# Precision Cancer Prevention of Esophageal Adenocarcinoma: A Lesson from Napoleon

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## Summary

A rapid and continuous rise in incidence of esophageal adenocarcinoma over the past four decades has been well documented in many developed countries across three continents. Among white males, who are in the highest risk demographic, incidence has risen 10-fold in the U.S. since the early 1970s. Incidence among males in the U.K. are among the highest in the world, and 50% higher than in the U.S. Unfortunately, treatments have not kept pace; unless their cancer is identified at a very early stage, most individuals will not survive a year after diagnosis. The beginnings of this widespread problem were first recognized over 25 years ago, yet rates have continued to rise against a backdrop of much improved understanding and management including the introduction of medical and surgical treatments aimed at reducing acid reflux, one of the most important risk factors; the availability of screening and surveillance programs for the precursor lesion Barrett's metaplasia; and the development of endoscopic therapies for prevention or treatment of early invasive cancer. We estimate that only about 7% of the 10,000 cases of esophageal adenocarcinoma diagnosed annually in the U.S. are identified through current approaches to cancer control, and trace pathways by which the remaining 93% are "lost." Based on emerging data on etiology and predictive factors coupled with new diagnostic tools, we suggest a five-tier strategy for prevention and control that begins with a wide population base and triages individuals into progressively higher risk strata, each with risk-appropriate prevention, screening and treatment options.

## Background

For nearly four decades, primary care physicians, gastroenterologists, surgeons and oncologists have been fighting a losing battle against a relentless opponent – esophageal adenocarcinoma. During this period, the cancer has undergone an impressive and continuous rise in incidence, from a true rarity in the early 1970s to the most common histologic type of esophageal cancer in many developed countries.[1–3] The most recent data from the U.S. Surveillance Epidemiology and End Results (SEER) registries show more than an eight-fold rise (from 0.3 to 2.7 per 100,000) in overall annual incidence between 1973 and 2011, and a

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10-fold increase (from 0.6 to 6.0 per 100,000) among white men (Figure 1).[4] Some of the highest incidence rates of esophageal adenocarcinoma in the world have been observed in the U.K. (9.4 per 100,000 males in the 2008–2010 time period.)[5] Treatment effectiveness has not substantially improved; currently about half of individuals newly diagnosed with the cancer succumb within a year, and fewer than 20% survive five years.[6]

These trends have occurred despite a background of improving medications and therapies that might have been expected to reduce risk of esophageal adenocarcinoma. For example H2-antagonists were introduced in the late 1970s, and the even more potent proton pump inhibitors a decade later. At appropriate doses these can essentially eliminate gastric acid production and minimize the symptoms of gastroesophageal reflux disease (GERD), which is a major risk factor for the cancer. Fundoplication was first described in the 1950s and gained popularity in the 1970s as a surgical means of strengthening the effectiveness of the lower esophageal sphincter and reducing or eliminating GERD. Unfortunately there is little evidence that these approaches substantially reduce incidence from esophageal adenocarcinoma.[7–10]

Increasingly, gastroenterologists have been focusing on the identification and long-term surveillance of persons with Barrett's metaplasia to facilitate identifying and treating pre-invasive or early-stage cancer. Photodynamic therapy began to be used in the 1990s as an endoscopic method of eliminating metaplastic or dysplastic cells of the esophagus, but has largely been dropped because of frequent side effects and lack of clear benefit.[11] More recently, endoscopic therapies such an endoscopic mucosal resection combined with ablation techniques such as radiofrequency ablation have advanced considerably, and become a common treatment for persons with high-grade dysplasia, a biomarker of high risk of neoplastic progression to esophageal adenocarcinoma, and have been proposed even for persons at lower risk.[12,13] These procedures have largely replaced esophagectomy, with its high morbidity and mortality, for persons deemed at high risk of developing invasive cancer, or a poor risk for surgery. However, the jury is still out regarding the effectiveness of surveillance coupled with endoscopic therapy, as very little evidence is available regarding the ultimate goal of reducing population mortality from esophageal cancer.

