Computational modelling suggests that Barrett’s oesophageal mucosa may be the precursor of all oesophageal adenocarcinomas

Kit Curtius, Joel H Rubenstein, Amitabh Chak, John M Inadomi

ABSTRACT

Objective Barrett’s oesophagus (BE) is a known precursor to oesophageal adenocarcinoma (OAC) but current clinical data have not been consolidated to address whether BE is the origin of all incident OAC, which would reinforce evidence for BE screening efforts. We aimed to answer whether all expected prevalent BE, diagnosed and undiagnosed, could account for all incident OACs in the US cancer registry data.

Design We used a multiscale computational model of OAC that includes the evolutionary process from normal oesophagus through BE in individuals from the US population. The model was previously calibrated to fit Surveillance, Epidemiology and End Results cancer incidence curves. Here, we also utilised age-specific and sex-specific US census data for numbers at-risk. The primary outcome for model validation was the expected number of OAC cases for a given calendar year. Secondary outcomes included the comparisons of resulting model-predicted prevalence of BE and BE-to-OAC progression to the observed prevalence and progression rates.

Results The model estimated the total number of OAC cases from BE in 2010 was 9970 (95% CI: 9140 to 11 980), which recapitulates nearly all OAC cases from population data. The model simultaneously predicted 8%–9% BE prevalence in high-risk males age 45–55, and 0.1%–0.2% non-dysplastic BE-to-OAC annual progression in males, consistent with clinical studies.

Conclusion There are likely few additional OAC cases arising in the US population outside those expected from individuals with BE. Effective screening of high-risk patients could capture the majority of population destined for OAC progression and potentially decrease mortality through early detection and curative removal of small (pre)cancers during surveillance.

INTRODUCTION

Oesophageal adenocarcinoma (OAC) is typically diagnosed when a patient presents with symptoms such as dysphagia. Unfortunately, the majority of these patients do not live past the first year of their diagnosis because by the time dysphagia develops, metastatic cancer is already present. In order to prevent this cancer or detect it at an earlier, more treatable stage, efforts are now made to identify patients with Barrett’s oesophagus (BE), the only known precursor to OAC. Identified BE patients are believed to have a 40–50-fold higher annual incidence of OAC than the general population. Metaplastic BE progresses through dysplasia to cancer. Advances in endoscopic eradication therapy for dysplastic BE discovered during surveillance of BE can now prevent cancer. However, most cancers arise in patients without previously diagnosed BE suggesting either inadequate screening strategies or, as a recent study proposes, the possible existence of a pathway independent from the BE pathway. In this study, we seek to answer a simple
question about the unseen origins of OAC: does overall OAC incidence reflect the number of cancers that would be expected to arise only from prevalent BE? In other words, do any OAC cases remain unaccounted for that ergo did not arise from the typical Barrett’s precursor pathway? The answer to this question will importantly guide research and public health efforts. If BE is the major or only precursor of OAC, then investigators should continue to focus on improving BE detection. If BE is not the major precursor of OAC, then research needs to focus on identifying alternative pathways and BE screening programmes will have limited impact on prevention and early detection of OAC.

In reality, very few individuals who have BE are ever offered an upper endoscopy, and therefore most BE remains asymptomatic and undiagnosed. Patients with gastro-oesophageal reflux disease (GERD) are technically the only subpopulation of the general public typically recommended BE screening because it is believed they have a 5-fold relative risk (RR) of developing long segment BE, yet even so only about 10% of GERD patients will receive an endoscopy. This indicates *underscreening*, likely because patients either do not complain of their GERD symptoms, they respond adequately to medical therapy, or were otherwise not deemed suitable high-risk by their physician to warrant an esophagogastroduodenoscopy. Nonetheless, the prevalence of BE in the general population is 1%–2%, whether diagnosed or not, and this is likely considerably higher in certain at-risk groups in the USA. The main concern is that the average rate to develop OAC in these patients is low—around 0.3% per year. Therefore, the majority of endoscopies are futile because patients either do not complain of their GERD symptoms, they respond adequately to medical therapy, or were otherwise not deemed suitable high-risk by their physician to warrant an esophagogastroduodenoscopy. Nonetheless, the prevalence of BE in the general population is 1%–2%, whether diagnosed or not, and this is likely considerably higher in certain at-risk groups in the USA. The main concern is that the average rate to develop OAC in these patients is low—around 0.3% per year. Therefore, the majority of endoscopies are futile in finding OAC. We aimed to answer whether all prevalent BE expected, diagnosed and undiagnosed in the US population, could account for all the incident OACs expected as progression rates would imply, to fit the national cancer registry data.

