Survival and development of health conditions after iron depletion therapy in C282Y-linked hemochromatosis patients

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ABSTRACT

BACKGROUND: We report long-term survival and development of selected health conditions in Ontario-based referred and screened C282Y homozygotes for hemochromatosis treated by phlebotomy compared with an untreated control group known to be without *HFE* mutations. **METHODS:** Patient characteristics and outcomes (all-cause mortality, liver cancer, diabetes, cirrhosis, hip or knee joint replacement, and osteoarthritis) were ascertained using a linked health administrative database held at ICES. Outcomes were assessed between groups without the outcome at baseline using Cox proportional hazards regression adjusted for age and sex. All C282Y homozygotes with elevated serum ferritin were treated by phlebotomy to reach serum ferritin of 50 µg/L. Our cohort included 527 C282Y homozygotes (311 men, 216 women, mean age 48 years) and 12,879 control participants (5,667 men and 7,212 women). **RESULTS:** C282Y homozygotes had an increased risk of all-cause mortality (aHR 1.44 [1.19–1.75], *p* <0.001); hepatocellular carcinoma (aHR 8.30 [3.97–17.34], *p* <0.001); hip or knee joint replacement (aHR 3.06 [2.46–3.81], *p* <0.001); osteoarthritis (aHR 1.72 [1.47–2.01], *p* <0.001); and cirrhosis (aHR 3.87 [3.05–4.92], *p* <0.001). C282Y homozygotes did not have an increased risk for diagnosis of diabetes) (aHR 0.84 [0.67–1.07], *p* = 0.16) during follow-up (median 17.7 y). **CONCLUSIONS:** C282Y homozygotes experience higher death and complication rates than individuals without *HFE* mutations, despite treatment by phlebotomy. Diabetes did not increase after phlebotomy therapy.

KEYWORDS: hemochromatosis; iron; iron overload; phlebotomy

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Though iron overload has been the defining feature of hemochromatosis, it is not clear that all the complications are caused by iron overload (1) or if iron depletion would prevent the future development of symptoms (2,3,4). In this study, the development of health conditions associated with C282Y-linked hemochromatosis and mortality after phlebotomy therapy are compared with a large untreated control population without *HFE* mutations.

STUDY DESIGN AND SETTING

We conducted a retrospective cohort study in Ontario—Canada's largest province—which provides universal access to health care through a single-payer system. Participant data were linked using unique encoded identifiers and analyzed at ICES. ICES is a prescribed entity under section 45 of Ontario's Personal Health Information Protection Act, which authorizes ICES to collect personal health information without consent for the purpose of analysis or compiling statistical information with respect to the management, evaluation, or monitoring of the allocation of resources to, or planning for, all or part of the health system. The use of data in this project was approved by the Western University Health Science Research Ethics Board. This study follows RECORD reporting guidelines (5).

Participants

Our cohort was derived from two sources: patients included C282Y homozygotes referred to University Hospital in London, Ontario between 1974 and 2018, and Ontario-based patients (C282Y homozygotes and controls without *HFE* mutations) screened during the Hemochromatosis and Iron Overload Study (HEIRS) study between 2000 and 2005 (1). We considered matching control participants based on age and gender, but we chose to include all available control participants without *HFE* mutations. The large sample size of the control population provides the best estimate of the clinical outcomes and a narrow confidence interval. The ICES database does not contain data on genetic testing, so ascertainment of C282Y homozygotes was not possible. C282Y homozygotes with an elevated serum ferritin (men >300 µg/L, women >200 µg/L) were treated by weekly 500 mL by phlebotomy until the serum ferritin was 50 µg/L (6). Maintenance therapy was individualized based on the monitoring of serum ferritin over the follow-up period. Periodic voluntary blood donation was recommended every 3 months for patients with persistent or rising serum ferritin. The therapy was supervised by a single physician in 95% of patients. The ICES database does not include laboratory data such as serum ferritin, so it was not compared with referred patients in this study. Serum ferritin at entry in all control patients without *HFE* mutations from the HEIRS study (including our 12,879 control participants) has been previously reported (1). Referred patients were evaluated for cirrhosis and liver failure, but this information was not available for the control population, so it was not compared. We have previously reported on cirrhosis in referred patients, which was 30% in male probands, and 7% in female probands (7). Due to the much broader referral period among University Hospital patients—which includes a period during which outcome data was unavailable at ICES—individuals from this group were only included if alive and in Ontario as of a randomly assigned index date that followed the distribution of index dates (the date of inclusion into the HEIRS study) for HEIRS patients. Where multiple records for an individual were present (for example, an individual was present in both sources), the earliest index date was assigned. In referred C282Y homozygotes, cirrhosis and hepatocellular carcinoma were diagnosed by triphasic imaging, alpha-fetoprotein, and biopsy in selected cases. No patient had chronic hepatitis B or C or alcoholic liver disease. This differs from our control population assessment, in which cirrhosis was based on a validated proxy for cirrhosis and hepatocellular carcinoma diagnosis was from public databases. Statistical comparisons were restricted to clinical outcomes where only ICES data was used. We have previously reported on our referred patients with regard to survival, liver pathology, serum ferritin, hepatocellular carcinoma (7,8), and alcohol abuse (9), and this was not reported since we did not have similar data on the control population. All patients with hepatocellular carcinoma as a complication of hemochromatosis at our centre have had cirrhosis.

