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List of Abbreviations:
SMR, standard mortality rate; CL, confidence limits; RH, relative hazards

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Abstract

Objective. The information concerning the morbidity and mortality of hereditary hemochromatosis is based primarily on clinical cohorts of symptomatic patients. The major aim of this study was to analyse the long-term prognosis for Swedish patients with this condition, with respect to both clinical features and survival, in relationship to the route by which the disease was detected.

Material and methods. 373 patients with hemochromatosis detected through routine health check-ups (n=153), family screening (n=44), symptoms of arthralgia (n=23), investigation of other diseases/symptoms (n=108) or signs of liver disease (n=45) were monitored for a mean period of 11.9±5.8 years. The degree of liver fibrosis and survival were analysed. ***Results.*** Overall survival among these patients was not significantly different from that of a matched normal population. The patients diagnosed through health check-ups and family screening were detected at an earlier age and had the highest rate of survival. Liver biopsy at the time of diagnosis revealed cirrhosis in 9% of those detected through the health check-ups and 5% in the case of family screening, compared with 13% for the group with arthralgia, 17% for other diseases/symptoms and 42% for liver disease.

Conclusion. Health check-ups and family screening allow detection of hereditary hemochromatosis at an earlier age and with less advanced liver fibrosis, although a few of these patients have already developed cirrhosis. Our study indicates that iron indices should be included in health check-ups, and if abnormal, should lead to further investigation.

Hereditary hemochromatosis is one of the most common inherited disorders with estimated prevalence of approximately 1:200-1:400 (1-3). It leads to an excessive absorption and accumulation of iron in the body with associated liver cirrhosis and risk for liver cancer. The majority of patients with this disorder carry a cysteine-to-tyrosine substitution at amino acid 282 (C282Y) in the protein encoded by the *HFE* gene, which was discovered in 1996 (4). This genotype is most frequent among individuals of Northern European origin, with one in thirteen of all inhabitants in Sweden (5). The symptoms and diseases associated hemochromatosis include fatigue, arthralgia, liver disease, heart failure, diabetes mellitus, abnormal skin pigmentation and impotence. Since many of these symptoms are non-specific, relatively common, and usually caused by other conditions. Therefore, hemochromatosis may easily be overlooked as the potential underlying cause (6).

A number of publications concerning the prognosis for patients with hemochromatosis revealed that individuals with symptomatic disease exhibit lower survival rates than sex- and age-matched controls, primarily due to their elevated mortality from liver cirrhosis (7-14). If treatment with phlebotomy is initiated prior to the development of cirrhosis, survival seems to be unaffected. The information concerning morbidity and mortality that is presently available is on clinical cohorts of patients diagnosed primarily on the basis of symptoms, i.e. at a relatively late stage of the disease.

In recent years the pros and cons of population screening for hemochromatosis have been debated. This relatively common and potentially life-threatening condition can effectively be prevented with inexpensive treatment, and its long asymptomatic phase allows detection prior to the onset of symptoms. However, some studies demonstrating a relatively low impact of hemochromatosis on morbidity and mortality at the population level have raised questions about the cost-effectiveness of screening programs, whereas other studies have shown cost-effectiveness of routine screening (1, 3, 15-20). In one such case, genetic screening for hemochromatosis at the

workplace was found to be feasible and acceptable, with a cost that was favourable in comparison to other workplace screening (21, 22).

To date, only a few analyses of the outcome for patients diagnosed with hemochromatosis at early stage have been published and in many of these studies the route via which the patients were identified is not described (8-10). In one case a significant frequency of hepatic fibrosis in asymptomatic patients was detected through regular health checks or family screening, but the long-term survival of such individuals detected through screening is poorly documented (22). Most importantly, information concerning the possible relationship between the route of detection and the prognosis is missing. Accordingly, the present investigation was designed to examine the relationships between different routes of detection and their clinical features, characteristics of liver biopsies and mortality of Swedish patients with hemochromatosis.

Patients and Methods

Patients

A cohort of 373 patients with hemochromatosis was recruited from nine university hospitals in Sweden. The clinical data for each patient were registered in the form of a detailed questionnaire and stored in a central registry at the Karolinska University Hospital.

