Received: 4 May 2023 | Revised: 2 November 2023 | Accepted: 4 November 2023

DOI: 10.1111/liv.15797

Liver INTERNATIONAL WILEY

ORIGINAL ARTICLE

Penetrance, cancer incidence and survival in *HFE* haemochromatosis—A population-based cohort study

Benedikt Schaefer[1] | Lorenz M. Pammer[1] | Bernhard Pfeifer[2,3] | Sabrina Neururer[2,3] | Maria R. Troppmair[1] | Marlene Panzer[1] | Sonja Wagner[1,4] | Elke Pertler[1,4] | Christian Gieger[5,6] | Florian Kronenberg[7] | Claudia Lamina[7] | Herbert Tilg[1] | Heinz Zoller[1,4]

[1]Department of Medicine I, Gastroenterology, Hepatology and Endocrinology, Medical University of Innsbruck, Innsbruck, Austria

[2]Division for Digital Medicine and Telehealth, UMIT TIROL-Private University for Health Sciences and Health Technology, Hall (Tyrol), Austria

[3]Tyrolean Federal Institute for Integrated Care, Tirol Kliniken Gmbh, Innsbruck, Austria

[4]Christian Doppler Laboratory for Iron and Phosphate Biology, Medical University of Innsbruck, Innsbruck, Austria

[5]Institute of Epidemiology, Helmholtz Zentrum München, German Research Center for Environmental Health, Neuherberg, Germany

[6]Research Unit of Molecular Epidemiology, Helmholtz Zentrum München, German Research Center for Environmental Health, Neuherberg, Germany

[7]Institute of Genetic Epidemiology, Medical University of Innsbruck, Innsbruck, Austria

Correspondence
Heinz Zoller, Christian Doppler Laboratory for Iron and Phosphate Biology, Department of Medicine I, Gastroenterology, Hepatology and Endocrinology, Medical University of Innsbruck, Anichstrasse 35, A-6020 Innsbruck, Austria.
Email: heinz.zoller@i-med.ac.at

Funding information
Austrian Federal Ministry for Digital and Economic Affairs; Christian Doppler Forschungsgesellschaft

Handling Editor: Luca Valenti

Abstract

Background and Aims: Haemochromatosis is characterized by progressive iron overload affecting the liver and can cause cirrhosis and hepatocellular carcinoma. Most haemochromatosis patients are homozygous for p.C282Y in *HFE*, but only a minority of individuals with this genotype will develop the disease. The aim was to assess the penetrance of iron overload, fibrosis, hepatocellular carcinoma and life expectancy.

Methods: A total of 8839 individuals from the Austrian region of Tyrol were genotyped for the p.C282Y variant between 1997 and 2021. Demographic, laboratory parameters and causes of death were assessed from health records. Penetrance, survival, and cancer incidence were ascertained from diagnosed cases, insurance- and cancer registry data. Outcomes were compared with a propensity score-matched control population.

Results: Median age at diagnosis in 542 p.C282Y homozygous individuals was 47.8 years (64% male). At genotyping, the prevalence of iron overload was 55%. The cumulative penetrance of haemochromatosis defined as the presence of provisional iron overload was 24.2% in males and 10.5% in females aged 60 years or younger. Among p.C282Y homozygotes of the same ages, the cumulative proportion of individuals without fibrosis (FIB-4 score < 1.3) was 92.8% in males and 96.7% in females. Median life expectancy was reduced by 6.8 years in individuals homozygous for p.C282Y when compared with population-matched controls ($p = .001$). Hepatocellular

Abbreviations: HCC, hepatocellular carcinoma; pIOL, provisional iron overload; LLN, lower limit of normal; ULN, upper limit of normal.

carcinoma incidence was not significantly higher in p.C282Y homozygotes than in controls matched for age and sex.

Conclusion: Reduced survival and the observed age-dependent increase in penetrance among p.C282Y homozygotes call for earlier diagnosis of haemochromatosis to prevent complications.

KEYWORDS
FIB-4, fibrosis, hepatocellular carcinoma, iron overload, malignancy

1 | INTRODUCTION

Haemochromatosis is a genetic disease characterized by progressive iron overload primarily affecting the liver.[1,2] Early disease manifestations of haemochromatosis include fatigue and other non-specific symptoms such as arthralgia. Advanced stages of the disease can be complicated by cirrhosis, hepatocellular carcinoma, diabetes and arthropathy.[3,4] The most common genotype associated with haemochromatosis is homozygosity for p.C282Y in *HFE*, which is present in >80% of patients. Rarely, the disease is caused by pathogenic variants in genes encoding haemojuvelin, hepcidin, transferrin receptor-2 and ferroportin.[5,6] The unifying pathogenesis is reduced functional hepcidin, which is the hormone that controls ingress of iron into the body and egress of iron from macrophages into the circulation.[7] Hepcidin normally inhibits the iron exporter ferroportin, which limits the release of iron from absorptive intestinal epithelial cells and macrophages.[8] Homozygosity for p.C282Y is associated with inappropriately low hepcidin expression, which results in elevated transferrin saturation and iron overload as biochemical hallmarks of haemochromatosis.[9] Adequate treatment of iron overload with therapeutic phlebotomy is effective in preventing clinical complications.[10]

In individuals homozygous for p.C282Y, the diagnosis haemochromatosis can be made when transferrin saturation and ferritin are elevated.[11] Documentation of hepatic iron overload by liver biopsy or magnetic resonance imaging are only required for treatment initiation in haemochromatosis patients not homozygous for p.C282Y.[1,12,13] Elevated transferrin saturation (TSAT) and high serum ferritin define penetrant disease in patients homozygous for the p.C282Y.[11,14,15] The reported penetrance of iron overload ranges broadly between 1% and 40%, which is mainly attributable to different study populations and definitions.[16–18]

Longitudinal studies have confirmed the progressive nature of the disease, showing that sex and alcohol consumption are major determinants of clinical disease expression.[11,19–22]

The present population-based cohort study was carried out to assess the age- and sex-dependent risk for the development of provisional iron overload in p.C282Y homozygotes. The long-term follow-up allowed us to also assess the life expectancy and cancer incidence in a real-life clinical setting and compare outcomes with a matched population-based control group.

