U.S. Preventive Services Task Force (USPSTF)

Screening for Hereditary Hemochromatosis

Systematic Review

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Contents

Abstract
Introduction
Background
Methods
Data Synthesis
Discussion
Conclusions
References
Notes
Copyright and Source Information

Abstract

Background: The U.S. Preventive Services Task Force (USPSTF) has not previously considered screening for hereditary hemochromatosis for a recommendation as a clinical preventive service for primary care clinicians.

Purpose: To conduct a focused systematic review of hereditary hemochromatosis screening relating to 2 USPSTF criteria, the burden of suffering and the potential effectiveness of a preventive intervention, to determine whether evidence is sufficient for a USPSTF recommendation.

Data Sources: MEDLINE®, CINAHL, and Cochrane Library databases from 1966 through February 2005. The authors supplemented literature searches with source materials from experts in the field and the bibliographies of key reviews and included studies.

Study Selection: Studies were retrieved to answer 3 key questions:

1. What is the risk for developing clinical hemochromatosis among those with a homozygous C282Y genotype?
2. Does earlier therapeutic phlebotomy of individuals with primary iron overload due to hereditary hemochromatosis reduce morbidity and mortality compared with treatment after diagnosis in routine clinical care?
3. Are there groups at increased risk for developing hereditary hemochromatosis that can be readily identified before genetic screening?

The authors critically appraised studies using quality criteria specific to their design.

Data Extraction: The authors abstracted all studies into evidence tables using condition definitions and diagnostic criteria.

Data Synthesis: Data were insufficient to define a very precise estimate of penetrance. Available data suggest that up to 38% to 50% of C282Y homozygotes may develop iron overload, with up to 10% to 33% eventually developing hemochromatosis-associated morbidity. Prevalence of C282Y homozygosity is higher in family members of probands and other high-risk patient groups defined by signs, symptoms, and phenotypic screening.

Limitations: This review considered genetic screening for *HFE*-related hereditary hemochromatosis in C282Y homozygotes only. Available research is limited, is based solely on observational designs, and is plagued by poor or inconsistent reporting.

Conclusions: Research addressing genetic screening for hereditary hemochromatosis remains insufficient to confidently project the impact of, or estimate the benefit from, widespread or high-risk genetic screening for hereditary hemochromatosis.

Return to Contents

Introduction

The U.S. Preventive Services Task Force (USPSTF) has not previously considered screening for hereditary hemochromatosis for a recommendation as a clinical preventive service for primary care clinicians. We examined key questions to assess hemochromatosis penetrance in C282Y homozygotes (key question 1), address health outcomes of therapeutic phlebotomy (key question 2), and examine the possibility of targeted genetic screening (key question 3). Key questions for this focused systematic review were limited to addressing critical evidence gaps in order for the USPSTF to recommend screening,[1,2] and were applied using strict and consistent definitions of disease, which are described in more detail below.

Return to Contents

Background

Condition Definition

Hemochromatosis was originally thought to be a rare idiopathic disorder characterized by end-stage disease (cirrhosis, diabetes, and bronzed skin) but is now recognized as having a hereditary component due to an autosomal recessive inherited disorder of iron metabolism.[3]

In hemochromatosis, body iron accumulates and can lead to iron overload.[4] In iron overload, excess iron is deposited in the liver, pancreas, heart, joints, and endocrine glands, resulting in tissue damage that can lead to disease conditions (such as cirrhosis, diabetes, heart failure, arthropathy, and impotence).[4-6] Iron overload can be primary (as in hereditary hemochromatosis) or secondary (for example, due to anemias with inefficient erythropoiesis or repeated blood transfusions).[7]

In 1996, 2 base-pair alterations, termed C282Y and H63D, of the *HFE* gene on the region of HLA-A on chromosome 6 were identified in hereditary hemochromatosis.[8] C282Y homozygosity is now recognized as the most common genotype in hereditary hemochromatosis.[9] Estimates are that 82% to 90% of cases of hereditary hemochromatosis among white persons occur in C282Y/C282Y homozygotes.[10] The other 10% to 18% of cases appear to be due to environmental factors or other genotypes. While other *HFE*-related and non-*HFE*-related genetic mutations are associated with hereditary hemochromatosis in a small number of cases,[4] other genotypes do not appear to be as strongly associated with hereditary hemochromatosis.[3,9]

