Exploration of Medicine

Open Exploration

Open Access Original Article

# Association between *GPX4* and *HMGCR* gene expression and cell proliferation in atypical hyperplasia of the breast

Danila Coradini*

Laboratory of Medical Statistics and Biometry, "Giulio A. Maccacaro", Department of Clinical Sciences and Community Health, University of Milan, 20133 Milan, Italy

***Correspondence:** Danila Coradini, Laboratory of Medical Statistics and Biometry, "Giulio A. Maccacaro", Department of Clinical Sciences and Community Health, University of Milan, Via Vanzetti 5, 20133 Milan, Italy. danila.coradini@gmail.com
**Academic Editor:** Andrea Nicolini, University of Pisa, Italy
**Received:** September 10, 2024 **Accepted:** November 15, 2024 **Published:** December 15, 2024

**Cite this article:** Coradini D. Association between *GPX4* and *HMGCR* gene expression and cell proliferation in atypical hyperplasia of the breast. Explor Med. 2024;5:950–9. https://doi.org/10.37349/emed.2024.00268

## Abstract

**Aim:** Using a dataset available from the NCBI Gene Expression Omnibus Repository, this in silico study investigated the differential expression of *GPX4*, the gene coding for the detoxifying enzyme glutathione peroxidase paired samples of AH (atypical hyperplasia) and corresponding histologically normal (HN) tissue from 17 women with AH and in four samples of normal breast tissue used as controls.

**Methods:** The study focused on the genes (*HMGCR*, *FDPS*, *FDFT1*, and *GGPS1*) involved in the production and breakdown of isopentenyl-diphosphate, a key component for GPX4 biosynthesis. It also explored the connection between the expression of *GPX4* and the genes (*CCND1*, *CDK4*, *CDK6*, and *CDKN1B*) associated with the cyclin D1-CDK4/6 complex.

**Results:** Compared to HN tissue, AHs exhibited higher levels of *GPX4* and *HMGCR*, supporting the functional connection between GPX4 synthesis and isopentenyl-diphosphate production. Additionally, AHs showed elevated levels of *CCND1* and *CDKN1B* and decreased levels of *CDK6*. Compared to normal breast tissue, HNs showed similar alterations, suggesting that ferroptosis escape and uncontrolled proliferation are early molecular events in the neoplastic transformation. Compared to HN tissue, AHs also expressed high levels of *GGPS1*, a downstream gene of *HMGCR*, which leads to the synthesis of geranylgeranyl-diphosphate, a molecule essential for the post-translational modification of the proteins involved in the regulation of the Hippo signaling pathway.

**Conclusions:** Although very preliminary, present results seem to suggest that blocking the mevalonate pathway by statins might, on the one hand, prevent AHs from escaping ferroptosis through depleting isopentenyl-diphosphate and, on the other hand, inhibit cell proliferation by controlling the Hippo pathway.

## Keywords

Atypical hyperplasia, *GPX4*, *HMGCR*, ferroptosis, cell proliferation

## Introduction

The term "atypical hyperplasia" (AH) of the breast refers to abnormal epithelial proliferative lesions that are not qualitatively or quantitatively abnormal enough to be classified as carcinoma in situ. Like most breast cancer precursors, AHs develop in the terminal duct lobular unit (TDLU), the basic functional structure of the mammary gland consisting of a bilayered ductal system ending in small glandular structures called acini [1], and are categorized into atypical ductal hyperplasia (ADH) and atypical lobular hyperplasia (ALH) based on their morphologic characteristics [2]. ADH consists of a proliferating epithelial cell population of luminal origin that strongly expresses the estrogen receptor (ER) [3]. ALH instead consists of small, round, uniform, and proliferating epithelial cells derived from the acinar population of the TDLU. These cells have an increased nucleus/cytoplasmic ratio and are E-cadherin negative [4].

Typically, AHs are found incidentally during routine screening mammography. Epidemiological evidence indicates that about 10% of breast biopsies reveal an AH and that patients with an AH at biopsy have a lifetime risk of 15%–20% of developing breast cancer [5, 6]. The standard care to prevent the progression of the AH toward invasive malignancies is surgical excision [7].

Molecular evidence has suggested that the increased proliferative activity of AHs and their progression to invasive cancer are mainly due to a failure in the balanced mechanism that controls cell proliferation and cell death [8]. However, the early events that trigger and promote the transformation of normal epithelial cells into hyperplasic cells are still unknown.

Accumulating evidence suggests that the long-term persistence in the breast tissue of some highly reactive oxygen species (ROS), reacting spontaneously with many cellular components, could play a crucial role in the transformation process [9]. In particular, the accumulation of lipid peroxides can cause extensive and irreversible damage to cell membranes and trigger ferroptosis, a form of non-apoptotic death [10].

Aimed at neutralizing the dangerous effects of ROS, preventing lipid peroxidation, and hampering ferroptosis activation, cells have developed a defense mechanism based on the detoxifying properties of glutathione peroxidases (GPX). In particular, GPX4, a selenocysteine-containing GPX, is the only member in this family of enzymes that can reduce complex lipid hydroperoxides even when embedded in membranes, thus preventing membrane disruption and ferroptosis activation [11, 12].