Key points

Genetic tests can identify people at risk for haemochromatosis, but not all with a positive test become sick. The present study shows that haemochromatosis patients with late diagnosis have shorter life expectancy than controls which can be attributed to cardiovascular risk factors. Liver cancer is a rare complication of haemochromatosis and further reduces life expectancy.

2 | METHODS

The present study was selected from patients referred to the Laboratory of Hepatology at the Department of Medicine, University Hospital of Innsbruck, for *HFE* genotyping between January 1997 and December 2021. Our Laboratory is the main diagnostic laboratory to perform this test in the county of Tyrol, Austria, during the study period and covers >95% of all *HFE* genotyping tests performed in this region. Of all 11088 patients who were referred to our department for the evaluation of suspected liver disease or haemochromatosis between 1997 and 2021, 8839 met the inclusion criterion of residence in Tyrol as defined by the postal code of their primary address registered with the national health insurance at the time of genotyping. (Figure 1).

Serum iron parameters and other laboratory test results at genotyping were retrospectively collected from the electronic health record and from the laboratory's database. Patient survival was assessed by inquiry of the national health insurance database on the 13th of January 2022. All deaths in Austria are registered in this database. Survival was calculated from date of birth to date of death. Patients alive on the 13th of January 2022 were censored accordingly for survival analysis. To compare the overall survival and hepatocellular carcinoma incidence of our haemochromatosis cohort with controls, a propensity score (based on age and sex, 2:1) matched cohort ($n=1088$) was modelled from the observed survival and age-adjusted cancer incidence in the general population of Tyrol as recorded in National death registry (Zentrales Sterberegister – Statistik Austria) for this region. Demographic data of all Tyrolean individuals were extracted from the National

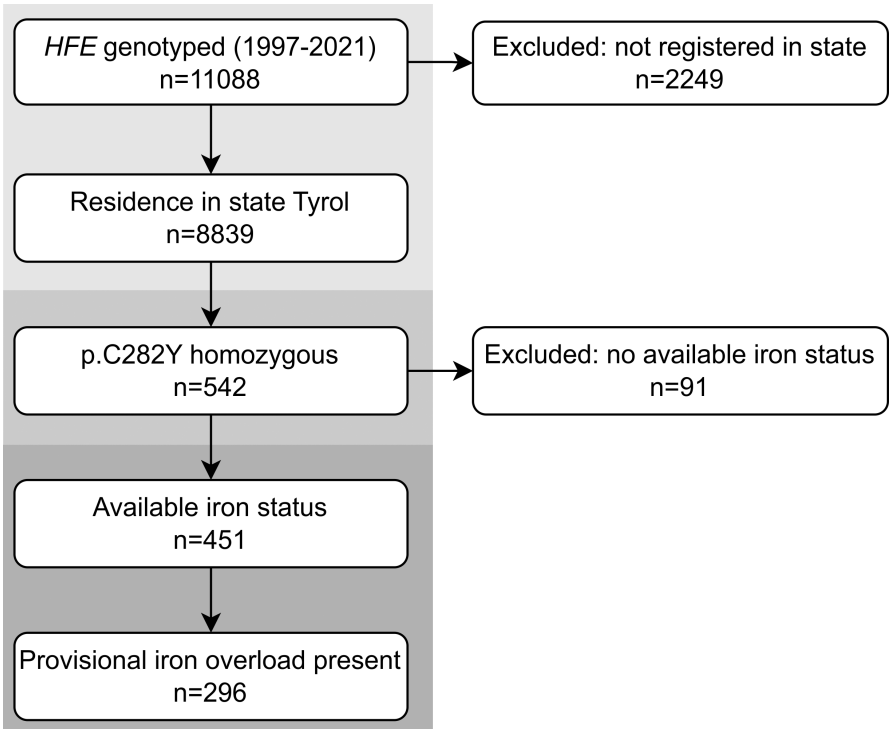

FIGURE 1 Study flow chart.

TABLE 1 Baseline characteristics of patients homozygous for p.C282Y.

	All	Female	Male
Number of patients with p.C282Y homozygosity	542	197 (36%)	345 (64%)
Median age at genotyping (year)	47.8 (35.3–60.1)	53.2 (37.8–63.7)	45.4 (34.0–56.8)
Serum iron (μmol/L)	*n* = 454	*n* = 170	*n* = 284
	34.1 (27.3–39.8)	31.6 (23.9–36.8)	36.2 (29.0–41.0)
Serum iron > ULN of 34.5 μmol/L (*n*)	49% (221)	35% (60)	57% (161)
Ferritin (μg/L)	*n* = 458	*n* = 170	*n* = 288
	580 (261–1127)	341 (170–628)	775 (419–1504)
Ferritin > ULN of 200 μg/L for females and 300 μg/L for males (*n*)	77% (354)	72% (123)	80% (231)
Transferrin (mg/dL)	*n* = 446	*n* = 166	*n* = 280
	193 (171–214)	193 (167–211)	193 (172–217)
Transferrin < LLN of 200 mg/dL (*n*)	58% (260)	59% (98)	58% (162)
Transferrin saturation (%)	*n* = 450	*n* = 169	*n* = 281
	74 (54–86)	67 (49–80)	79 (58–87)
Transferrin saturation > ULN of 45% (*n*)	85% (381)	81% (137)	87% (244)
C-reactive protein (mg/dL)	*n* = 392	*n* = 147	*n* = 245
	0.3 (0.1–0.7)	0.3 (0.1–0.7)	0.3 (0.1–0.7)
FIB-4 score			
<1.30	234 (62%)	95 (66%)	139 (60%)
≥1.30	143 (38%)	50 (34%)	93 (40%)
Median follow-up (year)	12.5 (7.3–17.6)	12.8 (7.2–17.6)	12.4 (7.5–17.7)
Cumulative follow-up (year)	6782.8	2487.5	4295.3
Any cancer diagnosis (#)	30	10	20
HCC diagnosis (#)	8	0	8

Note: Parametric variables are expressed as medians (25th and 75th percentile). Frequencies are reported as absolute numbers (percentages).

