Chapter 3

Risk Factors in Gastric Cancer

Jolanta Czyzewska

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1. Introduction

Gastric cancer is one of the most commonly occurring malignant cancers in the world. During the second half of the 20th century a drastic rise has been observed in the number of cases and deaths caused by this cancer. Gastric cancer is the second, after pulmonary cancer, cause of death due to malignant cancers in the world. There is a geographic diversification in the occurrence of gastric cancer. Most cases are recorded in Japan, China, South America, and significantly less in Western Europe and in the United States [1].

The frequency of the occurrence of gastric cancer throughout the world is conditioned by various factors. The following factors increase the risk of occurrence of gastric cancer: chronic atrophic gastritis with intestinal metaplasia, peptic ulcer, dysplasia, partial gastrectomy and polyps. Environmental factors which can cause an increase in the risk of occurrence of gastric cancer include, among others, dietary factors, smoking as well as a *Helicobacter pylori* infection [2].

2. Risk factors in gastric cancer

2.1. Age

One of the risk factors for contracting gastric cancer is age (above 45 years of age). The number of cases involving this tumor increases with age, reaching a peak between the ages of 50 and 70 [3,4]. Most deaths are recorded in the 55-75 age group; and the number of fatalities decreases after 75. The frequency of gastric cancer occurrence rising with age can be explained by the accumulation of somatic mutations connected with the occurrence of malignant tumors [5,1].

2.2. Sex

Gastric cancer definitely develops more often in men. The coefficient of contracting this type of cancer is 1.8 – 2 times higher for men in comparison to women. Generally, percentages show 68% of gastric cases to be men and only 32% to be women [3, 6].

2.3. Obesity

Obesity is one of the causes facilitating spreading of the cancer in the cardia since discharging of food contents into the esophagus can occur. Research results have indicated a 2.3- fold increase of the risk of contracting gastric cancer in the cardia in obese persons in comparison to non-obese people [4]. It has been shown that obesity in men (BMI ≥ 30 kg/m^2) was connected not only to an increased risk of development of gastric cancer but also of colorectal cancer, cancers of the liver and the gallbladder. In turn, obesity in women (BMI ≥ 30 kg/m^2) was tied to an increased risk of development of tumors of the liver, pancreas and breasts in women above 50 years of age [7].

2.4. Diet

Diet, especially one rich in salt, smoked or marinated foods, grilled meat or smoked fish, preserved food, rich in red meat, deficient in vitamins and antioxidants, significantly increases the probability of cancer occurrence. Salt and consumption of salted foods causes an increase in the risk of stomach cancer occurrence even up to 50-100%. This happens because sodium chloride damages the mucous membrane of the stomach leading to infections and consequently facilitates colonization and growth of *Helicobacter pylori*. Increasing the supply of salt while at the same time decreasing the number of consumed fruit and vegetables is particularly dangerous [2, 3, 8].

This risk can be reduced by increasing the amount of vegetables and fruit consumed. Increasing the number of consumed vegetables and fruit in every day diet reduces the risk of contracting gastric cancer by as much as 30-50%. It is connected to the antioxidant effect of the substances contained in vegetables such as ascorbic acid (vitamin C), carotenoids and tacopherols. Moreover, soy products and green tea reduce the risk of contracting this type of cancer. Catechins contained in green tea inhibit polyphenol nitrosation, have an anti-inflammatory and antineoplastic effect modulating the path of signal transfer, inhibiting cell proliferation and transformation, as well as inducement of apoptosis, and in effect inhibit the development of tumors [4,8].

Reducing the amount of chemically preserved products in the foods ingested also contributes to reducing the risk of gastric cancer occurrence. Antioxidants such as vitamins C and E, beta-carotene, or microelements like selenium, zinc or magnesium [2] have a protective effect.

