion of LGD patients (17%). However, most differences in these other parameters are small (model appendix) and therefore not likely to greatly influence results.

Second, this analysis is restricted to white males. We focused on this group because the majority of published data are derived from this group and including nonwhites and females to the analyses would add more uncertainty to the models. Third, for this analysis we have focused on differing progression rates from BE to EAC and have not accounted for other changes and uncertainties in variables, such as secular trend assumptions and assumptions concerning the preclinical sojourn times. Incorporating a secular trend could have effects on different parts of the model. It is not known whether these effects would be totally or partly caused by an increase in BE incidence or in a higher progression towards EAC in the BE population; thus, we decided not to model these effects. Since the preclinical to clinical sojourn times is a small part of the total BE to EAC sojourn time sequence the impact of varying the preclinical sojourn time is expected to be small compared to the current analysis.

Our analysis highlights the importance of research to diminish the uncertainty in BE prevalence and progression rate to malignancy in BE patients. Because these variables are closely correlated a reliable estimate of either would substantially reduce current uncertainty. Identification of the progression rate to malignancy using a Barrett's surveillance cohort to observe cancer development is difficult. Therefore we suggest a study to accurately estimate BE prevalence since this type of study does not require long-term follow-up and would be able to provide an answer to this important question in a shorter time frame.

In conclusion, our analysis illustrates that there is great uncertainty in the efficiency of treatment for Barrett's esophagus despite small variation in the effectiveness of therapy. This is due to the large variation in the numbers needed to treat based on the differing progression rates. Limiting treatment to patients with BE and HGD reduces the variability induced by uncertainty in progression. Estimates of the effectiveness and efficiency of BE screening and treatment will be highly speculative until this uncertainty is resolved.

Acknowledgments

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SUPPLEMENTARY INFORMATION

Table S1: Effectiveness and efficiency for varying intervention ages in case of Barrett's esophagus treatment.

	age 55-70		age 65-80		age 75-90	
Incidence reduction						
low progression	71%		62%		47%	
high progression	67%		58%		43%	
regression	65%		58%		47%	
Mortality reduction						
low progression	70%		66%		46%	
high progression	66%		64%		43%	
regression	69%		63%		58%	
Screening efficiency	NNS/case	NNS/death	NNS/case	NNS/death	NNS/case	NNS/death
low progression	590	869	470	628	646	982
high progression	605	883	510	663	715	1,079
regression	633	851	503	667	653	790
Treatment efficiency	NNT/case	NNT/death	NNT/case	NNT/death	NNT/case	NNT/death
low progression	14.2	21.0	14.3	19.1	21.0	31.9
high progression	6.5	9.4	6.5	8.5	10.8	16.2
regression	16.4	22.1	18.3	24.3	28.7	34.7

Number needed to screen to prevent one case: NNS/case, Number needed to screen to prevent one death: NNS/death, Number needed to treat: NNT

CHAPTER 7

The impact of endoscopic eradication for Barrett's esophagus on esophageal adenocarcinoma incidence and mortality: a comparative modeling analysis

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Submitted

ABSTRACT

Background: Esophageal adenocarcinoma (EAC) incidence increased dramatically over the past 40 years in Western countries and neither EAC incidence nor mortality has plateaued. New techniques for endoscopic eradication of the EAC precursor Barrett's esophagus (BE) such as radiofrequency ablation (RFA) are utilized to prevent progression to EAC. The efficacy and durability of endoscopic eradication are reported, but the long-term impact of eradicative treatment and recurrent disease on EAC incidence and overall mortality reduction has not been analyzed with comprehensive and robust simulation models using this recently updated clinical data. In this study we analyzed the impact of RFA for endoscopic eradication of BE with or without dysplasia on EAC incidence and mortality using a comparative simulation modeling approach.

Methods and Findings: This study includes the predictive modeling of endoscopic eradicative treatment (EET) using three previously established population-based EAC models calibrated to NCI-SEER data. The modeling of clinical aspects of EET was based on available clinical data for RFA and endoscopic mucosal resection (EMR). We simulated a hypothetical cohort of 60 year old patients with BE for whom multiple management strategies were tested, selected on initial dysplasia status and evaluated the simulation outcomes for EAC incidence and mortality reduction; required surveillance endoscopies and treatments including RFA and EMR and numbers of treatments needed to avert one EAC death (NTN/death).

A strategy to endoscopically eradicate BE with high-grade dysplasia will decrease EAC incidence by 50% (range 44%-58%) and EAC mortality by 46% (41%-53%) with NTN/death of 30 (26-34). If all BE (dysplastic and non-dysplastic) were eradicated, EAC incidence would incrementally decrease by 83% (81%-86%) and mortality by 80% (75%-85%). However, this reduction in EAC was associated with a four-fold increase in the number of treatments with an incremental NTN/death of 209 (132-316). Halting post-treatment surveillance after a recurrence-free period of 5-10 years has a negligible influence on NTN/death when eradicating only patients with HGD. The main limitation of our study is the extrapolation of shorter-term EET clinical data to long-term results.

Conclusions: The resources needed to achieve EAC mortality reduction increase substantially as patients with lower severity of disease are selected for treatment. From a resource efficiency perspective, the large NTN/death suggests that treatment benefits justify endoscopic eradication only among BE patients with HGD.

INTRODUCTION

The incidence of esophageal adenocarcinoma (EAC) has risen dramatically over the past four decades in the U.S. and much of the Western world, and unlike many other cancers, neither EAC incidence nor mortality has plateaued.[1] Barrett's Esophagus (BE), in which the normal squamous epithelium of the distal esophagus is replaced by an intestinal-type columnar epithelium, is a precursor for EAC.[2] Most societal guidelines recommend BE patients undergo endoscopic surveillance with tissue biopsy to grade the severity of precursor lesions and detect curable neoplasia.[3, 4] BE with no dysplasia progresses to EAC at a rate of less than 0.5% per year[5], while BE with high-grade dysplasia progresses at a rate of 6%-19% per year.[6]

New techniques for endoscopic eradication of BE such as endoscopic mucosal resection (EMR) and radiofrequency ablation (RFA) have become more widely utilized with the aim of preventing progression to EAC. Current American Gastroenterological Association (AGA) guidelines unequivocally recommend endoscopic eradicative therapy only for patients with high-grade dysplasia (HGD).[7] The incremental benefit for this therapy on low-grade dysplasia (LGD) and particularly non-dysplastic (ND) BE patients remains uncertain. Recent reports suggesting RFA decreases cancer incidence among subjects with BE and LGD might prompt increased utilization of eradicative therapy in this lower-risk population.[8] There is a growing evidence base regarding the efficacy and durability of RFA treatment.[9-15] The increasing availability of long-term data affords us the opportunity to analyze the impact of eradicative treatment on EAC incidence and overall mortality reduction using comprehensive and robust simulation models.

The National Cancer Institute's (NCI) Cancer Intervention and Surveillance Modeling Network (CISNET) includes three modeling groups who independently developed population-based models for the natural history of BE and EAC that share common calibration targets (Surveillance, Epidemiology, and End Results (SEER) cancer incidence and mortality data)[16] and were previously cross-validated through comparative modeling exercises.[17] Unique to CISNET is the ability to compare outcomes between models with differing structural assumptions, such as progression and regression from dysplasia, or the incorporation of molecular mechanisms of cancer development in the model structure. Sensitivity analyses on natural history assumptions and underlying model structures are thus built into our comparative modeling approach, strengthening our confidence in model results.

The aim of our current study was to analyze the impact of endoscopic eradication therapy on EAC mortality in a BE population. Specifically, we sought to describe the impact of multiple different strategies utilizing eradication therapy on EAC incidence and mortality and to estimate the number of surveillance endoscopies and treatments required to produce potential clinical benefits.

METHODS

CISNET-EAC models

Three distinct models for EAC were used to quantitatively estimate the effectiveness and efficiency of endoscopic ablative therapies. These EAC models were developed independently but have been refined through comparative modeling using common population benchmarks such as SEER incidence and mortality within NCI's CISNET modeling consortium. The models are the Multistage Clonal Expansion for EAC (MSCE-EAC) Model from the Fred Hutchinson Cancer Research Center (Seattle, WA) (FHCRC model), the Esophageal AdenoCarcinoma Model (EACMo) from the Massachusetts General Hospital (Boston, MA) (MGH model), and the Microsimulation Screening Analysis model from Erasmus University Medical Center (Rotterdam, The Netherlands) and University of Washington (Seattle, WA) (Erasmus/UW model). The CISNET-EAC models differ by modeling approach and structure, but all use a common set of calibration data on EAC incidence by age, stage, and calendar year from SEER (1975–2009). The FHCRC model uses a biological cell-based approach combining likelihood and microsimulation methods that focus on cell kinetics (mutations, cell division, death or apoptosis) including initiation of cells followed by clonal expansion, extinction, and biopsy-based detection of premalignant and malignant clones. The MGH model is a hybrid Markov state transition/ microsimulation model, and the Erasmus/UW model is a discrete-event microsimulation model. All three models assume a step-wise progression from ND BE towards dysplasia and EAC. The MGH and Erasmus/UW models include two grades of dysplasia: LGD and HGD, whereas the FHCRC model includes a singular grade of dysplasia: HGD.

For this analysis, all groups modified their original models to include additional modules containing the clinical details of RFA ablation and subsequent surveillance and management. Detailed technical profiles of each model are available online[18] and specific details about modeling endoscopic eradication are included the supplementary information.

Population simulated

Hypothetical cohorts for males and females and for 50-, 60- and 70-year old patients diagnosed with BE were followed for EAC incidence and mortality until death or age 100. Endoscopic surveillance and eradication therapy were discontinued at age 80. The cohorts analyzed were stratified by initial dysplasia status (high-grade dysplasia-HGD; low-grade dysplasia-LGD; BE no dysplasia- ND). Cancer risk was dependent on calendar year, birth cohort, age, and sex. Each model was calibrated to reproduce the cancer risks according to available SEER EAC incidence data.

Simulated strategies

We modeled and analyzed 5 strategies described in Table 1. In the 'Natural History' (NH) strategy there was no endoscopic screening or surveillance; patients came to medical attention only when a clinical cancer was diagnosed, at which point they would receive standard treatment. When a cancer was diagnosed, survival was modeled according to SEER survival data or survival of esophagectomy, depending on the modeling group (Supplementary information). The 'Surveillance' (S) strategy is that previously recommended by numerous societal guidelines prior to the widespread availability of endoscopic eradication therapy. The majority of societal guidelines base the interval of surveillance endoscopy solely on the histological grade of biopsy samples.7 The three endoscopic eradication treatment strategies varied by the histological point at which endoscopic eradication is first performed. In the 'HGD' strategy, patients with BE underwent endoscopic surveillance until HGD was detected on endoscopic biopsy, at which point the patient underwent treatment (figure 1). In the 'LGD' strategy, patients underwent treatment when any dysplasia (HGD or LGD) was detected on biopsy. In the 'BE' strategy, all BE patients underwent treatment at the start of the simulation regardless of degree of dysplasia.

Table 1. Characteristics of simulated interventions on Barrett's esophagus patient cohort.

Strategy	NDBE patients	LGD patients	HGD patients
Natural History (NH)	No intervention	No intervention	No intervention
Surveillance (S)	Surveillance endoscopy with biopsies every 3 years	Surveillance endoscopy with biopsies every 6 months in the first year, thereafter every year	Surveillance endoscopy with biopsies every 3 months
BE surveillance and HGD treatment (HGD)	Surveillance endoscopy with biopsies every 3 years	Surveillance endoscopy with biopsies every year	Endoscopic eradication therapy followed by surveillance*
BE surveillance and Dysplasia treatment (LGD)	Surveillance endoscopy with biopsies every 3 years	Endoscopic eradication therapy followed by surveillance*	Endoscopic eradication therapy followed by surveillance*
BE treatment (BE)	Endoscopic eradication therapy followed by surveillance*	Endoscopic eradication therapy followed by surveillance*	Endoscopic eradication therapy followed by surveillance*

BE: Barrett's esophagus, ND: No dysplasia, LGD: low-grade dysplasia, HGD: high-grade dysplasia
*All post-treatment surveillance intervals can be found in the appendix

Treatment characteristics

The efficacy and complications associated with endoscopic eradication therapy (EET) for BE were based on recently published data[19, 20] and expert opinion (table 2). Initial RFA treatment took place over a two-year period, and was in 55% of the patients preceded by EMR. Possible outcomes at the end of this period were complete eradication

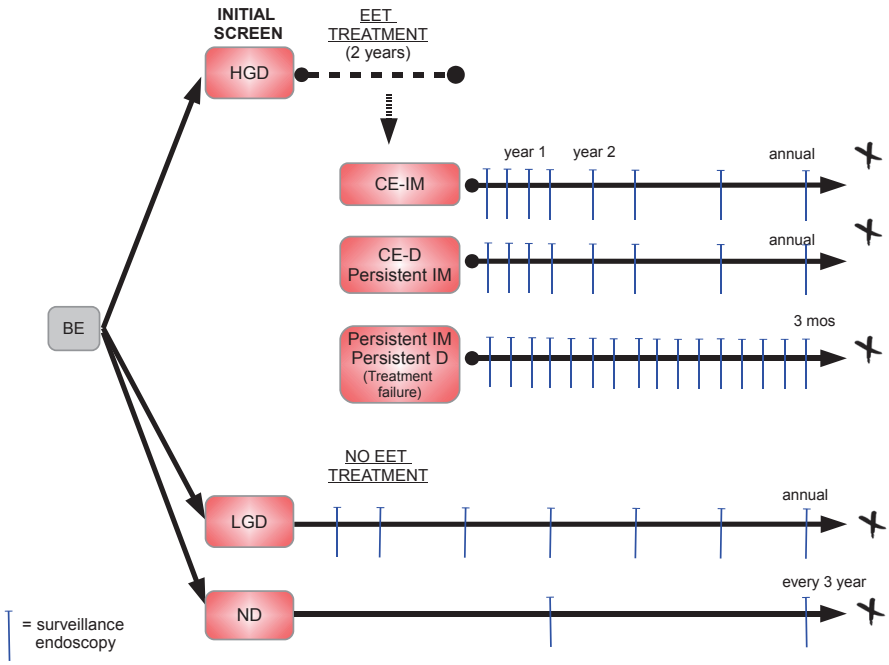

Figure 1. Barrett's esophagus patient flow chart for the HGD strategy. Additional charts for the treatment strategies can be found in the appendix.
HGDL High-grade dysplasia, LGD: Low-grade dysplasia, ND: No dysplasia, CE: Complete eradication, IM: Intestinal metaplasia (BE ND), D: High or Low-grade dysplasia, EET: Endoscopic eradication therapy. Strategy HGD: Endoscopic ablative therapy for HGD diagnosed patients strategy

of intestinal metaplasia (CE-IM), complete eradication of dysplasia (CE-D), or treatment failure (persistence of IM and/or D). After treatment failure, patients received endoscopic surveillance at pre-treatment intervals and were not given additional treatments. After treatment success (CE-IM or CE-D) patients were subject to a modified surveillance regimen that included additional endoscopies in the years immediately after the initial treatment period, with later endoscopies following at less frequent regular intervals. Full details of the post-treatment surveillance strategy for each treatment outcome and pre-treatment state are shown in the supplementary information. Following successful treatment patients could recur to BE, to their pre-treatment state or to a more advanced disease state. The probability of recurrence to BE was assumed to be constant over time and the distribution of post-recurrence states depended on the patient's pre-treatment state as estimated from observed clinical data (table 2). Patients with recurrences detected during post-treatment surveillance received "touch-up" RFA treatment (defined as circumferential or focal endoscopic RFA performed after the initial treatment period) and were monitored for further recurrences according to the post-treatment schedule described above. Patients were limited to a maximum of

Table 2. Common input parameters.

Parameter/Definition	Value	Source
Complications of therapy		
Complication rate from EGD	0.00013	[32,33]
Stricture rate with RFA at year 3	0.076	[34]
Perforations with RFA	0.0005	[4,35-39]
Proportion of patients receiving EMR treatments before RFA	0.55	[15]
Success of therapy in pre-treatment HGD patients		[19]
CE – IM and CE-D	88.89%	
Non CE-IM, CE-D	3.70%	
Non-CE-IM and Non-CE-D	*7.41%*	
Success of therapy in pre-treatment LGD patients		
CE – IM and CE-D	98.08%	
Non CE-IM, CE-D	0.00%	
Non-CE-IM and Non-CE-D	*1.92%*	
Success of therapy in pre-treatment NDBE patients		[20]
CE – IM	96.77%	
Non-CE-IM	3.23%	
Recurrence rates by baseline histologic grade and grade of recurrence		[28,29]
Annual recurrence rates after CE-IM		
Pre-treatment NDBE	7%	
Pre- treatment IND/LGD	11%	
Pre- treatment HGD	10%	
Recurrence histology pre- treatment NDBE		
NDBE	92%	
IND/LGD	6%	
HGD	2%	
IMC/EAC	0%	
Recurrence histology pre- treatment LGD		
NDBE	82%	
IND/LGD	14%	
HGD	2%	
IMC/EAC	2%	
Recurrence histology pre- treatment HGD		
NDBE	69%	
IND/LGD	15%	[32,33]
HGD	10%	
IMC/EAC	6%	

BE: Barrett's esophagus, ND: No dysplasia, LGD: low-grade dysplasia, HGD: high-grade dysplasia, IND: indefinite dysplasia, EGD: esophagogastroduodenoscopy, CE: complete eradication, IM: intestinal metaplasia, D: dysplasia, RFA: radiofrequency ablation, EAC: esophageal adenocarcinoma
*Expert consensus: panel of experts NS; SS; JI; CH; JR

three touch-ups. The model accounted for complications of endoscopy and ablation including perforation and stricture. A graphical representation of the simulated treatment strategies can be found in Figure 1 and in the supplementary information.

Outcomes

The main outcomes were presented for a 60-year-old male cohort (additional outcomes for female and various ages are shown in the supplementary files). The primary outcomes were EAC incidence and mortality reduction; total numbers of surveillance endoscopies and endoscopic eradicative treatments; numbers of treatments needed to avert one EAC death NTN death; life years gained; and complications of endoscopy and treatment. TheNTN death was calculated as the total number of ablative treatments divided by the number EAC deaths averted by a given strategy. We incorporated the total number of treatments needed to prevent one death because multiple treatments were needed per patient. Presenting the results as the number of patients needed to treat would underestimate the overall resources. Treatments included the number of EMR and RFA treatments. Incremental results compared the NTN death for a given strategy to the next-least invasive strategy by dividing the number of additional treatments by the additional EAC mortality reduction in the more invasive strategy.

Sensitivity analysis

We repeated our five base strategy simulation analyses with half and twice the base-case assumptions for the durability of successful treatment and for the efficacy of the initial treatment. In addition, we analyzed the effect of halting surveillance after a period of observed good health post-treatment (supplementary files table S1).

RESULTS

EAC incidence and mortality

Without surveillance, 85-134 EAC cases and 57-98 EAC deaths (ranges reflect differences between models) were expected to occur in 1,000 60-year old male BE patients (Table 3a). In all three models, surveillance led to down-staging and an average EAC mortality reduction of 25%; however, there was a 24% increase in cancer detection due to overdiagnosis (surveillance-detected EAC that would not have become clinically observed due to death from non-cancer causes).

The relative impact of the different treatment strategies was consistent across models. Compared to the surveillance only strategy, the HGD treatment strategy resulted in an average decrease in EAC diagnosis of 50% in the three models (range 44%-58%)

Table 3A. Main and incremental results per strategy and model.