resident registry (Zentrales Melderegister – Statistik Austria) – details see Supplementary Materials. This population was used to calculate the number of expected individuals homozygous for p.C282Y using the frequency of this genotype from the KORA cohort, which is a population-based study conducted in the nearby region of Augsburg, Germany.[23] Results were also compared with allelic frequencies in non-Finish European population published in gnomAD. Incident cancer diagnoses were assessed for our haemochromatosis cohort from the regional cancer registry (Tiroler Tumorregister, which is 'Gold certified' by the North American Association of Central Cancer Registries), where all incident cancer diagnoses are recorded.[24] The database was queried for all individuals referred for genotyping and the results were compared with expected cancer incidences, calculated from reported, age-standardized incidence rates, in the propensity score-matched cohort. Genomic DNA extraction from peripheral blood and genotyping were carried out as previously described using a validated TaqMan allelic discrimination assay (TaqMan SNP Genotyping assay for reference SNP ID number rs1800562 and rs1799945, ThermoFisher Scientific, Vienna, Austria).[25]

Penetrant disease was either defined as the presence of provisional iron overload (ferritin >300 μg/L for men and postmenopausal women, >200 μg/L for premenopausal women in association with transferrin saturation >55% for men and >45% for women) as previously described.[11] Advanced liver fibrosis was ruled out using a FIB-4 score >1.3 at the time of genotyping. Age of menopause was assumed with 54 years (median age of natural menopause in Europe).[26] Age-dependent penetrance of haemochromatosis was calculated by dividing the cumulative number of C282Y homozygous patients with penetrant disease by the cumulative number of expected C282Y homozygous individuals of the same age or younger. This ratio was iteratively calculated for each diagnosed patient with penetrant disease and the results plotted against age at diagnosis. The number of expected C282Y homozygous individuals was calculated from demographic data of the Tyrolean population from the national resident registry (Table S1) and genotype frequencies from the KORA cohort (Tables S2–S4).[23] Additional information can be found in the Supplementary Material.

Extracted data from electronic health records were collected in Microsoft Excel before performing statistical analyses in IBM Statistics SPSS v27.0 and R v4.0.3. Graphs were created using the package survminer and ggplot2. Alpha was set at 0.05 for statistical significance. This study complies with STROBE reporting guidelines and was approved by the local ethics committee of the Medical University of Innsbruck (protocol number: 1253/2019).

3 | RESULTS

In this cohort of 8839 individuals referred for HFE genotyping to a Hepatology clinic, the frequency for p.C282Y homozygosity was 6.1% (542) and the allele frequency for p.C282Y was 15.8%, which is higher in this than in the non-Finish European control populations as reported in the gnomAD database (15.8% vs. 5.7%, $p < .001$).[27]

Demographic data, clinical and biochemical findings of the p.C282Y homozygous patient cohort are summarized in Table 1. When male and female patients were compared, male patients were found to be significantly younger and had significantly higher serum iron, ferritin and transferrin saturation as compared to females at time of genotyping. The majority of patients had high serum iron, hyperferritinaemia and elevated transferrin saturation. Fibrosis could be ruled-out by a FIB-4 < 1.3 score in more female than male patients, but this difference did not reach statistical significance (Table 1).

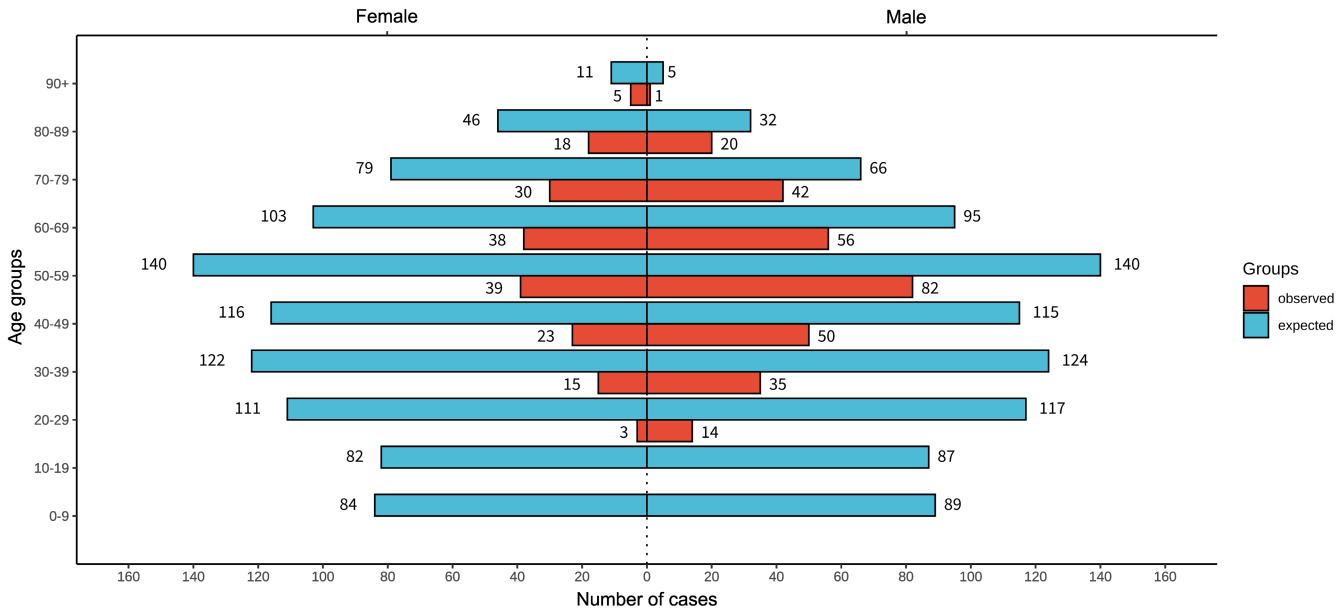

FIGURE 2 Comparison of expected and observed cases of individuals homozygote for p.C282Y grouped by sex. The number of expected patients for each group was calculated from regional allele frequencies and census data (details see Supplementary Material).

