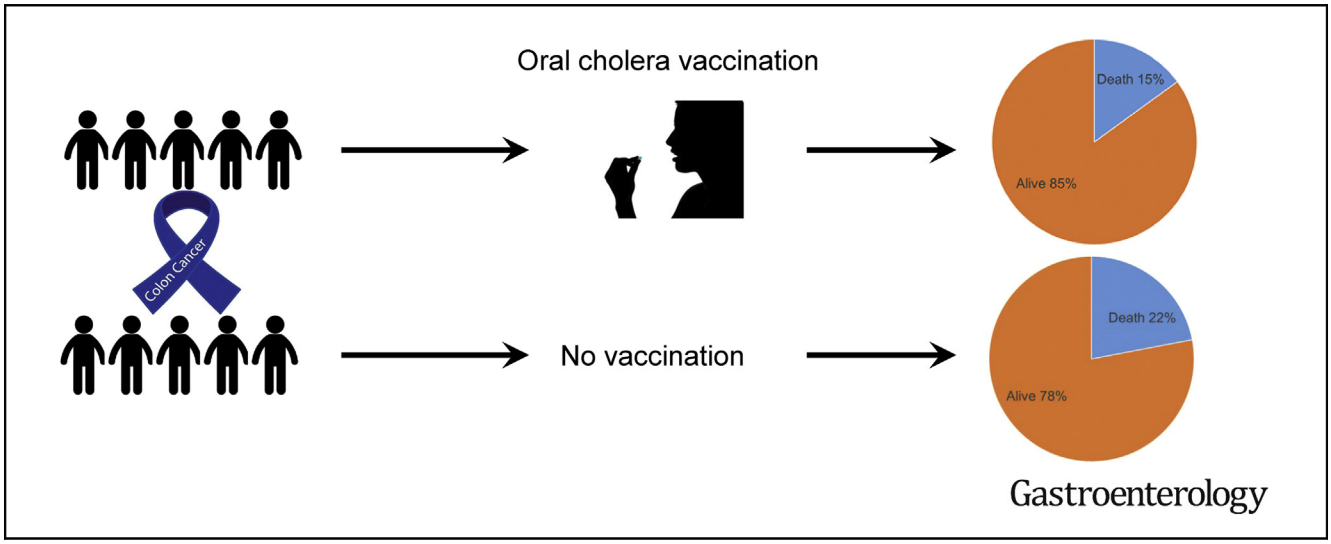
Gastroenterology 2018;154:86–92

CLINICAL AT

Cholera Vaccine Use Is Associated With a Reduced Risk of Death in Patients With Colorectal Cancer: A Population-Based Study

Jianguang Ji,[1] Jan Sundquist,[1,2] and Kristina Sundquist[1,2]

[1]Center for Primary Health Care Research, Lund University/Region Skåne, Sweden; [2]Department of Family Medicine and Community Health, Department of Population Health Science and Policy, Icahn School of Medicine at Mount Sinai, New York, New York



See Covering the Cover synopsis on page 6.

BACKGROUND & AIMS: Cholera toxin can act as a modulator of the immune response with anti-inflammatory effects; it reduces development of colon polyps in mouse models of colorectal cancer (CRC). We performed a population-based study to determine whether, in patients with a diagnosis of CRC, subsequent administration of the cholera vaccine (killed *Vibrio cholerae* O1 whole cells and recombinant cholera toxin B subunit) affects mortality. **METHODS:** We identified patients from the Swedish Cancer Register who were diagnosed with CRC from July 2005 through December 2012. These patients were linked to the Swedish Prescribed Drug Register to retrieve cholera vaccine use. We used Cox regression analysis to calculate the hazard ratio (HR) of death from CRC and overall mortality in patients with post-diagnostic use of cholera vaccine compared with matched controls. **RESULTS:** A total of 175 patients were diagnosed with CRC and given a prescription for the cholera vaccine after their cancer diagnosis. Compared with propensity score-matched controls and adjusted for confounding factors, patients with CRC who received the cholera vaccine had a decreased risk of death from CRC (HR, 0.53; 95% CI, 0.29–0.99) and a decreased risk of death overall (HR, 0.59; 95% CI, 0.37–0.94). The decrease in mortality with cholera vaccination was largely observed, irrespective of patient age or tumor stage at diagnosis or sex. **CONCLUSIONS:** In a population-based study, we associated administration of the cholera vaccine after CRC diagnosis with decreased risk of death from CRC and overall mortality.

Keywords: Cohort Study; Epidemiology; Register-based Study; Colon Cancer; Immune Regulation.

Colorectal cancer (CRC) is ranked as the third most common malignancy and the fourth most deadly cancer in the world.[1] In the United States, CRC is the third leading cause of cancer-related deaths in women and the second leading cause in men.[2] The incidence of CRC is lower in poor- and middle-income countries but is on the increase because of societal and economic development in these countries, as well as a shift to Western diets and lifestyles. CRC incidence tends to be stabilizing or decreasing in developed nations, such as the US and many European countries.[3,4] However, the incidence in these

Abbreviations used in this paper: **CI, confidence interval; CRC, colorectal cancer; CTA1, cholera toxin A1; CTB, cholera toxin B; HR, hazard ratio.**

Most current article

0016-5085/$36.00
https://doi.org/10.1053/j.gastro.2017.09.009

EDITOR'S NOTES

BACKGROUND AND CONTEXT

Cholera toxin can act as a modulator of the immune response with anti-inflammatory effects and it reduces development of colon polyps in mouse models of colorectal cancer (CRC).

