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Original Article

Computing lifetime incidence of esophageal adenocarcinoma and age-specific prevalence of Barrett's esophagus

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SUMMARY. **Barrett's esophagus is the precursor to esophageal adenocarcinoma. Esophageal adenocarcinoma detected from endoscopic surveillance programs accounts for <10% of all cases, suggesting majority of patients with Barrett's esophagus are likely unaccounted for. Previous observational studies have estimated the observed prevalence of Barrett's esophagus to be approximately 1%, but others suggest may be an underestimate. The aim of this study was twofold: (i) calculate lifetime risk of esophageal adenocarcinoma and (ii) estimate overall and age-specific prevalence of Barrett's esophagus. A tree cohort model was created for progression to esophageal adenocarcinoma from birth to death (100 years) for USA and Australian population. Lifetime risk of esophageal cancer and adenocarcinoma were necessary for calculating Barrett's esophagus prevalence. The model incorporated age- and sex-specific incidence data from national cancer registries: the Australian Institute of Health and Welfare and the Surveillance, Epidemiology, and End Results database for the USA. The model was calibrated using an optimization algorithm, which matched progression rates from Barrett's esophagus to esophageal adenocarcinoma with known national cancer data. A Monte Carlo simulation, with 10,000 iterations, was conducted to derive error margins. Estimates of age-specific and overall prevalence of Barrett's esophagus in the population were generated through a similar process. Results: The lifetime risk of esophageal cancer and adenocarcinoma in USA non-Hispanic White population was 0.56% and 0.36%, respectively, while it was somewhat higher at 0.81% and 0.61% (range 0.57%–0.65%) in the Australian population. Estimated overall prevalence of Barrett's esophagus was ∼3% (±0.3%) and ∼ 5.4% (±0.6%) in USA White and Australian populations (male and female). Prevalence for age brackets was estimated at 0.06% (±0.02%), 1.6% (±0.7%), 3.2% (±1.3%), 8% (±3%), and 12% (±4%) for USA, and 0.05% (±0.02%), 0.9% (±0.5%), 2.8% (±1.2%), 7% (±3%), and 12% (±4%) for Australian population for ages 0–29, 30–44, 45–59, 60–74, and 75+, respectively. Observed estimates of Barrett's esophagus prevalence are likely lower than projected overall prevalence. This study also presents age-specific prevalence estimates of Barrett's esophagus, which are key in developing screening programs for esophageal adenocarcinoma.**

KEY WORDS: **Barrett's esophagus, prevalence, esophageal adenocarcinoma, lifetime risk.**

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BACKGROUND

Esophageal adenocarcinoma is rising in incidence globally, especially in the developed nations.[1] The estimated incidence of esophageal adenocarcinoma varies across different countries and populations. Along with esophageal squamous cell carcinoma (ESCC), it is one of two major subtypes of esophageal cancer. It is currently believed that all esophageal adenocarcinoma develops through a metaplasia—dysplasia—neoplasia pathway commencing with Barrett's esophagus.[2]

A recent systematic review and meta-analysis of 103 studies concluded that the prevalence of Barrett's esophagus could be ~0.96% (95% CI 0.85%–1.04%), but the study found notable heterogeneity between studies.[3] This is conceivable because diagnosis of Barrett's esophagus can vary in studies due to factors such as biopsy compliance with Seattle protocol (four quadrant biopsy every 1–2 cm), histological definitions of metaplasia and dysplasia, and different sampled populations.

Estimating the true prevalence of Barrett's esophagus is challenging due to several factors. As an asymptomatic condition, many cases remain undiagnosed. Patients suspected of having Barrett's often present with gastroesophageal reflux disease (GERD) or reflux esophagitis symptoms and represent only a subset of cases.[4] Endoscopy populations may be biased, as symptoms can stem from other conditions like esophagitis. Additionally, less than 10% of esophageal adenocarcinoma cases are identified through Barrett's esophagus surveillance, with 90% diagnosed without prior Barrett's esophagus detection.[4] If all esophageal adenocarcinomas originate from Barrett's esophagus, this suggests a large undiagnosed population, with observed cases representing just the 'tip of the iceberg.' Some researchers estimate the true prevalence of Barrett's esophagus may be 5–9%.[4–6]

Ultimately, clinicians are limited by the late presentation of esophageal adenocarcinoma. Improving its survival requires earlier detection through cost-effective screening protocols. Screening success depends on both disease prevalence and tool accuracy. Understanding overall and age-specific prevalence can guide the development of targeted screening strategies. This study aimed to estimate the lifetime incidence of esophageal cancer using national registry data from Australia and the USA and to derive overall and age-specific prevalence of Barrett's esophagus. We hypothesized that Barrett's esophagus is more prevalent than previously reported, with higher rates in older age groups.