HFE mutations are fairly common in the United States, with 1 in 10 white persons heterozygous for the *HFE* C282Y mutation (carriers) and 4.4 homozygotes per 1000.[4,6] The frequency of C282Y homozygosity is much lower among Hispanic persons (0.27 in 1000), Asian Americans (<.0.001 per 1000), Pacific Islanders (0.12 per 1000), and black persons (0.14 per 1000).[11]

The availability of genotyping has permitted identifying persons who have the susceptible genotype but have little or no evidence of disease. Thus, individuals homozygous for the C282Y genotype can be characterized in 1 of 4 general stages: genetic predisposition without any other abnormality; iron overload without symptoms; iron overload with early symptoms; and iron overload with organ damage, especially cirrhosis.[4] Clinically recognized hereditary hemochromatosis is twice as common in males and occurs predominantly in white populations.[12]

While the natural history is not well understood, the condition appears to have a long latent period, with wide individual variation in biochemical expression.[13] This is because iron accumulation and disease expression are modified by environmental factors, such as blood loss from menstruation or donation, alcohol intake, diet, and comorbid disease (for example, viral hepatitis).[14,15] If symptomatic organ involvement develops, it generally occurs in mid-life with nonspecific signs and symptoms (such as unexplained fatigue, joint pain, and abdominal pain).[14] Age of onset is delayed in females,[16] perhaps because of blood loss

through menstruation.[3] The liver is the first target organ thought to be affected by iron accumulation.[17] and is central to both diagnosis and prognosis.[13]

While a clinical diagnosis is based on serum iron studies and clinical evaluation, documented iron overload relies on 1 of 2 methods: quantitative phlebotomy with calculation of the amount of iron removed, or liver biopsy with determination of quantitative hepatic iron.[18] Although liver biopsy was once essential to the diagnosis, it is currently used more as a prognostic tool.[19] While hepatic iron concentration greater than 283 µmol/g (reference range, 0 to 35 µmol/g) is associated with cirrhosis in C282Y homozygotes,[20] many patients with much higher levels do not have cirrhosis.[13] Even in the absence of systemic iron overload, iron accumulates when the liver is inflamed or cirrhosed because of other causes (such as alcoholic steatohepatitis, transfusion and chronic hemolytic disorders, or chronic viral hepatitis).[21]

Cirrhosis is a late-stage disease development and has been reported to shorten life expectancy.[22-25] Cirrhosis is also a risk factor for hepatocellular carcinoma.[13] and typically occurs between the ages of 40 and 60 years.[6] Cirrhosis prevention would be a major goal of screening and treatment.[26]

Prevalence and Burden of Disease

Estimates of the general population prevalence of hemochromatosis vary because of the long preclinical period and lack of a consistent "case" definition. The prevalence of cases of hemochromatosis defined biochemically (elevated serum iron indices) will be higher than the prevalence of cases based on documented iron overload, with or without clinical signs and symptoms. The prevalence will be lowest for cases based on diagnosed disease (cirrhosis, diabetes).[27] Experts have recommended defining iron overload as distinct from hemochromatosis,[4] and this provides an objective, although not universally accepted, standard for "early disease" based on documented increases in body iron stores.[27]

On the basis of clinically diagnosed hemochromatosis or hemochromatosis-compatible disease, 79,850 hemochromatosis-associated hospitalizations (2.3 per 100,000 residents) were projected in the United States over 18 years (1979 to 1997), although annual rates could not be reliably calculated.[28] Of 29 million deaths from 1979 to 1992, 4858 (0.017%) were consistent with hemochromatosis as an underlying cause.[12] Age-adjusted mortality rates for hemochromatosis-consistent deaths increased from 1.2 per million in 1979 to 1.8 per million in 1992. These rates were about twice as high in males as in females and in white persons as in nonwhite persons. Both of these estimates of the burden of disease

suggest a disease prevalence much lower than the prevalence of associated genetic mutations, which has fueled the debate about disease penetrance.

