The First Evidence of Hereditary and Familial Gastric Cancer in Latvia: Implications for Prevention

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Key words: *hereditary gastric cancer; familial gastric cancer; hereditary cancer; population screening.*

Summary. *Background and Objective. Gastric cancer is a frequent cause of cancer mortality. The prognosis of established tumor is unfavorable due to the propensity to spread and limited treatment efficiency. Therefore, prevention has a high significance. We tested a population screening approach in order to identify families with an increased gastric cancer load for further surveillance.*

Material and Methods. Population screening was performed by questionnaire reaching 76.6% of the population. Hereditary gastric cancer (HGC) syndrome was diagnosed if 3 mutually first-degree relatives with gastric cancer were reported in the kindred. Additional group (HGC2) of families with 2 first-degree relatives affected by gastric cancer was identified.

Results. The HGC syndrome was diagnosed in 0.11%, but HGC2 syndrome, in 0.4% probands. The gastric cancer frequency among blood relatives was 25.2% (95% CI, 20.6%–30.4%) in HGC, but 16.0% (95% CI, 13.8%–18.5%) in HGC2 families. The mean age at diagnosis of cancer was 56.9 years (95% CI, 53.4–60.3) in HGC and 62.5 years (95% CI, 60.1–64.8) in HGC2. The mean survival was 2.6 years (95% CI, 1.2–4.0).

Conclusions. Population screening identifies reasonable number of families with a high frequency of gastric cancer. The frequency of gastric cancer and an unfavorable course characterized by low survival justify surveillance in families with 2 or 3 first-degree relatives affected by gastric cancer. Population screening provides the age characteristics of the respective tumors in order to adjust the surveillance schedule.

Introduction

Gastric cancer is the second most common cause of cancer-related death in the world (1). In Baltic countries, the age-standardized incidence and mortality rates of gastric cancer exceed the average values for Europe showing the urgency of the problem (2). Once the gastric cancer has developed, the course is unfavorable urging to search for means of cancer prevention. Diet and *Helicobacter pylori* are well-known environmental risk factors (3). However, increasing evidence suggests an important role of hereditary factors. In order to prevent hereditary cancer or at least to diagnose it early, follow-up programs could be offered to persons subjected to increased hereditary cancer risk. This necessitates well-planned strategy in order to find out the target patients.

A positive family cancer history is a well-known risk factor for developing gastric cancer (3–5). The relative risk is 1.3–2.2 if second- or first-degree relatives are affected (3). Familial clustering is shown in approximately 10% of gastric cancer patients, and an autosomal dominant mode of inheritance with high penetrance is present in 3% of gastric cancer cases (6, 7).

Familial gastric cancer is a complex syndrome. The concept of familial gastric cancer involves the use of the Lauren classification (8) distinguishing a diffuse and intestinal type of gastric cancer. The hereditary diffuse gastric cancer (HDGC) is characterized by autosomal dominant inheritance of *E-cadherin/CDH1* mutations on chromosome 16q22 (9), first described in 3 Maori pedigrees with early-onset diffuse gastric cancer (10), and later shown in European families with aggregation of diffuse but not intestinal gastric cancer (11). Although initially truncating mutations were considered characteristic for HDGC (11), the clinically relevant *CDH1* mutations included also point mutations, small deletions, and insertions along the entire coding sequence (9, 12, 13). Founder mutations are rare, described in the original Maori families as well as in group of families originating from Newfoundland. Recurrent mutations are due to both independent mutational events and common ancestry (9). *CDH1* mutations are found in 53.1% of families with 2 gastric cancer cases per kindred in combination with at least one diffuse gastric cancer diagnosed before the age of 50 years (9, 12, 14) or in 30%–50% of HDGC patients (6).