METHODS

The study was conducted in four phases, as depicted in Figure 1. The first step calculated the lifetime incidence of esophageal cancer. A tree cohort model was created (TreeAge Pro version R2.1 2021), simulating progression from a healthy state to esophageal adenocarcinoma. Male, female, and combined sex cohorts in Australian and USA (non-Hispanic White) populations were modeled. The model started at birth of the starting population (age 0). The model's cycle length was 1-year, with a time horizon of 100 years.

Lifetime incidence of esophageal cancers

Age and sex-specific incidence data were available from the Australian Institute of Health and Welfare (AIHW) and Surveillance Epidemiology and End Results (SEER in USA). Data analysis was performed using Rstudio (R version 4.1.0; 2021-05-18). Health states included healthy, esophageal cancer (all subtypes), esophageal adenocarcinoma, and death (Fig. 3). The probability of progressing from a healthy state to esophageal adenocarcinoma depended on the characteristics of the starting population. Progression from a healthy state to esophageal adenocarcinoma was sourced from observed age specified incidence rates for esophageal cancer (AIHW database from 2000 to 2016[7]; SEER database 2000–2017[8]). For male and female populations, age-specified cancer incidence data were available from both AIHW and SEER data. For the Australian population, an assumption was made that esophageal adenocarcinoma represented 65–80% of all esophageal cancers, as this data was not provided in AIHW cancer registry.[9,10] The 10-year mortality for esophageal cancer was sourced from SEER data (from 2000 to 2017).

Model inputs

The probability of dying each cycle was based on sex and age-related all-cause mortality, and the probability of developing cancer was derived from the age-specified incidence of esophageal cancer (from AIHW). For Australian data, AIHW was used (Creative commons license 3.0, access date: 15 January 2021) and for USA data the SEER database and DevCan software (version 6.7.8.5; download date 2 February 2021).[8,11,12] When modeling the USA population, only White (non-Hispanic) ethnicity cancer incidence rates were used, as this population represented the largest proportion of patients with esophageal adenocarcinoma and demographically is more closely related to the Australian population. Age and sex specific (non-cancer) mortality was sourced from USA and Australian mortality life tables: for the Australian population from the Australian Bureau of Statistics (ABS; access date 6 April 2021)[13,14] and USA population from social security data.[15] A complete list of model inputs can be found in Table 1.[10,13,16,17]

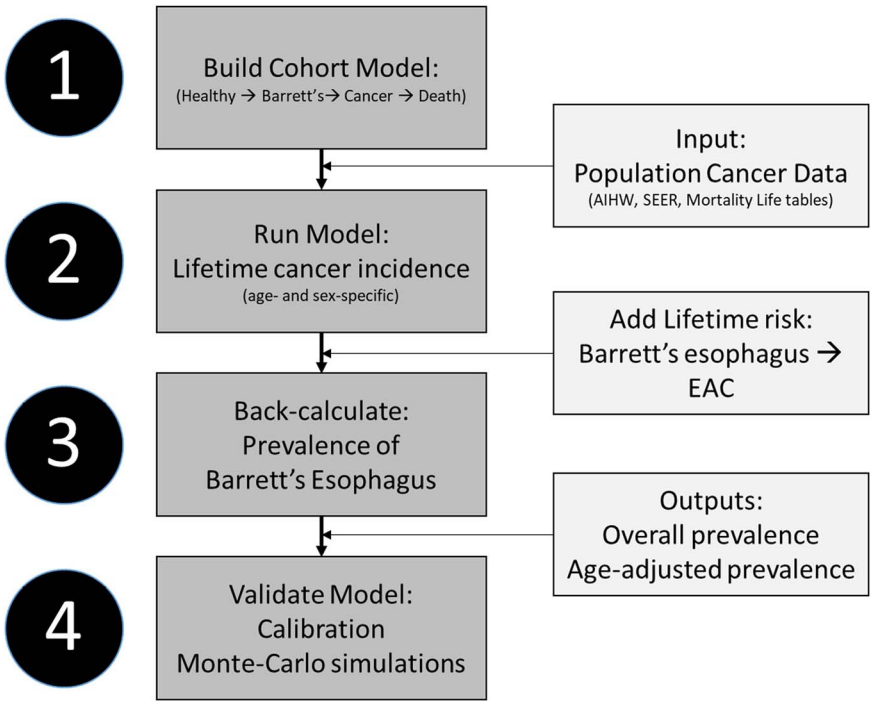

Fig. 1 Flow chart depicting stepwise processes in building, calibrating, and validating model for calculating the lifetime incidence of esophageal cancer and Barrett's esophagus prevalence.