Next, homozygous patients with available serum iron parameters at the time of genotyping were grouped by the presence or absence of provisional iron overload, as surrogate for haemochromatosis. *HFE* p.C282Y homozygotes with provisional iron overload, were more likely to be male, but not significantly older at genotyping when compared with individuals without

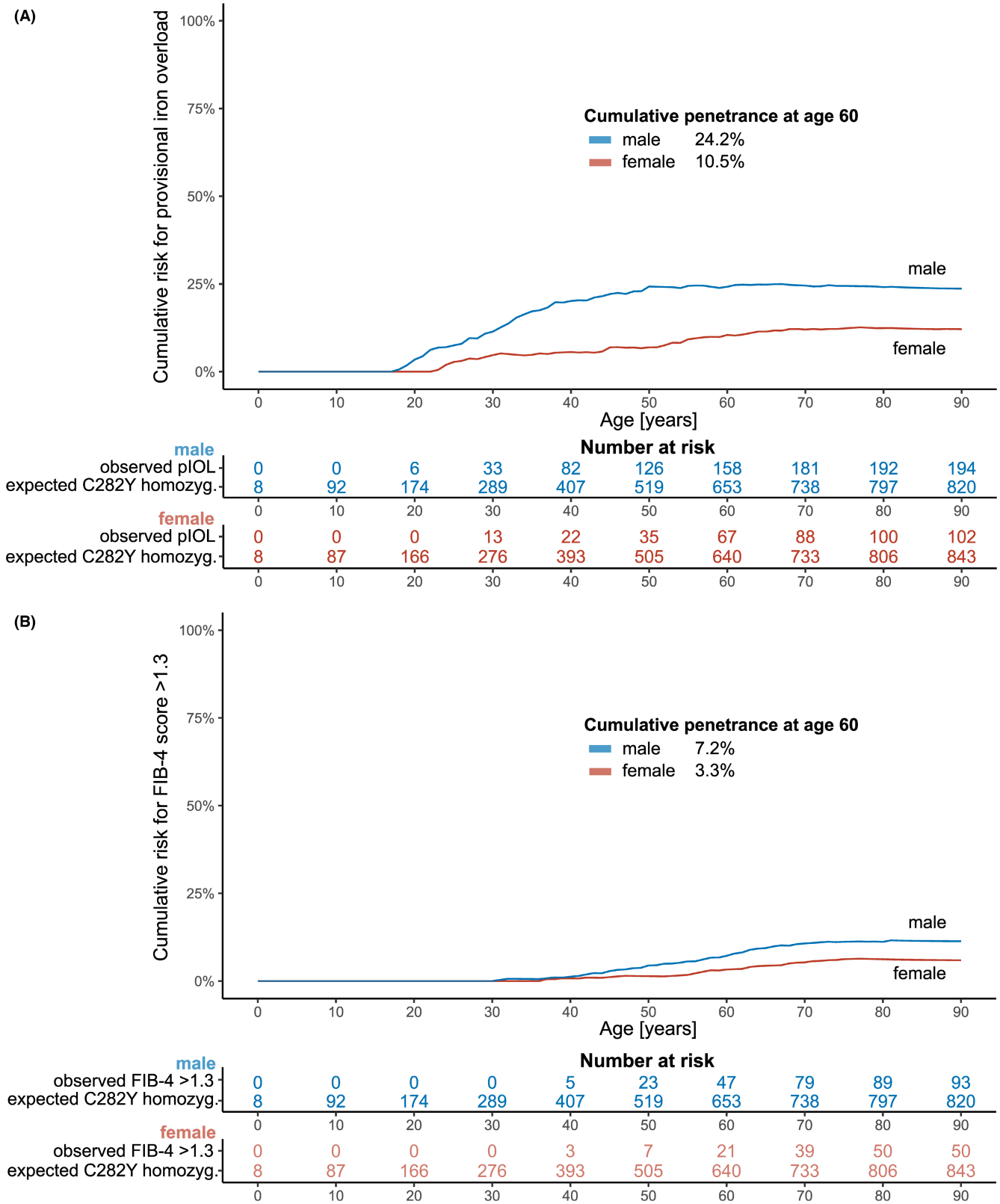

FIGURE 3 Cumulative age and sex-specific penetrance of (A) provisional iron overload or (B) of FIB-4 score ≥1.3 in p.C282Y homozygotes.

provisional iron overload. During a median follow-up of >10 years in both groups, incident cancer diagnoses and in particular hepatocellular carcinoma incidence rates were not significantly different (Table 1 and Table S5).

Figure 2 shows the age- and gender-distribution of diagnosed p.C282Y homozygotes and the number of expected p.C282Y homozygotes calculated from population data. This comparison shows that a larger proportion of males with p.C282Y homozygosity was diagnosed at relatively younger ages than females. The majority of male p.C282Y homozygotes were diagnosed in the 30–69 years age groups.

Age-dependent penetrance estimates of haemochromatosis defined as p.C282Y homozygosity with provisional iron overload or Fib-4 ≥ 1.3 for both sexes are shown in Figure 3.

During a median follow-up of 12.5 years, 30 patients were diagnosed with cancer, of whom 8 patients (all male) developed hepatocellular carcinoma (Table S7). Age-specific life expectancy and cancer incidence among p.C282Y homozygotes were compared with a propensity score-matched control population. As shown in Figure 4A, the life expectancy of individuals homozygous for p.C282Y was significantly reduced as compared with the matched control population. As shown in Figure 4B, median lifetime in p.C282Y homozygous patients who developed HCC was lowest with 69.7 years. Life expectancy in the group of patients with provisional iron overload or FIB-4 ≥ 1.3 at diagnosis was not significantly different from the group without provisional iron overload or FIB-4 < 1.3 at genotyping (Figure 4C,D).

Next, the observed age-dependent HCC incidence was compared with the modelled HCC incidence in the propensity score-matched control population. As shown in Figure 5A, no significant difference was noted. As all observed HCCs occurred in males, this analysis was repeated in p.C282Y homozygous patients as well as in modelled controls separated by sex. All p.C282Y homozygotes who developed HCC had a FIB4 > 1.3 at the time of genotyping and no HCCs were diagnosed in the group of patients with a FIB-4 < 1.3 at the time of genotyping. As shown in Figure 5B, no difference in HCC incidence was found when the analysis was confined to males or females.

In search for predictors of life expectancy in haemochromatosis patients, a Cox regression analysis was performed. As shown in Table 2, Tables S8 and S9, FIB-4 score as continuous variable, malignancy and cardiovascular risk factors were negatively associated with life expectancy. The strongest, independent predictor of survival was any cancer diagnosis. Younger age at diagnosis was a predictor of higher life expectancy in males after adjustment for FIB-4 and cancer. The causes of death could be assessed in 55 of 71 p.C282Y homozygote patients. In this cohort, cancer was the most common cause (45%) of death followed by cardiovascular disease (35%; Table S6). The most frequent comorbidities were steatosis (54.2%), smoking (39.3%) and arterial hypertension (37.2%) as detailed in Table S10.

