Research Article
Open Access
CrossMark

The role of the placenta in breast carcinogenesis in the offspring

Abstract

Introduction: Following the long-established hypothesis that breast cancer originates in utero under hormonal influence, the authors of this study aim to examine whether placental weight and morphology relate to an offspring's future risk of developing breast cancer.

Methods: A comprehensive search of the Pubmed and Scopus online databases for studies regarding the influence of the placental weight and morphology on an offspring's future breast cancer risk was performed. The search included articles published between 1990 and 2023.

Results: In total, five studies examining the issue under question emerged. Two studies found only a weak and non-significant positive association between placental weight and an offspring's breast cancer risk and two did not find any association at all. The fifth study demonstrated that increased placental volume elevated breast cancer risk in the offspring. The presence of a placental tumor was also strongly positively associated with cancer risk. Fibrin deposition and hemorrhage, on the other hand, had a protective effect.

Conclusion: Further prospective studies with long-term follow-up are needed in order to establish an association between placental morphology and a daughter's future breast cancer risk.

Keywords: placenta, breast cancer, weight, morphology, syncytiotrophoblast

Volume 14 Issue 6 - 2023

Nicole Dimitra Sarantis, Chrisostomos Sofoudis, Georgios Salvanos
Department of Obstetrics and Gynecology Helena Venizelou Maternal Hospital Athens Greece

Correspondence: Dr. Chrisostomos Sofoudis MD, PhD, MPH, PostDoc, Department of Obstetrics and Gynecology Helena Venizelou Maternal Hospital Athens Greece, Ippokratous 209, 11472, Athens, Greece, Email chrisostomos.sofoudis@gmail.com

Received: November 27, 2023 | **Published:** December 18, 2023

Introduction

Following Professor Trichopoulos' hypothesis in 1990 that breast cancer originates in utero under the influence of pregnancy estrogens,[1] there has been a cascade of scientific research in an endeavor to correlate various perinatal characteristics and endogenous maternal and placental hormones with an offspring's future cancer risk. However, to this day, there remains a great gap in evidence regarding the role of the placenta and its association to a daughter's developing breast cancer. Very few studies have examined how placental weight and morphology affect this risk and, so far, no conclusions have been reached. The aim of our study is to shed light on this issue by reviewing the relevant literature and exploring possible pathophysiological mechanisms linking placental characteristics to an offspring's breast cancer risk.

Breast cancer has become the most commonly diagnosed cancer, accounting for 1 in 8 cancer diagnoses. In 2020, 2.3 million cases were diagnosed globally and 685000 women died of it.[2] According to Eurostat, breast cancer incidence in Europe is estimated to be 144/100000, with Northern and Western European countries exhibiting the highest rates. Greece is estimated to have an incidence of 122.3/100000.[3] Similarly, according to the American Cancer Society, breast cancer incidence in the United States is 128.1/100000.[4] Various predisposing factors have been identified; the most important are older age, hormonal status, nulliparity, hormone replacement therapy, family history of breast cancer, atypical ductal and lobular hyperplasia, exposure to ionizing radiation, alcohol consumption, smoking and obesity. Of all breast cancer cases, only 10% are hereditary and are most often associated with mutations in the BRCA1 and BRCA1 genes, as well as the TP3 and PTEN genes. For staging,[5] which is the most important prognostic factor, the TNM classification has been adapted (Table 1); it is comprised of assessment of primary tumor size (T), condition of axillary lymph nodes (N) and presence of distant metastasis (M). Features such as the expression of steroid receptors (estrogen, progesterone), HER-2 receptor and cellular proliferation index Ki67 are also taken into account, especially when planning treatment.[4] Treatment must be individualized and may be surgical, radiotherapy, chemotherapy, hormonal and monoclonal antibody therapy or, most commonly, a combination thereof.

Table 1 Breast cancer classification system[5]

Tumor Size (T)	
Tx	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis (DCIS)	Ductal carcinoma in situ
Tis (Paget)	Paget disease not associated with invasive carcinoma or DCIS
T1	Tumor size <=20mm
T2	Tumor size >20mm but <=50mm
T3	Tumor size >50mm
T4	Tumor size with direct extension to the chest wall and/or the skin with macroscopic changes

Table 1 Continued...