The biosynthesis of GPX4 requires the presence of the isopentenyl-diphosphate, an intermediate of the mevalonate pathway, the core of the biosynthetic process leading to cholesterol (Figure 1), for transferring the unusual amino acid selenocysteine to the nascent catalytic site of GPX4 [13].

Since the emerging evidence suggests that tumor cells escape ferroptosis by producing high levels of the GPX4 enzyme, thus contributing to cell growth promotion, acquired drug resistance, and cancer progression [14–16], this in silico study aimed to investigate if, like invasive cancer, AHs overexpressed the *GPX4* gene when compared to the corresponding histologically normal (HN) tissue, and explore the relationship between the expression of *GPX4* and that of the genes involved in the production and breakdown of isopentenyl-diphosphate (namely, *HMGCR*, *FDPS*, *GGPS1*, and *FDFT1*). The study also investigated the relation between the expression of *GPX4* and that of genes coding for the elements of the cyclin D1-CDK4/6 complex, which controls the G1 phase of the cell cycle. Considering the diverse origins (ductal versus lobular portion of the TDLU) and a different risk of developing invasive cancer, ADH and ALH were analyzed separately.

## Materials and methods

### Patients and samples

The study utilized a dataset publicly available from the NCBI Gene Expression Omnibus (GEO) Repository (https://www.ncbi.nlm.nih.gov/geo/) identified by the GEO accession number GSE118432. As described in the original article [17], the study, which was approved by the Institutional Review Board of Baystate Health, Springfield, MA, under protocol number 182463, focused on women diagnosed with AH and with no

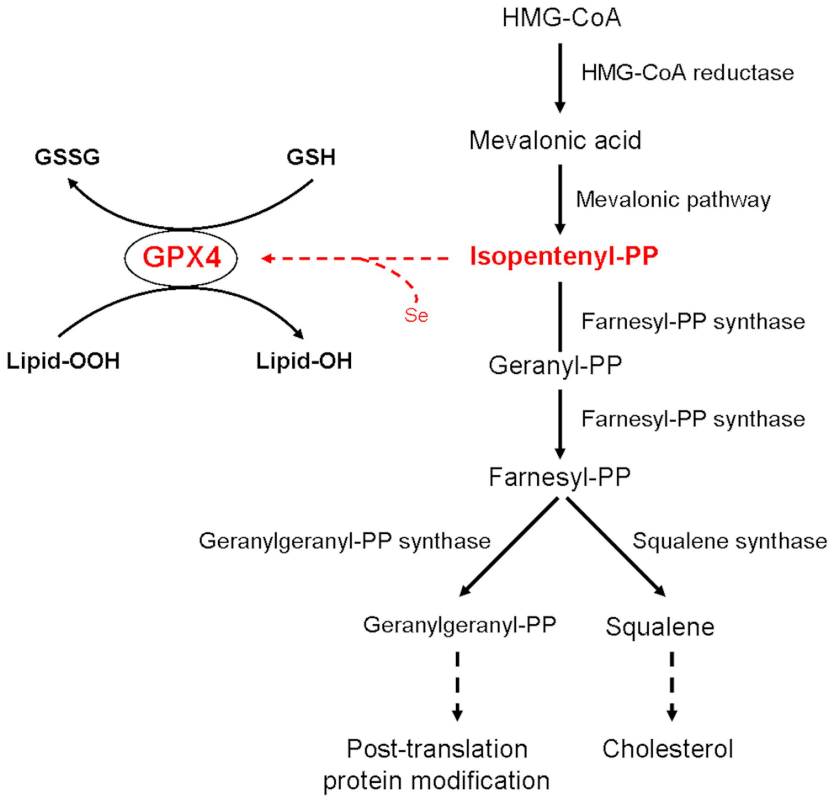


**Figure 1. Schematic description of the relationship between glutathione peroxidase 4 (GPX4) and isopentenyl-diphosphate (isopentenyl-PP) synthesis and metabolism.** Farnesyl-PP: farnesyl-diphosphate; Geranyl-PP: geranyl-diphosphate; Geranylgeranyl-PP: geranylgeranyl-diphosphate; GSH: glutathione; GSSG: glutathione disulfide; HMG-CoA: 3-hydroxy-3-methylglutaryl coenzyme-A; Lipid-OH: lipid alcohol; Lipid-OOH: lipid peroxide; Se: selenium. Solid arrows indicate the sequence of the enzymatic reactions whereas dashed arrows indicate the final biological event

prior history of breast cancer. Seventeen women with isolated AH on primary excisional biopsies and subsequent reduction mammoplasty participated in the study. Paired samples of AH and corresponding HN tissue were collected with informed consent from the patients. The HN tissue was collected at least 1 cm away from AH in the same formalin-fixed and paraffin-embedded tissue block or a different block. The case series comprised eight lobular lesions (ALH and/or classic lobular carcinoma in situ) and nine ductal lesions (ADH and/or flat epithelial atypia). Four independent samples of normal breast tissue (NOR) were collected to serve as a control. The complete transcriptome of the samples was evaluated using the [HuGene-1_0-st] Affymetrix Human Gene 1.0 ST Array [transcript (gene) version] (GEO accession GPL6244), and the expression estimates, which were filtered and $\log_2$ transformed, were uploaded in the GEO repository.