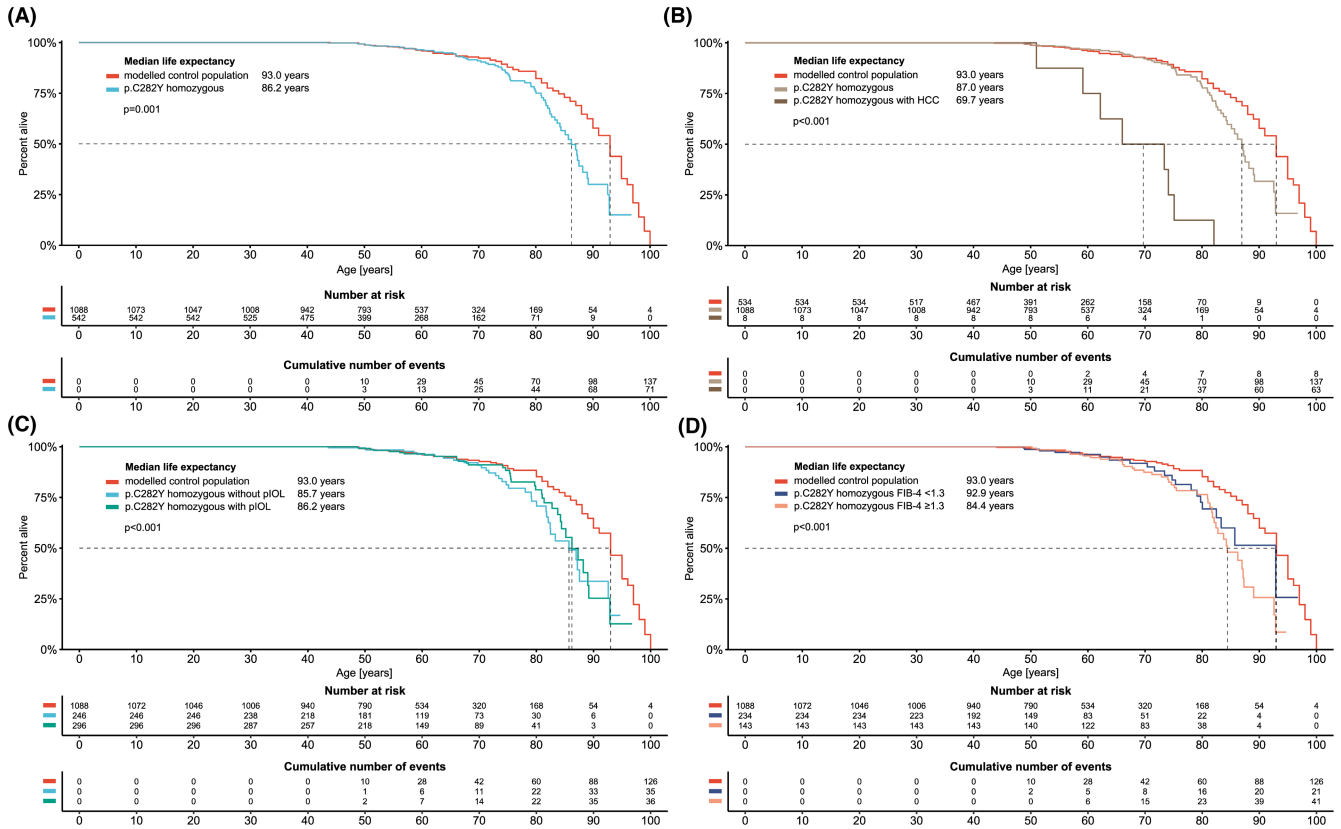

FIGURE 4 (A) Life expectancy of p.C282Y homozygotes (B) with and without HCC (C) with and without provisional iron overload (pIOL) and (D) FIB-4 score <1.3 or ≥1.3 compared with a modelled propensity score-matched control population.

4 | DISCUSSION

The present study was conducted to investigate the epidemiology, penetrance, cancer incidence and life expectancy in haemochromatosis patients. The study shows that the highest diagnostic rate of p.C282Y homozygous individuals was observed in the 50–59 age group. In this age group, over 50% of male and 28% of female cases expected from modelling were diagnosed.

The risk of developing iron overload in p.C282Y homozygotes is dependent on multiple factors including sex, age, study population

