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Research Article

The Impact of Obesity on the Rise in Esophageal Adenocarcinoma Incidence: Estimates from a Disease Simulation Model

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Abstract

Background: The United States has experienced an alarming and unexplained increase in the incidence of esophageal adenocarcinoma (EAC) since the 1970s. A concurrent increase in obesity has led some to suggest a relationship between the two trends. We explore the extent of this relationship.

Methods: Using a previously validated disease simulation model of white males in the United States, we estimated EAC incidence 1973 to 2005 given constant obesity prevalence and low population progression rates consistent with the early 1970s. Introducing only the observed, rising obesity prevalence, we calculated the incremental incidence caused by obesity. We compared these with EAC incidence data from the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) registry to determine obesity's contribution to the rise therein. Incidences were converted to absolute numbers of cases using U.S. population data.

Results: Using constant obesity prevalence, we projected a total of 30,555 EAC cases cumulatively over 1973 to 2005 and 1,151 in 2005 alone. Incorporating the observed obesity trend resulted in 35,767 cumulative EACs and 1,608 in 2005. Estimates derived from SEER data showed 111,223 cumulative and 7,173 cases in 2005. We conclude that the rise in obesity accounted for 6.5% of the increase in EAC cases that occurred from 1973 to 2005 and 7.6% in the year 2005.

Conclusion: Using published OR for EAC among obese individuals, we found that only a small percentage of the rise in EAC incidence is attributable to secular trends in obesity.

Impact: Other factors, alone and in combination, should be explored as causes of the EAC epidemic. *Cancer Epidemiol Biomarkers Prev; 20(11); 2450–6. ©2011 AACR.*

Introduction

According to the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) registry data, the incidence of esophageal adenocarcinoma (EAC) in the United States has increased 5-fold in the past 3 decades (1). There is no consensus regarding the cause of this rise in EAC incidence, although increasing gastroesophageal reflux disease (GERD), eradication of Helicobacter pylori infection, use of nonsteroidal anti-inflammatory drugs (2, 3), and obesity have been suggested (4). Of these risk factors, obesity has received particular attention as a potential causal factor in the rapid rise in EAC incidence (4, 5). Two meta-analyses found that the risk of EAC increased approximately 2- to 3-fold in overweight and obese individuals (6, 7) and additional studies found a higher risk of EAC in obese individuals than those who are simply overweight (7, 8), consistent with an exposure-response effect. Obesity has furthermore been found to be associated with symptoms of GERD and strongly associated with Barrett's esophagus (BE; refs. 3, 8, 9). These findings coupled with the high temporal correlation between obesity prevalence and EAC incidence have led to speculation that the increasing weight trends in the United States may be at least partially responsible for the increase in EAC incidence (7, 10, 11).

Previous epidemiologic studies, mainly case–control studies, were limited in their ability to estimate the contribution of obesity to the rapid rise of EAC incidence. Conducting a cohort study with sufficiently large sample size and follow-up period is difficult due to the low EAC incidence in the general population. However, mathematical models are able to simulate the natural history of EAC by integrating the best available biologic, epidemiologic, and clinical data. Such a model can be used to estimate the

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excess cases caused by obesity assuming a causal association. Other applications of such an approach have been shown in breast cancer (12, 13). We have previously used an EAC model to estimate the lives that could be saved under a national aspirin chemoprevention program (14, 15). The aim of this study was to estimate the excess risk for EAC attributable to obesity using a model constructed and validated with SEER data and the published literature.

Materials and Methods

Model overview

A previously developed and validated model of esophageal adenocarcinoma (EACMo; refs. 14, 16) was revised to analyze the contribution of obesity to the rise in EAC incidence in the United States over the study period of 1973 to 2005. EACMo is a Markov state transition model of esophageal carcinogenesis that tracks the transition of fractions of a population through 6 health states: Normal, Symptoms of GERD, BE, Undetected Cancer, Detected Cancer, and Death. Extensive details regarding the parameterization, calibration, and validation of the model can be found in a publicly available manuscript (14).

Analysis overview

The study conducted was a multiphase analysis. To help simplify and convey the process, the analysis is summarized into 5 phases; a more detailed description follows.

Dividing the population into obese and nonobese groups

The simulated U.S. population was initially divided by body mass index (BMI) into obese and nonobese groups and respective models.

Numerous simulations to provide numerous potential solutions

The models were run, with each simulation producing a different set of transition probabilities between the health states. The probabilities were randomly selected for each transition from within a wide clinically plausible range to produce ten billion (10^{10}) parameter sets (unique solutions).

