Original Research Article

DOI: http://dx.doi.org/10.18203/2349-2902.isj20171149

Possible mechanisms of development of carcinoma of breast in patients with early-onset cataract

Kaushal Deep Singh^{1*}, Shahbaz Habib Faridi¹, Mehershree Lodhi²

¹Department of Surgery, Jawaharlal Nehru Medical College, Aligarh, Uttar Pradesh, India ²Department of Microbiology, King George Medical University, Lucknow, Uttar Pradesh, India

Received: 05 February 2017 **Accepted:** 07 March 2017

*Correspondence: Dr. Kaushal Deep Singh, E-mail: drkdsm@gmail.com

Copyright: © the author(s), publisher and licensee Medip Academy. This is an open-access article distributed under the terms of the Creative Commons Attribution Non-Commercial License, which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

ABSTRACT

Background: A nation-wide population based retrospective cohort study from Taiwan in 2014 suggested a propensity of developing breast cancer in young females with early-onset cataract. One such patient presented to us who was a young non-obese female with a large lump in the right breast with skin nodules and bilateral painless progressive diminution of vision. Patient was diagnosed as locally advanced carcinoma of right breast with axillary metastasis (stage IIIB) and bilateral early-onset nuclear cataract. Mechanism of this possible association has never been described.

Methods: A comprehensive online English literature search was done using various electronic search databases. Different search terms related to pathogenesis of carcinoma breast and cataract, and their possible association, were used. An advanced search was further conducted by combining all the search fields in abstracts, keywords, and titles. **Results:** We summarized the data from the searched articles and found that there are certain biochemical pathways and genetic associations that link cancer to cataract. We identified four specific links between carcinoma breast and cataract (in some cases even early-onset cataract). The four mechanisms which explained this possible association included metabolic syndrome, action of reactive oxygen species, genetic polymorphisms and environmental factors. **Conclusions:** The evidence linking early-onset cataract with cancer is relatively new so possible mechanisms of development of breast cancer in patients with early-onset cataract needs to be elucidated. These plausible connections can further help to take up large scale molecular, biochemical, epidemiological and clinical studies to investigate this association in terms of cause-effect relationship. The impact this association can have, on understanding cataract and cancer pathogenesis; and its potential in reducing cancer incidence in patients with EOC, can be profound.

Keywords: Carcinoma breast, Early onset cataract, Glutathione, Glyphosate, Metabolic syndrome, Reactive oxygen species

INTRODUCTION

Cataract may be present in unilateral or bilateral forms in patients presenting with carcinoma breast. This is especially true for elderly post-menopausal females. Moreover, tamoxifen and raloxifene intake is also associated with development of cataract in breast cancer (BC) patients taking them. Age related/senile cataract is defined as cataract occurring in people >50 years of age,

unrelated to known mechanical, chemical, or radiation trauma.² But cataract may present in younger patients referred to as early-onset cataract (EOC). No definitive relationship was reported between cataract and breast cancer. However, in a recent nation-wide population based retrospective cohort study from Taiwan by Chiang et al, an increased incidence of BC was observed in patients presenting with EOC.² One such young non-obese female presented to us who had bilateral

progressive vision loss due to cataract for five years and subsequently she developed carcinoma of the right breast (Stage IIIB at presentation) (Figure 1). Patient had no history of trauma to eyes, watering, glares, floaters or redness of eyes; nor did she have diabetes mellitus or any other metabolic abnormality. We lost the patient as she died in an unfortunate road traffic accident. However, this interesting possible association motivated us to seek out the link between these two disease entities viz. breast cancer and early-onset cataract.



Figure 1: Right breast mass with bilateral early-onset cataract at presentation.

METHODS

A comprehensive online English literature search was done using various electronic search databases including "Med-line", "PubMed", "Scopus", "Web of Science" and "Google Scholar". Different search terms related to pathogenesis of carcinoma breast and cataract were used like "pathogenesis of carcinoma breast", "pathogenesis of cataract", "pathogenesis of early onset cataract", "cancer and cataract", "association between carcinoma breast and cataract", and "link between cancer and early onset cataract". An advanced search was also carried out by combining all search fields in keywords, abstracts and/or titles. Using these search terms, appropriate articles were selected for a comprehensive review. Investigation of literature was further supplemented by searching the referenced articles created by original investigators. Finally, all the selected articles were confirmed for duplications and excluded, if it was observed.