Table 1 Model Inputs

Type of Model Input	Value (mean ± SD)	Source
Starting age	0	
Time horizon	100 years (or death)	
Cycle Length	1 year	
All-cause mortality	Weighted average	Australian Bureau of Statistics-Weighted average Life tables (16) USA- Social Security Weight Average Life table (14)
Assumed % esophageal adenocarcinoma (of all esophageal cancers)	PERT distribution	Nguyen 2016 (24) Queensland Oncology Analysis System (OASys) data (15) Expert opinion
Probability of being diagnosed with esophageal adenocarcinoma (annual)	Age based incidence	AIHW (10) SEER (11, 17)
Chance of survival per annum	Based on esophageal cancer mortality per year post-diagnosis	SEER (17, 18)

Derivation of Barrett's esophagus prevalence

The second part of the study focused on using the lifetime incidence of esophageal adenocarcinoma from the above model to calculate the prevalence of Barrett's esophagus in male, female, and combined-sex cohorts for Australian and USA populations through a calibration process described below. Disease status included healthy, Barrett's esophagus, esophageal adenocarcinoma, and death (Fig. 3). As all esophageal adenocarcinoma was assumed to arise from Barrett's esophagus, the risk for progression to esophageal adenocarcinoma (EAC) for this cohort was assumed to be the inverse of the prevalence.

$$\text{Lifetime progression from Barrett's to EAC} = \frac{\text{Lifetime risk of EAC in general population}}{\text{Prevalence of Barrett's esophagus}}$$

This was rearranged to calculate the prevalence of Barrett's esophagus:

$$\text{Prevalence of Barrett's esophagus} = \frac{\text{Lifetime risk of EAC in general population}}{\text{Lifetime risk of progression from Barrett's to EAC}}$$

Model inputs

Initial age specific prevalence rates were estimated from several sources.[3,18,19] Data provided in a systematic review and meta-analysis[3] was extracted and analyzed for the prevalence of Barrett's esophagus at varying mean ages. A linear regression analysis was performed with prevalence as the outcome variable and mean age group as the predictor. Five age groups were devised, and the prevalence was predicted using a linear regression model from this data. The predicted prevalence values were used as the *initial* estimates for the model.

Initial inputs for the prevalence of Barrett's esophagus (overall and age-based prevalence) were systematically altered to match known long-term progression rates of esophageal adenocarcinoma.[20] Model calibration was performed using a constrained Bound Optimization By Quadratic Approximation method run for minimization.[21] Convergence criteria were determined as cumulative esophageal cancer percentage between 9% and 13%.[20] Resultant iterations were used to calculate the mean and standard deviation of prevalence of Barrett's esophagus in the community.

Model validation: Monte-Carlo simulations

After estimating the prevalence of Barrett's esophagus, model validation was performed through Monte-Carlo simulations (adjusting for input variable error). A beta distribution was generated for each of the calibrated variables described above (using mean and standard deviation). Other distributions included percentage of adenocarcinoma cases within the overall esophageal cancer cohort (for Australian data) using a pert distribution (likeliest 75%, minimum value of 65%, and maximum value of 80%) based on expert opinion and available literature.[9,10] Model outputs of 10,000 simulations were run and checked to confirm accuracy of calibration results.

RESULTS

Annual incidence of esophageal cancer

The annual incidence of esophageal cancer was higher in the Australian population (5–6 cases per 100,000 persons) compared to the USA population (4.5–5 cases per 100,000 persons) (Fig. 2). The highest incidence of esophageal cancer occurred between 80–90 years of life (combined sex 24.1 per 100,000 95% CI 23.2–25.1 per 100,000), with male incidence higher than female (male 43.4 per 100,000 95%CI 41.4–45.5 per 100,000; female 10.5 per 100,000 95%CI 9.7–11.4 per 100,000). In the USA population, (non-Hispanic) Whites had the highest incidence of esophageal adenocarcinoma, followed by Hispanic, Black, and Asian/Pacific Islander ethnicities (Fig. 2). The yearly incidence of esophageal adenocarcinoma was higher in Australians (4.0–4.6 cases per 100,000 persons) than USA Whites (3.2–3.5 cases per 100,000) (Fig. 2).

Cumulative incidence of Esophageal cancer

The cumulative percentage of cancer cases over a 100-year timeframe was interpreted as a lifetime risk of developing esophageal cancer. This is representative of all individuals between year 2000 and 2016 in the Australian population, and all individuals from 2000 to 2017 in the USA white population. In the Australian cohort, 0.81% developed esophageal cancer (all subtypes), while 0.61% developed esophageal adenocarcinoma. In the USA (non-Hispanic) Whites population, 0.61% developed esophageal cancer (all subtypes) and 0.56% developed esophageal adenocarcinoma (Table 2). The male-only cohort had a higher cumulative incidence of esophageal adenocarcinoma, compared to the female-only cohort. In the Australian population, 0.84% of the male cohort developed esophageal adenocarcinoma during the time horizon, compared to 0.4% of female cohort. In the USA White population, this was 0.4% in the male-only cohort and 0.11% in the female-only cohort.