Superior simulation selection

Two criteria were used: first, target OR; and second, fit to SEER EAC incidence. The top 1,000 simulations were deemed superior and selected.

Model projections over 33 years: scenarios 1 and 2

The superior parameter sets were used to project a hypothetical U.S. population from 1973 to 2005. In scenario 1, the simulation assumed that transition probabilities and all EAC risk factors including obesity prevalences remained constant over the study period. In scenario 2, the rising prevalence of obesity was incorporated into the model.

Assessing obesity contributions by comparing projections to SEER

Projected EAC cases in scenarios 1 and 2 were compared with SEER data and estimates of the number of cases attributable to obesity were calculated.

Analysis details

To isolate the effect of obesity on EAC incidence, we began by dividing the United States into 2 separate populations, obese and nonobese, at a BMI of 30. We then initially simulated each population independently. These 2 groups were recombined to recreate a whole U.S. population at a later point in the analysis when selecting simulations with superior results.

We ran separate simulations of the EAC model described above for each population. For each run, a parameter set (transition probabilities between health states) was randomly selected from within the bounds covering all reasonably likely rates for each transition (17), producing a wide and thorough sampling of potential progression rate combinations and resulting precancer health state prevalences and age-adjusted EAC incidences.

Ten billion (10^{10}) unique results from the simulations were generated and assessed. Two criteria were applied to select simulations that most accurately reflected the observed epidemiologic data in our calibration process. For the first selection criterion, we calculated the OR of GERD symptom prevalence and EAC incidence between the obese and nonobese groups from the model outputs. We selected simulations that produced OR consistent to within a factor of 2 of the values from the published literature: GERD OR = 1.94; EAC OR = 2.780; the target OR, ranges and references may be seen in Table 1. We also excluded any combinations with an OR less than 1, as this would have been inconsistent with published data and clinical plausibility

For the second selection criterion, the EAC incidences of simulations were compared with SEER EAC incidences averaged over the same period (1973–1977) and their χ^2 scores were calculated as a measure of their goodness of fit. The model was calibrated to the early years of the study period, or EAC incidences prior to the sharp increase. This process was consistent with the goal of producing model parameters (transition probabilities) preceding the secular trends and effects of obesity and other risk factors, both known and unknown. The first 5 years of the study period (1973–1977) were used instead of the first year alone (1973) to provide enough data points and lessen the risk of statistical noise resulting from small samples. The 1,000 simulations with the lowest χ^2 scores which also met the first (OR) criterion was deemed superior and therefore selected for use in the remainder of the analysis.

In scenario 1, we envisioned a static U.S. population where risk factors that would affect progression to EAC in the population, including the prevalence of obesity stayed at its average between 1973 and 1977, our basal rate (approximately 11%), over the ensuing 33-year study

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Table 1. Model inputs: parameters

Parameter	Value	Range	References
OR for effect of obesity on prevalence/incidence			
GERD symptoms prevalence	1.94	1.0–4.0	2, 3, 6, 8, 24–26
BE prevalence	[a]	0.99–4.0	9, 24, 27–33
EAC incidence	2.78	1.0–5.4	6, 7, 20, 34–38
Population prevalence (%)			
GERD symptoms prevalence	18.6	17.6–19.9	39–49
BE prevalence	4.2	0.8–25	40, 50–58
Annual transition rates between health states			
Normal to GERD symptoms	Derived from calibration	Derived from calibration	
Normal to BE	Derived from calibration	Derived from calibration	
GERD to BE	Derived from calibration	Derived from calibration	
BE to undetected EAC	Derived from calibration	Derived from calibration	
Undetected EACs detected (per year)	25%	11%–100%	59, 60

NOTE: This table describes the literature-derived values and ranges used as model input parameters. Population prevalences of GERD and BE are not themselves model parameters, but they are used to derive values for transition or progression from the "Normal" state to the "GERD" and "BE" states, respectively.

[a]A meta-analysis[32] could not find any statistically significant association between the effect of obesity and BE Prevalence; the effect is uncertain as published results have produced a wide range of result. Consequently, we did not use the OR for the effect of obesity on developing BE as part of our simulation selection criteria, but checked the OR to ensure that it was within the published range.

period. We recombined the populations by weighting the obese and nonobese populations by their respective proportions from the basal rate. Consequently, the resulting number of EAC cases in scenario 1 represented the expected number of EACs had obesity prevalence remained static over the years analyzed.

