The Hypothesis of Fetal Origin of Breast Cancer: An Update

Tongzhang Zheng, ScD[1*], Stephen Buka, ScD[1], Karl Kelsey, MD[1], George Papandonatos, PhD[1], Junhie Oh, BDS[2], Andreas Sjodin, PhD[3], Xichi Zhang, MPH[4], Zhengmin Qian, MD[5], and Kunchong Shi, MD[1]

[1]Department of Epidemiology, Brown School of Public Health, Brown University, 121 South Main Street, Providence, RI 02903, USA.

[2]Rhode Island Cancer Registry, Department of Health, 3 Capitol Hill, Providence, RI 02908, USA.

[3]Division of Laboratory Sciences (DLS), Centers for Disease Control and Prevention (CDC) Atlanta GA 30341-3724, USA.

[4]Washington Department of Public Health, PO Box 47903, Olympia, Washington 98504, USA.

[5]Institute for Global Health & Wellbeing College for Public Health & Social Justice, Saint Louis University, St. Louis, MO 63103, USA.

RESEARCH

Please cite this paper as: Zheng T, Buka S, Kelsey K, Papandonatos G, Oh J, Sjodin A, et al., The hypothesis of fetal origin of breast cancer: An update. Women's Health Research [2021] 3(2): 59-70.

***Corresponding Author:**

Tongzhang Zheng

Department of Epidemiology, School of Public Health, Brown University, 121 South Main Street, Providence, RI 02903, USA, Tel: 401-863-6365;

E-mail: tongzhang_zheng@brown.edu

Key Words: Breast cancer, fetal origin hypothesis, in utero exposures, windows of susceptibility.

INTRODUCTION

Breast cancer is the world's most prevalent cancer and the leading cause of cancer death among women worldwide [1-3]. While tremendous strides have been made, a substantial portion of breast cancer occurrence cannot be adequately explained by known risk factors [4-7]. Almost 30 years ago the eminent epidemiologist, Dr. Trichopoulos, hypothesized that breast cancer originates in-utero [8]. Interest in this hypothesis has increased markedly [9-23] including a very recent call for the specific examination of endocrine-disrupting chemicals that act during "windows of susceptibility" [9]. The fetal origin hypothesis of breast cancer proposes that in utero exposures [e.g., diethylstilbestrol use] alter fetal cell development and, thereby, trigger a chain of biologically linked events [impaired fetal growth, adverse birth outcomes, and postnatal accelerated growth] that ultimately leads to increased breast cancer risk among offspring [24-26]. Because of the lack of long-term longitudinal studies that start during pregnancy, most research testing this hypothesis has relied upon indirect measures of adverse pregnancy outcomes, such as maternal and infant anthropometry [e.g. pre-eclampsia, birth size] or perinatal factors [gestational age, twin birth] [26-35]. However, a recent report from a long-term cohort study [36] that directly measured levels of in utero exposure to Dichlorodiphenyltrichloroethane [DDT] strongly support the fetal origin hypothesis of breast cancer. Cohn et al. [36] based on the California Child Health and Development Study [CHDS] show that in-utero exposure to DDT is associated with breast cancer risk in female offspring, with a nearly 4-fold increased risk for those exposed to o,p'-DDT in the highest quartile. Notably, earlier studies of DDT/DDE exposure levels among adult women showed no such increased risk – evidence that in utero exposure may be a susceptibility window of breast cancer. Since adult

exposures fail to explain a substantial part of breast cancer occurrence, ascertaining whether there is, in fact, a fetal 'window of vulnerability' is an urgent scientific goal, essential to identifying new opportunities to potentially prevent breast cancer.

1. Indirect evidence that in utero exposure increases breast cancer risk

Because of the long induction period from birth to breast cancer occurrence in adulthood, early studies were forced to largely rely on indirect evidence using various proxies of in utero exposures (such as birth weight and length, and maternal weight gain) [26-29]. This evidence has been extensively reviewed [20, 21, 26-29, 37, 38] and is briefly summarized below.

1.1 Pregnancy complications as indicators of prenatal exposures and breast cancer in offspring: The pregnancy complications most intensively studied for their association with breast cancer risk among daughters include maternal pre-eclampsia or eclampsia. Studies showed that daughters of women who develop toxemia during pregnancy (preeclampsia/eclampsia) have a significant 10 to 60 percent lower risk of breast cancer than daughters of normotensive mothers. Perhaps similarly, daughters of mothers with a lifetime history of diabetes have also been found to be at a decreased risk of breast cancer, especially for premenopausal breast cancer [28, 29, 39]. These studies have viewed toxemia as a surrogate for low estrogen exposure in utero, supporting the hypothesis of a direct relationship between in utero estrogen levels and breast cancer risk among offspring.

1.2 Perinatal factors as surrogates of prenatal exposures and breast cancer in offspring: Various perinatal factors have been associated with breast cancer risk suggesting that in utero exposures are important in breast carcinogenesis. A relatively consistent positive association of breast cancer risk associated with birth weight and birth length strongly suggests in utero exposure influences on subsequent breast cancer risk [26, 27, 40-43]. Among positive reports, a U-shaped or J-shaped association was reported between birth weight and breast cancer risk in some studies [44-51] while a positive linear relationship has been found in other studies [24, 52-56]. Preterm birth is reported to be associated with an increased risk of breast cancer in some [13, 49, 56-58] but not all studies [44, 51-53, 59, 60]. Preterm birth female infants were found to have 10 to 20 times higher serum follicle-stimulating hormone concentrations compared with full term female infants [61], the raised serum concentrations of gonadotropins in preterm female infants might lead to ovarian hyper stimulation that increases estradiol concentrations and increase breast cancer risk [57, 62]. Twinning [29] particularly dizygotic twins [7, 63-65] that is associated with higher levels of pregnancy estrogens [66, 67] has been associated with an increased risk of breast cancer among offspring. Higher maternal age at delivery has been inconsistently associated with an increased risk of breast cancer in daughters [27-29] and it is known that concentrations of estrogen in maternal blood during pregnancy are higher in older women [68, 69]. These perinatal factors have been associated with pregnancy estrogens or insulin and insulin-like growth factors [8, 16] which are important regulators of somatic growth during fetal life and childhood [70]. It should be noted that high levels of IGFs (like estrogens) may also result in an increased number of stem cells and/or increased mitosis in the developing mammary gland [24].

