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HFE C282Y and H63D in adults with malignancies in a community medical oncology practice

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Abstract

Background: We sought to compare frequencies of HFE C282Y and H63D alleles and associated odds ratios (OR) in 100 consecutive unrelated white adults with malignancy to those in 318 controls.

Methods: Data from patients with more than one malignancy were analyzed according to each primary malignancy. For the present study, OR ≥ 2.0 or ≤ 0.5 was defined to be increased or decreased, respectively.

Results: There were 110 primary malignancies (52 hematologic neoplasms, 58 carcinomas) in the 100 adult patients. Allele frequencies were similar in patients and controls (C282Y: 0.0850 vs. 0.0896, respectively (OR = 0.9); H63D: 0.1400 vs. 0.1447, respectively (OR = 0.9)). Two patients had hemochromatosis and C282Y homozygosity. With C282Y, increased OR occurred in non-Hodgkin lymphoma, myeloproliferative disorders, and adenocarcinoma of prostate (2.0, 2.8, and 3.4, respectively); OR was decreased in myelodysplasia (0.4). With H63D, increased OR occurred in myeloproliferative disorders and adenocarcinomas of breast and prostate (2.4, 2.0, and 2.0, respectively); OR was decreased in non-Hodgkin lymphoma and B-chronic lymphocytic leukemia (0.5 and 0.4, respectively).

Conclusions: In 100 consecutive adults with malignancy evaluated in a community medical oncology practice, frequencies of HFE C282Y or H63D were similar to those in the general population. This suggests that C282Y or H63D is not associated with an overall increase in cancer risk. However, odds ratios computed in the present study suggest that increased (or decreased) risk for developing specific types of malignancy may be associated with the inheritance of HFE C282Y or H63D. Study of more patients with these specific types of malignancies is needed to determine if trends described herein would remain and yield significant differences.

Background

An increased prevalence of certain types of malignancy

has been reported in putative hemochromatosis heterozygotes characterized by iron phenotype criteria or family

studies [1-4]. However, discovery of the *HFE* gene on Ch6p and two common hemochromatosis-associated *HFE* missense mutations C282Y (exon 4; nt 845G→A) and H63D (exon 2; nt 187 C→G) [5] permits definition of hemochromatosis heterozygosity using molecular criteria. Subsequently, other investigators have reported that the frequency of C282Y in males with childhood acute lymphoblastic leukemia and in women with lung cancer is significantly increased [6,7]. The frequency of H63D was also significantly increased in adults with malignant gliomas [8]. Further, it has been postulated that increased susceptibility to malignancy of persons with C282Y could partly explain age-related reduction in the frequency of C282Y heterozygotes reported in Swedish people, a population with a high C282Y allele frequency [9]. However, it is unknown whether the frequencies of C282Y or H63D are generally increased (or decreased) in persons with diverse types of malignancy, as suggested by phenotype and family studies.

There are also reports of the frequencies of C282Y and H63D in adults with common types of malignancy, including plasma cell myeloma [10], myelodysplasia [11-13], acute non-lymphoblastic leukemia [14], and colon or rectal cancer [10,15], and in women with breast cancer [10]. In patients with many other types of malignancy, however, there are no reports of C282Y or H63D association. We evaluated the frequencies of C282Y and H63D and associated odds ratios (OR) for malignancy in 100 unrelated white adults treated in a community medical oncology and hematology practice in central Alabama and in control subjects from the same geographic area. We compared the present results with those in other reports, and discuss the pertinence of these observations to the association of common *HFE* mutations with malignancy in adults.

Methods

Selection of Study Subjects

The performance of this study was approved by the Institutional Review Board of Brookwood Medical Center. One hundred consecutive unrelated white adults (age \geq 18 years) with malignancy who were treated in a community medical oncology and hematology practice in central Alabama in 1996 – 1997 were included. Patients were referred for surgical adjuvant chemotherapy or management of advanced malignancy; the patients were otherwise unselected. We excluded a) persons whose only primary malignancy was non-melanoma skin cancer; b) persons with chemotherapy- or radiation-associated malignancies; and 3) persons with types of cancer transmitted as simple Mendelian traits. No patient had a diagnosis or family history of hemochromatosis at the time of referral for management of cancer. 318 apparently healthy white persons from the general population were used as

controls for C282Y and H63D frequencies [16,17]; a subset of 142 controls was used for *HFE* genotype frequencies [16].