Presence of Nodal Metastasis (N)	
cNX	Regional nodes cannot be assessed (previously removed)
cN0	No regional nodal metastasis
cN1	Metastases to movable ipsilateral level I and/or level II axillary nodes
cN2	Metastases to fixed or matted ipsilateral level I and/or level II axillary nodes; or metastases to ipsilateral internal mammary nodes without axillary metastases
cN3	Metastases to ipsilateral level III axillary nodes with or without level I and/or level II axillary metastases; or metastases to ipsilateral internal mammary nodes with level I and/or level II axillary metastases; or metastases to ipsilateral supraclavicular nodes
Distant Metastases (M)	
M0	No clinical or imaging evidence of distant metastases
cM0 (+)	No clinical or imaging evidence of distant metastases, but with tumor cells or deposits measuring <=0.2mm detected in circulating blood, bone marrow, or other nonregional nodal tissue in the absence of clinical signs and symptoms of metastases
cM1	Distant metastases on the basis of clinical or imaging findings
pM1	Histologically proven distant metastases in solid organs; or, if in nonregional nodes, metastases measuring >0.2mm

American Joint Committee on Cancer's Staging System for Breast Cancer -8th Edition

The idea that certain placental characteristics may predispose to breast cancer was born due to the fact that the placenta is in its essence a highly functional endocrine organ with multiple roles. It produces several hormones, including human placental lactogen, placental growth hormone, progesterone, estrogen, human chorionic gonadotropin, relaxin, chorionic adrenocorticotropin, cytokine growth factors and many others. Most importantly, the placenta delivers oxygen and nutrients to the fetus through the maternal-placental circulation. Furthermore, it acts as a selective barrier to maternal hormones and environmental pollutants and has the ability to inactivate them through placental enzymes. The mature placenta is a discoid organ that has, on average, a diameter of 22cm and a weight of 500gr.[6,7] Placental insufficiency and impaired trophoblast invasion result in obstetric pathological conditions, such as pre-eclampsia and fetal growth restriction. Therefore, due to this complex and multifaceted endocrine role of the placenta, the question of whether placental weight and morphology affect the risk of breast cancer in the offspring arises.

Methods

The authors of this article performed a comprehensive search of the Pubmed and Scopus online databases for studies regarding the influence of the placental weight and morphology on an offspring's future breast cancer risk. The search included articles published between 1990 and 2023. All articles reporting studies that examined breast cancer in the offspring in relation to either placental weight or placental morphological characteristics at birth were included, regardless of study design. We excluded studies that reported solely on hormones produced by the placenta and/or the fetus and their possible association to breast cancer risk. Studies regarding the mother's breast cancer risk were also, de facto, excluded.

Results

Only five relevant studies emerged from the aforementioned extended search. Their results are presented in Table 2. Out of the five studies that directly examined the issue under question, two found only a weak and non-significant positive association between placental weight and an offspring's breast cancer risk and two did not find any association at all. Only one study, the most recent of the five, exhibited promising results linking placental characteristics to breast cancer. This study, however, differed from the previous ones in that it did not simply examine placental weight but rather investigated placental morphology. It was demonstrated that increased placental volume (which encompasses three dimensions – the largest and the smallest diameter and the thickness in cm) elevated breast cancer risk in the offspring. The presence of a placental tumor was also strongly positively associated with cancer risk. Fibrin deposition and hemorrhage, on the other hand, had a protective effect. According to this study, therefore, it was the morphological characteristics rather than the actual weight that had a causative relation to breast cancer development.