Results per 1000 BE patients	NH	S	Incremental results compared to NH	HGD	Incremental results compared to S	LGD	Incremental results compared to HGD	BE	Incremental results compared to HGD* or LGD
FHCRC									
Number of surveillance endoscopies	0	5799	*+5799*	8984	*+3185*			5806	*-3178*
Number treatments	0	0	+0	926	+926			4902	+3977
Number of EAC cases	134	182	*+36%*	98	*-46%*			34	*-65%*
Number of EAC deaths	84	67	*-20%*	40	*-41%*			17	*-56%*
Life expectancy after diagnosis (years)	19.3	19.4	*+0.0*	19.7	*+0.3*			19.8	*+0.2*
Number of complications	0.0	0.8	*+0.8*	19.0	*+18.2*			96.1	*+77.1*
MGH									
Number of surveillance endoscopies	0	7175	*+7175*	7070	*+-106*	6541	*-529*	6382	*-159*
Number treatments	0	0	+0	863	+863	3033	+2169	5019	+1987
Number of EAC cases	85	110	*+29%*	46	*-58%*	31	*-34%*	16	*-49%*
Number of EAC deaths	57	42	*-27%*	19	*-53%*	13	*-32%*	6	*-52%*
Life expectancy after diagnosis (years)	20.5	20.6	*+0.1*	20.8	*+0.2*	20.9	*+0*	20.9	*+0.1*
Number of complications	0.0	0.9	*+0.9*	17.4	*+16.4*	59.0	*+41.7*	98.7	*+39.7*
Erasmus/UW									
Number of surveillance endoscopies	0	6506	*+6506*	6833	*+327*	6713	*-121*	5726	*-986*
Number treatments	0	0	+0	928	+928	2827	+1898	4501	+1674
Number of EAC cases	133	144	*+8%*	80	*-44%*	54	*-32%*	26	*-52%*
Number of EAC deaths	98	70	*-28%*	40	*-44%*	26	*-35%*	12	*-52%*
Life expectancy after diagnosis (years)	19.2	19.5	*+0.3*	19.8	*+0.4*	20.0	*+0.1*	20.1	*+0.2*
Number of complications	0.0	0.8	*+0.8*	18.7	*+17.8*	55.1	*+36.4*	87.3	*+32.3*

Table 3A. Main and incremental results per strategy and model. (continued)

Results per 1000 BE patients	**NH**	**S**	**Incremental results compared to NH**	**HGD**	**Incremental results compared to S**	**LGD**	**Incremental results compared to HGD**	**BE**	**Incremental results compared to HGD* or LGD**
Average all models	NH	S		HGD		LGD		BE	
Number of surveillance endoscopies	0	6494		7629		6627		5971	
Number treatments	-	-		906		2,930		4,808	
Number of EAC cases	117	145		75		42		25	
Number of EAC deaths	80	60		33		19		12	
Life expectancy after diagnosis (years)	19.6	19.8		20.1		20.4		20.3	
Number of complications	0.0	0.8		18.3		57.0		94.1	

EAC: esophageal adenocarcinoma, Strategies: NH: Natural History strategy; S: Surveillance strategy,HGD: Endoscopic ablative therapy for HGD diagnosed patients strategy; LGD: Endoscopic ablative therapy for dysplasia diagnosed patients strategy; BE: Endoscopic ablative therapy for all BE diagnosed patients strategy
* The incremental results for the FHCRC model are compared to the HGD strategy, while for the other groups these results are compared to the LGD strategy

Table 3B. Incremental numbers needed to treat to prevent one EAC death per strategy and model.

Incremental NTN/Death	**FHCRC**			**MGH**			**ERASMUS/UW**		
	Reference strategy			Reference strategy			Reference strategy		
Strategy:	S	HGD	LGD	S	HGD	LGD	S	HGD	LGD
HGD	34			39			30		
LGD				107	347		63	138	
BE	99	180		142	316 (dominated)	288	77	132 (dominated)	125

EAC: esophageal adenocarcinoma, Strategies: NH: Natural History strategy; S: Surveillance strategy, HGD: Endoscopic ablative therapy for HGD diagnosed patients strategy; LGD: Endoscopic ablative therapy for dysplasia diagnosed patients strategy; BE: Endoscopic ablative therapy for all BE diagnosed patients strategy

and EAC mortality reduction of 46% (range 41%-53%). The LGD treatment strategy (simulated by the MGH and ERASMUS/UW models only) resulted in a decrease in EAC diagnosis by 67% (range 62%-72%) and EAC mortality by 66% (range 63%-68%). Treating all BE patients at age 60 decreased the number of EAC cases by 83% (range 81%-86%) and the EAC mortality by 80% (range 75%-85%) (figure 2).

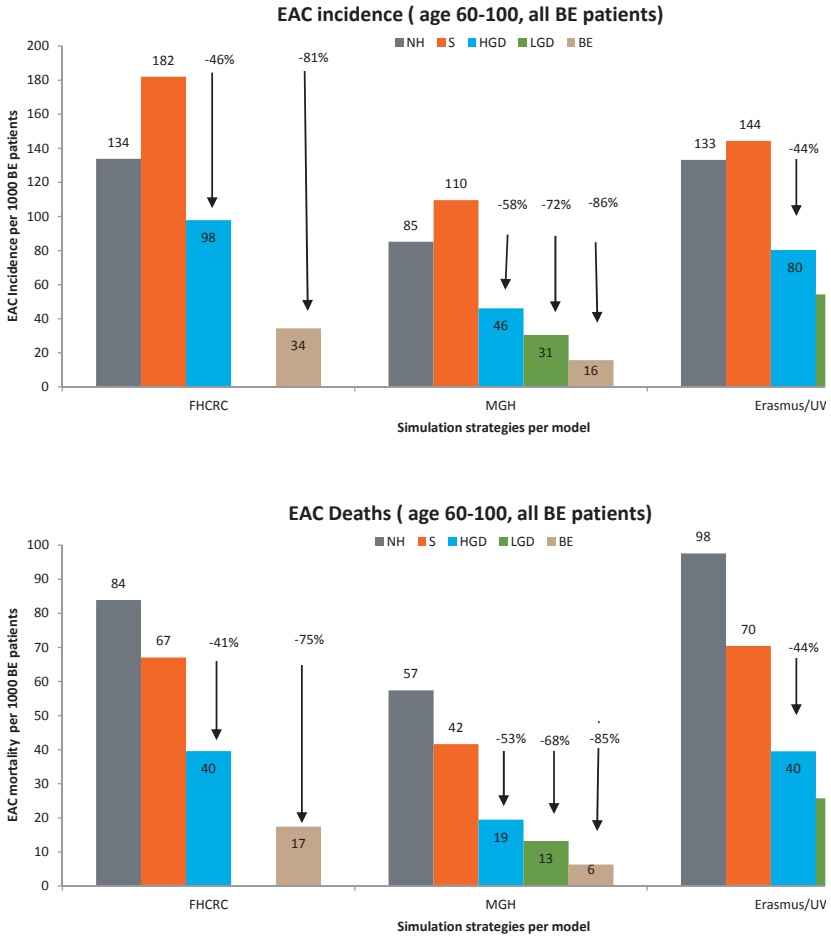

Figure 2. Figure 2 a shows the EAC incidence per 1000 BE patients per model and strategy. Figure 2b shows the EAC deaths per 1000 BE patients. The EAC incidence and mortality reductions are shown for the endoscopic eradicative treatment strategies compared to the strategy including only surveillance and no endoscopic eradicative treatment. The range in model estimates reflects differences in model structures and assumptions on BE prevalence and time to development of malignancy.

BE: Barrett's esophagus, EAC: esophageal adenocarcinoma, Strategies: NH: Natural History strategy; S: Surveillance strategy, HGD: Endoscopic ablative therapy for HGD diagnosed patients strategy; LGD: Endoscopic ablative therapy for dysplasia diagnosed patients strategy; BE: Endoscopic ablative therapy for all BE diagnosed patients strategy.

Resources required

The number of treatments differed across models, but showed similar patterns for each treatment strategy. On average 906 (range 863-928) treatments (including EMR, ablative treatments and touch-ups) needed to be performed in the HGD strategy. Also treating LGD patients increased the number of treatments by more than 200% to approximately 2,900 treatments (figure 3). Extending treatment to all BE patients further increased required treatments to 4,808 (range 4,501 -5,019). The expansion of treatment to patients with LGD and ND BE resulted in a slight decrease in surveillance endoscopies (-13% and -22% average decrease for LGD and BE strategy respectively) (table3a).

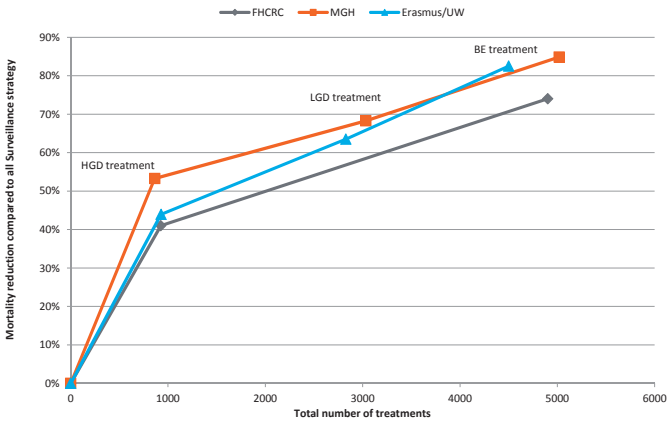

Figure 3. Mortality reduction compared to the total number of treatments per model and strategy.
BE: Barrett's esophagus, EAC: esophageal adenocarcinoma, Strategies: HGD: Endoscopic ablative therapy for HGD diagnosed patients strategy; LGD: Endoscopic ablative therapy for dysplasia diagnosed patients strategy; BE: Endoscopic ablative therapy for all BE diagnosed patients strategy.

Efficiency of treatment

The significant increase in treatments diminished the efficiency per treatment for the more inclusive strategies. The NTN/death for HGD treatment was a mean of 34 (range 30-39). In this strategy, relatively few treatments were required, resulting in a high mortality reduction (range 41%-53%). In contrast, the incremental NTN/death for LGD compared to HGD treatment was 347 and 138 in the MGH and ERASMUS/UW models, respectively. The incremental NTN/death for BE compared to HGD treatment was 180, 316, and 132 in the FHCRC, MGH, and the ERASMUS/UW models, respectively (table 3b).

Sensitivity analysis

For the HGD treatment strategy, the results of our models were robust to sensitivity analysis.. Comparing incremental NTN/death for the BE strategy with the HGD strategy, the results were most sensitive to the durability of successful treatment and for halting surveillance after a period recurrence-free post-treatment surveillance. However, halting post-treatment surveillance after a recurrence-free period of 5-10 years had negligible influence on NTN/death in the HGD strategy (supplementary files).

DISCUSSION

Our study shows that endoscopic eradication of HGD, specifically RFA, could result in substantial reductions in EAC incidence and mortality. However, extending treatment eligibility to patients with lower grades of dysplasia substantially increases the use of eradication therapy while diminishing the incremental effectiveness. This results in an unfavorable number needed to treat to prevent one EAC death if a strategy treating all patients with BE (including HGD, LGD and NDBE) is utilized.

The finding that EET may reduce EAC incidence and mortality is not surprising as the efficacy of the treatment is reported to be high and associated complication rates are relatively low. The more relevant issues to applying this therapy on a population basis are related to healthcare resource utilization, over-testing and over-treatment. Evaluation of the NTN to achieve additional mortality reduction for each strategy demonstrates eradicative therapy for patients with low-grade or no dysplasia results in diminishing returns. However, the mortality reduction that can be achieved by including non-dysplastic patients in the treatment strategy does not require substantially more treatments per cancer death averted compared to ablating patients with LGD. It appears that the diminishing impact of treatment expansion is due to the likelihood that ND and LGD patients will eventually receive treatment if they develop HGD. The additional deaths prevented by expansion of treatment result from cases that are rapidly developing EAC, or that are misclassified. In these instances, the HGD may not be diagnosed at endoscopy and it makes sense to treat these patients in an early stage.

The model results were most sensitive for the duration of successful treatment. Furthermore, all models support the decision to stop offering surveillance to HGD patients five years after successful RFA. All sensitive analyses had a relatively larger impact on the treatment strategies for low-grade and absent dysplasia.

Previously published cost-effectiveness studies agree that endoscopic eradication therapy is cost-effective when offered to HGD BE patients.[21-23]. One previous study evaluated the cost-effectiveness of RFA on varying dysplastic grades of BE, concluding that endoscopic ablative therapy was only cost-effective when offered to dysplastic

BE patients.[23] Our study similarly showed eradicative treatment is effective for all patients, and that treating patients with less severe or no dysplasia demands a major amount of resources. Prior studies used a single Markov model informed by clinical data available at the time of publication, but were not calibrated to US SEER incidence and mortality data. Our study used three simulation models that were independently calibrated to SEER data, which better equips them to assess cancer control strategies and patient guidelines.

A major strength of this study is the comparative modeling approach using results from independently developed models with common calibration targets. The comparative modeling approach helps to resolve major differences in model outputs and understanding of model uncertainties, which has been used in other CISNET comparative modeling analyses.[17, 24, 25] With this approach we were able to not only perform sensitivity analyses on the parameter estimates, but also on structural assumptions such as the possibility of regression from dysplasia, the incorporation of multiscale elements such as clonal expansion and other variations in the natural history of BE and EAC. Hence, although there are initial differences between our models when considering absolute malignant development and mortality among BE patients, this analysis showed considerable consistency between the models on the relative effectiveness and the NTN/death, demonstrating the robustness of our findings. Finally, we used the latest RFA data available in the field, collaborating with experts to verify the analysis and model inputs.

Our study is subject to several limitations. First, all of our models depict the biological progression following a specific sequence: BE without dysplasia, BE with dysplasia, preclinical cancer, and detected cancer. Although this is the commonly accepted paradigm for EAC carcinogenesis, not all EACs may follow this prescribed sequence in reality and alternative, heterogeneous pathways may exist within this paradigm.[26, 27] Second, the simulated endoscopic eradication results are dependent on assumptions about the durability and efficacy of endoscopic ablation. Recognizing these limitations, we have used the latest and best data available.[28,29] Our baseline assumption for efficacy on the initial treatment was based on data from ten of the best centers in the US in a highly regulated randomized controlled trial, which may raise the concern whether our models are too optimistic. However, our sensitivity analysis showed relatively low sensitivity for differing assumptions of efficacy of the initial treatment. Although we have used the latest available data regarding EET and more specifically RFA, limited availability of long-term outcomes necessitated translation of shorter-term data into model inputs to make longer-term projections. The accuracy of these projections may impact model outcomes. However, sensitivity analyses of these projections using a broad range of potential variables demonstrated our results

are robust. Thirdly, we have not incorporated the absolute excess risk of death in the BE cohort. More data is becoming available showing that the relative increased risk of all causes death was 21% for BE patients compared to the general population.[30] The majority of these deaths were actually not due to esophageal cancer, which reflects a higher competing risk for other cause mortality in BE patients resulting in lower EAC mortality rates. Finally, the definition of LGD is subject to large uncertainty because of interpretation bias. The models based the prevalence and progression rate of LGD to best available data, mainly from the U.S. Recently, Duits et al.[31] showed that when LGD is confirmed by experts, the risk for malignant progression is significantly higher than generally thought. When our models would assume that LGD is indeed approximating the malignant progression rate of HGD, the conclusions of our study may become more favorable towards EET treatment for LGD patients.

This study provides clinically important results about the effectiveness of RFA irrespective of costs. A strategy focusing only on cancer control with no consideration of cost would mandate treatment of all patients with BE given the 79% cancer mortality reduction expected under this approach. However, the primary utility of our study is in the projections of resource utilization necessary to achieve this goal. Our analysis highlights the large increment in endoscopic treatment numbers necessary to include LGD and NDBE patients in a population-based treatment program. These results may allow health policy decision makers to prioritize the use of this therapy in treatment algorithms based on their willingness to pay for the gains in cancer prevention outlined above, as well as the costs associated with its use in different healthcare systems. Furthermore, the large number of repeated endoscopic treatments represents a significant burden to individual patients. Lastly, it is expected that there will be a significant increase in esophageal stricture complications; however, these strictures are rarely serious and usually amenable to endoscopic treatment.

In conclusion, our comparative modeling analyses indicate that EET is an effective means of reducing EAC incidence and mortality. Benefit is predicted to be achieved across all patients with BE; however, the efficiency of eradication is substantially reduced if patients with LGD and no dysplasia are treated, and substantially more healthcare resources are required to avert a cancer death in these settings. These findings were consistent across all three esophageal CISNET models and were robust to sensitivity analyses of RFA efficacy and durability. Our results add further evidence to support RFA therapy to patients with HGD, and suggest that strategies targeting less severe disease will require close scrutiny for cost-effectiveness. Efficiency of care would be greatly enhanced through improved methods to stratify risk of cancer in lesser

forms of dysplasia and, therefore to better identify individuals who would benefit most from endoscopic therapy.

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SUPPLEMENTARY INFORMATION

Model profiles and endoscopic ablation modeling

Esophageal adenocarcinoma (EAC) is an important cancer to model because EAC incidence has increased over five-fold in the U.S. since 1975, risk factors driving these increasing trends are not well understood, current surveillance methods identify only a small fraction of individuals that later become EAC incident cases, and survival of EAC incident cases is generally very poor.

In brief, each model computes the life histories of a population of hypothetical individuals from birth (Erasmus/UW and FHCRC) or age 20 (MGH) to death and has a natural history component that tracks the progression of esophageal disease or precursor states preceding adenocarcinoma. All three models include the following health states: healthy, GERD symptoms, BE without dysplasia, BE with dysplasia, preclinical cancer, clinically diagnosed cancer, and death. The Erasmus/UW and MGH models further categorize dysplasia in BE into low-grade dysplasia (LGD) and high-grade dysplasia (HGD). In the current study, all EAC models followed a BE cohort. EAC would be diagnosed when no interventions are assumed if symptoms prompted endoscopic evaluation (clinical EAC). However, natural history can be interrupted by surveillance and/or endoscopic ablative therapy. These interventions allow for early detection on cancer, which potentially improves the survival of patients when diagnosed in an early malignant state.

For this study, the EAC CISNET models have been extended to predict the effectiveness and efficiency of surveillance and treatment for diagnosed BE patients, focusing on the impact of endoscopic ablative treatment on long term EAC mortality, with risk stratification by gender, age and dysplastic grade. Additionally the models evaluate the efficiency of the therapy in terms on surveillance endoscopies and treatments required.

The modeling approach for calculating the survival period after diagnosis of surveillance detected EAC and clinical EAC differs between the three models. The FHCRC model explicitly models the number of EAC surgeries (esophagectomies), which has more favorable outcomes for surveillance-detected patients, and generate a survival probability for these patients. The survival for clinically diagnosed patients is determined using calibration of SEER incidence and mortality. The MGH and the ERASMUS/UW models use the SEER-9 survival data that differ by cancer stage at the time of diagnosis. For surveillance detected EAC patients, the models adjust the survival according to malignant stage.

MGH Model

EACMo is a population-level Markov state transition model that depicts the natural history of EAC. A detailed description of this model can be found on the CISNET website. In order to allow for greater clinical realism particularly around endoscopic radiofrequency ablation (RFA), a microsimulation module was developed to augment the natural history model for this analysis. This supplement provides a description of this module and its implementation of the relevant screening, surveillance and treatment strategies.

A simulation was first run of the entire U.S. population within the population-level natural history model. When patients from the 1950 cohort reached the designated age (60 in the base case) for the beginning of screening the subpopulation with BE was identified and sequestered from simulation. The characteristics of this subpopulation were then used to initialize an individual-level microsimulation, which continued to simulate the progression of the disease in the presence of endoscopic surveillance and RFA treatment. Individual patients were simulated from the start of screening until death or age 100; the outcomes were then aggregated and combined with the output of the population-level simulation to produce the final results.

Prior to RFA treatment patients within the microsimulation could progress each cycle according to the transition probabilities of the natural history model. Endoscopy was performed at scheduled intervals based on detected health state; patients could receive RFA treatment based on the treatment strategy being analyzed, which was contingent on histologic status detected by endoscopic biopsy. The outcome (CE-IM, CE-D, or treatment failure) at the end of the initial treatment period was determined by a single random draw. Endoscopic surveillance schedules post-ablation depended on both the outcome of treatment and the pre-ablative health state of the patient.

In the event of treatment failure, patients remained in their pre-ablative health state, underwent endoscopic surveillance according to the same schedule prior to ablation, and received no further attempts at RFA treatment, essentially returning to their prior states. These patients could progress to more advanced disease states based on the transition probabilities from the natural history model.

Patients who received successful or partially successful treatment did not progress according to the natural history transition probabilities. Instead, there was a constant probability each cycle that a patient would undergo a recurrence event. When a recurrence event occurred, a second random draw based on a distribution would be performed to determine the post-recurrence state. Once in a post-recurrence state the patient could again progress in the same way as in the natural history model. If a patient was found by endoscopy and biopsy to have progressed beyond their diag-

nosed post-ablation state – that is, if endoscopic surveillance detected that a recurrence event had occurred – but had not yet progressed to cancer, the patient could receive touch-up RFA treatment, up to a maximum of 3 touchups after the end of the initial 2 year treatment period. Touch-up RFA was implemented in the same way as initial treatment in terms of the efficacy of ablation, the schedule of surveillance after treatment, and the modeling of recurrence.

ERASMUS/UW-EAC Model

Additional information can be found in the model appendix.