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The penetrance of *CDH1* mutations determines the lifetime risk of gastric cancer and confers also the risk for lobular breast carcinoma in females. Some estimates have been published. The lifetime risk for gastric cancer in mutation carriers was estimated as 70% (13). Alternatively, the cumulative risk of gastric cancer by the age of 75 years was estimated as 40% (95% confidence interval (CI), 12%–91%) for males and 63% (95% CI, 19%–99%) for females (9). Another groups have reported that the cumulative risk of gastric cancer by the age of 80 years was 67% (95% CI, 39%–99%) for men and 83% (95% CI, 58%–99%) for women (15) or, similarly, the lifetime risk for gastric cancer was 63%–83% for females and 40%–67% for males (16). The risk for lobular breast carcinoma in *CDH1* mutation-carrying females is 39%–40% (13, 15). The cumulative risk of female breast cancer by the age of 75 years was estimated as 52% (95% CI, 29%–94%) among the carriers of founder mutation in Newfoundland (9).

Variable diagnostic criteria can be applied. Family with 3 cases of concordant cancer among first or second-degree blood relatives can be considered a high-risk cluster (17). HDGC is defined clinically as a family that fits one of the following criteria: either 2 or more documented cases of diffuse gastric cancer in first- or second-degree relatives with at least one tumor diagnosed before the age of 50 or at least 3 documented cases of diffuse gastric cancer in first- or second-degree relatives independently of the age of onset (11). The criteria for *CDH1* testing are broader including also families with histologically confirmed diffuse type of gastric cancer in single family member only, individuals with diffuse gastric cancer before 40 years of age irrespectively of family history, and families with diffuse gastric cancer and lobular breast cancer (18). The diagnostic criteria of familial intestinal gastric cancer are adjusted to the incidence of gastric cancer in the corresponding population (11). In countries with a high gastric cancer rate, the criteria must be analogous to the diagnostic criteria of hereditary nonpolyposis colorectal cancer (HNPCC): 1) at least 3 relatives should have intestinal gastric cancer and one of them should be a first-degree relative of the other two; 2) at least 2 successive generations must be affected, 3) in one of the patients gastric cancer should be diagnosed before the age of 50. In contrast, in countries with a low incidence of gastric cancer, the criteria should be following: 1) 2 or more documented cases of intestinal gastric cancer in first- or second-degree relatives with at least one tumor diagnosed before the age of 50, or 2) at least 3 documented cases of intestinal gastric cancer in relatives at any age. Gastric cancer can also be a manifestation of HNPCC, Li-Fraumeni, familial adenomatous polyposis, or Peutz-Jeghers syndromes, diagnosed by the corresponding criteria (11).

If the kindred correspond to the HDGC criteria, genetic testing should be advised involving search for *CDH1* mutation in an affected patient and testing of the healthy family members. The mutation carriers have a significant lifetime risk of diffuse gastric cancer (11, 13), known for its propensity to a submucosal spread, marked difficulties in early endoscopic diagnostics, and dismal prognosis in advanced stages. Therefore, an option of prophylactic gastrectomy can be considered in mutation carriers taking into account that the average age of clinically detectable gastric cancer development in HDGC kindred is 38 years (11, 13) but the age range is wide, from 16 to 82 years (13). The earliest lethality is recorded at 16–20 years (9, 10); therefore, the prophylactic gastrectomy might be suggested even in 20–30-year-old males. It is suggested to carry out the prophylactic gastrectomy 5 years earlier than the youngest age of gastric cancer diagnosis in the family (6). In females, the impact of gastrectomy on pregnancy should be considered (9). Prophylactic gastrectomy might carry 1%–2% mortality, 10%–20% major acute morbidity and inevitable late morbidity as weight loss, dumping syndrome and diarrhea. As the prophylactic operations would be performed in healthy young adults, the expected mortality and rate of complications might be lower than after curative gastrectomy for gastric tumor in an elderly person (11). In the stomachs removed by prophylactic gastrectomy, foci of diffuse cancer are frequent. The rate of such operations that in fact are curative, not prophylactic, is 76.5%–100% (13, 19). The agreement rate for prophylactic gastrectomy is 45%–68% (9, 13). If the prophylactic gastrectomy is not acceptable, frequent surveillance gastroscopy with the best accessory techniques should be offered and combined by rigorous biopsies from any suspicious lesion. The gastroscopy should be performed once or twice per year (6, 11). At least 15 random mucosal biopsies must be provided for pathology (13). However, insufficient efficacy of chromoendoscopy, endoscopic ultrasound, random biopsies, and PET-CT has been demonstrated in *CDH1* mutation carriers (13). Magnetic resonance imaging of breast is advocated (6). Thus, possibilities for surveillance and intervention are already available and further development can be expected.

