Original Article

Eur J Breast Health
DOI: 10.4274/ejbh.galenos.2025.2025-7-1

Hemochromatosis: A Risk Factor for Breast Cancer? Systematic Review and Meta-Analysis

Megane Buttignol[1], Caroline Bouche[1], Manon Chrétien[2], Nicolas Taris[2], Tolga Ozmen[3], Carole Mathelin[1,4,5]

[1]Institut de Cancérologie Strasbourg Europe (ICANS), Strasbourg, France
[2]Unité d'oncogénétique Clinique, ICANS, Strasbourg, France
[3]Massachusetts General Hospital, Department of Surgery, Division of Gastrointestinal and Oncologic Surgery, Massachusetts, USA
[4]National Academy of Surgery, Paris, France
[5]Institut de Génétique et de Biologie Moléculaire et Cellulaire (IGBMC), Illkirch, France

ABSTRACT

Objective: Hereditary hemochromatosis and breast cancer are two major public health problems. The *HFE* gene variants C282Y and H63D, responsible for most cases of hemochromatosis, may contribute to carcinogenesis via iron overload, oxidative stress, and hormonal modulation. The aim of this study was to evaluate the association between *HFE* variants and breast cancer risk and propose a personalized surveillance strategy.

Materials and Methods: A systematic review and a meta-analysis were conducted according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. Eligible studies included case-control and cohort studies reporting breast cancer incidence in women with *HFE* gene C282Y and/or H63D variants. Data were pooled using a random-effects model. Subgroup analyses and meta-regressions explored sources of heterogeneity.

Results: Eight studies comprising 73,981 participants were included, published between 2000 and 2025. Among them, analysis of four revealed a link between hemochromatosis and breast cancer risk. In one study, a link was observed between the *HFE* C282Y allele and higher lymph node involvement, which may suggest an impact of hemochromatosis on tumor progression. By contrast, three studies did not find any link between the two diseases. Our meta-analysis showed a trend toward increased breast cancer risk in carriers of *HFE* variants, particularly C282Y homozygotes (odds ratio = 1.36, 95% confidence interval = 0.75–1.98). Substantial heterogeneity was present (I^2 >50%), but no tested covariates significantly explained this variation. Sensitivity analyses confirmed the robustness of the estimate.

Conclusion: In the absence of randomized trials with mortality endpoints, our findings do not yet justify changes in clinical practice. They nevertheless support prospective studies to assess whether women carrying these pathogenic variants, especially C282Y/C282Y homozygotes, could benefit from adapted breast cancer surveillance, potentially involving more frequent evaluations or advanced imaging to improve early detection.

Keywords: Breast cancer; genetic predisposition; hemochromatosis; iron overload; meta-analysis

Cite this article as: Buttignol M, Bouche C, Chrétien M, Taris N, Ozmen T, Mathelin C. Hemochromatosis: a risk factor for breast cancer? Systematic review and meta-analysis. Eur J Breast Health. [Epub Ahead of Print]

Key Points

- Hereditary hemochromatosis is a common genetic disorder in individuals of European descent, and its main pathogenic variants, C282Y and H63D, may contribute to carcinogenesis through iron overload and oxidative stress.
- This meta-analysis included eight studies and over 53,000 participants to assess the association between *HFE* gene mutations and breast cancer risk.
- Although the pooled analysis did not show a statistically significant association, a consistent trend toward increased breast cancer risk, particularly in C282Y homozygotes, was observed.
- The heterogeneity between studies could not be explained by genotype, zygosity, publication year, or methodological quality, but sensitivity analyses confirmed the robustness of the findings.
- An intensified screening protocols for individuals carrying *HFE* pathogenic variants is proposed, particularly homozygous C282Y carriers. Pending further data, we propose risk-adapted screening for these individuals, which may include more frequent clinical evaluations and imaging, potentially incorporating additional modalities such as ultrasound or breast magnetic resonance imaging.

Corresponding Author:
Carole Mathelin MD; c.mathelin@icans.eu

Received: 04.07.2025
Accepted: 13.08.2025
Epub: 05.09.2025

Introduction

Breast cancer and hereditary hemochromatosis are both relatively common diseases, especially among individuals of European ancestry. Emerging evidence suggests a potential association between the two, with iron overload implicated as a possible contributing factor in breast cancer development. Breast cancer is the most common cancer in women with an estimated 2,296,840 new cases worldwide in 2022. It also remains the leading cause of cancer-related death in women, accounting for roughly 666,103 deaths every year (1). Breast cancer incidence and mortality regularly rise, with over 3 million new cases and more than a million deaths expected by 2040. Hereditary hemochromatosis is one of the most common genetic diseases in populations of Northern European origin, with an estimated homozygous prevalence of between 1/200 and 1/400 (2).

Hereditary hemochromatosis is an autosomal recessive genetic disorder due to excessive iron absorption, resulting in a toxic accumulation of iron in the organs, particularly in the liver, heart, pancreas and joints (3). The most common form of hereditary hemochromatosis is associated with biallelic pathogenic variations of the *HFE* gene located on chromosome 6, especially the C282Y and H63D pathogenic variants (type 1), particularly in Northern Europeans with around 1 in 200 homozygous for C282Y, and 1 in 10 heterozygous for C282Y, but other genes are also associated to a minor extent, such as *HJV* or *HAMP* (type 2) in juvenile forms, *TfR2* (type 3) and *FPN* (type 4). The common characteristic of these pathogenic variants is that they interfere with the signal system responsible for hepcidin synthesis (2, 4), leading to increased intestinal iron absorption. Excess iron is then stored as ferritin in tissues, resulting in progressive toxicity, particularly in vital organs (3).

