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Gastric cancer beyond chronic stress

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Abstract
Cancer has been one of the biggest silent killers during the 20ths and 21st centuries. In addition to this disease, one of the social factors that promote the chances of having diseases is stress. Recent studies have shown that chronic stress can lead to gastric cancer by activating adrenergic signaling pathway which plays a fundamental role in tumorigenesis. Furthermore, the plasma levels of catecholamines and cortisol elevate in stressful situations. These hormones play a role in inducing progress and metastasis of gastric carcinoma. Stress management has been a vital factor for the people of this century. Although stress is not well-explained clearly, recent studies have shown that people with low income, loads of work, family problems, etc. are of environmentally challenging and present a high possibility of being victim to gastric neoplasms and other diseases.

Running title: Gastric cancer beyond chronic stress

Keywords: gastric cancer, chronic stress, cortisol, sympathetic response, endoscopy

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Introduction

Maintaining a work-life balance in the 21st century can present significant challenges leading to several mental problems such as stress, depression, and etc. These psychological issues can lead to the releasing of stress hormones with neurotoxic effects. The abnormal hormones are released from hypothalamus-pituitary-adrenal (HPA) axis and additionally, stress-related catecholamines level is also increased. These abnormally released hormones mimic a response of the sympathetic nervous system which can proceed to slowing down of the digestive processes [1]. Chronic inflammation can initiate a cascade of cellular changes contributing to gastric cancer when left untreated.

Gastric cancer has taken the 5th place among cancer deaths and the fourth leading cause of cancer-related mortality, with over one million new cases and approximately 770,000 deaths reported annually. East Asia, Eastern Europe and South America are the most affected regions with non-cardia gastric cancers. Unhealthy diet (e.g., very salty foods, nitrosamines), *Helicobacter Pylori* infections and the long-term use of NSAIDS (non-steroidal inflammatory drugs) are typical risk factors of gastric adenocarcinoma [2]. Whereas, the localized tumors in the early stages can mostly be excised. For the late stages, only the lifespan of the patient can be extended through systemic chemotherapy, targeted therapies (e.g., Trastuzumab for HER2-positive tumors), or immunotherapy.

The tumorigenesis of gastric cancer involves multiple genetic and molecular changes. Chronic inflammation caused by *Helicobacter Pylori* infection or prolonged stress exposure can induce DNA damages, epigenetic modifications and activation of the oncogenic pathway. The Wnt/β-catenin, NF-κB, and PI3K/Akt signaling pathways play a role in promoting uncontrolled cell proliferation while mutations in tumor suppressor genes (TP53, CDH1) contribute to malignant neoplasms. Gastric adenocarcinomas mostly arise in the antrum and body of the stomach, starting from precancerous lesions (atrophic gastritis, intestinal metaplasia, dysplasia) to invasive carcinomas [3].

It is essential to acknowledge that managing stress in cancer patients could be challenging but this process is a vital need to be proceed. A study illustrates that practicing yoga or meditation, getting enough sleep and starting an exercise routine show benefits for the patients [4]. Moreover, pharmacological approaches such as prescribing a variety of antidepressants for stress typically include tricyclic agents (TCAs), selective serotine-reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs). These drugs have shown significant changes in cancer patients [5].

Chronic stress

Stress is a health-threatening psychological condition which cannot be cured overnight. A variety of social factors influence an individual's daily life

