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Recent trends in the study of *Helicobacter pylori* developing stomach cancer in human

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Abstract
The microbial origin of cancer is at present realized as one of the most important causes of developing cancer in human. And, recently, it appears that the same subject has been found to be discussed in much detail by the microbial oncologists as one of the causes of cancer development. Barry Marshal and Robin Warren have investigated a similar carcinogenic bacteria named *Helicobacter pylori* developing cancer in human stomach. The present paper is an attempt to review the recent trends in researches carried on in the field of *H. pylori* infections and their magnifications of developing a variety of cancers in human for the last 15 years.

Keywords: *Helicobacter pylori,* human stomach cancer

1. Introduction
Helicobacter pylori is an ubiquitously distributed Gram negative bacteria usually found in human stomach causing duodenal ulcers and stomach cancers in human. The bacteria was isolated and identified by Barry Marshal and Robin Warren in 1982 from a person suffering from gastritis and gastric ulcers, a condition, in fact not known previously to be linked in any way with their microbial origin of cancer. Further, despite the patients infected with this bacteria are usually found asymptomatic and even their simple colonization of bacteria often do not cause a disease, it has always been associated with a number of upper gastrointestinal tract ailment and disorders in human. Some of the symptomatic distinguishing features of *H. pylori* infections are found as nausea and vomiting, abdominal cramps, difficult swallowing, burping and bloating, gastritis with gastric ulcers, diarrhoea, helitosis, heartburn and feeling of hunger especially in the morning. The present paper deals with the study of highlighting the infection of *Helicobacter pylori* causing ulcer and stomach cancer in human.

2. Methodology
The present paper is prepared on the basis of recent researches done so far in the field of stomach cancer caused by *Helicobacter pylori* in human. Several research papers were consulted to explore the facts and mechanisms of developing and disseminating this bacterial origin of cancer in the human society.

3. Results and Discussion
Helicobacter pylori is a potent oncogenic bacteria. Nearly, half of the worlds population are having this bacteria in their stomach (Chang and Parsonnet 2010) [11]. This bacteria has been colonizing the human stomach for the last 58000 years (Linz *et al.* 2007) [31]. Nearly, 60% of all stomach cancers and 5.5% of all cancers are caused by the *H. pylori* (Parkin 2006) [45]. Similarly, 10% of *H. pylori* carriers usually showed the symptoms of peptic ulcer and 3% gastric adenocarcinoma of which 0.1% was suffering from mucosa-associated lymphoid tissue (MALT) lymphoma (Peek and Crabtree 2006, Kondo *et al.* 2009 and Shanks and El-Omar 2009)[28, 48, 55]. These infections are very easily acquired during the course of childhood via oral-fecal or oral-oral mode of transmission (Everhart 2000) [17]. Approximately, 1 million cases are diagnosed every year, establishing fourth most common cancer of the world. Men are suffered twice than women. Most of the peoples are suffering at the age of 47 to 50 years (Blaser *et al.* 1995) [5]. This has been enough unfortunate for us to mention for *H. pylori* that once the bacteria colonizes in the stomach or in intestine it persists there life long and our immune system is quite incapable of removing the same making it the second leading cause of stomach related deaths worldwide (Lydia *et al*. 2010 and Panchal *et al*. 2003) [33, 44].
H. pylori is classified as a class 1 carcinogen by the International Agency for Research on Cancer (IARC, 1994) [23]. *H. pylori* is a Gram negative, spiral bacterium that colonizes the stomach in 50% of all humans. It continues in countries with high socioeconomic strata, the infection is rather less common than in developing countries where virtually everyone may be infected. The infection is usually asymptomatic in most of the individuals but to cause peptic ulcer. Such ulcers are more common in the duodenum at the specific site of upper corpus region of the stomach due to excess acids production by *H. pylori* infection (Mudd *et al*. 1980, Chipman 1982, Goldin *et al.* 1985, Carboni *et al*. 1988, Graham 1997, Hahm *et al*. 1997, Zhao *et al*. 2005, Burnstein *et al*. 2009 and Cho *et. al*. 2010) [8, 10, 13, 14, 20, 21, 22, 40, 68]. For decades, we thought that human stomach ulcers are developed due to stress, ingestion of more spicy foods, chain smoking or other lifestyle habits. But, in the year 2005, when Barry Marshall and Robin Warren were awarded the Nobel prize for physiology and medicine this is proved that *Helicobacter pylori* is a potent carcinogen causing stomach cancer in human (Van Der Weyden *et al.*

2005) [66]. The *H. pylori* infection in stomach produces an increased inflammatory response and higher risk of gastric adenocarcinoma with chronic hypochlorhydria associated with iron deficiency (Peek and Blaser 2002, Stolte *et al*. 2002, Peter and Beglinger 2007, Lydia *et al*. 2010, Paul *et al*. 2013, Zucca *et al*. 1998 and Morgner *et al*. 2000) [33, 37, 46, 47, 49, 60, 70]. *H. pylori* produces gastric MALT lymphoma as well as diffuse large-B-cell lymphoma (Peek and Crabtree 2006) [48]. Though, the *H. pylori* infection is common but the identification of individuals with high risk of cancers has been a very tedious job. Because, most of the persons who colonized the bacteria never develop cancer (Shanks and El-Omar 2009) [55]. And, it might be due to the genetic diversity of microbe and the host concerned (Lydia *et al*. 2010) [33]. Now, there are some techniques available to identify the persons with high risk of cancer having colonization of bacteria. These techniques include the genome sequencing of *H. pylori* measurable phenotypes (Cag A phosphorylation) and practical animal models (Akopyants *et al*. 1998 and Blaser and Berg 2001) [1, 4]. In addition, a good number of researches have carried out to investigate the mechanism responsible for virulence of *H. pylori* as follows