Diagnosis is based on elevated ferritin and transferrin saturation coefficient >45%, combined with a screening for homozygous or compound heterozygous pathogenic variants of the *HFE* gene, in particular C282Y and H63D (2, 5). Hereditary haemochromatosis is a disease with low clinical penetrance. Despite the frequency of pathogenic variants, only a minority of patients develop symptomatic hemochromatosis, with around 10–30% of homozygous men developing a significant overload. The rate is less significant in women due to menstrual loss and pregnancy.

Targeted screening is recommended, with systematic screening of first-degree relatives if a family member is homozygous for C282Y or has clinical haemochromatosis, with a genetic test carried out immediately in addition to the ferritin and transferrin saturation coefficient assays (6-8). Systematic screening of the general population is not justified, due to low clinical penetrance, the risk of overdiagnosis and anxiety in healthy carriers, and the presence of a simple and effective treatment.

The main treatment for hemochromatosis consists of regular phlebotomies to reduce iron levels. Other approaches include the use of iron chelators in certain cases, particularly in patients who cannot undergo frequent phlebotomies (9).

Iron is indispensable, yet overload is carcinogenic. Excess, particularly the readily absorbed heme iron in red meat, drives oxidative stress, free-radical DNA damage and higher serum-ferritin levels, all linked to increased cancer risk (10). In breast tissue, iron synergizes with estrogens metabolites to generate reactive species, a process intensified in post-menopause when iron stores rise (11, 12). Moreover, hemochromatosis often coexists with diabetes and obesity, that are both additional breast cancer risk factors. Hemochromatosis is known to increase the risk of liver carcinomas and other cancers. However, to date, scientific data remain contradictory in terms of breast carcinoma (11).

The objective of this literature review and meta-analysis was to assess the link between hemochromatosis and breast cancer and to propose a personalized surveillance for these patients.

Materials and Methods

This review was guided by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines (prismastatement.org).

Study Identification and Selection

Eligible publications were retrieved by searching for the PubMed database, published between 2000 and 2025, using the terms "hemochromatosis", "*HFE* pathogenic variants" and "breast cancer".

Inclusion Criteria and Exclusion Criteria

Eligible studies were included in this review according to following criteria: publications that evaluated the association between *HFE* gene pathogenic variants and cancer risk; these publications were designed as prospective and retrospective cohort studies, case-control studies, meta-analysis and systematic reviews.

Studies were excluded when they were a case-only study, case-report, or abstract; without sufficient data; and publications concerning animals.

Only articles published in English or French were considered.

We have included a flow chart to describe the publications selection process (Figure 1). Previously two published meta-analyses were not included in our meta-analysis to avoid potential data duplication.

A meta-analysis was conducted to estimate the association between hereditary hemochromatosis-related pathogenic variants (notably C282Y and H63D) and breast cancer risk. Effect sizes extracted from the included studies were primarily expressed as odds ratios (OR) with 95% confidence intervals (CIs). The primary analysis used a random-effects model to account for between-study heterogeneity and to compute a pooled OR with a corresponding 95% CI.

Heterogeneity was assessed using Cochran's Q statistic and the I^2 index. In cases of substantial heterogeneity (I^2 >75%), subgroup analyses were conducted according to pathogenic variant**s** type (C282Y, H63D, or combined) and zygosity (homozygous, heterozygous, compound heterozygous). Meta-regressions weighted by the inverse of the variance were performed to evaluate the effect of potential moderators (year of publication, pathogenic variants type, zygosity, and methodological quality). A leave-one-out sensitivity analysis was performed to assess the robustness of the pooled estimate.

Statistical Analysis

Potential publication bias was explored using visual inspection of a funnel plot and formally tested using Egger's regression test. Statistical analyses were performed using the software JASP (version 0.19.3 for Apple Silicon, www.jasp-stats.org). Assistance with the construction of data tables, supplementary calculations, and the generation of figures (annotated forest plots, meta-regressions, sensitivity analysis, Egger's test) was provided by ChatGPT (OpenAI, GPT-4) under supervised use, without automation of methodological decisions or unvalidated interpretations.