Outcomes

We followed participants to identify a series of outcomes previously linked to hemochromatosis (1,4,7,8,10–19): hepatocellular carcinoma, chronic liver disease, cirrhosis, knee or hip replacement, osteoarthritis, diabetes, and all-cause death. We also looked back for evidence of these outcomes in the patient's health history. For each outcome, individuals were censored at index if the outcome was already present. During follow-up, individuals were also censored upon death or at the end of the observation window (for most outcomes, December 31, 2019; for death, March 31, 2020). Complete concept definitions are provided in Table 1.

Covariates

We obtained covariates for the cohort at index including age, sex, health history (pneumonia in past 3 years; osteoporotic fracture in past 5 years), and

Table 1: Covariate concept definitions and codes

Variable	Data source	Definition description	Standardized codes applied
Age	RPDB	Age of the individual at index, years. Categories for this variable include <30; 30–39; 40–49; 50–59; 60+	
Sex	RPDB	Biological sex of the individual	
Congestive heart failure	CHF (20)	Presence in the database indicates the individual has a history of congestive heart failure	
Diabetes	ODD (21)	Presence in the database indicates the individual has a history of diabetes	
Rheumatoid arthritis	ORAD (22)	Presence in the database indicates the individual has a history of rheumatoid arthritis	
Osteoarthritis	DAD	At least one health care encounter in any of the listed data sources occurring within 5 years prior to index or during the follow-up period having a code related to osteoarthritis	ICD-9: 715
	NACRS		ICD-10: M15; M16; M17; M18; M19; M47
	OHIP		OHIP dx: 715
Pneumonia	DAD	At least one health care encounter in any of the listed data sources occurring within 3 years prior to index or during follow-up having a code related to pneumonia	ICD-9: 480; 481; 482; 483; 484; 485; 486
	NACRS		ICD-10: J12; J13; J14; J15; J16; J17; J18
	OHIP		OHIP dx: 498
Chronic liver disease	DAD	At least one health care encounter in any of the listed data sources occurring within 5 years prior to index having a code related to chronic liver disease	ICD-9: 070; 571; 573; 2750; 2751; 4561; 4562; 5722; 5723; 5724; 5728; 7824; 7891; 7895; V026
	NACRS		ICD-10: B16; B17; B18; B19; I85; R17; R18; R160; R162; B942; Z225; E831; E830; K70; K713; K714; K715; K717; K721; K729; K73; K74; K753; K754; K758; K759; K76; K77
	OHIP		OHIP dx: 571; 573; 070 OHIP fee: Z551; Z554
Dementia	DEMENTIA (24)	Presence in the database indicates the individual has a history of dementia	
Parkinson's disease	DAD	At least one health care encounter in any of the listed data sources occurring within 5 years prior to index or during follow-up having a code related to Parkinson's disease	ICD-9: 3320
	NACRS		ICD-10: G20
	OHIP		OHIP dx: 332
Recent osteoporotic fracture	DAD	At least one health care encounter in any of the listed data sources occurring within 3 years prior to index with a code related to an osteoporotic fracture	ICD-9: 812; 8056; 8057; 808; 813; 8210; 8211; 8200; 8201; 8208; 8209; 8202; 8203
	NACRS		ICD-10: S422; S52; S720; S721; S722; S321; S322; S324; S323; S325; S327; S328; S723