## Gene selection

In addition to *GPX4*, which codes for glutathione peroxidase 4, eight genes were selected for the study. Of these genes, four code for crucial enzymes involved in isopentenyl-diphosphate synthesis and metabolism (Figure 1): *HMGCR* (3-hydroxy-3-methylglutaryl coenzyme-A reductase), which encodes the enzyme that converts HMG-CoA into mevalonic acid; *FDPS* (farnesyl-diphosphate synthase), which encodes the enzyme that catalyzes the synthesis of the farnesyl-diphosphate with geranyl-diphosphate as an intermediate step; *FDFT1* (farnesyl-diphosphate farnesyltransferase 1), which encodes the enzyme that catalyzes the formation of squalene, the committed intermediate in the biosynthesis of cholesterol and sterols; *GGPS1* (geranylgeranyl-diphosphate synthase 1), which encodes the enzyme that converts geranyl-diphosphate to geranylgeranyl-diphosphate, an essential element for the post-translational geranylgeranylation of the proteins. The other four genes code for the components of the cyclin D1-CDK4/6 complex: *CCND1* (cyclin D1), *CDK4* (cyclin-dependent kinase 4), *CDK6* (cyclin-dependent kinase 6), and *CDKN1B* (cyclin-dependent kinase inhibitor 1B) [18].

### Statistical analysis

Shapiro-Wilk was used to test normal distribution. The non-normal distribution was expressed with median and interquartile range (IQR), and non-parametric tests were used. Wilcoxon test was used for paired samples. For non-paired samples, Kruskal-Wallis and Wilcoxon tests were used. Spearman correlation coefficient was used to evaluate the correlation between genes. R Core Team version 4.1.2 (http://www.R-project.org) was used to analyze. $P < 0.05$ was defined as statistically significant.

## Results

### *GPX4* expression in atypical hyperplasia and corresponding histologically normal tissue

Kruskal-Wallis test indicated that AHs expressed a significantly higher level of *GPX4* than the corresponding HN tissue, which in turn expressed a statistically significant higher level of *GPX4* than normal tissue (Figure 2A). In particular, the Wilcoxon test indicated that all the comparisons were statistically significant (HN versus NOR: 0.94 vs. 0.73, $P = 0.0176$; AH versus HN: 1.15 vs. 0.94, $P = 0.0229$; AH versus NOR: 1.15 vs. 0.73, $P = 0.0063$).

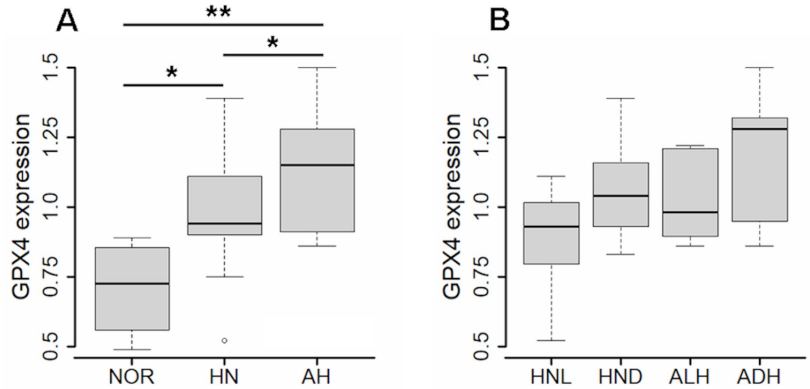


**Figure 2. Expression of *GPX4* gene in normal tissue, histologically normal tissue and atypical hyperplasia.** (**A**) Expression of *GPX4* in atypical hyperplasia (AH, $N = 17$), corresponding histologically normal (HN, $N = 17$) tissue, and normal breast tissue (NOR, $N = 4$). (**B**) Expression of *GPX4* in atypical lobular hyperplasia (ALH, $N = 8$), atypical ductal hyperplasia (ADH, $N = 9$), and corresponding HN tissue [respectively, HNL (HN lobular), $N = 8$, and HND (HN ductal), $N = 9$]. The differences were evaluated by the unpaired Wilcoxon test; values of $P < 0.05$ were considered statistically significant, and marked as * ($P < 0.05$) and ** ($P < 0.01$)

When ALH and ADH were analyzed individually, the level of *GPX4* in the two subtypes was not statistically different. Likewise, the level of *GPX4* did not differ in the HN tissue adjacent to the two AH subtypes (Figure 2B).

### Expression of the genes involved in the control of the G1-phase of the cell cycle and their association with *GPX4*

Kruskal-Wallis test indicated that AHs expressed a level of *CCND1* higher than the corresponding HN tissue or NOR (Figure 3A) as confirmed by the Wilcoxon test, according to which AH versus HN: 0.96 vs. 0.76, $P = 0.0099$, and AH versus NOR: 0.96 vs. 0.75, $P = 0.0011$.