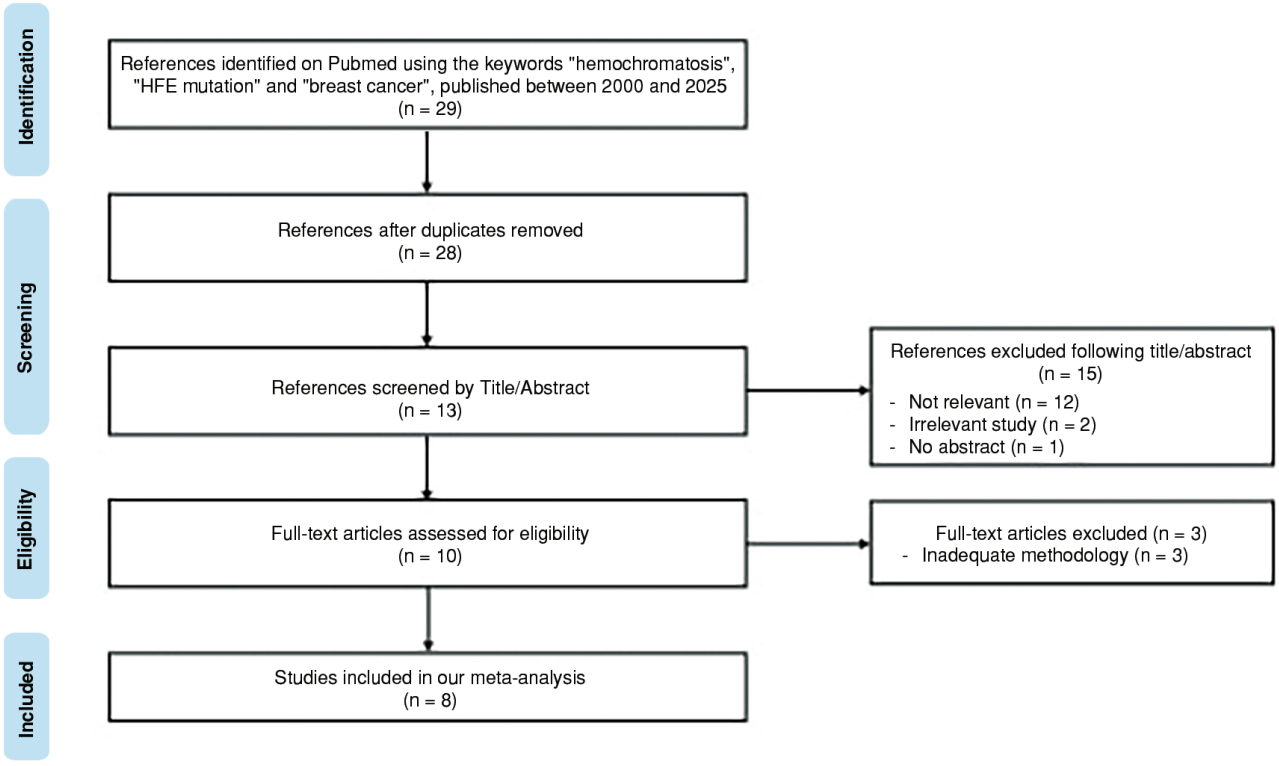

Figure 1. Flow chart showing the studies selection

Results

The various studies included in the meta-analysis are summarized in Table 1.

1. Studies Reporting No Significant Association Between Hemochromatosis and Breast Cancer Risk

A multicenter retrospective cohort study was conducted in eight university hospitals in Sweden from 1997 to 2017 with 3,645 persons carrying homozygous or compound heterozygous *HFE* pathogenic variants, matched by age, sex and country of residence to 36,423 population-based reference individuals. This study showed no significant difference compared to reference individuals for the risk for breast cancer [hazard ratio (HR) = 1.08, 95% CI = 0.73–1.60] (12).

Similarly, a prospective European study of 451,143 participants from the UK Biobank, aged 40 to 70 years, over an average duration of 11.6 years, evaluated the risks of non-hepatic cancers in carriers of *HFE* pathogenic variants. The study found an increased risk of prostate cancer in men homozygous for C282Y pathogenic variants, but no increased risk for other types of cancer, including breast cancer in women for either the *HFE* pathogenic variant C282Y and/or H63D (H63D+/+ HR = 1.09 95% CI = 0.96-1.25, p = 0.19; C282Y+/+ HR = 0.90, 95% CI = 0.69–1.18, p = 0.45; C282Y+/H63D+ HR = 0.99, 95% CI = 0.87–1.14, p = 0.93) (13).

This is also the case for a Brazilian case-control study, which evaluated 68 patients with operable breast cancer, with a mean age of 54.2 years, compared with a control population of 85 women with no family history of cancer and no use of hormonal therapies. There was no association between H63D and C282Y pathogenic variants in the *HFE* gene and breast cancer risk (C282Y+/+ OR = 0.34, 95% CI = 0.14–1.91; H63D+/+: OR = 0.53, 95% CI = 0.40–1.58) (14).

A German study involving 688 women under the age of 80 years, of Caucasian origin, and all diagnosed with breast cancer within the previous six months, analyzed 19 polymorphisms in genes involved in iron metabolism, including the *HFE* gene. The results showed no significant differences in allele or genotype frequencies between breast cancer patients and controls, suggesting that these variants do not have a direct effect on breast cancer incidence (C282Y +/- OR = 0.92, 95% CI = 0.65–1.37; H63D +/- OR = 0.87, 95% CI = 0.67–1.13; H63D +/+ OR = 0.79, 95% CI = 0.37–1.71). However, a possible association was observed between the *HFE* C282Y allele and higher lymph node involvement in patients, which may suggest a link with tumor progression. This observation, however, was limited by the small sample size (15).