Considering the remarkable progress in the hereditary gastric cancer research, we designed our study with the aim to evaluate the importance of the hereditary gastric cancer by population frequency of the given syndrome, the associated cancer rate among blood relatives and impact of hereditary gastric cancer in the total gastric cancer burden as well as the implications for cancer prevention assessing the health status of the identified persons and the

age characteristics of malignant tumor in the hereditary gastric cancer pedigrees.

Material and Methods

The investigation was designed as population screening for hereditary cancer in the Valka district within the frames of the project "The development of hereditary cancer prophylaxis in Estonia and Latvia" co-financed by European Union Interreg IIIB Neighbourhood program. The Valka district is a geographic area in the northeast of Latvia. In collaboration with family physicians, 18 642 retrospective family cancer histories were collected from adult inhabitants representing 76.6% of the Valka population. The study was carried out from September 2005 until June 2007. The inclusion criteria comprised adult age, agreement to participate in the study, and registered place of residence within Valka district. No recruitment restrictions were applied for upper age limit, gender, ethnicity, or health status. Among the responders, there were 10 438 women (56.0%) and 7904 men (42.4%). The study was approved by the Central Commission of Medical Ethics of Latvia. Written informed consent was obtained from all patients.

Information on family cancer history was collected using a questionnaire. The participants reported the presence and localization of tumors in kinsmen (father, mother, grandparents, siblings, children, grandchildren, siblings of parents, and other blood relatives), as well as the age of the patient in the time of the diagnosis. If the patient died because of the tumor, the age at death was ascertained as well. Additional questions were asked about the treatment modalities (e.g. radiation therapy and chemotherapy, extent of operation) of affected persons in order to verify the presence and location of cancer. The interview took 45 minutes to complete.

The filled questionnaires were analyzed in the Hereditary Cancer Institute, Rīga Stradiņš University. If hereditary cancer syndrome was diagnosed the corresponding persons were invited for repeated consultation to explain the syndrome entity and to provide written prophylactic recommendations concerning further surveillance and/or additional investigations. Hereditary gastric cancer (HGC) syndrome was diagnosed if 3 mutually first-degree blood relatives in kindred were diagnosed with gastric cancer. In addition, families with 2 mutually first-degree blood relatives affected by gastric cancer were identified and included into additional group (HGC2) for further analysis.

Data obtained during secondary consultations were applied in order to identify mutually related families. In this way, the possibility to include any affected person repeatedly in the analysis due to several kindred relationships was eliminated.

Descriptive statistical analysis was performed using CIA (Confidence Interval Analysis) software (20). The population frequency of hereditary cancer syndrome was calculated as the ratio between the number of probands diagnosed with the syndrome and the size of study group. The data about the age of tumor diagnostics, age of tumor-related death, and survival of the affected persons were evaluated after detailed analysis of the relationships between different pedigrees. The cancer frequency in the revealed families was calculated as the ratio between the number of affected blood relatives and the whole number of blood relatives in the corresponding blood line. The ratio between gastric cancer cases in HGC and/or HGC2 families and all reported gastric cancer cases in the pedigrees of study population was calculated as well. Data about cancer presence in spouses were recorded although excluded from the diagnostics of hereditary cancer. Spouse correlation was calculated as the ratio of number of couples presenting a history of gastric cancer in both members over the number of couples with at least one case of gastric cancer.

Results

The population screening disclosed 21 cases of hereditary gastric cancer syndrome (Fig. 1). In addition, 74 families were included in HGC2 group. This is the first documented evidence of HGC in Latvia. The population frequency of HGC was 0.11% (95% CI, 0.07%–0.17%) but of HGC2 – 0.4% (95% CI, 0.32%–0.50%). HGC was the most frequent hereditary cancer syndrome in Valka population. The gastric cancer cases occurring within HGC families constituted 4.4% (95% CI, 3.5%–5.5%) but within combined group of HGC/HGC2 families – 13.9% (95% CI, 12.3%–15.7%) of all reported gastric cancer cases in the pedigrees of study population.