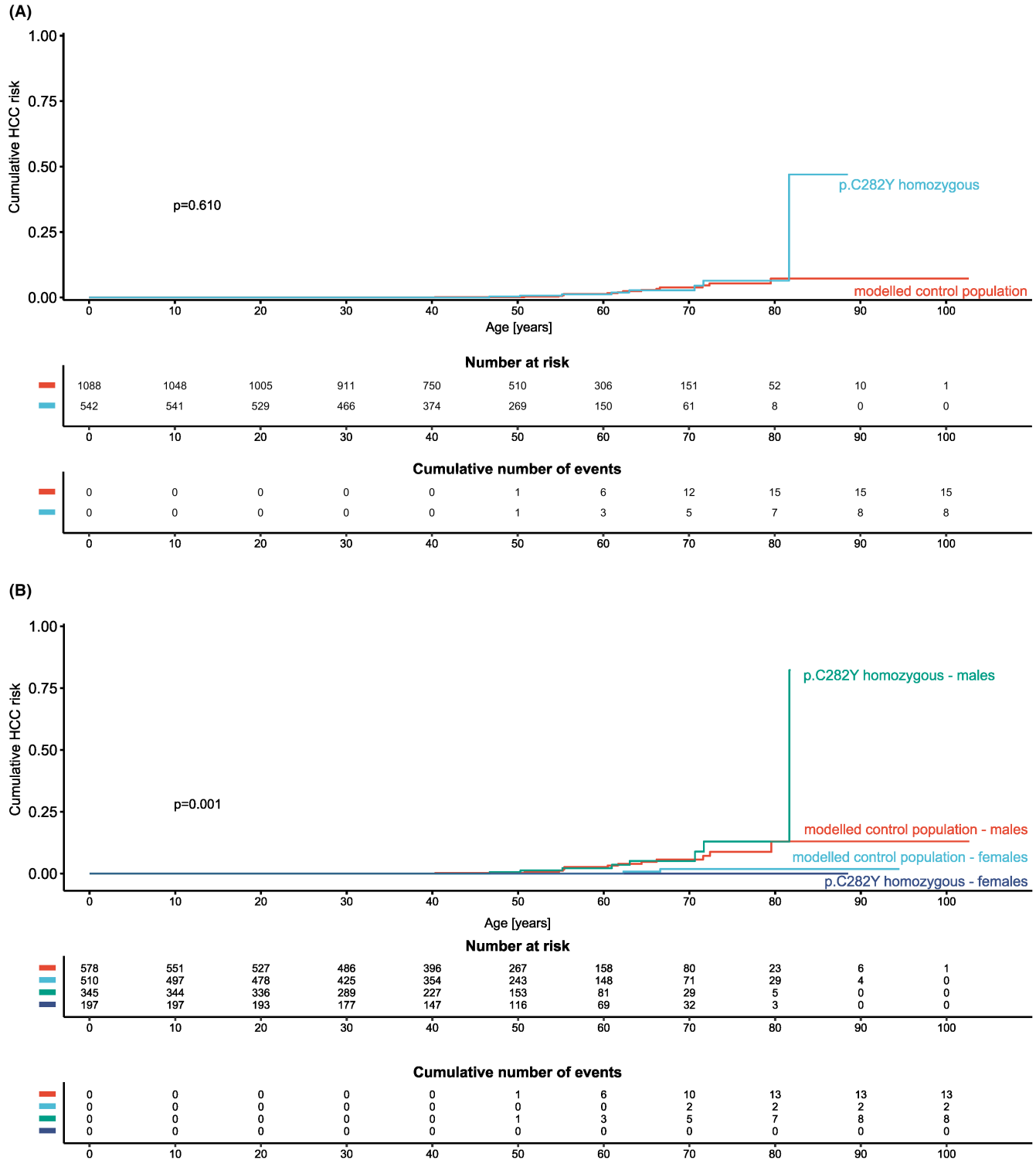

FIGURE 5 (A) Cumulative lifetime HCC risk for p.C282Y homozygotes compared with a modelled propensity score-matched control population. (B) Cumulative lifetime HCC risk for p.C282Y homozygotes compared with a modelled propensity score-matched control population stratified by sex.

TABLE 2 Cox regression of life expectancy.

	Female					Male				
	Univariate			Multivariate		Univariate			Multivariate	
Variable	*n* (events)	HR [95% CI]	*p*	HR [95% CI]	*p*	*n* (events)	HR [95% CI]	*p*	HR [95% CI]	*p*
Age at diagnosis (years)	181 (26)	0.977 [0.93–1.03]	.392	–	–	317 (45)	0.967 [0.93–1.00]	.060	0.932 [0.892–0.974]	.002
Iron (μmol/L)	157 (22)	1.006 [0.96–1.05]	.793	–	–	262 (39)	0.989 [0.96–1.02]	.430	–	–
logFerritin (μg/L)	157 (23)	1.002 [0.67–1.50]	.992	–	–	265 (39)	1.029 [0.83–1.27]	.793	–	–
Transferrin (mg/dL)	153 (22)	0.998 [0.98–1.01]	.789	–	–	258 (39)	0.996 [0.99–1.01]	.404	–	–
Transferrin Saturation (%)	156 (23)	1.003 [0.99–1.02]	.662	–	–	258 (39)	0.997 [0.99–1.01]	.623	–	–
CRP (mg/dL)	135 (21)	1.065 [1.00–1.13]	.043	1.054 [0.989–1.124]	.105	226 (40)	1.075 [0.97–1.19]	.175	–	–
FIB-4	134 (22)	1.252 [1.04–1.51]	.018	1.239 [1.040–1.475]	.016	216 (40)	1.423 [1.14–1.78]	.002	1.481 [1.182–1.856]	<.001
Any cancer diagnosis	181 (26)	3.002 [1.34–6.72]	.008	3.198 [1.224–8.354]	.018	317 (45)	2.440 [1.33–4.48]	.004	2.140 [1.053–4.352]	.036
Provisional iron overload at genotyping	181 (26)	0.825 [0.45–1.50]	.528	–	–	317 (45)	0.892 [0.56–1.41]	.623	–	–

and definition of penetrant disease. For the present study, penetrant disease was defined as provisional iron overload. This definition has been adopted from previous studies and was chosen, because current guidelines are based on the same criteria for diagnosis and treatment indication.[1,11,15,28] For the assessment of haemochromatosis penetrance defined as liver fibrosis, FIB-4 could also be used as a surrogate, where a threshold of <1.3 has been suggested to exclude significant fibrosis.[29,30] Recent guidelines recommend that patients with haemochromatosis and a FIB-4 ≥ 1.3 should be investigated for the presence of liver disease.[31]

Analysis of disease penetrance, as performed in this study, allows age- and sex-dependent risk estimation. Data shown result from combined effects of diagnostic rate and penetrance, which limits penetrance estimates in children and adolescents, where HFE haemochromatosis is rare.[32] Disease penetrance estimates in adults are more reliable and represent a lower bound, because they are based on all diagnosed patients with provisional iron overload. These data are a quantitative representation of age-dependent increase in disease penetrance.

Homozygotes for p.C282Y had a 6.8 year shorter life expectancy when compared with a control population matched for sex and age at genotyping. Still, median life expectancy was 86.2 years among haemochromatosis patients, who were diagnosed at a median age of 47.8 years. This also explains the high median life expectancy of 93 years in the control population, who were matched for the age at diagnosis of the control population. The reduced life expectancy of haemochromatosis patient indicates that patients were either diagnosed too late or inadequately treated. Previous studies have shown normal or even higher life expectancy for adequately treated haemochromatosis patients.[33,34] However, the fact that the presence of provisional iron overload at diagnosis was not associated with reduced survival, indicates that late diagnosis rather than inadequate treatment determines life expectancy in this cohort. Treatment outcome could not be ascertained for most patients, which represents a limitation of our study. Elevated transferrin saturation was observed in 85% of p.C282Y homozygous individuals at diagnosis but only 49% had elevated serum iron concentrations highlighting the poor diagnostic performance of this test alone. This highlights the importance of genetic diagnosis to identify individuals at risk, in whom lifestyle modification and surveillance for iron overload could prevent disease. The present study found a high rate of comorbidities, such as steatosis, arterial hypertension, smoking or a history of harmful drinking that negatively affect life expectancy. Individuals with haemochromatosis might be particularly susceptible to the detrimental effects of this comorbidities that are preventable by early diagnosis.