FHCRC: MSCE-EAC Multiscale Screening Model

The multistage clonal expansion (MSCE) model for EAC includes an initial stochastic transition rate to convert a section of the normal squamous epithelium in the esophagus to generate a BE segment, with separate transition rates for individuals with or without gastroesophageal reflux disease (GERD). Cells within the BE segment are assumed to be at risk for progression through a multistage clonal expansion process to develop EAC. The MSCE-EAC model includes two rate-limiting mutations to transform BE cells to premalignant cells that undergo a slow clonal expansion process, followed by a third rate-limiting mutation to generate malignant cells that also undergo clonal expansion, but at a faster rate. In contrast to earlier multistage clonal expansion (MSCE) formulations of the EAC incidence model[40, 41] the MSCE-EAC multiscale screening model includes the explicit computation of the number and sizes of premalignant (HGD) clones and their spatial appearance within an idealized crypt-structured BE segment as a function of how long a patient had BE.42 This description also includes the stochastic development of malignant clones representing preclinical cancer, which may be detected on a biopsy as a screen-detected cancer case. Symptomatic, incident cancers occur by a stochastic detection process. Biological parameters were estimated via likelihood maximization fitting EAC incidence data.[17]

The MSCE-EAC model simulates the joint distribution of premalignant and malignant clones sizes before cancer is detected in a symptomatic patient. Thus, we are able to predict the potential presence (or absence) of malignant cells in biopsies that harbor a sufficiently large number of dysplastic crypts to be subjected to closer examination for the presence of malignant cancer. The results presented in the main text are based on use of the standard (Seattle) biopsy protocol which requires quadrant biopsies every 1-2 cm along the BE segment. Factors contributing to the sensitivity for detection of HGD or cancerous lesions include the minimum aberrant tissue fraction in the biopsy necessary for diagnosis, the spacing between biopsy samples, and the size of biopsy forceps. The general efficacy of biopsy sampling remains highly uncertain due to vari-

ability in biopsy sampling between practitioners and due to considerable uncertainties in the histological assessment of the biopsied tissues. For the Results in the main text, we employed a biopsy detection sensitivity of 40%.[42] For the 60 year old screened males with BE, this assumption yields a prevalence of 2.8% for initial screen-detected cancers and 4.7% for initial HGD cases.

FHCRC: Surveillance and RFA Treatment

During surveillance, the MSCE-EAC model explicitly simulates the growth (in numbers) of any and all BE crypts, HGD crypts, and malignant crypts as a BE patient ages. For each patient, given a randomly generated size of the BE segment and simulated number and sizes of the neoplastic lesions at any given time, we also simulate the biopsy procedure at every surveillance screen to determine a possibly different diagnosis based on the highest grade of tissue found on biopsy. After a simulated screen of a BE patient for detection of HGD and preclinical EAC at a specified screening age, the MSCE-EAC model also allows the explicit modeling of an ablative treatment, such as radio frequency ablation (RFA). Specifically, assuming that ablation decimates the number of BE, dysplastic, and malignant crypts by specific fractions, the simulation modifies the size of a patient's BE segment along with any concurrent HGD and/or malignant lesions during ablative treatment. For the results shown in the main text, we assumed an efficacy of 70% removal of all cell types during an RFA treatment or touch-up based on calibration to published recurrence rates during surveillance.[13, 19]

FHCRC: Survival

Once a malignant lesion is screen-detected, a BE patient may undergo surgery, whether endoscopic mucosal resection or esophagectomy. We utilized data from the Surveillance and End Results (SEER) registry to model cause-specific EAC survival and cure rate trends by stage and age category (ages 50-59, 60-60, 70-84), using the CANSURV program to fit a lognormal survival model to the data while estimating temporal trends on the shape and cure parameters.[43] After controlling for age and stage, survival for men and women did not differ significantly, but the estimated cure rates for local stage diagnosis were significantly higher than for regional or distant diagnoses. The all-stage EAC survival curves for each age category were adjusted to account for ablation or surgical resection by fitting the cure model parameters based on a study of 430 patients undergoing ablation and 1586 patients undergoing esophagectomy that were identified in SEER between 1998-2009.[44] Separate models were developed for EAC cause specific survival by age group, with or without ablation or surgical resection, while accounting for censoring and other cause death by matching cure rates at 2003.5 (midpoint of the 1998-2009 SEER follow-up data from Wani et al.) at age 63.4 (mean patient age for surgical resection), or age 70.5 for ablation.

Table S1. Input and sensitivity parameters

	Base values			Lower value			Upper value		
Durability of successful treatment									
	Pre-treatment histology			**Pre-treatment histology**			**Pre-treatment histology**		
	NDBE	IND/LGD	HGD	NDBE	IND/LGD	HGD	NDBE	IND/LGD	HGD
Annual recurrence probability	7.0%	10.7%	10.0%	3.5%	5.4%	5.0%	14.0%	21.5%	20.0%
Efficacy of the initial treatment									
Success of therapy in pre-treatment HGD patients									
CE – IM and CE-D		0.89			0.78			0.94	
Non CE-IM, CE-D		0.04			0.07			0.02	
Non-CE-IM and Non-CE-D		0.07			0.15			0.04	
Success of therapy in pre- treatment LGD patients									
CE – IM and CE-D		0.98			0.96			0.99	
Non-CE-IM and Non-CE-D		0.02			0.04			0.01	
Success of therapy in pre- treatment n NDD patients									
CE – IM		0.97			0.94			0.98	
Non CE-IM		0.03			0.06			0.02	
Halting surveillance after a period of observed good health post-treatment									
	Until death or age 80 (follow patients up to age 100)			STOP surveillance when 5 year remained CE-IM, after achievement CE-IM of initial endoscopic therapy			STOP surveillance when 10 year remained CE-IM, after achievement CE-IM of initial endoscopic therapy		

EAC: esophageal adenocarcinoma, CE: Complete eradication, IM: intestinal metaplasia, D: dysplasia, ND: no dysplasia, BE: Barrett's esophagus, IND: indefinite dysplasia, LGD: low-grade dysplasia, HGD: high-grade dysplasia

Table S2. Post-treatment surveillance strategies.

Patient characteristic	Surveillance interval	Source
Surveillance endoscopy interval after CE-IM of HGD patient (state = NORMAL)	Q3 months for one year then q6 months for one year then annual	[45]
Surveillance endoscopy interval after CE-IM of LGD patient (state = NORMAL)	Q6 months for 2 years then annually for 2 years, then every three years	*Expert consensus**
Surveillance endoscopy interval after CE-IM of NDBE patient (state = NORMAL)	every three years	*Expert consensus**
Surveillance endoscopy interval after CE-D, none CE-IM of HGD patient (state=IM/BE ND)	Q3 months for one year then q6 months for one year then annual	*Expert consensus**
Surveillance endoscopy interval after CE-D, none CE-IM of LGD patient (state=IM/BE ND)	Q3 months for one year then q6 months for one year then annual	*Expert consensus**
Surveillance endoscopy interval after non CE-D, none CE-IM of HGD patient (state = HGD)	Every three months	*Expert consensus**
Surveillance endoscopy interval after non CE-D, none CE-IM of LGD patient (state = LGD)	q6 months for one year then annual	*Expert consensus**
Surveillance endoscopy interval after none CE-IM of ND patient (state = ND)	Every three years	*Expert consensus**

BE: Barrett's esophagus, ND: No dysplasia, LGD: low-grade dysplasia, HGD: high-grade dysplasia, IND: indefinite dysplasia, EGD: esophagogastroduodenoscopy, CE: complete eradication, IM: intestinal metaplasia, D: dysplasia, RFA: radiofrequency ablation, EAC: esophageal adenocarcinoma
*Expert consensus: panel of experts NS; SS; JI; CH; JR

Table S3. All Female results: Incremental numbers needed to treat to prevent one EAC death per strategy and model.

Incremental NTN/Death	FHCRC			MGH			ERASMUS/UW		
	Reference strategy			Reference strategy			Reference strategy		
Strategy:	S	HGD	LGD	S	HGD	LGD	S	HGD	LGD
HGD	31			57			119		
LGD				169	1,027		245	399	
BE	101	177		248	1,060	1,100	229	293 (dominated)	196

EAC: esophageal adenocarcinoma, Strategies: NH: Natural History strategy; S: Surveillance strategy, HGD: Endoscopic ablative therapy for HGD diagnosed patients strategy; LGD: Endoscopic ablative therapy for dysplasia diagnosed patients strategy; BE: Endoscopic ablative therapy for all BE diagnosed patients strategy

Table S4. All Male surveillance start age 50, 60 and 70: Incremental numbers needed to treat to prevent one EAC death per strategy and model.

Incremental NTN/Death									
Age 50-100		**FHCRC**			**MGH**			**ERASMUS/UW**	
		Reference strategy			Reference strategy			Reference strategy	
Strategy:	S	HGD	LGD	S	HGD	LGD	S	HGD	LGD
HGD	31			36			29		
LGD				93	320		55	123	
BE	71	110		118	299	274	64	118	111
Age 60-100		**FHCRC**			**MGH**			**ERASMUS/UW**	
		Reference strategy			Reference strategy			Reference strategy	
Strategy:	S	HGD	LGD	S	HGD	LGD	S	HGD	LGD
HGD	34			39			30		
LGD				107	347		63	138	
BE	99	180		142	316 (dominated)	288	77	132 (dominated)	125
Age 70-100		**FHCRC**			**MGH**			**ERASMUS/UW**	
		Reference strategy			Reference strategy			Reference strategy	
Strategy:	S	HGD	LGD	S	HGD	LGD	S	HGD	LGD
HGD	37			43			32		
LGD				130	391		75	146	
BE	170	412		200	409	424	111	170	191

EAC: esophageal adenocarcinoma, Strategies: NH: Natural History strategy; S: Surveillance strategy, HGD: Endoscopic ablative therapy for HGD diagnosed patients strategy; LGD: Endoscopic ablative therapy for dysplasia diagnosed patients strategy; BE: Endoscopic ablative therapy for all BE diagnosed patients strategy

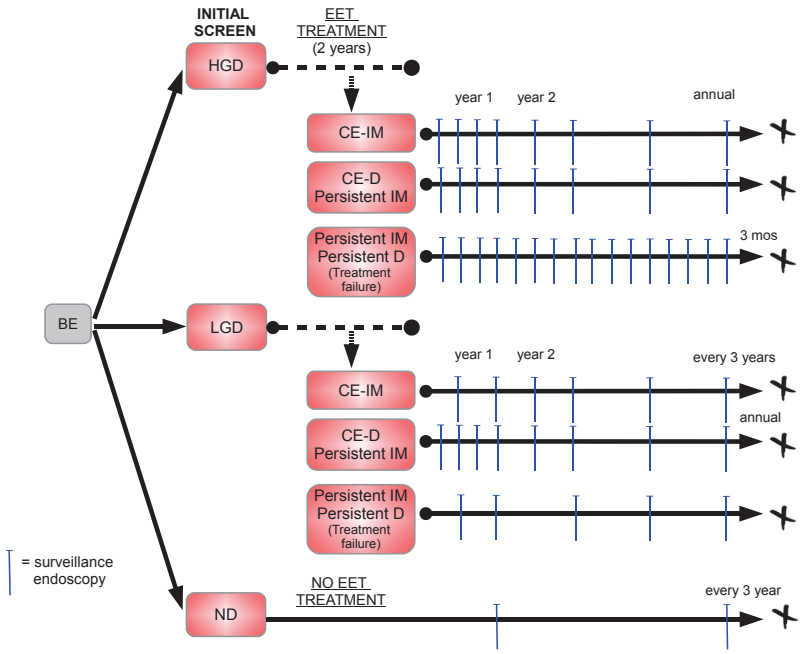

Figure S1a. BE patient flow diagram for strategy LGD
HGD: High-grade dysplasia, LGD: Low-grade dysplasia, ND: No dysplasia, CE: Complete eradication, IM: Intestinal metaplasia (BE ND), D: High or low-grade dysplasia, EET: Endoscopic eradication therapy. Strategy LGD: Endoscopic ablative therapy for dysplasia diagnosed patients strategy

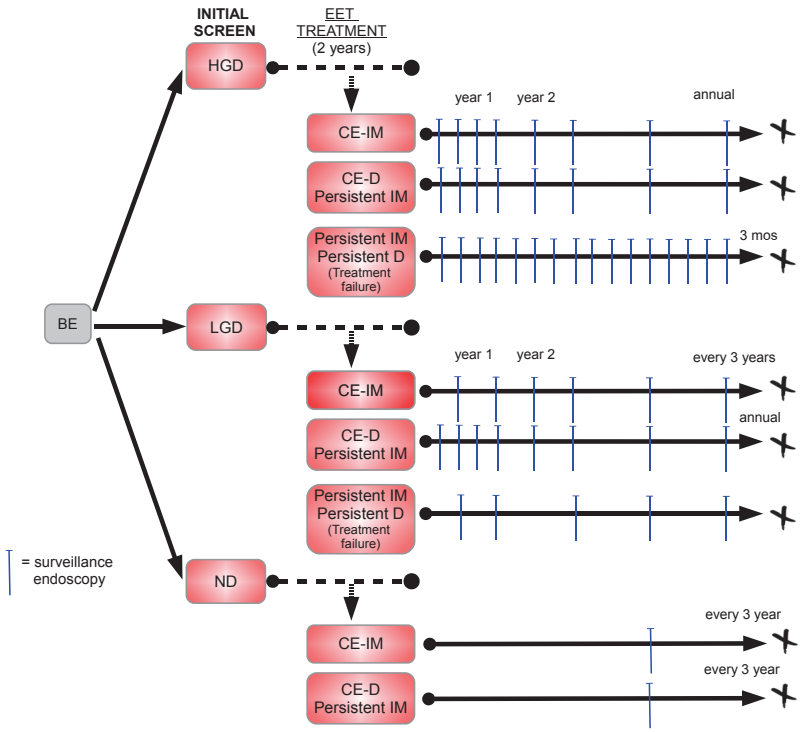

Figure S1b. BE patient flow diagram for strategy BE

HGD: High-grade dysplasia, LGD: Low-grade dysplasia, ND: No dysplasia, CE: Complete eradication, IM: Intestinal metaplasia (BE ND), D: High or low-grade dysplasia, EET: Endoscopic eradication therapy. Strategy BE: Endoscopic ablative therapy for all BE diagnosed patients strategy

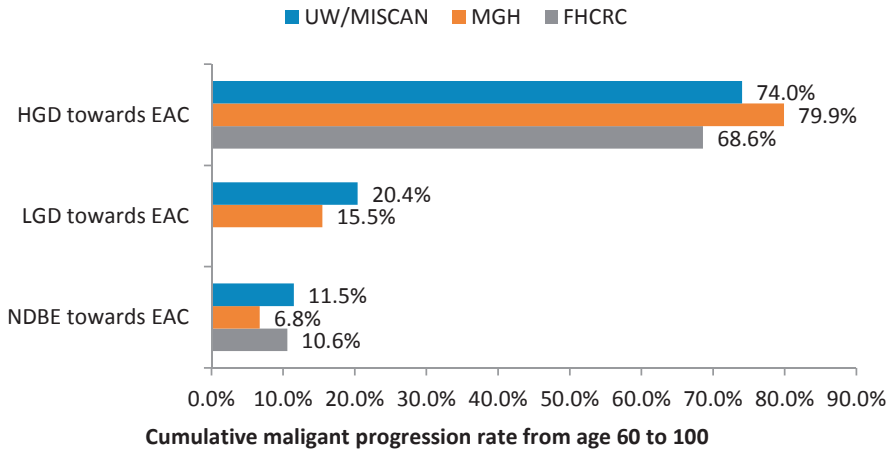

Figure S2. Progression rates in each model. The figure shows the development from BE to EAC in terms of progression rates in case of no interventions, which is, in the natural history of the disease. The cumulative progression rates towards EAC are shown following patients from age 60 having a certain initial phase (NDBE, LGD or HGD).

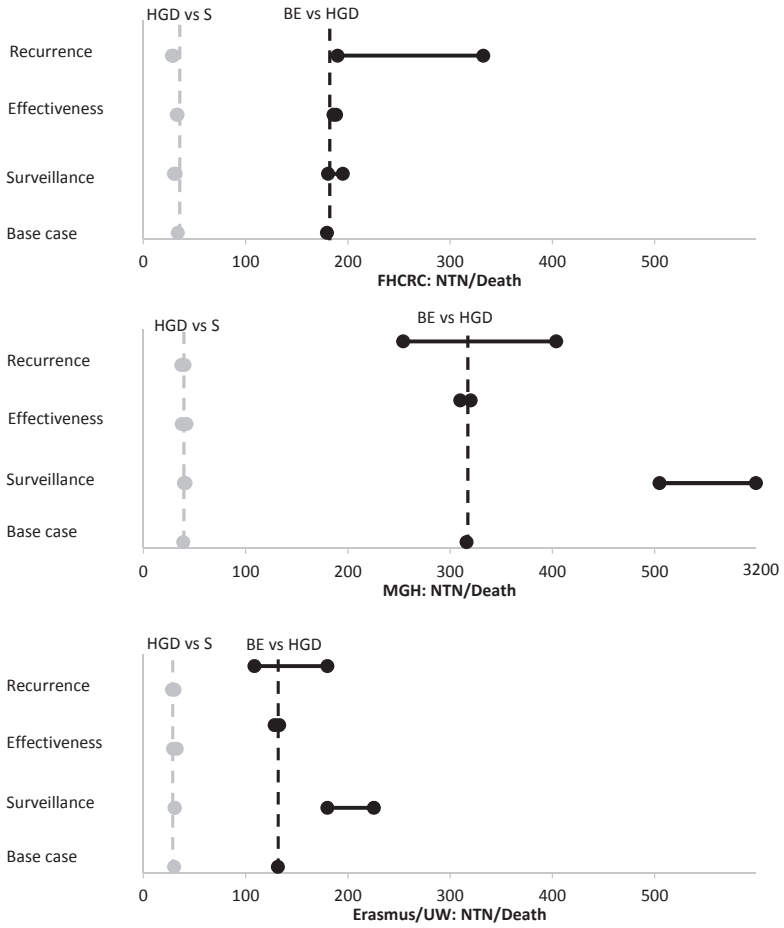

Figure S3. The incremental number of treatments needed to prevent 1 EAC death (NTN/Death) per model for the various sensitivity analyses. The incremental outcomes of two strategies are shown: the additional treatments needed to prevent 1 EAC death in case of HGD treatment compared to the strategy where only surveillance is applied (grey dots). Next to this, the incremental NTN/death when applying treatment to all BE patients compared to treatment for only HGD patients is presented (black dots). The lines represent the base case value.

BE: Barrett's esophagus; S: Surveillance strategy, HGD: Endoscopic ablative therapy for HGD diagnosed patients strategy; LGD: Endoscopic ablative therapy for dysplasia diagnosed patients strategy; BE: Endoscopic ablative therapy for all BE diagnosed patients strategy.

CHAPTER 8

General discussion

8

This chapter begins by addressing each of the research questions stated in the introduction and proceeds to discuss the methodological considerations and the interpretations of the results The chapter continues with implications for future research directions, followed by the main conclusions and recommendations.

8.1 MAIN FINDINGS

Part I: Natural history and secular trends of esophageal adenocarcinoma

Research question 1: Can changes in lifestyle trends explain esophageal adenocarcinoma (EAC) incidence trends?

> International trends in obesity, smoking and alcohol consumption, are discordant with the trends in EAC incidence. Other important for the increase in EAC incidence in the three observed countries must be present.

The trends in obesity and other lifestyle-associated factors have been hypothesized to be important drivers of the increase in EAC incidence. We tested this hypothesis by comparing changes in these factors with changes in EAC incidence over time between three western countries. In 1980, the EAC incidence was similar among the Netherlands, Spain and the United States (0.46 – 0.63 per 100,000 population). EAC incidence increased in all, with the largest increase observed in the Netherlands, followed by the United States and Spain (estimated annual percentage of change = 9.7 % , 7.4 % and 4.3 % respectively). With regard to obesity, increasing trends were seen in all three countries. However, the absolute rate of the trends do not support obesity to be the driver of the increase in EAC since the country-sequencing of EAC incidence and obesity prevalence differ (the Unites States has the highest obesity rates while the Netherlands ranked first on EAC incidence). The change in rates over time seems to support the hypothesis that obesity is a driver for EAC development since the EAC incidence and obesity prevalence is increasing in all countries. However, looking more specifically, Spain has a smaller increase than the Unites States in EAC incidence (1980-2004), but a greater increase in obesity prevalence (1987-2009). Furthermore, the Netherlands has a greater increase in EAC incidence than the Unites States (1975-2009), but a similar increase in obesity prevalence (1981-2009). Smoking showed a reverse trend compared with EAC among all three countries in the last 20 years. The absence of an observed decrease in EAC incidence suggests smoking is not an important risk factor. The absolute smoking rates merely support that smoking is a driver of

EAC when the lag time is larger than 50 years. For alcohol, the highest consumption rates are seen in Spain, while their EAC incidence rates are lowest among the three countries.. For absolute rates, the country-sequencing of alcohol consumption is not in accordance with the country-sequencing of EAC incidence.

Research question 2: What is the estimated future EAC incidence and mortality?

> The models show that EAC incidence and mortality rates likely continue to increase until 2030, although the rate of the increase seems to with advancing birth cohorts.