While there is some room for optimism due to the improved treatments available, if Figure 1 is taken to heart, one can only conclude that primary and secondary prevention efforts in response to this mounting problem, which was first identified in the late 1980s,[14] have had minimal impact, at least on a population basis. Where did we go wrong?

## The road taken

A key reason for the failure of the current paradigm is that we are not identifying the "at risk" population very effectively. The current strategy can be construed as representing not a war on esophageal adenocarcinoma, but rather a war on Barrett's esophagus. However, for the majority of individuals, Barrett's esophagus is a benign condition which usually remains undiagnosed. In fact there is evidence that the metaplastic epithelium protects against the inflammatory and erosive effects of bile and acid reflux.[15,16] In addition, some cases of esophageal adenocarcinoma may occur without associated Barrett's metaplasia, or in an

ultra-short columnar tongue which may not be endoscopically visible. Far from a "lightning strike," this war seems more akin to Napoleon's long, cold and ultimately fruitless march on Moscow in 1812–1813.[17] It is well known how that ended for soldiers and citizens on both sides, with vastly overstretched resources contributing to the rapidly diminishing size of Napoleon's army over time, space and temperature, as famously depicted by Charles Minard (reproduced in Figure 2.)

A similar graphical depiction ("Napoleogram"; Figure 3) can describe the current situation in terms of the overall burden of esophageal adenocarcinoma, the subgroups considered for diagnostic and surveillance endoscopy tests, and the rapidly diminishing number of esophageal adenocarcinoma cases which can be found in these subgroups, despite large expenditures for such endoscopic procedures.[18] Figure 3 is divided into four panels estimating incidence rates and numbers of cases arising in: (A) the overall adult population, (B) those with and without recurrent symptoms of GERD, (C) those who do and do not receive screening endoscopy, and (D) those with and without diagnosed Barrett's esophagus.

## Panel A

In the U.S. approximately 17,000 cases of esophageal cancer are diagnosed per year[19] of which almost 60% (10,000) are adenocarcinomas.[1] Over 99% occur in persons 40 years of age or older, a population of approximately 150M, yielding a crude incidence rate of 6.7 per 100,000.[19,20]

## Panel B

Population-based studies in the U.S. and Sweden indicate that about 40% of esophageal adenocarcinoma cases (4,000 per year) occur among persons without chronic symptoms of GERD (i.e., heartburn and/or regurgitation once per week or more.)[21,22] They comprise approximately 80% of the adult population (120M persons), and experience a crude annual incidence rate of 3.3 per 100,000 (upper section of panel B, labeled "GERD–").[23–25] The remaining cases (6,000) occur among the 20% of the adult population (30M) who report GERD symptoms at least once per week,[23–26] yielding an annual incidence rate of 20 per 100,000 (lower section of panel B, labeled "GERD+".) Comparing crude incidence rates in persons with and without chronic GERD symptoms yields a relative risk for esophageal adenocarcinoma of about six, which is consistent with published studies.[25,26]

## Panel C

Among those with recurrent symptoms of GERD, only a small proportion, estimated at 10% (3M persons),[18] undergo endoscopy in a given year to i) identify those with Barrett's metaplasia for enrollment in surveillance, ii) follow up those known to have Barrett's metaplasia, and/or iii) screen for early esophageal adenocarcinoma (or other treatable conditions such as ulcer) which has not yet given rise to alarm symptoms.[27] Assuming that those who undergo endoscopy do not represent a random selection of those with GERD symptoms, but rather, those with slightly higher risk (estimated at 30% higher in Panel C) due to reasons such as symptom severity, clinical acumen, etc., their annual incidence would be 26 per 100,000. The remaining 27M persons with recurrent GERD symptoms who do not

undergo endoscopic screening would therefore experience a slightly lower annual incidence of 19.3 per 100,000, yielding 5,220 cases in this group.