Table 2 Studies examining breast cancer risk in relation to placental characteristics

Author (year)	Country	Design	Sources	Birth cohort	Year of follow-up	Case number	Control number	Unit of risk measurement	Exposure measure	Result (95% ci)	Adjustment for covariates
Ekbom et al.[24]	Sweden	Nested Case-Control Study	Hospital Records, National Cancer Registry	1874-1954	1958-1990	458	1197	OR	Placental weight (quartile): Lowest, Second, Third, Highest	A positive correlation between placental weight and breast cancer risk that was not, however, statistically significant	Age, Birth date

Citation: Sarantis ND, Sofoudis C, Salvanos G. The role of the placenta in breast carcinogenesis in the offspring. *Obstet Gynecol Int J.* 2023;14(6):203–207. DOI: 10.15406/ogij.2023.14.00721

Table 2 Continued...

Author (year)	Country	Design	Sources	Birth cohort	Year of follow-up	Case number	Control number	Unit of risk measurement	Exposure measure	Result (95% ci)	Adjustment for covariates
Ekbom et al.[23]	Sweden	Nested Case-Control Study	Hospital Records, National Registry	1874-1961	1958-1994	1068	2727	OR	Placental weight (quartile): Lowest, Second, Third, Highest	A weakly positive but non-significant correlation between placental weight and breast cancer risk	Menopausal status, age at diagnosis
Vatten et al.[18]	Norway	Case-Control Study	Hospital Records, National Registry	1910-1970	1959-1997	373	1150	OR	Placental weight (gr): <500, 500-590, 600-700, >=710	No association between placental weight and breast cancer risk	Age at first birth, parity
Sandvei et al.[29]	Norway	Prospective cohort	Hospital Records, National Registry	1920-1966	1961-2012	870	21521	OR	Placental weight (gr): <560, 560-619, 620-699, 700-779, >=780, Per 150gr increment	No association between placental weight and breast cancer risk	Age at first birth, parity, maternal height, adult height, adult body mass index
Cirillo et al.[8]	U.S.A	Prospective cohort	Hospital Records, California Cancer Registry	1960-1963, 1965-1966	1992-2012	137	8751	HR	Placental volume (cm3), placental fibrin deposition, evidence of hemorrhage in the placenta, placental cysts, placental tumor	Higher placental volume and presence of placental tumor associated with increased risk of breast cancer, fibrin deposition and hemorrhage have a protective effect	Maternal ancestry, maternal body mass index, gestational age, maternal history of breast cancer, year of birth, parity, age at pregnancy, maternal education, total family income

CI, confidence interval, OR, odds ratio, HR, hazard ratio

Discussion

In 1990, Professor Trichopoulos first expressed the idea that carcinogenesis starts in utero due to the effect of maternal estrogens on the offspring's developing mammary gland.[1] Since then, multiple mechanisms have been proposed and are still under investigation. It is inevitable, therefore, that, since the placenta functions as a hormone-producing organ, an effort should be made to examine its possible influence on breast cancer development.

The idea that the intrauterine environment predisposes to adult disease is based on two concepts, as described by Cirillo et al.[8]: a) fetal growth and metabolism, mediated by the placenta, act to pre-program adult homeostasis and cell metabolism, which are crucial to cancer development in later life and b) the similarities between the placental trophoblast cells and malignant tumor cells, both of which utilize proliferation, migration and invasion in order to survive. The placenta holds a key role in both concepts.[8]

Regarding the first concept, the fact that increased birth weight and/or birth length is associated with increased breast cancer risk in the offspring has been established by multiple studies.[8–18] Intrauterine growth is dependent on efficient placental function,[19] reasonably leading, therefore, to the question under study, that is the assumption that placental function affects breast cancer risk. Lagiou et al.[19] suggested as a second fact pointing to this direction the positive association between placental weight and cord blood insulin-like growth factor (IGF)-1.[19] IGF-1 is synthesized by both the placenta and the fetus and is present in both syncytiotrophoblast and cytotrophoblast during all stages of gestation.[20] IGF-1 is implicated both in fetal growth and breast cancer etiology.[17,21,22]

Citation: Sarantis ND, Sofoudis C, Salvanos G. The role of the placenta in breast carcinogenesis in the offspring. *Obstet Gynecol Int J.* 2023;14(6):203–207. DOI: 10.15406/ogij.2023.14.00721

As to the second concept, impaired trophoblast invasion and placentation have been linked to a protective effect on developing breast cancer in later life.[23,24] Ekbom et al. suggested that preeclampsia significantly reduces breast cancer risk. Vatten et al.[25] corroborate the protective role of preeclampsia but attribute it to the significantly raised levels of alpha-fetoprotein in the umbilical cord in pregnancies with severe preeclampsia. Alpha-fetoprotein has an anti-estrogenic effect and could, thus, lower future risk for breast cancer in the offspring. It is, however, worth noting that not all authors agree on the effects of preeclampsia. Troisi et al.[16] did not find any association between maternal preeclampsia and an offspring's breast cancer risk in their respective study.