The incidence of EAC has increased five-fold in the United States since 1975. The aim of our study was to estimate future United States EAC incidence and mortality rates and to shed light on the potential drivers in the disease process that are conduits for the dramatic increase in EAC incidence. Our study used three population-based models of EAC that were developed through the National Cancer Institute's (NCI) Cancer Intervention and Surveillance Modeling Network (CISNET). These independent mathematical models were calibrated to U.S. EAC incidence and incidence-based mortality rates from 1975 to 2010. The models differed in model structure and design, from biologically based modeling at the cellular level to empirically based simulations of natural histories. The models were consistent with one another in their model fits to the Surveillance, Epidemiology, and End Results (SEER) data and projections to 2030 for total EAC incidence and mortality rates. The predicted ranges of incidence and mortality rates for all males in 2030 predicted by the three models are 8.4 to 10.1 and 5.4 to 7.4 cases per 100,000 person years, respectively. The localized EAC incidence rates exhibited the slowest increases, followed by regional and advanced EAC. The models suggested a strong birth cohort effect on the progression rates with increasing progression rates in younger birth cohorts up to the cohorts born in 1940, followed by a leveling off in the progression rates of the cohorts born after 1940. For the period from 2011 to 2030, we estimate that there will be between 142,000 and 186,000 cumulative EAC deaths in the United States, which is nearly twice the number of EAC deaths that occurred between 1991 and 2010. The models identify modification of cancer progression rates (modeled as a birth cohort effect) as an important driver of the observed temporal trends for EAC incidence and mortality. The specific causes of the historical increase in EAC incidence and mortality remain unclear. However, our joint modeling of potential drivers of the increasing incidence and mortality trends implies an enhanced Barrett's esophagus (BE)to EAC progression as significant factor, in addition to trends that may be driving up the prevalence of BE in the United States

population as predicted by the Massachusetts General Hospital (MGH) and Erasmus/ UW-EAC models.

Research question 3: Can we reconcile published data and accurately estimate the EAC incidence in BE using simulation modeling?

> In the first 5 years following diagnosis, the rate of progression from BE to EAC is likely to more closely approximate the lower estimates reported by population-based studies than the higher estimates reported by prospective studies, in which EAC is detected by surveillance. Clinicians should use this information to explain to patients their short-term and long-term risk of developing EAC if no action is taken, and discuss the risks and benefits of surveillance.

We hypothesize that the difference in estimates of progression rates between prospective and population-based studies could be explained by the practice of endoscopic surveillance performed in prospective studies, resulting in earlier detection of preclinical cancers. The aim of this study was to provide an accurate estimate for the clinical cancer incidence in BE by reconciling published data. The underlying value for progression to EAC of our model including realistic diagnostic inaccuracy, the clinical progression rate, was estimated at 0.07% annually for 65- year old BE (without dysplasia (ND) and with low-grade dysplasia (LGD)) to EAC with a 5 year follow up. This clinical progression rate increased to 0.37% annually when evaluated after a 10 year follow up. The same disease model predicted an annual progression rate of 0.19% and 0.36% for the population-based and prospective design respectively with an average follow up length of 5 years. After 20 years these progression rates each increased to 0.63%–0.65% annually, corresponding with a 9.1%–9.5% cumulative cancer incidence. The difference between progression rates of the two designs decreased from 91% and 21% after 5 and 10 years, to 9% and eventually 5% after 15 and 20 years of follow up. Our results suggest that the gap between the published progression rates from population based studies and prospective studies can be largely explained by differences in study design, more specifically by the differences in the surveillance intensity. Performing endoscopic surveillance in individuals with BE leads to earlier detection of cancers and thus to a higher cumulative EAC incidence after a given length of follow up. In the situation without surveillance, a proportion of these cancers (those not overdiagnosed) would have developed symptoms that led to clinical cancer diagnosis later on. However, given closure of the study, e.g. after five years, some of these cancers would have been observed only in the situation with surveillance. In our simulations, significant differences between the study designs impact the progression rates when

the follow up length is less than 10 years, which is mainly explained by our assumption of diminishing surveillance over time.

Part II: Possibilities for early detection and intervention

Research question 4: What is the current knowledge on possibilities for earlier detection of EAC and the benefits of early detection on the burden of EAC in the population?

> The early detection of EAC by means of screening on population level has not yet been successful; signs, symptoms and risk factors in the general population are not exclusively predictive for EAC. New modalities are emerging including genetic- and epigenetic markers that might provide higher predictive values for BE and progressive BE in the general population. There is no definite evidence, only strong suggestions that early detection of EAC by means of surveillancein a high risk population, e.g. BE patients is effective. To improve cost effectiveness, surveillance should be optimized by improving risk stratification in this high risk population.

The aim of this study was to summarize the current evidence on whether early detection of EAC and its precursors is possible. 1376 articles were retrieved from searching various databases. After exclusion of duplicates and screening of title and abstract, 197 titles were included for full text screening. Eventually 49 articles were included.

We stratified the predictive value of signs, symptoms and risk factors by the outcomes of EAC, BE and malignant potential (where BE and/or EAC were one combined outcome measure). We found a number of risk factors which were significantly associated with EAC development in the general population. The highest associations were found for daily symptoms of gastro-esophageal reflux disease (GERD) (Odds Ratio (OR:7.4), more than 20 years of GERD symptoms (OR: 5.4), more than 30 pack years of smoking (OR: 6.1), and family history (OR: 12.8). However, the predictive value of these risk factors is low. A prediction model for early detection of EAC in the general population by Hippisley-Cox and Coupland[1] including many of the risk factors of this review had a positive predictive value for the actual diagnosis of EAC of only 1.2%. For BE, the strongest associations were found with cytokines interleukins(IL) showing ORs between 1.8 and 9.5 for varying types. An increased waist to hip ratio and male gender showed a moderately increased risk of BE (OR: 1.9-4.1).

Early detection of EAC by surveillance of BE seems to lead to health benefits in terms of higher survival and higher quality of life as shown in the included cohort studies. BE

diagnosis and adherence to a BE surveillance program before the diagnosis of high-grade dysplasia (HGD) or EAC was found to significantly improve the probability of survival. However, none of these studies were designed as a randomized controlled trial, resulting in no definite evidence for health benefits.

The cost effectiveness of screening and surveillance has only been assessed in modeling studies. Surveillance in dysplastic patients was more cost effective than surveillance in ND BE patients. Improved adherence to guidelines in terms of adhering to the recommended surveillance intervals in combination with a higher proportion of HGD patients treated with endotherapy (ET) can reduce costs compared to a lower proportion of HGD patients treated with ET. Two additional studies showed that the ultra-thin endoscopy and cytosponge are more cost effective than standard endoscopy for screening and surveillance as both lead to more Quality Adjusted Life Years (QALY) gained and lower costs with the use of one of these diagnostic modalities. In summary, surveillance for BE seems to be effective in terms of increasing the health benefits of patients identified due to early detection, but cost-effectiveness of surveillance is controversial and highly dependent on risk of EAC which has a high level of uncertainty.

In terms of demographic and clinical factors we found that nodularity (OR: 2.0-7.7) and dysplasia (OR: 3.7-9.7) are predictive for progression to HGD and EAC. Length of the BE segment, esophagitis and length of hiatal hernia have a weaker association with malignant development. For genetic and epi-genetic markers, the strongest association with malignant development within BE patients are found with aneuploidy (OR: 5.9) and tetraploidy with increased 4N (OR: 1.4-12.0). Methylation of a combination of genes has a high specificity for the prediction of progression towards EAC.

Research question 5: What is the influence of uncertainty in the risk of EAC development in patients with BE on the expected effectiveness and efficiency of hypothetical screening and treatment interventions?

> There is great uncertainty in the efficiency of treatment for BE despite small variation in the effectiveness of therapy. This uncertainty is due to the large variation in the numbers needed to treat based on the differing progression rates. Limiting treatment to BE patients with HGD reduces the variability induced by uncertainty in progression.

Estimates for the annual progression rate from BE to EAC vary widely. In this explorative study we quantified how this uncertainty affects the estimates of effectiveness and efficiency of screening and treatment for EAC using microsimulation modeling. For this analysis we calibrated 3 different models varying in progression rates (0.12% vs

0.42% annual progression rate) and model structure (regression between dysplastic states is allowed versus not allowed). Furthermore we assumed perfect diagnostic accuracy and perfect successful treatment. The BE prevalence was highest in the model with regression [3.3% for age 60-65] followed by low progression [2.9% for age 60-65] and high progression [1.3% for age 60-65]. The differences in EAC incidence and mortality reduction from screening and treating all BE were negligible between the three models but were more pronounced for strategies only including treatment for dysplasia or HGD. The maximum clinical incidence reduction (the maximum possible incidence reduction when assuming perfect surveillance and perfect treatment) was greatest in the strategy incorporating treatment of all patients with BE [58%-62%], followed by dysplasia treatment [26%-42%] and HGD treatment [4%-13%]. Differences in the EAC development in the untreated BE population directly reflect differences in the progression rates between the models. In case of treatment limited to dysplasia, 7.5% of the ND BE developed into EAC in the high-progression model, whereas in the low progression and the regression models less than 3.5% developed into EAC. The number of treatments differ in each model because this is influenced by the variation in BE prevalence. Given this variation in number of treatments and the minor differences in effectiveness of screening and treatment, large differences are seen in the number of patients needed to treat to prevent one EAC case (NNT/case) as well as in the number of patients needed to treat to prevent one EAC death (NNT/death). The all-BE treatment strategy is most efficient in the high-progression model (NNT/death is 8.5), followed by the low-progression model (NNT/death is 19.1) and the regression model (NNT/death is 24.3) Almost no differences in the efficiency of HGD treatment are found between the three models.

Research question 6: What is the long-term impact of endoscopic eradicative treatment (EET) on population EAC incidence and mortality?

> EET is reducing EAC incidence and mortality effectively. Benefit is predicted to be achieved across all patients with BE; however, the efficiency of eradication is substantially reduced if patients with LGD and no dysplasia are treated, and substantially more healthcare resources are required to avert a cancer death in these settings.

New techniques for endoscopic eradication of the EAC precursor BE such as radiofrequency ablation (RFA) are utilized to prevent progression to EAC. The durability of RFA has been a concern. The aim of our current study was to analyze the impact of endoscopic eradication therapy on EAC mortality in a BE population through simulation modeling incorporating the latest clinical data. Specifically, we sought to describe

the impact of different strategies utilizing eradication therapy on EAC incidence and mortality and to estimate the number of surveillance endoscopies and RFA treatments required to produce potential clinical benefits. Our study used three validated population-based models of EAC that were developed through CISNET. Without surveillance, 85-134 EAC cases and 57-98 EAC deaths (ranges reflect differences between models) were expected to occur in 1,000 BE patients followed from age 60 until death or age 100. In all three models, surveillance led to down-staging of cancer phase and overdiagnosis of EAC cases. However, there was an average EAC mortality reduction of 25% (42-70 EAC deaths per 1000 BE patients). The relative impact of the different treatment strategies was consistent across models. Compared to the surveillance only strategy, the HGD treatment strategy resulted in an average decrease in EAC diagnosis of 50% in the three models and EAC mortality reduction of 46%. Treating all BE patients at age 60 decreased the number of EAC cases by 83% and the EAC mortality by 80%. The number of treatments differed across models, but showed similar patterns for each treatment strategy. On average 906 ablative treatments (including RFA, touch-ups and Endoscopic Mucosal Resections (EMR)) for 1,000 BE patients needed to be performed when treating only patients with HGD. Also treating BE patients with LGD increased the number of treatments by more than 200% to approximately 2,900 treatments per 1,000 BE patients. Extending treatment to all BE patients further increased required treatments to 4,808 per 1,000 BE patients. The significant increase in treatments diminished the efficiency per treatment for the more invasive strategies. The mean number of treatments needed to prevent one EAC death (NTN/death) for the HGD treatment strategy was 34. In this strategy, relatively few treatments were required, resulting in a high mortality reduction. The incremental NTN/death for treatment of all BE patients compared to the HGD treatment strategy was 160, 283, and 116 in the FHCRC, MGH, and the Erasmus/UW models, respectively.

8.2 METHODOLOGICAL CONSIDERATIONS

The chapters in this thesis are predominantly based on the outcomes of microsimulation models. In addition we performed a trend analysis for which we will consider the methodological issues in this chapter.

Trend analysis

Analyzing time trends between countries has limitations. First, definitions of predictors and outcomes can differ between various data sources. For example, the morphology codes for EAC incidence which are used in the data registries differed slightly between Spain, U.S. and the Netherlands. Second, there were variations in ages, collection

methods and inclusion criteria between the three countries for the risk factors. These differences are not expected to highly impact the total EAC incidence and the prevalence of risk factors and are therefore considered to be negligible. Third, the available time horizons of the data differed between countries for lifestyle-associated factors and EAC incidence trends. However, the overlapping periods were sufficient for testing our hypothesis whether these factors could be main drivers for the increasing EAC incidence. Furthermore, the level of detail for the risk factors we studied was limited. We did not identify the quantity of smoking by country and sex, and the composition of cigarettes for each country. The distribution of alcohol consumption in the population and the type of alcohol consumption would reflect more specific trends. As for the study design, two main difficulties should be noted. As results of ecological analyses are evaluated on population level, they may not reflect associations at the individual level. Next to this we cannot analyze interactions between the joint lifestyle factors and development of EAC in this study design. Despite the limitations of this study and study design, this analysis enabled us to identify differences in EAC incidence and risk factors between countries and provided new insights in the role of lifestyle-associated risk factors on the increasing EAC incidence trend.

Microsimulation modeling

Microsimulation models are extremely useful for the exploration of effects for screening, surveillance and treatment on EAC incidence and mortality reduction. However, one should take into account that the quality of the modeling results is directly influenced by the quality of the model inputs. Making assumptions about the natural history of disease is inherent to disease modeling. The extent to which these assumptions can be informed through data is limited due to the non observability of the disease progression process. In addition there are no randomized controlled trials, informing us on the effects of surveillance and treatment interventions, available. When data is scarce, hypotheses have to be made with the help of experts to consider a model structures and model inputs that approximate reality. This does not imply that the natural history of EAC is completely unknown. Some indirect inferences can be made from published literature and EAC incidence data which are used as calibration target when fitting the model.

The dysplasia states in the model are based on most commonly published data. We assumed that the sequence towards malignancy always starts with a BE without dysplasia, followed by low-grade and high-grade dysplasia. Although there is data available for indefinite dysplasia, we choose not to implement this to avoid further complexity and uncertainty in our model. The malignant stages are divided into local, regional and advanced state since our data source (SEER-9 U.S.A. cancer registry) presents the cancer incidence in those three phases. A perhaps more controversial

choice of our model is the possibility of regression, as we implemented the possibility for HGD and LGD to regress towards a stage with less dysplasia. In chapter 6, we discussed the uncertainty of this assumption and developed models that only include the possibility of progression to a higher dysplasia stage. Critique against the possibility of regression includes the major amount of misclassification due to sample error and pathological interpretation. However, there are studies where the Seattle biopsy protocol (four-quadrant biopsies at 2 cm intervals) was performed in combination with expert agreement on the pathological dysplasia grade that continuously showed regression of the higher dysplastic stage. Based on various expert opinions and these studies we assumed that regression is part of the natural course of the disease and implemented this in all further models.

The models were al calibrated to age-specific SEER-9 U.S. incidence and incidence-based mortality data. In chapter 3 we calibrated on the yearly data from 1975 to 2009 in order to optimize secular trend effects. Although we were able to provide estimates for the age, period and birth cohort effects that are driving the secular changes in EAC incidence, we are aware that these effects incur a high level of uncertainty. There are two main difficulties when addressing age, period, and cohort effects. First, there is an identification problem; multiple solutions for the combination of these effects in terms of drift and rate can explain the secular observed trend. Second, there is uncertainty to which element of the natural history (BE incidence and/or BE progression) the effects apply; also in this case multiple solutions are possible. In order to decrease the uncertainty in parameters due to the secular trend effects in birth cohort and period, we additionally established cross sectional models excluding secular effects for chapter 4, 6 and 7. These models were calibrated on the average recent EAC incidence over a 10-year time frame, optimizing only the age specific parameters for BE incidence.

8.3 INTERPRETATION OF FINDINGS

Natural history and secular trends of EAC

The increase in EAC has alarmed patients and doctors over the past few decades. The mystery of the disease and its increasing incidence has not yet been resolved. This thesis starts off with an evaluation of the cancer incidence trends in the Netherlands, United States and Spain. The evaluation of cancer incidence and mortality trends can give important insights in the changes of disease proliferation in the population over time. The influence of demographic and genetic risk factors will cause differences in incidence trends between countries, providing us valuable information when considering possibilities for prevention. Our results indicate that other drivers besides obe-

sity, smoking and alcohol consumption are likely responsible for the major increase in EAC incidence.

In chapter 2, we postulate several alternative explanations for the increasing EAC incidence. First, the time trends might reflect changes in diagnostics. With the refinement of various diagnostic modalities and the increased use of endoscopy among patients with GERD symptoms or BE, increased diagnosis might be a reason for the observed increased incidence of EAC. Although there has also been a concomitant increase in EAC mortality, this could be caused by sticky diagnosis or misattribution bias.[2] Second, a reclassification of tumors could result in an observed increase in EAC incidence. However, changes in reclassification of tumors would be expected to show corresponding reductions in tumors adjacent to the esophagus, which have not been observed: gastric cardia incidence has remained stable in all of the examined countries for the last two decades. In addition, we observed a steady rise of EAC incidence, instead of a discrete change that would represent reclassification influences. Finally, although the trends imply that obesity, smoking and alcohol are not the primary causes for the rise in EAC incidence, it is possible that the effect of these risk factors could be masked by an unknown protective factor with differential prevalence across the countries. A plausible explanation for the increasing EAC trend in our view is the decrease in *H.Pylori* infection in the population.

We used microsimulation modeling in chapter 3 to project the future EAC incidence and mortality resulting from our assumptions on the plausible drivers for EAC increase. We assumed that two mechanisms are responsible for the observed trend in EAC: the decrease in *H.Pylori* infection and the introduction of Proton Pump Inhibitors (PPI). We assumed that having *H.Pylori* infection protects against BE and EAC and decreases with birth cohort since 1885.[3] Consequently we modeled the disappearing *H.Pylori* infection effect as a birth cohort effect increasing the BE incidence rate and the rate of progression from BE to EAC (transition parameters). For PPI use, we assume that this has a protective effect against EAC development, and was introduced after 1988 (period effect). Since PPI is generally used by GERD patients, we considered that it might only influence BE patients and therefore we modelled a protective period effect by reducing the rate of progression from BE to EAC. Furthermore we modeled age effects on the BE incidence. After establishing how the effects would be modelled, we calibrated the model optimizing the absolute rates of the effects.

The extrapolation of the birth and period effects were used to estimate the EAC incidence and mortality between 2009 and 2030. The model estimates that the birth cohort effect plateaus around birth cohort 1945 for both males and females. As a consequence,

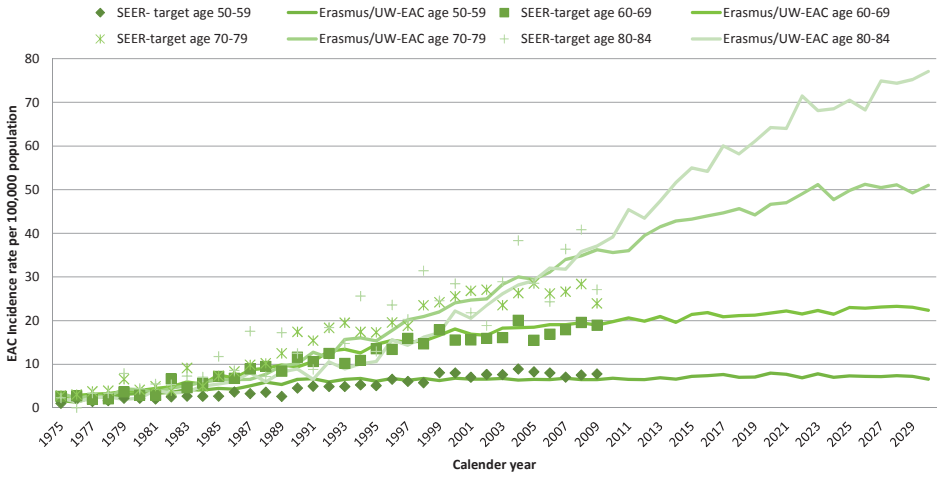

Figure 1. Real and predicted all male U.S. esophageal adenocarcinoma incidence per age group predicted by Erasmus/UW-EAC

EAC incidence plateaus after 2009 for age groups born after 1945, and still increases for older age groups (figure 1). Overall, both males and females are predicted to experience a trend of increasing EAC incidence after 2010. The estimated protective effect from PPI's in our model for both males and females was small and resulted in a minimal plateauing effect on EAC incidence. Our model assumptions did unfortunately result in a lack of fit for EAC incidence in older age groups, showing a continued increase in EAC incidence after 2010 while the other two CISNET modeling groups found an plateauing EAC incidence in older birth cohorts (chapter 3). Although the other models might have a better fit, they have not based their secular trend effects on hypotheses for the driving mechanisms behind the EAC increase. After recognizing the uncertainty in secular trend effects and the lack of fit of the incidence rates in older age groups, we decided to use non-secular models in chapter 4, 6 and 7. These non-secular models were calibrated on most recent EAC incidence providing more robust estimates for age specific parameters due to the exclusion of uncertain cohort and period effects.

