Understanding Cancer Incidence in Barrett’s Esophagus: Light at the End of the Tunnel

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The main importance of Barrett’s esophagus, a metaplastic change in the epithelial lining of the esophagus, is that its presence is a harbinger of increased risk of esophageal adenocarcinoma. Given the rapidly increasing incidence of esophageal adenocarcinoma, the management of Barrett’s esophagus becomes a prominent clinical question.

The cancer risk in patients with Barrett’s esophagus matters. The magnitude of this risk drives important clinical and research decisions: Does the potential benefit of screening, surveillance, or treatment outweigh the potential risk? If the incidence is extremely low, then methods to detect Barrett’s esophagus, survey it for early cancers with endoscopic biopsies, or even ablate the metaplastic mucosa are unlikely to provide a net benefit. The potential benefit to a few people may be exceeded by the negative consequences to many others, which include a small risk of physical harm from the required invasive procedures and the psychological harm of being labeled with a precancerous condition.

A population-based determination of the incidence of esophageal adenocarcinoma among patients with Barrett’s esophagus has been surprisingly elusive, leading to ambiguity regarding important clinical and research decisions. In the current issue of the Journal, Bhat et al. (1) provide one of the first estimates of incidence from a large multicenter population. As suggested by these authors, published cost-effectiveness analyses, upon considering both the risks and the benefits of endoscopic screening or surveillance, suggest that surveillance would be a reasonable and cost-effective choice if the rate of progression to cancer is high (eg, one cancer for every 100–200 patients per year) but would be a costly choice if the rate of progression is low (eg, one cancer for every 400 patients per year) (2). Other authors have suggested that in a population that has been screened just once to “clear out” the prevalent cancers, subsequent surveillance would be costly relative to the number of lives saved if the cancer incidence were less than one cancer for every 54 patients per year (3).

The study by Bhat et al. (1) addresses several crucial questions:

1. **What is the risk of progression to cancer in a general population?** The authors suggest that the risk is somewhat lower than what has been estimated by most prior studies. However, in most estimates, the study included persons without intestinal metaplasia, who would not have been considered to have traditional “Barrett’s esophagus” in the United States. The author’s estimated cancer risk for persons with intestinal metaplasia was only slightly lower than prior estimates (4,5).

2. **Does the risk differ between patients with vs those without intestinal metaplasia on biopsy?** The authors report that cancer risk is statistically significantly lower in persons without intestinal metaplasia (vs with metaplasia) on the initial biopsy. Furthermore, their incidence figures suggest that persons who are consistently without intestinal metaplasia, after repeated sampling, are even more unlikely to develop cancer.

3. **Does the risk change over time?** Almost all cost-effectiveness models assume that the risk of cancer progression is constant over time; the current study is among the first adequately powered evaluations to show that cancer detection is relatively steady over time.

4. **Does the risk vary by age and sex?** Current clinical recommendations imply that surveillance, if performed, would likely provide the greatest benefit to men and to persons older than 50 years. The current study supports these hypotheses by finding that the risk of esophageal cancer is substantially higher among men than women and among older persons compared with those who are younger than 50 years.

This important study, however, still leaves several important gaps mainly because the investigators lacked detailed endoscopic data. The presence of a visually abnormal esophageal lining is a crucial requirement for diagnosing Barrett’s esophagus in most clinical studies. For the current study, entry into the cohort required only columnar mucosa on an esophageal biopsy; it is unclear how many patients actually had visible changes of Barrett’s esophagus on endoscopy. Such misclassification could meaningfully bias the results: if a moderate proportion did not have visible changes, and if the risk in that group was lower than among persons who had visible changes, then the average cancer risk may be artificially low.

The finding that a relatively small proportion of patients had more than one endoscopic examination was interesting because it raises the possibility that some subclinical cancers might remain undetected. Undetected cancers might partly explain the difference in cancer incidence between this study and others from centers that use vigorous regular endoscopic surveillance programs. It is unknown what proportion of such cancers would cause clinical disease, especially among more elderly patients with competing causes of mortality.

In summary, the current study, which was conducted in a large general population, provides general support for many paradigms underlying current thoughts about the management of Barrett’s esophagus (6). First, patients without intestinal metaplasia, and especially patients with multiple examinations who lack metaplasia, are at relatively low risk of malignant progression; such patients are less likely to benefit from surveillance or treatment.
Second, patients with intestinal metaplasia are at increased risk of cancer, which may make surveillance cost-effective if surveillance or treatment is effective (an unproved tenet to date). Third, esophageal and gastric cardia cancer risk is greater in men than in women with Barrett’s esophagus, and risk is greater in people older than 50 years than in younger people. Last, the rate of detection is fairly constant over time.

Key avenues for future investigation include the determination of whether surveillance or treatment (eg, ablation or chemoprevention) actually decrease cancer deaths and the development of better techniques for risk stratification. The study by Bhat et al. (1) can help inform the development of more meaningful “personalized” risk scores that incorporate demographic, biochemical, and genetic factors. Such scores have been evaluated in other malignancies and medical conditions (7,8). Ongoing molecular studies also offer the promise of more accurate reproducible methods for stratifying patients into high- vs low-risk groups, beyond the current relatively crude methods that depend on subjective microscopic criteria of intestinal metaplasia and dysplasia (9,10).

References

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