(Continued)

Variable	Data source	Definition description	Standardized codes applied
			CCP: 9101; 9121; 9141; 9111; 9131; 9052; 9104; 9124; 9054; 9114; 9134; 9104; 9124; 9054; 9114; 9134; 935; 936
			CCI: 1TV73; 1TV74; 1TV03; 1VC73; 1VC74; 1VC03; 1VC80; 1VA73; 1VC73; 1VA74; 1VA53; 1VC74; 1VA80
	OHIP		OHIP fee: F014; F022; F023; F025; F026; F028; F030; F032; F033; F046; F024; F027; F031; Z203; F095; F096; F097; Z211
Cirrhosis	DAD	At least one health care encounter in any of the listed data sources occurring within 3 years prior to index or during follow-up having a code related to cirrhosis	ICD-9: 4561; 5712; 5715
	NACRS		ICD-10: K700; K702; K73; K754; K758; K759; K760; B180; B181; B182; B188; B189
	OHIP		OHIP dx: 571
All-cause death	RPDB	Death due to any cause	
Liver cancer	OCR	Diagnosis during follow-up with a liver tumour site	Topography code = C220
Knee or hip joint replacement	DAD	At least one health care encounter in any of the listed data sources occurring during follow-up having a code related to knee or hip joint replacement	CCP: 9351; 9359; 9341
	NACRS		CCI: 1VA53; 1VG53
	OHIP		OHIP fee: R241; R439; R440; R481; R491; R553; R244; R248; R441; R442; R482; R483; R509

Data source: RPDB = ICES Registered Persons Database; CHF = Congestive heart failure; ODD = Ontario diabetes database; ORAD = Ontario rheumatoid arthritis database; DAD = Canadian Institute for Health Information Discharge Abstract Database; NACRS = Canadian Institute for Health Information National Ambulatory Care Reporting System; OHIP = Ontario Health Insurance Plan database
Standardized codes: ICD-9 = International Classification of Diseases Version 9; ICD-10 = International Classification of Diseases Version 10 (Canadian Version); OHIP fee = Ontario Health Insurance Plan fee codes; CCP = Canadian Classification of Diagnostic, Therapeutic and Surgical Procedures; CCI = Canadian Classification of Health Interventions; OHIP dx = Ontario Health Insurance Plan Diagnosis Codes

comorbidities [congestive heart failure (20), diabetes (21), rheumatoid arthritis (22), osteoarthritis, chronic liver disease (23), dementia (24), Parkinson's disease (24), and cirrhosis (23)] (Table 2). Covariate concept definitions, including codes, are provided in Table 1.

STATISTICAL METHODS

We describe cohorts at index using a combination of one-way ANOVA, Kruskal–Wallis, and chi-square tests, as appropriate. We also provide standardized differences, which assess differences between group means as a percentage of the pooled standard deviation (a difference of >10% is considered

significant). The standardized difference is the difference between two group means divided by the standard deviation of pooled groups. It is not as susceptible to identifying a statistically significant difference that is not clinically significant with large sample sizes as hypothesis testing is, which is why it is used in the analysis of large datasets (25).

We then report crude and event rates per 100 person-years. The hazard of receiving a given outcome for C282Y homozygotes was summarized using an adjusted hazard ratio (aHR) from a multivariate Cox proportional hazards model adjusted for age and sex. We ensured the proportional hazards

