Helicobacter pylori-associated malignancies:

Genetics, Epidemiology and Gastric Cancer Risk

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Stellingen

Behorende bij het proefschrift

***Helicobacter pylori* – associated malignancies**

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1. Naast een coloscopie ter preventie van darmkanker moeten patiënten met het Lynch syndroom ook een gastroscopie ondergaan voor vroeg-detectie van maagkanker. (*dit proefschrift*)
2. Accurate evaluatie van de mucosa van de maag binnen een jaar na de diagnose MALT lymfoom is noodzakelijk vanwege het gelijktijdige risico op maagkanker. (*dit proefschrift*)
3. Een scoringssysteem gebaseerd op atrofische veranderingen van het maagslijmvlies is slecht reproduceerbaar en leidt daardoor tot een onbetrouwbare voorspelling van het maagkanker risico. (*dit proefschrift*)
4. Een negatieve familie-anamnese voor maagkanker is een slechte indicator om af te zien van een maagonderzoek ter preventie van maagkanker in patienten met het Lynch syndroom. (*dit proefschrift*)
5. Conventionele wit licht endoscopie is onvoldoende voor het aantonen van pre-maligne maagafwijkingen. (*dit proefschrift*)
6. Niet alles wat gemeten wordt is waardevol en niet alles wat waardevol is kan worden gemeten. (*Albert Einstein*)
7. Ondanks het scherpere zicht leidt het hebben van een multifocale bril bij ouderen tot hogere kosten in de zorg. (*Haran M, et al. BMJ 2010*)
8. Absence of evidence is not the evidence of absence. (*Altman DG, et al. BMJ 1995*)
9. De lange periode tussen het submitten en publiceren van een artikel leidt ten tijde van een epidemie tot meer doden. (*Xing W, et al. PloS Med 2010*)
10. Het eten van een reep chocolade is goed voor de gezondheid: het verbetert de hartfunctie, het voorkomt tandbederf en het bevordert met name bij vrouwen de gemoedstoestand. (*Medisch contact 2008*)
11. Als chaos en drukte wetenschappelijke creativiteit bevorderen, is het hebben van een 1-persoonskamer minder bevorderlijk voor de promotie dan het hebben van een 7-persoonskamer.

Summary

Helicobacter pylori infection affects at least 50% of the world population. The chronic inflammation caused by *H. pylori* can progress to pre-malignant gastric lesions, gastric adenocarcinoma and gastric MALT lymphoma. The widespread high prevalence of *H. pylori* explains that gastric cancer remains the fourth most common cancer and second leading cause of cancer related death worldwide. For these reasons, data on epidemiology and screening and surveillance options for gastric cancer in patients with *H. pylori*-associated malignancies may lead to a reduction in gastric cancer mortality.

In the first chapter the aims and outline of this these are described.

In the second chapter of this thesis we describe a pilot study on the association between *H. pylori* susceptibility and genetic factors. Overall, 277 *H. pylori*-positive patients and 728 *H. pylori*-negative patients were included in this study. Three single nucleotide polymorphisms (SNPs) in two loci demonstrated a significant association with *H. pylori* infection ($p \leq 0.05$). All three SNPs resided in unannotated regions, two on chromosome 2 (rs17015126 and rs1816653) and one on chromosome 11 (rs1939842). For these SNPs combined p-values and Odds ratios were calculated for the total cohort. All showed suggestive genome-wide associations with *H. pylori* with an OR of 2.5 (95% CI 1.7-3.5; p = 2.8 x 10-7) for rs17015126, an OR of 2.7 (95% CI 1.7-4.4; p = 2.6 x 10-5) for rs1816653 and an OR of 0.6 (95% CI 0.5-0.8; p = 2.9 x 10-5) for rs1939842. Unfortunately, the precise identity of these SNPs and the function of the nearest genes remain unknown. Therefore, future (basic) research is

necessary to confirm this association and to provide insights in identity of the underlying loci.

In the third chapter we evaluated the epidemiology of gastric MALT lymphoma, and the gastric adenocarcinoma risk of patients with gastric MALT lymphoma. Firstly, we demonstrated that the incidence of gastric MALT lymphoma increased from 1991-1997. However thereafter, a rapid decline in gastric MALT lymphoma incidence was observed. This decline is in part explained by the declining *H. pylori* prevalence in Western countries. Furthermore, we showed that patients with gastric MALT lymphoma had a 6-fold increased risk for gastric cancer in comparison with the general population ($p<0.001$). In 90% of patients with diagnosis of gastric cancer, gastric cancer was diagnosed simultaneously or after gastric MALT lymphoma diagnosis, with a median interval of 6.0 years (range1-7). We concluded that accurate endoscopic and histologic re-evaluation after diagnosis for gastric MALT lymphoma is highly warranted.