1.3 Postnatal accelerated growth and risk of breast cancer: Evidence strongly suggests that accelerated postnatal or early childhood growth predicts later breast cancer and modifies the relationship between birth size and breast cancer risk [24, 71-73]. A UK national cohort study showed that the effect of birth weight on breast cancer differ significantly based on height at age 7 years, suggesting a significant interaction between birth weight and childhood growth on breast cancer risk [24]. Another UK report showed that women who grow faster in childhood were at particularly increased risk of breast cancer [72]. Studies

have shown that rapid childhood growth increases breast cancer risk and in utero effects may be modified by childhood growth velocity. A cohort study of 117,415 Danish women showed that high birth weight, earlier age of peak growth [between ages 8 – 14 years], high stature at 14 years, low BMI at 14 years were independent risk factors for breast cancer [73]. A systematic review [74] showed that rapid catch-up growth of LBW neonates following reduced intrauterine development is a more important factor than LBW alone for adult diseases.

1.4 Intrauterine diethylstilbestrol [DES] exposure and breast cancer in offspring: DES is a synthetic estrogen widely used by pregnant women in the 1950s and 1960s to reduce the risk of fetal loss [75]. Studies showed that women exposed to DES in utero are at an increased risk of developing breast cancer [76-79]. Daughters of mothers who took DES during pregnancy have two times higher breast cancer risk than women who were not exposed to it [78-81]. This risk may extend to their granddaughters as well [76]. The reason for the increased breast cancer risk of DES in utero exposure may not only be due to elevated pregnancy estrogenic environment, but may also be attributable to epigenetic alterations that target genes regulating stem cells and prevent differentiation of their daughter cells [5]. Strikingly, DES use during pregnancy has also been associated with a higher risk of SGA and preterm birth among offspring [82] comparable to the outcomes observed following in utero DDE exposure by Longnecker et al. [35] and several smaller studies [30-34].

2. Direct and quantitative evidence that in utero DDT exposure increases breast cancer risk

Cohn's cohort study [36] is the only direct, quantitative study to date to prospectively link in utero DDT exposure to increased risk of breast cancer in offspring. In studying DDT exposure and breast cancer risk, Cohn and colleagues creatively used blood samples largely collected 1-3 days after delivery from the California Child Health and Development Study [CHDS] to investigate breast cancer risk in two generations: a] the female offspring; and b] the pregnant mothers themselves.

2.1 Study of offspring linking in utero DDT exposure to breast cancer risk: In a nested case control study, Cohn et al. [36] quantitatively assessed o,p'-DDT, p,p'- DDT, and p,p'-DDE levels in blood samples collected 1-3 days after delivery for 118 breast cancer cases and 354 controls among the female offspring. Out of the 3 measured DDT isomers, the study found that elevated maternal perinatal serum o,p'-DDT significantly predicted a nearly 4-fold increase in the daughter's risk of breast cancer. Cohn's nested case control study is the only direct, quantitative study to date to prospectively link in utero DDT exposure to increased risk of breast cancer in offspring and thus filled a major gap by directly measuring DDT exposures soon after birth and breast cancer risk in offspring.

2.2 Studies of mothers by age of first DDT exposure and age at diagnosis of breast cancer: Using the same blood samples collected 1-3 days after delivery, Cohn et al. conducted two prospective, nested case–control studies of DDT exposure and breast cancer among the mothers themselves. The blood samples were collected when female study participants were, on average, approximately 26 years old [83, 84]. Accordingly, due to the long half-life of DDT, presence of DDT during pregnancy presumably reflected exposure at earlier ages. The authors combined information on levels of DDT [during pregnancy] and secular trends in DDT exposure in the US to generate several new findings. The first nested case control study [83] involving 129 cases and 129 controls found that, out of the 3 measured DDT isomers [o,p'-DDT, p,p'- DDT, and p,p'-DDE], high levels of serum p,p´-DDT during pregnancy predicted a statistically significant 5-fold increased risk of breast cancer, for a specific subset of women. That is, women who were born after 1931, and who were under 14 years of age in 1945, when DDT came into widespread use. The authors concluded that exposure to p,p´-DDT early in life [before puberty], but not later, may increase breast cancer risk. The recently published second nested case control study [84]

involving 153 new cases and 432 controls presented the joint effects of p, p'-DDT, age at first exposure, and age at diagnosis on breast cancer risk. Among women estimated to have first been exposed before age 3 years [based on age in 1945], p, p'-DDT was associated with increased risk of early breast cancer [< 50 years] but not later breast cancer [ages 50–54 years]. Among women estimated to have been first exposed from ages 3 to 13 years, p, p'-DDT was associated with increased risk of both early and late breast cancer. Among women first exposed after age 13 years, p, p'- DDT was associated only with increased risk of later breast cancer [ages 50–54 years]. Based on these results, the study concluded that risk of breast cancer associated with DDT exposure depended on timing of first exposure and diagnosis age, supporting the hypothesis that early life is a critical vulnerability window for mammary cancer [85-87].

In conclusion, these nested case control reports are significant because previous studies of body levels of DDT/DDE and other organochlorines in adult women and breast cancer in the US, including our own, were largely negative [88-94] Cohn's findings [36, 83, 84] suggest that risk of breast cancer associated with DDT exposure depends upon timing of exposure – with exposure that starts in utero and possibly very early life (but not in adulthood) determining breast cancer effects.