Table 2: Description of the cohort at index

	No. (%)*				
	Total (N = 13,406)	C282Y homozygote (n = 527)	Wild type (n = 12,879)	p-value	Standardized difference[†]
Demographics					
Age at index date, years					
Mean (SD)	49.00 (13.78)	48.14 (15.61)	49.04 (13.70)	0.145	6%
Median (IQR)	48 (39–58)	49 (38–58)	48 (39–58)	0.811	1%
<30	2,734 (20.4)	81 (15.4)	2,653 (20.6)	<0.001	13%
30–39	3,615 (27.0)	128 (24.3)	3,487 (27.1)		6%
40–49	3,002 (22.4)	128 (24.3)	2,874 (22.3)		5%
50–59	3,100 (23.1)	126 (24.0)	2,974 (23.1)		2%
≥60	950 (7.1)	62 (11.8)	888 (6.9)		17%
Sex = male	5,512 (41.1)	309 (58.6)	5,203 (40.4)	<0.001	
Comorbidities and health history					
Congestive heart failure	223 (1.7)	12 (2.3)	211 (1.6)	0.256	5%
Diabetes	1,268 (9.5)	61 (11.6)	1,207 (9.4)	0.085	7%
Rheumatoid arthritis	164 (1.2)	6 (1.1)	158 (1.2)	0.863	1%
Osteoarthritis[‡]	1,478 (11.0)	84 (15.9)	1,394 (10.8)	<0.001	15%
Recent osteoporotic fracture[§]	168 (1.3)	15 (2.8)	153 (1.2)	<.001	12%
Chronic liver disease[§]	891 (6.6)	186 (35.3)	705 (5.5)	<0.001	80%
Pneumonia[§]	582 (4.3)	37 (7.0)	545 (4.2)	0.002	12%
Dementia	NR	≤5	25 (0.2)	0.985	0%
Parkinson's disease[§]	NR	≤5	42 (0.3)	0.83	1%
Cirrhosis[‡]	77 (0.6)	20 (3.8)	57 (0.4)	<0.001	23%

Unless otherwise specified
† A standard difference >10% is statistically significant ([25])
‡ Evidence within 5 years prior to index
§ Evidence within 3 years prior to index
IQR = Interquartile range; NR = Not recorded

assumption was met. Throughout, small cells (fewer than 6) are suppressed to protect patient privacy. We conducted all analyses using SAS statistical software, version 9.4 (SAS Software, Cary, NC, USA).

RESULTS

We included 13,406 patients (527 C282Y homozygotes and 12,879 patients without *HFE* mutations) from both sources after exclusions ([Figure 1]). C282Y homozygotes were more likely male (58.9% versus 40.4%). They were not substantially more likely to have chronic conditions other than cirrhosis (3.8% versus 0.4%), chronic liver disease (35.4% versus 5.5%), and osteoarthritis (16% versus 10.8%). They were also more likely to have selected health history events (osteoporotic fracture, 2.9% versus 1.2%; pneumonia, 7.0% versus 4.2%) ([Table 2]).

The aHRs of selected outcomes for C282Y homozygotes compared with wild-type participants are summarized in [Table 3]. The median follow-up time was 17.7 years. Liver cancer rates are lower than the UK Biobank study ([10]) and earlier studies ([7]), but cirrhosis rates are similar to previous studies in referred patients ([11],[12],[13]) and much higher than a population-based study from Newfoundland, Canada ([4]).
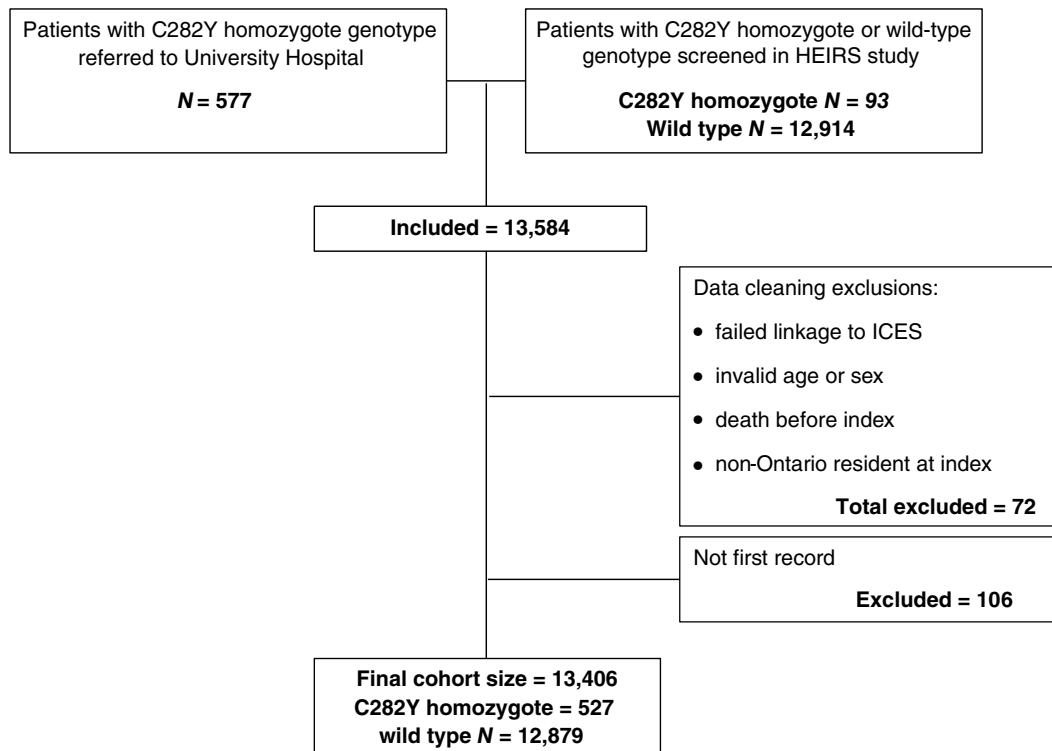
Figure 1: Cohort creation