Prevalence of Barrett's esophagus

The overall prevalence of Barrett's esophagus from published meta-analysis has been reported to be 0.96% (0.85%–1.07%). Prevalence data from 66 studies with complete data were extracted and plotted against the reported mean age[3] as shown in Figure 3. Studies reporting higher mean ages tended to have a higher prevalence of Barrett's esophagus. A linear regression model was used to predict values of defined age cut-offs namely 30–44, 45–59, and 60–74 years with predicted prevalence of 5.8%, 5.02%, and 12.8%, respectively. Age cut-offs under 30 years and over 75 years did not have adequate data and thus did not yield reliable predictive values. The predicted prevalence values were used as initial estimates for model calibration of an age-specific Barrett's esophagus prevalence.

Model calibration with stated convergence criteria yielded approximately 2600 iterations. From these iterations, transition probability distributions were created, and the model was run for 10,000 simulations to check and confirm the calibrated estimates. Resulting mean and standard deviation of prevalence estimates are reported in Table 3.

The relationship between Barrett's esophagus prevalence and the lifetime risk of esophageal adenocarcinoma for a flat prevalence and age-specific prevalence is shown in Figure 5 and Figure 6, respectively. Modeling a flat overall prevalence percentage for a cohort of Barrett's esophagus patients revealed an estimated community prevalence rate 2.5–3.7%

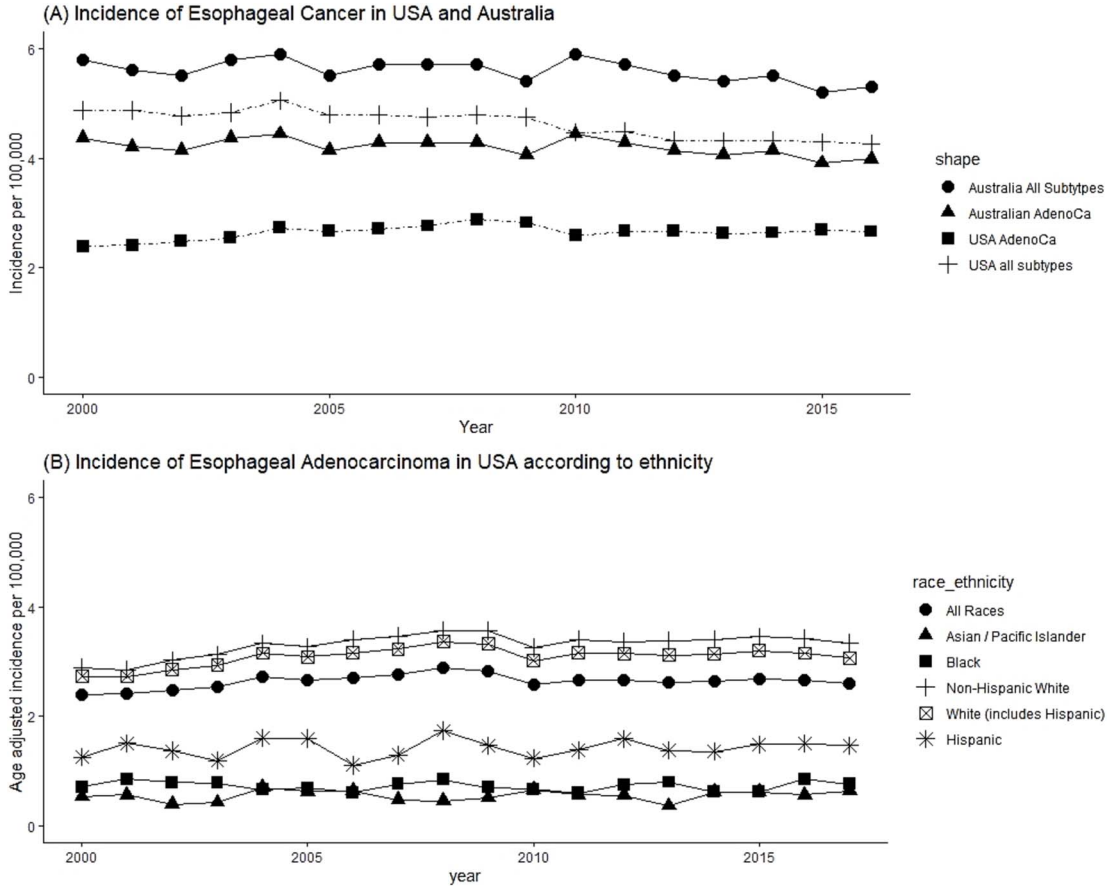

Fig. 2 (A) Differences in incidences of esophageal cancer between USA and Australia (SEER and AIHW sources, respectively). The solid lines represent Australian data, while the dashed lines represent American data. Incidence of Esophageal adenocarcinoma is higher in Australia. (B) Differences in age-adjusted incidence of esophageal adenocarcinoma in United States between ethnicities. Non-hispanic white population carries the highest risk, with Black and Asian populations account for the lowest.