The age distribution of probands diagnosed with HGC and HGC2 is reflected in Fig. 2. The probands mostly were oncologically healthy themselves. In HGC syndrome, gastric cancer had been diagnosed in 1 proband – a 74-year-old female. Another proband, a 58-year-old female, had a history of breast cancer at the age of 41. Among the 74 cases of HSC2 syndrome, 6 probands were affected by cancer in different locations. No cases of gastric cancer were observed. Endometrial cancer was reported in 2 probands at the age of 53 and 63 years, respectively. There were also single cases of urinary bladder, prostate, ovarian, and colorectal cancer.

In total, 225 patients affected by gastric cancer were reported among blood relatives in HGC and HGC2 families. There were 126 men (57.5%; 95% CI, 50.9%–63.9%) and 93 women (42.5%; 95% CI, 36.1%–49.1%) among the patients. In order to characterize the course of HGC in Valka population, the

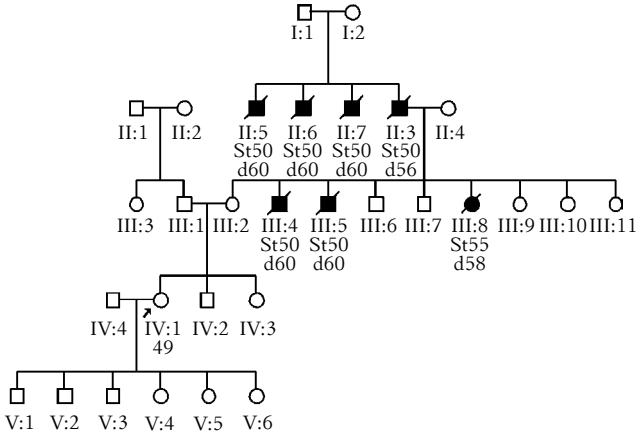

Fig. 1. Pedigree affected by hereditary stomach cancer manifesting in multiple persons in 2 generations

St, gastric cancer; d, dead. The age of cancer diagnostics is shown by number following the diagnosis, and the age of death is shown by the number, following the abbreviation "d". The proband is indicated by an arrow.

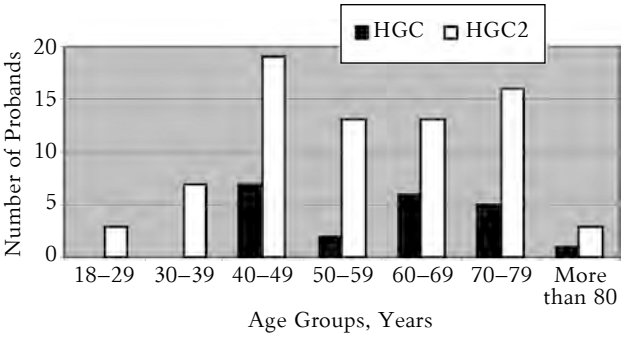

Fig. 2. The age distribution of probands diagnosed with hereditary gastric cancer syndrome

HGC, hereditary gastric cancer; HGC2, families with 2 gastric cancer cases in first-degree relatives

data about tumor diagnostics and cancer-related death in all affected persons from HGC and HGC2 groups are represented in Table 1. There was a trend toward earlier age of tumor diagnostics in the HGC than in the HGC2. The age at death was statistically significantly lower in the HGC. Twelve affected persons (5.4%; 95% CI, 3.1%–9.2%) were alive. The survival is presented in Table 1 as well.

The frequency of gastric cancer among blood relatives was 18.2% (225/1235; 95% CI, 16.2%–20.5%) in the whole group of HGC and HGC2, 25.2% (76/302; 95% CI, 20.6%–30.4%) in HGC families and 16.0% (149/933; 95% CI, 13.8%–18.5%) in HGC2.

Among HGC pedigrees, no other cancer cases were present in 8 of the 21 families featuring a cancer frequency of 27.4% (95% CI, 19.8%–36.5%). In the remaining HGC families, the following cancers were reported: 9 endometrial, 4 lung, 3 breast and 3 colorectal cancer cases, single cases of unspecified gynecological, pancreatic, laryngeal and urinary bladder cancer as well as a single case of a hematological malignant tumor. In isolated cases, the malignant tumor was found in the brain or liver.