The inclusion of patients in the cohort started in 1996, with follow-up of patients until December 2006. The patients were diagnosed during the period of 1977 to 2005. The diagnoses were based on clinical history, a physical examination, serum levels of iron and ferritin and the degree of transferrin saturation, HFE mutation and/or liver biopsy. Most patients were diagnosed with homozygous C282Y mutation in the HFE analysis (n=228, 61%). Before the availability of HFE analysis, all patients had a liver biopsy positive for iron overload according to Scheuer (iron deposits of 3+, or 4+, predominantly in hepatocytes) (23) to support the diagnosis. The degree of fibrosis was graded as none, fibrosis or cirrhosis. Among the genotyped patients, they were all subjected to a liver biopsy if they had a homozyogous C282Y mutation and a serum ferritin over

1000 ug/L. In some patients who were included in the study, the diagnosis were made with biochemical data and a liver biopsy before HFE analysis was available, and a later HFE analysis showed that they were not homozygous for the HFE mutation. These patients are still included since they were diagnosed with the criteria valid at that time. In all cases, diagnosis was confirmed by either both HFE mutation and liver biopsies (n=197, 53%), or analysis of the *HFE* mutation (n=62, 17%) or examination of a liver biopsy (n=114, 31%).

The mutation analyses were thus performed in 259 (69%) patients. These revealed that 228 (88%) of the genotyped patients were homozygous for C282Y, 2 homozygous for H63, and 7 homozygous for the wild-type gene. Five were heterozygous for C282Y and the wild-type gene (wt), 8 heterozygous for H63D/wt, and 9 compound heterozygous (C282Y/H63D). Homozygous C282Y mutations were found in 114/127 (90%) of genotyped patients who were detected through health check-ups, 29/32 (91%) for those via family screening, 11/13 (85%) for those via symptom of arthralgia, 59/70 (84%) for patients via other diseases/symptoms, and 15/17 (88%) of those detected due to liver disease.

Patients with porphyria cutanea tarda or secondary iron overload, e.g. from repeated blood transfusions were excluded from the study. Diagnoses of cancer, and the causes and date of death for all patients in this study were obtained from the Cancer Registry and Cause of Death Register, respectively, at the Swedish National Board of Health and Welfare. Sex-, age and calendar year-specific mortality rates were also retrieved from the National Board of Health and Welfare, who collects the information for all Swedish residents, i.e. general population. This study was approved by the regional ethical committee at the Karolinska Institute.

Routes of detection

Five alternate routes for detection of hemochromatosis were identified from the questionnaire: 1) regular health check-ups (n=153, 41%), 2) family screening (n=44, 12%), 3) symptoms of arthralgia (n=23, 6%), 4) other diseases/symptoms (n=108, 29%) and 5) liver disease (n=45, 29%).

Hemochromatosis was detected through blood tests performed by general practitioners or through company health care providers in the group detected through health check-ups. None of these patients had sought health care or were referred to hospital due to symptoms. The group detected by family screening consisted of relatives to probands diagnosed with hemochromatosis and were tested initially for their serum levels of iron, transferrin saturation and ferritin. The fourth group consisted of patients examined due to the presence of, e.g., cardiovascular disease, inflammatory bowel disease, or symptoms such as vertigo, abdominal discomfort, insomnia, or muscle pain. Patients in the fifth group were investigated as a result of either clinical and/or biochemical signs of liver disease.

Additional Data Concerning the Patients

The age, sex and date at the time of diagnosis were recorded for all patients. Alcohol consumption was categorised as <20 grams/day, 20-80 grams/day or >80 grams/day, the latter being considered excessive consumption. The presence of fatigue, arthralgia, diabetes mellitus, as well as the results of laboratory tests such as serum levels of iron and transferrin saturation and ferritin, were all noted. The amount of stored iron was calculated from the amount of iron removed during the initial, intensive, period of venesection, and 1000 ml blood was estimated to contain 0.5 gram iron. Intensive venesection was continued until the ferritin level reached 40-50 mg/l, after which he patients received maintenance treatment.

Statistical Methods

For comparison of qualitative variables, expressed as percentages, $\chi 2$ analysis was employed. Quantitative variables, expressed as means and standard deviations, were compared with Student's *t*-test. The actuarial probabilities of death were calculated by the Kaplan-Meier method. Standardised mortality rates (SMR) were calculated by dividing the number of deaths observed by the number of deaths expected among individuals of the same age and sex and during the same

calender years in the general population. The 95% confidence intervals for the SMR were calculated assuming a Poisson distribution for the number of deaths observed, with a lower limit > 1.0 indicating a significant increase in mortality. Differences between subgroups with respect to survival rates were tested with Cox proportional hazard regression. Univariate analyses and multivariate analyses were performed using Cox proportional hazard regression to estimate risk factors for mortality. For univariate analyses, factors as age at the time of diagnosis, diabetes, liver fibrosis/cirrhosis, gender and alcohol consumption were tested. Relative hazards and age-adjusted relative hazards for mortality were calculated. Those risk factors which were found to be significant for mortality in univariate analyses were then tested in multivariate analyses. All analyses were two-sided and a P-value of < 0.05 was considered to be statistically significant. Data analysis was performed with the SAS 9.2 software (Cary, NC, USA).