### Panel D

Endoscopic investigation of persons with recurrent GERD symptoms generally reveals Barrett's metaplasia to be present in at least 8% of initial endoscopies, depending on the population being considered.[28–31] Assuming 8% prevalence of Barrett's metaplasia (240,000 persons) and an annual rate of progression to EA of approximately 0.3% (300/100,000),[32] then 720 cases (about 7%) will have been diagnosed as a consequence of current prevention activities. A few esophageal adenocarcinoma cases would still be observed among persons for whom Barrett's is not found at endoscopy, perhaps due to Barrett's being missed, a rapidly developing cancer or an adenocarcinoma not arising in Barrett's epithelium. Given the numbers above (8% prevalence of Barrett's and a progression rate of 0.3% in persons positive for Barrett's), it can be calculated that 60 esophageal adenocarcinomas would arise in this group, reflecting an incidence rate of 2.2 per 100,000 per year. We are not aware of published incidence rates for comparison.

## Challenges

Under- and over-diagnosis are increasingly being recognized as significant challenges for many cancers in devising screening and surveillance programs that are both economically sensible and effective in reducing mortality.[33] These challenges are particularly apparent in the current approach to control of esophageal adenocarcinoma, as described in Figure 3, which paradoxically yields both over- and under-diagnosis.

Under-diagnosis occurs because more than 90% of cases arise outside of endoscopic diagnosis and surveillance programs.[34] Current U.S. "best practice" advice states that, in the absence of alarm symptoms, endoscopic investigation is indicated only in those with recurrent GERD symptoms who do not respond to proton pump inhibitors.[27] Thus, a large fraction of cases (about 40%) are missed simply because they do not report sufficient symptoms of GERD.[25,26] Most of these 4,000 individuals will eventually be diagnosed only after they develop alarm symptoms, at which time the cancer is typically too far advanced for effective treatment. Another estimated 52% of cancer cases will have had recurrent GERD symptoms, but were never investigated. Reasons for this are not clear, but likely involve a combination of patient characteristics, physician characteristics, and issues of access to health care. They too are usually diagnosed at a late stage, and consequently have a very poor prognosis.

Conversely, over-diagnosis occurs because most (95%) individuals who do undergo periodic surveillance do not develop the cancer in their lifetime, and thus contribute to overstretching healthcare resources.[16,33] Within the current paradigm, simply performing upper endoscopies on a larger proportion of persons with reflux symptoms would only worsen the over-diagnosis problem without materially improving population mortality from esophageal adenocarcinoma. Importantly, it is still not clear whether individuals diagnosed through surveillance programs in the community setting actually experience improved survival.[34–37]

## A different direction

If Napoleon had paused as he neared Moscow to fully contemplate the likely outcome of his campaign, taking into account how poorly it had progressed up to that point, he might have changed course and chosen a different path, saving hundreds of thousands of lives in the process. An opportunity of similar magnitude presents itself today, as modeling indicates that the incidence of esophageal adenocarcinoma will continue to increase through 2030, and that approximately 160,000 deaths attributable to this cancer will occur in the U.S. alone over the next two decades.[38] A lesson we can learn from Napoleon is the importance of recognizing when an approach is not working, and resources are stretched too thin, so that a different direction can be plotted and tried.

Analysis of the neglected and uninvestigated subpopulations depicted in Figure 3 might give us a new perspective regarding the individuals on whom we should focus our efforts in a renewed, more scientifically focused attempt to win this war. One promising approach to cancer prevention is to consider each risk factor, or predictor, in its most important and cost-effective context, i.e., "precision cancer prevention." Current approaches presume that reflux is the single overriding risk factor.[25,26] However, there are a number of other strong risk factors for esophageal adenocarcinoma that have been identified;[39–46] hence it is now possible to categorize individuals into more precise risk groups, each of which can be targeted for further investigation and/or prevention interventions in a manner that is appropriate for their absolute risk (annual incidence) of esophageal adenocarcinoma.