Table 2 Model outputs: Cumulative percentage of cohort progressing to cancer over the time horizon in the general population (base scenario)

Lifetime Risk (100 years)	All Esophageal Cancers		Esophageal Adenocarcinoma only			
	Australian model	United States model	Australian model	United States model	Australian 70%	Australian 80%
General population	0.81%	0.56%	0.61%	0.36%	0.57%	0.65%
Male (general population)	1.20%	0.89%	0.84%	0.40%	0.78%	0.9%
Female (general population)	0.48%	0.25%	0.40%	0.11%	0.37%	0.43%

Table 3 Estimated age and sex related prevalence of Barrett's esophagus in USA (non-Hispanic White) and Australian populations

Population	Non-Age-Specific	Age Specific (years)				
	Overall	0–29	30–44	45–59	60–74	75+
USA population						
Combined sex	3.0% ± 0.3%	0.06% ± 0.02%	1.6% ± 0.7%	3.2% ± 1.3%	8% ± 3%	12% ± 5%
Male only	5.3% ± 0.6%	0.16% ± 0.07%	3.2% ± 1.3%	5.2% ± 2.5%	11% ± 5%	10% ± 4%
Female only	1.0% ± 0.1%	0.05% ± 0.01%	0.7% ± 0.3%	2.2% ± 1%	5% ± 2%	7% ± 4%
Australian Population						
Combined sex	5.4% ± 0.6%	0.05% ± 0.02%	0.9% ± 0.5%	2.8% ± 1.2%	7% ± 3%	12% ± 4%
Male only	7.4% ± 0.8%	0.51% ± 0.18%	1.8% ± 1.1%	5.4% ± 2.1%	10% ± 3%	14% ± 5%
Female only	3.4% ± 0.4%	0.06% ± 0.02%	0.8% ± 0.4%	1.2% ± 0.5%	7% ± 3%	10% ± 4%

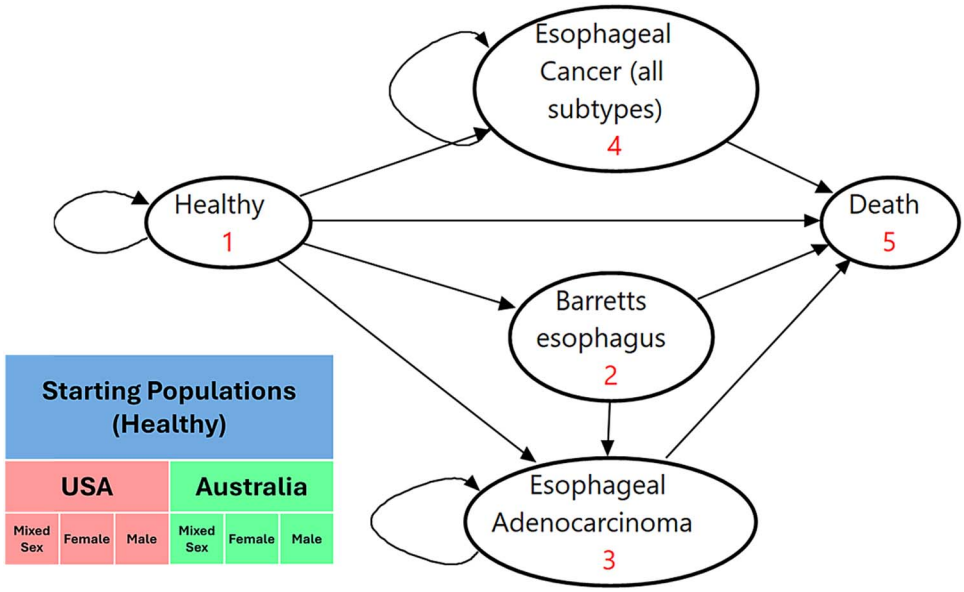

Fig. 3 Movements across health states. Starting populations were healthy female, male, or mixed USA and Australian individuals. Model outputs were progression to cancer and death.

(mean 3%) for US data and 4.3–6.4% (mean 5.4%) for Australia (Fig. 5). Mean prevalence estimates for subgroups are shown in Table 3. Of note, Australian males had the highest overall prevalence of Barrett's esophagus at 7.4% (± 0.8%), while US females had the lowest at 1% (± 0.1%). At a Barrett's esophagus prevalence value of 0.96% (meta-analysis estimate), the model predicted 44.5% of the general Australian population with Barrett's esophagus and 30% of USA population with Barrett's esophagus would develop esophageal adenocarcinoma at the end of the time horizon (Fig. 5). This is much higher than the observed rates of progression from Barrett's esophagus to adenocarcinoma in the literature, and hence likely implausible.