2. Studies Reporting a Significant Association Between hemochromatosis and Breast Cancer Risk

In contrast to the studies described above, Kallianpur et al. (16) found a strong association between C282Y pathogenic variants in the *HFE* gene and an increased risk of breast cancer, with significant public health implications, particularly for hemochromatosis genetic screening and breast cancer prevention. They compared the frequency of C282Y pathogenic variants in a population of 168 patients who underwent chemotherapy or blood cell transplants for cancer treatment between 1995 and 1998 at the Vanderbilt University Medical Center in Tennessee. The study compared breast cancer patients with those treated for non-breast cancers, including hematologic cancers, as well as a sample of cancer-free individuals from a Tennessee clinic and national population data. The frequency of at least one C282Y allele in breast cancer cases was higher (36.6%, 5 homozygotes/10 heterozygotes) than in the Tennessee clinic population (12.7%, p<0.001), the general population (12.4%, p<0.001), and similarly selected non-breast cancer cases (17.0%,

Table 1. Studies evaluating the association between *HFE* gene mutations and breast cancer risk

	Author (reference)	Study type (*n* = 73,981)	Year	Average age (years)	Country	*HFE* mutation	Results
No link between HC and breast cancer	Abraham et al. (15)	Case-control (*n* = 1,412)	2005	58.7	Germany	C282Y, H63D	C282Y: OR = 0.92, 95% CI = 0.65–1.37 H63D: OR = 0.79, 95% CI = 0.37–1.71
	Batschauer et al. (14)	Case-control (*n* = 153)	2011	54.12	Brazil	C282Y, H63D	C282Y: OR = 0.34, 95% CI = 0.14–1.91 H63D: OR = 0.53, 95% CI = 0.40–1.58
	Hagström et al. (12)	Retrospective cohort (*n* = 40,057)	2021	52.6	Sweden	C282Y, H63D	HR = 1.08, 95% CI = 0.73–1.60
	Atkins et al. (13)	Prospective cohort (*n* = 9,238)	2022	56.8	United-Kingdom	C282Y, H63D	H63D: HR = 1.09, 95% CI = 0.96–1.25 C282Y: HR = 0.90, 95% CI = 0.69–1.18 C282Y/H63D: HR = 0.99, 95% CI = 0.87–1.14
Link between HC and breast cancer	Kallianpur et al. (16)	Case-control (*n* = 5,510)	2004	53.0	United States of America	C282Y	OR = 2.55, 95% CI = 1.35–4.81
	Gunel-Ozcan et al. (19)	Case-control (*n* = 188)	2006	41.0	Türkiye	H63D	HR = 2.05, 95% CI = 1.12–3.75
	Kondrashova et al. (20)	Case-control (*n* = 360)	2006	53.2	Russia	H63D	HR = 4.4, 95% CI = 1.4–14.1
	Osborne et al. (17)	Prospective cohort (*n* = 17,063)	2010	48.3	Australia	C282Y	C282Y: HR = 2.39, 95% CI = 1.24–4.61

HC: Hemochromatosis; HR: Hazard ratio; OR: Odds ratio; CI: Confidence interval

p = 0.008). The probability of developing breast cancer increased with the number of C282Y alleles (p = 0.010), and serum iron analysis confirmed higher levels in breast cancer patients carrying these pathogenic variants (16).

Similarly, a prospective cohort study using data from the Melbourne Collaborative Cohort Study followed 28,509 participants aged between 27 and 75 years, enrolled from 1990 to 1994, for an average of 14 years to examine the link between pathogenic C282Y in *HFE* and cancer risk, particularly for breast, colon, and prostate cancer. The study demonstrated a significant 2.39-fold increase in breast cancer risk among individuals homozygous for C282Y pathogenic variant (HR = 2.39, 95% CI 1.24–4.61, p = 0.01). However, compound heterozygous C282Y/H63D individuals did not show an increased breast cancer risk (HR = 1.16, 95% CI = 0.74–1.84) (17).

A meta-analysis published in 2016, including 36 studies with 87,028 participants (13,680 cancer cases and 73,348 controls), also found a trend towards an approximately two-fold increased breast cancer risk in patients with C282Y homozygous pathogenic variant of *HFE* (OR = 2.14, 95% CI 1.24–3.70, p = 0.673). However, no increased breast cancer risk was demonstrated in patients with H63D pathogenic variants of the *HFE* gene (18), contrary to Gunel-Ozcan et al. (19), who found a significant difference in a retrospective study comparing the frequency of C282Y and H36D pathogenic variants in the *HFE* gene among Turkish women with breast cancer and healthy controls, suggesting that H63D pathogenic variants might be associated with a two-fold increased breast cancer risk (HR = 2.05, 95% CI 1.12–3.75, p = 0.02).

Similarly, another case-control study was conducted to determine the frequency of C282Y and H63D pathogenic variants in the *HFE* gene in Russian women with hormone-dependent cancers, including breast, ovarian and endometrial cancer. There was a significant increase in the risk of breast cancer in women over 57 years with heterozygous or homozygous H63D pathogenic variants (HR = 4.4, 95% CI = 1.4–14.1, p = 0.002). This association was not found for C282Y pathogenic variants (20).

A meta-analysis was conducted by Zhang et al. (21), including 20 studies in total published between 1999 and 2005, of which seven assessed the risk of breast cancer in patients with C282Y pathogenic variants of the *HFE* gene, with a total of 2,353 cases and 19,171 controls, as well as five studies concerning the risk of breast cancer in patients with H63D pathogenic variants of the *HFE* gene, with a total of 1,570 cases and 2,449 controls. An association was found only in patients who were homozygous for the C282Y pathogenic variant

(OR = 1.76, 95% CI = 1.05–2.94, p = 0 .425), suggesting an increased risk of breast cancer in this population. No association was found between H63D pathogenic variants in *HFE* and an increased risk of breast cancer (21).

