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Exploring Gastric Cancer Risk Factors and Screening Methods: What Can Change in the US?

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ABSTRACT: Stomach cancer is one of the leading causes of cancer-related deaths worldwide. It often develops silently; although advancements in treatments have improved results, it is still very difficult to treat, especially if diagnosed late. Early diagnosis is crucial to improving gastric cancer survival. Unfortunately, there is no screening program for gastric cancer currently in the U.S. This leads to the delay of the diagnosis of gastric cancer, impacting survivability. There are various causes and risk factors, including a *Helicobacter pylori* infection, a high-salt diet, and a lack of screenings. Some ethnic groups have higher *H. pylori* infection rates. The tendency in salt consumption differs depending on ethnic cuisines. It is important that the screening programs are developed by taking into account the differences among ethnic groups within the country. This literature review first covers three main risk factors: *H. pylori* infection, salt intake, and demographics. It then investigates the screening program of the country, Japan, where they were able to reduce gastric cancer rates. Examining such successful programs can help improve the screening methods of multi-ethnic countries such as the U.S.

KEYWORDS: Medical and Health Sciences, Public Health, Cellular Immunology, High-Salt Diet, *H. Pylori*, Risk Stratification.

Introduction

Stomach cancer, also known as gastric cancer, is one of the leading causes of cancer-related deaths worldwide. Though incidence and mortality rates of gastric cancer have been declining, according to GLOBOCAN estimates, there were more than 1 million gastric cancer cases in 2020, resulting in around 768,800 deaths.[1] It is generally a slow-developing cancer, and early-stage gastric cancer may not cause any noticeable symptoms. In many cases in the U.S., it is not diagnosed until it has spread significantly because cancer screening is not routine.

Though the exact cause of gastric cancer is unknown, there are known risk factors that increase the chances of developing gastric cancer. In addition to family history and certain genetic conditions, hereditary diseases such as Lynch syndrome and familial adenomatous coli, Epstein-Barr virus, alcohol consumption, gender, type A blood, stomach surgery, obesity, aging, and smoking also increase risk.[2,3] Several studies have found diet factors that could prevent the risk of gastric cancer, such as intake of citrus fruits, a Mediterranean diet, dairy products, Vitamins C, A, and E, dietary fibers, and cruciferous vegetables;[4] however, consuming smoked, salted, and processed foods can increase the risk of gastric cancer. *H. pylori* infections can also cause chronic inflammation in the stomach lining.[3] In addition, *H. pylori* induces genetic mutations by damaging DNA in tumor suppressor genes, leading to increased rates of cancer as well.[5]

There are three major types of gastric cancers. Adenocarcinoma is the most common, originating from the glandular cells of the stomach. Lymphoma, the next most common type, develops in the lymphatic tissue. The rarest is a gastrointestinal stromal tumor, which develops in the muscle or connective tissue of the stomach wall.[6] Treatments vary based on the stage and location of the cancer, including chemotherapy, radiation therapy, targeted therapy, immunotherapy, and palliative care.

Gastric cancer might not create any noticeable symptoms until the cancer has progressed for a while, and its symptoms are also often vague. Gastric cancer is commonly misdiagnosed or diagnosed too late because of the ambiguity of its symptoms. Common symptoms are poor appetite, unintentional weight loss, abdominal pain, feeling full without eating much, heartburn or indigestion, nausea and vomiting, vague discomfort in the abdomen, swelling or fluid buildup in the abdomen, blood in the stool, fatigue, anemia, and jaundice.[7]

This literature review examines the gastric cancer prevalence by ethnic groups within the U.S. and explores the possibility of improving screenings. Certain ethnic groups have dietary preferences and high salt intake that elevates the risk of gastric cancer. Certain ethnic groups also have higher *H. pylori* infections, which is a risk factor, as well. Immigrating into the U.S. would not immediately change their dietary preferences but also would not eradicate *H. pylori*, leaving their risk factor unchanged, yet they would not receive the necessary routine cancer screenings in the U.S. Therefore, It is likely that the gastric cancer rates of the immigrant populations who are from the areas where people have cuisine with higher salt intake and have high *H. pylori* infections will remain high.