Clinical and Laboratory Methods

The diagnosis of each primary cancer was established with histology; flow cytometry, chromosome analysis, *in vitro* demonstration of erythropoietin-independent colony growth, or *bcr/abl* oncogene analysis were also used, as appropriate. The presumptive diagnosis of hemochromatosis was based on persistent transferrin saturation ($>60\%$ for men and $>55\%$ for women) [16]. Iron overload was defined as otherwise unexplained elevation of serum ferritin concentration (>300 ng/mL in men, >200 ng/mL in women), 3+ or 4+ intrahepatocytic iron visualized by Perls' acid ferrocyanide staining, or hepatic iron index ≥ 1.9 [18-20]. Testing for C282Y and H63D using genomic DNA was performed as previously described; absence of detectable C282Y or H63D was defined as wt (wild type) [15,16]. Testing for other *HFE* missense mutations was not performed because these are uncommon in white persons in central Alabama [17].

Literature Search

A computerized and manual search was performed to identify reports of case series of persons with malignancies in whom *HFE* mutation analysis had been performed.

Statistical Considerations

The present data set consisted of observations on 100 persons who collectively had 110 primary malignancies; data on non-melanoma skin cancer that occurred in the present patients were not evaluated. Data from persons with more than one primary malignancy were categorized for analysis according to each primary malignancy. Descriptive data are presented as enumerations, percentages, or frequencies. C282Y or H63D frequencies and *HFE* genotype frequencies in patients with malignancy were compared with those in control subjects using chi-square analysis or Fisher's exact test (when a number in a cell was <5) [21]. A value of $p < 0.05$ was defined as significant. Odds ratios (OR) were computed as previously described [22]; OR were not calculated in malignancy categories in which C282Y or H63D were not detected. For the present study, we defined an OR of ≤ 0.5 or ≥ 2.0 to be decreased or increased, respectively.

Results

General Characteristics of Patients, Malignancies, and Control Subjects

In patients with malignancies, there were 50 men and 50 women. The average age at first diagnosis of malignancy was 64 ± 14 years (range 20 – 96 years). Two patients were diagnosed to have hemochromatosis associated with C282Y homozygosity after diagnosis of malignancy.

Table 1: HFE C282Y and H63D Allele Frequencies in 50 Adults with 52 Hematologic Malignancies.*

Classification of Malignancy (no. of cases) †	C282Y	Odds Ratio (value of p)	H63D	Odds Ratio (value of p)
B-cell non-Hodgkin lymphoma (12)	0.1667	2.0 (0.3461)	0.0833	0.5 (0.5848)
B-cell chronic lymphocytic leukemia (9)	0.0555	0.6 (0.9355)	0.0555	0.4 (0.4957)
Plasma cell myeloma (6)	0.0833	0.9 (0.7398)	0	-(0.8538)
Myelodysplasia (13)	0.0385	0.4 (0.6331)	0.1923	1.4 (0.6582)
Myeloproliferative disorders (7)	0.2143	2.8 (0.2597)	0.2857	2.4 (0.2755)
Acute Leukemia (5)	0.1000	1.1 (0.6579)	0	-(0.9565)

* Frequencies of C282Y and H63D were compared to those in 318 controls; odds ratios were not calculated in categories in which C282Y or H63D alleles were not detected. † B-cell non-Hodgkin lymphoma included high, intermediate, and low histologic grades in two, four, and six cases, respectively. B-cell chronic lymphocytic leukemia included one case of hairy cell leukemia. Plasma cell myeloma was IgG-specific in five cases and IgA-specific in one case. Myelodysplasia included eleven cases of refractory anemia (nine with ringed sideroblasts), and two cases of refractory anemia with excess blasts in transformation. Myeloproliferative disorders included six cases of polycythemia rubra vera and one case of Ph-positive chronic myelogenous leukemia. Among the six patients who had polycythemia rubra vera, two were heterozygous for C282Y, one was a compound C282Y/H63D heterozygote, one was homozygous for H63D, and two did not have C282Y or H63D. The one patient with Ph-positive chronic myelogenous leukemia was heterozygous for H63D. There were three cases of acute non-lymphoblastic leukemia and two cases of acute lymphoblastic leukemia (1 T-cell, 1 B-cell). One man had both B-cell chronic lymphocytic leukemia and plasma cell myeloma, one man had B-cell chronic lymphocytic leukemia and non-small cell carcinoma of the lung, and one man had B-cell non-Hodgkin lymphoma, adenocarcinoma of the rectum, and adenocarcinoma of the kidney. One woman had polycythemia rubra vera and non-Hodgkin lymphoma.