**METHODS**

The question above is too complex to answer on the ‘back of an envelope’ because published *average* rates of progression are dependent on age, birth cohort and calendar year. In particular for OAC, age-specific incidence rates vary drastically between men and women. This complexity of timescales involved in normal to premalignant BE to OAC progression has necessitated the creation of quantitative models that analyse cancer incidence rates, and project these trends into the future for public health risk assessments and planning. Models also quantify the potential impact of progression rates measured in clinical studies on hypothesetical intervention and surveillance scheduling in efficacy and cost-effectiveness studies. Such models allow us to perform quantitative, comparative analyses on the benefits versus harms of proposed screening and surveillance protocols against watch-and-wait strategies; these simply cannot be done heuristically due to the complex nature of cancer evolution.

In this study, we model both the onset of BE and the progression of BE to OAC. As a brief background, the multistage clonal expansion model for OAC (herein referred to as the MSCE-OAC model, but also referred to as the MSCE-EAC model elsewhere) is a stochastic model for development of OAC during patient lifetime that includes probabilities of developing BE at various ages, followed by initiation of dysplastic and malignant cell clones in BE with parameters for growth and progression of individual clones to cancer (figure 1). The *inputs* only include GERD prevalence (calibrated to age-specific and sex-specific estimates) and OAC age-specific and sex-specific incidence curves provided by Surveillance, Epidemiology and End Results (SEER) registry. The BE prevalence and neoplastic progression rates are calibrated to fit those inputs, that is, they are not based on observed BE prevalence nor neoplastic progression rates from empiric studies. Briefly, the model includes a GERD-stratified risk curve to develop BE, which is modelled as an age-dependent rate of exponential BE onset each calendar year with an unknown baseline parameter \( \nu_p \). The patient-specific BE lengths can vary, derived from a Beta distribution with general population mean length set to 2–3 cm. Beyond \( \nu_p \), the baseline constant rate for BE onset, the additional model parameters govern the evolutionary dynamics for dysplastic and malignant growth and OAC detection. The model parameters have been previously calibrated such that the resulting hazard functions fit to OAC age-specific and sex-specific incidence curves provided by SEER registry. We found during rigorous model selection with likelihood

![Figure 1](https://gut.bmj.com/content/70/14/1435-1440.10.1136/gutjnl-2020-321598)