Results

Clinical and laboratory features at the time of diagnosis

The mean age at the time of diagnosis was 48±14 years, and was significantly lower for males than females (46.4±13.5 vs. 52.3±14.8 years; $P < 0.001$) (Table 1). The lowest mean ages were exhibited by the patients identified by routine health check-ups or family screening, with significantly higher mean ages for those detected on the basis of symptoms of arthralgia or liver disease ($P < 0.001$). The 373 patients were followed for a mean period of 11.9±5.8 years (range 1.5-28.6 years). The follow-up time was 11.6±5.1 years in the case of routine health check-ups, 10.4±6.1 years in the group identified by family screening, 12.0±6.2 years in the case of arthralgia, 11.5±6.2 years for other diseases/symptoms and 15.4±5.5 years for patients with liver disease (health check-ups vs. liver disease; $P < 0.001$).

Fatigue was less prevalent in those detected via a routine health check-up than on the basis of symptoms of liver disease ($P < 0.001$), arthralgia ($P = 0.02$) or other diseases/symptoms ($P < 0.001$, Table 1). Moreover, arthralgia occurred at a significantly lower frequency in the group identified

via health check-ups than those with symptoms of liver disease ($P = 0.006$) or other diseases/symptoms ($P = 0.002$). The frequency of diabetes mellitus was significantly lower in the health check-up group than in the group with liver disease ($P < 0.001$), but not significantly different from that in the other groups.

The mean serum level of ferritin was significantly lower in those detected through health check-ups than due to liver disease ($P < 0.001$), or arthralgia ($P < 0.001$), but not significantly different from those with other diseases/symptoms or identified through family screening. The amount of stored iron in the liver was significantly higher in the patients initially exhibiting signs of liver disease ($P < 0.001$) or arthralgia ($P < 0.001$), than in the health check-up group.

Results of liver biopsies

Liver biopsy was performed in 311 patients (83%). A total of 56 patients (15%) exhibited cirrhosis at the baseline liver biopsies (Table 1 and 2). Cirrhosis was present in 19 (42%) among those identified on the basis of liver disease, 18 (17%) of those with other diseases/symptoms, 3 (13%) with arthralgia, and in those detected through health check-ups or family screening, 14 (9%) and 2 (5%), respectively. The frequency of cirrhosis was significantly higher among the group with liver disease ($P < 0.0001$), or other diseases/symptoms ($P = 0.02$) than among those detected through health check-ups. Fibrosis was observed in 120 of the patients (32%). As shown in Table 2, fatigue, arthralgia and diabetes mellitus were more common, and the mean amount of stored iron significantly higher in the patients with cirrhosis than those without cirrhosis (all $P < 0.001$).

Survival

The causes of death for the 46 patients who died during follow-up are presented in Table 3. Only one (13%) patient had died due to liver-related death (liver failure or liver cancer) among those detected through health check-ups and none among those detected through family screening,, in comparison to 8 (42%) patients among those with liver disease ($P < 0.001$). The standardised

mortality rates were significantly elevated in the group with liver disease and among patients with liver cirrhosis (Table 4).

The cumulative overall survival rates of 96% at 5 years, 91% at 10 years, 88% at 15 years and 72% at 20 years did not differ significantly from those of sex- and age-matched individuals in the general population during the same calendar years (Figure 1). However, survival among those detected on the basis of liver disease was significantly reduced ($P < 0.001$), which was not the case for the other routes of detection. Moreover, the survival of patients with liver cirrhosis or diabetes mellitus was significantly lower than for those without these conditions ($P = 0.001$ in both cases; Fig. 2).