There were 110 primary malignancies. Each of ninety-one patients had one primary malignancy, and nine persons had two or more primary malignancies. There were 52 hematologic malignancies, including 27 B-cell neoplasms and 25 cases of myelodysplasia, myeloproliferative disorders, or acute leukemia (Table 1). There were 58 diagnoses of carcinoma; 37 were adenocarcinomas of the female breast, adenocarcinomas of the colon or rectum, or non-small cell carcinomas of the lung (Table 2). Among controls, there were 158 men and 160 women. Their average age at the time of HFE mutation analysis was 52 ± 15 years (range 18 – 86 years).

Frequencies of HFE C282Y and H63D Alleles and HFE Genotypes

The frequencies of C282Y were 0.0850 in 100 patients and 0.0896 in 318 controls ($p = 0.9565$; OR = 0.9). The frequencies of H63D were 0.1400 in 100 patients and 0.1447 in 318 controls ($p = 0.9663$; OR = 0.9). In patients with malignancy, allele frequencies were similar in men (C282Y 0.9000; H63D 0.14000) and women (C282Y 0.8000; H63D 0.1400). The HFE genotype frequencies in patients and in control subjects were: C282Y/C282Y: 0.0200, patients and 0.0031 controls ($p = 0.2873$, OR = 6.5); H63D/H63D 0.0300 patients and 0.0315 controls ($p = 0.7970$, OR = 0.9); C282Y/H63D: 0.0500 patients and 0.0535 controls ($p = 0.9029$, OR = 0.9); C282Y/wt: 0.0800 patients and 0.1195 controls ($p = 0.3589$, OR = 0.6); H63D/wt: 0.1700 patients and 0.1730 controls ($p = 0.9355$, OR = 0.9); and wt/wt: 0.6500 patients and 0.6195 controls ($p = 0.6658$, OR = 1.1).

Each of ten patients had two detectable HFE mutations (HFE genotypes C282Y/C282Y, C282Y/H63D, or H63D/

H63D). A man with Burkitt lymphoma and a woman with adenocarcinoma of the tail of the pancreas had the genotype C282Y/C282Y; both had elevated serum transferrin saturation values and iron overload. A hemochromatosis phenotype or iron overload was not detected in other patients. Five patients were C282Y/H63D compound heterozygotes (1 patient each with B-cell chronic lymphocytic leukemia, adenocarcinoma of the colon, non-small cell carcinoma of the lung, and adenocarcinoma of the prostate, and another patient with polycythemia rubra vera and non-Hodgkin lymphoma). Three patients had the genotype H63D/H63D (1 patient each with polycythemia rubra vera, myelodysplasia, and adenocarcinoma of the breast).

Frequencies of HFE C282Y and H63D Alleles and HFE Genotypes in Patients with Two or More Malignancies

In the nine patients, C282Y frequency was 0.0555 ($p = 0.9355$, OR = 0.6) and H63D frequency was 0.1667 ($p = 0.9385$, OR = 1.2). Their HFE genotypes were C282Y/H63D ($n = 1$), H63D/wt ($n = 2$), and wt/wt ($n = 6$).

Frequencies of HFE C282Y and H63D Alleles in Subgroups of Malignancies

In 50 patients with hematologic malignancies, the frequency of C282Y was 0.1000 and the frequency of H63D was 0.1100; these are similar to the corresponding frequencies in control subjects (0.0896 and 0.1447, respectively). A subgroup of 27 patients had B-cell malignancies (non-Hodgkin lymphoma, chronic lymphocytic leukemia, plasma cell myeloma, or B-cell acute lymphoblastic leukemia). The frequency of C282Y in the B-cell malignancies subgroup was similar to that in control subjects (0.1111 vs. 0.0896; $p = 0.7396$, OR = 1.3). However, the