Discussion

1. H. Pylori :

H. pylori is classified as a carcinogen, meaning it is known to cause cancer in humans.[8] This bacterium causes chronic inflammation of the stomach lining, leading to the loss of stomach lining cells, which are then replaced inappropriately with intestinal cells, a phenomenon known as metaplasia.[9]

The inflammation can disrupt cell signaling and trigger DNA damage, leading to increased genetic mutations, which can directly exacerbate the risk of cancer development. There are certain *H. pylori* strains more strongly associated with gastric cancer. The eradication of *H. pylori* reduces the risk of gastric cancer, especially when treated before atrophic or metaplastic changes occur.[8]

Screening and treatment of *H. pylori* infections in high-risk populations is crucial. Endoscopic surveillance is recommended for patients with atrophy, intestinal metaplasia, or dysplasia. Various biomarkers, such as serum pepsinogen and gastrin-17, can help in the risk stratification. Public health strategies can also lower gastric cancer incidence.[8]

There have been a variety of scientific studies that show a high salt diet exacerbates *H. pylori*'s ability to cause cancer. A study was done on Mongolian gerbils infected with either a wild-type strain of the bacteria with the *CagA* gene intact or a *CagA* knockout mutant. The *CagA* gene encodes a protein that acts as both a virulence factor and an oncoprotein. It gets injected into cells during infection with *CagA*+ *H. pylori* bacteria, where it disrupts cell signaling and growth pathways, promoting unrestrained growth and cancer development. They were then fed either a standard diet or a high salt diet (of 8 ~ 8.75% sodium chloride) for 4 months post-infection. It was found that 100% of gerbils infected with the wild-type *CagA*+ strain with a high salt diet developed gastric adenocarcinoma in 4 months. Meanwhile, only 58% of the wild-type *CagA*+ strain-infected animals on a regular diet developed cancer. None of the animals infected with the *CagA* mutant developed cancer, even with a high salt diet.[5] These findings suggest that in this model, *CagA* is required for *H. Pylori*'s oncogenicity, which is exacerbated by a high salt diet.

In other words, it was found that a high salt diet made the gastric inflammation response to *H. pylori* much worse. The high salt diet increased gastric inflammation severity, elevated gastric pH, increased parietal cell loss, and also caused a notably higher expression of pro-inflammatory cytokines and reduced levels of hepcidin, a peptide hormone. High-salt conditions increased *CagA* gene expression both in vitro and in vivo (in mice). Relegated *CagA* transcription also correlated with increased delivery of the *CagA* oncoprotein into host cells, driving inflammation and carcinogenic changes.[5]

In conclusion, a high salt diet significantly elevates gastric cancer risk in the presence of *CagA*+ *H. pylori*. This effect is driven by increased bacterial virulence (*CagA* expression) and enhanced mucosal damage/ inflammation. Interventions should focus on reducing salt intake alongside proactive *H. pylori* management.

2. Salt in the Body:

2.1. The Role of Salt in the Body:

Our immune system can defend against cancer by recognizing and killing mutated and cancerous cells, but salt can contribute to a cancer-promoting environment through the presence of low-level inflammation. Salt plays a crucial role in the body, but exacerbates *H. pylori*'s capacity to cause cancer through effects on bacteria and the immune system.[5] There are many other ways salt impacts the immune system, various cells, and structures within the body. These can have negative effects, including increased cell death in certain types of cells, and either diminished or enhanced effector functions.

2.2. The Role of Salt in Gastric Cancer:

Salt impacts different cells in the body, but the effects are often dose and context-dependent. For example, a high salt diet is beneficial in some cell types or increases cellular proliferation, while it might be pro-inflammatory for other cells. Sodium can be stored in high concentrations in certain tumors and sites of inflammation throughout the body. It was found that high salt levels can lead to apoptosis, or cell death, in certain cell types and can diminish cellular proliferation. On the other hand, moderately increased salt concentrations led to improved T cell proliferation.[10] Below are five examples of cells that are affected by a high salt diet and can potentially lead to increased gastric cancer risk.