HEIRS = Hemochromatosis and iron overload study

Table 3: Adjusted hazard of developing selected outcomes during follow-up among C282Y homozygotes, compared with wild-type patients

	Adjusted* hazard ratio (95% CI)			
	HR	Lower CL	Upper CL	*p*-value
All-cause death	1.436	1.182	1.745	0.0003
Liver cancer	8.297	3.97	17.341	<0.001
Knee or hip joint replacement	3.063	2.461	3.811	<0.001
Diabetes	0.844	0.667	1.067	0.1567
Cirrhosis	3.872	3.047	4.920	<0.001
Osteoarthritis	1.719	1.472	2.007	<0.001

* Adjusted for age and sex

After adjusting for age and sex, C282Y homozygotes had a 44% increased hazard of experiencing all-cause death (aHR 1.44 [95% CI 1.18–1.75]). They are over eight times more likely to experience hepatocellular carcinoma (aHR 8.30 [95% CI 3.97–17.34]) (Table 2). C282Y homozygotes are nearly four times more likely to experience cirrhosis during the follow-up (aHR 3.87 [95% CI 3.05–4.92]), over three times more likely to experience hip or knee replacement (aHR 3.06 [95% CI 2.46–3.81]) and are 72% more likely to develop osteoarthritis (aHR 1.72 [95% CI 1.47–2.01]). C282Y homozygotes were not more likely to develop diabetes during follow-up. Outcomes are compared between male and female C282Y homozygotes in Table 4 and between screened and referred patients in Table 5.

DISCUSSION

Since the discovery of the *HFE* gene in 1996 (26), there have been conflicting opinions about the clinical expression of the C282Y mutation of the *HFE* gene1 (4,12–19) and the efficacy of phlebotomy therapy in preventing long-term medical complications. Population studies using genetic testing have identified many non-expressing C282Y homozygotes, most commonly in young women (1). Earlier studies in referred patients may have introduced a referral bias and overestimated the morbidity and mortality (19). In this study, we have included both screened and referred C282Y homozygotes (Table 5) and non-*HFE* controls linked to health administrative data permitting identification of health outcomes over a median observation window of 17.7 years.

Table 4: Outcomes by sex

	Male			Female		
	Homozygote, No. (%) (n = 309)	Wild type, No. (%) (n = 5,203)	χ^2 (p-value)	Homozygote, No. (%) (n = 218)	Wild type, No. (%) (n = 7,676)	χ^2 (p-value)
Death	75 (24.27)	992 (19.07)	4.8 (0.03)	33 (15.14)	992 (12.92)	1.03 (0.31)
Diabetes	48 (15.53)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Cirrhosis	59 (19.09)	965 (18.55)	1.14 (0.28)	24 (11.01)	1,164 (15.16)	2.95 (0.08)
Osteoarthritis	141 (45.63)	229 (4.40)	125.9 (<0.001)	19 (8.72)	291 (3.79)	13.9 (<0.001)
Knee or hip joint replacement	52 (16.83)	1,571 (30.19)	31.5 (<0.001)	98 (44.95)	2,857 (37.22)	5.9 (0.01)