Table 1 describes five separate risk strata that could be considered, ranging in annual cancer incidence from about 7/100,000 in the general population and the general practice settings, to 1,000-fold higher (7,000/100,000) among those in a tertiary care setting for management of those at highest risk. Incidence in the lowest two tiers is based on SEER data;[4] whereas incidence in the highest tier (7% per year) represents an approximate minimum risk at which surgical or endoscopic interventions might be reasonably applied.[47] Incidence in the third and fourth strata are set to be 10- and 100-fold higher than the general population to illustrate the separation in risk that might be achieved with current information together with resources that may be available in the near future. The sub-populations triaged to higher risk strata would be correspondingly reduced by 10-fold (or more) per level, depending on the sensitivity of such classification schemes.

In the general population (stratum 1), the main modifiable risk factors include obesity, cigarette smoking and diet low in fruit and vegetables.[48,49] It should be noted that although chronic GERD is a key risk factor, it is not easily addressed at the general population level.[26] Given the well-recognized importance of these three factors for multiple other cancers, as well as for cardiovascular disease and other health outcomes, the marginal importance of the relatively rare occurrence of esophageal adenocarcinoma is quite small in driving public policy towards improvements in these adverse exposures. Nevertheless, it is still important to recognize that improvements in population healthy behaviors might actually have as large or larger impact on incidence and mortality from esophageal adenocarcinoma than the other more targeted interventions discussed below, as well as treatment of those with the cancer.[50,51]

In the office of the primary care provider (<u>stratum 2</u>), the absolute risk of a particular patient over 40 years of age might be considered about the same as in the general population, but here the possibilities are much greater for educating both provider and patient as to modifiable risk factors, and for those sufficiently motivated, actually encouraging modest behavioral changes.[29,52] Given the additional information resources available in this setting, e.g., medical and family history,[53] physical examination, blood/urine measures (as effective biomarkers are identified),[54–57] and knowledge of their independent associations with cancer risk, a risk assessment tool, or risk calculator, can be used to educate and motivate, as well as to identify those at a higher level of risk who should be considered for additional investigation.[51,58] While no highly penetrant germline mutations for esophageal adenocarcinoma have been identified, there is evidence for a significant polygenic hereditary component,[59] and the list of common mutations conferring small differences in risk is growing.[60–63] Eventually germline mutations might contribute to the risk prediction algorithms. This stratum is one context in which a substantial improvement in referral decisions can be made rather easily. Rather than relying primarily on reflux symptom history, ten or more risk factors, all easily assessed, can be integrated into a single risk calculation, and only those above a threshold (e.g., ten-fold higher is used as the example in Table 1) can be triaged to the next assessment stage.[29]

Traditionally, the next level of assessment has involved referral to a gastroenterologist for endoscopy in order to visualize abnormalities, including columnar epithelium, and to collect biopsies for histologic assessment. Ultra-thin transnasal endoscopes have been developed but they still require significant investment for the hardware and skilled operators more suited to the secondary care provider.[64,65] Recently, several new less invasive non-endoscopic approaches have shown promise for use in primary care (<u>stratum 3</u>). A tethered capsule has been created using volume laser endomicroscopy which uses frequency domain optical coherence tomography that can rapidly scan the esophageal lumen at a thirty micron lateral resolution to allow this device to be used for screening for BE.[66] In addition molecular screening of the esophagus using non-invasive methods soon may be shown to be practical.[67] For example, Cambridge University have developed the Cytosponge which can be used in the office setting without sedation and then the retrieved esophageal epithelial cells are assessed in a diagnostic assay for BE which detects Trefoil Factor 3 (TFF3).[68] This technique has a sensitivity of 80–90% depending on the length of the Barrett's segment with a specificity of around 92%.[69] It has also recently been shown to be able to identify lesions affecting the *p53* gene, as an indicator of high grade dysplasia, with sensitivity of 86% and specificity of 100% and further clinical trials are ongoing. Such molecular tests might also detect early cancers that have not necessarily arisen in BE. [70,71] These emerging tests are still experimental but to the extent that tissue-based markers (e.g., cell surface or somatic genetic markers) from the capsule sponge or other non-invasive techniques, in concert with other risk factors,[72–74] can be demonstrated to differentiate the minority with substantially increased risk (again, ten-fold higher is used as the example in Table 1) who can be referred to secondary care, from the majority whose absolute risk remains low, then a substantial improvement in clinical practice would be achieved.[75] For those who remain in stratum 3, chemopreventatives (e.g., aspirin, statins) might be considered as well as stronger