**Figure 1** The stochastic, multiscale model for OAC development (MSCE-OAC) includes conversion from normal squamous epithelium in the oesophagus to BE metaplasia with BE onset rate \( \nu(t) \), which is a function of a baseline rate \( \nu_0 \) and age-dependent prevalence of GERD \( \rho(d) \) (see Methods for details). Two-hit processes with rates \( \mu_0, \mu_1 \), initiate a premalignancy (eg, inactivation of tumour suppressor gene \( TP53 \) in nondysplastic BE due to mutation/copy number alteration in a BE daughter cell creates first cell of a high grade dysplasia lesion). Premalignant cell growth rates are defined as \( \alpha_p = \text{divison rate}, \beta_p = \text{death/differetiation rate per year} \). Malignant transformation with rate \( \rho \) creates the first cell of a preclinical clone that can grow with rates \( \alpha_M = \text{division rate}, \beta_M = \text{death/differetiation rate per year} \). Size-based probability \( \rho \) for detection of preclinical malignant clone can lead to patient-specific time of incident OAC. BE, Barrett’s oesophagus; OAC, oesophageal adenocarcinoma; GERD, gastro-oesophageal reflux disease; MSCE-OAC, multistage clonal expansion for oesophageal adenocarcinoma.
of whom were born around 1950
dysplastic BE to published estimates.
Research Initiative (CORI) for more than 150
which included endoscopic reports from the Clinical Outcomes
and on cost-
the BE prevalence and the resulting BE-
online supplemental material for equation details), along with
patient-
specific and sex-
model to estimate the number of OAC cases using the US age-
BE the precursor of all OAC? T o do this, we first applied the
elucidate an answer to our general public health question—’Is
OAC (see
the expected number of OAC cases in an at-
fit the incidence data, robust to sensitivity analyses (figure 2).
With these fits, the model outputs used for this study include
expected number of OAC cases in at-risk population
at a given year calculated using the hazard function $h_{oac}$ (see
influence of patient-specific molecular BE dwell time on future OAC risk,
and on cost-effectiveness of endoscopic eradication therapy for
certain BE risk groups during surveillance.15
In our original
studies on sensitivity of biopsy sampling tech-
niques for detection of small dysplastic lesions,14 on influence of
patient-specific molecular BE dwell time on future OAC risk,19
and on cost-effectiveness of endoscopic eradication therapy for
BE risk groups, and on the BE-to-OAC progression rates (predicted specific to age, sex and birth cohort).
This model has been used and improved in comparative analyses within the NCI Cancer Intervention and Surveillance Modelling Network consortia for the past 9 years, which has enabled numerous studies on sensitivity of biopsy sampling tech-
niques for detection of small dysplastic lesions,14 on influence of
BE prevalence and the resulting BE-to-OAC progression rates (predicted specific to age, sex and birth cohort).

RESULTS

First, Vaughan and Fitzgerald estimated that the newly diagnosed number of cases for ages greater than 40 to be roughly around
10,000 total in the USA every year based on data from 2010
with an average OAC incidence rate across all age groups.7
With the Markov model framework, we can analytically compute
the OAC hazard function and estimate the expected number of
diagnosed OAC cases by age and year separately for men and
women when considering also population data. As a starting
point using 2010 census person-year data,20 the model predicts
that about 2.2 million adults had prevalent BE in 2010, which is
around 1.6% of the general US population over age 40. Then,
for age groups greater than 40 in both sexes of all races, our
single-age calibrated model estimated that the expected number
of new OAC cases diagnosed in 2010 was equal to 9,970 (95% CI: 9,140 to 11,980).

We also computed the analogous estimate for OAC cases using incidence rates quoted directly from the SEER registry for ages
40–90, which was found to be 9,400 OAC cases total in 2010.12
Thus, the estimate generated by our computational model of
progression from BE to OAC is closely consistent with the total
number of OAC cases reported in SEER, which also aligns with
the 10K incident cases quoted by Vaughn and Fitzgerald.5
The model therefore suggests that over 90% of OAC cases are attrib-
utable to BE.

Second, we considered what the model simultaneously
predicted for BE prevalence and BE-to-OAC progression rates
in order to achieve the expected ~10K cases. Breaking down
the contributions of the 2.2 million total BE patients estimated
above, the model predicted BE prevalence to be 1.9%–2.4% in
men and 0.4%–0.5% in women in the general US population
ages 45–55 in 2010 (figure 3A). These predictions concur with
best estimates5,6 and influence the total OAC cases predicted
by the multistage model. To further explore implications for
high-risk patients, we note that the model predicted a BE prev-
ance of 7.9%–9.3% in US men with symptomatic GERD who
are cancer-free ages 45–55 in 2010 when the RR of BE vs non-
GERD individuals is assumed to be RR=5 (figure 3B). This is
also consistent with the estimate of 8% provided by Vaughan and Fitzgerald\(^1\) for prevalence of cancer-free BE diagnoses among GERD patients who undergo an upper endoscopy. Further, the model’s predicted age-specific BE prevalence curves by sex were consistent with previous results on BE prevalence from the CORI study\(^20\) (figure 3A). Compared with our model results and 8% quoted above\(^1\) for high-risk groups, the CORI study independently found similar BE prevalence in white men with GERD of 6.3% for ages 40–49 and 9.3% for ages 50–59 (figure 3B). To account for likely heterogenous RR of developing BE in GERD populations based on symptom onset age, BE length and other factors,\(^4\)\(^–\)\(^22\)\(^–\)\(^26\) we also considered a range of fixed values (RR=2–6) and found age-specific trends broadly consistent to overall BE prevalence results in CORI. Observed BE prevalence in white women undergoing screening was less precise in the CORI study data yet still coincided with our predictions for women (figure 3B).