Microsimulation modeling can also be used to explore uncertainties in the natural history of the disease. We used a non-secular model to reconcile published data and accurately estimate the EAC incidence in BE in chapter 4. Our study revealed that early detection of EAC is causing higher published estimates for the BE to EAC progression on short term, while the underlying progression rate is actually much lower. The model, calibrated on average cancer incidence in the male population between 2000 -2009 and on a 0.18% annual progression rate in a population-based design including partial surveillance, showed an average clinical progression rate (clinically diagnosed cancers in a situation without intervention) from diagnosed non-dysplasia(ND) or LGD to EAC

of 0.07%, 0.37% and 0.53% % annually for 5, 10 and 15 years of follow up (from age 65) when performing no surveillance at all and accounting for diagnostic inaccuracy.

Our calibrated model showed that after 15 years of follow up from age 65, 5.7% of the true positive ND patients have developed EAC. For true-positive LGD and HGD the malignant development was 13.1% and 75.4% (figure 2). The results of this model are in line with published data. The study of Den Hoed[4] calculated that for an average follow-up period of 15 years, the malignant progression rate was 0.66% annually with a cumulative incidence of 10%. Furthermore their study revealed that the mean intervals between BE diagnosis and either HGD or EAC, death or end of follow-up were 10.8, 12.6 and 25.5 years.

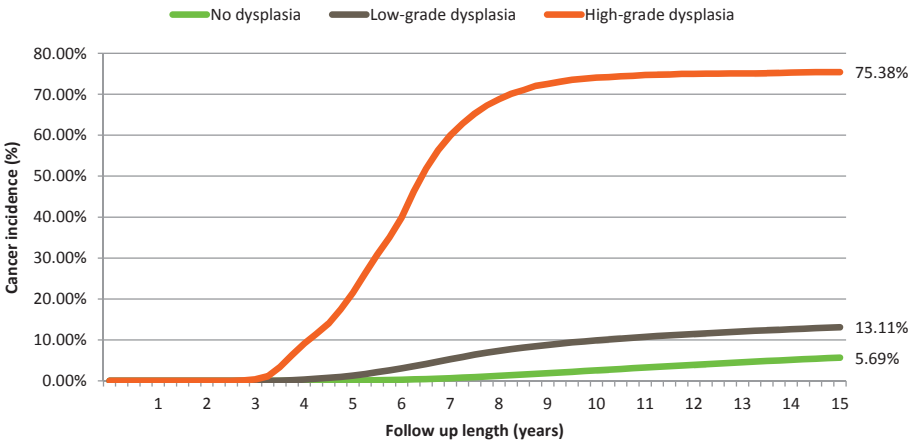

Figure 2. A: Cumulative cancer incidence in ND, LGD and HGD patients of age 65 over a 15 year time frame

The BE prevalence in our model between age 60-65 was 1.4% in the male population which in combination with the progression rate results in the fitted 2000-2009 EAC incidence. This is relatively low if we compare this rate with previously published studies estimating the BE prevalence in the adult population to be around 1-2.[5] We optimized the incidence rate of BE per 10-year age groups and over age 85 for patients with and without symptoms of GERD (GERD patients having a 6-fold increased risk for BE). Figure 3a shows the BE incidence in the male population, and Figure 3b shows the incidence found in the total population in the recently published Masclee study.[6] The large decrease in the optimized BE incidence for age 70-80 can be explained by the fairly low EAC incidence for age 85-100, on which the model was calibrated. Assuming an increasing BE incidence up to age 80 would result in an overestimation of cancers in the oldest age group.

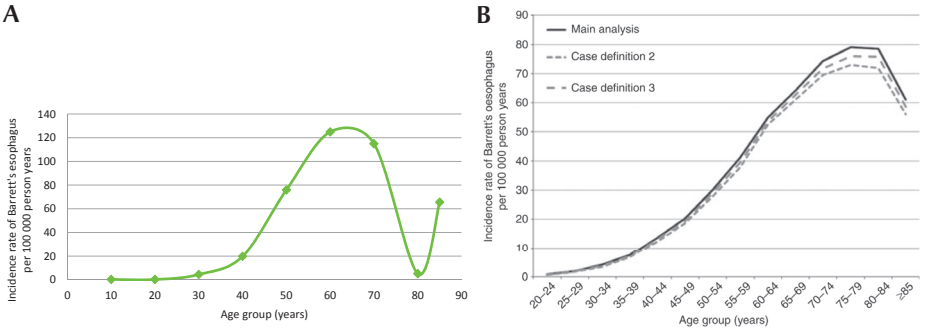

Figure 3. A: Male BE incidence in our model B: Overall BE incidence of Masclee (2013)[6]

On average, in the male population aged 20-100 years, the incidence ratio (IR) of BE in the model was 42.9/100 000 person-years (PY), this is slightly higher than the published rate of 39.6/100 000 PYs for males in the Netherlands.[7]

The simulations in chapter 4 including a population-based design with partial surveillance and a cohort design with 100% surveillance predicted annual progression rates of 0.19% and 0.36% in an average follow up length of 5 years. Figure 4 shows that the annual progression rates increase and that the cancer incidence rates of different study designs converge to each other on the long term, because cancers detected during surveillance are diagnosed within a short time frame, while diagnosis is delayed in the non-surveillance cohort.

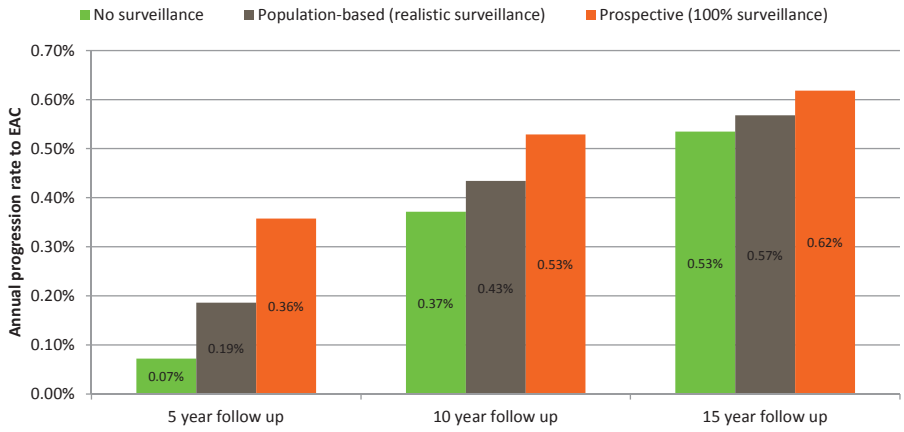

Figure 4. Average annual progression rates (from BE ND+LGD to EAC) for different lengths of follow up and surveillance interventions for a male 65-year old cohort

For total HGD and EAC development, the long time horizon results show that 0.5%-1% of the simulated 65-year old cohort will be diagnosed with HGD or early EAC which would not have progressed to clinical cancer when performing no surveillance at all (figure 5). This is in line with a recently published study showing that incidence rates may increase when including patients with HGD as endpoint, as they receive treatment and will not progress further to EAC. Over a follow up period of 5 year, a cancer progression rate of 0.18% annually was found. Including HGD patients, the progression rate increased to 0.48% annually.[8]

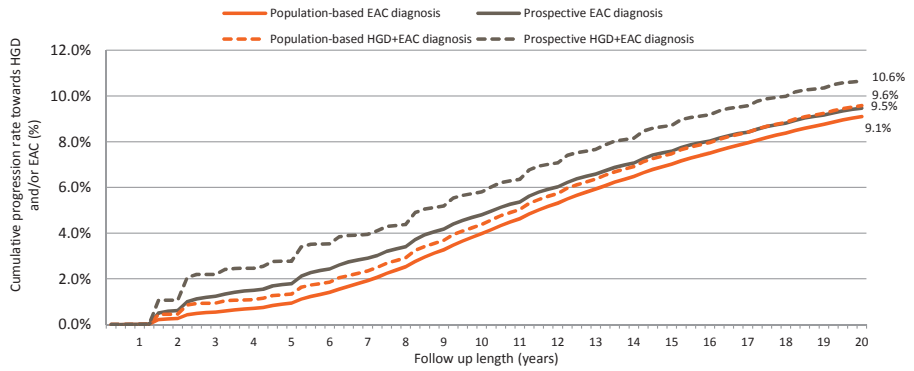

Figure 5. Cumulative incidence rate over time when in the population-based design (orange) and prospective design (grey)

Because of surveillance there is early detection of cancers, which results in a 0.19% annual progression rate for a 5 year follow up for the population-based estimate (incorporates a small part of patients receiving surveillance), and a 0.36% progression rate for the prospective estimate (all patients receive surveillance). This might be defined as progression rate including surveillance bias, as this progression rate includes not only the clinically diagnosed cancers, but additionally early detected cancers. After 5 years, the difference between the progression rates is fairly large, however after a long follow up period the difference is almost negligible. The long term absolute difference in cancer incidence depends on how much surveillance is performed in the long run. Clinicians informing their patients should use the clinical rate to express their risk (short and long term, whatever is more relevant for the particular patient) if no action is undertaken, and then discuss the risks (cancer diagnosis at earlier age with the possibility of overdiagnosis) and benefits (less invasive treatment and improvement of prognosis) of surveillance.

Possibilities for early detection and intervention

The spectacular increase in EAC incidence and mortality has led to an extensive increase of research concerning BE and EAC interventions. Therefore part II of this thesis studies the possibilities of early EAC detection and intervention. We reviewed the evidence for early detection possibilities in chapter 5. We gained some insights in the risk factors, symptoms and signs that are predictive for BE and EAC in the general population and the predictors for progression in a BE population (table 1). These predictors can enable us to identify individual-based risk, where after interventions can be tailored on the person-based characteristics.

Table 1. Risk factors for BE and EAC

	Strong associations	Moderate associations
Predictors for BE	Cytokines interleukins (IL)	Increased waist to hip ratio, Male gender
Predictors for EAC	Daily symptoms of GERD, More than 20 years of GERD symptoms, More than 30 pack years of smoking, Family history	Weekly GERD symptoms, <10-15 year GERD symptoms, Obese (10 years ago), Smoking
Predictors for BE and EAC as combined outcome	Cytokine interleukins, Male gender	Race, Age, PPI use, Hiatus hernia
Predictors for EAC in BE	Nodularity, Dysplasia, DNA content abnormalities, p53 loss of heterozygosity (LOH), Leukocyte telomere length	Length of the BE segment, Esophagitis, Length of hiatal, Aneuploidy, Tetraploidy, Methylation

BE: Barrett's esophagus; EAC: Esophageal adenocarcinoma; GERD: gastro-esophageal reflux disease

The review revealed that the possibilities for BE screening are limited and that the available risk-factors cannot be used in a screening program due to insignificant predictive value. Since the evidence for the effectiveness of BE surveillance is scarce, one could argue that as long as we don't know whether surveillance of BE patient is (cost-) effective, putting forward a screening program for BE should not be considered an option. There is a lack of randomized controlled trials proving the effectiveness of surveillance, and furthermore the observational studies show conflicting results. There is better evidence for the effectiveness of RFA treatment, however uncertainty in BE natural history and the underlying risk for EAC development is crucial when evaluating cost effectiveness of screening and treatment for BE.

In chapter 5 we showed that based on varying plausible assumptions concerning the BE progression rate the possibility of dysplastic regression, the effectiveness when treating all BE patient was robust. However, the resources required to gain that effectiveness varied considerably when treating all BE patients: screening and treatment

of all BE requires up to 3 times more patients to be treated per death prevented in a situation with regression compared with a situation with high progression. This is caused by the differences between models in the BE prevalence in the population. Finally, the smaller number of patients treated when limiting therapy to patients with (high-grade) dysplasia results in smaller differences in the efficiency of treatment between the models.

When comparing differences in NNT/death and NNS/death between our models with literature for other screening programs, we found that outcomes for efficiency of screening in terms of numbers needed to invite (NNI) are reported for breast cancer screening. A recent meta-analysis reported 1904 NNI/death, with a large 95% confidence interval between 929 and 6378 NNI/death.[8] Thus, the reported variation of NNI/death within the 95% confidence interval holds a 7-fold variation, while our results reported variation between models up to 3-fold for the NNT/death. Modeling studies reporting the influence of the uncertainty of input parameters and model structures on cancer screening also showed considerable differences for effectiveness of screening. A study that compared various CISNET models with varying modeling approaches, structures and input assumptions for the simulation of colonoscopy screening showed that the maximum clinical incidence reduction (MCLIR) after disease removal at age 65-80 varied from 51% to 90% between models, implying a difference of 80% in incidence reduction between models.[9] In our study the largest differences were seen in case of HGD treatment resulting in a difference of 230% in incidence reduction. A recent paper investigated the benefits and harms of computed tomography lung cancer screening strategies by five comparative simulation models. Differences in modeling results for the number of persons who were no longer dying of lung cancer varied between 177 and 863 per 100,000 individuals, which is a 5-fold difference in mortality reduction.[10] In our study the differences in modeling results for the number of persons who were no longer dying of EAC varied between 14.5 and 15.6 per 100,000 individuals assuming all BE treatment, and between 3.9 and 5.1 per 100,000 individuals assuming only HGD treatment, reflecting the low incidence of EAC in the general population.

We considered the low-progression rate model with possibility of dysplastic regression to be most plausible based on our model fit and the results of chapter 4 showing that high progression rates are caused by detection bias due to surveillance. As a result, interventions for BE will less likely be cost-effective. After studying the potential effect of uncertainties in progression rates on hypothetical interventions, we evaluated the results for realistic surveillance and treatment interventions. For this model we included the possibility of dysplastic regression in the model structure, and calibrated on a low malignant progression rate as these are our most plausible assumptions.

In addition to our Erasmus/UW-EAC model, the study used two additional CISNET models with various structures and assumptions in order to account for uncertainties in the natural history of the disease. All models simulated the effect of EET on EAC incidence and mortality. We simulated a 60-year old BE cohort (including ND, LGD and HGD patients) and applied surveillance and/or EET according to dysplastic grading for various strategies. Without surveillance, 85-134 EAC cases and 57-98 EAC deaths were expected to occur in 1,000 60-year old BE patients. The ranges reflect differences between models in BE prevalence and malignant progression rate due to the varying model structures and assumptions. In all three models, surveillance led to down-staging and an average EAC mortality reduction of 25%, from 57-98 EAC deaths to 42-70 EAC deaths per 1,000 BE. However, there was a 24% increase in cancer detection (from 85-134 EAC cases to 110-182 EAC cases per 1,000 BE) due to early detection, partly caused by overdiagnosis (surveillance-detected EAC that would not have become clinically observed due to death from non-cancer causes). EET treatment was effective in each model, although the number of treatments (EMR and RFA treatments) substantially increased when patients with lower dysplasia grades were included in the treatment strategy . The average number of EAC cases detected decreased from 142 per 1,000 BE patients when only applying surveillance, to 75, 42 and 25 per 1,000 BE patients when performing EET treatment for HGD patients, all dysplastic patients and all BE patients respectively.

Our study shows that endoscopic eradication of HGD, specifically by RFA, could result in substantial reductions in EAC incidence and mortality. The additional deaths prevented by expansion of treatment to lower grades of dysplasia result from cases that are rapidly developing EAC, or that are misclassified HGD and/or EAC patients diagnosed as ND or LGD BE. In these instances, the HGD may not be diagnosed at endoscopy and it makes sense to treat these patients in an early stage. However, extending treatment eligibility to patients with lower grades of dysplasia substantially increases the use of eradication therapy while diminishing the incremental effectiveness. This result in an unfavorable number of treatments needed to prevent one EAC death if a strategy treating all patients with BE (including HGD, LGD and NDBE) is used.

8.4 IMPLICATIONS FOR FUTURE DIRECTIONS

Natural history and secular trends of EAC

For the Netherlands, incidence rates up to 2013 are publicly available, showing us a small decrease in incidence in 2012 and 2013. It would be interesting to evaluate the forthcoming trend per age group in order to explain the birth cohort, age, and period

effects of the disease. Knowing the effect in terms of birth cohort, age and period gives us the opportunity to find applicable risk factors in line with these effects.

Modeling can be improved if the drivers of the disease are more certain. Future research should focuses on diminishing the uncertainty in secular trend effects by incorporating risk factors directly in the model. In chapter 2 we have assumed that *H.Pylori* was driving the increase in EAC incidence in our microsimulation model. After calibration we found a reasonable fit for the EAC incidence with this assumption. Future research should be done by data-analysis to support whether our assumption is plausible. Demographic trends of *H. Pylori* infection or a proxy for this variable can reveal relevant associations by examining the change in risk-factors and EAC incidence over time.

Possibilities for early detection and intervention

In general, early detection of EAC consists of two parts. The first part is the ability to find the precursor BE in the general population. The second part is the ability to stratify patients with BE for risk of progression to EAC, in order to adequately provide treatment and surveillance. One could argue that as long as we don't know whether surveillance of BE patient is (cost-) effective, screening for BE should not be considered an option. On the other hand, currently only 10% of the diagnosed EAC is observed in patients with a previous diagnosis of BE. This means that to truly combat the increase in EAC one also needs to target the total population. This can only be achieved if diagnostic methods are found that are less invasive and less costly than the current conventional endoscopy. Ideally, these diagnostic methods should be able to distinguish high risk BE patients from low risk BE patients to enable risk-stratified surveillance and treatment and unburden health-care resources and avoid exploding health costs. At the moment there is uncertainty about the effectiveness of early detection due to the lack of available evidence from randomized controlled trials. Since it is ethically impossible to perform such a trial, modeling can be used to identify the effectiveness of emerging interventions and key areas for improvement of current EAC screening, surveillance and treatment. We will discuss the main areas on which future research should focus in order to enhance current knowledge and possibilities for early detection and intervention of EAC.

As the detection of BE and EAC is done by endoscopic diagnosis followed by pathological confirmation, detection rates are dependent on the sensitivity, the specificity and the accuracy characteristics of the diagnostic test. Advanced technology on diagnostic modalities are continuously changing current practice and should be accounted for in simulation models. In terms of the current accuracy characteristics, the evaluation of early detection and intervention is biased because outcomes are subjective to misclas-

sification. Misclassification can be caused by sampling error when biopsy specimens are taken and by interpretation error by pathologists when grading the biopsy. The latter is especially observed when grading LGD, which is influencing the predictive value of malignant progression within these patients. When diagnosis of LGD made by a general pathologist is reviewed by an expert panel the diagnosis is most often downgraded to negative for dysplasia.[11,12] In one study, the malignant progression rate in confirmed LGD patients is even similar to the progression rate of HGD patients.[11] The altering definitions of dysplasia are constraining the possibilities for optimizing intervention decisions, as effectiveness of interventions are highly dependent on malignant progression rates. For emerging diagnostic modalities, new endosopic imaging techniques are improving detection rates of dysplasia and early cancers allowing more targeted biopsies. In addition, there are promising results for the cytosponge, which is an alternative diagnostic modality for the conventional endoscopy. The cytosponge includes a biomarker panel with high detection values for BE and more specifically BE with higher risks for malignant progression. Improving detection rates, decreasing the misclassification rates and identifying high risk patients by these new modalities will enable the individualized risk stratification and provide opportunities for screening in larger populations in the future.

Decision analytic models are extremely useful for exploration of the effects of interventions and to highlight which knowledge gaps exist. However, large uncertainties in the disease development and determinants of the disease diminish the robustness and increase bias in model results on possibilities for early detection and effectiveness of interventions. Main uncertainties in the disease development are the incidence of BE and the prevalence of BE in the population, the progression rates from BE towards EAC and the sojourn times between preclinical EAC and clinical EAC. First, current knowledge about BE incidence in the general population and risk factors for BE is scarce and hard to study because BE is partly asymptomatic. Secondly, the incubation time from BE to EAC and in between dysplasia states is a significant model feature because this uncertainty highly influences the outcomes of the most pressing questions within the EAC field: what is the malignant progression rate from BE towards EAC and are there possibilities to individualize the malignant progression rates by risk stratification? The last decade the research concerning predictors for BE and EAC has increased extensively. Multiple studies are focusing on finding demographic, clinical, genetic and epi-genetic factors aiming to increase the ability to accurately predict progression towards EAC. Although current literature does provide ranges for malignant progression and their determinants, the published estimates are variable. In future research, population-based studies and cohort studies should continuously be used to derive the clinical progression rate from BE to EAC and to determine predictors for progres-

sion. Especially new data over a long follow up period could be used to support our findings in chapter 4 concerning early detection bias due to surveillance frequency and long-term clinical progression rates.

Cohort studies researching cancer incidence in BE, predictors for progression and outcomes for surveillance and treatment interventions are continuously improving our understanding on the consequences of interventions for BE and EAC. The studies provide us valuable information on the impact of surveillance and treatment practice on cancer incidence, which can be used by clinicians to inform their patients on the risks (cancer diagnosis at earlier age with the possibility of overdiagnosis) and benefits (less invasive treatment and improvement of prognosis) of interventions. In addition, prospective cohort studies offer the possibility to estimate duration and significance of screen detectable disease and the sensitivity of surveillance for these precursors. This typically could be done by modeling, by simultaneous calibration to studies with varying levels of surveillance and treatment. To this end, a good description of the interventions and surveillance versus symptom detected cancers by length of follow up in empirical studies is mandatory.