3. Direct evidence showing that in utero exposure to DDT/DDE may trigger a cascade of biologically linked events that ultimately contributes to increased risk of breast cancer among offspring

Using a South African birth cohort, Murray et al. [95] recently reported that p,p'-DDT and p,p'-DDE serum concentrations were associated with hypertensive disorders of pregnancy while an earlier study by Savitz et al. [96] did not find an association of DDT exposure with preeclampsia . Several studies have also reported an increased risk of hypertension associated with higher levels of DDT exposure [97-102].

A large cohort study by Longnecker et al. [35] measured serum levels of p,p′-DDT and p,p′-DDE and found that in utero exposure to p,p′-DDE significantly increased SGA risk. A significant dose response relationship was reported between maternal p,p′-DDE levels during pregnancy and adverse birth outcomes. The adjusted SGA ORs for each increasing quintile of DDE were 1, 1.9, 1.7, 1.6, 2.6, respectively (trend p=0.04). Longnecker's findings have since been replicated by several smaller studies [30, 34, 103-111] including our own [112] although some discrepancies remain [113-115].

Importantly, a recent study from Berkeley using the South Africa VHEMBE birth cohort showed that maternal serum p,p'-DDT concentration was consistently and positively associated with accelerated postnatal growth, including higher BMI-for-age in girls aged at 1 and 2 years of age [116]. A recent small cohort study from California involving 240 children showed that in utero exposure to DDT and DDE affected early childhood growth and significantly increased the risk of obesity at 12 years among boys, while non-significantly increasing the obesity risk among girls [117]. A study from China [118] showed that women exposed to the highest quartile of DDT/DDE had a significantly younger age at the time of menarche than those in the lowest quartile. A recent report from the Child Health and Development Studies by Cirillo et al. [119] showed that grand maternal perinatal serum DDT is associated with granddaughter's early menarche and adult obesity, the risk factors for female breast cancer.

This collective evidence begins to illuminate a general model for the fetal origins of breast cancer associated with DDT exposure in utero. Namely, that in utero exposure to DDT impairs fetal development, results in subsequent early childhood accelerated growth and, eventually, increased risk for breast cancer among adult offspring.

4. Biological Plausibility

Experimental studies have shown that fetal life is an important window of susceptibility for mammary cancer [120-125]. In humans, however, the underlying mechanisms

linking in utero exposures to subsequent breast cancer among offspring are not fully understood. In utero exposures may increase the number of breast stem cells during the fetal period and, therefore, the number at risk of malignant transformation. The likelihood of breast cancer occurrence depends on the number of mammary tissue specific stem cells and this is determined early in life, notably in utero or during immediate postnatal life [17-19]. In utero exposures can modify the epigenome and epigenetic modifications in the fetus might lead to changes in mammary gland development, such as increased vulnerability of epithelial targets [perhaps stem cells] for malignant transformation that alter the susceptibility to factors that can initiate breast cancer [19]. Breast tissue undergoes rapid proliferation and development in utero, which creates a fertile soil for cancer initiation representing a critical window of increased susceptibility for mammary carcinogenesis [8, 10, 17, 18, 126-128]. Thus, breast cancer may be diagnosed over the lifetime but begin in utero.

5. Major gaps in studying the fetal origin hypothesis

• Studies of fetal origin hypothesis to date have largely relied upon indirect evidence. Most previous studies of the fetal origin hypothesis of breast cancer have been based on indirect evidence of breast cancer risk associated with various proxies of in utero exposures (such as birth weight, birth length) as summarized previously. This is mainly due to the fact that the induction period is long from in utero exposure to breast cancer in adulthood taking about 50-60 years, but there is a general lack of long-term longitudinal prenatal cohort studies with direct prospective measures (bio specimens) of the prenatal environmental milieu.

• Studies that explicitly test the "fetal origin of breast cancer" hypothesis in the same cohort population have been sorely lacking. No prior study, including the prior DDT-breast cancer study [36], the DDT-adverse birth outcome study [30-35] and the DDT-early childhood growth and menarche studies [116-119] has directly examined, in the same cohort population, the extent to which in utero exposure to DDT is associated with intrauterine growth restriction (e.g., SGA), subsequent accelerated growth and – ultimately- increased risk of breast cancer.

• Cohn's DDT-breast cancer study [36] is the only published longitudinal study so far with the ability to investigate whether in utero DDT exposure significantly increases the risk of breast cancer. It is important to both extend these findings and test DDT-related fetal origin hypotheses. Millions of current adult women were heavily exposed in utero and are potentially at increased risk of breast cancer [36].

• Need to test in utero exposure to multiple environmental pollutants and breast cancer risk. It is needed to determine the relationship between in utero exposure to multiple environmental pollutants and breast cancer risk in offspring, including persistent organic pollutants (POPs), metals and other environmental pollutants. These pollutants could jointly produce their impact or confound each other while their effects are evaluated in testing the fetal origins hypothesis of breast cancer.

CONCLUSION

As stated previously, although tremendous efforts have been made, a substantial portion of breast cancer occurrence cannot be adequately explained by known risk factors. If we are to make headway in preventing breast cancer, we must further enhance our understanding of the etiology of this disease, critically highlighting its modifiable risk factors. Only in this way can we positively impact the occurrence of the disease that is currently the leading cause of cancer death among women worldwide. Both the direct and indirect evidence strongly supports the hypothesis of fetal origin of breast cancer. It is critically important to advance our understanding of the hypothesis by ascertaining whether there is a fetal 'window of vulnerability' for breast cancer as proposed, which is essential to identifying new opportunities to prevent breast cancer considering the fact that adult exposures fail to explain a substantial part of breast cancer occurrence.