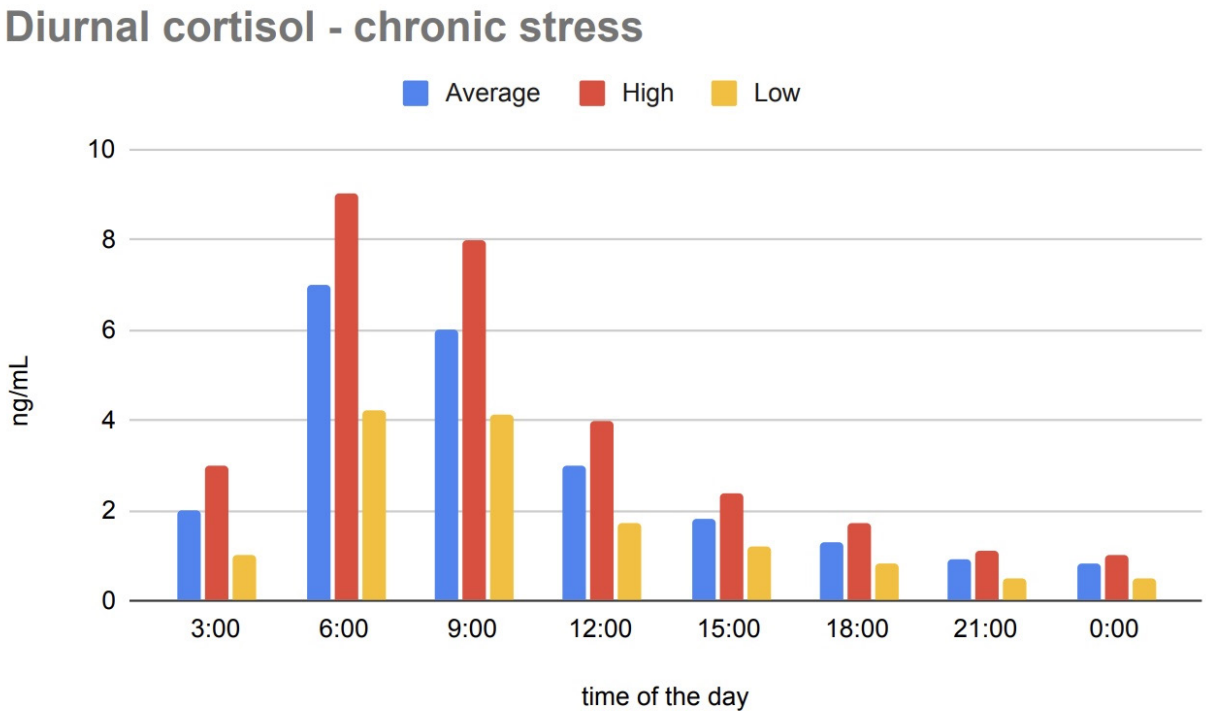

FIGURE 1 Cortisol levels according to 24hours of the day [9]

as well as reflects psychological well-being. The research provides load of work, lack of social interaction, financial instability, and other personal issues are the key contributors of stress [6]. In 2018, the researchers were shocked to find out that 85% of adults experience stress at some point throughout their life. According to research by Mutad.MP, 1 in 5 people has been experiencing stress every day. In addition, gender and age are also the factors which should not be forgotten to mention. Forth stated that women are enduring this psychological distress more than men do and around a quarter of women admitted to experiencing stress everyday based on their looks, insecurities and sexual harassment. The data shows that age group of people between 16 and 24 are experiencing this psychological problem more than other age groups [7]. This is because of the massive pressure to succeed [6]. Some doctors state that measuring daily cortisol level is a must for a patient who is suffering from chronic stress. Many pharmacies sell cortisol measuring kits which are convenient to use at home. Normal cortisol level indicates between 5 and 23 mcg/dl when it is measured at 8am but 3-13 mcg/dl when measured at 4pm. **Figure 1** shows the ranges for 24 hours cortisol level. The level of cortisol during in the morning can be seen higher than other parts of the day. Normally, stress hormones levels return to normal after fight-or-flight conditions. But in conditions such as chronic stress, this can lead to prolonged catecholamines release mimicking sympathetic responses [8].

Prolonged sympathetic response

The autonomic nervous system is composed of sympathetic and parasympathetic nervous systems. Parasympathetic nervous system is primarily responsible for regulating normal physiological functions while sympathetic nervous system is induced during stressful (fight-or-flight) situations such as encountering an immediate threat. These situations trigger the release of catecholamines from adrenal medulla and cause the change of some body mechanisms. Increased heart rate, decreased motility and secretion of digestive tract, bronchiolar dilation, inhibited insulin secretion, etc. are sympathetic responses [10]. Prolonged sympathetic response can lead to slowing of the digestive system functions. It can lead to improper digested particles which the nutrients cannot be absorbed or passed onto small intestines. Chronic exposure to these conditions may contribute to an increased risk of gastric pathologies, including gastric cancer. Persistent dysregulation of digestive processes, coupled with prolonged exposure to stress induced catecholamines, has been implicated in inflammatory and oncogenic pathways, highlighting the need for further research into the long-term effects of sympathetic overactivation on gastric health.

Molecular mechanisms

The studies have shown that the patients with chronic stress experience elevated level of catecholamines and epinephrine [11]. These hormones have an agonist effect on adrenoceptor beta 2 which is a well-known G protein-coupled receptor. When experiencing stress, the angiogenesis of tumor is promoted and leads to the malignant growth of tumor cells [3]. This is because stress trigger ADRB2 gene that encodes B2AR via cAMP-protein kinase A signaling pathway and this regulates multiple cellular processes like cytokine production, cell motility and trafficking which will lead to progression of GC eventually [12]. Stress behaviors increase angiogenesis and promote tumor growth as well. In addition, recent studies have shown that PlexinA1 which is a member of semaphorin and plexin family shows a massive influence on gastric cancer cells progression. This study also proved that patients with plexin A1 has lower survival than normal patients [3].