3. The Present Meta-Analysis

We conducted a meta-analysis to investigate the association between hereditary hemochromatosis-related pathogenic variants (primarily C282Y and H63D) and the risk of breast cancer. This included eight studies with a total of 73,981 patients. Our meta-analysis was carried out with two additional recent studies, dating from 2021 and 2022, with non-negligible sample sizes, which the meta-analyses by Lv et al. (18) and Zhang et al. (21) did not provide.

a. Pooled Effect

The random-effects model estimated a pooled OR of 1.36 (95% CI = 0.75–1.98) for breast cancer among carriers of hemochromatosis pathogenic variants. Although the point estimate suggested an increased risk, between-study heterogeneity was substantial (Q = 88.4, df = 11, p<0.001; τ^2 = 0.96).

b. Subgroup Analyses

• By Mutation

Subgroup analysis by mutation type (C282Y, H63D, combination) did not reveal significant differences between groups (F = 0.183, p = 0.835). The type of mutation did not explain the observed heterogeneity.

• By Zygosity

Similarly, zygosity (homozygous vs. heterozygous/compound heterozygous) was not a significant moderator (F = 0.009, p = 0.927).

• By Design and Quality

Meta-regression incorporating study design (cohort vs. other) and methodological quality (high vs. low) showed no significant effect. Design (cohort); β = +0.06 (log OR), p = 0.69; Quality (high); β = -0.43 (log OR), p = 0.19. These variables did not account for heterogeneity (Adjusted R^2 = –0.005).

c. Meta-Regression

Additional meta-regression assessed the effects of mutation (C282Y), zygosity (homozygous), and year of publication. C282Y mutation; β = -0.10 (log OR), p = 0.55; Homozygosity; β = +0.10 (log OR), p = 0.53; year of publication; β = -0.006 (log OR), p = 0.58. None of these factors significantly influenced effect size variability (adjusted R^2 = -0.19).

d. Publication Bias

Funnel plot inspection revealed no evident asymmetry. Egger's regression intercept was not significant (p = 0.41), suggesting no publication bias.

e. Sensitivity Analysis

Leave-one-out sensitivity analysis showed that no single study significantly influenced the pooled estimate. The OR remained stable across exclusions (Figure 2).

Discussion and Conclusion

The international literature reveals contrasting results regarding the association between hemochromatosis and breast cancer. On the one hand, some studies, such as those by Hagström et al. (12) and the UK Biobank (13), showed no significant increase in the risk of breast cancer in individuals who were homozygous for C282Y pathogenic variants in the *HFE* gene. In contrast, some studies such as those by Kallianpur et al. (16) and Osborne et al. (17) indicated a significant link between these pathogenic variants and an increased risk of developing breast cancer. Several methodological and biological factors may explain these discrepancies. Firstly, differences in study design, sample size and length of follow-up considerably influence the results. For example, the study by Kallianpur et al. (16) is based on a smaller cohort. In contrast, large-scale studies such as the UK Biobank study (13) benefit from greater statistical power but may not capture specific sub-populations at risk, such as menopausal women.

The variable clinical penetrance of hereditary hemochromatosis associated with *HFE* pathogenic variants, particularly C282Y homozygosity, has important implications for patient monitoring in the context of cancer risk. Although only 10% to 33% of individuals with this genotype develop clinically manifest hereditary hemochromatosis, a significantly larger proportion exhibit elevated biochemical markers of iron overload, including increased serum ferritin and transferrin saturation. This discrepancy between biochemical and clinical expression highlights the need for an individualized follow-up strategy, rather than a genotype-based approach alone. Compound heterozygotes and H63D homozygotes typically present with mild elevations in iron indices, but these are generally not associated with progressive iron-related organ damage unless additional risk factors are present (22).

From a pathophysiological point of view, the mechanisms linking excess iron to breast carcinogenesis remain complex and yet incompletely elucidated. The role of oxidative stress induced by excess iron, implicated in DNA damage and genomic instability, is an argument in favor of a carcinogenic influence. In addition, the interaction between iron and estrogens suggested by Marques et al (23) and Wyllie and Liehr (24) could explain why this risk is more marked in post-menopausal women, where the increase in iron stocks coincides with alterations in hormonal metabolism. Finally, contradictory results are also emerging concerning the involvement of the H63D pathogenic variant in the *HFE* gene. While the meta-analysis by Lv et al. (18) shows no significant association, the study by Gunel-Ozcan et al. (19) suggested an increased risk of breast cancer in women with these pathogenic variants. These disparities highlight the importance of continuing investigations with more specific studies incorporating more parameters, such as menopausal status, environmental factors and metabolic co-morbidities.