We are well aware that there are not many prenatal cohorts available for directly testing the fetal origin hypothesis by linking prenatal exposure to fetal development, pregnancy complication, adverse birth outcomes, postnatal and early childhood growth and adiposity, age at menarche, and ultimately breast cancer risk in offspring. Until the current prenatal cohort studies mature and are available for studying the hypothesis, efforts could still be made by testing the relationship between prenatal exposures and various indirect measures involving early life events (such as adverse birth outcomes, postnatal and early childhood growth and adiposity, and age at menarche) since these events have been linked to the risk of breast cancer, and are in fact likely to be the intermediate steps in the causal pathways—reflecting the chain of biologically linked events from the same in utero exposures that lead to increased susceptibility of the tissue to further insults – ultimately, leading to increased risk of breast cancer in the offspring. These early life events may mediate the association between in utero exposures and breast cancer risk. By advancing the fetal origin hypothesis, these efforts may lead to refine strategies and reach the ambitious goal of identifying new opportunities to prevent and control this deadly disease.

Acknowledgements

Funding for this project was provided in part by ES032876, ES029082, and ES031391.

REFERENCES

1. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, Bray F. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA: Cancer J Clin 2021; 71: i, 191-280.
2. Siegel RL, Miller KD, Fuchs HE, Jemal A. Cancer Statistics, 2021. CA Cancer J Clin 2021; 71:7-33.
3. World Health Organization. Breast Cancer. 2021, March 26.
4. Swerdlow AJ, Wright LB, Schoemaker MJ, Jones ME. Maternal breast cancer risk in relation to birthweight and gestation of her offspring. Breast Cancer Res 2018; 20:110.
5. Troisi R, Bjørge T, Gissler M, Grotmol T, Kitahara CM, Myrtveit Saether SM, et al. The role of pregnancy, perinatal factors and hormones in maternal cancer risk: a review of the evidence. J Intern Med. 2018; 283:430-45.
6. Ginsburg O, Bray F, Coleman MP, Vanderpuye V, Eniu A, Kotha SR, et al. The global burden of women's cancers: a grand challenge in global health. Lancet 2017; 389: 847–60.
7. American Cancer Society. Breast Cancer Facts & Figures 2017-2018. Atlanta: American Cancer Society, Inc. 2017.
8. Trichopoulos D. Hypothesis: does breast cancer originate in utero? Lancet 1990; 335:939-40.
9. Kripke M, Brody JG, Hawk E, Hernandez AB, Hoppin PJ, Jacobs MM, et al. Rethinking Environmental Carcinogenesis. Cancer Epidemiol Biomark Prev 2020; 29:1870–5.
10. Ekbom A, Trichopoulos D, Adami HO, Hsieh CC, Lan SJ. Evidence prenatal influences on breast cancer risk. Lancet 1992; 340:1015-18.
11. Anbazhagan R, Gusterson BA. Prenatal factors may influence predisposition to breast cancer. Eur J Cancer 1994; 30A1-3.
12. Adami HO, Persson I, Ekbom A, Wolk A, Ponten J Trichopoulos D. The aetiology and pathogenesis of human breast cancer Mutat Res 1995; 333:29-35.
13. Ekbom A, Hsieh CC, Lipworth L, Adami HQ, Trichopoulos D. Intrauterine environment and breast cancer risk in women: a population-based study.J. Natl. Cancer Inst. 1997; 89:71–6.
14. Simmen FA, Simmen RCM. The maternal womb: a novel target for cancer prevention in the era of the obesity pandemic. Eur J Cancer Prev 2011; 20:539-48.
15. Trichopoulos D. Intrauterine environment, mammary gland mass and breast cancer risk. Breast Cancer Res 2002; 5:42-4.