Another issue that has been examined is the fact that several studies demonstrate increased breast cancer risk in dizygotic twins compared to monozygotic or singletons.[17,26,27] According to Troisi et al.,[17] this difference in risk may be attributed to the higher hormonal exposure of dizygotic twins received by two placentae or one larger single placenta compared to monozygotic pregnancies, two-thirds of which have one placenta. This theory, however, has also been refuted by other studies, albeit older ones.[28]

It is evident that all theories that have been suggested in an attempt to explain the in utero origins of breast cancer in the offspring have the direct or indirect influence of the placenta as a common denominator. Yet, research is lacking and, thus, further research must be conducted in order to understand the true role of the placenta in the process of carcinogenesis.[29]

Conclusion – suggestions

In conclusion, the role of the placenta in association to breast carcinogenesis, still evades us. Multiple theories have been postulated by scientists venturing to answer this long-standing question, yet no conclusive evidence exists with regard to the placental characteristics that may influence future breast cancer risk in the offspring. We believe that in order to decipher the role of the placenta, more prospective studies are needed. These studies would follow patients for the development of breast cancer from birth until late age and would specifically examine the weight and other morphological characteristics of the placenta at birth, as well as levels of different maternal and fetal hormones, while adjusting for possible confounding factors. This, of course, requires not only the coordination of obstetricians, breast surgeons and pathologists on a 24-hour basis, but it also necessitates that institutions make provisions for a very extended time of follow up, which may be the main reason behind the limited number of studies that have been undertaken so far. Such tremendous effort, though, would provide us with an immense amount of information and could even be adapted to other forms of cancer as well.

Acknowledgments

None.

Funding

None.

Conflicts of interest

All authors disclose no conflict of interests.