Neutrophils are an innate immune cell type that responds quickly to the first infection, but can also be found in gastric cancer tumors. They are responsible for causing acute inflammation. The effect of a high salt diet on neutrophils is dependent on the timing of the exposure. Specifically, if a neutrophil is activated and then encounters high salt concentrations, its effector function is improved.[10] However, if a neutrophil is pretreated with high salt concentration before activation, it has less effector function and increased apoptosis.[11] Importantly, it was found in a human study that a high salt diet inhibited neutrophil function, suggesting the potential for reduced cancer-fighting capacity during gastric cancer.[11] These findings highlight that salt has time and context-dependent effects on neutrophil activity, which may contribute to the increased risk of cancer associated with a high salt diet.

Natural killer cells are important in the anti-cancer immune response: they kill tumor cells and produce IFNg, a cytokine that puts the rest of the immune system and neighboring cells on high alert. They recognize the absence of MHC I expression, a mechanism used by tumor cells to evade immune detection. A study performed in healthy mice showed that a high salt diet suppressed proliferation, activation, and natural killer cell function.[12] Interestingly, another study performed in tumor-bearing mice showed increased natural killer cell function in response to a high salt diet due to diminished PD-1 expression and increased IFNg production by natural killer cells.[13] Therefore, the interaction between NK cells and salt during gastric cancer deserves further exploration.

Macrophages are another type of innate immune cell. Their basic functions are: phagocytosis, a process where cells engulf and internalize large particles; antigen presentation, and immune modulation. Macrophages are commonly categorized into two subsets: M1 and M2 macrophages. M1 macrophages mediate the immune response to bacteria and intracellular pathogens, and are polarized by inflammatory stimuli. M2 macrophages, on the other hand, are anti-inflammatory, existing in settings such as asthma and allergy. High salt diets generally favor M1-like macrophages, meaning a high salt diet favors inflammatory protein production and inhibits anti-inflammatory protein production.[10] This likely contributes to the chronic inflammation that supports gastric cancer development.

CD4+ Helper T cells orchestrate an immune response and tailor it to a specific pathogen type or disease state (such as bacteria, virus, helminth, or cancer). Different subtypes are impacted by a high salt diet in a variety of ways. Th17 cells are a subset of helper T cells that play an important role in controlling extracellular bacteria and fungi at the mucosal surfaces and are abundant in the gut. A high salt diet promotes differentiation into pathogenic Th17 cells in the presence of Th17 polarizing cytokines.[10] Additionally, a high salt diet reduces the presence of the L. murinus bacteria, which promotes pathogenic Th17 differentiation.[14] Regulatory T cells are another subset of CD4+ helper T cells. These cells suppress T cell-derived inflammation. Salt reduced regulatory T cells and their proliferation. This means that salt has the potential to push the T cell balance into the pro-inflammatory direction, which in turn has a high potential to play a role in the chronic inflammatory process that supports gastric cancer development and progression.[10]

CD8+ T cells, also known as cytotoxic T cells, kill cells expressing mutated or cancer-associated proteins on cell surfaces via MHC I expression. Research on salt's effect is currently conflicting. In one experiment, the anti-tumor immunity of CD8 T cells was enhanced on a high salt diet.[15] Meanwhile, in another study, CD8 T cell activation was diminished due to impacts on antigen-presenting cells.[16] These studies highlight the complex interplay between a high salt diet and CD8 T cell effector functions.

In conclusion, though salt is an essential mineral and necessary for various bodily functions, there are a multitude of ways that salt can affect various cells in the body and eventually contribute to the development of gastric cancer. However, their effects are often dependent on their quantity and context.