In chapter 6, we have elaborated on the use of EET, and more specifically RFA as first-line treatment for BE patients. As we analyze the effectiveness of emerging treatments on mortality reduction and efficiency by resources needed to obtain effectiveness in long term, the results of clinical trials inform and determine our simulation results as the available data is extrapolated by our simulations. For this reason it is essential to use most recent data available concerning effectiveness and durability of EET and emerging treatment methods. Additional information concerning predictors for recurrence and effectiveness are becoming available as cohorts are followed over long term. Data on complications due to EET such as buried crypts and long term outcomes for the recurrence rates are necessary to accurately describe long-term risks for adverse events after EET. Using most recent data on risk-stratified effectiveness and durability of treatment for BE, but also for early EAC, will improve possibilities for optimizing risk-stratified treatment strategies.

In order to adequately specify the effects of interventions, costs and quality adjusted life years (QALY) should be considered in future modeling studies. In chapter 7 we analyzed that the health care resources needed to achieve additional EAC mortality reduction is huge, and especially when surveillance after treatment and additional treatments are given over a long period after initial diagnosis, one should consider the costs of interventions. Cost-effectiveness studies will enlarge the understanding of the EAC burden on the population compared with other diseases and allow decision-

makers to optimize health-care resources for cancer prevention in the general population.

In terms of modeling, it is of high importance to get a better understanding of the progression of the disease such that more realistic assumptions can be made, improving future projections and simulation results on effectiveness of intervention. Until these uncertainties in the natural course of the disease are diminished, future modeling of interventions should always consider multiple sensitivity analyses on their parameters to reflect biases in their predictions. We have discussed the main areas on which future research should focus, in order to obtain more realistic and higher quality data which can be used to strengthen the results of microsimulation modeling and advance our understanding of esophageal cancer and cancer control interventions to diminish the burden of this disease.

8.5 MAIN CONCLUSIONS

- The increase in esophageal adenocarcinoma incidence in the United States and the Netherlands is significantly greater than the increase in Spain. Concomitant trends in obesity, smoking, and alcohol consumption do not support their driving role in this increase. Other important causative factors for the increase in esophageal adenocarcinoma incidence must therefore be present.
- The increase in esophageal adenocarcinoma incidence and mortality rates in the United States from 1975-2009 is predominantly driven by a birth cohort effect. The model estimates that the birth cohort effect plateaus for younger birth cohorts. As a consequence the increase in esophageal adenocarcinoma incidence and mortality will slowly decline in the future.
- The projected trends for the United States esophageal adenocarcinoma incidence and mortality are likely to continue to increase between 2009 and 2030.
- More than two-third of the difference in progression rates of Barrett's esophagus patients between population-based studies and prospective studies can be explained by detection bias from endoscopic surveillance in the latter studies. Given the uncertainties in surveillance intensity and diagnostic accuracy, detection bias may even explain all of the difference between varying published progression rates.
- The underlying clinical progression rate to esophageal adenocarcinoma is closer to that observed in population-based studies and was estimated expected to be 0.37% annually after a 10-year of follow up length for 65-year old non- and low-grade dysplastic Barrett's esophagus patients.

- There is no definitive evidence, only suggestive evidence that early detection of esophageal adenocarcinoma in Barrett's esophagus patients is effective. Cost effectiveness of surveillance is increased when applied to Barrett's esophagus patients with dysplasia. To further improve cost effectiveness, surveillance should be optimized by improving risk stratification in Barrett's esophagus patients.
- Efficiency of treatment for patients with high-grade dysplasia is robust for natural history assumptions; however, the effectiveness of treatment is variable when changing natural history assumptions. Extending treatment to patients with lower grades and without dysplasia reduces variability in treatment effectiveness but increases variability in treatment efficiency induced by uncertainty in natural history assumptions.
- Comparative modeling analyses indicate that endoscopic eradicative treatment is an effective means of reducing EAC incidence and mortality. Benefit is predicted to be achieved across all patients with Barrett's esophagus. However, substantially more treatments and endoscopies are required to avert a cancer death when treatment is given to patients with lower grades and without dysplasia.
- Our results add further evidence to support endoscopic eradicative treatment, more specifically radiofrequency ablation, in high-grade dysplastic patients. Strategies targeting less severe disease are not likely to be cost-effective.

8.6 MAIN RECOMMENDATIONS

- Reduction in esophageal adenocarcinoma must rely on identification of causative factors responsible for the increase in incidence seen in the last few decades. Global trend analysis on the prevalence of *H. Pylori* infection over time should be performed to evaluate the hypothesis that the increase in esophageal adenocarcinoma incidence is caused by the diminished protective effect of *H. Pylori* infection.
- For the Netherlands, esophageal adenocarcinoma incidence rates up to 2013 are publically available, showing a small decrease in incidence in 2012 and 2013. We recommend to evaluate the forthcoming incidence trends by age group in order to explain the birth cohort, age, and period effects of the disease. Knowing the effect in terms of birth cohort, age and period gives us the opportunity to find applicable risk factors in line with these effects.
- In terms of modeling, it is of high importance to get a better understanding of the progression of the disease such that more realistic assumptions can be made, improving future projections and simulation results on effectiveness of interventions. Until these uncertainties in the natural course of the disease are resolved, we recommend that future modeling of interventions should always consider multiple

sensitivity analyses on their parameters to assess the robustness of their predictions for uncertainties in the natural history.

- The so called clinical progression rate (clinically diagnosed esophageal adenocarcinomas that will develop in Barrett's esophagus patients in a situation without intervention) is the only definition which is unambiguous and should be used by modelers and clinicians for risk interpretation.
- Modelers must make the distinction between the progression rate to clinical cancer in the situation without surveillance, and progression rate with surveillance, including surveillance detected pre-clinical cancers. For (calibration to) the former, it is recommended that models use the lower end of the published estimates, approximating the clinical progression rate in order to prevent overestimation of cancer incidence without surveillance. Using this estimate will provide more valid cost-effectiveness calculations of surveillance and treatment.
- Clinicians should inform their patients on the risks (cancer diagnosis at earlier age with the possibility of overdiagnosis) and benefits (less invasive treatment and improvement of prognosis) of surveillance.
- Radio-frequency ablation should be applied to patients with high-grade dysplasia. Strategies targeting less severe disease will be effective in terms of mortality reduction, but will pose a substantially higher burden on patients and health care resources.
- Although radiofrequency ablation for Barrett's esophagus patients with low-grade and no dysplasia is effective, the efficiency of treatment is low and the cost-effectiveness for treatment of these patients remains controversial. Future research should focus on identifying new markers for progression in patients with low-grade or no dysplasia, because stratification of surveillance and treatment recommendations on these risk factors could greatly increase the efficiency of care of Barrett's esophagus patients.
- Our understanding of esophageal adenocarcinoma and cancer control interventions would be greatly enhanced when future research will focus on long term data from population-based studies and cohort studies considering long term clinical progression rates from BE to EAC and to predictors for progression.
- Microsimulation modeling should focus on (new studies): 1) adding risk stratification in modeling to predict on individual risk level for patients and to optimize risk-stratified surveillance and treatment protocols. 2) Screening possibilities and effect of current screening and new methods on total EAC mortality. 3) Cost-effectiveness and decreasing burden on health care resources.

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SUMMARY

Introduction

Esophageal adenocarcinoma (EAC) is a disease with a high fatality rate and although its incidence among the population is low, the rising incidence over time is an alarming trend. The last four decades the incidence of EAC has experienced a 7-fold rise. On the contrary, the incidence of squamous cell carcinoma (SCC) has decreased and plateaued, making EAC the most prevalent type of esophageal cancer since the 90s. EAC is most common among older males. EAC originates from Barrett's epithelium (BE), a premalignant condition in which the normal squamous epithelium of the distal esophagus is replaced by columnar epithelium containing goblet cells. The development of EAC is a gradual process, in which metaplastic epithelium evolves to low-grade dysplasia, high-grade dysplasia and eventually EAC. Currently around 92% of the diagnosed EAC is found at first endoscopy, that is, without an earlier confirmed BE diagnosis. In contrast, only a small percentage of the patients diagnosed with BE (6-11%) will eventually develop EAC. The risk for malignant progression in BE is positively correlated to the grade of dysplasia found at endoscopy and biopsies. However, endoscopic surveillance, using conventional histological diagnosis of dysplasia lacks proper discriminative power to separate patients with a very low risk for malignant progression from those who have a high risk. The presence of a premalignant stage provides the opportunity to prevent the development of BE related adenocarcinoma by early detection and BE treatment. Although there is reasonable evidence that treatment for BE with high-grade dysplasia is effective, effectiveness of surveillance and treatment interventions for lower grades of dysplasia is controversial due to unknowns in the malignant risk and disease proliferation of EAC.

The overarching goal of this thesis is to gain insight into the unknowns of the natural history of EAC, and to predict the impact of these unknowns to inform decision making concerning the early detection and treatment of EAC. The first part of this thesis focuses on the natural history of EAC and explores the trends in EAC incidence and mortality and drivers of those trends. The second part explores trends in EAC control and possibilities for early detection. As new treatments are emerging, we studied the effects of new treatments and interventions.

Secular trends of EAC incidence and the natural history of EAC

Chapter 2 examines the trends of EAC incidence among the United States, the Netherlands and Spain. Each trend showed an increase over time, however the highest increase was seen in the Netherlands. In our analysis, we took the trend evaluation to a higher level including lifestyle-associated risk factors. The trends in obesity and other

lifestyle-associated factors have been hypothesized to be important drivers of the EAC increase. We tested this hypothesis by comparing changes in these factors with changes in EAC incidence over time between the three western countries. Data on EAC incidence trends were abstracted from the SEER-9 registry for the United States, from multiple cancer registries in Spain and from Eindhoven Cancer Registry in the Netherlands. In addition, we collected trend data on obesity, smoking, and alcohol consumption. The trend data were analyzed using log-linear regression. In 1980, the EAC incidence was similar among the three countries ((0.46 – 0.63) per 100,000). EAC incidence increased in all, with the largest increase observed in the Netherlands, followed by the United States and Spain (estimated annual percentage of change = 9.7, 7.4, 4.3%, respectively). However, this pattern was not observed in lifestyle factors associated with EAC. With regard to obesity, the United States clearly has had the highest prevalence rates both in the past and in the present. For alcohol, the highest consumption rates are seen in Spain. Smoking showed a reverse trend compared with EAC among all three countries in the last 20 years. We concluded that the international trends in EAC incidence do not match corresponding trends in lifestyle-associated factors including obesity. Our findings suggest that other factors must overrule the association of obesity, smoking and alcohol consumption with EAC in order to explain the increasing time trends in EAC. In **chapter 3** we explored the drivers of the increasing EAC incidence by simulation modeling of age, period and birth cohort effects. With the help of experts and current knowledge on risk factors that are influencing EAC incidence we made assumptions concerning the type of effect (age, period, birth cohort) of these risk factors and the influence on the EAC sequence (BE incidence and/or BE progression. We calibrated the Erasmus/UW-EAC model on United States incidence and mortality data from 1975-2009 optimizing the drifts of the 3 different effects on BE incidence and BE progression. The model was used to make projections for EAC incidence and mortality between 2009 and 2030. We used a comparative modeling approach to project EAC incidence and mortality to year 2030 with the three EAC modeling groups of the Cancer Intervention and Surveillance Modeling Network (CISNET) consortium. Importantly, all three models identified birth cohort trends affecting cancer progression as a major driver of the observed increases in EAC incidence and mortality. All models predict that incidence and mortality rates will continue to increase until 2030 but with a plateauing trend for recent male cohorts. The predicted ranges of incidence and mortality rates (cases per 100,000 person years) in 2030 are 8.4 to 10.1 and 5.4 to 7.4, respectively, for males, and 1.3 to 1.8 and 0.9 to 1.2 for females. Estimates of cumulative cause-specific EAC deaths between both sexes for years 2011 to 2030 range between 142,300 and 186,298, almost double the number of deaths in the past 20 years. To gain more insight into the underlying progression rates from BE to EAC we calibrated a non-secular model to reconcile published data and

to predict cancer incidence in **chapter 4.** Literature shows a wide variation between estimates of progression and we hypothesized that a large part of this variation is due to early detection of EAC in cohorts where surveillance is frequently applied. We calibrated a model onto average incidence rates of 2000-2009, and optimized the BE incidence and cancer development of BE in order to fit published estimates of the population-based and prospective cohort design incurring different levels of frequent surveillance. The model showed that the clinical progression is actually very low and that proportion and adherence to surveillance is of crucial influence on average annual progression rates. For the first 5 year of follow up, the model reproduced the 0.19% average annual rate of progression observed in population-based studies; the same disease model predicted a 0.36% annual rate of progression in studies with a prospective design (0.41% reported in published articles). After 20 year these rates each increased to 0.63%–0.65% annually, corresponding with a 9.1%–9.5% cumulative cancer incidence. Between these periods, the difference between the progression rates of both study designs decreased from 91% to 5%. Thus, in the first 5 year after diagnosis, the rate of progression from BE to EAC is likely to more closely approximate the lower estimates reported from population-based studies than the higher estimates reported from prospective studies in which EAC is detected by surveillance. Clinicians should use this information to explain to patients their short-term and long-term risk if no action is taken, and discuss the risks and benefits of surveillance.

Possibilities for early detection and intervention

In **chapter 5** we systematically reviewed the possibilities of early detection for EAC on different aspects by performing a literature search for articles published between 2002 and 2013 (Medline, PubMed). We summarized evidence on possibilities of early detection of EAC based on predictive signs, symptoms and risk factors; decreasing doctor/patient delay; screening and surveillance for EAC and its precursor lesion Barrett's esophagus (BE); risk factors for progression to EAC in BE patients under surveillance and whether early detection of EAC led to improved prognosis. We included 49 papers in our study. Risk factors for (precursors of) EAC were male gender, waist-to- hip ratio, gastro-esophageal reflux symptoms and genetic factors. However, early detection on the basis of (a combination of) these risk factors in the general population did not lead to earlier detection of EAC. Scarce evidence indicates that patient- and doctor-delay did not negatively impact survival of EAC. Observational studies show that patients diagnosed in a surveillance program for BE had a better survival than those diagnosed outside such a program. Modeling studies suggest that surveillance for BE can be effective in patients with dysplasia, while cost-effectiveness improves by stratification of patients based on risk factors for carcinogenesis. Esophagitis, nodularity, BE segment length, dysplasia and detecting aneuploidy/tetraploidy or methylation in biopsies

from BE are predictors for malignant progression. We found that although surveillance and treatment of BE patients seems beneficial, both effectiveness and efficiency of interventions would be greatly enhanced if these patients could be risk-stratified. The influence of uncertainty in cancer progression rates in BE patients on hypothetical screening and treatment interventions was evaluated in **chapter 6.** In line with the results from the systematic review, we found that this uncertainty has a large influence on outcomes for hypothetical surveillance and treatment interventions. We calibrated two models with differing assumptions in progression rate (0.12% vs. 0.42%). The BE prevalence differed between models in order to reach the EAC incidence in combination with the targeted progression rate. In addition, a third model was calibrated in which we allowed regression of dysplasia in combination with a low progression rate. Assuming a perfect screening and treatment intervention for all patients with BE, the maximum EAC mortality reduction (64%-66%) and the NNS per death prevented (470-510) were similar across the 3 model versions. However, three times more people needed to be treated to prevent 1 death (24 v. 8) in the 0.12% regression model compared with the 0.42% progression model. Restricting treatment to those with dysplasia or only high-grade dysplasia resulted in smaller differences in number of patients needed to treat (2-3 to prevent one EAC case) but wider variation in effectiveness (mortality reduction of 15%-24%). This study demonstrated that the current uncertainty surrounding BE progression is unlikely to lead to large differences in estimates of the effectiveness of BE screening and treatment in the strategy of treatment for all patients with BE. However, if treatment is restricted to BE patients with dysplasia, treatment effectiveness varies widely and is dependent on BE progression assumptions. Furthermore, the resources required to gain that effectiveness vary considerably when treating all BE patients: screening and treatment of all BE requires up to 3 times more patients to be treated per death prevented in a situation with regression compared with a situation with high progression. Finally, the smaller number of patients treated when limiting therapy to patients with dysplasia results in smaller differences in the efficiency of treatment between the models. In **chapter 7** we evaluated the effectiveness and efficiency for realistic surveillance and treatment interventions. As the efficacy and durability of endoscopic eradication are reported, the long-term impact of endoscopic eradicative treatment (EET) and recurrent disease on EAC incidence and overall mortality reduction has not been analyzed with comprehensive and robust simulation models using this recently updated clinical data. In this study we have used three different CISNET models with various structures and assumptions in order to account for uncertainties in the natural history of the disease. All models simulated the effect of EET on EAC incidence and mortality. We simulated a 60-year old BE cohort and applied surveillance and/or EET according to dysplastic grading for various strategies. A strategy to endoscopically eradicate BE with high-grade dysplasia will decrease

EAC incidence by 50% (range 44%-58%) and EAC mortality by 46% (41%-53%) with number of treatments needed to avert one death (NTN/death) of 30 (26-34). If all BE (dysplastic and non-dysplastic) were eradicated, EAC incidence would incrementally decrease by 83% (81%-86%) and mortality by 80% (75%-85%). However, this reduction in EAC was associated with a four-fold increase in the number of treatments with an incremental NTN/death of 209 (132-316). Halting post-treatment surveillance after a recurrence-free period of 5-10 years has a negligible influence on NTN/death when eradicating only high-grade dysplasia. The resources needed to achieve EAC mortality reduction increase substantially as patients with lower severity of disease are selected for treatment. From a resource efficiency perspective, the large NTN/death suggests that treatment benefits justify endoscopic eradication only among BE patients with high-grade dysplasia.

General discussion

We discussed the uncertainties in the natural history of EAC and the impact of interventions on outcomes for BE patients in **chapter 8**. Although literature concerning BE and risk stratification has emerged the last few years, major issues concerning predictors for progression in the general and BE population has not yet been resolved. Using a microsimulation model, we assessed the influence of uncertainties in parameter assumptions on intervention outcomes and explored the effects driving EAC incidence and mortality. Although there are a lot of unknowns associated with the disease, optimizing intervention strategies and risk-stratified guidelines will lead to EAC incidence and mortality reduction. More specific research towards predictive factors for progression and effectiveness of treatments and additionally the implementation of those research results into microsimulation models is needed to verify how to optimize BE management in order to obtain more benefits and minimize harm for the patients.

SAMENVATTING

Oesophagus adenocarcinoom (OAC) is een ziekte met een slechte prognose en in de afgelopen 40 jaar is de incidentie van OAC in Nederland met meer dan 700% gestegen. OAC ontstaat uit het voorstadium Barrett oesophagus, oftewel Barrett-slokdarm (BO), een premaligne aandoening van de slokdarm waarbij het normale plaveiselcelepitheel van het slijmvlies van de slokdarm veranderd is in afwijkend cilindrisch epitheel met intestinale metaplasie. Maligne progressie naar OAC in een BO is een stapsgewijs proces waarbij intestinale metaplasie zich ontwikkelt naar laaggradige dysplasie, naar hooggradige dysplasie en vervolgens naar OAC. Slechts een klein deel van de adenocarcinomen wordt ontdekt in een Barrett-slokdarm surveillance programma (ca. 7,6% van alle adenocarcinomen). Het overgrote deel van adenocarcinomen wordt dus gediagnosticeerd als de kanker reeds ontwikkeld is. Aan de andere kant ontwikkelt ook niet elke Barrett-slokdarm gedurende het leven zich tot adenocarcinoom (6%-11% van gediagnosticeerde Barrett-slokdarm). Het risico op carcinogenese in Barrett-slokdarm is gecorreleerd aan de dysplasiegraad gevonden bij het endoscopisch onderzoek, maar met name de diagnose laaggradige dysplasie heeft te weinig voorspellende waarde om patiënten met een laag en hoog risico goed te kunnen onderscheiden.

Het bestaan van een premaligne voorstadium (BO) geeft de mogelijkheid om de ontwikkeling van OAC te voorkomen door middel van endoscopische surveillance en behandeling. Momenteel is er redelijk bewijs om aan te nemen dat behandeling van BO met hooggradige dysplasie (HGD) effectief is, maar het bewijs voor de effectiviteit van surveillance en behandeling van BO met lagere of geen dysplasie is controversieel. Onzekerheden over het maligne risico en de ziekte proliferatie van OAC zijn hiervan de oorzaak.

Het doel van dit proefschrift is om inzicht te verkrijgen in het natuurlijk beloop van OAC en om de invloed van onzekerheden in het BO naar OAC proces op vroege opsporing en interventie in kaart te brengen. Het eerste deel van dit proefschrift richt zich op het natuurlijk beloop van OAC en verkent de trends in OAC incidentie en mortaliteit en mogelijke oorzaken van deze trends. Het tweede deel van dit proefschrift richt zich op de mogelijkheden van vroege opsporing en behandeling van OAC.