16. Schernhammer ES. In utero exposures and breast cancer risk: joint effect of estrogens and insulin like growth factor? Cancer Causes Control 2002; 13:505-8.
17. Baik I, Becker PS, DeVito WJ, Lagiou P, Ballen K, Quesenberry PJ, et al. Stem cells and prenatal origin of breast cancer, Cancer Causes Control 2004; 15:517–30.
18. Trichopoulos D, Lagiou P, Adami HO. The crucial role of the number of mammary tissue specific stem cells. Breast Cancer Res 2005; 7:13-7.
19. Hilakivi-Clarke L, de Assis S. Fetal origins of breast cancer. Trends Endocrinol Metabol 2006; 17:340-8.
20. Potischman N, Troisi R. In utero and early life exposure in relation to risk of breast cancer. Cancer Causes Control 1999; 10:561-73.
21. Hanf V, Hanf D. Reproduction and breast cancer risk. Breast Care (Basel). 2014; 398-405.
22. Tehranifar P, Cohn BA, Flom JD, Protacio A, Cirillo P, Lumey LH et al. Early life socioeconomic environment and mammographic beast density. BMC Cancer 2017; 17-41.
23. Calkins K, Devaskar SU. Fetal origins of adult disease. Curr Probl Pediatr Adolesc Health Care. 2011; 41:158-76.
24. De Stavola BL, Hardy R, Kuh D, Santos Silva ID, Wadsworth M, Swerdlow AJ. Birthweight, childhood growth and risk of breast cancer in a British cohort. Br J Cancer 2000; 83:964-8.
25. Ben-Shlomo Y, Kuh D. A life course approach to chronic disease epidemiology: concenptual models, empirical challenges and interdisciplinary perspectives. Int J Epidemiol 2002; 31:285-93.
26. Schmid D, Willett WC, Ding M, Michels KB. Maternal and infant anthropometric characteristics and breast cancer incidence in the daughter. Sci Rep 2020; 10:2550.
27. Barber LE, Bertrand KA, Rosenberg L, Battaglia TA and Palmer JR. Pre- and perinatal factors and incidence of breast cancer in the Black Women's Health Study. Cancer Causes Control 2019; 30:87–95.
28. Xue F, Michels KB. Intrauterine factors and risk of breast cancer: a systematic review and meta-analysis of current evidence. Lancet Oncol 2007; 8:1088-100.
29. Park SK, Kang D, McGlynn KA, Garcia-Closas M, Kim Y, Yoo KY et al. Intrauterine environments and breast cancer risk: meta-analysis and systematic review. Breast Cancer Res. 2008:10–R8.
30. Kezios KL, Liu X, Cirillo PM, Cohn BA, Kalantzi OI, Wang Y et al. Dichlorodiphenyltrichloroethane (DDT), DDT metabolites and pregnancy outcomes. Reprod Toxicol. 2013; 35:156-64.
31. Bergonzi R ,De Palma G, Specchia C, Dinolfo M, Tomasi C, Frusca T, et al. Persistent organochlorine compounds in fetal and maternal tissues: evaluation of their potential influence on several indicators of fetal growth and health. Sci Total Environ 2011; 409:2888-93.
32. Arrebola JP, Cuellar M, Bonde JP, González-Alzaga B, Mercado LA. Associations of maternal o,p'-DDT and p,p'-DDE levels with birth outcomes in a Bolivian cohort. Environ Res 2016; 151:469-77.
33. Xu C, Yin S, Tang M, Liu K, Yang F, Liu W. Environmental exposure to DDT and its metabolites in cord serum: Distribution, enantiomeric patterns, and effects on infant birth outcomes. Sci Total Environ 2017; 15; 580:491-8.
34. Chevrier J, Rauch S, Crause M, Obida M, Gaspar F, Bornman R,et al. Associations of Maternal Exposure to Dichlorodiphenyltrichloroethane and Pyrethroids With Birth Outcomes Among Participants in the Venda Health Examination of Mothers, Babies and Their Environment Residing in an Area Sprayed for Malaria Control. Am J Epidemiol. 2019; 188:130-40.
35. Longnecker MP, Klebanoff MA, Zhou H, Brock JW. Association between maternal serum concentration of the DDT metabolite DDE and preterm and small-for-gestational-age babies at birth. Lancet 2001; 358:110-14.
36. Cohn BA, Merrill ML, Krigbaum NY, Yeh G, Park JS, Zimmermann L et al. DDT exposure in utero and breast cancer. J Clin Endocrinol Metab 2015; 100:2865-72.

37. Potischman N, Troisi R, Vatten L. Chapter 11: A life course approach to cancer epidemiology, in: A Life Course Approach to Epidemiology, Second Edition, D. Kuh and Y. Ben-Shlomo, ed, Oxford University Press Oxford 2004.
38. Okasha M, McCarron P, Gunnell D, Smith GD. Exposures in childhood, adolescence and early adulthood and breast cancer risk: a systematic review of the literature, Breast Cancer Res Treat 2003; 78:223–76.
39. Stephansson O, Granath F, Ekbom A, Michels KB. Risk of breast cancer among daughters of mothers with diabetes: a population-based cohort study. Breast Cancer Res 2010; 12:14.
40. Spracklen CN, Wallace RB, Sealy-Jefferson S, Robinson JG, Freudenheim JL, Wellons MF, et al. Birth Weight and Subsequent Risk of Cancer. Cancer Epidemiol 2014; 38: 538 -43.
41. Silva Idos S, De Stavola B, McCormack V, Collaborative Group on Pre-Natal Risk Factors and Subsequent Risk of Breast Cancer. Birth size and breast cancer risk: re-analysis of individual participant data from 32 studies. PLoS medicine 2008; 30:5:e193.
42. Xu X, Dailey AB, Peoples-Sheps M, Talbott EO, Li N, Roth J. Birth weight as a risk factor for breast cancer: a meta-analysis of 18 epidemiological studies. J Women's Health 2009; 18:1169-78. Doi:10.1089/jwh.2008.1034
43. Troisi R, Grotmol T, Jacobsen J, Tretli S, Toft-Sørensen H, Gissler M, et al. Perinatal characteristics and breast cancer risk in daughters: a Scandinavian population-based study. J Dev Orig Health Dis 2013; 4:35–41.
44. Innes K, Byers T, Schymura M. Birth characteristics and subsequent risk for breast cancer in very young women. Am J Epidemiol 2000; 152: 1121–8.
45. Titus-Ernstoff L, Egan KM, Newcomb PA, Ding J, Trentham-Dietz A, Greenberg ER, et al. Early life factors in relation to breast cancer risk in postmenopausal women. Cancer Epidemiol Biomark Prev 2002; 11:207-10.
46. Sanderson M, Williams MA, Malone KE, Stnaford I, Emannuel I, White E, et al. Perinatal factors and risk of breast cancer. Epidemilology 1996; 7:34-7.
47. Ahlgren M, Sørensen T, Wohlfahrt J, Haflidadóttir A, Holst C, Melbye M. Birth weight and risk of breast cancer in a cohort of 106,504 women. Int J Cancer 2003; 07:997-1000.
48. Mellemkjaer L ,Olsen ML ,Sørensen HT, Thulstrup AM, Olsen J, Olsen JH. Birth weight and risk of early onset breast cancer (Denmark). Cancer Causes Control 2003; 14:61-4.
49. Kaijser M, Akre O, Cnattingius S, Ekbom A. Preterm birth, birth weight, and subsequent risk of female breast cancer. Br. J. Cancer 2003; 89:1664–6.
50. Barba M, McCann SE, Nie J, Vito D, Stranges S, Fuhrman B, et al. Perinatal exposures and breast cancer risk in the Western New York Exposures and Breast Cancer Study. Cancer Causes Control 2006; 17:395-401.
51. Innes KE, Byers TE. First pregnancy characteristics and subsequent breast cancer risk among young women. Int J Cncer 2004; 112:306-11.
52. Michels KB, Trichopoulos D, Robins JM, Rosner BA, Manson JE, Hunter DJ, et al. Birth weight as a risk factor for breast cancer. Lancet 1996; 348:1542–6.
53. Hübinette A, Lichtenstein P, Ekbom A, Cnattingius S. Birth characteristics and breast cancer risk: a study among like-sexed twins. Int J Cancer 2001; 91:248–51.
54. Kaijser M, Litchtenstein P, Granath F, Erlandsson G, Cnattingius S, Ekbom A. In utero exposures and breast cancer: a study of opposite-sexed twins. J Natl Cancer Inst 2001; 93:60–2.
55. Vatten LJ, Mæhle BO, Lund Nilsen TI, Tretli S, Hsieh CC, Trichopoulos D, et al. Birth weight as a predictor of breast cancer: a case–control study in Norway. Br J Cancer 2002; 86:89–91.
56. McCormack VA, dos Santos Silva I, De Stavola BL, Moshen R, Leon D, Lithell HO. Foetal growth and subsequent risk of breast cancer: results from a long-term follow-up of a Swedish cohort of over 5000 women. BMJ 2003; 326:248–51.
57. Ekbom A, Erlandsson G, Hsieh C, Trichopoulos D, Adami H O, Cnattingius S. Risk of breast cancer in prematurely born women. J. Natl. Cancer Inst 2000; 92:840–1.