Among HGC2 pedigrees, no other cancer cases were present in 24 of the 74 families having a gastric cancer frequency of 18.9% (95% CI, 14.4%–24.2%). In the remaining HGC2 families, the following cancers were reported: 12 endometrial and 2 cervical, 11 lung, 7 colorectal, 6 breast, 6 renal, 5 urinary bladder, 3 ovarian, 3 unspecified gynecologic, 3 pancreatic cancer, and 2 prostate cancer cases as well as 2 cases of head and neck cancer and single cases of esophageal and thyroid cancer. There were 8 cases of brain tumor and 4 cases of hematological malignancy. In 6 cases, the malignant tumor was found in the liver, but in 5 cases, in the abdominal cavity. In 9 cases, the location of cancer in the affected person was not known to the proband. The frequency of most common extragastric tumors is presented in Table 2.

Combining all families affected by stomach cancer only vs. other families, the frequency of stomach cancer was 21.4% (95% CI, 17.5%–26.0%) vs. 16.9% (95% CI, 14.6%–19.6%).

The data describing the presence and exact location of malignant tumors in both persons were obtained about 191 spouse couples belonging to the HGC pedigrees. Among these couples, at least 1 case of gastric cancer was present in 83 families but there were only 3 cases of gastric cancer in both

Table 1. The Characteristics of Hereditary Gastric Cancer Course by Population Screening Data

Diagnosis	Event	Age, Years			
		Range	Mean	SD	95% CI
Combined Group	Diagnosis	30–95	60.9	11.8	58.9–62.9
	Death	30–96	63.0	12.3	61.2–64.8
	Survival	0–20	2.5	3.7	1.9–3.1
HGC	Diagnosis	30–83	56.9	10.7	53.4–60.3
	Death	30–90	58.3	12.2	55.3–61.3
	Survival	0–20	2.6	4.1	1.2–4.0
HGC2	Diagnosis	34–95	62.5	11.8	60.1–64.8
	Death	37–96	65.6	11.6	63.4–67.6
	Survival	0–20	2.4	3.5	1.7–3.1

CI, confidence interval; HGC, hereditary gastric cancer, HGC2, families with 2 gastric cancer cases in first-degree relatives.

Table 2. The Frequency of Most Common Extra-Gastric Tumors Among Blood Relatives of Families Affected by Hereditary Gastric Cancer

Origin of Extra-Gastric Tumor	HGC		HGC2	
	Number	Proportion, % (95% CI)	Number	Proportion, % (95% CI)
Endometrial cancer	9	6.3 (3.1–12.4)	12	3.0 (1.7–5.2)
Lung	4	1.3 (0.5–3.4)	11	1.2 (0.7–2.1)
Breast	3	1.0 (0.3–2.9)	6	0.6 (0.3–1.4)
Colorectal	3	1.0 (0.3–2.9)	7	0.8 (0.4–1.5)
Pancreatic	1	0.3 (0.1–1.9)	3	0.3 (0.1–0.9)
Urinary bladder	1	0.3 (0.1–1.9)	5	0.5 (0.2–1.2)
Hematological	1	0.3 (0.1–1.9)	4	0.4 (0.2–1.1)
Brain	1	0.3 (0.1–1.9)	8	0.9 (0.4–1.7)
Kidney	0	0 (0–1.3)	6	0.6 (0.3–1.4)

HGC, hereditary gastric cancer; HGC2, group of families with 2 first-degree relatives affected by gastric cancer; CI, confidence interval.

spouses. Thus, spouse correlation for gastric cancer was low (3.6%; 95% CI, 1.2%–10.1%).

Discussion

Gastric cancer is an important healthcare problem in Latvia. The age-standardized incidence rate of gastric cancer in Latvia is higher than in European Union – 28.6 cases and 14.6 cases of gastric cancer (per 100 000) were reported in men and women, respectively, in Latvia. The EU age-standardized incidence rate is lower: 18.2 cases and 8.1 cases per 100 000 are reported in men and women, respectively (2). The dynamics of the gastric cancer incidence rate in Latvia is shown in Figure 3. The age-standardized mortality rate in Latvia is also at least twice higher than reported in the EU: 27.5 cases and 12.0 cases per 100 000 in men and women, respectively, versus 12.2 cases and 5.7 cases per 100 000 in men and women, respectively, in the EU (2).