Genetic abnormalities and risk factors

Gastric cancer arises from multiple factors, where both environmental and genetic influences play a role in the development and occurrence of the disease [13]. Compared to familial and genetic factors, environmental risk factors can significantly elevate the chance of gastric cancer [14]. Genetic predisposition may modify the impact of environmental and dietary exposures, resulting in the high variation of gastric cancer incidence observed globally.

Environmental factors have a major role in influencing the risk of developing gastric cancer [14,15]. Such environmental factors include *Helicobacter pylori* infections, dietary variations, smoking, and excessive alcohol consumption [14]. *Helicobacter pylori* (H. pylori) infection is considered to be the most impactful risk factor for gastric cancer particularly in individuals with ATM, BRCA1, BRCA2, or PALB2 pathogenic mutations, whereas the regional variance in gastric cancer incidence is influenced by diet [16].

Individuals with positive family histories of gastric cancer are more likely to have the disease themselves, especially if they have first degree relatives (parent, sibling, or child) diagnosed with stomach cancer [16]. Positive family history may heighten the risk of stomach cancer due to either shared genetic factors or shared environmental risk factors, e.g., the transmission of H. pylori from parents to children [2]. Males exhibit a higher prevalence of gastric cancer than females and the incidence rate increase progressively with age [17]. A significant proportion of stomach tumors have been shown to contain particular genes, including p53 tumor suppressor genes, APC, and MCC. E-cadherin, a molecule that facilitates a calcium dependent adhesion, plays a crucial role in the gastric carcinogenesis cascade [18]. In cases of genetic susceptibility, a single

mutant CDH1 allele is passed down as hereditary transmission. If there is an acquired mutation in the second allele of the E-cadherin gene, it leads to a failure in intracellular adhesion, ultimately resulting in heightened intracellular permeability. Families with gastric cancer have been found to have a wide range of mutations in this region [18]. Inherited syndromes account for only 1-3% of gastric cases. The remaining cases of stomach cancer are sporadic, and no significant high-penetrance genes have been identified for them [17]. These inherited conditions include hereditary diffuse gastric cancer (HDGC), familial adenomatous polyposis (FAP), Lynch syndrome (HNPCC), and Peutz-Jeghers syndrome (PJS) [16-18].

Signs and symptoms

The signs and symptoms of most stomach cancers cannot be found until cancer cells spread out of the stomach, and earlier stages do not usually show any visible signs. But in countries such as South Korea and Japan where screening of stomach cancer is routine, gastric cancer can be found in the earlier stages [19]. The most common visible signs and symptoms include:

- Noticeable weight loss
- Anorexia
- Abdominal pain
- Heartburn or indigestion
- Nausea and vomiting
- Edema in the abdomen
- Blood in stool
- Jaundice if the cancer cells have spread to the liver.

Having these symptoms do not usually mean cancer but could indicate viral infections or an ulcer [19].

Diagnosis

The technique of the greatest importance is upper gastrointestinal endoscopy (UGIE) with biopsies to detect premalignant conditions and gastric cancer [20]. Early diagnosis is important for both prognosis and choosing treatment plan. Considering non-modifiable risk factors such as increasing age, male gender, family history of GC, hereditary syndromes and modifiable risk factors like alcohol or tobacco abuse, obesity, high salt intake and persistent H. pylori infection, the main biological risk factor, is also important in addition to endoscopy. When a questionable spot such as a depressed or elevated area, a flat pale or erythematous area is found during UGIE, determining the lesion with white light endoscopy (WLE) and virtual chromoendoscopy (VCE) or magnifying endoscopy (ME) is required to look for demarcation line which indicates mucosal pattern transition. If the lesion presents the demarcation line and either microvascular or microsurface pattern is irregular, it is considered as a neoplastic one [21]. To assess the serosal invasion in patients with gastric cancer as a preoperative measure, CAD (computer aided diagnosis) system with DEsCT (dual-energy spectral computed tomography) is used as well [22].