encouragement to modify lifestyle (e.g., smoking cessation, improved diet, weight loss, increased physical activity.)[44,46,76–81]

Those calculated to be at higher risk based all of the previously collected risk factor information would then be considered to have entered <u>stratum 4</u> under care of a secondary care provider. This group would be much smaller in size than the number of persons with recurrent GERD symptoms in the general population (1.5M vs. 30M), but have a much higher average risk. Here, an absolute risk of 700/100,000 (0.7% per year) (for example) would likely prompt an endoscopy with multiple patterned biopsies as well as biopsies directed at visible abnormalities. Information based on endoscopy and biopsy, such as somatic genetic abnormalities[70,74,82] and histologic findings[83] would then define whether the patient could be referred back to stratum 3, entered into surveillance (remaining in stratum 4) and perhaps or be triaged to the highest risk stratum.[71]

Persons entering <u>stratum 5</u> (tertiary care provider) would have an average absolute risk of developing esophageal adenocarcinoma of 7/100 (7%) per year, based on the example in Table 1. Surgical or endoscopic interventions proven to lower risk of mortality from esophageal adenocarcinoma could be offered to this group, who could then be returned to stratum 4 for continuing surveillance.

## Conclusions

Efforts over the past several decades directed towards primary prevention and early diagnosis of esophageal adenocarcinoma have had very little impact at the population level in curtailing its rapidly increasing morbidity and mortality. Fortunately, much has been learned from epidemiologic and clinical studies during this period regarding etiologic and other predictive risk factors (e.g., lifestyle, demographics, anthropometry, genetic, and tissue-based biomarkers), while new techniques and devices are being developed which offer promising opportunities for integrating what is now known about the development of the cancer into a scientifically sound clinical practice protocol.

Such a protocol would be designed to start with a wide population base, including many who are ignored by current practices, and triage individuals into progressively higher risk strata, each with risk-appropriate prevention, screening and treatment options. Risk assessment methods would also be stratum-specific. At the lowest strata there would be minimal intervention and simple, cost-effective tools, whereas in the higher risk groups clinicians would make use of increasingly precise, but also increasingly invasive and expensive tools. Hence, the careful selection of tests and prevention activities at different stages should be favorable economically, in contrast to the current scenario of enrolling more and more patients into endoscopic surveillance with little regard to their absolute risk, and therefore little population benefit. Some of the technologies mentioned are still in research and development, and are not yet available for widespread adoption. In addition, development and validation of risk prediction algorithms for the middle three strata are important aspects of this approach. Such efforts have already begun, although they have been based on limited data and settings;[29,84] thus a good deal of development and validation work in this area remains, but the potential reward is high.