Monitoring iron status in *HFE* pathogenic variant carriers is particularly relevant in oncology, as emerging evidence suggests a link between iron excess and tumor progression. High circulating iron levels and transferrin saturation have been associated with increased risk of distant metastasis in breast cancer, possibly via promotion of oxidative stress, immune evasion, and pro-metastatic niche formation. In a retrospective monocentric study conducted at the University Hospitals of Leuven, De Troy et al. (25) examined the relationship between iron metabolism markers at the time of early-stage breast cancer diagnosis and the risk of developing distant metastases. Among

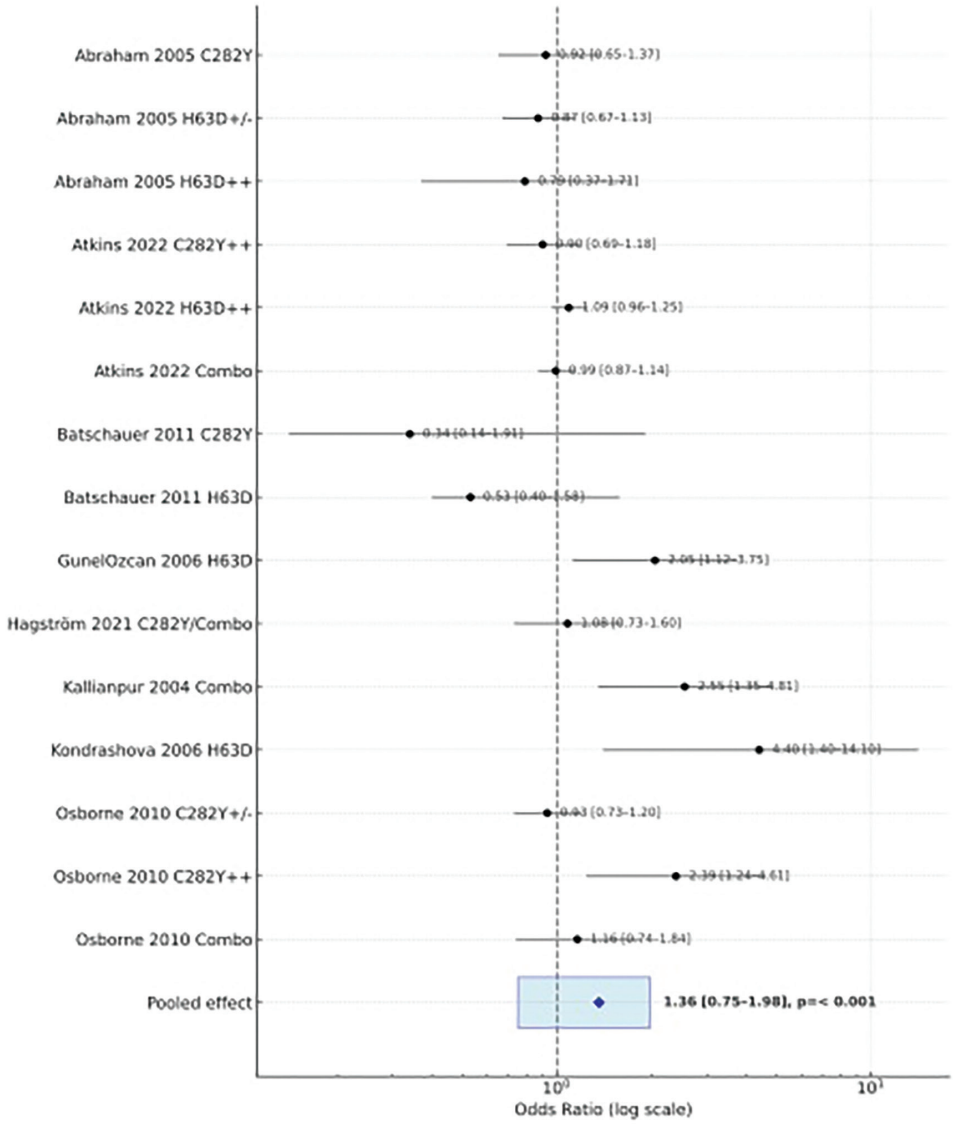

Figure 2. Meta-analysis of the association between hereditary hemochromatosis-related pathogenic variants and breast cancer risk

1,113 women with unilateral, unifocal breast cancer and available iron profiles (serum iron, ferritin, and transferrin saturation) measured within six weeks of diagnosis, 10% developed secondary metastases during a median follow-up of seven years. Multivariate Cox regression analysis showed that a 10% increase in transferrin saturation was associated with a 19% increase in metastatic risk (HR = 1.19, 95% CI = 1.02–1.38), and a 10 μg/dL increase in serum iron was associated with a 6% increase in metastatic risk (HR = 1.06, 95% CI = 1.01–1.12). In contrast, ferritin levels were not significantly associated with the occurrence of metastases. No associations were found between iron status and the metastatic site or tumor molecular subtype. The findings suggest that elevated circulating iron and iron saturation at diagnosis may contribute to the formation of a pro-metastatic microenvironment and support the potential benefit of targeting iron metabolism, for example through iron chelation or ferroptosis induction, as a therapeutic strategy in breast cancer.

In this context, iron overload may act not only as a metabolic comorbidity but also as a modifier of cancer behavior. Environmental and physiological factors, such as age, sex, alcohol intake, metabolic syndrome, viral hepatitis, and menopausal status, significantly influence the progression to clinical iron overload and may synergize with cancer-related pathways. Furthermore, secondary genetic modifiers (e.g., *HAMP*, *HJV*, or *BMP* variants), high dietary heme iron intake, or the use of acid suppression therapy can further modulate iron burden and therapeutic requirements (22).