2.5. Stimulants

The risk of gastric cancer development correlates with the frequency and duration of smoking cigarettes. A nearly 5-fold increase occurs in the probability of contracting this disease in

persons who smoke over 20 cigarettes a day and using alcohol more than 5 times in a two week period of time. Furthermore, the probability of contracting this type of cancer increased approximately 1.3 times for passive smokers in comparison to people who do not smoke and are not passive smokers. This is caused by the carcinogenic effects contained in cigarette smoke (for example tar and its polycyclic hydrocarbons) [3-5,9]. Carcinogens are able to form covalent bonds with DNA, which alters the correct function of the DNA and can lead to the development of gastric cancer [10].

Similarly, overuse of spirits, especially those with high alcohol content, significantly increases the risk of contracting gastric cancer and other tumors of the digestive tract (cancers of the mouth, throat, larynx and esophagus). Overconsumption of alcohol (4 or more drinks a day) is connected to a significant increase in the risk of contracting gastric cancer, equally for smokers as well as non-smokers (10). Alcohol stimulates the production of gastric juices and gastric motility. Intragastric supply of 70-100% ethanol causes extensive mucous membrane damage, with simultaneous reduction of blood flow in the blood vessels of the stomach, reduced generation of mucus, increase in the activity of proinflammatory cytokines (including IL-1), tumor necrosis factor alpha (TNFα), the level of leucotriene B4 and causing of oxidative stress [11].

Ethanol is not a carcinogen but the nitrosamines present in alcoholic beverages, especially in vodka, can be responsible for heightened risk of gastric cancer development. Acetic aldehyde, a metabolite of ethanol, is a known to be a carcinogen in animals. Acetic aldehyde created during ethanol metabolizing is mainly eliminated from the organism by aldehyde dehydrogenase-2 (ALDH2). ALDH2 is polymorphic and in people it has two alleles: ALDH2*1 and ALDH2*2. Reduced activity of the enzyme ALDH2*2 in homozygous individuals results in approximately 6-20 times higher level of acetic aldehyde in blood in comparison to homozygote ALDH2*1 and is connected with an elevated risk of developing gastric cancer [10].

2.6. Medicines

Aspirin is one of the medicines which increase the risk of contracting gastric cancer. For people who regularly take aspirin the risk of contracting gastric cancer increases up to 30%. Regular application of non-steroid anti-inflammatory drugs (NSAID) increased the risk of developing peptic ulcers and digestive tract bleeding, while at the same time, depending on the dosage, decreasing the growth of *H. pylori* and bacterial virulence factors. Aspirin increases the permeability of the external bacterial membrane causing an increased sensitivity of *H. pylori* to antibiotics [12]. Occurrence of damage to the gastric mucosa (bleeding and ulceration of the stomach, duodenum and small intestine) connected to aspirin intake at a dosage of 75-325 mg/day has been described. In patients taking aspirin occasionally bleeding of the digestive tract occurred 5.5 times more often and in patients regularly taking this drug approximately 7.7 times more frequently in relation to persons who did not take aspirin [13]. Furthermore, aspirin significantly decreases the amount of claudin-7, a protein produced by the MNK28 cells, connected to damage of the digestive tract and aspirin related dysfunction of the epithelium in the stomach. Aspirin related concentration decrease of the protein clau-

din-7 has been completely eradicated by the SB-203580 (inhibitor p38MAPK) treatment. These results demonstrate that the protein claudin-7 plays a significant role in the occurrence of aspirin related dysfunction of the stomach and that the activation of p28MAPK also takes a part in this dysfunction [14].

On the other hand it has been shown that patients who regularly take NSAIDs had a significantly reduced risk of gastric cancer occurrence in relation to persons occasionally taking these drugs or not taking them at all. However, the protective role of the NSAIDs was observed only in patients with non-cardia gastric cancer [15].