Seculaire trends in OAC incidentie en het natuurlijk beloop van OAC

Trends in obesitas en andere levensstijl factoren worden vaak gezien als belangrijke oorzaken van deze stijging in OAC incidentie. In **hoofdstuk 2** hebben we deze hypothese getest door de absolute en relatieve veranderingen in deze risicofactoren te vergelijken met veranderingen in OAC incidentie door de tijd heen tussen drie westerse

landen. In 1980 was de OAC incidentie bijna gelijk in alle drie landen (0.46-0.63 per 100.000 populatie). Vanaf dit moment steeg de incidentie in alle drie landen, waarbij de snelste stijging werd gezien in Nederland, gevolgd door de Verenigde staten en tot slot Spanje (geschat jaarlijks percentage van verandering is respectievelijk 9.7%, 7.4% en 4.3%). Dit patroon werd echter niet gezien in de levensstijl factoren die geassocieerd worden met OAC. In de Verenigde Staten was de prevalentie van obesitas het hoogst over de gehele periode, terwijl Spanje de hoogste alcoholconsumptie had. Roken liet een inverse trend met OAC zien in alle drie landen over de afgelopen 20 jaar en het ontbreken van een daling in OAC incidentie suggereert dat roken geen grote verklarende factor is. Deze analyse geeft aan dat trends in OAC in de Verenigde Staten, Spanje en Nederland niet verklaard kunnen worden door trends in obesitas, roken en alcohol consumptie en dat er andere factoren moeten zijn die deze levensstijl factoren op OAC overschaduwen. Terugdringing van oesophagus adenocarcinoom sterfte moet daarom worden gezocht in identificatie van deze andere factoren.

In **hoofdstuk 3** hebben we de verklarende factoren voor de stijging in EAC verkend door middel van simulatie van leeftijd, periode en geboorte-cohort effecten. Dit onderzoek bestond uit een vergelijkende model analyse in samenwerking met twee andere OAC model groepen van het "Cancer Intervention and Surveillance Network" (CISNET). De modellen werden gekalibreerd op OAC incidentie- en sterftedata van 1975 tot 2009, waarbij de hoogte en veranderingen van leeftijd, periode en geboorte-cohort effecten op de BO incidentie en progressie werden geoptimaliseerd. Dezelfde modellen werden vervolgens gebruikt om de incidentie en mortaliteit na 2009 te projecteren. De drie modellen identificeerden dat het geboorte-cohort effect de grootste invloed had op de geobserveerde stijging in OAC incidentie en mortaliteit. Hiernaast voorspelden alle modellen dat de kanker incidentie en mortaliteit zal blijven stijgen tot 2030. De totale OAC mortaliteit tussen 2011 en 2030 werd geschat op 142.300 -186.298 gevallen, wat bijna het dubbele is van het aantal gevallen in de afgelopen 20 jaar.

Een belangrijke onbekende in de ontwikkeling van OAC is de onderliggende progressie kansen van BO naar OAC. Er is een grote variatie in de literatuur in schattingen van progressie, en onze hypothese was dat een groot deel van deze variatie te verklaren is door vroege detectie van OAC in cohorten waar surveillance wordt toegepast. Om deze hypothese te toetsen hebben we in **hoofdstuk 4** een niet-seculair simulatie model ontwikkeld, gekalibreerd op de kanker incidentie tussen 2000-2009. Rekening houdend met de mate van surveillance hebben we de progressie van BO naar OAC gekalibreerd op basis van de progressiekansen in populatie-studies (0.18%) en vervolgens met dat model voorspellingen gedaan voor progressie zonder surveillance (gedefinieerd als de klinische progressie kans) en progressie in prospectieve cohort studies met surveillance. Ons model liet zien dat de klinische progressie erg

laag is en dat de frequentie en proportie van surveillance in BO patiënten van grote invloed is op de gemiddelde progressie kans. Voor de eerste 5 jaar na BO diagnose reproduceerde het model de 0,19% jaarlijkse progressie kans geobserveerd in de populatie studies. Hetzelfde model voorspelde een jaarlijkse progressie kans van 0,07% zonder surveillance en van 0,36% in cohorten met een prospectieve onderzoeksopzet met intensievere surveillance (0,41% jaarlijkse kans in literatuur). Deze gemiddelde kansen stegen naar 0,63%-0,65% voor beide onderzoeksopzetten na 20 jaar met een cumulatieve kanker incidentie van 9,1%-9,5%. We concludeerden dat in de eerste 5 jaar na diagnose de progressie kans van BO naar OAC het beter benaderd wordt door de lagere schattingen uit populatie studies dan door de hogere schattingen uit prospectieve-cohort studies waar OAC gedetecteerd wordt door surveillance. Clinici zouden dan ook deze informatie moeten gebruiken om hun patiënten te informeren over de korte en lange termijn risico's op OAC in een situatie zonder interventie, waarna de voor- en nadelen van surveillance bediscussieerd kunnen worden.

Mogelijkheden voor vroege opsporing en interventie

In **hoofdstuk 5** hebben we met behulp van een systematische literatuuronderzoek de mogelijkheden voor vroege opsporing van OAC onderzocht op basis van artikelen gepubliceerd tussen 2002-2013 (Medline, PubMed). Hoewel er aanwijzingen op basis van observationeel onderzoek zijn dat surveillance van Barrett-slokdarm patiënten kan leiden tot sterftedaling als gevolg van een adenocarcinoom, is dit niet vastgesteld in gerandomiseerd onderzoek. Modelleerstudies laten zien dat surveillance van BO patiënten met een hoog risico op OAC progressie kosteneffectief is, en dat bij laag-risico patiënten surveillance alleen kosteneffectief is bij een lang surveillance-interval. Laaggradige dysplasie, endoscopisch zichtbare afwijkingen (nodulariteit), de lengte van het Barrett-segment en oesophagitis lijken belangrijke voorspellers te zijn voor OAC risico. Dysplasie gradering is op dit moment de meest gebruikte marker voor progressie, maar vaststelling van dysplasie is moeilijk, omdat die onderhevig is aan variabiliteit in pathologische interpretatie en sampling error. Naast dysplasie is de bruikbaarheid van geen van de andere bovengenoemde factoren (alleen of in combinatie) voor maligne predictie gevalideerd.

De invloed van de onzekerheid van de progressie kans op de effectiviteit en efficientie van surveillance en behandeling is onderzocht in **hoofdstuk 6.** In deze studie hebben we twee modellen ontwikkeld met verschillende aannamen in progressie kans (0,12% vs. 0,42% jaarlijkse kans). Hiernaast werd een derde model ontwikkeld waarin we de mogelijkheid van regressie van dysplasie graad toevoegden aan de modelstructuur in combinatie met een lage progressie kans. We simuleerden perfecte screening en behandeling voor alle BO patiënten in de drie verschillende modellen en vergeleken de effectiviteit en efficiëntie. Er was weinig variatie tussen de drie

modellen in mortaliteitsreductie (64-66%) en het aantal screenings per voorkomen OAC sterfte (470-510). Daarentegen moesten wel drie keer zoveel mensen behandeld worden om één sterfgeval te voorkomen (24 vs. 8) in het 0,12% regressie model vergeleken met het 0.42% progressie model. Het enkel behandelen van BO patiënten met HGD resulteerde in kleinere verschillen in het aantal behandelingen per voorkomen sterfgeval (2-3), maar een grotere variabiliteit in de effectiviteit van de behandeling (mortaliteitsreductie tussen 15% tot 24%).

In **hoofdstuk 7** hebben we de effectiviteit en efficiëntie van realistische surveillance en behandel interventies onderzocht. Hoewel in de literatuur reeds gepubliceerd is over de werkzaamheid van endoscopische ablatie voor BO op de korte termijn, was de effectiviteit en het terugkeren van de ziekte op lange termijn nog niet geanalyseerd op basis van de meest recente klinisch beschikbare data. Op basis van deze recente klinische data hebben de drie CISNET modelgroepen een 60-jarige BO cohort gesimuleerd voor verschillende strategieën van endoscopische behandeling. De strategieën varieerden in het moment waarop endoscopische behandeling werd toegepast. De strategie waarbij alle BO patiënten met HGD endoscopisch behandeld werden resulteerde in een 50% (range tussen de 3 modellen 44% - 58%) OAC incidentie reductie en een 46% (41% - 53%) EAC mortaliteit reductie. Er waren 30 (26-34) behandelingen nodig om een OAC sterfgeval te voorkomen. De strategie waarbij alle BO patiënten (zowel met als zonder dysplasie) endoscopisch werden behandeld, resulteerde in 83% (81% -86%) OAC incidentie reductie en 80% (75% - 85%) OAC mortaliteit reductie. Hiervoor waren echter vier keer zoveel behandelingen noodzakelijk, resulterend in 209 (132-316) additionele benodigde behandelingen per extra voorkomen sterfgeval. Deze resultaten suggereren dat behandeling enkel efficiënt is wanneer deze wordt toegepast in BO patiënten met HGD.

MODEL APPENDIX

GENERAL MODEL OVERVIEW

The Erasmus/UW-EAC model (before, UW/MISCAN-EAC model) is a semi-Markov microsimulation model for esophageal adenocarcinoma (EAC). The population is simulated individual by individual and each person can evolve through discrete disease states. However, instead of modeling yearly transitions with associated transition probabilities, the Erasmus/UW model generates durations in states. With the assumption of exponential distribution of the duration in each state, this way of simulating leads to similar results as a Markov model with yearly transition probabilities. The advantage of the Erasmus/UW-EAC model is that durations in a certain state need not necessarily be a discrete value but can be continuous. The Erasmus/UW-EAC model uses the Monte Carlo method to simulate all events in the program. Possible events are birth and death of a person, Barrett's incidence, and transitions from one state of disease to another. The basic structure of the Erasmus/UW model is separated in three main parts:

- demography part
- natural history part
- screening part

These parts are not physically separated in the program, but it is useful to consider them separately.

Demography Part

The individual life histories are simulated in the demography part of the model. For each person, a birth date and death date is simulated for other causes than EAC. The distribution of births and deaths can be adjusted to represent the simulated population.

Natural history part

We assume that EAC develops through precursor Barrett's esophagus (BE). For each individual in the simulated population a personal risk index is generated. A minority of the population has symptomatic gastro-esophageal reflux disease (GERD), giving them a higher risk of developing BE during their lifetime. The development of BE is generated according to this personal risk index and an age specific incidence of onset. The sequence from the onset of BE to EAC diagnosis is governed by sojourn times between the different states. BE starts in a state with no dysplasia (ND), after which dysplasia can develop. Two states of dysplasia are defined: low-grade (LGD) and high-grade dysplasia (HGD). There is a possibility that regression from HGD to LGD and from LGD to ND

occurs. The probability to regress or progress is dependent on a transition rate matrix, and is therefore also influenced by the sojourn time. The probability of regression, progression and the according sojourn times can be calculated as follow:

$Probability\ of\ regression\ in\ state\ i = \frac{R_{ir}}{R_{ir}+R_{ip}}$, where *i*: current state LGD or HGD, *r*: regress, *p*: progress, *R*: rate

$Probability\ of\ progression\ in\ state\ i = \frac{R_{ip}}{R_{ir}+R_{ip}}$, where *i*: current state LGD or HGD, *r*: regress, *p*: progress, *R*: rate

$Sojourn\ time\ in\ state\ i = \frac{1}{R_{ir}+R_{ip}}$, where *i*: current state LGD or HGD, *r*: regress, *p*: progress, *R*: rate

From HGD malignant cells can arise that can transform from this stage to preclinical localized EAC, which can sequentially progress into regional and distant preclinical EAC. In each of these three states, there is a probability of the cancer being diagnosed. The sojourn times between these described states are exponentially distributed, and in some states (BE ND, BE LGD and BE HGD) age dependent. Because most sojourn times extend beyond the demography-generated age of death from other causes, only a small proportion of the population develops EAC from BE. The survival after clinical diagnosis depends on the cancer stage, and the year of diagnosis (period effect reflecting survival improvement over time).

Screening part

The development of EAC can be interrupted by screening. Screening can detect BE, the dysplasia states and preclinical cancers. BE and dysplasia can be removed using treatment. Usually the cancers will be found in an earlier stage than with clinical diagnosis. In this way screening reduces EAC incidence or EAC death.

Integration of the three model components

For each individual, the demography part of the model simulates a time of birth and a time of death of other causes than EAC, creating a life history without EAC. Subsequently the onset of BE is simulated for that individual. For most individuals no dysplasia is generated. In the case of progressive BE, dysplasia may develop and HGD transforms into a malignant carcinoma, causing symptoms and eventually resulting in death from EAC. When a person dies from EAC before he dies from other causes, his death age is adjusted accordingly. This procedure is explained in Figure A1. In this example the life history of a person is shown who develops BE, preclinical EAC and consequently clinical EAC which causes death before the age of death from other causes. The combination of life history without cancer and the development of cancer through BE is shown in the bottom line.

After the life history of a person is adjusted for EAC, the history can also be adjusted for the effects of screening (figure A2). After screening, BE with or without dysplasia is

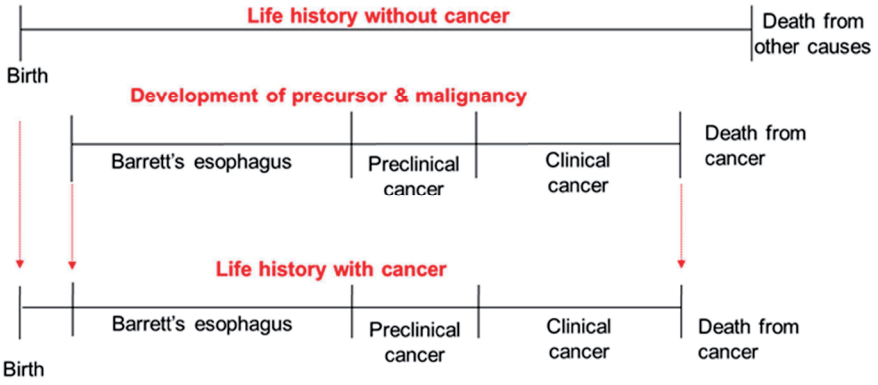

Figure A1| Modeling natural history into life history

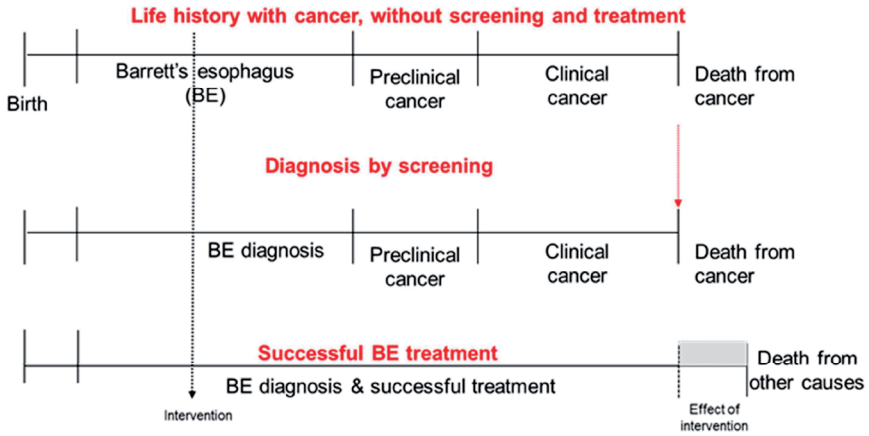

Figure A2| Modeling screening and treatment interventions into life history

removed by treatment. This results in a combined life history for EAC in the presence of interventions. BE is removed at the time of screening and this individual does not develop cancer because the precursor has been removed. Therefore the person dies from other causes and the effect of screening is the difference in life-years in between the simulation without intervention and the simulation with intervention. The effects of different intervention strategies can be compared by applying them to identical natural histories. If one is solely interested in modeling the natural history of disease, the screening part is not necessary.

MODEL QUANTIFICATION CHAPTER 3 "EXPLORING THE RECENT TREND IN ESOPHAGEAL ADENOCARCINOMA INCIDENCE AND MORTALITY USING COMPARATIVE SIMULATION MODELING"

Using microsimulation modeling we aimed to explain and project the increasing trend of EAC over time by modeling the driving effects on the natural history of EAC, using a secular trend model. In general, a combination of the BE incidence in the population and the progression rate from BE towards EAC are responsible for the EAC incidence in the total population, which is the main calibration target in the secular trend model. Calibrating our model to the U.S. EAC incidence between 1975 and 2009, there were a number of assumptions we made concerning the drivers of the increase and the effect on the natural history. We addressed the origin of the effects (age, period and birth cohort) and rate they would apply on (BE incidence and/or BE progression) according to expert opinion and current knowledge concerning risk factors in the field. For this analysis we developed a secular trend model, including age-, period-, and birth cohort effects.

Demography parameters

There are two types of demography parameters: birth tables and life tables. The life tables were derived from the life tables published by the National Center for Health Statistics.[27]

Natural history parameters

The average prevalence rate of GERD in the population is estimated to be around 20%[2-5]; therefore we have a fixed 20% of the total population that suffers from symptomatic GERD. The onset of BE was fitted per age group (i.e. this is a calibration parameter) and differs between individuals with and without GERD symptoms. We assume that 40% of total BE prevalence comes from individuals without and 60% from people with GERD symptoms (i.e. a relative risk of 6).

Secular trend modeling: age, cohort and period effects

We assumed that two mechanisms are responsible for the observed trend in EAC: the decrease in *Helicobacter Pylori* infection and the introduction of Proton Pump Inhibitors (PPI). We assumed that having *H. Pylori* infection is protective against BE and EAC. Based on Sonnenberg et al., we assumed that *H. Pylori* decreases with birth cohort since 1885. Consequently we modeled the disappearing *Helicobacter Pylori* infection effect as a birth cohort effect increasing the BE incidence rate and the rate of progression from BE to EAC (transition parameters). This birth cohort effect is modeled as a sigmoid function, in which we assume that the increase in rates occurs between birth

cohorts 1885 and 1985. We have restricted that half of the total birth cohort effect occurs between birth cohort 1910 and 1940. We have optimized the point at which the effect increases, *t*, the height of the increase, *h* (separate for BE incidence and transition parameters), and the slope of the increase, *s* (separate for BE incidence and transition parameters) for the sigmoid function $h / (1+exp(-s \cdot (x-t)))$. For PPI use, we assume that this has a protective effect against EAC development. Because PPI was introduced after a certain period of time, we modeled the protective effect of PPI as a sigmoid period effect. We have restricted the period effect between calendar years 1988–2030. For the period effect also the point at which the effect decreases *t*, the height of the effect *h* and the slope of the effect *s* is optimized for the sigmoid function $h / -(1+ exp(-s \cdot (x-t)))$. Age effects are modeled within the BE incidence, where the BE incidence rate is optimized for each ten-year age group.

Calibration process

The model is calibrated to fit several calibration targets in order to optimize the unknown natural history parameters: the EAC incidence from 1975-2009, and the BE to EAC progression rate of 0.18% between 1995-2010. The incidence of BE per 10-year age group, the birth cohort effects, the period effects, the sojourn times in BE ND, the transition rates of regression and progression in LGD and HGD and the sojourn times in the preclinical states were optimized in the calibration process.

Projection of the trend to 2030

The projection of the trend from 2009 to 2030 is a result of the birth cohort and period effects which are optimized to reach the EAC incidence from 1975 to 2009. The model estimates that the birth cohort effect plateaus around birth cohort 1945 for both males and females. As a consequence, EAC incidence plateaus after 2009 for age groups born after 1945 and still increases for older age groups. Overall, both males and females are predicted to experience an increasing trend after 2010. The estimated protective effect from PPI's in our model is estimated to be modest for both males and females, resulting in a minimal plateauing effect on EAC incidence.

MODEL QUANTIFICATION CHAPTER 4 "AN ACCURATE CANCER INCIDENCE IN BARRETT'S ESOPHAGUS: A BEST ESTIMATE USING PUBLISHED DATA AND MODELING"

For this analysis we developed two different models (perfect model, realistic model) varying in natural history assumptions. The natural history part simulates the development of EAC in the population. The current models used in this paper do not include

an increasing secular trend for the EAC increasing incidence over time. Because the focus of this paper is on effectiveness and efficiency, we decided that it could be best compared with the simulation of a cohort excluding secular trend effects before and after 2000-2009.

Demography parameters

There are two types of demography parameters: birth tables and life tables. The life tables were derived from the life tables published by the National Center for Health Statistics.[27]

Natural history parameters

The parameters for the natural history are directly estimated from data or fit to reference data, based on expert opinion, or calibrated to fit the model. The average prevalence rate of symptomatic GERD is around 20%[2-5]; therefore we have a fixed input parameter for which 20% of the total population suffers from symptomatic GERD.