Although several studies have investigated the association between *HFE* pathogenic variants and breast cancer risk, none have specifically reported on the histological subtypes of breast cancer in women with hereditary hemochromatosis. The current literature predominantly focuses on genetic associations, iron metabolism, and overall cancer incidence, without detailing tumor morphology or receptor status. Furthermore, while some studies suggest an increased prevalence of breast cancer in *HFE* pathogenic variant carriers, particularly those with H63D or C282Y variants, data regarding the age of onset remain limited. Notably, one study conducted in a Russian population found that the breast cancer risk associated with the H63D pathogenic variant increased significantly in women over the age of 57 years (20).

This meta-analysis offers several significant strengths compared to previous investigations on the association between hereditary

hemochromatosis and breast cancer risk. First, all included studies are recent, published in the last 20 years. Second, it integrates data from a geographically and ethnically diverse set of populations, including studies from Europe (Germany, Sweden, UK, Russia, Türkiye), North and South America (USA, Brazil), and Australia. This diversity enhances the generalizability of the findings across different genetic backgrounds and environmental contexts. Third, the included studies allow for stratified analysis by specific *HFE* genotypes (C282Y homozygotes, H63D carriers, compound heterozygotes), enabling a more nuanced assessment of genotype-specific cancer risks, particularly in women. This meta-analysis incorporates data from large-scale, prospective cohort studies such as the UK Biobank and the Melbourne Collaborative Cohort Study, which provide high-quality, population-based evidence with long-term follow-up. Moreover, age- and sex-stratified data enable the evaluation of potential effect modifiers, such as menopausal status, which may influence the penetrance of *HFE* mutations.

Our meta-analysis indicated a potential association between C282Y and H63D pathogenic variants in *HFE* and an increased risk of breast cancer. Although this trend did not reach statistical significance, the observed signal justifies further investigation through large-scale studies with reduced heterogeneity to better determine this relationship and potentially warrant adjusting breast surveillance in carriers. Indeed, the UK Age Trial, a randomized study of 160,921 women, showed that annual mammography from ages 40 to 48 years of age reduced breast cancer mortality by 25% in the first 10 years (risk ratio = 0.75, p = 0.029), with one death prevented per 1000 women screened. No long-term increase in overdiagnosis or other mortality was observed (26).

Breast cancer and hereditary hemochromatosis are two major public health problems. While the present meta-analysis did not demonstrate a significant association between *HFE* pathogenic variants, especially C282Y and H63D, and breast cancer risk, a consistent trend toward increased risk, especially among C282Y homozygotes, was observed.

Given the absence of randomized trials with mortality endpoints, our findings cannot justify changes in clinical practice at this stage. However, they provide a rationale for future prospective studies to assess whether women carrying these pathogenic variants, especially C282Y/C282Y homozygotes, might benefit from adapted breast cancer surveillance strategies. Such research could help determine whether personalized screening approaches, potentially incorporating more frequent evaluations or advanced imaging modalities, would improve early detection in this probable genetically predisposed population.

Ethics

Ethics Committee Approval: This meta-analysis is based on data extracted from previously published studies. No new human or animal subjects were involved, and no ethical approval was required.

Informed Consent: This meta-analysis is based on data extracted from previously published studies. No new human or animal subjects were involved, and no ethical approval was required.

Footnotes

Authorship Contributions

Surgical and Medical Practices: M.B., C.B., M.C., N.T., T.O., C.M.; Concept: M.B., C.M.; Design: M.B., C.M.; Data Collection or Processing: M.B.; Analysis or Interpretation M.B., C.B.; Literature Search: M.B., M.C., N.T.; Writing: M.B.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