When ALH and ADH were considered individually (Figure 3B), the expression level of *CCND1* was similar in the two AH subtypes (0.95 and 0.96, respectively) and higher than the corresponding HN tissue even not in a statistically significant manner [ALH versus HNL (HN lobular): 0.95 vs. 0.73, $P = 0.0584$; ADH versus HND (HN ductal): 0.96 vs. 0.76, $P = 0.0742$].

As regards the other components of the cyclin D1-CDK4/6 complex, while the expression of *CDK4* was similar in all tissues (Figure 3C), also when ALH and ADH were considered individually (Figure 3D), the expression of *CDK6* significantly decreased in AHs and corresponding HN tissue when compared to NOR (Figure 3E) as confirmed by the Wilcoxon test according to which AH versus HN: –0.03 vs. 0.02, $P = 0.0221$, and AH versus NOR: –0.03 vs. 0.23, $P = 0.0089$. The expression of *CDKN1B*, on the contrary, showed an

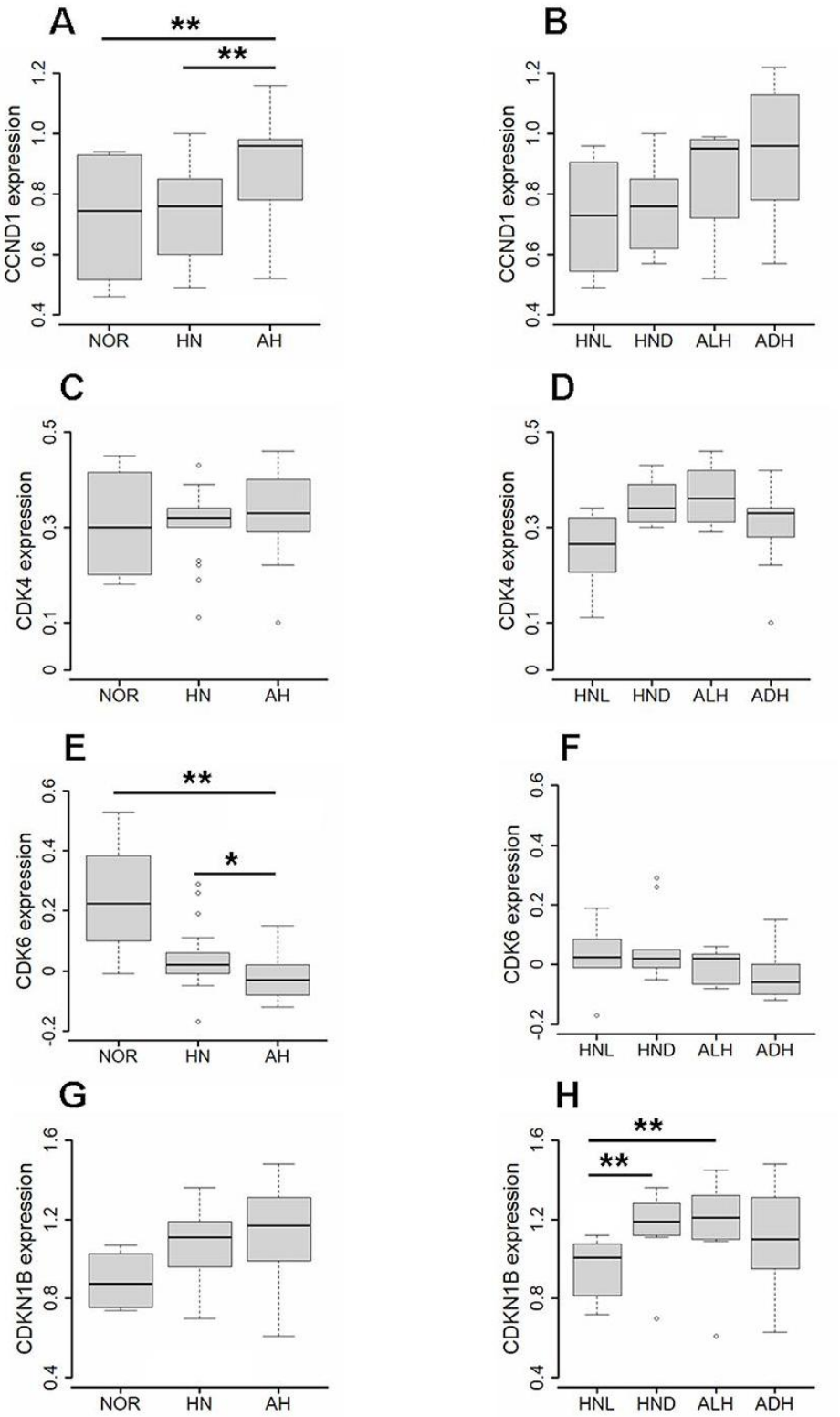


**Figure 3. Expression of *CCND1*, *CDK4*, *CDK6*, and *CDKN1B* gene in normal tissue, histologically normal tissue and atypical hyperplasia.** (**A**) Expression of *CCND1* in atypical hyperplasia (AH, *N* = 17), corresponding histologically normal (HN, *N* = 17) tissue, and normal breast tissue (NOR, *N* = 4) evaluated by the unpaired Wilcoxon test. (**B**) Expression of *CCND1* in atypical lobular hyperplasia (ALH, *N* = 8), atypical ductal hyperplasia (ADH, *N* = 9), and corresponding HN tissue (respectively, HNL, *N* = 8, and HND, *N* = 9) evaluated by the paired Wilcoxon test. (**C**) Expression of *CDK4* in AH, HN, and NOR subgroups evaluated by the unpaired Wilcoxon test. (**D**) Expression of *CDK4* in ALH, ADH, HNL, and HND subgroups evaluated by the paired Wilcoxon test. (**E**) Expression of *CDK6* in AH, HN, and NOR subgroups evaluated by the unpaired Wilcoxon test. (**F**) Expression of *CDK6* in ALH, ADH, HNL, and HND subgroups evaluated by the paired Wilcoxon test. (**G**) Expression of *CDKN1B* in AH, HN, and NOR subgroups evaluated by the unpaired Wilcoxon test. (**H**) Expression of *CDKN1B* in ALH, ADH, HNL, and HND subgroups evaluated by the paired Wilcoxon test. Values of $P < 0.05$ were considered statistically significant and marked as * ($P < 0.05$) and ** ($P < 0.01$)

increasing trend in AHs and corresponding HN tissue when compared to NOR (Figure 3G), although the difference did not reach statistical significance (AH versus NOR: 1.17 vs. 0.88, $P = 0.0648$, and HN versus NOR: 1.11 vs. 0.88, $P = 0.0911$).