The rates of mortality were higher in the arthralgia and liver disease groups than among those identified via a health check-up ($P = 0.009$ and $P < 0.001$, respectively) (Fig 3, Table 5). The difference remained in the case of liver disease, but not arthralgia, after adjustment for age at the time of diagnosis. The mortality rates of health check-ups, family screening and other diseases/symptoms did not differ significantly. The mortality rates for patients with fibrosis or cirrhosis were higher than the corresponding rate for those without fibrosis at the time of the initial liver biopsy ($P = 0.01$ and $P < 0.001$, respectively). After adjustment for age at the time of diagnosis, the differences between patients with cirrhosis and those with or without fibrosis remained significant, whereas no difference was seen between patients with and without fibrosis. Univariate analysis using Cox proportional hazard regression demonstrated significant correlations with reduced survival for older age at the time of diagnosis (10-year increments; $P < 0.001$), diabetes ($P = 0.001$) and liver fibrosis/cirrhosis ($P < 0.001$), but not for gender or alcohol consumption. Multivariate analysis was then performed with variables of age at the time of diagnosis, diabetes and liver fibrosis/cirrhosis. Cirrhosis and more advanced age ($P = 0.003$ and $P < 0.001$, respectively) were those identified as significant prognostic factors for reduced survival in multivariate analysis.

Discussion

The present cohort of 373 patients with hereditary hemochromatosis, detected by different routes with the most frequent being regular health check-ups and followed-up as long as 28.6 years (mean= 11.9 years) demonstrates that the detection routes are of importance for prognosis, since the percentage of patients with cirrhosis was much higher if patients had already developed symptoms.

To our knowledge, no reports regarding the long-term survival of patients detected through health check-ups have been published previously. In agreement with previous findings (7, 9, 10, 12), survival among our non-cirrhotic patients did not differ from that of a matched general population, while the survival of cirrhotic patients was reduced. In the present study, all patients with a serum level of ferritin $\geq$ 1000 μg/l had been subjected to liver biopsy. Thus, virtually all patients with cirrhosis should have been identified, since such a high serum level of ferritin is strongly associated with the presence of this condition (24-26).

The method we used for inclusion of patients is a commonly used one but not ideal. All patients should have been diagnosed and treated, and should be possible to follow-up. We have included patients in this cohort since 1996, but the diagnosis was already made before this year in certain patients. Thus this study is not truly prospective. Since we have used Swedish registries with a 99% coverage of causes of death and other events, we do not however lack information about prognosis. The patient selection may though be regarded as a problem since we did not use a true epidemiological approach. However, our study does not aim to survey the hemochromatosis phenotype in individuals detected through population screening using genotyping. Instead, the different routes of detection reported in the present study represent how patients are discovered in a clinical setting. In two previous publications we have compared the patient groups reported in this study with a larger cohort from the Swedish national registries and found them to be representative of patients with hemochromatosis in Sweden (13, 14).

It is not known whether patients with asymptomatic hemochromatosis will generally develop liver cirrhosis, or whether these constitute a subpopulation with better prognosis (27). It remains

unclear if early detection is beneficial, since, for ethical reasons, no randomised trials designed to answer this question have been performed. Cirrhosis was already present in some of our patients detected through health check-ups, thus progressive disease is found even in this group. Without an early detection and treatment, the liver damage in these patients would most probably have worsened eventually leading to the development of symptoms. The frequency of cirrhosis in our patients identified via health check-ups or family screening is higher than that reported by Powell and colleagues (22). Liver cirrhosis was present in 6.3% of their patients identified via health check-ups and in 2.2% via family screening at the time of diagnosis of hemochromatosis, while in other investigations, this condition was found to be present in 1-7% of the patients identified through family screening (28-30). The rate of liver biopsy varied between 34 and 92% in these studies (28-30). Clearly, the frequency of cirrhosis detected may vary among different groups of patients and be influenced by how frequently liver biopsies are performed. In the present case, liver biopsy was performed on 86% of the patients detected through health check-ups, while the corresponding rate in the study conducted by Powell and co-workers was 61%. However, follow-up data are lacking in other comparable reports. In the group of health check-ups, males were predominant (79%) and although the mean age was low (45 years), this might have affected the relatively high number of patients with cirrhosis. Penetrance of hemochromatosis and presence of cirrhosis are usually higher among males, whereas females develop the disease and its complications later in life, probably due to menstrual blood loss (22, 28).