NEW FINDINGS

The researchers show that patients with CRC who received the cholera vaccine had a decreased risk of death from CRC and a decreased risk of death overall.

LIMITATIONS

This study did not include information about medical treatment of CRC.

IMPACT

Cholera vaccine might be used as adjuvant therapy for patients with CRC.

countries is still the highest in the world, most likely because of the high consumption of processed and unprocessed meat, which can lead to dysregulation of colonic microbial metabolism.[1] In addition, the hygiene hypothesis, ie, because of lack of exposure to microbes during childhood, was originally introduced for autoimmune and allergic diseases and later was expanded to include neoplasia, which might account for the association between microorganisms and CRC.[5] Recent evidence from human studies and animal models suggests a possible link between gut microbiome and CRC, but the role of gut microbiome in the formation of CRC remains elusive.[6–9] Infectious agents, as well as their products, can cause a wide range of host immune responses, which might be related to cancer development and/or progression. Certain types of pathogens might lead to antitumor immune responses and decrease the risk of cancer.[5] One possible mechanism is that gut bacteria antigens might play an important role in the regulation of immune responses.[10–13] Oral administration of cholera toxin can down-regulate the accumulation of neutrophil, up-regulate the regulatory T cell accumulation and IL-10 production in the colonic mucosa, leading to a reduction of colonic polyps in the mouse model.[10] In addition, other immune cell populations, such as macrophages and NK cells, are also up-regulated when administrated with cholera toxin.[10–13] Based on existing evidence, we hypothesized that post-diagnostic use of cholera vaccine, which includes both killed whole cells of Vibrio cholera O1 and recombinant cholera toxin B (CTB) subunit, in CRC patients might be associated with an improved prognosis. We retrieved data from several national registers in Sweden and studied the risk of CRC mortality and overall mortality among CRC patients who were cholera vaccine users after their cancer diagnosis, and compared them with matched controls. To the best of our knowledge, this is the first nationwide population-based study to explore the association between post-diagnostic use of cholera vaccine and the risk of mortality in CRC patients.

Methods

Study Population

This retrospective cohort study was approved by the Ethics Committee at Lund University, Sweden. First we identified all patients diagnosed with CRC between July 2005 and December 2012 from the Swedish Cancer Register by using the 10th International Classification of Disease (ICD-10) codes C18, C19, and C20. The Swedish Cancer Registry was founded in 1958 and is maintained by the National Board of Health and Welfare. In Sweden, it is compulsory for clinicians and pathologists/cytologists to report all newly diagnosed cancers to the cancer registry. At present, the Swedish Cancer Registry has an estimated greater than 90% completeness of nationwide coverage.[14] Tumor characteristics according to the TNM system, including the size of tumor, nodal status, and presence of metastatic disease, have been recorded in the register since 2002.[15] T shows primary tumor size; N tells whether the tumor has spread to nearby lymph nodes; and M indicates whether the cancer has spread (metastasized) to other body organs. Numbers or letters after T, N, and M provide more details about each of these factors. The numbers 0 through 4 indicate increasing severity.[16] The T, N, and M categories were used to determine and create stage at diagnosis of CRC,[17] which ranged from stage I (the least advanced) to stage IV (the most advanced). The stage at diagnosis of CRC was defined as follows: stage I (T1 or T2 N0 M0), stage II (T3 or T4 N0 M0), stage III (any T N1 or N2 M0), and stage IV (any T or N M1).[17]

We further linked these CRC patients to the Swedish Prescribed Drug Registry to retrieve information about cholera vaccine use. The Swedish Prescribed Drug Register was established in July 2005 by the National Board of Health and Welfare. It includes information about drug utilization and expenditures for all prescribed drugs for the entire population in Sweden. All drugs are classified according to the Anatomical Therapeutic Chemical (ATC) classification system. The ATC code J07AE01 was used to identify individuals who had been prescribed and dispensed with the cholera vaccine. In Sweden, cholera vaccine is sold under the product name *Dukoral*, which is composed of small amounts of inactivated Vibrio cholera O1 and recombinant CTB subunit (not the holotoxin). The cholera toxin is composed of 6 protein subunits: a single copy of the A subunit and 5 copies of the B subunit. When infected by Vibrio cholera, the B subunit ring of the cholera toxin firstly binds to GM1 gangliosides (expressed on all mammalian nucleated cells) on the surface of target cells. The entire toxin complex is then endocytosed by the cell and the cholera toxin A1 (CTA1) chain is released, further activating adenylate cyclase and leading to severe dehydration. CTB subunit is not toxic by itself, but it does have an immuno-adjuvant function. Thus a recombinant CTB subunit is an important component in cholera vaccine to induce effective immune response but without side effects. In total, we found 175 CRC patients who had used cholera vaccine after their cancer diagnosis. To mitigate the selection bias of using cholera vaccine, we did multiple logistic regression analyses for the whole CRC cohort including all the covariates listed in Table 1, and controlled for the remaining imbalance by using nearest neighbor propensity scores matching. The propensity score is the probability of treatment assignment conditional on observed baseline characteristics. We did a 1-to-3 match so the 2 groups of patients had the same/similar