When ALH and ADH were analyzed individually, *CDK6* was found expressed similarly in the two AH subtypes and their corresponding HN tissue (Figure 3F), whereas *CDKN1B* was significantly less expressed in the HN surrounding ALH than the HN surrounding ADH (HNL versus HND: 1.01 vs. 1.19, $P = 0.0093$) or ALH (HNL versus ALH: 1.01 vs. 1.21, $P = 0.0078$) (Figure 3H).

Correlation analysis indicated that in addition to the differential expression found in AH compared to the corresponding HN or NOR, *CCND1*, *CDK6*, and *CDKN1B* genes significantly changed their interrelationship according to the tissue. While in NOR, *CCND1* was highly associated with both genes (*CCND1*CDK6*: $r = 0.80$ and *CCND1*CDKN1B*: $r = 0.81$), in HN tissue, the association profile changed depending on the AH subtype. Thus, the HN tissue adjacent to ALH showed a correlation degree between *CCND1* and *CDK6* similar to that of the NOR ($r = 0.80$), which substantially decreased in ALH ($r = 0.49$); in the HN tissue adjacent to ADH, the degree of correlation between the two genes decreased dramatically ($r = 0.33$) and disappeared in ADH ($r = 0.10$). Furthermore, the positive association of *CCND1* with *CDKN1B* decreased significantly in both AH subtypes (ALH: $r = 0.49$ and ADH: $r = 0.57$) and corresponding HN tissue (HNL: $r = 0.38$ and HND: $r = 0.41$). Conversely, the correlation analysis showed a substantial increase in the degree of association between *CDKN1B* and *GPX4* in both AH subtypes (ALH: $r = 0.81$ and ADH: $r = 0.78$) when compared to the corresponding HN tissue (HNL: $r = 0.45$ and HND: $r = 0.44$).

## Expression of the genes involved in the production and metabolism of isopentenyl-diphosphate and their association with *GPX4*

Statistical analysis indicated that, of the genes involved in the production and metabolism of isopentenyl-diphosphate, only *GGPS1* was differentially expressed in AHs compared to the corresponding HN tissue (AH versus HN: 0.77 vs. 0.61, $P = 0.0141$) and that, when ALH and ADH were considered individually, the ADH subtype expressed a higher level of *GGPS1* than ALH (ADH versus ALH: 0.82 vs. 0.62, $P = 0.0236$) (Figure 4).

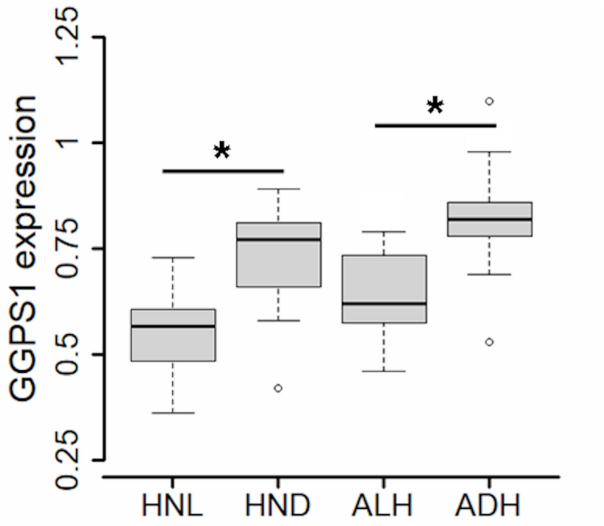


**Figure 4. Expression of *GGPS1* gene in atypical lobular hyperplasia (ALH, *N* = 8), atypical ductal hyperplasia (ADH, *N* = 9), and corresponding HN tissue (respectively, HNL, *N* = 8, and HND, *N* = 9) evaluated by the paired Wilcoxon test.** Values of $P < 0.05$ were considered statistically significant and marked as * ($P < 0.05$)