3. Demographics of Gastric Cancer:

There are also demographic factors that contribute to gastric cancer risks. Gastric cancer is more common in older people, with the average age of diagnosis being 68. Men are more likely to develop it than women. Ethnic background also plays a large part; in the US, it is more common in Hispanic, African American, Native American, and Asian/Pacific Islander populations compared to the non-Hispanic white population. Within the Asian population, Korean, Vietnamese, Japanese, and Chinese people have a higher risk.[17]

Generally, countries with a high incidence of gastric cancer also have high *H. pylori* prevalence rates, such as developing countries, South Korea, China, and Japan. However, in some regions, such as South Asia and Africa, the incidence of gastric cancer is relatively low while the prevalence of H pylori is very high.[17] The reason for this may be the presence of a non-gastric-cancer type of *H. pylori* strain rather than one that promotes gastric cancer.[8]

Recently, an increasing incidence has been observed in populations younger than 50 years in the U.S. and the UK. A study found that despite the declining trend in the overall incidence rate, the incidence rate of people younger than 45 years in some countries showed an increasing trend, especially in countries with a low overall incidence rate, such as the UK, the U.S., and the Netherlands. Especially for the U.S. and the UK, this trend may be due to their highest obesity rates in adults, children, and adolescents, which would influence the rates of gastric cancer.[17] This suggests that further studies are needed to determine exactly why gastric cancer rates are increasing in younger populations across the world.

4. Screening In the U.S.:

The U.S. Preventive Services Task Force has not issued any formal recommendations on routine screening for *H. pylori* infection in asymptomatic adults. There are also no standard or routine screening tests to detect stomach cancer in people at average risk. This is due to the relatively low incidence of stomach cancer in the U.S. and the fact that there seems to be no major benefit in spending resources on it for the general population. However, early diagnosis of gastric cancer is essential, especially for those at higher risk, as a late diagnosis often leads to more fatal outcomes.[18]

The American College of Gastroenterology (ACG) suggests testing and treating *H. pylori* in specific high-risk groups, including: individuals with gastric atrophy, intestinal metaplasia, or dysplasia; patients with a history of early gastric cancer resection; first-degree relatives of individuals with gastric cancer; individuals from regions with high gastric cancer incidence (e.g., East Asia, South America, etc.); and patients with certain hereditary cancer syndromes. Screening in the U.S. is usually only done for those who are considered to have a higher risk, such as those who have genetic diseases or those with a family history.

In addition, screenings for the first-generation immigrants from high-incidence gastric cancer regions and possibly other non-white racial and ethnic groups, those with a family history of gastric cancer in a first-degree relative, and individuals with certain hereditary GI polyposis or hereditary cancer syndromes are recommended.[18]

The most common method to screen for gastric cancer is an upper endoscopy, which is the best test for screening or surveillance in individuals at increased risk for gastric cancer. With an endoscopy, doctors can visually check the esophagus, stomach, and the first part of the upper intestine, enabling direct visualization to endoscopically stage the mucosa and identify areas of concerning neoplasia. It also enables biopsies for further histologic examination and mucosal staging. Both endoscopic and histologic staging are key for risk stratification and determining whether ongoing surveillance is indicated and at what interval.[19]

Endoscopists should ensure that all individuals with confirmed gastric atrophy with or without gastric intestinal metaplasia (GIM) undergo risk stratification. Individuals with severe atrophic gastritis and/or multifocal or incomplete GIM are likely to benefit from endoscopic surveillance, particularly if they have other risk factors for gastric cancer, for example, family history. If the individual has a family history of gas-

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tric cancer or multiple risk factors for gastric cancer, ongoing screening should be considered as well. Endoscopic surveillance should be considered every 3 years; however, intervals are not well defined, and shorter intervals may be advisable in those with multiple risk factors, such as severe GIM that is anatomically extensive.[19] This highlights the importance of personalized medicine specific to each patient's circumstances.

5. Gastric Cancer In Asian Populations in the U.S.:

In the U.S., gastric cancer consists of 1.5% of all new cancers nationally.[20] However, different ethnic groups within the U.S. have different levels of gastric cancer risk. It is known that Asian populations are at a particularly high risk for gastric cancer, even if they're living in the U.S. They are only about 6% of the U.S. population, thus contributing to statistical underrepresentation in gastric cancer incidence at the population level.[20]

In California, the public health system keeps track of health data by ethnicity. It is known that Vietnamese, Korean, Chinese, and Japanese people have a significantly elevated risk of gastric cancer. Koreans have the highest risk at 13 times that of non-Hispanic white people. Vietnamese people's risk is seven times higher, while Japanese and Chinese people have a risk of around five times higher.[21]

Moreover, the prevalence of *H. pylori* infection is much higher in countries outside of the U.S., especially those in Asia. The rate of *H. pylori* infection in the U.S. is only about 10 to 20% for all populations. In Asian countries, however, it is as high as 80%. It is known that recent immigrants from these high-incidence of *H. pylori* countries remain at high risk.[21] Therefore, immigrants from these areas should still stay vigilant about gastric cancer prevention, and communicate to their physicians that they may be an abnormal case compared to the typical US population.