2.7. *H. pylori* infection

In many studies a close connection has been shown between a *Helicobacter pylori (H. pylori)* infection and an infection of the mucous membrane of the stomach wall, peptic ulcer and cancer [4]. The World Health Organization (WHO) classified *H. pylori* as a group 1 carcinogen, even though the exact mechanism through which this bacterium contributes to the development of gastric cancer is not completely understood [5]. It has been ascertained that in patients with an *H. pylori* infection the risk of the development of gastric cancer increases seven fold in comparison with a group of people without such an infection. It seems that an *H. pylori* infection connected with cagA genes (cytotoxin-associated gene A) and VacA (valulocating cytotoxin A) induces a more severe infection [6]. These genes are responsible for the production of cytotoxins which increase virulence. Especially the presence of *Helicobacter pylori* CagA + contributes to the rise of the risk of carcinogenesis occurrence. CagA intensifies immunological response, and through stimulation releases IL-8, a chemokine which leads to damage to the mucosa [4,16,17]. Additionally, *Helicobacter pylori* produce large amounts of urease which breaks urea into ammonia and carbon dioxide. The ammonia neutralizes the hydrochloric acid contained in stomach juices leading to it gaining a higher pH therefore making it easier for the bacteria to survive and reproduction [18]. Chronic inflammation caused by a *Helicobacter pylori* infection can result in damage to cell DNA by disrupting antioxidant processes, while at the same time raising the level of reactive forms of oxygen, as well as the amount of nitric oxide (NO), eventually elevating the risk of carcinogenesis. What is more, *Helicobacter pylori* causes the release of interleukins such as IL-1β, IL-6, IL-8, IL-18 as well as of the tumor necrosis factor α (TNF-α), through this intensifying the immunological response of the body and development of cancer[19, 16, 20].

H. pylori have a carcinogenic effect in the stomach through one of two possible mechanisms:

i. direct transformation of the stomach's mucous membrane using the metabolic products of the body or

ii. quick transformation of the mucosa cells causing infection related damage to the mucous membrane which may elevate the risk of DNA damage, predisposing the mucosa to transformation by absorption or endogenic mutagens [21] and byproducts of the infection [22] such as peroxides and hydroxyl ions which can cause oxidative damage, mutation and malignant transformation [23].

Furthermore, it has been proven that the eradication of *H. pylori* in patients below the age of 40 can reduce the risk of gastric cancer occurrence [24].

2.8. Epstein-Barr virus infection

The Epstein-Barr virus (EBV) is a herpes gamma virus, which causes opportunistic lymphomas in immunologically compromised hosts, and in individuals without immunologic suppression. Mechanisms of EBV- related tumorigenesis may include:

- DNA methylation, which regulates host gene expressions and signal pathway through viral proteins
- viral small RNAs that can target host genes
- altered expression of microRNAs (miRNA) of host cells and
- other epigenetic alterations (chromatin conformation and histone modification) [25].

It has been shown that the frequency of EBV infections in patients with gastric cancer differs in different countries and ranges from 1.3% to 20.1%, an average of approximately 10%. In association with the presence of the EBV in cancerous cells this type of gastric cancer has been called the EBV-associated gastric carcinoma (EBVaGC). EBVaGC is a non-endemic disease since it is distributed throughout the world. This carcinoma shows some distinct clinicopathologic characteristics, such as male predominance, predisposition to the proximal part of the stomach, and a high proportion in diffuse-type gastric carcinomas. Also, EBVaGC shows some characteristic of molecular abnormality, like global and nonrandom CpG-island methylation of the promoter region of many cancer-related genes (p16, p73, CDH1). EBVaGC presents a relatively favorable prognosis [26-30].

2.9. Socioeconomic status

Throughout the world in 2002 2/3 of gastric cancer cases have been recorded in less developed nations. The poorest countries, especially African nations, stand out as having a relatively low morbidity coefficient for this type of tumor. However, this is caused by insufficient diagnosis and status of medical care [19]. Performance of some professions such as: butcher, farmer or fisherman predisposes one to an elevated risk of developing stomach cancer. This is associated with being exposed to herbicides or nitrates during work. Other professions exposed to a greater danger of carcinogenesis are: mechanic, manager, production supervisor as well as craftsmen, people working in stone quarries, metal industry, food industry, cooks, people working in laundries and cleaning personnel [19,31].