Likewise, the HN tissue surrounding ADH expressed a higher level of *GGPS1* than the HN tissue surrounding ALH (HND versus HNL: 0.77 vs. 0.57, $P = 0.0274$). Correlation analysis (Figure 5) showed that also the association of *GPX4* with *GGPS1* increased significantly in ADH and the corresponding HND tissue (respectively, $r = 0.75$, $P = 0.0205$ and $r = 0.72$, $P = 0.0369$) whereas, in ALH and corresponding HNL tissue, the association of the two genes was (respectively, $r = 0.37$, $P = 0.3652$ and $r = 0.55$, $P = 0.1710$) similar to that found in NOR ($r = 0.40$, $P = 0.2912$).

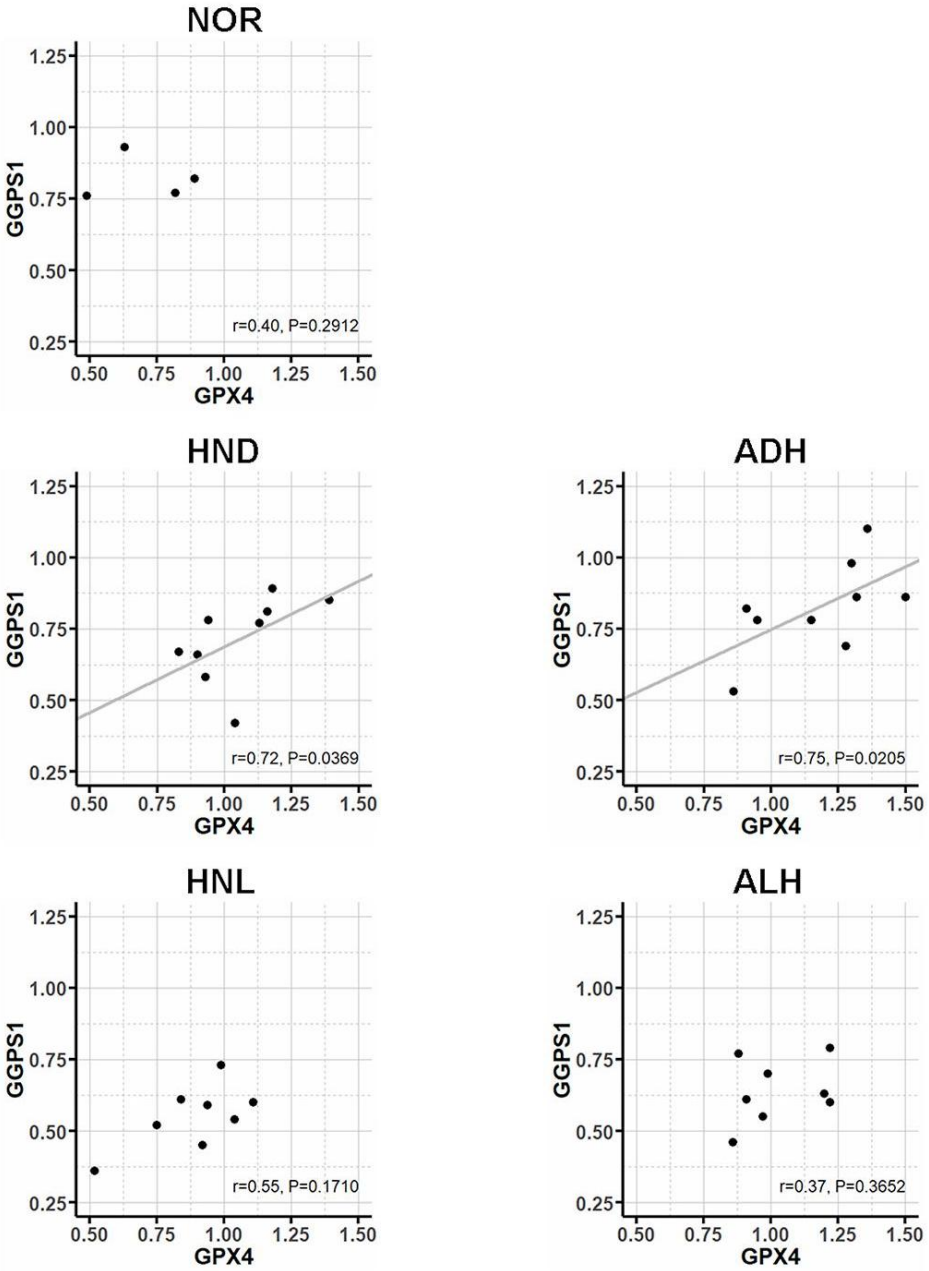


**Figure 5. Correlation between the expression of *GPX4* and *GGPS1* gene in normal breast tissue (NOR, *N* =4), atypical ductal hyperplasia (ADH, *N* = 9), atypical lobular hyperplasia (ALH, *N* = 8), and corresponding HN tissue (respectively, HNL, *N* = 8, and HND, *N* = 9) evaluated by Spearman correlation coefficient**