In summary, collecting and summarizing the data of gastric cancer through general population-level statistics puts minority groups in the U.S. at a strong disadvantage. Developing a screening policy incorporating differences by ethnic groups is a potentially better approach to address this issue.

6. Screening in Countries with High Gastric Cancer Rates:

Japan and Korea have national stomach cancer screening programs because the incidence of gastric cancer is very high. Early identification improves the outcome of gastric cancer treatment. However, in the U.S., because screening is not done regularly, it often isn't diagnosed early enough. This has huge impacts on outcomes, as only 30% of patients who are diagnosed with stomach cancer in the U.S. reach the five-year survival mark, while in Japan and Korea, it is 60 to 70%.[2] Overall, this demonstrates the effectiveness of proper screening protocols.

6.1. Epidemiology and Risk Stratification of Gastric Cancer in Japan:

Gastric cancer is the second leading cause of cancer incidence in Japan, though its mortality has decreased over the past few decades, often attributed to the decline in *H. pylori* prevalence.

In Japan, gastric cancer caused nearly half of all cancer deaths in the 1960s; however, the proportion continues to decline.[2] The number of gastric cancer deaths that had remained similar for the past few decades, 50,000, has also begun declining since 2011. In 2021, gastric cancer was ranked third in the number of deaths after lung cancer and colorectal cancer, constituting 42,000 deaths.[22] However, more than 40,000 people still lose their lives to gastric cancer every year; gastric cancer has the second-highest *incidence* rate at 12.9%, following colorectal cancer, meaning it is still very prevalent. Overall, while the total number of cases is still rising and deaths are leveling off due to an increase in incidence and deaths among the elderly, the age-standardized incidence and mortality rates of gastric cancer are decreasing.[2]

In Japan, radiographic examination has been conducted since the 1960s as a secondary preventive measure for gastric cancer. The revised 2014 Japanese Guidelines for Gastric Cancer Screening approved gastric endoscopy for use in population-based screening, together with radiography. Currently, the government of Japan recommends either radiography or gastroscopic examination for gastric cancer screening. However, there are some barriers, such as participation rate, endoscopic capacity, equal access, and cost-effectiveness.[2] One way to combat costs is through risk stratification.

As mentioned before, there are a multitude of factors that can increase the risk of getting gastric cancer. Recently, it has been reported that approximately one-fifth of diffuse-type gastric cancers (a subtype of gastric cancer characterized by poorly differentiated cancer cells that infiltrate the tissue individually),[23] in Japan, were attributable to the combination of alcohol intake and defective ALDH2 allele or CDH1 variants. In addition, individuals can be categorized by gastric cancer risk based on *H. pylori* infection status and suggestive cancer risk during endoscopic examination. A study examining the accuracy of a *H. pylori* infection diagnosis found that the specificity of detecting uninfected, existing, or current infections is very high (>90%).[2] As a safeguard, however, an *H. pylori* antibody test is also recommended.

The Kyoto classification of gastritis includes factors such as moderate-to-severe gastric atrophy, enlarged gastric folds, nodular gastritis, xanthoma, and map-like redness. Additionally, this risk classification by endoscopic examination was confirmed to have very high accuracy. The commonly used gastric cancer risk classification system is the "ABC method," a combined assay for serum anti-*H. pylori* IgG antibody and serum pepsinogen (PG) levels.[2] A study reported a strong correlation between the ABC classification system and radiological findings in relation to the risk of gastric cancer.[24]

According to the 2019 Basic Survey of National Life, 54.2% of men and 45.1% of women 40 - 90 years of age have undergone gastric cancer screening, with the target value being 50%.[2] In addition, while the gastric cancer-adjusted mortality rate has naturally decreased, the number of *H. pylori*-negative people has increased in recent years. Unfortunately, it is noted that in the future, it may be necessary to categorize individuals based on their risk factors for gastric cancer, and analyze them in terms of the necessity for an endoscopy and a determination of a screening interval. In other words, the methods used in Japan are not only very effective but also widely used, and are constantly being revised to optimize both cost and efficiency.