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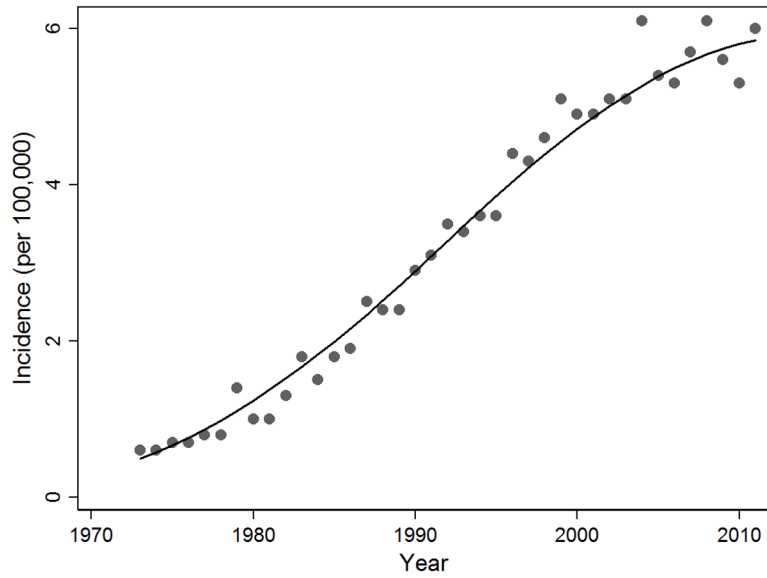
**Figure 1.**
Esophageal adenocarcinoma incidence in white males, United States, 1973–2011.
[Surveillance, Epidemiology, and End Results (SEER) Program (www.seer.cancer.gov)
SEER*Stat Database: Incidence - SEER 9 Regs Research Data, (with SEER Delay Factors)
Nov 2013 Sub (1973–2011) <Katrina/Rita Population Adjustment> National Cancer
Institute, DCCPS, Surveillance Research Program, Surveillance Systems Branch, released
April 2014, based on the November 2013 submission.]
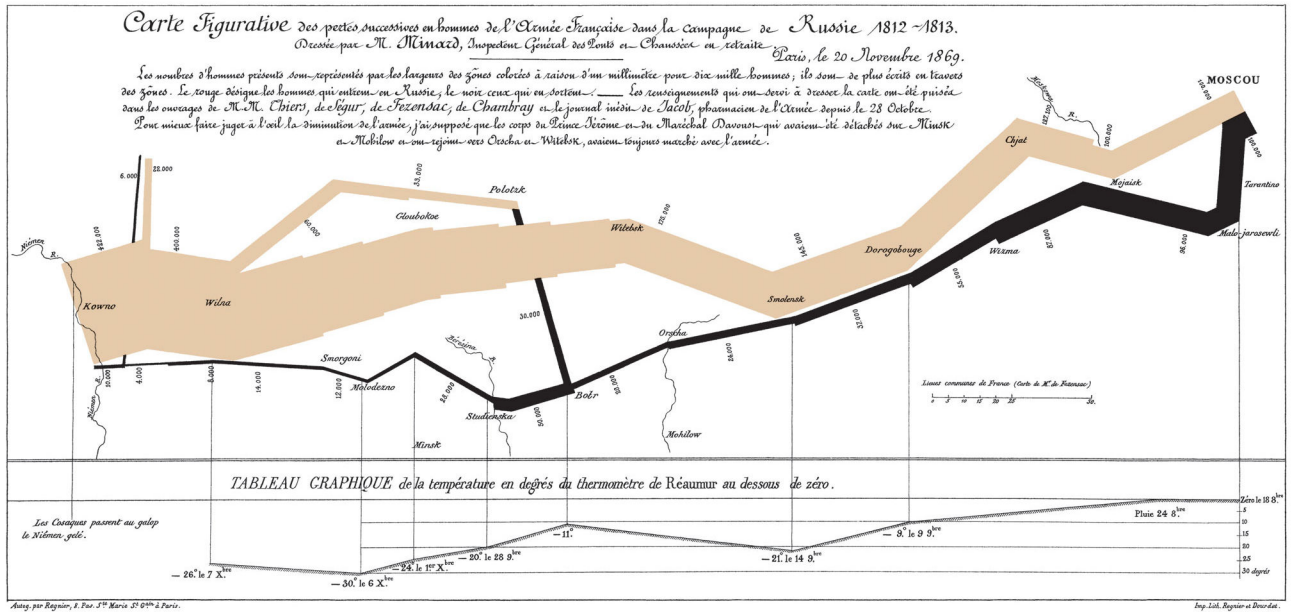
**Figure 2.**
The size of Napoleon's army, represented by the width of the line, dwindled from almost 500,000 to about 10,000 during his invasion of Russia (gray), and return to France (black) during the extremely cold winter of 1812–1813. (Charles Minard, 1869; public domain)
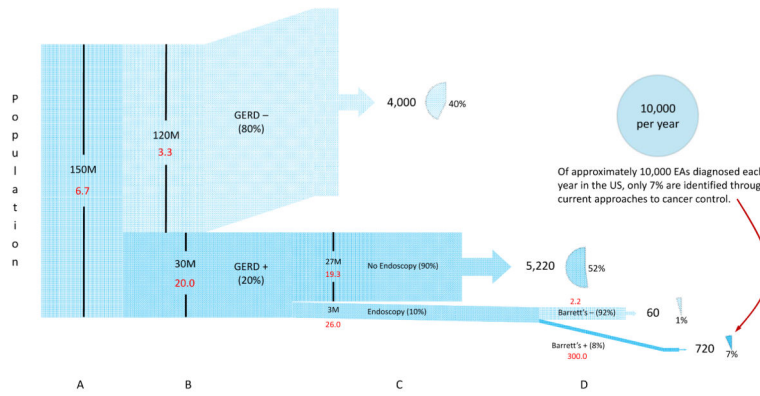
**Figure 3.**
The current approach to control of esophageal adenocarcinoma identifies only about 7% of the cases via screening and surveillance, with most of the remainder diagnosed because of alarm symptoms, usually indicative of later stage disease. Approximately half (52%) of the cases arise in persons with reflux symptoms who are not investigated through endoscopy or other means. Numbers in red indicate the estimated annual incidence rate in each population subgroup. See text for details.