The onset of BE was fitted per age group, which we call an optimized parameter. The parameter is relaxed and its final value results from the optimal calibrated model. Asymptomatic BE (no GERD symptoms) is a calibration target of the model, calibrated to be 40% of the total prevalence of BE in the model.[7, 8] The exponential scale parameter for the time from a preclinical state to clinical detection is restricted within the range of 2-9 years for each individual.[9, 10] When evaluating the whole simulated population, the average time from onset of preclinical cancer to the diagnosis of clini-

Appendix Table 1 |Estimation of LGD and HGD prevalence within the BE population at age 60-65

Author	Sample size	LGD prevalence	Rate	Sample size	HGD prevalence	Rate
Bonelli[1]	205	18		205	0	
Clark, Ireland, Peters, et al. [2]	70	8		70	3	
Conio [3]	177	4		177	3	
GOSPE [4]	69	6		69	1	
Hirota, Loughney, Lazas, et al. [5]	63	5		63	1	
Katz, Rothstein, Schned, et al. [6]	102	5		-	-	
Rex, Cummings, Shaw, et al. [7]	65	3		65	0	
Sharma, Weston, Morales, et al. [8]	177	17		177	3	
Sharma, Morales, Bhattacharyya, et al.	59	5		59	0	
Spechler, Robbins, Rubins, et al. [10]	115	4		-	-	
Weston, Krmpotich, Makdisi, et al. [11]	60	15		60	0	
Weston, Krmpotich, Cherian, et al. [12]	108	20		108	8	
Weston, Badr and Hassanein [13]	99	18		99	6	
Total	**1369**	**128**	**9.35%**	**1152**	**25**	**2.17%**

cal EAC is calibrated to be within the range of 45 years, which is a calibration target of the model. Using published studies we estimated the proportion of LGD and HGD in a BE population (table 1), being 2.2% HGD, 9.4% LGD, and 88.4% non-dysplastic BE, which were used as calibration targets in the models. Furthermore, the EAC incidence is calibrated to the total SEER esophageal cancer incidence rates from 2000 to 2009. The assumption that differs between the models is the natural history parameter of the yearly progression rate from BE (ND+LGD) to EAC. The realistic model assumed 0.18% progression rate with partial surveillance and adherence with realistic diagnostic inaccuracy endoscopies. The realistic model incorporated clinical EAC and detected EAC (EAC diagnosed at surveillance endoscopy).

Surveillance parameters

We have used a one-time screening examination at age 65 in the calibration, in which every person is categorized as having BE ND or BE LGD, incorporating false-positive ND and LGD patients. 38% (52%) of the ND(LGD) diagnosed patients will go to surveillance, getting their next endoscopy after 2 (1.4) years. At each endoscopy the patient will be categorized into a dysplastic state or cancer, and can be detected. After the first surveillance endoscopy, 46% of the patients will not adhere to the next endoscopy, and will not be offered any subsequent surveillance in our model. When they develop symptomatic EAC, the patient will be diagnosed with clinical EAC. The remaining patients in the surveillance cohort will be offered surveillance every 3 years (ND), 1 year (LGD) and 3 months (HGD) until cancer detection or death. The stage-specific survival of patients with surveillance-detected cancer is assumed to be the same as the survival of patients with cancers clinically diagnosed in the same stage.

Calibration Process

The Erasmus/UW-EAC model is calibrated to fit several calibration targets in order to optimize the unknown natural history parameters. For all three models, the incidence of BE per 10-year age group, the sojourn times in BE ND, the transition rates of regression and progression in LGD and HGD and the sojourn times in the preclinical states have to be optimized (table 2).

During the optimization the Pearson chi-square Goodness of fit function was minimized on the basis of the number of observed and expected rates. The deviation of each of the four main calibration targets (SEER-EAC incidence rates per age group, annual progression rate from BE to EAC, proportions of dysplasia and average preclinical sojourn time) were summed to calculate the overall Goodness of fit of the model given a certain set of parameters. The search for new parameters was performed following the Nelder-Mead simplex method.

Appendix Table 2| Main natural history assumptions and results of the Erasmus/UW-EAC realistic model

Model parameter/value	Value in realistic model	Source	Parameter characteristic*
Symptomatic GERD prevalence	20% of the total population	Prevalence studies 14-17	Fixed Input
BE from symptomatic GERD population	60% of total BE is from symptomatic GERD population	Published estimates 4, 18	Fixed Input
BE prevalence age 60-64	1.4%	BE onset per 10 year age group	Optimized parameter
Percentage of LGD in total BE at age 60-65	8.2%	Derived from published studies	Calibration target: 9.4%
Percentage of HGD in total BE at age 60-65	1.2%	Derived from published studies	Calibration target: 2.2%
Annual progression rate from diagnosed BE (ND+LGD) to clinical EAC	0.07%		Optimized parameter
Annual progression rate from diagnosed BE (ND+LGD) to clinical and detected EAC	0.18%	*Published estimates 19-24. Definition: 5 year follow up from age 65*	Calibration target: 0.18% in realistic model
Average sojourn time from preclinical cancer to clinical cancer, given transition	5.0	Published estimates 25, 26	Calibration target: 4-5 year
Average time in BE to next transition	6.7	Exponential sojourn times: BE ND to LGD	Optimized parameter
Average time in LGD to next transition	1.0	LGD to BE ND or HGD	
Average time in HGD to next transition	1.1	HGD to LGD or Preclinical Localized	
Regression transition probability		Regression transition probability	Optimized parameter
P(LGD to ND BE)	88%		
P(HGD to LGD)	15%		

*Fixed input: the parameter is defined as a fixed input of the model, Optimized parameter: the parameter is relaxed and is optimized during calibration of the model, the value is a result of the model; Calibration target: the model is calibrated to fit the fixed calibration targets as good as possible. Model is furthermore calibrated on the SEER-9 EAC incidence data from 2000-2009 for all males. GERD: Gastro-esophageal reflux disease; BE: Barrett's esophagus; ND: No dysplasia; LGD: Low-grade dysplasia; HGD: High-grade dysplasia; EAC: Esophageal adenocarcinoma

The regression and progression transition probabilities are highly correlated with the progression rate from BE towards EAC, which hampers the ability to identify these parameters. Although there are a large number of feasible parameter solutions, there is one optimal parameter solution resulting in the best fit which can be found in the calibration process.[11]

MODEL QUANTIFICATION CHAPTER 6 "UNCERTAINTY IN BARRETT'S ESOPHAGUS PROGRESSION RATES TO ESOPHAGEAL ADENOCARCINOMA: IMPACT ON EFFICIENCY OF SCREENING AND TREATMENT"

For this analysis we developed three different models varying in model structure and natural history assumptions. To vary the underlying structural assumptions of the model, we developed two options for the natural history part, the first one being the progression model and the second one being the regression model. The current models used in this paper do not include an increasing secular trend for the EAC increasing incidence over time. Because the focus of this paper is on effectiveness and efficiency, we decided that it could be best compared with the simulation of a cohort excluding secular trend effects before and after 1998-2009.

Progression model

We assume that EAC develops through precursor Barrett's esophagus (BE). For each individual in the simulated population a personal risk index is generated. A minority of the population has symptomatic gastro-esophageal reflux disease (GERD), giving them a higher risk of developing BE during their lifetime. The development of BE is generated according to this personal risk index and an age specific incidence of onset. The sequence from the onset of BE to EAC diagnosis is governed by sojourn times between the different states. BE starts in a state with no dysplasia (ND), after which dysplasia can develop. Two states of dysplasia are defined: low-grade (LGD) and high-grade dysplasia (HGD). From high-grade dysplasia, malignant cells can arise that can transform from this stage to preclinical localized EAC, which can sequentially progress into regional and distant preclinical EAC. In each of these three states, there is a probability of the cancer being diagnosed. The sojourn times between these described states are exponentially distributed, and in some states (BE ND, BE LGD and BE HGD) age dependent. Because most sojourn times extend beyond the demography-generated age of death from other causes, only a small proportion of the population develops EAC from BE. The survival after clinical diagnosis depends on the cancer stage and the year of diagnosis (period effect reflecting survival improvement over time).

Regression model

In the regression model an additional possibility to transit between states is added. BE still starts with no dysplasia, after which LGD and HGD can develop. From HGD, malignant cells can arise with can transform this stage to preclinical localized EAC. In the regression model, however, there is a possibility that regression from HGD to LGD and from LGD to ND occurs. The probability to regress or progress is dependent on a transition rate matrix and is therefore also influenced by the sojourn time. The probability of regression, progression and the according sojourn times can be calculated as stated in the general model overview.

Screening part

During screening BE, with or without dysplasia, is removed by a hypothetical treatment. This results in a combined life history for EAC in the presence of screening. BE is removed at the time of screening and this individual does not develop cancer because the precursor has been removed. Therefore the person dies from other causes and the effect of screening is the difference in life-years in between the simulation without screening and the simulation with screening.

Demography parameters

There are two types of demography parameters: birth tables and life tables. The life tables were derived from the life tables published by the National Center for Health Statistics.[27]

Natural history parameters

Different from the model described in chapter 4, the EAC incidence is calibrated to the total SEER esophageal cancer incidence rates from 1998 to 2009.

There are two assumptions that differ between the models. The first assumption differs in the natural history parameter of the yearly progression rate from BE (ND+LGD) to EAC, which was assumed 0.12% or 0.42% and set as a different calibration target in the models. The second assumption differs in the used model structure for the possibility to regress. We optimized the regression probabilities for the transitions from LGD to ND and from HGD to LGD to fit the calibration targets.

Intervention parameters

We have used a one-time perfect screening examination at age 65 in the simulation, in which every person is correctly categorized as having no BE, BE, LGD, HGD and EAC. Perfect treatment is modeled to manage patients depending on their treatment strategy. The first strategy includes treatment for all patients in whom BE is diagnosed with and without dysplasia; the second strategy treats only dysplastic patients (LGD and

Appendix Table 3 | Natural history assumptions and results for the three versions of the Erasmus/UW-EAC model

Model parameter/value	Value low- progression model	Value high- progression model	Value regression model	Source	Parameter characteristic*
Symptomatic GERD prevalence	20% of the total population	20% of the total population	20% of the total population	Prevalence studies 14-17	Fixed input
BE from symptomatic GERD population	60% of total BE is from symptomatic GERD population	60% of total BE is from symptomatic GERD population	60% of total BE is from symptomatic GERD population	Published estimates 4, 18	Fixed Input
Sojourn times preclinical cancer (years)	2-9	2-9	2-9	Published estimates 25, 26	Fixed Input
BE prevalence age 60-64†	2.9%	1.3%	3.3%	Optimized BE onset per 10 year age group	Optimized parameter
Percentage of LGD in total BE at age 60-65	8.3%	17.3%	10.8%	Derived from published studies	Calibration target: 9.4%
Percentage of HGD in total BE at age 60-65	2.5%	2.6%	1.6%	Derived from published studies	Calibration target: 2.2%
Annual progression rate from BE (ND+LGD) to EAC	0.12%	0.42%	0.12%	*Published meta-analysis 19-23, 28 Definition: 5 year follow up from age 65*	Calibration target: 0.12%, 0.42% and 0.12% respectively
Average time BE to LGD (years)‡	16.0	12.2	10.7	Optimized exponential sojourn times: BE to LGD	Optimized parameter
Average time LGD to HGD (years)	6.4	6.0	2.7	LGD to HGD	
Average time HGD to Preclinical Localized (years)	2.7	1.2	1.8	HGD to Preclinical Localized	
Average sojourn time to preclinical cancer (years)	4.7	4.8	4.7	Published estimates 25, 26	Calibration target: 4-5 years
Regression transition probability				Optimized regression transition probability	Optimized parameter
P(LGD to ND)			76%		
P(HGD to LGD)	n.a.	n.a.	15%		

n.a.: Not applicable; *Fixed input: the parameter is defined as a fixed input of the model, Optimized parameter: the parameter is relaxed and is optimized during calibration of the model, the value is a result of the model; Calibration target: the model is calibrated to fit the fixed calibration targets as good as possible; †: Figure A1 shows the BE and dysplasia prevalence of the models more specifically per age group; ‡The average duration between one state to the next state.

HGD); the final strategy treats only patients with HGD When treatment is performed it is assumed the person will never develop BE again and will die of other causes than EAC. The stage-specific survival of patients with screen-detected cancer is assumed to be the same as the survival of patients with cancers clinically diagnosed in the same stage.

Calibration process

For all three models, the incidence of BE per 10-year age group, the sojourn times in BE ND and the sojourn times in the preclinical states have to be optimized. In the progression models the sojourn times in LGD and HGD must also be included in the parameters to optimize, while in the regression model the transition rates of regression and progression in LGD and HGD must be included (table 3).

MODEL QUANTIFICATION CHAPTER 7 "THE IMPACT OF ENDOSCOPIC ERADICATION FOR BARRETT'S ESOPHAGUS ON ESOPHAGEAL ADENOCARCINOMA INCIDENCE AND MORTALITY: A COMPARATIVE MODELING ANALYSIS"

For this study, additional modules for modeling the characteristics of endoscopic ablation were inserted to the model. For endoscopic ablation, the outcome of the initial two-year endoscopic treatment for each individual patient is randomly drawn at the start of the treatment. In case of treatment failure, the patient remains in endoscopic surveillance at an interval in accordance to their pre-ablative dysplastic grade. In case of treatment success, the patient will be in complete eradication of dysplasia with persistent metaplasia (CE-D) or complete eradication of dysplasia and intestinal metaplasia (CE-IM) after two years. In the first case, we assume that the patient is in the BE non-dysplastic (ND) phase having the same assumptions as our natural history model. In the latter case, the patient stays in the CE-IM state for sojourn time randomly selected from an exponential distribution. If the patient transits to the next state (recurrence/progression), they will immediately transit to the state of histological recurrence. Furthermore, the patient will have a higher probability of recurrence in a higher state if the patient would have developed EAC in the natural history model. After generating this new life-history for this individual, the model simulated the surveillance according to the inputs after RFA. Surveillance can detect recurrent stages of BE and dysplasia and EAC. In the case of recurrent stages of BE, a new endoscopic ablation sequence is inserted, and the process as described is started again; generating new life histories for the patient. In this new life history the durations and probability of developing EAC are set. After determining this new life history, surveillance is inserted in the model ac-

cording to post-RFA surveillance intervals described in the common input parameters. A maximum number of three touch ups is allowed.

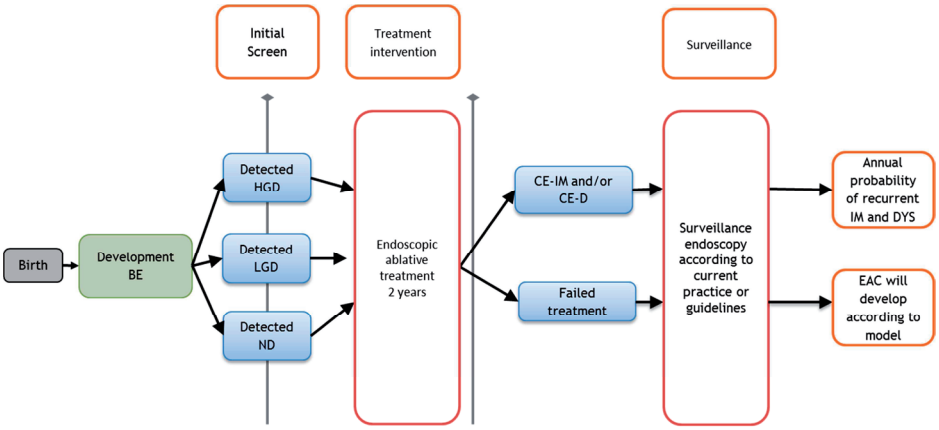

Figure A3| Simulation of Barrett's esophagus treatment and surveillance

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p.s. Yes! Mijn werkstuk is eindelijk af! Daarnaast kan ik eindelijk in één zin uitleggen wat ik doe zonder dat mensen water zien branden (toch?).

CURRICULUM VITAE

Sonja Kroep was born on the 23rd of December 1985, in Bleiswijk, the Netherlands. In 2004, she completed her secondary education at the Melanchton College Rotterdam, where after she started studying 'Econometrics and Management Science' at the Erasmus University Rotterdam. She obtained her Master of Science degree in 2011 with a specialization in 'Operations Research and Quantitative Logistics'. She wrote a Master's thesis about the expectation patterns and planning possibilities of the Post Anesthesia Care Unit. From 2010 to 2011 she worked as a business management consultant at the Operation Room Department, and as a business intelligence consultant at the Business Intelligence Center of the Erasmus Medical Center. Since 2011, she is employed as a junior researcher at the department of Public Health at the Erasmus University Medical Center in Rotterdam, where she developed the microsimulation model Erasmus/UW-EAC. An important part of the research is performed within the Cancer Intervention and Surveillance Modeling Network (CISNET), which is an international consortium of NCI-sponsored investigators that use statistical modeling to improve the understanding of the natural history and progression of cancer and to evaluate the effect of cancer control interventions. The research findings on the natural history of EAC and the impact and possibilities of early detection of EAC are presented in this thesis.

PUBLICATIONS

Kroep S, Lansdorp-Vogelaar I, Rubenstein JH, Lemmens VE, van Heijningen EB, Aragonés N, van Ballegooijen M, Inadomi JM. Comparing trends in esophageal adenocarcinoma incidence and lifestyle factors between the United States, Spain, and the Netherlands. Am J Gastroenterol. 2014 Mar;109(3):336-43.

Kong CY, **Kroep S,** Curtius K, Hazelton WD, Jeon J, Meza R, Heberle CR, Miller MC, Choi SE, Lansdorp-Vogelaar I, van Ballegooijen M, Feuer EJ, Inadomi JM, Hur C, Luebeck EG. Exploring the recent trend in esophageal adenocarcinoma incidence and mortality using comparative simulation modeling. Cancer Epidemiol Biomarkers Prev. 2014 Jun;23(6):997-1006.

Kroep S, Lansdorp-Vogelaar I, van der Steen A, Inadomi JM, van Ballegooijen M. The Impact of Uncertainty in Barrett's Esophagus Progression Rates on Hypothetical Screening and Treatment Decisions. Med Decis Making. 2014 Oct 2.

Kroep S, Lansdorp-Vogelaar I, Rubenstein JH, de Koning HJ, Meester R, Inadomi JM, van Ballegooijen M. An Accurate Cancer Incidence In Barrett's Esophagus: A Best Estimate Using Published Data And Modeling. Gastroenterology. 2015 Apr 29.

PHD PORTFOLIO

Summary of PhD training and teaching

Name PhD student: Sonja Kroep
Erasmus MC Department: Public Health
PhD period: 2011-2015
Promotor: Prof.dr. H.J. de Koning
Supervisor: Dr. I. Lansdorp-Vogelaar

1. PhD training

	Year	Workload (ECTS)
General courses		
Specific courses Nihes		
Social Epidemiology	Summer 2011, Rotterdam	1.4
Cancer epidemiology	Spring 2012, Amsterdam	1.4
Bayesian Statistics	Spring 2012, Rotterdam	1.4
Planning of Screening and Surveillance	Spring 2012, Rotterdam	1.4
Survival Analysis	Summer 2012, Rotterdam	1.9
Prognostic factors	Summer 2013, Rotterdam	0.7
Seminars and workshops		
Seminars at the department of Public Health, Erasmus MC, Rotterdam	2011-2015, Rotterdam	5.7
Minicursus Methodologie van Patiëntgebonden Onderzoek en Voorbereiding van Subsidieaanvragen	Spring 2012, Rotterdam	0.1
Biostatistics: Variable Selection Minicourse	Spring 2012, Rotterdam	0.1
Methodology club, MGZ, Erasmus MC Rotterdam	2011-2015	1.0
Society of medical decision making, Probabilistic Decision Analytic Models in Excel	Autumn 2014	0.1
Society of medical decision making, Individual-Level State-Transition Modeling Using Excel and VBA	Autumn 2014	0.1
Presentations		
Presentations at Cancer Intervention and Surveillance Modeling Network (CISNET) meetings, National Cancer Institute, USA	2011-2015	6.0
Oral presentation. Research meeting at the department of Public Health, Erasmus MC, Rotterdam	Autumn 2013	0.6
Oral presentation, Department of gastroenterology, University of Washington, Seattle, USA	Spring 2013	0.6
Society of medical decision making, oral presentation, Miami, USA	Autumn 2014	0.6
(Inter)national conferences		
Amsterdam Life Endoscopy, visit	Winter, 2012	0.3

UEGW, Visit and poster presentation, Amsterdam	Winter, 2012	0.6
Society of medical decision making, Visit and poster presentation, Phoenix, USA	Winter, 2012	0.6
OESO, Visit and poster presentation, Paris, France	Summer 2013	0.6
Digestive Disease Week, visit, Chicago, USA	Spring 2014	0.3
Society of medical decision making, Visit and two poster presentations for Lee Lusted Moderated Poster Session	Autumn 2014	0.6
Other International traineeship, Seattle, USA	Spring 2014	5.1
Peer reviews for PLOS one	2014	0.5

2. Teaching

Lecture assistant Planning of Screening and Surveillance	Spring 2014	0.1
Supervising intern	Summer 2014	0.3
Checking Methodology essays medical students, Erasmus University Rotterdam	Winter, 2015	0.7