While these statistics are probably underestimates, primarily because of underdiagnosis,[29] the extent of this underestimation is not clear. The prevalence of hemochromatosis-attributable morbid conditions (such as cirrhosis, diabetes, arthralgias, and fatigue or other symptoms) has been proposed as an estimate of the burden due to undiagnosed disease, particularly since diagnosis may commonly be delayed as a result of the nonspecific nature of hemochromatosis-related signs and symptoms.[30] Since these signs and symptoms are also prevalent and nonspecific, however, relevant evidence must establish their prevalence due to iron overload, or their excess prevalence in association with iron overload compared with controls.

In a previous study, 297 middle-aged patients with previously undetected hereditary hemochromatosis (homozygous for C282Y) had a higher prevalence of diagnosed osteoarthritis, knee symptoms, hypothyroidism, and use of antihypertensive or thyroid replacement medications than sex- and age-specific controls.[31] However, general health, mental health, and 52 other questionnaire-based and clinical examination-based measures of cardiovascular, respiratory, and liver diseases were not statistically different between case-patients and controls.

In another cross-sectional comparison of 124 C282Y screening-detected adult homozygotes with 22,394 wild-type/wild-type genotypic controls, common symptoms (chronic fatigue, joint symptoms, impotence, and limited general health) and signs (diabetes) were no more frequent in C282Y homozygotes than controls.[32] While the relative risk for physician-diagnosed liver problems or hepatitis was increased (relative risk, 2.1 [95% CI, 1.1 to 4.0]), the proportion of C282Y homozygotes with liver problems was modest (10%).

Similarly, in the Hemochromatosis and Iron Overload Screening (HEIRS) study, C282Y homozygotes had an increased odds of self-reported liver disease (odds ratio, 3.28 [CI, 1.49 to 7.22]) compared with wild-type controls. Almost one fourth, however, were not identified by screening.[11] Clearly, the prevalence of hemochromatosis-attributable morbid conditions is not a simple, reliable way to estimate the disease burden associated with hemochromatosis.

Rationale for Population Screening

Screening for hemochromatosis or iron overload is theoretically attractive and has been widely discussed over the past 10 to 15 years, with renewed interest and a focus on hereditary hemochromatosis since the discovery of the *HFE* mutations.[4,33-36] Although

hereditary hemochromatosis appears to be ideal for population screening [7,16,37-39] and for a "new paradigm for genetics and public health",[34] inadequacies in the evidence supporting genetic screening for hereditary hemochromatosis have precluded widespread support for population-based screening.[4,9,34,40]

Aims of Focused Systematic Review

This review addresses 2 major uncertainties in the evidence: "How much disease is actually caused by *HFE* mutations?" and "Does therapeutic phlebotomy treatment, initiated through earlier identification of those with hereditary hemochromatosis, lead to better outcomes?" We also considered evidence for high-risk (as opposed to general population) screening.

Return to Contents

Methods

We focused on hereditary *HFE*-associated hemochromatosis due to C282Y homozygosity in persons of northern European descent, which is the most prevalent form of hereditary hemochromatosis in the United States. Other *HFE* and non-*HFE* genetic mutations are much rarer causes of hemochromatosis,[41] and data for their disease association are more sparse than those for C282Y homozygosity.[9]

Key Questions

We developed 3 explicit questions with supporting definitions (Appendix Table 2), in conjunction with USPSTF leads and Agency for Healthcare Research and Quality (AHRQ) staff.

- Key question 1: What is the risk for developing clinical hemochromatosis among those with a homozygous C282Y genotype?
- Key question 2: Does earlier therapeutic phlebotomy of individuals with primary iron overload due to hereditary hemochromatosis reduce morbidity and mortality compared with treatment after diagnosis in routine clinical care?
- Key question 3: Are there groups at increased risk for developing hereditary hemochromatosis that can be readily identified before genetic screening?