In a sensitivity analysis, we also found these results to be robust to varying GERD prevalence in the model input for men and women in the population (see online supplemental material and online supplemental figure S1). When assuming smaller values of RR that lead to reduced BE prevalence in the GERD subpopulations for both sexes (see online supplemental material for details, online supplemental figure S2), the model still predicts that the majority of expected OACs (over 90%) develop in BE patients.

Finally, we previously found using this model that, for individuals born after 1940, the range of progression rates from BE-to-OAC was 0.10%–0.20% for men, and this was about twice as high as we found for women.\(^13\) These are plausibly low rates compared with current best estimates.\(^11\)\(^\)\(^–\)\(^27\) Taken together, these secondary outcomes support the plausibility of our model’s predictions for numbers of OAC cases from BE annually.

The modelling results above imply that, even in the most conservative probability estimates, less than 10% of all annual OAC cases are unaccounted for beyond those expected to arise from BE. If there were a more significant alternate non-BE pathway than these numbers imply, then this model (which does not include a non-BE pathway) would have estimated either a much lower predicted population incidence of OAC than what was observed in SEER or shown greater inconsistencies with BE studies. In the latter case, the model would have estimated a greater prevalence of BE than what has been observed, and/or a greater rate of neoplastic progression among non-dysplastic BE than observed.

**DISCUSSION**

Based on the published epidemiology of BE and OAC, our analysis suggests that a major alternative non-BE pathway to OAC is an unlikely scenario. The existence of such an alternative pathway was suggested by a retrospective analysis of macroscopic reports of OAC specimens diagnosed without BE in two cohorts from the USA and UK by Sawas and colleagues; however, their study conclusions remain speculative due to some important limitations including (1) a lack of longitudinally followed cases to OAC from non-BE patient oesophageal tissue and (2) the plausibility that small BE segments were completely overtaken by malignant expansions and thus were unmeasurable at cancer diagnosis.\(^7\)\(^0\) Moreover, our result that BE is the main origin of OAC does not necessarily refute the existence of differing phenotypes for OAC—the finding that the presence of BE was associated with better survival could plausibly be explained by the theory that more aggressive cancers are likely to replace the precursor BE more readily than less aggressive cancers. The stochastic nature of our model allows for variation...
in progression across a population and we explored a wide range of parameter values for rates defining the stochastic process from birth to clinical OAC and reached similar results, but there is still ultimately some uncertainty.

Indeed, genetic and epigenetic analyses have also consistently shown BE and OAC to be very similar,28–31 and one study that sought genomic differences between adenocarcinomas with and without BE failed to reveal molecular differences between the two.52 Nonetheless, this is fortunate news that, with adequate uptake, screening for BE by upper endoscopy or minimally invasive non-endoscopic technologies16–33 could potentially identify and enrol all patients who are at risk for developing OAC into a surveillance programme.