Prevalence, expectedly, increased with age, seen to be minimal in the first 30 years of life and maximum after age 75. This was estimated at 0.06% (±0.02%), 1.6% (±0.7%), 3.2% (±1.3%), 8% (±3%), and 12% (±4%) for USA, and 0.05% (±0.02%), 0.9% (±0.5%), 2.8% (±1.2%), 7% (±3%), and 12% (±4%) for Australian population for ages 0–29, 30–44, 45–59, 60–74, and 75+, respectively. Female cohorts had a lower prevalence of Barrett's esophagus, with the USA female population demonstrating the lowest means across all ages (0.05%, 0.7%, 2.2%, 5%, and 7% in ages (years) 0–29, 30–44, 45–59, 60–74, and 75+, respectively). Conversely, the Australian male cohort had the highest prevalence of Barrett's esophagus with mean values 0.51%, 1.8%, 5.4%, 10%, and 14% across ages (years) 0–29, 30–44, 45–59, 60–74, and 75+, respectively.

DISCUSSION

Our study estimates the lifetime risk of developing esophageal cancer and esophageal adenocarcinoma in Australian and USA total, male, and female populations using a tree cohort model. Working backwards from observed data (i.e., the population incidence of esophageal adenocarcinoma and the lifetime risk of conversion from Barrett's esophagus to esophageal adenocarcinoma), we estimated the population prevalence of Barrett's esophagus to be approximately 3% (± 0.3%) for the white USA population and 5.4% (± 0.6%) for the general Australian population.

Our study highlights an apparent discrepancy between the prevalence of Barrett's esophagus as reported in the literature, the estimated annual rate of progression, and the incidence of esophageal adenocarcinoma reported in national cancer databases, an issue that has been raised at several conferences previously.[22] Marques de Sa *et al.*[3] synthesised data from 103 studies, to provide what would seem convincing evidence of Barrett's prevalence ~0.96% (95% CI 0.85%–1.04%). Only a handful of studies have examined the prevalence of Barrett's esophagus through random sampling and estimated it to be between 0.5% and 1%.[23–25] Even though the prevalence of Barrett's esophagus has been reported at ~1%, a sampling bias cannot be ruled out. If the prevalence of Barrett's esophagus is accurate at ~1%, and all esophageal adenocarcinoma arises from Barrett's esophagus, then the modeled lifetime risk of a patient with Barrett's esophagus developing esophageal adenocarcinoma would be 44.6% in Australian population and 30% in USA population (Fig. 5), which is implausible. Either the prevalence of Barrett's esophagus is 4–7× fold higher than current estimations or there is an alternative explanation. Other highly reputable computation modeling studies have also concluded similarly that the prevalence of NDBE must be higher at ~5–9% to account for the esophageal adenocarcinoma that are found outside

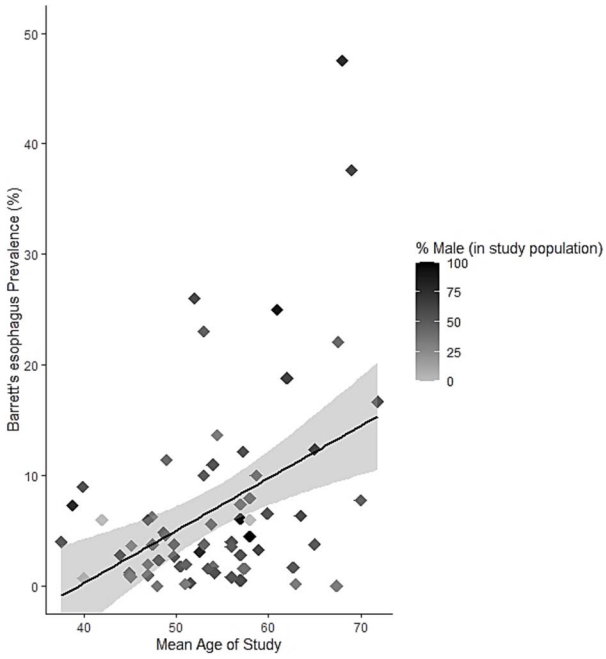

Fig. 4 Prevalence of Barrett's Esophagus reported in 66 studies compared to mean age. Higher prevalence is seen in studies with higher mean ages. The line is a fit of data using linear regression. Percentage of male patients was between 50% and 75% in most studies.

of surveillance programs.[6,26,27] This discrepancy may be due to undiagnosed cases resulting from the asymptomatic nature of Barrett's esophagus. Additionally, it could be that the development of Barrett's esophagus and its progression to esophageal adenocarcinoma varies across different age groups.