2.10. Migration

A reduction in the incidence of cancer is observed in an event of migration from an environment with a high risk coefficient to those having a lower coefficient, for example, migration of citizens of Japan to the United States. A significant fall in the occurrence of gastric cancer is observed in persons of Japanese origin born in the United States in comparison to recent immi-

grants [9]. Studies done on immigrants to the United States from countries with a high risk of gastric cancer occurrence, such as Japan or Poland, showed that subsequent generations of émigrés to the USA slowly become similar through following generations to native citizens of the country of settlement, meaning the risk of contracting the disease decreases [6].

2.11. Peptic ulcer

Patients suffering from gastric cancer often report having long lasting peptic ulcer disease of the stomach or the duodenum or gastrointestinal reflux disease. The symptoms of the diseases mentioned above and symptoms of early stages of gastric cancer are practically indistinguishable if correct forms of diagnostics are not utilized [32].

2.12. Family history of gastric cancer

Family history of gastric cancer has been studied in many regions including Eastern Asia, North America, Northern Europe and the nations of the Mediterranean region. Most cases of family history of gastric cancer have been recorded in the countries of the Mediterranean while the fewest cases of this type of disease have occurred in the countries of Western Europe. Additionally, it has been shown that family history of gastric cancer more often concerns women than men [33].

Occurrence of gastric cancer within a family significantly increases the risk of carcinogenesis. This is connected with similar environmental conditions in which a given family lives, genetic predispositions, habits, like smoking tobacco or a *Helicobacter pylori* infection [34,35]. Development of gastric cancer is observed in approximately 10 – 15% of people with the disease previously occurring among family members. Furthermore, the danger connected with the occurrence of gastric cancer in immediate family increases about 2 – 3 fold in families who are hereditarily degenerate [9,3]. Approximately 30% of gastric cancer cases connected to earlier occurrence of this tumor in family is linked to a mutation in the e-cadherine coding CDH1 gene [36].

Mutations in the e-cadherine coding gene (CDH1) lead to the inhibition of the reuptake of e-cadherine by the product of the APC gene as a result of which an intensification of the inflammatory response is observed. This results in an emergence of linitis plastica, a cancer which develops without the presence of *Helicobacter pylori* infection or chronic gastritis [4].

2.13. Level of pepsinogen in serum

Pepsinogen is a proenzyme of pepsin, a digestive enzyme produced in the mucous membrane of the stomach. Two subtypes of pepsinogen can be distinguished (sPG): pepsinogen I and pepsinogen II. Both subtypes are produced by chief cells, mucous neck cells and fundic glands. Pepsinogen II is also produced by the pyloric gland cells. When atrophy develops in the stomach, chief cells and fundic glands are replaced by pyloric gland cells, which leads to a decrease of the pepsinogen I level while the level of pepsinogen II remains unchanged. For this reason low levels of pepsinogen I and II are a good indicator of atrophic gastritis. Chronic atrophic gastritis is a precursor of gastric cancer, especially intestinal-type cancers. Hence des-

ignation of the level of pepsinogen in serum or the calculation of the coefficient of pepsinogen I/II is a good screening assay for gastric cancer. The ≤ 59 ng/ml level of pepsinogen I in serum and the ≤3.9 value of the coefficient of pepsinogen I/II have been regarded as the most predictive. The sensitivity of this test was 71% while the specificity reached 69.2% [37].

2.14. Single Nucleotide Polymorphisms (SNAPs)

2.14.1. Polymorphism of IL1B

Interleukin 1 beta (IL1B) is a proinflammatory cytokine which regulates the expression of some particles taking part in the inflammation process. It has been shown that the two functionally important polymorphisms in the promoter region, IL1B-31T/C and -511C/T, are connected to an increased risk of developing gastric cancer [38, 39].