6.2. Future Directions for Screenings:

In various national screening programs, including in Japan's, the recommended age for gastric cancer screening is set to after 50 years of age due to a decrease in gastric cancer incidence within the younger population and cost-related reasons.[2] Korea, Singapore, and the U.K. have similar age thresholds. Specifically in Singapore, Chinese Singaporeans older than 50 years old who have a higher risk of gastric cancer have been targeted by the national screening program.[25] In the future, different screening intervals might be determined based on the individual's background and general gastric cancer risk.

As mentioned before, the incidence of gastric cancer depends on risks such as *H. pylori* infection status or atrophic gastritis. The Korean, the U.K., and Japanese national programs recommend repeated gastric cancer screening every 2 to 3 years.[2] However, high-quality subsequent studies are required to determine the best follow-up interval for endoscopic screening. In 2020, a study introduced new testing strategies and conducted a nationwide research study to set a standard interval for risk-specific screenings.[26] If low-risk individuals could be picked out early and brought into the screening programs, their intervals could be lengthened. The results will hopefully increase the efficiency of classifying the risk of various individuals and appropriately determine their individual screening intervals. The results could also help establish a system that targets specific population groups and increases the accessibility of necessary screening by efficiently utilizing limited resources.[2]

7. Conclusion:

Asian populations, especially Korean, Vietnamese, Japanese, and Chinese people, are at a particularly high risk for gastric cancer, even if they're living in the U.S. Since national rates of gastric cancer are low in the U.S., early screening and detection methods are not prioritized. However, it should be acknowledged by physicians that minority groups and recent immigrants are not well represented in the national statistics, putting them at a strong disadvantage, and that these high-risk populations deserve proper screening protocols as part of their preventative care.[21]

A prevention strategy that could be implemented immediately and at low cost for this specific subpopulation is education. People who are at high risk should be notified and educated so they can discuss with their doctors about their risks and potential controllable changes that can be made. Even in various areas within the U.S. where there's a large percentage of Asian and Asian American patients and doctors, many don't know that they and other Asians and Asian Americans are at higher risk for gastric cancer.[21] Therefore, it is crucial for specific ethnicities and those at higher risk of gastric cancer to be notified earlier to prevent gastric cancer and to get diagnosed early.

While it is known that recent immigrants in high-incidence countries are at high risk, there isn't enough good data on children of immigrant parents. However, it is reasonable to infer that the diets of recent immigrants will not change quickly enough to create a drastic change in gastric cancer prevalence, as food is an important part of culture. This dietary preference will also likely carry on to their children as well, though perhaps at a lesser rate due to assimilation. Furthermore, *H. pylori* is transmitted between people, highlighting another potential source of increased risk in immigrant families. Therefore, such a population should be studied in the U.S. to determine appropriate screening methods.

In the U.S., there are currently no stomach cancer screening guidelines for people at average risk of the disease. They have not been proven to be effective in reducing death from gastric cancer in the general U.S. population, and are thought to lead to unnecessary medical procedures, emotional distress, and cost.[27] Due to this, only those who have a substantial risk factor, such as a genetic or hereditary factor, would be considered.

Japan successfully implemented screening and risk stratification policies to improve outcomes in gastric cancer, showing it is feasible and beneficial to have a simplified strategy for gastric cancer screening and surveillance for high-risk individuals in the U.S. In this case, individuals could be stratified based on race, *H. pylori* infection status, and family history of gastric cancer. In addition, it would be beneficial to determine regular and frequent screening intervals for older individuals who are first or second-generation immigrants from high-risk regions of the world, such as East Asia. It would also be beneficial to begin endoscopic screening in individuals with a family history of gastric cancer earlier on, and use the various markers and treatments available for determining the *H. pylori* infection status.