Table 2: HFE C282Y and H63D Allele Frequencies in 54 Adults with 58 Carcinomas.*

Histology, Primary Site of Malignancy (no. of cases) †	C282Y	Odds Ratio (value of p)	H63D	Odds Ratio (value of p)
Adenocarcinoma of breast (18)	0.0278	0.3 (0.3269)	0.2500	2.0 (0.1386)
Adenocarcinoma of colon or rectum (12)	0.0417	0.4 (0.6445)	0.1250	0.8 (0.9725)
Non-small cell carcinoma of lung (7)	0.1429	1.7 (0.7360)	0	-(0.7631)
Adenocarcinoma of prostate (4)	0.2500	3.4 (0.3230)	0.2500	2.0 (0.6602)
Adenocarcinoma of undetermined primary site (4)	0	-(0.7841)	0	-(0.7267)
Hepatocellular carcinoma (4)	0.1250	1.5 (0.7841)	0.1250	0.8 (0.7267)
Adenocarcinoma of kidney (3)	0	-(0.8695)	0	-(0.6668)
Adenocarcinoma of stomach (3)	0	-(0.8695)	0.1667	1.2 (0.6668)
Miscellaneous (3)	0.3333	‡	0.1667	‡

* Frequencies of C282Y and H63D were compared to those in 318 controls; odds ratios were not calculated in categories in which C282Y or H63D alleles were not detected. † All cases of adenocarcinoma of the breast occurred in women. Two women had both adenocarcinoma of the breast and B-chronic lymphocytic leukemia; two other women had both adenocarcinoma of the breast and adenocarcinoma of the colon or rectum. One man had both B-chronic lymphocytic leukemia and non-small cell carcinoma of the lung, one man had non-small cell carcinoma of the lung and adenocarcinoma of the stomach, and a third man had B-cell non-Hodgkin lymphoma, adenocarcinoma of the rectum, and adenocarcinoma of the kidney. None of the cases of hepatocellular carcinoma were associated with iron overload. Miscellaneous category includes one case each of primary peritoneal adenocarcinoma, adenocarcinoma of the pancreas, and primary cutaneous melanoma. ‡ OR and values of p are not reported for this subgroup because it is composed of a heterogeneous group of malignancies.

frequency of H63D in this subgroup was lower than that in controls (0.0556 vs. 0.1447 controls; $p = 0.1055$, OR = 0.4). 23 patients had myeloid malignancies (myelodysplasia, myeloproliferative disorders, or acute non-lymphoblastic leukemia). In this subgroup, the frequencies of C282Y (0.1042; 5/48) ($p = 0.8888$, OR = 1.2) and H63D (0.1875; 9/48) ($p = 0.5512$, OR = 1.4) were similar to the corresponding frequencies in control subjects. C282Y and H63D frequencies in individual diagnostic categories are displayed in Table 1. In the six patients who had polycythemia rubra vera (Table 1), HFE allele frequencies were 0.2500 for C282Y ($p = 0.1817$, OR = 3.4) and H63D ($p = 0.5031$, OR = 2.0), respectively.

The frequencies of C282Y and H63D in 54 patients with carcinomas were 0.0818 and 0.1455, respectively; these values are similar to the corresponding frequencies in control subjects. In 18 women with adenocarcinoma of the breast, the OR associated with C282Y was 0.3, and the OR associated with H63D was 2.0 (Table 2). In 12 patients with adenocarcinoma of the colon or rectum, the frequencies of C282Y and H63D were lower than corresponding values in control subjects, but these differences were not statistically significant (Table 2). In patients with carcinomas of other primary sites, C282Y and H63D frequency values were similar to respective frequencies in control subjects (Table 2).

Discussion

The present 100 consecutive adult patients with malignancy were 12 years older than the 318 control subjects, on average, yet the corresponding frequencies of HFE C282Y and in the patients and in control subjects were similar. This is consistent with most studies that demon-

strate that the frequency of the C282Y allele is constant or nearly so at all ages [23,24]. The corresponding frequencies of HFE C282Y and H63D in the patients and controls were also similar. Overall, the occurrence of C282Y or H63D was not associated with an increased (or decreased) OR for malignancy in the present study. Nonetheless, the present observations do not exclude the possibility that an increased (or decreased) risk of developing specific types of malignancy may be associated with common HFE mutations.