Population screening for hereditary cancer is a possibility to identify healthy persons at higher cancer risk thus giving an input in the early diagnostics and prevention of cancer (21) as performance of the prophylactic measures in this group could improve the results of cancer care. The population screening

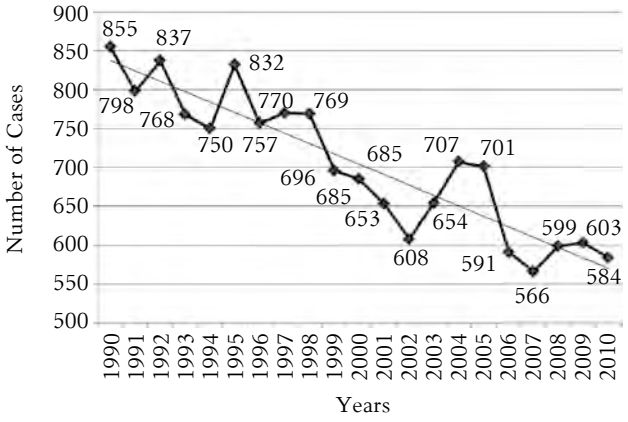

Fig. 3. The dynamics of gastric cancer incidence rate in Latvia over years 1990–2010

A trend line is added to show the general tendency.

programs for hereditary cancer still are in the stage of development (22); therefore, our experience might be valuable for other centers planning and setting up programs with similar goals. Taking into account the abovementioned reasons and our objectives, we carried out the population screening for hereditary cancer in Valka district. In our experience, it was easily manageable. The population compliance during screening program was sufficiently high (76.6%) in accordance with the published experience from the population screening in Poland, mentioning a population participation rate of 74.0% (22).

The clinical diagnostics of HGC is embarrassed by the variety of diagnostic criteria. The criteria for hereditary diffuse and familial intestinal gastric cancer differ by the number of affected relatives, the degree of kinship, and the presence or absence of age limit. However, in Latvian population, the information about the cancer type in older relatives cannot be obtained due to several historical reasons. Such information is also too specific to be obtained from probands (18). Therefore, our criteria were based on the assumption that 3 cases of concordant cancer among the blood relatives points toward high risk of this tumor and 2 cases – toward moderate risk (18) and on the observations of minor relative risk differences in dependence on the cancer type (intestinal or diffuse) in affected probands (3). Although the published criteria of high risk familiar cancer cluster include also the presence of particular cancer in second degree relatives (18), we limited our criteria to a more conservative approach diagnosing HGC or HGC2 syndromes on the basis of gastric cancer presence in mutually first-degree relatives.

The high frequency of gastric cancer in the identified Valka families as well as a statistically significant difference in cancer frequency among HGC and HGC2 groups shows the appropriateness of the applied clinical criteria based on the number of affected first-degree relatives. The difference also confirms the model of risk stratification into high- risk group identified by the presence of

at least 3 affected first-degree blood relatives, and moderate-risk group, characterized by the presence of concordant cancer in 2 first-degree blood relatives. Thus, a history of gastric cancer in 3 mutually first-degree relatives can show high risk, but in 2 – moderate although elevated risk. Although differentiation between hereditary diffuse and familial intestinal gastric cancer is important, it can be difficult if no ancient medical documentation (including Lauren classification data) is available. In such situation, the applied criteria may help identify the need for surveillance.

Due to different methodology of calculation, it is not possible to compare exactly the frequency of gastric cancer in the affected Valka families with the lifetime risk for gastric cancer in *CDH1* mutation carriers. Cautious illustrative comparison shows that the frequency is lower (13, 15) or close to the estimates of gastric cancer risk (9) in *CDH1* mutation carriers. An additional reason for the discrepancy is the fact that in our study all the blood relatives were included in the analysis as in the absence of mutation analysis there was no possibility to exclude persons without mutation. Naturally, this reduces the frequency estimates.