Stages of gastric adenocarcinomas

Gastric adenocarcinomas can be staged from 0 to 4 according to TNM system. In stage 0 which is known as carcinoma in situ, the abnormal cells could be confined in mucosa but they have not started spreading. During stage 1 which can be divided into stage 1A and 1B, we can see that cancer cells have been metastasized to mucosa and submucosa. In addition, these cells are starting to extend to 1 or 2 lymph nodes nearby. The invasion through submucosa and 3 to 6 lymph nodes by adenocarcinomas can be researched in stage 2 of gastric cancer. But in the stage 3, the involvement of more lymph nodes can be seen because cancer cells have already invaded to the muscular layer and have metastasized nearly 7 to 15 lymph nodes. During this stage, adenocarcinomas may have also been spread to nearby organs such as liver, lungs, kidneys, etc. At the time of end-stage (stage 4), cancer cells have been fully metastasized to the other organs including distant lymph nodes and the tissue lining of the abdominal wall [23].

Management of gastric cancer

The management of gastric adenocarcinomas rely upon the stages which differentiate whether the tumors are localized or already metastasized. The tumors of earlier stages (0, 1 and 2) which have not invaded the mucosa are eligible for successfully resection [24]. In the treatment of stage 0 gastric cancer with Endoscopic mucosal resection, an endoscope is used for eliminating abnormal tissues despite using surgery. During stage 1, certain medications such as cisplatin, leucovorin, oxaliplatin, capecitabine, etc. are prescribed alone or in combination [25]. Targeted therapies for example HER2 targeted agents such as trastuzumab show a noticeable effect on HER2 positive gastric cancers [24]. Besides, gastrectomy is the most recommended therapy for stage 2 and 3 although it can also be proceeded during the earlier stages. Throughout gastrectomy, the surgeons abolish all or part of the stomach and the nearby lymph nodes which have been invaded by cancer cells. The drugs which were prescribed in stage 1 can still be used during these stages. In the end stage, palliative therapy is the most appropriate management. This therapy focusses on extending the lifespan of the patients rather than curing the diseases. For the HER2 negative gastric cancer, chemotherapy is administered and for HER2 positive, pembrolizumab which is an immunotherapeutic monoclonal antibody and tar-

geted therapy drug trastuzumab in combination with chemotherapy are approved by many oncologists. If the patient feels any uncomfortable symptoms such as blockage in the stomach, radiation therapy should be performed to reduce the size of the tumor [25].

Conclusions

Chronic stress has been a massive risk factor of many diseases for centuries. It is due to the always changing living standards such as busy working environment, separation from the community or loneliness, etc. For people whose family members had experienced cancer at one point throughout their lives should be very careful with their own lifestyles as they may have the inherited oncogenes. Gastric cancer can be a result of chronic stress in that the person is experiencing prolonged sympathetic activity caused by abnormal hormonal release. In addition, stress can activate certain receptors such as Plexin A1 and ADBR2 which can enhance tumor activity. Several environmental factors such as unhealthy diet and lack of exercise can also promote the risk of having gastric cancer. There are several diagnostic methods available for annual checkup. Cancer patients can also be relieved with certain medications according to the stages of the tumor progression.

Ethical approval

The study was a descriptive one. No human or animals were a subject of examinations.

Acknowledgments

Not applicable.

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Conflict of interest

The authors declare no conflict of interest.