2.14.2. Polymorphism of IL-8

IL-8 is a member of the α-chemokine family which acts as a strong chemoattractant and neurofilia activator. It has been suggested that this interleukin is strongly associated with the processes of carcinogenesis, angiogenesis, adhesion, invasion and metastasis. Hull et al. demonstrated the presence of a polymorphism of a single nucleotide in the -251 (A/T) position from the transcription starting place in a region closer to the promoter as well as a connection between the presence of the allele IL-8-251A and an increase in the production of IL-8 and an elevated risk of gastric cancer development in the cardia. The presence of the IL-8 251AA genotype was connected with increased risk of gastric cancer development in an Asian population, mainly Han Chinese as well as in intestinal-type cancer [41,42].

2.14.3. Polymorphism of IL-10

Interleukine-10 (IL-10) is an anti-inflammatory cytokine which regulates the cell immunological response. In the gene coding IL-10 three polymorphic promoter variants, located in positions -1082 (A>G), -819 (T>C) and -592 (A>C) have been discovered. These variants are connected with an elevated production of IL-10 and an increased risk of the occurrence of gastric cancer, especially the intestinal non-cardia gastric cancer. What is more, polymorphism of the gene coding IL-10 in combination with environmental factors, such as cigarette smoking or an *H. pylori* infection creates favorable conditions for the occurrence and progression of gastritis and carcinogenesis [43]. Additionally, polymorphism of IL-10 can influence the immune system by changing the activity of the NK, T cells and macrophages and in this manner influence the disease progression [44].

2.14.4. Polymorphism of IL-17A and IL-17F

Interleukin 17A and 17F are inflammatory cytokines, which play a critical role in inflammation and probably in cancer. An association has been found between IL-17F A7488G polymorphisms and the risk of intestinal-type gastric cancer. This polymorphism may influence the multi-steps of gastric carcinogenesis. Furthermore, patients having IL-17F 7488GA geno-

type had increased risk of large tumor size and lymph- node metastasis. Positive associations have been found between IL-17A 197AG genotype and elderly onset, early TNM stage and poorly differentiated gastric cancers [45].

2.14.5. Polymorphism of TLR2 and TRL4

TRLs are important innate immunity receptors. TRL2 and TRL4 promote transcription of genes involved in immune response activation including nuclear factor kappa B (NF-κB). TRL2 activates NF-κB in response to *H. pylori* infection, causing the expression of IL-8. TRL4 up regulated in gastric epithelial cell infected by *H. pylori*; expression of the TRL4 protein has been demonstrated in chronic active gastritis and in gastric tumor cells. It has been demonstrated that the presence of the TRL2-169 to -174del I TRL4+896G (Asp299Gly) polymorphic variant can increase the risk of gastric cancer development, especially the non-cardia intestinal-type [46-49].

2.14.6. Polymorphism of TP53

The TP53 gene is one of the most frequent targets for genetic mutations. The p53 pathway is crucial for effective prevention of genetically damaged cell propagation, either directly, by its participation in DNA repair mechanisms, or indirectly by induction of apoptosis. TP53 72ArgArg seems to be the survival factor for gastric cancer patients more advanced in years, while the TP53 Pro-A1 plays the same role in younger patients with this type of tumor. Additionally tumors at more advanced stages (III and IV) showed TP53 intron 3 A2A2 genotype carriers [50-52].

2.15. Gene mutations

2.15.1. CDH1 mutation

The germline CDH1 mutation is associated with the development of hereditary cancer syndrome, called hereditary diffuse gastric cancer (HDGC). Germline mutation of the CDH1 gene has also been discovered in patients with sporadic early onset gastric cancer (EOGC). Mutation of this gene has been described for the first time in 1998 in New Zealand in a Maori family with history of diffused gastric cancer. Various types of CDH1 gene mutations such as deletion, inertia, nonsense, and truncating have been described. The risk of developing gastric cancer with the occurrence of a non-missense mutation of the CDH1 gene is high at >80%, while with the occurrence of a missense mutation of this gene the risk has not been defined [53-55].

CDH1 gene (E-cadherin gene), is one of the most important tumor suppressor genes in gastric cancer. The mutations, chromosomal deletions, epigenetic modifications have been reported as a mechanisms, that cause CDH1 inactivation. Somatic CDH1 mutations have been found in about 50% of diffuse gastric cancer, germline mutations have been reported in familial gastric cancers.