Within the 103 studies examined in the meta-analysis,[3] data extracted from 66 studies suggests a trend to higher prevalence in studies reporting higher mean age (Fig. 4). As Barrett's esophagus is often asymptomatic, it is conceivable that its prevalence rises with age.[18] This was seen by Rubenstein *et al.*, who conducted a cross-sectional study looking at patients undergoing endoscopy, finding a peak in Barrett's esophagus prevalence in the sixth decade of life.[28] This finding is consistent with our results coinciding with the peak in esophageal cancer in the mid-80s, and assumed latency period of 15–20 years.[29] Further evidence can be found in esophagogastroduodenoscopies performed for patients undergoing colorectal screening in USA (above 50 year olds). The prevalence of Barrett's esophagus in these patients was found to be around higher at 6.8%,[30–32] lying within the range of our estimates (Table 3).

The strength of our study is twofold: (i) drawing from population level data to estimate lifetime risk of esophageal adenocarcinoma in the general population and merging with best available data on lifetime risk of progression from Barrett's esophagus to adenocarcinoma and (ii) estimating age-specific prevalence rates, which have not been presented previously. Barrett's esophagus surveillance is expensive and invasive, performs poorly in cost-effectiveness studies, and only detects 10% or less of the total patients who develop esophageal adenocarcinoma.[4] Other than symptoms of GERD, Barrett's esophagus is an asymptomatic disease. Consequently, its incidence and progression leads to late presentation of esophageal adenocarcinoma. It is likely that this group of individuals have undetected Barrett's esophagus and screening high risk individuals at the correct age/period could improve the detection rate of esophageal adenocarcinoma to improve overall survival. Understanding age-related prevalence is crucial, as it directly impacts the effectiveness of screening tools. This age-specific prevalence data provides valuable insights for designing targeted, cost-effective screening programs for Barrett's esophagus and esophageal adenocarcinoma, particularly when considering novel biomarkers, whose sensitivity and specificity vary with disease prevalence. Targeted screening for individuals aged 55 in males and 65 in females is likely to enhance detection rates when using accurate diagnostic tools such as endoscopy or Cytosponge.[33–35]

As with any computational study, this work has limitations related to model inputs which necessarily require assumptions and estimations for unavailable data, our study does rely on population cancer data and assumption that all esophageal adenocarcinoma arises from Barrett's esophagus. Population cancer data is the best available data, but it might be under-reported. This is an important feature in interpreting our results as the prevalence of Barrett's esophagus is likely to be higher than currently believed. Additionally, esophageal cancer subtypes are not reported

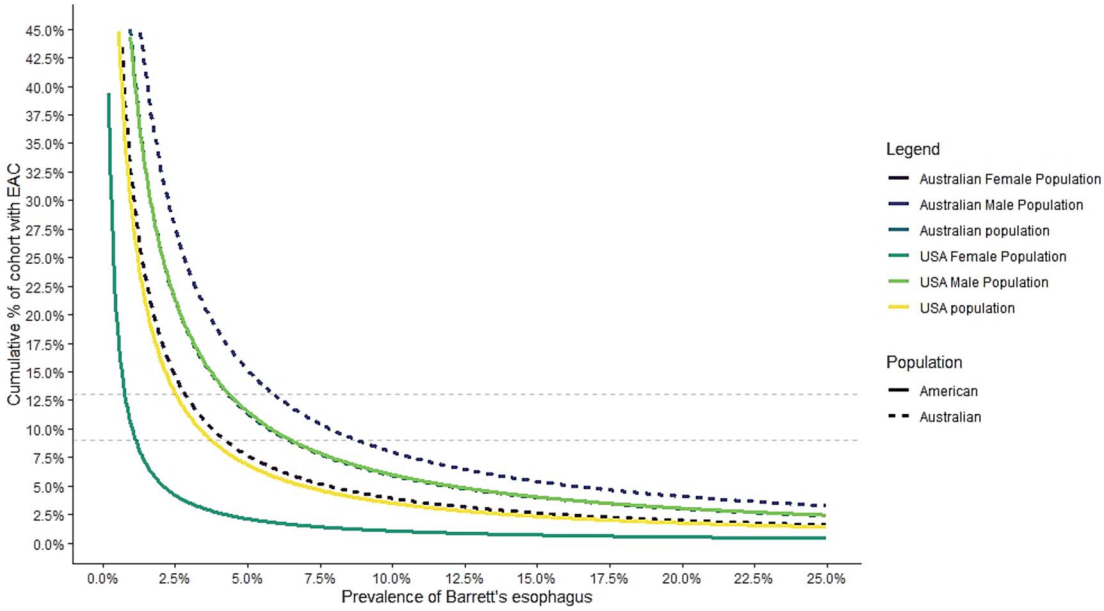

Fig. 5 Progression of a cohort of individuals with Barrett's esophagus to esophageal adenocarcinoma (EAC) in American and Australian population based on various prevalence (overall/flat). A high prevalence of Barrett's esophagus indicates each individual has a lower probability of progression to EAC, given its observed population incidence.