RESULTS

Early-onset cataract (EOC) is thought to be due to insufficient anti-oxidative function.^{2,3} Carcinogenesis is similarly related to oxidative stress and oxidative damage.⁴ This anti-oxidative insufficiency may occur as a result of faulty anti-oxidative and/or deoxyribonucleic acid (DNA) repair or due to overproduction of reactive oxygen species (ROS) which leads to oxidative damage to cellular macromolecules, genomic instability and uncontrolled cell proliferation.⁴ This similar mechanism might explain the propensity of development of certain

cancers in patients with EOC. The mechanisms which we found in our literature review for the possible association between BC and EOC included metabolic syndrome, action of reactive oxygen species, genetic polymorphisms and environmental factors.

DISCUSSION

We describe here the possible mechanisms linking EOC with BC which we found during our literature review. Table 1 summarizes all the studies which explain the various possible links between EOC and BC.

Table 1: Studies explaining the various possible links between Early-onset cataract and Breast cancer.

Possible links between early- onset cataract and breast cancer	Studies explaining the possible mechanisms
Metabolic Syndrome	Forte et al ⁶ - Diabetes and obesity are linked closely and both in-turn are associated with an increased incidence of solid tissue cancers.
	Tan et al ⁸ - Metabolic syndrome is associated with all three types of cataracts.
	Paunksnis et al ⁹ - Increased odds of cataract formation in middle-aged females with arterial hypertension, obesity and hypertriglyceridemia.
Reactive Oxygen Species	Klaunig et al ⁴ , Martinez-Outschoorn et al ¹³ - ROS alter gene expression patterns and thus contribute to carcinogenesis through oxidative stress in fibroblasts which then proliferate uncontrollably. Augusteyn et al ¹⁴ - ROS lead to lens opacification through oxidative damage to lens proteins.
	West et al ¹⁵ - Oxidative damage associated with ultraviolet light plays a key role in the development of cataracts.
Genetic Factors	Saadat et al ¹⁷ - Increased incidence of cataract in subjects with the null genotype of GSTM1.
	Sohail et al ¹⁹ - Polymorphisms of GSTM1, GSTT1, GSTP1 and GSTO2 have been shown to be associated with increased risk of developing breast cancer.
Environmental Factors	Swanson et al ²¹ - Increased use of glyphosate in the United States has been demonstrated with increase in the incidence and/or death rate of multiple diseases (including cataract) and several cancers (like breast cancer, liver cancer etc.). Stout et al ²² - Glyphosate induced a statistically significant cataractous lens formation in male as well as female rats. Séralini et al ²⁵ - Female rats fed with GM
	Séralini et al ²⁵ - Female rats fed with GM maize treated with glyphosate had very high propensity of developing mammary fibroadenomas and adenocarcinomas

ROS - reactive oxygen species; GST - glutathione S-transferase; GM - genetically modified.

Metabolic syndrome

Patients with metabolic syndrome suffer from problems like obesity, dyslipidemia, hypertension, diabetes and insulin resistance.⁵ Forte et al found that diabetes and obesity are linked closely and both in-turn are associated with an increased incidence of solid tissue cancers.⁶ Chen et al found a two- to three-fold increase in the risk of hepatocellular carcinoma (HCC) in patients with diabetes.⁷ Tan et al reported in their study that metabolic syndrome is associated with all three types of cataracts (nuclear, cortical, and posterior sub-capsular cataracts).⁸ Similarly, Paunksnis et al reported increased odds of cataract formation in middle-aged females with arterial hypertension, obesity and hypertriglyceridemia.⁹

Diabetes and hyperglycemia are known to promote the glycation of lens proteins and the hyperosmotic effects of sorbitol on lens fibers through the aldose reductase pathway. Leptin has been shown to be involved in cataract formation. People with hyperlipidemia are likely to have hyperleptinemia and leptin resistance. Hence, hyperlipidemia may promote cataract formation. Thus, we saw that metabolic syndrome can be the biochemical link between cancer and cataract as it acts as a precursor to both.

Reactive oxygen species (ROS)

ROS alter gene expression patterns and thus contribute to carcinogenesis through oxidative stress in fibroblasts which then proliferate uncontrollably. Als ROS lead to lens opacification through oxidative damage to lens proteins. Moreover, oxidative damage associated with ultraviolet light plays a key role in the development of cataracts. Henceforth, if the anti-oxidative function is maleficent at a younger age, EOC may occur because ROS-damaged DNA cannot be repaired, leading to a higher cancer possibility in young adults.