58. Vatten LJ, Romundstad PR, Trichopoulos D, Skjaerven R. Pregnancy related protection against breast cancer depends on length of gestation. Br J Cancer 2002; 87:289–90.
59. Sanderson M, Williams MA, White E, Daling IR, Holt VL, Malone KE,et al. Validity and reliability of subject and mother reporting of perinatal factors. Am J Eidemiol 1998; 147:136-40.
60. Sanderson M, Daling IR, Doody DR, Malone KE. Perinatal factors and mortality from breast cancer. Cancer Epidmiol Biomark Prev 2006; 15:1984-7.
61. Tapanainen J, Koivisto M, Vihko R, Huhtanien I. Enhanced activity of the pituitary gonadal axis in premature human infants. J Clin Endocrinol Metab 1981; 52:235-8.
62. Service RF. New role for estrogen in cancer. Science 1998:279:1631–3.
63. Braun MM, Ahlbom A, Floderus B, Briston LA, Hoover RN. Effect of twinship on incidence of cancer of the testis, breast andother sites (Sweden). Cancer Causes Control 1995; 6:519-24.
64. Swerdlow AJ, De Stavola BL, Swanwick MA, Maconochic NES. Risks of breast and testicular cancers in young adult twins in England and Wales: evidence on prenatal and genetic etiology. Lancet 1997; 350:1723-8.
65. Cerhan JR, kushi H, Olson JE, Rich SS, Zheng W, Folsom AR et al. Twinship and risk of postmenopausal breast cancer. J Natl Cancer Inst 2000; 92:261-5.
66. Duff GB Brown JB. Urinary oestriol excretion in twin pregnancies. J Obstel Gynaecol 1974; 81:695-700.
67. Trapp M, Kato K, Bohnet HG, Gerhard I, Weise HC, Leidenberger F. Human placental lactogen and undconjugated estriol concentrations in twin pregnancies: monitoring of fetal development in intrauterine growth retardation and single intrauterine fetal death. Am J Obstet Gynecol 1986; 155:1027-33.
68. Panagiotopoulou K, Katsouyanni K, Petridou E, Garas Y, Tzonou A, Trichopoulos D, Petridou E. Tobacco smoking, pregnancy estrogens, and birth weight. Epidemiology 1990; 1:247-50.
69. Panagiotopoulou K, Katsouyanni K, Petridou E, Garas Y, Tzonou A, Trichopoulos D. Maternal age, parity, and pregnancy estrogens. Cancer Causes Control 1990; 1:119-24.
70. Holly J. Insulin-like growth factor-I and new opportunities for cancer prevention. Lancet 1998; 351:1373-5.
71. Lucas A, Fewtrell JM, Cole TJ. Fetal origins of adult disease-the hypothesis revisited. BMJ 1999; 319:245-9.
72. De Stavola BL, dos Santos Silva, McCormack V, Hardy RJ, Kuh DJ, Wadsworth ME. Childhood growth and breast cancer. Am J Epidemiol 2004; 159:671-82.
73. Ahlgren M, Melbye M, Wohlfahrt J, Sørensen TI. Growth patterns and the risk of breast cancer in women. N Engl J Med 2004; 351:1619-26.
74. Kelishadi R, Haghdoost AA, Jamshidi F, Aliramezany M, Moosazadeh M. Low birthweight or rapid catch-up growth: which is more associated with cardiovascular disease and its risk factors in later life? A systematic review and cryptanalysis. Paediatr Int Child Health 2015; 35:110-23.
75. Noller K, Fish CR. Diethylstilbestrol usage: its interesting past, important present, and questionable future. Med Clin North Am 1974; 58:739-810.
76. Hilakivi-Clarke L. Maternal exposure to diethylstilbestrol during pregnancy and increased breast cancer risk in daughters. Breast Cancer Res 2014; 16:208.
77. Hatch EE, Palmer JR, Titus-Ernstoff L, Noller KL, Kaufman RH, Mittendorf R, et al. Cancer risk in women exposed to DES in utero. JAMA 1998; 280:630-4.
78. Hoover RN, Hyer M, Pfeiffer RM, Adam E,Bond B, Andrea L. Cheville AL, et al. Adverse health outcomes in women exposed in utero to diethylstilbestrol. New Eng J Med 2011; 365:1304-14.
79. Palmer JR, Wise LA, Hatch EE, Troisi R, Titus-Ernstoff L, Strohsnitter W, et al. Prenatal DES exposure and risk of breast cancer. Cancer Epidemiol Biomark Prevent 2006; 15:1509–14.
80. Weiss HA, Potischman NA, Brinton LA, Brogan D, Coates RJ, Gammon MD, et al. Prenatal and perinatal risk

factors for breast cancer in young women. Epidemiology 1997; 8:181–7.