CANCER SITE	CASES	(%) BOTH SEXES	ASR (world)
lip, oral cavity	263	2,1	3.9
Nosopharynx	84	0,7	1.2
other pharynx	135	1,1	0.2
Oesophagus	482	3,8	7.0
Stomach	**989**	**7,8**	**14.1**
Colorectum	1233	9,7	17.3
Liver	748	5,9	10.8
Gallbladder	145	1,1	2.0
Pancreas	277	2,2	3.9
Laryngx	151	1,2	2.3
Lung	1608	12,7	23.0
malanoma of skin	197	1,6	2.8
Kaposi sarcoma	34	0,3	0.5
Breast	1383	10,9	39.0
cervix uteri	529	4,2	15.2
corpus uteri	287	2,3	8.2
Ovary	225	1,8	6.3
Prostate	913	7,2	28.5
Testis	52	0,4	1.5
Kidney	271	2,1	3.9
Bladder	386	3	5.3
brain, nervous system	238	1,9	3.5
Thyroid	212	1,7	3.1
Hodkin lymphoma	67	0,5	1.0
non-Hodkin lymphoma	355	2,8	5.1
multiple myeloma	102	0,8	1.5
Leukemia	351	2,8	5.1

Table 1. Estimated new cancer cases (thousands), ASRs (per 100,000) and cumulative risks (percent) by sex and cancer site worldwide, 2008 [64].

CANCER SITE	DEATHS	(%) BOTH SEXES	ASR (world)
lip, oral cavity	127	1.7	1.9
Nosopharynx	51	0.7	0.8
other pharynx	95	1.3	1.4
Oesophagus	406	5.4	5.8
Stomach	**738**	**9.7**	**10.3**
Colorectum	608	8.0	8.2
Liver	695	9.2	10.0
Gallbladder	109	1.4	1.5
Pancreas	266	3.5	3.7
Laryngx	82	1.1	1.2
Lung	1378	18.2	19.4
malanoma of skin	46	0.6	0.6
Kaposi sarcoma	29	0.4	0.4
Breast	458	6.0	12.5
cervix uteri	274	3.6	7.8
corpus uteri	74	1.0	2.0
Ovary	140	1.8	3.8
Prostate	258	3.4	7.5
Testis	9	0.1	0.3
Kidney	116	1.5	1.6
Bladder	150	2.0	2.0
brain, nervous system	174	2.3	2.6
Thyroid	35	0.5	0.5
Hodkin lymphoma	30	0.4	0.4
non-Hodkin lymphoma	191	2.5	2.7
multiple myeloma	72	1.0	1.0
Leukemia	257	3.4	3.6

Table 2. Estimated cancer deaths (thousands), ASRs (per 100,000) and cumulative risks (percent) by sex and cancer site worldwide, 2008 [64].

REGION	MALE	FEMALE
Eastern Africa	4.0	3.3
Middle Africa	1.7	1.8
Northern Africa	2.9	1.9
Southern Africa	0.7	0.5
Western Africa	3.3	2.6
Caribbean	2.4	1.6
Central America	7.7	6.5
South America	29.3	17.9
Northen America	15.1	9.4
Eastern America	408.2	193.1
South-Eastern Asia	24.9	18.4
South-Central Asia	41.9	26.2
Western Asia	9.2	5.6
Cenral and Eastern Europe	43.3	30.6
Northern Europe	7.8	4.9
Southern Eutope	20.0	12.9
Western Europe	16.5	10.9
Australia/New Zealand	1.5	0.8
Melanesia	0.2	0.1
Micronesia/Polynesia	0.0	0.0

Table 3. Estimated numbers of new gastric cancer cases (thousands) by sex and regions, 2008 [64].