Genetic factors

Genetic polymorphisms occurring in genes predisposing to carcinogenesis or cataractogenesis are another possible factor linking EOC with cancer.16 One of the most wellknown cancer-related polymorphic genes encoding for enzymes involved in free radical metabolism is the glutathione S-transferase (GST) gene system.¹⁷ GST are phase II iso-enzymes that safeguard against endogenous oxidative stress and exogenous toxins. They are involved in the detoxification of a variety of electrophilic compounds generated by ROS damage to intracellular molecules including DNA. Saadat et al found an increased incidence of cataract in subjects with the null genotype of GSTM1 (odds ratio-1.51; p<0.05).¹⁷ The polymorphisms of GSTM1, GSTT1, GSTP1 and GSTO2 have been shown to be associated with increased risk of developing breast cancer, HCC and skin cancers. 19 Thus, the polymorphism of GST may be a possible link between EOC and carcinogenesis.

Environmental factors

Wide use of chemicals in our daily lives could also be a potential link relating EOC and cancer. Glyphosate is one such herbicide which is now a major crop management strategy for pre-harvest desiccation of perennial weed control especially with genetically modified (GM) crops.²⁰ The increased use of glyphosate in the United States has been demonstrated with increase in the incidence and/or death rate of multiple diseases (including cataract) and several cancers (like breast cancer, liver cancer etc.).²¹

Multiple genotoxic and potentially carcinogenic metabolites of fructose are plausibly present in foods derived from glyphosate-resistant crops, or as a contaminant in glyphosate-based products, or as a breakdown product generated endogenously following glyphosate exposure. These include glyoxylate, glyoxal and methylglyoxal. Stout et al ²² conducted a study between 1987 and 1989 and found that glyphosate induced a statistically significant (p<0.05) cataractous lens formation in male as well as female rats. Methylglyoxal is implicated in cataract development by inducing endoplasmic reticulum stress in human lens epithelial cells, and activating an unfolded protein response leading to overproduction of ROS and altering the cellular redox balance toward lens oxidation.²³ In vitro studies have also confirmed that glyphosate stimulates proliferation of human breast cancer cells when present in concentrations of parts per trillion.²⁴ This effect is specific to hormone-dependent cell lines, and is mediated by the ability of glyphosate to act as an estrogenic agent.

A study on rats conducted by Séralini et al demonstrated that female rats fed with GM maize treated with glyphosate had very high propensity of developing mammary fibroadenomas and adenocarcinomas.²⁵ Glyphosate also impairs metabolism of toxic phenolic compounds such as nonylphenols, diethylstilbestrol, and bisphenol A; all widely recognized to possess estrogenic activity, thus having an indirect potential impact on increasing risk of breast cancer.²⁰ Use of glyphosate possesses a real possible risk linking development of BC and EOC. Our patient was also involved in agricultural activities since the age of 16 years.

CONCLUSION

The evidence linking early-onset cataract with cancer is relatively new and needs to be studied in more detail especially in terms of controlled studies. These plausible connections can further help to take up large scale molecular, biochemical, epidemiological and clinical studies to investigate this association in terms of cause-effect relationship. The impact this association can have, on understanding cataract and cancer pathogenesis; and its potential in reducing cancer incidence in patients with EOC, can be profound.