The population screening brought the first documented evidence of hereditary and familial gastric cancer in Latvia. In a hypothetic population that would be equal in size to the population of Latvia but have the same ethnic, gender and age composition as Valka population, the detected population frequency would be equivalent to 2524 probands affected by definitive HGC syndrome and 9178 probands affected by HGC2 syndrome.

The frequency of gastric cancer both in HGC and HGC2 pedigrees exceeds the cumulative risk (0–74 years) in the European Union constituting 1.62% in men and 0.68% in women (23). Accordingly, surveillance should be offered to both groups. It should be started early as the youngest cases of gastric cancer in the identified families were diagnosed early – at 30 years and 34 years, respectively, in the HGC and HGC2 groups. Even earlier cancer development (at 16–20 years) has been described (9, 10, 13). The frequency of gastric cancer does not differ significantly in dependence on the presence of other cancers in the pedigree. Thus, these data do not influence the surveillance for gastric cancer. Endometrial cancer is the most common extragastric cancer. As its frequency exceeds the cumulative risk in European Union females (aged 0–74 years) constituting 1.5% (23), surveillance can be considered especially if a family history is remarkable for the presence of endometrial cancer. The combination of gastric and endometrial cancer and brain tumors may suggest a peculiar variant of Lynch syndrome in a subgroup of HGC (24, 25).

Although the familial risk might be explained not only by heredity but also by shared environmental factors the applied criteria allow detecting a risk group and could be recommended for practical use. However, the low spouse correlation points toward an importance of the genetic background. The role of environmental factors was not analyzed in the present study as such information would not be reliable regarding older medical information. It should also be emphasized that analysis of familial predisposition does not exclude the interaction between genetic and environmental factors.

The age distribution of the probands showed a wide plateau at the age interval of 30–70 years. As the mean age of cancer diagnostics in HGC and HGC2 pedigrees was 56.9 and 62.5 years, respectively, at least part of the probands were younger, and thus, surveillance would be started at proper time. The oncological health status of probands also was appropriate for the surveillance as only 1 proband has gastric cancer herself. However, the seemingly beneficial health status of probands might partially be attributable to the rapid course of gastric cancer eliminating the affected persons from the population and decreasing their chance to be included in the population screening as probands. The course of the tumor was aggressive – only 5.4% (95% CI, 3.1%–9.2%) of the affected persons were alive at the time of population screening. The mean survival was only 2.5 years.

The gastric cancer in HGC and HGC2 families in Valka population constitutes 13.9% (95% CI, 12.3%–15.7%), but in HGC – 4.4% (95% CI, 3.5%–5.5%) of all reported gastric cancer cases. These values slightly exceed the published estimates (6) describing familial clustering in 10% of gastric cancer patients and an autosomal dominant mode of inheritance in 3% of patients. The high frequency of gastric cancer in the identified families confirms the expedience of the used criteria; therefore, the higher finding could be considered true for Valka population. It is possible that a higher proportion of hereditary cancer in a particular location can be expected in a population subjected to general a high frequency of this cancer (2) as the environmental carcinogenic factors lessen the influence of the evolutionary pressure striving to eliminate the carriers of harmful mutations.

The high frequency of gastric cancer in the affected families, the unfavorable course, and low survival demand preventive means. Biannual chromoendoscopy with multiple biopsies can be offered. Surgical prophylaxis in the setting of genetic testing for *CDH1* mutations could become an effective solution for hereditary diffuse gastric cancer. Thus, population screening has identified hereditary and familial gastric cancer as an important, previously

unrecognized problem that can be approached by surveillance and surgery.

Conclusions

Hereditary gastric cancer is an important goal in oncology with significant implications for prevention. Up to 13.2% of gastric cancer cases potentially could be prevented identifying the target families by a population screening approach with a simple questionnaire. The gastric cancer frequency among blood relatives in these families is significantly increased reaching 25.2%. The number of affected blood relatives is an important diagnostic criterion. The high frequency of gastric cancer and an unfavorable course characterized by low survival, justify surveillance in the families with 2 or 3 gastric cancer cases among first-degree blood relatives. The recommendation for surveillance is further enhanced by the possibility to start observation in healthy probands and the population frequency of the syndrome of 0.54% not posing a great burden on the healthcare system.

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Statement of Conflicts of Interest

The authors state no conflict of interest.

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