Note: Numbers of patients with hepatocellular carcinoma are too small to perform χ^2 analysis

Table 5: Outcomes in screened and referred C282Y homozygotes

	Screened*, No. (%) (n = 135)	Referred†, No. (%) (n = 392)	χ^2 (p-value)
Death	22 (16.29)	86 (21.94)	1.96 (0.16)
Cirrhosis	19 (14.07)	59 (15.05)	0.07 (0.78)
Knee or hip joint replacement	24 (17.78)	65 (16.58)	0.34 (0.56)

* Screened refers to a C282Y homozygote discovered during a population screening study
† Referred is a C282Y homozygote referred to a specialty clinic by a primary care physician

Liver complications, including cirrhosis and hepatocellular carcinoma, are the most serious and life-threatening and account for most disease-related mortality (4,7,8,10,11,12,27). Early treatment of hemochromatosis by phlebotomy has been demonstrated to prevent cirrhosis and hepatocellular carcinoma (28). Regression of liver fibrosis has also been reported after phlebotomy therapy (28–30), but complete reversal of cirrhosis is uncommon. In the current study, treated C282Y homozygotes had over eight times the risk of hepatocellular carcinoma compared with a large control population without *HFE* mutations. A larger sample of untreated C282Y homozygotes identified by genochip array analysis in the UK Biobank study had a hazard ratio of 15.5

(27). They predicted that 7.2 % of male homozygotes would develop hepatocellular carcinoma by age 75 years. The reduced hazard ratio for hepatocellular carcinoma in our study is not directly comparable, but improvement in fibrosis by phlebotomy therapy is a potential factor. It is possible in both studies that the follow-up period was not extended long enough to capture all eventual liver cancer cases. C282Y homozygotes in the present study had a nearly four times hazard of experiencing cirrhosis during the observation window, which could be a conservative estimate since liver biopsies were not done in all cases. A recent report from Newfoundland reported cirrhosis in 5.8% of C282Y homozygotes (4). Previous studies have suggested that hemochromatosis patients today may have a less severe phenotype than previously reported in earlier studies (31).

C282Y homozygotes were over three times more likely to require hip and knee joint replacements. Similar results were previously reported (32), and iron depletion has not been shown to improve arthropathy of hemochromatosis in most studies (33). C282Y homozygotes were 71% more likely to have evidence of osteoarthritis during the observation window. Both osteoarthritis and rheumatoid arthritis were more common in the UK Biobank study, with odds ratios of 2.01 and 2.23 (10). Arthropathy of hemochromatosis has often been shown to be the presenting complaint in women, and it can have a major deleterious effect on quality of life (34).

Although hemochromatosis was originally called "bronze diabetes," we did not demonstrate an increased rate of diabetes, similar to several previous population-based studies (1,13,27). We previously

demonstrated that most hemochromatosis patients with diabetes have insulin resistance, not low insulin from iron in the pancreas (35). The clinical factors associated with insulin resistance (obesity, metabolic syndrome) are also very common in the control population, which may explain why there is no increased risk of diabetes in the hemochromatosis cohort. Phlebotomy therapy was expected to possibly improve existing symptoms and prevent new symptoms from developing in C282Y homozygotes. This study demonstrates that cirrhosis, hepatocellular carcinoma, joint replacement, and osteoarthritis continue to occur after iron depletion. Hepatocellular carcinoma has rarely been reported in non-cirrhotic hemochromatosis patients (36), but an early diagnosis and treatment prior to the development of cirrhosis is likely the best strategy to prevent cirrhosis and hepatocellular carcinoma.

Limitations

We rely on health administrative data for the detection of outcomes. We used validated case definitions where possible for outcomes, but certain outcomes (in particular, osteoarthritis) have unknown operating characteristics in administrative data, which may result in misclassification. Certain individuals in the referral group have a blackout period of years or decades before starting their observation window. We do not know what happened before, whether it be treatment, or health outcomes, that might affect their behaviour. Data has been previously reported on cohorts of C282Y homozygotes that were untreated (27,37–39) but may not be directly comparable to our patient cohorts.

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