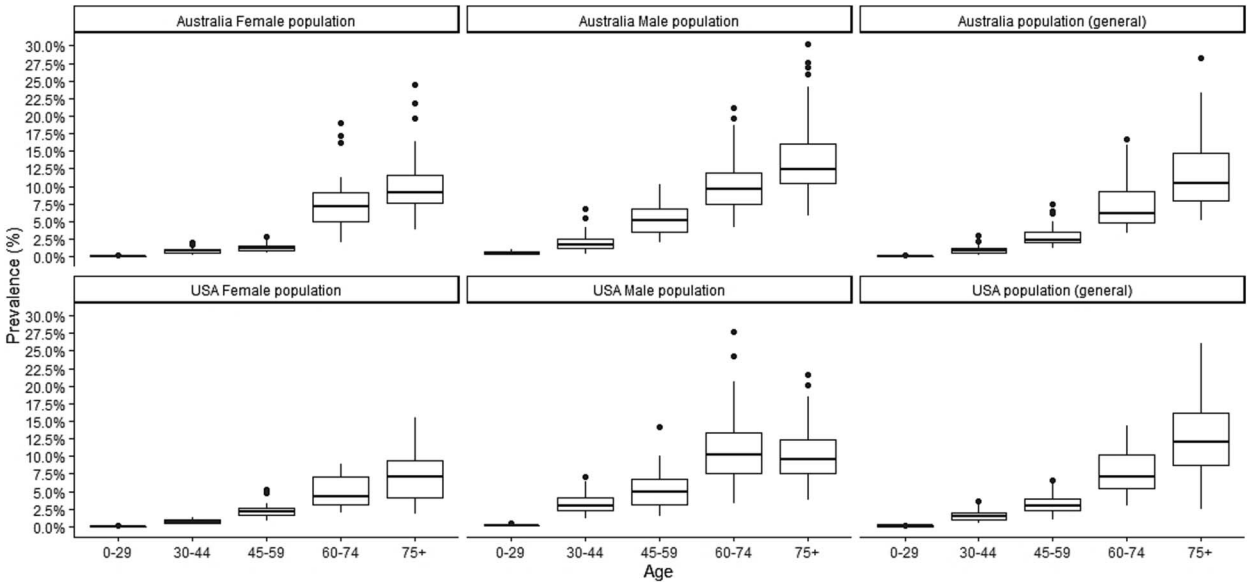

Fig. 6 Boxplot of calibrated age and sex related prevalence rates of Barrett's esophagus in Australian and American (non-Hispanic White) populations.

separately in the AIHW cancer incidence data, or in any public registries in Australia. Adenocarcinoma rates for Australian populations had to be estimated based on scant literature evidence and expert opinion. We assumed that adenocarcinoma represents 65–80% of all esophageal cancers in Australia. This rate was derived from published rates from the States of Queensland (~65%) and South Australia (69.6%), so it is a reasonable assumption.[9,10] In a subgroup of studies in the meta-analysis[3] from Western countries, the prevalence of Barrett's esophagus was 2.3% (95% CI 0.42–4.2%). As western countries have a predominantly Caucasian population, particularly the elderly component of those populations, it is likely possible our model estimates a higher prevalence due to this feature. Other limitations involved the estimation of initial prevalence rates of different age groups by pooling data from other studies. Unfortunately, a meta-regression controlling for fixed and random effects was outside the scope of this study. Instead, a regression analysis was applied to allow us to estimate initial values (Fig. 4), which were then calibrated to targets from higher level evidence to mitigate effects of this limitation.

The second limitation to consider is the assumption that all esophageal adenocarcinoma arises from Barrett's esophagus. While Barrett's esophagus is the only known precursor to esophageal adenocarcinoma, alternate pathways have been proposed. These include the potential transformation of stem cells from esophageal submucosal glands or the gastric cardia into intestinal-type metaplasia, which can progress to esophageal adenocarcinoma.[36,37] However, the precise mechanisms of these alternate pathways remain unclear, and there is debate whether these represent metaplasia of esophageal origin or reflect a broader spectrum of cellular changes leading to dysplasia and adenocarcinoma. For now, Barrett's esophagus is still believed to account for most or all the current cases of esophageal adenocarcinoma.

CONCLUSION

We sought to estimate the lifetime risk of developing esophageal cancer and adenocarcinoma in the general population and address the current incongruence between low reported prevalence rates of Barrett's esophagus and observed risks of progression to adenocarcinoma. Additionally, an age-specific prevalence estimate is calculated for future screening strategies for earlier detection of esophageal adenocarcinoma. While these estimates are based on population level data and modeling, they remain speculative and do not prove this phenomenon. However, short of performing hundreds or thousands of research endoscopies in a large representative sample of the general population, there are few alternative methods for estimating the true prevalence of Barrett's esophagus in the community.

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