81. Sanderson M, Williams MA, Daling JR,Holt VL, Malone KE, Self SG, et al. Maternal factors and breast cancer risk among young women. Paediatr Perinat Epidemiol 1998; 12:397–407.
82. Hatch EE, Troisi R, Wise LA, Titus-Ernstoff L, Hyer M, Palmer JR, et al. Preterm birth, fetal growth, and age at menarche among women exposed prenatally to Diethylstilbestrol (DES). Reprod Toxicol. 2011; 31:151-7.
83. Cohn BA, Wolff MS, Cirillo PM, Sholtz RI.DDT and breast cancer in young women. New data on the significance of age at exposure. Environ Health Perspect 2007; 115:1406-14.
84. Cohn BA, Cirillo PM, Terry MB. DDT and breast cancer: prospective study of induction time and susceptibility windows. JNCI 2019; 111:1-8.
85. Newnham JP. and Ross MG. Early Life Origins of Human Health and Disease. ISBN: 978-3-8055-9139-3 e-ISBN: 978-3-8055-9140-9
86. Rudel RA, Fenton SE, Ackerman JM, Euling SY, Makris SL. Environmental exposures and mammary gland development: state of the science, public health implications, and research recommendations. Environ Health Perspect. 2011; 119:1053-61.
87. Fenton SE, Reed C, Newbold RR. Perinatal environmental exposures affect mammary development, function, and cancer risk in adulthood. Annu Rev Pharmacol Toxicol. 2012; 52:455-79.
88. Ingber SZ, Buser MC, Pohl HR, Abadin HG, Murray HE, Scinicariello F. DDT/DDE and breast cancer risk: a meta-analysis. Regul Toxicol Pharmacol 2013; 67:421-33.
89. Zheng T, Holford T, Tessari J, Mayne ST, Zahm SH, Owens PH, et al. Oxychlorodane and trans-nonachlor in breast adipose tissue and risk of female breast cancer. J Epidemiol Statistics 2000; 5:153-60.
90. Zheng T, Holford T, Mayne ST, Tessari J, Owens PH, Zahm SH, Ward B, Carter D, Boyle P. Risk of breast cancer associated with serum PCBs and DDE. Cancer Epidemiol Biomark Prevent 2000; 9:167-74.
91. Zheng T, Holford T, Mayne ST, Tessari J, Owens PH, Zahm SH, et al. Environmental exposure to hexachlorobenzene and risk of female breast cancer in Connecticut. Cancer Epidemiol Biomark Prevent 1999; 8:407-11.
92. Zheng T, Holford T, Mayne ST, Ward B, Carter D, Owens PH, et al. DDE and DDT in breast adipose tissue and risk of female breast cancer. Am J Epidemiol 1999; 150:453-8.
93. Zheng T, Holford T, Mayne ST, Owens PH, Ward B, Carter B, et al. □-benzene hexachloride in breast adipose tissue and risk of breast carcinoma. Cancer 1999; 85:2212-8.
94. Laden F, Collman G, Iwamoto K, Alberg AJ, Berkowitz GS, Freudenheim JL, et al. DDE and PCBs and breast cancer: combined analysis of five US studies. J Natl Cancer Inst 2001; 93:768-773.
95. Murray J, Eskenazi B, Bornman R, Gaspar F, Crause M, Obida M, et al. Exposure to DDT and hypertensive disorders of pregnancy among South African women from an indoor residual spraying region: The VHEMBE study. Environ Res 2018; 162:49-54.
96. Savitz DA, Klebanoff MA, Wellenius GA, Jensen ET, Longnecker MP. Persistent organochlorines and hypertensive disorders of pregnancy. Environ Res 2014; 132:1–5.
97. Valera B, Jorgensen ME, Jeppesen C, Bjerregaard P. Exposure to persistent organic pollutants and risk of hypertension among inuit from Greenland. Environ Res 2013; 122:65-73.
98. La Merrill M, Cirillo PM, Terry MB, Krigbaum NY, Flom JD, Cohn BA. Prenatal exposure to the pesticide ddt and hypertension diagnosed in women before age 50: a longitudinal birth cohort study. Environ. Health Perspect 2013; 121:594-9.
99. Valera B, Ayotte P, Poirier P, Dewailly E. Associations between plasma persistent organic pollutant levels and blood pressure in inuit adults from Nunavik. Environ Int 2013; 59:282-9.
100. Lind PM, Penell J, Salihovic S, van Bavel B, Lind L. Circulating levels of p,p-DDE are related to prevalent

hypertension in the elderly. Environ Res 2014; 129:27-31.