REGION	MALE	FEMALE
Eastern Africa	3.8	3.1
Middle Africa	1.6	1.7
Northern Africa	2.7	1.8
Southern Africa	0.6	0.5
Western Africa	3.1	2.5
Caribbean	1.8	1.2
Central America	6.4	5.6
South America	24.2	15.1
Northen America	7.6	5.2
Eastern America	274.3	144.2
South-Eastern Asia	20.1	15.3
South-Central Asia	39.5	24.1
Western Asia	8.1	4.9
Cenral and Eastern Europe	38.2	26.6
Northern Europe	5.4	3.6
Southern Eutope	14.6	9.8
Western Europe	11.1	7.9
Australia/New Zealand	0.9	0.6
Melanesia	0.2	0.1
Micronesia/Polynesia	0.0	0.0

Table 4. Estimated numbers of gastric cancer deaths (thousands) by sex and regions, 2008 [64].

2.15.2. DNA methylation

DNA methylation is an epigenetic mechanism regulating transcription which in cancer is attributed to the inappropriate silencing of tumor suppressor genes, or loss of oncogene repression. Methylation pattern of DNA can be useful in assessing the risk of cancer occurrence, prognosis and success of treatment. Aberrant DNA methylation appears in early stages of carcinogenesis, which makes it especially useful to predict the risk of contracting cancer. Methylated DNA is stable and has a high detectability (as much as 1:1000 particles) in biological fluids. What is more, in cancer patients DNA methylation can be an indicator of an answer for applied chemotherapy as well as can indicate a shorter time of post-operative survival [56-59].

2.15.3. RUNX3 promoter methylation

Runt-related transcription factor (RUNX3), a member of the runt domain family of transcription factors, plays an important role in the signaling path of the TGF-β (transforming growth factor β). In many reports not only the role of the RUNX3 in the correct development but also in the progression of cancer has been demonstrated. It has been shown that in younger gastric cancer patients the methylation of the RUNX3 promoter was associated with histological type and level of tumor differentiation. It has been suggested that RUNX3 promoter methylation or down-regulation of the RUNX3 gene may be related to a poor prognosis [60,61].

2.15.4. CHRF promoter methylation

CHRF (checkpoint with FHA and RING finger) is an important tumor suppressor gene. CHRF encodes a protein within the FHA and RING finger domain that governs transition from prophase to metaphase in the mitotic checkpoint pathway. Aberrant methylation of the CHRF gene is a frequent event in gastric cancer. The methylation rate of CHRF gene in stomach carcinoma was significantly higher than in paired normal gastric mucosa and it was associated with poorly differentiated tumor cells. Also, CHRF gene methylation was associated with the degree of malignancy of gastric cancer. The CHRF mRNA or protein expression level was down-regulated or loss [62,63].

3. Conclusion

Gastric carcinogenesis is a complex multistep process resulting from the interaction between genome and environmental factors. Many exogenous factors seem to contribute to the initiation of carcinogenesis in the stomach, including diet (especially high in salt, smoked or pickled foods, grilled meats or smoked fish), chronic a trophic gastritis with intestinal metaplasia, gastric ulcer, dysplasia, and partial resection of gastric polyps. Others risk factors for this cancer is chemical agents and infections, e. g. caused by Helicobacter pylori and Epstein- Barr virus. Also, genetic factors, such as blood group A, familial polyposis and the

presence of gastric cancer among family members play a role in the development of this cancer. This group of factors also include radiation or pernicious anemia. Additionally, dysfunction of CDH1 gene (E-cadherin-coding gene) together with mutation have been found in diffuse-type gastric carcinoma. Mutation in CDH1 is a genetic defect found in approximately 1/3 of familial gastric cancers such as hereditary diffuse gastric cancers (HDGC). Also, the presence of single nucleotide polymorphisms (SNPs) in several genes can modulate the risk of gastric cancer.

Knowledge of various risk factors for stomach cancer can help to determined the risk of development this cancer. Also, a small change in diet or lifestyle can significantly reduce this risk.

Author details

Jolanta Czyzewska*

Address all correspondence to: czyzyk15@op.pl

Department of Clinical Laboratory Diagnostics Medical University of Bialystok, Bialystok, Poland

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