References

1. Trichopoulos D. Hypothesis: does breast cancer originate in utero? *Lancet*. 1990;335(8695):939–940.
2. Arnold M, Morgan E, Rumgay H, et al. Current and future burden of breast cancer: Global statistics for 2020 and 2040. *Breast*. 2022;66:15–23.
3. Dafni U, Tsourti Z, Alatsathianos I. Breast cancer statistics in the European union: incidence and survival across European countries. *Breast Care (Basel)*. 2019;14(6):344–353.
4. Smolarz B, Nowak AZ, Romanowicz H. Breast cancer–epidemiology, classification, pathogenesis and treatment (Review of Literature). *Cancers (Basel)*. 2022;14(10):2569.
5. Kalli S, Semine A, Cohen S, et al. American joint committee on cancer's staging system for breast cancer. 8th edn. What the radiologist needs to know. *Radiographics*. 2018;38(7):1921–1933.
6. Burton GJ, Fowden AL. The placenta: a multifaceted, transient organ. *Philos Trans R Soc Lond B Biol Sci*. 2015;370(1663):20140066.
7. Cindrova–Davies T, Sferruzzi–Perri AN. Human placental development and function. *Semin Cell Dev Biol*. 2022;131:66–77.
8. Cirillo PM, Cohn BA. Gestational biomarkers of daughter's breast cancer in the Child Health and Development Studies. *Reprod Toxicol*. 2020;92:105–111.
9. Ahlgren M, Sorensen T, Wohlfahrt J, et al. Birth weight and risk of breast cancer in a cohort of 106,504 women. *Int J Cancer*. 2003;107(6):997–1000.
10. Kaijser M, Lichtenstein P, Granath F, et al. In utero exposures and breast cancer: a study of opposite–sexed twins. *J Natl Cancer Inst*. 2001;93(1):60–62.
11. McCormack VA, dos Santos Silva I, Koupil I, et al. Birth characteristics and adult cancer incidence: Swedish cohort of over 11,000 men and women. *Int J Cancer*. 2005;115(4):611–617.
12. Mellemkjaer L, Olsen ML, Sorensen HT, et al. Birth weight and risk of early–onset breast cancer (Denmark). *Cancer Causes Control*. 2003;14(1):61–64.
13. Michels KB, Trichopoulos D, Robins JM, et al. Birthweight as a risk factor for breast cancer. *Lancet*. 1996;348(9041):1542–1546.
14. Schmid D, Willett WC, Ding M, et al. Maternal and infant anthropometric characteristics and breast cancer incidence in the daughter. *Sci Rep*. 2020;10(1):2550.
15. Stavola BL, Hardy R, Kuh D, et al. Birthweight, childhood growth and risk of breast cancer in a British cohort. *Br J Cancer*. 2000;83(7):964–968.
16. Troisi R, Grotmol T, Jacobsen J, et al. Perinatal characteristics and breast cancer risk in daughters: a Scandinavian population–based study. *J Dev Orig Health Dis*. 2013;4(1):35–41.
17. Troisi R, Potischman N, Hoover RN. Exploring the underlying hormonal mechanisms of prenatal risk factors for breast cancer: a review and commentary. *Cancer Epidemiol Biomarkers Prev*. 2007;16(9):1700–1712.
18. Vatten LJ, Maehle BO, Lund Nilsen TI, et al. Birth weight as a predictor of breast cancer: a case–control study in Norway. *Br J Cancer*. 2002;86(1):89–91.
19. Lagiou P, Hsieh CC, Samoli E, et al. Associations of placental weight with maternal and cord blood hormones. *Ann Epidemiol*. 2013;23(11):669–673.
20. Hiden U, Glitzner E, Hartmann M, et al. Insulin and the IGF system in the human placenta of normal and diabetic pregnancies. *J Anat*. 2009;215(1):60–68.
21. Innes K, Byers T, Schymura M. Birth characteristics and subsequent risk for breast cancer in very young women. *Am J Epidemiol*. 2000;152(12):1121–1128.

22. Trichopoulos D, Lagiou P, Adami HO. Towards an integrated model for breast cancer etiology: the crucial role of the number of mammary tissue–specific stem cells. *Breast Cancer Res*. 2005;7(1):13–17.

23. Ekbom A, Hsieh CC, Lipworth L, et al. Intrauterine environment and breast cancer risk in women: a population–based study. *J Natl Cancer Inst*. 1997;89(1):71–76.

24. Ekbom A, Trichopoulos D, Adami HO, et al. Evidence of prenatal influences on breast cancer risk. *Lancet*. 1992;340(8826):1015–1018.

25. Vatten LJ, Romundstad PR, Odegard RA, et al. Alpha–foetoprotein in umbilical cord in relation to severe pre–eclampsia, birth weight and future breast cancer risk. *Br J Cancer*. 2002;86(5):728–731.

26. Cerhan JR, Kushi LH, Olson JE, et al. Twinship and risk of postmenopausal breast cancer. *J Natl Cancer Inst*. 2000;92(3):261–265.

27. Hsieh CC, Lan SJ, Ekbom A, et al. Twin membership and breast cancer risk. *Am J Epidemiol*. 1992;136(11):1321–1326.

28. Swerdlow AJ, De Stavola BL, Swanwick MA, et al. Risks of breast and testicular cancers in young adult twins in England and Wales: evidence on prenatal and genetic aetiology. *Lancet*. 1997;350(9093):1723–1728.

29. Sandvei MS, Lagiou P, Romundstad PR, et al. Size at birth and risk of breast cancer: update from a prospective population–based study. *Eur J Epidemiol*. 2015;30(6):485–492.

Citation: Sarantis ND, Sofoudis C, Salvanos G. The role of the placenta in breast carcinogenesis in the offspring. *Obstet Gynecol Int J.* 2023;14(6):203–207. DOI: 10.15406/ogij.2023.14.00721