101. Henriquez-Hernandez LA, Luzardo OP, Zumbado M, Camacho M, Serra-Majem L, Alvarez-Leon EE, et al. Blood pressure in relation to contamination by polychlorobiphenyls and organochlorine pesticides: results from a population-based study in the canary islands. Environ Res 2014; 135:48-54.
102. Arrebola JP, Fernandez MF, Martin-Olmedo P, Bonde JP, Martin-Rodriguez JL, Exposito J, et al. Historical exposure to persistent organic pollutants and risk of incident hypertension. Environ Res 2015; 138:217-23.
103. O'Leary JA, Davies JE, Edmundson WF, Feldman M. Correlation of prematurity and DDE levels in the fetal whole blood. Am J Obstet Gynecol 1970; 106:939.
104. Procianoy RS, Schvartsman S. Blood pesticide concentration in mothers and their newborn infants. Relation to prematurity. Acta Paediatr Scand 1981; 70:925-8.
105. Saxena MC, Siddqui MK, Seth TD, Krishna Murti CR, Bhargava AK, Kutty D. Organochlorine pesticides in specimen from women undergoing spontaneous abortion, premature or full term delivery. J Anal Toxicol 1981; 5:6-9.
106. Wassermann M, Ron M, Bercovici B, Wassermann D, Cucos S, Pines A. Premature delivery and organochlorine compounds: polychlorinated biphenyls and some organochlorine insecticides. Environ Res 1982; 28:106-12.
107. Karmaus W, Zhu X. Maternal concentration of polychlorinated biphenyls and dichlorodiphenyl dichloroethylene and birth weight in Michigan fish eaters: a cohort study. Environ Health 2004; 3:1.
108. Ribas-Fito N, Sala M, Cardo E, Mazón C, De Muga ME, Verdú A, et al. Association of hexachlorobenzene and other organochlorine compounds with anthropometric measures at birth. Pediatr Res 2002; 52:163–7.
109. Torres-Arreola L, Berkowitz G, Torres-Sanchez L, López-Cervantes M, Cebrián ME, Uribe M, et al. Preterm birth in relation to maternal organochlorine serum levels. Ann Epidemiol 2003; 13:158–62.
110. Saxena MC, Siddiqui MKJ, Bhargava AK, Seth TD, Krishnamurti CR, Kutty D. Role of chlorinated hydrocarbon pesticides in abortions and premature labor. Toxicology 1980; 17:323–31.
111. Wojtyniak BJ, Rabczenko D, Jonsson BAG, Zvezdauy V, Pedersen HS, Rylander L, et al. Association of maternal serum concentrations of 2,2', 4,4'5,5'-hexachlorobiphenyl (CB-153) and 1,1-dichloro-2,2-bis (p-chlorophenyl)-ethylene (p,p'-DDE) levels with birth weight, gestational age and preterm births in Inuit and European populations. Environmenl Health 2010; 9:56.
112. Guo H, Jin Y, Cheng Y, Leaderer B, Lin S, Holford TR, et al. Prenatal exposure to organochlorine pesticides and infant birth weight in China. Chemosphere 2014; 110:1–7.
113. Bjerregaard P, Hansen JC. Organochlorines and heavy metals in pregnant women from the Disko Bay area in Greenland. Sci Total Environ 2000; 245:195–202.
114. Gladen BC, Shkiryak-Nyzhnyk ZA, Chyslovska N, Zadorozhnaja TD, Little RE. Persistent organochlorine compounds and birth weight. Ann Epidemiol 2003; 13:151–7.
115. Rogan WJ, Gladen BC, McKinney JD, Carreras N, Hardy P, Thullen J,et al. Neonatal effects of transplacental exposure to PCBs and DDE. J Pediatr 1986; 109:335–41.
116. Coker E, J Chevrier, Rauch S, Bradman A, Obida M, Madelein Crause M, et al. Association between prenatal exposure to multiple insecticides and child body weight and body composition in the VHEMBE South African birth cohort. Environ Int 2018; 113:122-32.
117. Warner M, Ye M, Harley K, Kogut K, Bradman A, Eskenazi B. Prenatal DDT exposure and child adiposity at age 12: The CHAMACOS study 2017; 159:606-12.
118. Ouyang F1, Perry MJ, Venners SA, Chen C, Wang B, Yang F,et al. Serum DDT, age at menarche and abnormal menstrual cycle length. Occup Environ Med 2005; 62:878-84.
119. Cirillo PM, Merrill MAL, Krigbaum NY, Cohn BA. Grandmaternal Perinatal Serum DDT in Relation to Granddaughter Early Menarche and Adult Obesity: Three Generations in the Child Health and

Development Studies Cohort. Cancer Epidemiol Biomarkers Prev 2021; 30:1480-8.

120. Tomatis L. Overview of perinatal and multigeneration carcinogenesis. In: Napalkov NP, Rice JM, Tomatis L, Yamasaki H, eds. Perinatal and Multigeneration Carcinogenesis (IARC Scientific publications No. 96). Lyon: International Agency for Research on Cancer, pp 1-15. 1989.
121. Napalkov NP. Prenatal and childhood exposure to carcinogenic factors. Cancer Detect Prev 1986; 9:1-7.
122. Boylan ES, Calhoon RE. Transplacental action of DES on mammary carcinogenesis in female rats give one or two dose of 7,12-dimethylbenz(a)anthracene. Cancer Res 1983; 43:4879-84.
123. Soto AM, Brisken C, Schaeberle C, Sonnenschein C. Does cancer start in the womb? Altered mammary gland development and predisposition to breast cancer due to in utero exposure to endocrine disruptors. J Mammary Gland Biol Neoplasia 2013; 18:199-208.
124. Russo J, Gusterson BA, Rogers AE, Russo IH, Wellings SR, van Zwieten MJ. Biology of disease: comparative study of human and rat mammary tumorigenesis. Lab Invest 1990; 62:244-78.
125. Birnhaum ISW, Fenton SE. Cancer and developmental exposure to endocrine disruptors. Environ Health Perspect 2003; 111:389-94.
126. Ronckers CM, Erdmann CA, Land CE. Radiation and breast cancer: a review of current evidence. Breast Cancer Res 2005; 7:21-32.
127. Moolkavgar SH, Day NE, Stevens RG. Two-stage model for carcinogenesis: epidemiology of breast cancer in females. J Natl Cancer Inst 1980; 65:559–69.
128. Yen SCC. Endocrinology of pregnancy. In: Creasy RK, Resnic R, eds. Maternal-Fetal Medicine. Philadelphia: WB Saunders, 1989; 375-403.

PEER REVIEW

Not commissioned. Externally peer reviewed.