Survival status and cancer incidence could be reliably assessed from national health insurance and cancer registry. The median follow-up period of over 12 years is also sufficiently long to assess cancer incidence. In our study, hepatocellular cancer incidence was not increased in homozygous p.C282Y patients when compared with a propensity score-matched control cohort. Previous studies reported a higher cancer incidence in p.C282Y homozygotes when compared with matched controls.[35–38] Our study provides longitudinal

data on cancer incidence. A likely explanation for this difference is that median age in our cohort was 6–8 years lower than in previous studies. This is further supported by the notion that incidence for HCC was lower in the Swedish cohort study (mean age at diagnosis: 52.6 years) than in the UK biobank study (mean age at baseline: 56.9 years). Further, data from the Swiss haemochromatosis cohort identified age at diagnosis as the strongest predictor for the development of HCC.[39] In accordance with all previous studies, male sex was confirmed as a major risk factor for HCC development in haemochromatosis.[40]

Age and potential liver fibrosis indicated by FIB-4 score as continuous variable were identified as main predictors of survival by Cox regression analysis. In Kaplan-Meier analysis, FIB-4 at a cut-off of 1.3 could not discriminate patients with impaired life expectancy. This apparent difference could be explained by a threshold effect, where in haemochromatosis significant fibrosis may be associated with different FIB-4 scores as compared with other aetiologies. A previous biopsy-based study demonstrated a good accuracy of the FIB-4 score in haemochromatosis.[31]

In conclusion, data from this population-based long-term follow-up study highlights the advances made during the era of genetic diagnosis of haemochromatosis. *HFE* genotyping allows identification of individuals at risk of developing iron overload at pre-symptomatic disease stages. Screening programs have not been introduced for haemochromatosis because disease penetrance had been considered too low.[20] Still, life expectancy is lower in patients homozygous for p.C282Y compared with a matched control population, which is not attributable to increased cancer risk.

ACKNOWLEDGEMENTS

The KORA study was initiated and financed by the Helmholtz Zentrum München—German Research Center for Environmental Health, which is funded by the German Federal Ministry of Education and Research (BMBF) and by the State of Bavaria. Data collection in the KORA study is done in cooperation with the University Hospital of Augsburg.

FUNDING INFORMATION

The financial support by the Austrian Federal Ministry for Digital and Economic Affairs, the National Foundation for Research, Technology and Development and the Christian Doppler Research Association is gratefully acknowledged.

CONFLICT OF INTEREST STATEMENT

BS reported receiving personal fees from Pharmacosmos A/S, and Vifor Pharma, and grants and personal fees from AbbVie, and Gilead outside the submitted work. HZ reported receiving grants, personal fees, and nonfinancial support from AbbVie, Gilead, Pharmacosmos A/S, and Vifor Pharma; personal fees from Merck; personal fees and nonfinancial support from Bayer; grants from Merck Sharp & Dohme; and honoraria for lecturing from Bristol-Myers Squibb, Medice, Merz, and Novartis outside the submitted work.

DATA AVAILABILITY STATEMENT

Data, analytic methods, and study materials will be made available on request.

ORCID

Heinz Zoller https://orcid.org/0000-0003-1794-422X

REFERENCES

1. EASL clinical practice guidelines on haemochromatosis. *J Hepatol*. 2022;77(2):479-502.
2. Girelli D, Busti F, Brissot P, Cabantchik I, Muckenthaler MU, Porto G. Hemochromatosis classification: update and recommendations by the BIOIRON society. *Blood*. 2022;139(20):3018-3029.
3. Pilling LC, Tamosauskaite J, Jones G, et al. Common conditions associated with hereditary haemochromatosis genetic variants: cohort study in UK biobank. *BMJ*. 2019;364:k5222.
4. Ellervik C, Birgens H, Tybjaerg-Hansen A, Nordestgaard BG. Hemochromatosis genotypes and risk of 31 disease endpoints: meta-analyses including 66,000 cases and 226,000 controls. *Hepatology*. 2007;46(4):1071-1080.
5. Powell LW, Seckington RC, Deugnier Y. Haemochromatosis. *Lancet*. 2016;388(10045):706-716.
6. Brissot P, Pietrangelo A, Adams PC, de Graaff B, McLaren CE, Loréal O. Haemochromatosis. *Nat Rev Dis Primers*. 2018;4:18016.
7. Pietrangelo A. Hemochromatosis: an endocrine liver disease. *Hepatology*. 2007;46(4):1291-1301.
8. Nemeth E, Tuttle MS, Powelson J, et al. Hepcidin regulates cellular iron efflux by binding to ferroportin and inducing its internalization. *Science*. 2004;306(5704):2090-2093.
9. Bridle KR, Frazer DM, Wilkins SJ, et al. Disrupted hepcidin regulation in HFE-associated haemochromatosis and the liver as a regulator of body iron homoeostasis. *Lancet*. 2003;361(9358):669-673.
10. Prabhu A, Cargill T, Roberts N, Ryan JD. Systematic review of the clinical outcomes of iron reduction in hereditary hemochromatosis. *Hepatology*. 2020;72(4):1469-1482.
11. Allen KJ, Gurrin LC, Constantine CC, et al. Iron-overload-related disease in HFE hereditary hemochromatosis. *N Engl J Med*. 2008;358(3):221-230.
12. Henninger B, Rauch S, Zoller H, Plaikner M, Jaschke W, Kremser C. R2*-relaxometry of the pancreas in patients with human hemochromatosis protein associated hereditary hemochromatosis. *Eur J Radiol*. 2017;89:149-155.
13. Adams P, Altes A, Brissot P, et al. Therapeutic recommendations in HFE hemochromatosis for p.Cys282Tyr (C282Y/C282Y) homozygous genotype. *Hepatol Int*. 2018;12(2):83-86.
14. European Association for the Study of the Liver. EASL clinical practice guidelines on haemochromatosis. *J Hepatol*. 2022;77(2):479-502.
15. Kowdley KV, Brown KE, Ahn J, Sundaram V. ACG clinical guideline: hereditary hemochromatosis. *Am J Gastroenterol*. 2019;114(8):1202-1218.
16. Beutler E, Felitti VJ, Koziol JA, Ho NJ, Gelbart T. Penetrance of 845G--> A (C282Y) HFE hereditary haemochromatosis mutation in the USA. *Lancet*. 2002;359(9302):211-218.
17. Jacobs EM, Hendriks JC, Marx JJ, et al. Morbidity and mortality in first-degree relatives of C282Y homozygous probands with clinically detected haemochromatosis compared with the general population: the HEmochromatosis FAmily study (HEFAS). *Neth J Med*. 2007;65(11):425-433.
18. Bulaj ZJ, Ajioka RS, Phillips JD, et al. Disease-related conditions in relatives of patients with hemochromatosis. *N Eng J Med*. 2000;343(21):1529-1535.
19. Andersen RV, Tybjaerg-Hansen A, Appleyard M, Birgens H, Nordestgaard BG. Hemochromatosis mutations in the