Constant and early gastric cancer screening in the appropriate populations would be highly helpful, especially as a late diagnosis of gastric cancer is a major risk factor that affects the mortality of the diagnosed individual. A specific and targeted screening system has been shown to have a survival benefit, as seen in East Asian countries. Implementing such targeted screening systems in the U.S. should also be beneficial to reduce gastric cancer-related mortality in underrepresented populations that have historically been underserved by a generalized medical system.

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References

1. Wu, X.; Chen, L.; Cheng, J.; Qian, J.; Fang, Z.; Wu, J. Effect of Dietary Salt Intake on Risk of Gastric Cancer: A Systematic Review and Meta-Analysis of Case-Control Studies.
2. Yashima, K.; Shabana, M.; Kurumi, H.; Kawaguchi, K.; Isomoto, H. Gastric Cancer Screening in Japan: A Narrative Review. **2022**.
3. *What is Stomach Cancer?*. Illinois Department of Public Health. https://dph.illinois.gov/topics-services/diseases-and-conditions/cancer/type/stomach.html#:~:text=Bacterial%20infection,Gender (accessed 07-03-25).

DOI: 10.36838/IJHSR89.284

4. Wu, B.; Yang, D.; Yang, S.; Zhang, G. *Dietary Salt Intake and Gastric Cancer Risk: A Systematic Review and Meta-Analysis*. Frontiers. https://www.frontiersin.org/journals/nutrition/articles/10.3389/fnut.2021.801228/full?wbraid=Ck0KCAiAutyfBhBkEj0AtM2iJQvKyvyvgcr3aEzBni3j_JT0QuvxPvjqV_caq0vvbXrFg8Z6fPoIp-Qt90WpiOFLdYlmRqbbAQoGgISWg.
5. Gaddy, J. A.; Radin, J. N.; Loh, J. T.; Zhang, F.; Washington, M. K.; Peek Jr., R. M.; Algood, H. M. S.; Cover, T. L. High Dietary Salt Intake Exacerbates Helicobacter Pylori-Induced Gastric Carcinogenesis. **2013**.
6. *What Is Stomach Cancer?*. American Cancer Society. https://www.cancer.org/cancer/types/stomach-cancer/about/what-is-stomach-cancer.html (accessed 07-14-25).
7. *11 Common Early Signs of Stomach Cancer.* University of Kansas Cancer Center. https://www.kucancercenter.org/news-room/blog/2021/01/11-common-early-signs-stomach-cancer (accessed 06-28-25).
8. Correa, P.; Piazuelo, M. B. The Gastric Precancerous Cascade. **2012**. https://doi.org/10.1111/j.1751-2980.2011.00550.x.
9. *Intestinal Metaplasia.* Cleveland Clinic. https://my.clevelandclinic.org/health/diseases/22215-intestinal-metaplasia (accessed 2025-08-12).
10. Willebrand, R.; Kleinewietfeld, M. The Role of Salt for Immune Cell Function and Disease. **2018**. https://doi.org/10.1111/imm.12915.
11. Jobin, K.; Stumpf, N. E.; Schwab, S.; Eichler, M.; Neubert, P.; Rauh, M.; Adamowski, M.; Babyak, O.; Hinze, D.; Sivalingam, S.; Weisheit, C.; Hochheiser, K.; Schmidt, S. V.; Meissner, M.; Garbi, N.; Abdullah, Z.; Wenzel, U.; Holzel, M.; Jantsch, J.; Kurts, C. A High-Salt Diet Compromises Antibacterial Neutrophil Responses through Hormonal Perturbation. **2020**. https://doi.org/10.1126/scitranslmed.aay3850.
12. Zeng, X.; Li, Y.; Lv, W.; Dong, X.; Zeng, C.; Zeng, L.; Wei, Z.; Lin, X.; Ma, Y.; Xiao, Q. A High-Salt Diet Disturbs the Development and Function of Natural Killer Cells in Mice. https://doi.org/10.1155/2020/6687143.