Most of our patients (228/259, 88%) carried homozygous C282Y mutations, while others didn't. The latter group was all subjected to liver biopsies with findings of positive iron overload for a diagnosis of hemochromatosis. To reflect our clinical setting, all patients including those without homozygous C282Y mutations were included. One route for the detection of hemochromatosis employed here was based on symptoms of arthralgia, but the relationship between these two conditions is controversial (3, 17, 31), mainly because arthralgia is so common in the population. In our study, arthralgia was more common among those with liver disease than in patients detected

through health-check-ups. Those detected through health check-ups, or on the basis of arthralgia or other diseases/symptoms had been identified primarily due to abnormal liver or iron blood samples, whereas family screening involved genotyping. This difference could explain the substantially lower serum level of ferritin in the latter group.

The debate concerning population screening for hemochromatosis is still ongoing. In central regions of Sweden, the prevalence of hemochromatosis has been estimated to be as high as 1/200 (32), but the incidence has not yet been determined by genetic screening of large groups. In the present investigation health check-ups were most often provided at workplaces and our findings are therefore limited in terms of population screening. Perhaps additional test/s for detecting hemochromatosis in connection with health check-ups, may allow early and relatively inexpensive detection of this treatable disease. Determination of serum levels of ferritin has been suggested in this situation, since this can reveal most patients at risk for developing liver disease related to iron overload (33).

In conclusion, our patients with hemochromatosis detected through health check-ups or family screening were diagnosed at an earlier age and with less advanced liver fibrosis, although a few of them have already developed cirrhosis. Our study indicates that iron indices should be included in health check-ups, and if abnormal, should lead to further investigation.

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FIGURE LEGEND

Figure 1.

Cumulative survival curves for the patients diagnosed via health check-ups in comparison to a matched, general population. The standard deviations for the patient values are shown.

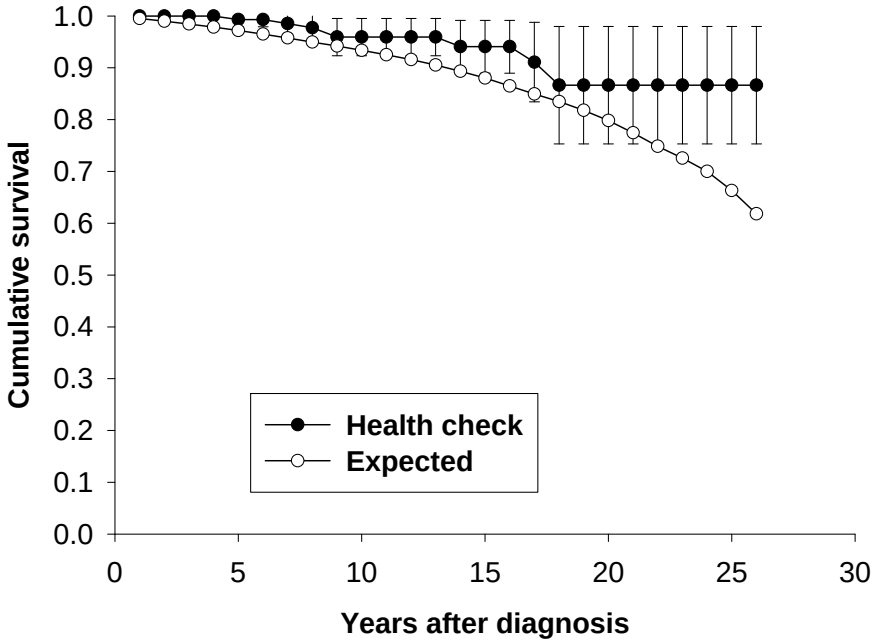
Figure 2.

Cumulative survival among 373 Swedish patients with hemochromatosis in relationship to the route of detection.

Figure 3.

A. Cumulative survival among cirrhotic (n=56) and non-cirrhotic (n=254) patients with hemochromatosis. B. Cumulative survival among diabetic (n=41) and non-nondiabetic (n=282) patients.

Fig 1.


