

DOI: 10.5455/msm.2021.33.119-123

Received: Apr 25 2021; Accepted: Jun 16, 2021

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ORIGINAL PAPER

Mater Sociomed. 2021 Jun; 33(2): 119-123

# Neonatal Birth Weight of the Woman as a Risk Factor for Breast Cancer in her Life: a Case-Control Bicentric Study

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## ABSTRACT

**Background:** It is a global fact that the birth weight is increasing during the years around the world and for this reason it is very important to be examined as a potential risk factor for breast cancer. According to data from World Health Organization, breast cancer is the second most frequent malignancy across the world, after lung cancer, in Europe including Greece in incidence and mortality for women between the ages 0-85 years old. **Objective:** The aim of this study was to investigate a possible association between neonatal birth weight of the women and breast cancer risk in Greek women. Although that many studies concluded that birth weight is positively related with breast cancer reinforcing the theory that breast cancer may originate in utero, some studies found no association. Moreover, the results from previous studies are inconsistent maybe due to several factors such as the study design and the number of cases. **Methods:** This study was a case-control retrospective bicentric study. The case group included 238 women with breast cancer, while the control group included 153 women without breast cancer who consulted in two breast clinics in Greece. In all women, a clinical examination and breast ultrasound were achieved. Moreover, digital bilateral mammography was performed in patients older than 40 years. **Results:** According to Fisher's exact analysis, there is a statistically significant relationship between the higher women's neonatal birth weight and the risk for breast cancer ( $p < 0.001$ ). More specifically in the group of women with breast cancer, 61% of them had more than 3500 grams birth weight, in contrast with 7.8 % in the control group. In our cohort, women who had birth weight more than 3500

grams are more likely to develop breast cancer in their life. **Conclusion:** Our study trend to show that the increased neonatal birth weight may influence future risk of breast cancer. However, further studies with larger number of participants are needed in order to clarify the role of birth weight as a complementary risk factor of breast cancer.

**Keywords:** Breast cancer, neonatal birth weight, breast malignancy, breast cancer risk factors.

## 1. BACKGROUND

It is a global fact that the birth weight is increasing during the years around the world (1) and for this reason it is very important to be examined as a potential risk factor for breast cancer. According to data from World Health Organization (2), breast cancer is the second most frequent malignancy across the world, after lung cancer, in Europe including Greece in incidence and mortality for women between the ages 0-85 years old. Analytically, the incidence was 24.5% and the mortality reached 15.5% in 2020, worldwide. In Europe the percentage of incidence was 25.8% and the mortality 16.3%. Specifically, in Greece the percentage of incidence (27.5%) and mortality (17.4%) was the highest (2). This heterogeneity may be the result of the existence of multiple risk factors (lifestyle, genetic factors, environment etc.). In addition, it is acceptable that in more developed countries the opportunities for treatment are superior and therefore the changes of survival tend to be greater. Therefore, the percentage of mortality seems to be decreased in these countries. Due to the fact that the risk factors of breast cancer vary, they could

be separated in two categories; classic and «non-classic». Many haven't been substantiated and birth weight is one of them. This risk factor belongs to «non-classic» category.

## 2. OBJECTIVE

The purpose of this study is to investigate the relationship between birth weight and risk of breast cancer in our community.

## 3. MATERIAL AND METHODS

### Study design

This research is a case-control bicentric study. We collected the data of the patients who consulted in two breast clinics in Greece, between 2016 and 2019. The 391 participants included in the study were divided in two groups. Specifically, the case-group included 238 women with breast cancer confirmed after breast surgical procedure by the histopathological analysis. Conversely, the control group included 153 healthy women, who were examined with clinical examination, breast ultrasound and/or bilateral digital mammography. All the women of the two different groups were evaluated in the same period of time, after a written informed consent.

### Data analysis

The obtained information regarding neonatal birth weight and the presence or absence of breast cancer was submitted to the SPSS and we also used Fisher's Exact Test.

## 4. RESULTS

Our series consists of 391 women, of whom 238 are patients with breast cancer (60.9%) and 153 are healthy (39.1%) (Table 1).

The mean age of the patients in the study at the onset

		CASE/CONTROL			
		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	Breast cancer patients	238	60.9	60.9	60.9
	Healthy women	153	39.1	39.1	100.0
	Total	391	100.0	100.0	

Table 1. Number of participants in the study.

of the disease was 58 years. The maximum value of the age of the patients at the onset of the disease was 94 years, while the minimum value was 26 years. For the healthy participants, the mean age at the time of completing the questionnaire was 56 years, the maximum age was 82 years and the minimum age was 20 years.

Of the 391 participants, 32 (8.2%) had a neonatal birth weight <2500g, 115 (29.4%) had a neonatal birth weight of 2500-3000g, 87 (22.3%) had a neonatal birth weight >3000-3500g, 91 (23.3%) had a neonatal birth weight >3500-4000g and 66 (16.9%) >4000g.

Of the 238 patients with breast cancer, 12 (5%) had a neonatal birth weight <2500g, 37 (15.5%) had a neonatal birth weight of 2500-3000g, 44 (18.5%) had a neonatal birth weight >3000-3500g, 83 (34.9%) had a neonatal birth weight >3500-4000g and 62 (26.1%) >4000g.

Also, of the 153 healthy participants, 20 (13.1%) had a neonatal birth weight <2500g, 78 (51%) had a neonatal birth weight of 2500-3000g, 43 (28.1%) had a neonatal birth weight >3000-3500g, 8 (5.2%) had a neonatal birth weight >3500-4000g and 4 (2.8%) >4000g.