References

1. Sanders DJ. A review: the agents and actions of sympathetic nerve and catecholamine inhibition of gastric mucosal function. Agents Actions. 1976;6(4):385-8; DOI:10.1007/BF01973207.
2. Yang L, Ying X, Liu S, Lyu G, Xu Z, Zhang X, Li H, Li Q, Wang N, Ji J. Gastric cancer: epidemiology, risk factors and prevention strategies. Chin J Cancer Res. 2020;32(6):695-704; DOI:10.21147/j.issn.1000-9604.2020.06.03.
3. Lu Y, Cheng D, Pang J, Peng Y, Jin S, Zhang X, Li Y, Zuo Y. Chronic stress promotes gastric cancer progression via the adrenoceptor beta 2/PlexinA1 pathway. Cell Stress Chaperones. 2024;29(1):201-15; DOI:10.1016/j.cstres.2024.02.001.
4. Khajuria A, Kumar A, Joshi D, Kumaran SS. Reducing stress with yoga: a systematic review based on multimodal biosignals. Int J Yoga. 2023;16(3):156-70; DOI:10.4103/ijoy.ijoy_218_23.
5. Hsieh YH, Chiu WC, Lin CF, Chan HL, Liang HY, Lee Y, McIntyre RS, Chen VC. Antidepressants and Gastric Cancer: A Nationwide Population-Based Nested Case-Control Study. PLoS One. 2015;10(11):e0143668; DOI:10.1371/journal.pone.0143668.
6. Piao X, Xie J, Managi S. Continuous worsening of population emotional stress globally: universality and variations. BMC Public Health. 2024;24(1):3576; DOI:10.1186/s12889-024-20961-4.
7. Matud MP, Díaz A, Bethencourt JM, Ibáñez I. Stress and psychological distress in emerging adulthood: a gender analysis. J Clin Med. 2020;9(9):2859; DOI:10.3390/jcm9092859.
8. Noushad S, Ahmed S, Ansari B, Mustafa UH, Saleem Y, Hazrat H. Physiological biomarkers of chronic stress: a systematic review. Int J Health Sci (Qassim). 2021;15(5):46-59.
9. Russell GM, Durant C, Ataya A, Papastathi C, Bhake R, Woltersdorf W, Lightman S. Subcutaneous pulsatile glucocorticoid replacement therapy. Clin Endocrinol (Oxf). 2014;81(2):289-93; DOI:10.1111/cen.12470.
10. Silverthorn DU. Human physiology: an integrated approach. 8th ed. Benelux: Pearson; 2019. 984 p.
11. Menon G, El-Nakeep S, Babiker HM. Gastric Cancer [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 [cited 2025 Jan 22]. 34 p. Available from: https://www.ncbi.nlm.nih.gov/books/NBK459142/.
12. Cole S, Sood A. Molecular pathways: beta-adrenergic signaling in cancer. Clin Cancer Res. 2012;18(5):1201-6; DOI:10.1158/1078-0432.CCR-11-0641.
13. Machlowska J, Baj J, Sitarz M, Maciejewski R, Sitarz R. Gastric cancer: epidemiology, risk factors, classification, genomic characteristics and treatment strategies. Int J Mol Sci. 2020;21(11):4012; DOI:10.3390/ijms21114012.
14. Oh DY, Choi KS, Shin HR, Bang YJ. Public awareness of gastric cancer risk factors and disease screening in a high risk region: a population-based study. Cancer Res Treat. 2009;41(2):59-66; DOI:10.4143/crt.2009.41.2.59.
15. Shah D, Bentrem D. Environmental and genetic risk factors for gastric cancer. J Surg Oncol. 2022;125(7):1096-1103; DOI:10.1002/jso.26869.
16. National Cancer Institute. Genetics of gastric cancer (PDQ®) – health professional version [Internet]. Bethesda (MD): National Cancer Institute; 2025 [cited 2025 Jan 27]. Available from: https://www.cancer.gov/types/stomach/hp/gastric-genetics-pdq/.
17. Karimi P, Islami F, Anandasabapathy S, Freedman ND, Kamangar F. Gastric cancer: descriptive epidemiology, risk factors, screening, and prevention. Cancer Epidemiol Biomarkers Prev. 2014;23(5):700-13; DOI:10.1158/1055-9965.EPI-13-1057.
18. Zali H, Rezaei-Tavirani M, Azodi M. Gastric cancer: prevention, risk factors and treatment. Gastroenterol Hepatol Bed Bench. 2011;4(4):175-85.
19. Sugano K. Screening of gastric cancer in Asia. Best Pract Res Clin Gastroenterol. 2015;29(6):895-905; DOI:10.1016/j.bpg.2015.09.013.
20. Axon A. Symptoms and diagnosis of gastric cancer at early curable stage. Best Pract Res Clin Gastroenterol. 2006;20(4):697-708; DOI:10.1016/j.bpg.2006.03.015.
21. Gonçalves N, Chaves J, Marques- Sá I, Dinis-Ribeiro M, Libânio D. Early diagnosis of gastric cancer: endoscopy and artificial intelligence [Internet]. Best Pract Res Clin Gastroenterol. 2025 [cited 2025 Jan 24]. Available from: https://doi.org/10.1016/j.bpg.2025.101979/.
22. Li C, Shi C, Zhang H, Hui C, Lam KM, Zhang S. Computer-aided diagnosis for preoperative invasion depth of gastric cancer with dual-energy spectral CT imaging. Acad Radiol. 2015;22(2):149-57; DOI:10.1016/j.acra.2014.08.006.
23. National Cancer Institute. Stomach cancer stages [Internet]. Bethesda (MD): National Cancer Institute; 2023 [cited 2025 Jan 25]. Available from: https://www.cancer.gov/types/stomach/stages/.
24. Guan WL, He Y, Xu RH. Gastric cancer treatment: recent progress and future perspectives. J Hematol Oncol. 2023;16(1):57; DOI:10.1186/s13045-023-01451-3.
25. National Cancer Institute. Stomach cancer treatment by stage [Internet]. Bethesda (MD): National Cancer Institute; 2023 [cited 2025 Jan 25]. Available from: https://www.cancer.gov/types/stomach/treatment/by-stage/.