Cumulative survival
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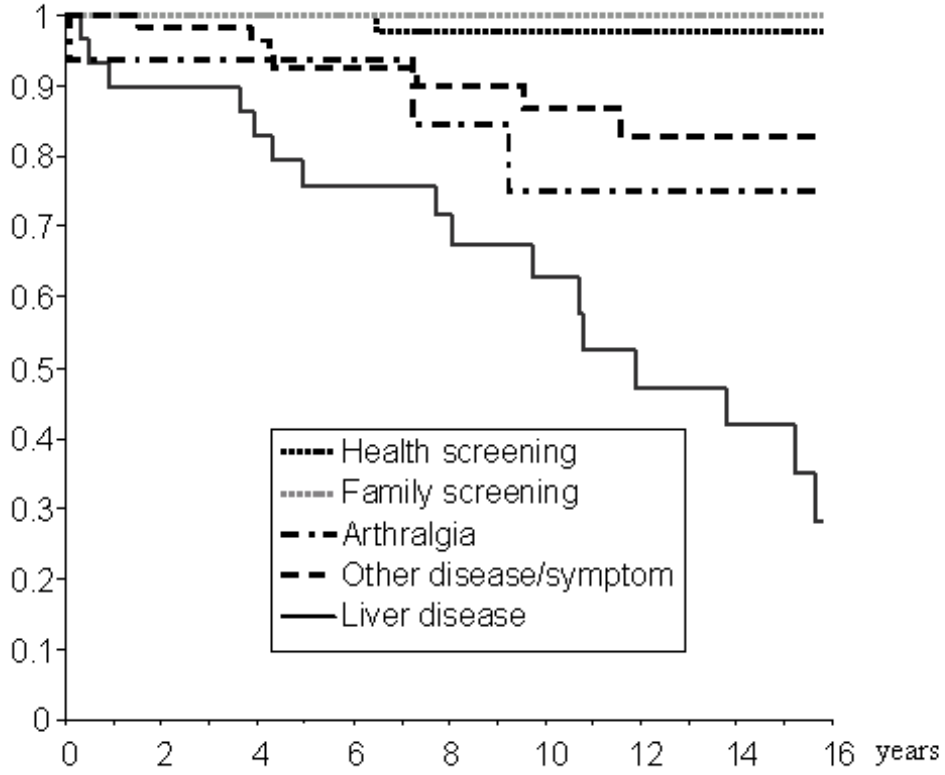
Years after diagnosis
Health check
Expected

Fig 2.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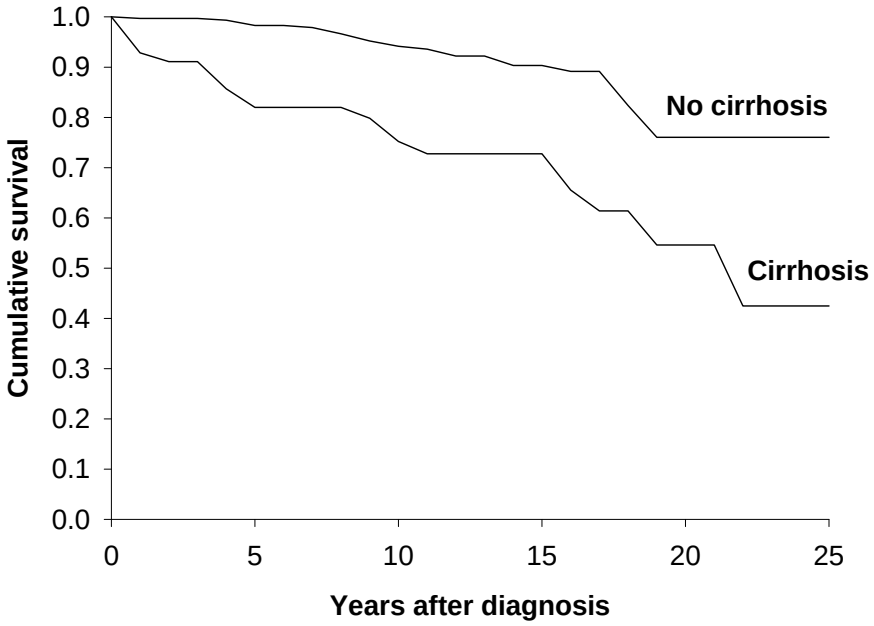
Health screening
Family screening
Arthralgia
Other disease/symptom
Liver disease

Fig 3

A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Cumulative survival
No cirrhosis
Cirrhosis
0
5
10
15
20
25
Years after diagnosis