For scenario 2, we incorporated secular trends of the rising obesity prevalence, whereas everything else in the model remained the same as in scenario 1. The populations were recombined by weighting, as in scenario 1, but weighted by their observed obesity prevalences for the corresponding calendar year as seen in Fig. 1. These obesity prevalences were derived using National Health and Nutrition Examination Surveys (NHANES; 1971–2006) which were fit to regression models to create continuous BMI values between surveys (18).

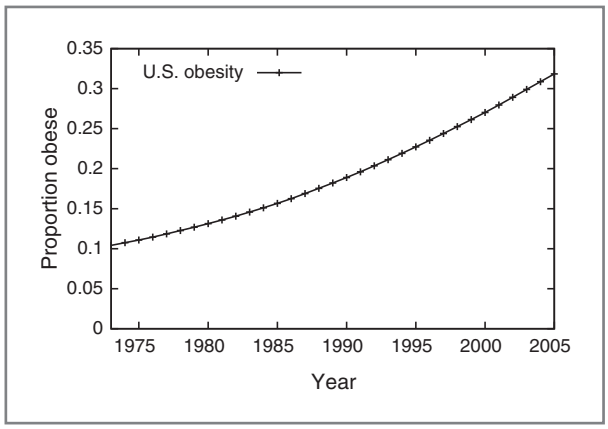

Figure 1. Obesity prevalences from 1973 to 2005 for U.S. White Males besity prevalences used for scenario 2, which incorporates the rising prevalences over the study period (1973–2005) are plotted. The prevalence of obesity, defined as BMI > 30kg/m^2, rises from 11% of the population in 1973 to 32% in 2005.

Each scenario's incidence and SEER incidence was weighted with the United States white male population for the corresponding year, providing the number of EAC cases each year, and summed over the study period, providing the total number of EACs over the study period.

This difference in number of cases between scenarios 1 and 2 was the contribution of obesity toward the rise in EAC incidence. The difference between SEER data and scenario 1 was the total rise in EAC incidence. The ratio of the 2 differences, the increase from obesity divided by the full increase, was taken to be obesity's fractional contribution to the rise in EAC incidence: (scenario 2—scenario 1)/(SEER—scenario 1). This contribution was calculated for both the full-study period and the final year, 2005, alone.

Acknowledging the uncertainty in the published ORs of EAC incidence in obese individuals compared with individuals who are not obese, a sensitivity analysis was done to explore the impact on the model's projections with varying ORs. In particular, we calculated the ORs necessary to reproduce SEER EAC incidence (both cumulative incidence over the study period and for the final year of study, 2005).

Results

Table 2 and Fig. 2 display the primary results of the analysis, EAC incidence estimates for scenarios 1 and 2,

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Table 2. Number of EAC cases in the United States by year

	Annual EAC incidence (number of cases)				
Year	**Scenario 1**	**Scenario 2**	**SEER data**	**From obesity**	**Total rise**
1975	806	806	746	0	−60
1980	825	857	1,138	32	314
1985	855	929	1,958	75	1,103
1990	903	1,038	3,507	135	2,604
1995	979	1,197	4,334	218	3,355
2000	1,056	1,378	6,332	322	5,276
2005	1,151	1,608	7,173	457	6,022
Total	30,555	35,767	111,223	5,212	80,668

NOTE: Numbers of EAC cases from scenarios 1 and 2 and estimated from SEER data are presented by sampled year and cumulatively in the final row. The fifth column, "From obesity," is the difference between scenario 2 and scenario 1, which is the number of cases attributed to the rise in obesity. The final column, entitled "Total rise," is the difference between SEER and scenario 1.

along with SEER registry data are presented over the study time period. The juxtaposed plots of the respective data in Fig. 2 succinctly summarize the study results, with differences visually highlighted. Both results from Table 2 and Fig. 2 are the weighted average of the 1,000 superior simulations. Scenario 1, where all risk factors remained constant, resulted in 30,555 EAC cases cumulatively from 1973 to 2005 and 1,151 cases in. 2005; as expected, EAC incidences remained relatively flat. Scenario 2, where secular trends in obesity were incorporated into the model projected, resulted in 35,767 cases cumulatively and 1,608 in. 2005; these figures are higher reflecting obesity's effect on the progression rates to EAC. SEER data estimates (incidence weighted by population figures) show 111,223 cases cumulatively and 7,173 cases in 2005. In Table 2, the fifth column is the difference between scenario 2 and 1 which is the estimated number of cases attributable to obesity. The sixth and final column is the difference between SEER and scenario 1, or the total rise in the number of cases. Using the calculation detailed in the Methods section, or dividing the number in fifth column by the number in the sixth column, these data show that obesity accounts for 6.5% (5,212/80,668) of EAC cases in the United States between 1973 and 2005, and 7.6% (457/6,022) of cases in 2005.