In the present combined B-cell neoplasm cases, there was a lower OR in patients with H63D. This may have been attributable largely to Non-Hodgkin lymphoma cases, in which we observed an increased OR associated with C282Y and a decreased OR with H63D. There were no cases of Hodgkin lymphoma in the present series, although there was no increase in frequency of C282Y in 121 persons with Hodgkin lymphoma in Wales [25]. In the present patients with B-chronic lymphocytic leukemia, OR associated with C282Y and H63D were not increased or decreased; we are unaware of other reports of HFE allele frequency in B-chronic lymphocytic leukemia. In the present patients with myeloma, the C282Y frequency was similar to that in control subjects, consistent with observations in Swedish and Finnish patients with myeloma [10,26,27].

HFE allele frequencies in the present patients with myelodysplasia were similar to those in control subjects, consistent with previous reports [11-13,27]. In contrast, C282Y and H63D frequencies were greater in Hungarian patients with myelodysplasia than in corresponding control subjects in whom HFE mutation frequencies are lower than

those typically observed in western regions of Europe [28,29]. In the seven present patients with a myeloproliferative disorder (six of whom had polycythemia rubra vera), C282Y and H63D were associated with increased OR. In 68 patients in Finland with chronic myelogenous leukemia, essential thrombocythemia or polycythemia rubra vera, the frequencies of C282Y and H63D were similar to those of population controls [27]. In the present series, C282Y and H63D frequencies and associated OR were not significantly different in patients with acute non-lymphoblastic leukemia than in control subjects, consistent with previous reports [14]. Further, these data are in agreement with previous reports that post-chemotherapy iron overload in adults with acute leukemia is not typically attributable to the inheritance of common *HFE* alleles [30,31].

In Swedish and Australian patients with sporadic colon or rectal cancer, C282Y and H63D allele frequencies were similar to those in corresponding control subjects, and the relative risks for cancer were not increased (or decreased) [10,15]. The present results are in agreement with these reports. In contrast, a case-control study of North Carolina subjects indicates that the OR of the occurrence of colon cancer in persons with C282Y or H63D was increased [31]. The frequencies of C282Y and H63D were similar in Swedish women with breast cancer and in control subjects, and neither allele was associated with increased (or decreased) risk for breast cancer [10]. In the present study, however, the occurrence of H63D was associated with an increased OR. Observations in the small number of lung cancer cases in the present study suggest that more evaluation of the possible relationship of C282Y and H63D to this common form of malignancy is needed. In a recent study, the prevalence of C282Y in women with lung cancer was significantly greater than that in men with lung cancer or in control subjects with head and neck cancer [7]. In four men with prostate cancer in the present study, occurrence of C282Y and H63D were associated with increased OR, but we were unable to identify reports of other case series of this common malignancy.

In hemochromatosis patients, the prevalence of non-hepatoma malignancies was higher than normal in some studies [33-40] but not in others [41-43]. The increased prevalence of C282Y homozygotes in the present patients could be attributed to a greater likelihood to develop non-hepatoma malignancy in persons with hemochromatosis, or to an ascertainment bias for malignancy and hemochromatosis in patients referred to hematology and medical oncology practices. The prevalence of primary liver cancer is also increased in putative hemochromatosis homozygotes identified by phenotype, in hemochromatosis associated with C282Y homozygosity, and in persons with C282Y who do not have hepatic cir-

rhosis [39,44,45]. In the present study, however, the two patients with hemochromatosis and C282Y homozygosity did not have primary liver cancer. The OR associated with C282Y and H63D in four present patients with primary liver cancer were not increased or decreased. This is consistent with previous observations that the frequency of C282Y and H63D in persons with hepatocellular carcinoma is similar to that in normal control subjects [46].

There are uncertainties about the conclusions of the present and related studies. The postulate that there could be an increased incidence of malignancy in persons with common *HFE* mutations is supported by some reports [6,25,47]. However, some of the present results suggest that the OR to develop other types of malignancy may be decreased, although there were few patients in each of several diagnosis categories for analysis. We did not study adults with primary central nervous system malignancies, primary gynecologic malignancies (e.g., carcinomas of the endometrium, ovary, or cervix), urothelial malignancies, soft-part sarcomas, primary bone cancers, or Hodgkin disease. Some of these malignancies are uncommon, and some patients are typically not referred to medical oncology and hematology practices. None of the present patients were children. With few exceptions [6,25,47], the relationship of common *HFE* mutations to neoplasia in childhood has not been reported. It is possible that patients with earlier stages of carcinoma at diagnosis may have different frequencies of C282Y or H63D than persons with similar malignancies that were more advanced at diagnosis. However, this is unlikely in patients with colon and rectal cancer [15]. There is variability in the frequency of *HFE* alleles and *HFE* genotypes in persons with hemochromatosis in different subpopulations [48-50]. For example, the reported frequency of C282Y in population control subjects in studies of malignancy varies from 0.0140 [8] to 0.0850 (present study) [8,10,15]. The allele frequencies of C282Y and H63D in the central Alabama whites are relatively great (0.0896 and 0.1447, respectively) [16,17]. Thus, a positive or negative association of malignancy with *HFE* genotype in a population in which the frequency of *HFE* mutations is relatively high may be due to chance association with other genetic or environmental factors. Contrariwise, a significantly increased relative risk of malignancy may be more readily demonstrated in populations in which C282Y or H63D frequencies are lower [8,29]. Thus, patient age at diagnosis, type of malignancy, expectations of medical management, stage at diagnosis, and race, ethnicity, and population of origin are important potential sources of variability which must be considered in interpreting results of the present and similar reports, and in designing future studies.