B

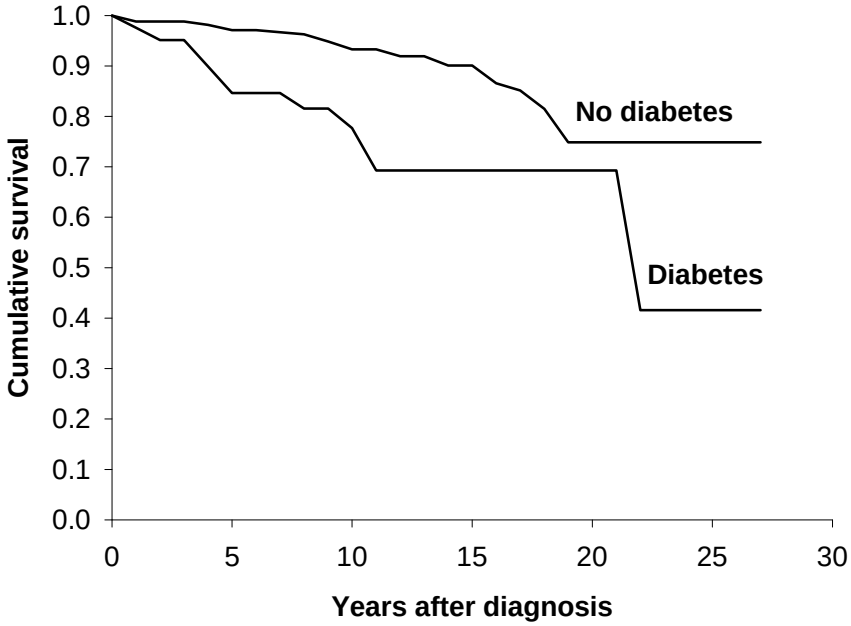
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
Cumulative survival
No diabetes
Diabetes
0
5
10
15
20
25
30
Years after diagnosis

Table 1 The clinical and laboratory features of patients with hemochromatosis at the time of diagnosis. These patients are grouped according to how the disease was detected. The data are expressed as the number of patients (% of all of the patients) or means ±SD.

Clinical features and findings from the examination of liver biopsies	All patients (n= 373)	Health check-ups (n=153)	Family screening (n=44)	Arthralgia (n=23)	Other diseases/ Symptoms (n=108)	Liver disease (n=45)
Age at diagnosis (yrs)	48 ± 14	45 ± 13	45 ± 12	54 ± 13	50 ± 15	54 ± 15
Gender						
Male	266 (71%)	121 (79%)	27 (61%)	17 (74%)	69 (64%)	34 (76%)
Female	107 (29%)	32 (21%)	17 (39%)	6 (26%)	39 (36%)	11 (24%)
Alcohol consumption						
<20 g/day	242 (65%)	102 (67%)	27 (61%)	12 (52%)	75 (69%)	26 (58%)
20-80 g/day	70 (19%)	30 (20%)	7 (16%)	6 (26%)	16 (15%)	11 (24%)
>80 g/day	3 (1%)	0 (0%)	1 (2%)	1 (4%)	0 (0%)	1 (2%)
Unknown	58 (16%)	21 (14%)	9 (20%)	4 (17%)	17 (16%)	7 (16%)
Fatigue	86/295 (29%)	19/127 (15%)	8/32 (25%)	7/18 (39%)	35/82 (43%)	17 (47%)
Arthralgia	124/337 (37%)	34/143 (24%)	12/38 (32%)	23/23 (100%)	38/92 (41%)	21 (50%)
Diabetes Mellitus	41/323 (13%)	11/137 (8%)	0/34 (0%)	3/22 (14%)	13/89 (15%)	14 (33%)
Serum ferritin †	1311 ±1607	1083 ±1349	763 ±774	2384 ±2577	1326 ±1738	2036 ±1635
Transferrin saturation‡	78 ±18	77 ±17	69 ±21	77 ±20	81 ±17	79 ±17
Amount of iron§ β (range)	5.7 ±4.6 (0.4-37.5)	4.8 ±3.3 (0.7-24)	5.7 ±3.9 (1.1-16.2)	9.1 ±5.2 (2.5-20)	5.3 ±3.9 (0.4-6.2)	8.7 ±7.6 (1.6-37.5)
Fibrosis in liver biopsy						
None	135 (36%)	72 (47%)	16 (36%)	6 (26%)	36 (33%)	5 (11%)
Fibrosis	120 (32%)	48 (31%)	9 (20%)	13 (57%)	30 (28%)	20 (44%)
Cirrhosis	56 (15%)	14 (9%)	2 (5%)	3 (13%)	18 (17%)	19 (42%)
Not performed	62 (17%)	19 (12%)	17 (39%)	1 (4%)	24 (22%)	1 (2%)

*: in μkat/l , †: in mg/l, ‡:, in %, §: in gram. β: data missing in 68/373 patients.

Table 2. The clinical and laboratory features of patients with or without cirrhosis at the time of diagnosis of hemochromatosis.