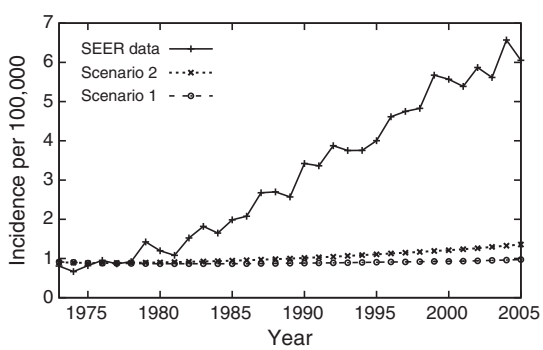

Figure 2. EAC incidence by year: simulation results compared with SEER data in this figure, EAC incidences over the study period (1973–2005) are plotted for scenarios 1 and 2 next to SEER data for direct visual comparison.

Because there was uncertainty regarding model inputs, particularly obesity's effect on progression risk to EAC, sensitivity analysis was done to explore and delineate parameter's effect on model results or projections. Specifically, we aimed to determine the point or threshold value for the obesity-related ORs in order for scenario 2 to reproduce SEER EAC incidence. We found the OR would have to be at least 77 (or >87 for 2005 EAC incidence), substantially higher than the OR of 2.78 used in our base case analysis and reported in the literature (see Table 3).

Discussion

The goal of our study was to estimate the impact of obesity on the witnessed rise in EAC incidence since the early 1970s. The etiology of the dramatic increase in EAC incidence has not been explained, although many have postulated that the concomitant and parallel trend in obesity prevalence is suggestive of a causal relationship (7, 10, 11). However, these studies only qualitatively compared the rise in EAC incidence with obesity. Our analysis is unique in that we integrate the obesity prevalence as a model input to produce a quantitative estimation of obesity's contribution.

Within the context of the limited data and means to study this hypothesis, we used a previously validated simulation disease (EACMo) and performed a thought experiment. We imagined a world where obesity and EAC incidence remained static since the early 1970s (scenario 1). This world served as a baseline to introduce a single, and therefore isolated, factor into the model: changes in obesity prevalence over the study period (scenario 2). Comparisons between scenarios 1 and 2 and to actual

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Table 3. Obesity effects, sensitivity analysis

OR	Cumulative cases	2005 cases
	Percent of SEER cases	
2.8	**6.5%**	**7.6%**
5	17%	15%
10	26%	24%
20	35%	33%
50	57%	53%
77	100%	95%
87	106%	100%
100	115%	108%

NOTE: The results of the sensitivity analysis are presented where the OR for obesity's impact on EAC, which was 2.8 in the base case analysis, is varied and the threshold for the OR where scenario 2 reproduces SEER data is determined. Column 2 is cumulative cases and column 3 is incidence in 2005.

SEER EAC incidence data allowed us to estimate what percentage of the rise in EAC incidence was due to obesity. Short of a modeling and simulation methodology, it would not have been possible to conduct this analysis.

Our findings suggest that the increase in obesity in the U.S. population only accounts for a small portion of the concurrent increase in EAC incidence. Our data affirm our hypothesis, estimating that 6.5%, a relatively small proportion, of the increase in EAC incidence in the United States is attributable to rising obesity prevalence in the United States over the 3-decade–period studied.

Our finding that obesity's contribution was minor was consistent with a few observations. First, the rise in both obesity and EAC seemed to occur simultaneously, whereas if obesity were indeed playing a pivotal causal role, we would expect a temporal lag between the rises in obesity and EAC, as observed in other examples such as the effect of aspirin on colorectal cancer (19). One of the suggested mechanisms behind the proposal of obesity causing EAC is that obesity increases abdominal pressure on the stomach leading to more GERD symptoms, more cases of BE, and ultimately more EAC cases, a sequence of events involving several steps and that would take at least a few years to occur (20). In fact, a recent publication suggests that the EAC incidence was rising a full decade prior to significant increases in obesity prevalence in the United States (21). Second, EAC continues to be significantly more common in men than in women; however, the rise in obesity is more marked in the latter group (22). Some have postulated that gender differences in the distribution of adipose tissue within the body play a role in this phenomenon (8), with men more likely to have central abdominal obesity than women. The slope of the increase in EAC incidence seems too precipitous for obesity to be the only explanation. Our data suggest that other causes, such as hormonal differences between genders (8), synergies between factors, or other factors hitherto unsuspected or unstudied are contributing significantly to the rise in EAC incidence.