In addition, the prevalence and severity of pre-malignant gastric lesions in patients with gastric MALT lymphoma may indicate an increased gastric cancer risk. Therefore in chapter four we evaluated the differences between the prevalence of pre-malignant gastric lesions in gastric MALT lymphoma patients with a subsequent diagnosis of gastric cancer and those without. No differences were demonstrated in the prevalence and severity of pre-malignant gastric lesions of gastric MALT lymphoma patients with a subsequent diagnosis of gastric cancer or those without. However, surprisingly, advanced pre-malignant gastric lesions were common in both patients with subsequent gastric cancer and patients without gastric cancer development. This indicated that endoscopic and histopathologic surveillance with

specific attention to the severity of pre-malignant gastric lesions after diagnosis of gastric MALT lymphoma is highly warranted.

In the fifth till seventh chapter we evaluated screening and surveillance options for patients with pre-malignant gastric lesions. In the fifth chapter we described a large cohort of 119 patients with a previous diagnosis of intestinal metaplasia or dysplasia and 98 patients with no diagnosis of advanced precursor lesions. We demonstrated that serum leptin levels can serve as extra tool to predict patients with high gastric cancer risk in combination with the established risk factors, in particular male sex, advancing age, and low serum pepsinogen I levels. However, our results showed that the additional value of this non-invasive marker is rather low. In the sixth chapter, we presented a cohort of 43 patients with a previous diagnosis of intestinal metaplasia and dysplasia. These patients underwent surveillance endoscopy with conventional white light and narrow band imaging (NBI). We showed that the sensitivity for the detection of advanced pre-malignant gastric lesions was 71% for NBI and 51% for the conventional white light endoscopy. We concluded therefore that NBI considerably increases the diagnostic yield of the detection of gastric intestinal metaplasia and dysplasia, compared to routine WLE. NBI therefore seems superior to WLE in the surveillance of patients with advanced gastric precursor lesions.

We proposed in the seventh chapter a new histological staging system for estimating gastric cancer risk in patients with pre-malignant gastric lesions. This new staging system was based on the grading of intestinal metaplasia (OLGIM) instead of the recently proposed OLGA staging system which is based on the grading of atrophic gastritis. We showed that the interobserver agreement was substantial for atrophic gastritis (kappa value=0.6) and almost perfect for intestinal metaplasia (kappa

value=0.9). In addition, the interobserver agreement was improved for all stages of the OLGIM compared to the OLGA. Moreover, the correlation with the severity of gastritis remained at least as strong. Therefore, we concluded that the OLGIM may be preferred over the OLGA for the prediction of gastric cancer risk in patients with pre-malignant gastric lesions.

In addition to the increased gastric cancer risk in patients with gastric MALT lymphoma and pre-malignant gastric lesions, Lynch syndrome mutation carriers seem to have an increased gastric cancer risk, too. In chapter 8 of this thesis we described the incidence trends of gastric cancer and the gastric cancer risk in a cohort of 2014 mutation carriers. In total, 32 (1.6%) Lynch syndrome mutation carriers were diagnosed with gastric cancer. Firstly, we showed that the standardized incidence rate of gastric cancer in Lynch syndrome mutation carriers decreased from 4.0 (95% CI 1.5-8.6) in the years 1970-1979 to 2.1 (95% CI 0.6-5.3) in 1990-1999 (p=0.03). Secondly, we demonstrated a lifetime risk of developing gastric cancer of 8.0% for males and 5.3% for females (p=0.02). This risk was particularly increased in patients with MLH1 and MSH2 mutations. For these reasons, we concluded that the incidence of gastric cancer showed a non-significant decrease during the past decades and that surveillance upper GI-endoscopy for Lynch syndrome patients carrying an MLH1 or MSH2 mutation should be considered, due to the substantial gastric cancer risk in these patients.

In chapter 9 of this thesis, we evaluated the risk of esophageal squamous cell carcinoma in patients with gastric atrophy, since an explanation for this association remains largely unclear. Of the 97728 patients that were included with a first

diagnosis of gastric atrophy, 126 patients developed ESCC. An overall relative risk of 2.2 was demonstrated for the development of ESCC in gastric atrophy patients. However, the risk of ESCC did not increase with the severity of gastritis, with relative risks of 2.1 for development of ESCC in patients with intestinal metaplasia and 2.3 for patients with dysplasia. Moreover, a similar association was demonstrated between gastric atrophy and small cell lung carcinoma. Hence, a causal relationship between gastric atrophy and the development of ESCC seems unlikely.

In the remaining chapters the main findings of this thesis are discussed and future directions for further research on *H. pylori*-associated malignancies are provided.