general population: iron overload progression rate. *Blood*. 2004;103(8):2914-2919.
20. Whitlock EP, Garlitz BA, Harris EL, Beil TL, Smith PR. Screening for hereditary hemochromatosis: a systematic review for the U.S. preventive services task force. *Ann Intern Med*. 2006;145(3):209-223.
21. Hagstrom H, Ndegwa N, Jalmeus M, et al. Morbidity, risk of cancer and mortality in 3645 HFE mutations carriers. *Liver Int*. 2021;41(3):545-553.
22. Fletcher LM, Dixon JL, Purdie DM, Powell LW, Crawford DH. Excess alcohol greatly increases the prevalence of cirrhosis in hereditary hemochromatosis. *Gastroenterology*. 2002;122(2):281-289.
23. Holle R, Happich M, Löwel H, Wichmann HE. KORA—a research platform for population based health research. *Gesundheitswesen*. 2005;67(Suppl 1):S19-S25.
24. Tumorregister Tirol. Inzidenz und Mortalität bösartiger Neubildungen in Tirol. 2019; https://www.iet.at/page.cfm?vpath=register/tumorregister, 2022
25. Schaefer B, Mandorfer M, Viveiros A, et al. Heterozygosity for the alpha-1-antitrypsin Z allele in cirrhosis is associated with more advanced disease. *Liver Transpl*. 2018;24(6):744-751.
26. Dratva J, Gómez Real F, Schindler C, et al. Is age at menopause increasing across Europe? Results on age at menopause and determinants from two population-based studies. *Menopause*. 2009;16(2):385-394.
27. Karczewski KJ, Francioli LC, Tiao G, et al. The mutational constraint spectrum quantified from variation in 141,456 humans. *Nature*. 2020;581(7809):434-443.
28. Bacon BR, Adams PC, Kowdley KV, Powell LW, Tavill AS. Diagnosis and management of hemochromatosis: 2011 practice guideline by the American Association for the Study of Liver Diseases. *Hepatology*. 2011;54(1):328-343.
29. Sterling RK, Lissen E, Clumeck N, et al. Development of a simple noninvasive index to predict significant fibrosis in patients with HIV/HCV coinfection. *Hepatology*. 2006;43(6):1317-1325.
30. EASL clinical practice guidelines on non-invasive tests for evaluation of liver disease severity and prognosis—2021 update. *J Hepatol*. 2021;75(3):659-689.
31. Chin J, Powell LW, Ramm LE, Hartel GF, Olynyk JK, Ramm GA. Utility of serum biomarker indices for staging of hepatic fibrosis before and after venesection in patients with hemochromatosis caused by variants in HFE. *Clin Gastroenterol Hepatol*. 2021;19(7):1459-1468.e1455.
32. Griffiths WJH, Besser M, Bowden DJ, Kelly DA. Juvenile haemochromatosis. *Lancet Child Adolesc Health*. 2021;5(7):524-530.
33. Milman N, Pedersen P, Steig T á, Byg KE, Graudal N, Fenger K. Clinically overt hereditary hemochromatosis in Denmark 1948-1985: epidemiology, factors of significance for long-term survival, and causes of death in 179 patients. *Ann Hematol*. 2001;80(12):737-744.
34. Bardou-Jacquet E, Morcet J, Manet G, et al. Decreased cardiovascular and extrahepatic cancer-related mortality in treated patients with mild HFE hemochromatosis. *J Hepatol*. 2015;62(3):682-689.
35. Adams PC. Hepatocellular carcinoma in hemochromatosis: where or when? *Digest Dis Sci*. 2022;68:12-13.
36. Adams PC, Richard L, Weir M, Speechley M. Survival and development of health conditions after iron depletion therapy in C282Y-linked hemochromatosis patients. *Can Liver J*. 2021;4(4):381-390.
37. Natarajan Y, Patel P, Chu J, et al. Risk of hepatocellular carcinoma in patients with various HFE genotypes. *Digest Dis Sci*. 2022;68:312-322.
38. Atkins JL, Pilling LC, Masoli JAH, et al. Association of hemochromatosis HFE p.C282Y homozygosity with hepatic malignancy. *JAMA*. 2020;324(20):2048-2057.
39. Nowak A, Giger RS, Krayenbuehl PA. Higher age at diagnosis of hemochromatosis is the strongest predictor of the occurrence of hepatocellular carcinoma in the Swiss hemochromatosis cohort: a prospective longitudinal observational study. *Medicine (Baltimore)*. 2018;97(42):e12886.
40. Grosse SD, Gurrin LC, Bertalli NA, Allen KJ. Clinical penetrance in hereditary hemochromatosis: estimates of the cumulative incidence of severe liver disease among HFE C282Y homozygotes. *Genet Med*. 2018;20(4):383-389.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Schaefer B, Pammer LM, Pfeifer B, et al. Penetrance, cancer incidence and survival in *HFE* haemochromatosis—A population-based cohort study. *Liver Int*. 2024;44:838-847. doi:10.1111/liv.15797