It is difficult to compare reports of the prevalence of malignancy in cohorts of putative hemochromatosis heterozygotes characterized by phenotype criteria and family relationships [1-4] to those performed using *HFE* mutation testing. In epidemiology studies that use data modeling techniques, iron phenotype data are typically adjusted for common disease-related variables that cause abnormal serum iron concentrations, transferrin saturation values, or serum ferritin concentrations values, thus excluding many study subjects from final analysis [2,51]. Phenotypes of hemochromatosis heterozygotes ascertained in HLA-based family studies or in *HFE*-based studies are quite variable [38,52]. Thus, using phenotype criteria to identify C282Y or H63D heterozygotes is often unreliable. In some studies, presumed hemochromatosis heterozygotes were ascertained only by self-reported kinship to a putative hemochromatosis homozygote in questionnaire surveys [53]. In family-based studies in which *HFE* mutation or other DNA-based testing is not used, non-paternity is an additional source of error (1.0 – 1.4% non-paternity in American Caucasians) [54,55].

The basis for the putative association of common *HFE* mutations and malignancy is unknown. Some C282Y heterozygotes and many persons with hemochromatosis, regardless of *HFE* genotype, have increased body iron content [1,16,52]. Excess iron could act as a carcinogen due to oxidative stress [44], activate oncogenes [56], impair cytotoxic activity of macrophages [56,57], promote activation, growth, or proliferation of malignant cells [44,59], or induce modifications in the immune system [44]. *HFE* C282Y may alter iron delivery to tumor cells via transferrin receptor and thus affect their growth rate [60]. Inheritance of the transferrin receptor allele S142G (Ch3) was associated with an increased OR for development of myeloma, colorectal cancer, or breast cancer in adults who also had *HFE* C282Y [10]. Common *HFE* mutations may be markers linked to other alleles that promote (or inhibit) neoplasia. For example, Ch6p haplotypes characterized by HLA-A3, B7 are associated with inheritance of *HFE* C282Y [16,61]. Similarly, HLA-A3 and B7 have been associated with increased risks to develop certain types of malignancy [62-64]. In childhood acute lymphoblastic leukemia, the frequency of C282Y is significantly increased in males [6], but the Ch6p alleles HLA-DRB4 (-DR53) and tumor necrosis factor₂-alpha have an even greater positive association with childhood acute lymphoblastic leukemia than does C282Y [24,47]. These associations and the lack of a gene-dosage effect suggest that C282Y in childhood acute lymphoblastic leukemia may be a marker linked to another Ch6p gene involved in leukemia susceptibility [23].

Conclusions

In 100 consecutive adults with malignancy evaluated in a community medical oncology practice, frequencies of *HFE* C282Y or H63D were similar to those in the general population. This suggests that C282Y or H63D is not associated with an overall increase in cancer risk. However, odds ratios computed in the present study suggest that increased (or decreased) risk for developing specific types of malignancy may be associated with the inheritance of *HFE* C282Y or H63D. Study of more patients with these specific types of malignancies is needed to determine if trends described herein would remain and yield significant differences.

Competing Interests

None declared.

Authors Contributions

JB evaluated and managed patients, conceived the study, participated in data collection and statistical evaluation, and wrote part of the manuscript. LB evaluated and managed patients, and participated in data collection. RA participated in laboratory evaluation of the patients and in statistical evaluation of data, and wrote part of the manuscript. All authors approved the final version of the manuscript.

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