References

1. Data visualization tools for exploring the global cancer burden in 2022. [Internet]. 2022. Available from: https://gco.iarc.fr/today/data/factscheets/cancers/20-Breast-fact-sheet.pdf [Crossref]
2. Brissot P, Pietrangelo A, Adams PC, de Graaff B, McLaren CE, Loréal O. Haemochromatosis. Nat Rev Dis Primers. 2018; 4: 18016. (PMID: 2962005) [Crossref]
3. Allen KJ, Gurrin LC, Constantine CC, Osborne NJ, Delatycki MB, Nicoll AJ, et al. Iron-overload-related disease in HFE hereditary hemochromatosis. N Engl J Med. 2008; 358: 221-230. (PMID: 18199861) [Crossref]
4. Pietrangelo A. Hereditary hemochromatosis: pathogenesis, diagnosis, and treatment. Gastroenterology. 2010; 139: 393-408, 408.e1-e2. (PMID: 20542038) [Crossref]
5. Feder JN, Gnirke A, Thomas W, Tsuchihashi Z, Ruddy DA, Basava A, et al. A novel MHC class I-like gene is mutated in patients with hereditary haemochromatosis. Nat Genet. 1996; 13: 399-408. (PMID: 8696333) [Crossref]
6. Bacon BR, Adams PC, Kowdley KV, Powell LW, Tavill AS; American Association for the Study of Liver Diseases. Diagnosis and management of hemochromatosis: 2011 practice guideline by the American Association for the Study of Liver Diseases. Hepatology. 2011; 54: 328-343. (PMID: 21452290) [Crossref]
7. European Association For The Study Of The Liver. EASL clinical practice guidelines for HFE hemochromatosis. J Hepatol. 2010; 53: 3-22. (PMID: 20471131) [Crossref]
8. Kowdley KV, Brown KE, Ahn J, Sundaram V. ACG Clinical Guideline: hereditary hemochromatosis. Am J Gastroenterol. 2019; 114: 1202-1218. Erratum in: Am J Gastroenterol. 2019; 114: 1927. (PMID: 31335359) [Crossref]
9. Kawabata H. The mechanisms of systemic iron homeostasis and etiology, diagnosis, and treatment of hereditary hemochromatosis. Int J Hematol. 2018; 107: 31-43. (PMID: 29134618) [Crossref]
10. Fonseca-Nunes A, Jakszyn P, Agudo A. Iron and cancer risk--a systematic review and meta-analysis of the epidemiological evidence. Cancer Epidemiol Biomarkers Prev. 2014; 23: 12-31. (PMID: 24243555) [Crossref]
11. Crownover BK, Covey CJ. Hereditary hemochromatosis. Am Fam Physician. 2013; 87: 183-190. (PMID: 23418762) [Crossref]
12. Hagström H, Ndegwa N, Jalmeus M, Ekstedt M, Posserud I, Rorsman F, et al; Swedish Hepatology Study Group (SweHep). Morbidity, risk of cancer and mortality in 3645 HFE mutations carriers. Liver Int. 2021; 41: 545-553. (PMID: 33450138) [Crossref]
13. Atkins JL, Pilling LC, Torti SV, Torti FM, Kuchel GA, Melzer D. Hereditary hemochromatosis variant associations with incident nonliver malignancies: 11-year follow-up in UK biobank. Cancer Epidemiol Biomarkers Prev. 2022; 31: 1780-1787. (PMID: 35709753) [Crossref]
14. Batschauer AP, Cruz NG, Oliveira VC, Coelho FF, Santos IR, Alves MT, et al. HFE, MTHFR, and FGFR4 genes polymorphisms and breast cancer in Brazilian women. Mol Cell Biochem. 2011; 357: 247-253. (PMID: 21625954) [Crossref]
15. Abraham BK, Justenhoven C, Pesch B, Harth V, Weirich G, Baisch C, et al; GENICA Network. Investigation of genetic variants of genes of the hemochromatosis pathway and their role in breast cancer. Cancer Epidemiol Biomarkers Prev. 2005; 14: 1102-1107. (PMID: 15894659) [Crossref]

16. Kallianpur AR, Hall LD, Yadav M, Christman BW, Dittus RS, Haines JL, et al. Increased prevalence of the HFE C282Y hemochromatosis allele in women with breast cancer. Cancer Epidemiol Biomarkers Prev. 2004; 13: 205-212. (PMID: 14973098) [Crossref]

17. Osborne NJ, Gurrin LC, Allen KJ, Constantine CC, Delatycki MB, McLaren CE, et al. HFE C282Y homozygotes are at increased risk of breast and colorectal cancer. Hepatology. 2010; 51: 1311-1318. (PMID: 20099304) [Crossref]

18. Lv YF, Chang X, Hua RX, Yan GN, Meng G, Liao XY, et al. The risk of new-onset cancer associated with HFE C282Y and H63D mutations: evidence from 87,028 participants. J Cell Mol Med. 2016; 20: 1219-1233. (PMID: 26893171) [Crossref]

19. Gunel-Ozcan A, Alyilmaz-Bekmez S, Guler EN, Guc D. HFE H63D mutation frequency shows an increase in Turkish women with breast cancer. BMC Cancer. 2006; 6: 37. (PMID: 16503999) [Crossref]

20. Kondrashova TV, Neriishi K, Ban S, Ivanova TI, Krikunova LI, Shentereva NI, et al. Frequency of hemochromatosis gene (HFE) mutations in Russian healthy women and patients with estrogen-dependent cancers. Biochim Biophys Acta. 2006; 1762: 59-65. (PMID: 16216474) [Crossref]

21. Zhang M, Xiong H, Fang L, Lu W, Wu X, Wang YQ, et al. Meta-analysis of the association between H63D and C282Y polymorphisms in HFE and cancer risk. Asian Pac J Cancer Prev. 2015; 16: 4633-4639. (PMID: 26107216) [Crossref]

22. Barton JC, Parker CJ. HFE-related hemochromatosis. 2000 Apr 3 [updated 2024 Apr 11]. In: Adam MP, Feldman J, Mirzaa GM, Pagon RA, Wallace SE, Amemiya A, editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2025. (PMID: 20301613) [Crossref]

23. Marques O, da Silva BM, Porto G, Lopes C. Iron homeostasis in breast cancer. Cancer Lett. 2014; 347: 1-14. (PMID: 24486738) [Crossref]

24. Wyllie S, Liehr JG. Release of iron from ferritin storage by redox cycling of stilbene and steroid estrogen metabolites: a mechanism of induction of free radical damage by estrogen. Arch Biochem Biophys. 1997; 346: 180-186. (PMID: 9343364) [Crossref]

25. De Troy J, Fendt SM, Hatse S, Neven P, Smeets A, Laenen A, et al. Plasma iron levels at early breast cancer diagnosis are associated with development of secondary metastases: a single-center retrospective cohort study. Breast Cancer (Auckl). 2025; 19: 11782234251317070. (PMID: 39927294) [Crossref]

26. Duffy SW, Vulkan D, Cuckle H, Parmar D, Sheikh S, Smith RA, et al. Effect of mammographic screening from age 40 years on breast cancer mortality (UK Age trial): final results of a randomised, controlled trial. Lancet Oncol. 2020; 21: 1165-1172. (PMID: 32800099) [Crossref]