## Discussion

The finding that AHs expressed a level of the *GPX4* gene higher than the surrounding HN tissue suggests that they could exploit the detoxifying property of this enzyme to escape ferroptosis. Furthermore, the observation that the HN tissue expressed a higher level of *GPX4* compared to NOR indicates that the overexpression of *GPX4* is an early molecular event that may predispose the normal tissue to transform into AH and proliferate. The differential expression of the genes that control the G1 phase of the cell cycle (specifically, the increased expression of *CCND1* and *CDKN1B* and the substantial decrease in the expression of *CDK6*) along with the significant increase in the association between *CDKN1B* and *GPX4*, further supports the link between ferroptosis escape and cell proliferation.

As regards the association between the mevalonate pathway and GPX4 biosynthesis, present findings indicated that AHs expressed high levels of *HMGCR* compared to the corresponding HN tissue, in line with the augmented requirement of isopentenyl-diphosphate because of *GPX4* overexpression. Remarkable is also the finding that AHs overexpressed *GGPS1*, which encodes for the enzyme that synthesizes

geranylgeranyl-diphosphate, a molecule playing an essential role in the posttranslational prenylation of several proteins, including Rho GTPases, which act as molecular switches in various cell processes and signaling pathways, including the Hippo signaling pathway [19]. By controlling the nuclear translocation of the Yes-associated protein (YAP) coactivator, the Hippo signaling pathway regulates the expression of several genes involved in cell proliferation promotion and apoptosis inhibition [20, 21]. The observation that ADHs, the most aggressive of the two AH subtypes, expressed higher levels of *GGPS1* compared to ALHs, along with the finding that in ADHs and the corresponding HN tissue, the expression of *GGPS1* associated with that of *GPX4* suggests that the propensity of ADH to proliferate and transform into invasive cancer could be the result of the concomitant escape from ferroptosis, inhibition of the Hippo pathway, YAP activation, and cell proliferation.

In this complex scenario, the mevalonate pathway should play a crucial role in providing the isopentenyl-diphosphate required for the biosynthesis of GPX4 and the geranylgeranyl-diphosphate necessary for Rho GTPases prenylation.

Although the findings are based on a small case series and lack support from immunohistochemical evaluation of the corresponding proteins, current results suggest that using statins to inhibit HMG-CoA reductase could be a safe and effective approach to prevent the progression of AHs (especially ADHs) to invasive cancer, resulting in the concurrent promotion of ferroptosis and inhibition of Rho GTPase prenylation. Anyway, further clinical studies are needed to confirm this promising therapeutic approach.

## Abbreviations

ADH: atypical ductal hyperplasia

AH: atypical hyperplasia

ALH: atypical lobular hyperplasia

CCND1: cyclin D1

CDK: cyclin-dependent kinase

CDKN1B: cyclin-dependent kinase inhibitor 1B

FDFT1: farnesyl-diphosphate farnesyltransferase 1

FDPS: farnesyl-diphosphate synthase

GEO: Gene Expression Omnibus

GGPS1: geranylgeranyl-diphosphate synthase 1

GPX: glutathione peroxidases

HMGCR: 3-hydroxy-3-methylglutaryl coenzyme-A reductase

HN: histologically normal

HND: histologically normal ductal

HNL: histologically normal lobular

NOR: normal breast tissue

ROS: reactive oxygen species

TDLU: terminal duct lobular unit

YAP: Yes-associated protein

## Declarations

### Author contributions

DC: Conceptualization, Investigation, Writing—original draft, Writing—review & editing.

### Conflicts of interest

The author declares that she has no conflicts of interest.

### Ethical approval

The study utilized summary statistics from the publicly available dataset, the NCBI Gene Expression Omnibus (GEO) Repository. The original study was approved by the Institutional Review Board of Baystate Health, Springfield, MA, under protocol number 182463. As such, this research did not involve direct contact with human participants or the collection of new personal data, and therefore, ethical approval was not required.

### Consent to participate

This study analyzed secondary data from the NCBI Gene Expression Omnibus (GEO) Repository. Therefore, consent to participate is not required.

### Consent to publication

Not applicable.

### Availability of data and materials

The datasets analyzed for this study can be found in the NCBI Gene Expression Omnibus (GEO) Repository (https://www.ncbi.nlm.nih.gov/geo/).

### Funding

Not applicable.