**Table 1**

Prevention approaches appropriate for specific strata of absolute risk (annual incidence) of esophageal adenocarcinoma.

| Stratum | Annual incidence | Setting (population) | Additional resources available | Additional risk factors assessed | Potential prevention activities |
|---|---|---|---|---|---|
| 1 | 7/100,000 | General population 40+ (150M) | | • Obesity<br>• Cigarette smoking<br>• Diet | • Reduce exposures on societal level |
| 2 | 7/100,000 | Primary Care (150M) | • Questionnaire<br>• History<br>• Examination<br>• Blood | • Demographics (age, sex, race)<br>• Recurrent reflux symptoms<br>• Family history<br>• Potential biomarkers based on blood/urine | • Education of patient and physician of risk factors<br>• Interventions to reduce risk factors on individual level<br>• Risk assessment for further evaluation |
| 3 | 70/100,000 (.07%) | Primary care (15M) | • Non-invasive esophageal tissue sampling (e.g., "Cytosponge") | • Additional potential biomarkers based on blood/urine<br>• Cell surface or genetic markers based on tissue | • Above activities<br>• Chemopreventatives (e.g., aspirin)<br>• Risk assessment for referral and further evaluation |
| 4 | 700/100,000 (.7%) | Secondary care (1.5M) | • Endoscopy with esophageal biopsy | • Germline genetic factors<br>• Somatic genetic abnormalities<br>• Histologic characteristics | • Above activities<br>• Periodic surveillance<br>• Risk assessment for referral for intervention |
| 5 | 7,000/100,000 (7%) | Tertiary care (150K) | | | • Surgical or endoscopic intervention<br>• Referral back to secondary care for continued surveillance and risk assessment |