- Induction of gastric epithelial apoptosis by *H. pylori* has been reported by Moss *et al*. 1996 [39].
- Not only the genes responsible for the colonization of infection have been identified but the complete genome sequencing of the *H. pylori* have also been worked out by Shimoyama *et al*. 1997 and Kavermann *et al*. 2003 [26, 56].
- *H. pylori* causes DNA damage in gastric epithelial cells (Hahm *et al*. 1997) [22].
- Cag A protein formed during the course of infection causes mitotic impairment and induces chromosomal instability in host (Umeda *et al*. 2009) [65].
- Chronic *H. pylori* infections induce gastric mutations in animal model experiments (Touati *et al*. 2003) [62].

However, there are some environmental factors reported which establishes and enhances the incidence of disease. For example, tobacco smoking increases the risk for gastric adenocarcinoma among *H. pylori* – infected individuals (Siman *et al*. 2001) [58]. Similarly, gastric carcinoma is more easily developed in persons with *H. pylori* infection having high salt intake. It damages the gastric mucosa allowing the entry of carcinogens into the gastric tissue (Beevers *et al*. 2004, Tsugane 2005, Kato *et al*. 2006 and Ganez *et al*. 2008)[3, 18, 25, 64]. But, one thing to be worth mentioning here that *H. pylori* coinfection with helminth in children has shown the low incidence with gastric carcinoma. How it happens is a matter of further research (Whary *et al*. 2005 and Du *et al*. 2006)[15, 67]. In the early stages of infection, eradication of *H. pylori* and the treatment with antibiotics cures the patient (Stolte *et al*. 2002, Romano and Cuomo 2004, Cai *et al*. 2005, Suzuki *et al*. 2010, Lopes *et al*. 2014, Molina-Infante and Gisbert 2014) [33, 37, 46, 47, 49, 60, 70]. Vaccination against H. pylori infections has also been suggested in young children as a means to prevent the stomach cancer (Giuseppe *et al*. 2009, Nina *et al*. 2013 and Amin Abadi 2016) [2, 19, 43].

Helicobacter pylori has also been found to be involved in some other diseases like lung cancer (Philippou *et al*. 2004, Ece *et al*. 2005, Najafizadeh *et al*. 2007, and Zhuo *et al*. 2009) [16, 41, 50, 69], gall bladder cancer and cholecystitis (Chen *et al*. 2007, Nath *et al*. 2010, and Rani kanthan *et al*. 2015) [12, 42, 51] and colorectal cancer (Breuer-Katschinski *et al*. 1999, Siddheshwar *et al*. 2001, Limberg *et al*. 2002, and Robertson *et al*. 2009) [7, 30, 53, 57]. In addition, various other *Helicobacter* species like *H. felis* and *H. heilmanni* are also reported to cause certain diseases including stomach cancer (Regimbeau *et al*. 1998, Morgner *et al*. 2000, Ierachi *et al*. 2001, Trebesius *et al*. 2001, Cai *et al*. 2005, Singhal and Sepulveda 2005 and Chang and parsonnet 2010) [9, 11, 24, 37, 52, 59, 63] and gall bladder and biliary tract cancer with gall stones and cholecystitis by *H. bilis* and *H. hepaticus* (Matsukura *et al*. 2002, Kobayashi *et al*. 2005, Bohr *et al*. 2007, Mortel *et al*. 2009, Nath *et al*. 2010 and Rani Kanthan *et al*. 2015) [6, 27, 35, 38, 42, 51].

The testing for *H. pylori* infection is always recommended if the patients are suffering from peptic ulcers or even low grade MALT lymphoma is present. The various tools are usually adapted to examine the *H. pylori* infection given as under

- Endoscopy
- Blood antibody test
- Stool antigen test
- Carbon urea breath test
- Urine ELISA test

Though, these methods as described above are helping us a lot in detecting the bacteria in patients suffering from *H. pylori* infections; perhaps, the only accurate method has always been there as histological examinations of endoscopic biopsy either associated with rapid urease test or microbial cultures.

Since, in most of the cases the infection is asymptomatic without being developed in cancer, we should nothing more to worry about it but to be alert in future. Moreover, if any one develops the cancer in future, certainly it is his bad luck (Masroor *et al*. 2018) [34]. In addition, the first line treatment often includes the eradication of bacteria allowing the ulcer to heal with the help of suitable antibiotics with appropriate proton pump inhibitors. Proton pump inhibitors (PPIs) lower the stomach acid. It helps the antibiotics to work more effectively. Similarly, the choice of drugs are clarithromycin, amoxicillin and omeprazole as triple therapy prescribed for a week (Kumar and Vidyarthi 2018) [29].

4. Conclusion

One of the most important bacteria causing cancer in human is *Helicobacter pylori*. Though, this is overlooked since long because of their as usual asymptomatic inhabitants in the stomach of human and only some of the people developed ulcers and more rarely cancers. At this juncture, we are unfortunately unable to understand that how and why these peoples develop cancer in future. Scientists are not sure why it affects some people differently than others. The authors felt the need of early diagnosis and treatment of *H. pylori* infections, if the similar symptoms as described in the paper are seen.

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6. Conflict of Interest

The authors have declared no conflict of interest. They have approved the final version of the manuscript contributing equally.

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