Data Sources

We developed literature search strategies and terms for each key question (Appendix Table

1) and conducted 4 separate literature searches (for key questions 1, 2, and 3 and for background) in the MEDLINE®, CINAHL, and Cochrane Library databases from 1966 through February 2005. Literature searches were supplemented with source material from experts in the field and by examining the bibliographies of included studies. A single investigator reviewed abstracts, and a second reviewer independently reviewed all excluded abstracts. Interreviewer discrepancies were resolved by consensus.

Study Selection

Using inclusion criteria developed for each key question (described in Appendix Table 2), we reviewed 1,886 abstracts for inclusion in all key questions (Figure, 24 KB). Literature searches were focused for each key question but were reviewed with all key questions in mind. We reviewed 134 full-text articles for key question 1, 69 articles for key question 2, and 55 articles for key question 3. Two investigators rated all included articles for quality, as well as those excluded for quality-related reasons, using the USPSTF criteria (Appendix Table 3). Excluded articles are listed in Appendix Tables 4 to 6.

Data Extraction and Quality Assessment

To overcome the inconsistent uses of terminology in the literature, we adopted the set of terms in the Appendix for extracting data from studies into tables in a consistent format. We also established *a priori* screening and diagnostic criteria for elevated iron measures and iron overload due to hereditary hemochromatosis to guide our review and to establish comparability between studies (Table 1). Data were abstracted into evidence tables by a single reviewer and checked by a second reviewer (Appendix Tables 7 to 10).

We critically appraised studies according to USPSTF methods.[67] using quality criteria specific to their design (Appendix Table 3). To augment criteria provided for nonrandomized studies of treatment effectiveness, we added criteria from the Cochrane Non-Randomised Studies Methods Group.[68] We eliminated any case series or nonrandomized comparative treatment study that used a nonsystematic method of case accrual. We critically evaluated reported results, including the comparability of constructed comparison groups, concerning whether confounding factors (age, sex, alcohol intake, population prevalence of C282Y homozygosity, and comorbid liver disease) and secular trends in disease diagnosis and medical care were adequately considered. We eliminated studies with possible serious biases.

Data Synthesis

Studies were extremely heterogeneous and could not be easily synthesized quantitatively.

To evaluate whether our review identified adequate data to create one or more outcomes tables for illustrating the expected yield from screening, we used an approach adapted from a previous report.[35] We considered whether there were adequate data for genetic screening of 2 different screening populations (general population and family-based). Insufficient data were available to create a reliable outcomes table for either screening approach since very few studies reported results for all required measures (genotype, iron measures, iron overload, and disease) among screening study participants, resulting in extremely small numbers for within-study morbidity estimates. Therefore, we summarized screening data in tables, as described later.

We selected data from studies that met minimum a priori criteria for 3 variables:

1. Screening positive for elevated iron measures
2. Documented iron overload.
3. Morbidity due to clinical hemochromatosis.

For iron overload and morbidity, we calculated 2 proportions (selected and all). Among patients selected for further evaluation, we reported the proportion of positives among those who were actually tested for iron overload or morbidity (maximum penetrance) and, for all, the proportion who screened positive among all those evaluated at the first screening step (minimum penetrance). We evaluated whether results were similar enough to combine across studies and, when they were, we quantitatively combined study results for each variable to generate a single point estimate for that variable.

We reported a range of results for any variable for which individual study results were too different to be meaningfully combined. We did not include individual study results with 10 or fewer patients in the denominator to define a range, but we did include these results if they could be combined with other results in a single variable estimate. Study results were reported as raw numbers for denominators of 10 or fewer.

Role of the Funding Source

This research was funded by AHRQ under a contract to support the work of the USPSTF. The USPSTF members participated in the initial design and reviewed interim results and the final evidence review. Although AHRQ had no role in the study design, data collection, or synthesis, AHRQ staff reviewed interim and final evidence reports and distributed the initial evidence report for external content review by 7 outside experts, including representatives of professional societies and federal agencies. The subsequently revised systematic review on which this manuscript is based is available at http://www.ahrq.gov/clinic/serfiles.htm.

Return to Contents
Proceed to Next Section

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