## References

1. Figueroa JD, Pfeiffer RM, Patel DA, Linville L, Brinton LA, Gierach GL, et al. Terminal duct lobular unit involution of the normal breast: implications for breast cancer etiology. J Natl Cancer Inst. 2014;106:dju286. [DOI] [PubMed] [PMC]
2. Page DL, Rogers LW. Combined histologic and cytologic criteria for the diagnosis of mammary atypical ductal hyperplasia. Hum Pathol. 1992;23:1095–7. [DOI] [PubMed]
3. Martinez AP, Cohen C, Hanley KZ, Li XB. Estrogen Receptor and Cytokeratin 5 Are Reliable Markers to Separate Usual Ductal Hyperplasia From Atypical Ductal Hyperplasia and Low-Grade Ductal Carcinoma In Situ. Arch Pathol Lab Med. 2016;140:686–9. [DOI] [PubMed]
4. Page DL, Kidd TE Jr, Dupont WD, Simpson JF, Rogers LW. Lobular neoplasia of the breast: higher risk for subsequent invasive cancer predicted by more extensive disease. Hum Pathol. 1991;22:1232–9. [DOI] [PubMed]
5. Visscher DW, Frank RD, Carter JM, Vierkant RA, Winham SJ, Heinzen EP, et al. Breast Cancer Risk and Progressive Histology in Serial Benign Biopsies. J Natl Cancer Inst. 2017;109:djx035. [DOI] [PubMed] [PMC]
6. Donaldson AR, McCarthy C, Goraya S, Pederson HJ, Sturgis CD, Grobmyer SR, et al. Breast cancer risk associated with atypical hyperplasia and lobular carcinoma in situ initially diagnosed on core-needle biopsy. Cancer. 2018;124:459–65. [DOI] [PubMed]
7. Degnim AC, King TA. Surgical management of high-risk breast lesions. Surg Clin North Am. 2013;93:329–40. [DOI] [PubMed]
8. Danforth DN. Molecular profile of atypical hyperplasia of the breast. Breast Cancer Res Treat. 2018;167:9–29. [DOI] [PubMed]

9. Ambrosone CB. Oxidants and antioxidants in breast cancer. Antioxid Redox Signal. 2000;2:903–17. [DOI] [PubMed]
10. Dixon SJ, Lemberg KM, Lamprecht MR, Skouta R, Zaitsev EM, Gleason CE, et al. Ferroptosis: an iron-dependent form of nonapoptotic cell death. Cell. 2012;149:1060–72. [DOI] [PubMed] [PMC]
11. Yang WS, SriRamaratnam R, Welsch ME, Shimada K, Skouta R, Viswanathan VS, et al. Regulation of ferroptotic cancer cell death by GPX4. Cell. 2014;156:317–31. [DOI] [PubMed] [PMC]
12. Seibt TM, Proneth B, Conrad M. Role of GPX4 in ferroptosis and its pharmacological implication. Free Radic Biol Med. 2019;133:144–52. [DOI] [PubMed]
13. Warner GJ, Berry MJ, Moustafa ME, Carlson BA, Hatfield DL, Faust JR. Inhibition of selenoprotein synthesis by selenocysteine tRNA[Ser]Sec lacking isopentenyladenosine. J Biol Chem. 2000;275:28110–9. [DOI] [PubMed]
14. Wang S, Wei W, Ma N, Qu Y, Liu Q. Molecular mechanisms of ferroptosis and its role in prostate cancer therapy. Crit Rev Oncol Hematol. 2022;176:103732. [DOI] [PubMed]
15. Sekhar KR, Cyr S, Baregamian N. Ferroptosis Inducers in Thyroid Cancer. World J Surg. 2023;47:371–81. [DOI] [PubMed]
16. Zhang W, Jiang B, Liu Y, Xu L, Wan M. Bufotalin induces ferroptosis in non-small cell lung cancer cells by facilitating the ubiquitination and degradation of GPX4. Free Radic Biol Med. 2022;180:75–84. [DOI] [PubMed]
17. Gregory KJ, Roberts AL, Conlon EM, Mayfield JA, Hagen MJ, Crisi GM, et al. Gene expression signature of atypical breast hyperplasia and regulation by SFRP1. Breast Cancer Res. 2019;21:76. [DOI] [PubMed] [PMC]
18. Graña X, Reddy EP. Cell cycle control in mammalian cells: role of cyclins, cyclin dependent kinases (CDKs), growth suppressor genes and cyclin-dependent kinase inhibitors (CKIs). Oncogene. 1995;11:211–9. [PubMed]
19. Etienne-Manneville S, Hall A. Rho GTPases in cell biology. Nature. 2002;420:629–35. [DOI] [PubMed]
20. Yu FX, Guan KL. The Hippo pathway: regulators and regulations. Genes Dev. 2013;27:355–71. [DOI] [PubMed] [PMC]
21. Zhao B, Wei X, Li W, Udan RS, Yang Q, Kim J, et al. Inactivation of YAP oncoprotein by the Hippo pathway is involved in cell contact inhibition and tissue growth control. Genes Dev. 2007;21:2747–61. [DOI] [PubMed] [PMC]