13. Rizvi, Z. A.; Dalal, R.; Ssadhu, S.; Kumar, Y.; Kumar, S.; Gupta, S. K.; Tripathy, M. R.; Rathmore, D. K.; Awasthi, A. High-Salt Diet Mediates Interplay between NK Cells and Gut Microbiota to Induce Potent Tumor Immunity. **2021**. https://doi.org/10.1126/sciadv.abg5016.
14. Wilck, N.; Matus, M. G.; Kearney, S. M.; Olesen, S. W. Salt-Responsive Gut Commensal Modulates TH17 Axis and Disease. **2017**. https://doi.org/10.1038/nature24628.
15. Luo, M.; Shao, B.; Yu, J.; Liu, T.; Liang, X.; Lu, L. Simultaneous Enhancement of Cellular and Humoral Immunity by the High Salt Formulation of Al(OH)3 Adjuvant. **2017**.
16. Popovic, Z. V.; Embgenbroich, M.; Chessa, F.; Nordstrom, V.; Bonrouhi, M.; Hielscher, T. Hyperosmolarity Impedes the Cross-Priming Competence of Dendritic Cells in a TRIF-Dependent Manner. **2017**.
17. Lin, J.; Lin, J.-X.; Lin, G.-T.; Huang, C.-M.; Zheng, C.-H.; Xie, J.-W.; Wang, J.; Chen, Q.-Y.; Li, P. Global Incidence and Mortality Trends of Gastric Cancer and Predicted Mortality of Gastric Cancer by 2035. **2024**.
18. C. Shah, S.; Wang, A. Y.; Wallace, M. B.; Hwang, J. H. AGA Clinical Practice Update on Screening and Surveillance in Individuals at Increased Risk for Gastric Cancer in the United States: Expert Review. **2025**.
19. *Screening and surveillance in patients at high risk for gastric cancer.* AGA. https://gastro.org/clinical-guidance/screening-and-surveillance-in-patients-at-high-risk-for-gastric-cancer/ (accessed 07-16-25).
20. Katella, K. *Stomach Cancer Is Still a Risk for Many People.* Yale Medicine. https://www.yalemedicine.org/news/stomach-cancer-gastric-cancer (accessed 07-19-25).
21. Moskal, E. *Stomach cancer hits Asian populations harder*. Stanford Medicine. https://med.stanford.edu/news/insights/2022/12/stomach-cancer-asians.html#:~:text=Japan%20and%20Korea%20have%20national,is%2060%25%20to%2070%25 (accessed 07-03-25).
22. *National Cancer Center Center for Cancer Control and Information Services*. Cancer Information Services. https://ganjoho.jp/public/index.html (accessed 08-12-25).
23. Assumpção, P. P.; Barra, W. F.; Ishak, G.; Coelho, L. G. V.; Coimbra, F. J. F. The Diffuse-Type Gastric Cancer Epidemiology Enigma. **2020**. https://doi.org/10.1186/s12876-020-01354-4.
24. Miki, K. Gastric Cancer Screening by Combined Assay for Serum Anti-Helicobacter Pylori IgG Antibody and Serum Pepsinogen Levels - "ABC Method." *87*, 7, 405-414 **2011**. https://doi.org/10.2183/pjab.87.405.
25. Zhou, H. J.; Dan, Y. Y.; Naidoo, N.; Li, S. C.; Yeoh, K. G. A Cost-Effectiveness Analysis Evaluating Endoscopic Surveillance for Gastric Cancer for Populations with Low to Intermediate Risk. **2013**. https://doi.org/10.1371/journal.pone.0083959.
26. Hamashima, C.; Yoshimura, K.; Fukao, A. A Study Protocol for Expanding the Screening Interval of Endoscopic Screening for Gastric Cancer Based on Individual Risks: Prospective Cohort Study of Gastric Cancer Screening. **2020**.
27. *Stomach Cancer Screening.* Emory Winship Cancer Institute. https://winshipcancer.emory.edu/cancer-types-and-treatments/stomach-cancer/screening.php#:~:text=Screening%20for%20Stomach%20Cancer,high%20risk%20for%20the%20disease (accessed 08-20-25).

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