Prior studies that have analyzed obesity's contribution to the increase in EAC were observational, mainly case–control studies. These types of analyses have limited abilities to estimate the role of obesity in the rise of EAC incidence due to their retrospective nature and the presence of potential bias and competing risks. In addition, a cohort study with sufficient sample size and long enough follow-up period has not been done previously because of the low incidence of EAC in the general population. Currently, a large clinical trial (AspECT) is underway in the United Kingdom that has recruited more than 2,000 patients with BE and plans to follow the cohort for more than 8 years (23). This study will provide important observational data regarding progression to EAC from BE and may provide additional prospective data regarding obesity's effect on EAC incidence. However, AspECT was primarily designed and statistically powered to assess the effects of aspirin and acid suppression on progression rates, rendering any obesity analyses secondary or post-hoc and, even with the large numbers and follow-up period, underpowered.

Using simulation modeling techniques, we were able to examine the uncertainty surrounding the estimates and provided a way to test and evaluate a wide range of potential transition probabilities and see which correspond to various natural histories.

There were a few limitations in our model which could be addressed in future research and analyses. First, there are limited data to inform model inputs. The annual rates of progression from GERD to BE and from there to EAC are the most salient examples, and there remains significant uncertainty regarding the effect of obesity on progression to EAC. Second, our analysis focused on white males. We chose to perform our analysis in the patient group for which the most empiric clinical data existed, and that group is white males. As previously mentioned, EAC incidence in the past and present, as well as the aforementioned sharp increase therein, is most notable in white males. Furthermore, although specific empirical data regarding precursor health states such as BE are limited in white males, they are even more lacking for females and nonwhites. Therefore, including females and nonwhites in the model would introduce yet another level or dimension of uncertainty. The purpose of our study was to test a scientific hypothesis, not to guide clinical practice or inform public health policy and in this context we believe building a model of white males is justifiable because of the precision we gain in our analysis. In addition, some analyses suggest that waist circumference may be superior to BMI as a predictor of EAC among males and females (20, 24). Ideally our model would have included such markers of central obesity; however, our analysis only simulated males, where there is a strong correlation between high BMI values and the presence of central obesity. Therefore, using BMI alone may have been

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adequate. Another limitation to our analysis was that we modeled obesity dichotomizing the population using a BMI of 30 as a cut off value; consequently, those with intermediate BMI values, or overweight, were not incorporated, potentially leading to an underestimate of the impact of obesity and raising concerns about the validity of the conclusion. Although the incorporation of waist circumference and an overweight category into our model would have been interesting and potentially worthwhile, the lack of sufficient data to adequately inform model inputs made this unfeasible. Finally, our sensitivity analysis that explores the association between obesity and EAC provides some insight into how model projections would change with differing estimates of the impact of obesity. To estimate the impact of the increase in obesity on EAC, we isolated obesity as a specific risk factor and then incorporated it into scenario 2. We acknowledge that this methodology has the limitation of assuming an overly simplified system where no potential interactions exist. However, an advantage of these simplifying assumptions is an analysis that is more transparent and readily comprehensible.

Future trial data from studies such as AspECT (23) that carefully track the natural history of those with BE could improve understanding of obesity's impact on progression to EAC, confirming or contradicting the ORs we derived from prior published studies. However, our sensitivity analysis finds that the OR would have to be unrealistically high to reproduce the actual increase in EAC incidence with our model framework. Future epidemiologic and modeling analyses should focus on searching for additional risk factors, synergies between risk factors, and identifying potential subsets of the population that are at highest risk for this cancer that still affects a relatively small percentage of the population, but is undergoing a dramatic rise in incidence.

The message of our analysis is not that obesity is acceptable because the associated increased risk of EAC is not substantial but instead that we need to search for other hypotheses to better explain and understand the alarming rise in EAC incidence. We chose to focus on and isolate a single putative contributing factor. Our conclusion is that unless there is significant synergy with other hypothesized contributors or substantial heterogeneity of effect within a subgroup of the population, obesity is not a major cause of the 500% rise in EAC.

Disclosure of Potential Conflicts of Interest

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