Feature	Cirrhotic patients	Non-cirrhotic patients
Number	56	255
Mean age at the time of diagnosis (years)	54 ± 11	47 ± 14
Gender		
Male	42 (75%)	185 (73%)
Female	14 (25%)	69 (27%)
Alcohol consumption		
<20 g/day	31 (55%)	172 (68%)
20-80 g/day	18 (32%)	42 (17%)
>80 g/day	2 (4%)	1 (0.4%)
Unknown	5 (9%)	39 (15%)
Fatigue	19/45 (42%)	53/225 (24%)
Arthralgia	27/49 (55%)	83/244 (34%)
Diabetes Mellitus	20/54 (37%)	21/241 (9%)
Serum ferritin†	3079 ± 2380	1142 ± 1276
Transferrin saturation‡	81.5 ± 15.5	77.0 ± 19.2
Amount of stored iron§	9.8 ± 7.2	5.6 ± 3.7

†: in mg/l, ‡: in %, §: in gram.

Table 3. The causes of death in 46 patients with hemochromatosis in relationship to the route of detection.

	All patients (n=373)	Health check-ups (n=153)	Family screening (n=44)	Arthralgia (n=23)	Other diseases or symptoms (n=108)	Liver disease (n=45)
No. of deaths of all patients (%)	46 (12%)	8 (5%)	2 (5%)	5 (22%)	12 (11%)	19 (42%)
Cause of death no. (%) of all deaths						
Liver-related	*12 (26%)*	*1 (13%)*	*0*	*1 (20%)*	*2 (16%)*	*8 (42%)*
Liver failure	8 (17%)	1 (13%)	0	1 (20%)	1 (8%)	5 (26%)
Liver cancer	4 (9%)	0	0	0	1 (8%)	3 (16%)
Other cancer	8 (17%)	2 (25%)	1 (50%)	1 (20%)	1 (8%)	3 (16%)
Cardiovascular	11 (24%)	4 (50%)	0	1 (20%)	4 (33%)	2 (11%)
Other causes	15 (33%)	1 (13%)	1 (50%)	2 (40%)	5 (42%)	6 (32%)

Table 4. Standardised mortality rates (SMR) for 373 patients with hemochromatosis in relationship to the route of detection and presence or absence of cirrhosis and/or diabetes. The numbers of deaths observed among the patients were divided by the numbers of deaths expected among individuals of the same sex and age and during the same calendar year in the general population. Significant findings are shown in bold.

	No.of deaths observed	No of deaths expected	SMR	95% CL
All groups of patients	46	49.4	0.98	0.88-1.04
Routes of detection				
Health check-ups	8	14.4	0.91	0.95-1.06
Family screening	2	2.9	0.99	0.98-1.01
Arthralgia	5	4.9	1.00	1.00-1.00
Other diseases	12	15.1	0.95	0.83-1.06
Liver disease	19	12	**1.53**	**1.01-1.28**
Liver biopsy findings				
Cirrhosis	19	11.3	**1.68**	**1.08-3.23**
No cirrhosis	8	6.5	1.24	0.61-2.54
Diabetes	11	9.1	1.21	0.70-2.18
No diabetes	30	37.6	0.80	0.56-1.14

Table 5. Univariate analyses employing Cox proportional hazard regression were performed. Relative hazards (RH) and age- adjusted relative hazards (10- year increments) for mortality of our patients with hemochromatosis in relationship to gender, age, presence or absence of cirrhosis, and/or diabetes, and route of detection are shown. Significant findings are indicated in bold.

Parameters	RH	*P* value	RH (age adjusted)	*P* value (age adjusted)
Age (10- year increments)	2.37	**< 0.001**	-	-
Findings upon liver biopsy				
Fibrosis vs. no fibrosis*	3.01	**0.01**	1.96	0.13
Cirrhosis vs. no fibrosis*	6.74	**< 0.001**	4.42	**0.001**
Cirrhosis vs. Fibrosis*	2.15	**0.02**	2.22	**0.01**
Diabetes	3.09	**0.001**	2.45	**0.01**
Routes of detection				
Family screening vs. health check-ups*	0.89	0.88	0.83	0.81
Other disease vs. health check-ups*	2.10	0.09	1.31	0.54
Arthralgia vs. health check-ups*	4.22	**0.009**	2.18	0.18
Liver disease vs. health check-ups*	6.75	**<0.001**	3.89	**0.001**

*= reference condition