Although the overall progression to OAC is low in patients diagnosed with BE, for those selected BE patients who have high grade dysplasia and/or early OAC detected during surveillance, effective treatment can save lives. In this way, our analysis reinforces the primary goal in BE screening for OAC prevention—that effective surveillance of the entire BE population could potentially prevent the majority of mortality caused by OAC in the general population. Further, by mathematically analysing the time-dependent nature of cumulative risk of BE in GERD patients, we can also use our multistage model framework to improve identification of at-risk populations by optimising the timing of initial screening recommended for BE in symptomatic GERD.34 Although current intensive ‘one-size-fits-all’ surveillance strategies35–40 would lead to high costs for those over-diagnosed BE screen cases and surveillance strategies clearly need to improve, we conclude that there is a strong rationale for screening for BE to reduce OAC mortality.

**Author affiliations**
1Centre for Genomics and Computational Biology, Barts Cancer Institute, School of Medicine and Dentistry, Queen Mary University of London, London, London, UK
2Division of Biomedical Informatics, Department of Medicine, University of California San Diego, La Jolla, California, USA
3Division of Gastroenterology, University of Michigan, Ann Arbor, Michigan, USA
4Center for Clinical Management Research, Ann Arbor Veterans Affairs Medical Center, Ann Arbor, Michigan, USA
5Division of Gastroenterology and Liver Disease, University Hospitals Cleveland Medical Center, Case Western Reserve University School of Medicine, Cleveland, Ohio, USA
6Department of Medicine, University of Utah School of Medicine, Salt Lake City, Utah, USA

**Twitter** Kit Curtius @yosoykit

**Acknowledgements** The authors thank the NIDDK Clinical Outcomes Research Initiative (CORI) for access to endoscopy data.

**Contributors** KC: statistical analysis; obtained funding; JHR: acquisition of data; analysis and interpretation of data; drafting of the manuscript; critical revision of the manuscript for important intellectual content; KC, AC and JMI: study concept and design; acquisition of data; analysis and interpretation of data; drafting of the manuscript; critical revision of the manuscript for important intellectual content; JMI: obtained funding.

**Funding** This work was supported by funding from NIH grants CINET U01 CA152926, U01 CA199336 (JM, KC and JHR), K24 DK080941 (JMI and KC) and a UKRI Rutherford Fund Fellowship (KC). JHR is also supported by NIH grant U54 CA163059 (BETREN). AC is supported by NIH grants U54 CA163060 and P50 CA150964.

**Competing interests** KC, JHR and JMI declare no potential conflicts of interest. AC has founders shares and stock options in LucidRx, serves as a consultant to LucidRx, has sponsored research with LucidRx and has a royalty interest in patents licensed to LucidRx. He is also a consultant for Intercar Diagnostics and receives research support from C2 Therapeutics/Pentax.

**Patient consent for publication** Not required.

**Provenance and peer review** Not commissioned; externally peer reviewed.

**Data availability statement** All data relevant to the study are included in the article or uploaded as Supplementary material. All data used in our analysis are publicly available. CORI data can be accessed through application with ethical approval to NIDDK (https://niddkrepository.org/studies/cori/). All equations are provided either in Figures and Supplementary material or were previously published along with model parameters. Code to solve equations was developed in R (V 3.6.1). Computational scripts are available at: github.com/yosoykit/BETRNET_Results

**Supplemental material** This content has been supplied by the author(s). It has not been vetted by BMJ Publishing Group Limited (BMJ) and may not have been peer-reviewed. Any opinions or recommendations discussed are solely those of the author(s) and are not endorsed by BMJ. BMJ disclaims all liability and responsibility arising from any reliance placed on the content. Where the content includes any translated material, BMJ does not warrant the accuracy and reliability of the translations (including but not limited to local regulations, clinical guidelines, terminology, drug names and drug dosages), and is not responsible for any error and/or omissions arising from translation and adaptation or otherwise.

**Open access** This is an open access article distributed in accordance with the Creative Commons Attribution 4.0 Unported (CC BY 4.0) license, which permits others to copy, redistribute, remix, transform and build upon this work for any purpose, provided the original work is properly cited, a link to the license is given, and indication of whether changes were made. See: https://creativecommons.org/licenses/by/4.0/.

**ORCID iD**
Kit Curtius http://orcid.org/0000-0002-2678-0960

**REFERENCES**


1439