Funding: No funding sources Conflict of interest: None declared

Ethical approval: The study was approved by the

institutional ethics committee

REFERENCES

- Wickerham DL, Costantino JP, Vogel VG, Cronin WM, Cecchini RS, Ford LG, et al. The use of tamoxifen and raloxifene for the prevention of breast cancer. Recent Results Cancer Res. 2009;181:113-9.
- Gupta VB, Rajagopala M, Ravishankar B. Etiopathogenesis of cataract: an appraisal. Indian J Ophthalmol. 2014;62(2):103-10.
- 3. Chiang CC, Lin CL, Peng CL, Sung FC, Tsai YY. Increased risk of cancer in patients with early-onset cataracts: A nationwide population-based study. Cancer Sci. 2014;105(4):431-6.
- Klaunig JE, Kamendulis LM, Hocevar BA. Oxidative stress and oxidative damage in carcinogenesis. Toxicol Pathol. 2010;38:96-109.
- Farrell GC, Larter CZ. Nonalcoholic fatty liver disease: from steatosis to cirrhosis. Hepatology. 2006;43:S99-112.
- 6. Forte V, Pandey A, Abdelmessih R, Forte G, Whaley-Connell A, Sowers JR, et al. Obesity, diabetes, the cardiorenal syndrome, and risk for cancer. Cardiorenal Med. 2012;2(2):143-62.
- Chen CL, Yang HI, Yang WS, Liu CJ, Chen PJ, You SL, et al. Metabolic factors and risk of hepatocellular carcinoma by chronic hepatitis B/C infection: a follow-up study in Taiwan. Gastroenterology. 2008;135(1):111-21.
- 8. Tan JS, Wang JJ, Mitchell P. Influence of diabetes and cardiovascular disease on the long-term incidence of cataract: the Blue Mountains eye study. Ophthalmic Epidemiol. 2008;15:317-27.
- Paunksnis A, Bojarskiene F, Cimbalas A, Cerniauskiene LR, Luksiene DI, Tamosiunas A. Relation between cataract and metabolic syndrome and its components. Eur J Ophthalmol. 2007;17(4):605-14.
- Stitt AW. Advanced glycation: An important pathological event in diabetic and age related ocular disease. Br J Ophthalmol. 2001;85:746-53.
- 11. Gomez-Ambrosi J, Salvador J, Fruhbeck G. Is hyperleptinemia involved in the development of age related lens opacities? Am J Clin Nutr. 2004;79:888-9.
- 12. Narin F, Atabek ME, Karakukcu M, Narin N, Kurtoglu S, Gumus H, et al. The association of plasma homocysteine levels with serum leptin and apolipoprotein B levels in childhood obesity. Ann Saudi Med. 2005;25(3):209-14.
- 13. Martinez-Outschoorn UE, Balliet RM, Rivadeneira DB, Chiavarina B, Pavlides S, Wang C, et al. Oxidative stress in cancer associated fibroblasts drives tumor-stroma co-evolution: A new paradigm for understanding tumor metabolism, the field effect and

- genomic instability in cancer cells. Cell cycle (Georgetown, Tex). 2010;9(16):3256-76.
- 14. Augusteyn RC. Protein modification in cataract: possible oxidative mechanisms. In: Duncan G, ed. Mechanisms of Cataract Formation in the Human Lens. London: Academic Press; 1981:72-111.
- West SK, Longstreth JD, Munoz BE, Pitcher HM, Duncan DD. Model of risk of cortical cataract in the US population with exposure to increased ultraviolet radiation due to stratospheric ozone depletion. Am J Epidemiol. 2005;162(11):1080-8.
- Hayes JD, Flanagan JU, Jowsey IR. Glutathione transferases. Annu Rev Pharmacol Toxicol. 2005;45:51–88.
- Saadat I, Ahmadi Z, Farvardin-Jahromi M, Saadat M. Association between cataract and genetic polymorphisms of GSTM1, GSTT1, and GSTO2 with respect of work place. Mol Vis. 2012;18:1996-2000.
- Vineis P. Cancer as an evolutionary process at the cell level: an epidemiological perspective. Carcinogenesis. 2003;24:1-6.
- 19. Sohail A, Kanwal N, Ali M, Sadia S, Masood AI, Ali F, et al. Effects of glutathione-S-transferase polymorphisms on the risk of breast cancer: a population-based case-control study in Pakistan. Environ Toxicol Pharmacol. 2013;35(2):143-53.
- Samsel A, Seneff S. Glyphosate, pathways to modern diseases iv: cancer and related pathologies. J Biol Phys Chem. 2015;15(3):121-59.
- Swanson NL, Leu A, Abrahamson J, Wallet B. Genetically engineered crops, glyphosate and the deterioration of health in the United States of America. J Org Syst. 2014;9:6-37.
- 22. Stout LD, Ruecker FA. Chronic study of glyphosate administered in feed to albino rats. Unpublished Study, Project No. MSL-10495. Monsanto Agricultural Company (2,175 pp.) Submitted to the US EPA MRID #416438-01; September 26, 1990.
- Palsamy P, Bidasee KR, Ayaki M, Augusteyn RC, Chan JY, Shinohara T. Methylglyoxal induces endoplasmic reticulum stress and DNA demethylation in the Keap1 promoter of human lens epithelial cells and age-related cataracts. Free Radic Biol Med. 2014;72:134-48.
- Thongprakaisang S, Thiantanawat A, Rangkadilok N, Suriyo T, Satayavivad J. Glyphosate induces human breast cancer cells growth via estrogen receptors. Food Chem Toxicol. 2013;59:129-36.
- 25. Séralini G-E, Clair E, Mesnage R, Gress S, Defarge N, Malatesta M, et al. Republished study: long-term toxicity of a Roundup herbicide and a Roundup-tolerant genetically modified maize. Environ Sci Eur. 2014;26(1):14.

Cite this article as: Singh KD, Faridi SH, Lodhi M. Possible mechanisms of development of carcinoma of breast in patients with early-onset cataract. Int Surg J 2017;4:1394-7.