		Neonatal birth weight					Total	
		<2500g	2500-3000g	>3000-3500g	>3500-4000g	>4000g		
Breast cancer	Yes	Count	12	37	44	83	62	238
		ExpectedCount	19.5	70.0	53.0	55.4	40.2	238.0
		% withincancer	5,0%	15.5%	18.5%	34.9%	26.1%	100.0%
		% withinWeight_of_Birth	37.5%	32.2%	50.6%	91.2%	93.9%	60.9%
		% of Total	3.1%	9.5%	11.3%	21.2%	15.9%	60.9%
		Residual	-7,5	-33.0	-9.0	27.6	21.8	
		StandardizedResidual	-1.7	-3.9	-1.2	3.7	3,4	
	No	Count	20	78	43	8	4	153
		ExpectedCount	12.5	45.0	34.0	35.6	25.8	153.0
		% withincancer	13.1%	51.0%	28.1%	5,2%	2.6%	100.0%
Total		% withinWeight_of_Birth	62.5%	67.8%	49.4%	8.8%	6.1%	39.1%
		% of Total	5.1%	19.9%	11,0%	2,0%	1,0%	39.1%
		Residual	7.5	33.0	9.0	-27.6	-21.8	
		StandardizedResidual	2.1	4.9	1.5	-4.6	-4.3	
		Count	32	115	87	91	66	391
		ExpectedCount	32.0	115.0	87.0	91.0	66.0	391.0
		% withincancer	8.2%	29.4%	22.3%	23.3%	16.9%	100.0%
		% withinWeight_of_Birth	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%
		% of Total	8.2%	29.4%	22.3%	23.3%	16.9%	100.0%

Table 2. Neonatal birth weight of the participants.

	Value	df	Asymptotic Significance (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)	Point Probability
Pearson Chi-Square	116.436 <sup>a</sup>	4	.000	.000		
Likelihood Ratio	131.641	4	.000	.000		
Fisher's Exact Test	129.155			.000		
Linear-by-Linear Association	100.360 <sup>c</sup>	1	.000	.000	.000	.000
McNemar-Bowker Test	.	.	. <sup>b</sup>			
N of Valid Cases	391					

Table 3. Association of neonatal birth weight with the risk of breast cancer.

Consequently, we observed that breast cancer patients had a higher neonatal birth weight compared to the healthy participants (Table 2). In fact, women who weighed >3500g were more likely to develop breast cancer (OR = 18.3).

With the usage of Fisher's Exact Test, it was observed that there is a statistically significant correlation between the neonatal birth weight of women with breast cancer and those who do not (Fisher's Exact Test = 129,155, Exact sig <0.001). More specifically, 61% of women weighing >3500g have breast cancer which means that women who had a neonatal birth weight >3500g were more likely to have breast cancer (Table 3).

## 5. DISCUSSION

Many studies have tried over the years to consider the birth weight as a possible risk factor for breast cancer. Michels et al in 1996 discovered a possible relation between perinatal factors and especially, birth weight with breast malignancy. For the collection of the data, questionnaires were used. 582 mothers of nurses with breast cancer and 1.569 mothers of nurses without breast cancer were enrolled. The birth weight was separated in 5 categories ( $\geq 4000$  g, 3.500-3.999 g, 3.000-3.499 g, 2.500-2.999 g and < 2.500 g). A relationship with breast cancer was come out and specifically the highest relative risk was observed for the birth weight group 3.500-3.999 g (3). This result corresponds absolutely with our study and particularly in both studies the same cut-off regarding birth weight group was found to have the highest risk for breast malignancy.

Additionally, a large cohort study was carried out by Ekbohm et al. In this analysis, 3.795 women participated and 1.068 were diagnosed with breast cancer. The data were collected from 5 different hospitals in Sweden. At this case-control study 10 possible risk factors were probed and birth weight-length was also included. Overall, no association was indicated between birth weight and breast cancer, but when the placenta weight was adjusted the risk of breast malignancy was elevated (4). These survey data are adverse to ours.

The possible association between birth weight and breast cancer was also investigated in a population of very young women (14-37 years old) by Innes et al in 2000. A total number of 484 women were diagnosed with breast malignancy during the period 1978-1995 and the majority of them were 30.3 years old. A J-shaped correlation was found between birth weight and breast cancer. Particularly, women born  $\geq 4.500$  g had three times greater risk to develop breast cancer (5). To sum up, this analysis is coincident with our study.

Similarly, the association between birth weight and risk of breast cancer was discussed in a supplementary published study of Vaten et al. The total number of women, who participated in this study, was 1.523 (1.150 without history of breast cancer and 373 diagnosed with breast cancer). According to their results, women with birth weight  $\geq 3.730$  g had 40 % increased risk of breast cancer (6). This result is related to our data.

Furthermore, the possibility of birth weight as a risk factor for breast cancer was examined in a large cohort study of 106.504 Danish women (7). A linear increase was observed between birth weight and risk of breast cancer. Particularly, for every 1 kg increase in birth weight, the probability of breast cancer was per 9 % grown. This result was independent of menopausal status and age of the women. So, it is easily understood, that their outcome is related our results.

Another study with contrasting findings, had investigated the possible correlation between birth weight and breast cancer (8). 4.505 women were enrolled finally at this study. After 23.5 years of follow-up, no association between birth weight and breast cancer was found. This association was stronger for young women (< 40 years), who were born > 3.500 g (RR = 2.19). In conclusion, this result comes in disagreement to our study.

Moreover, Xue et al published a meta-analysis which included 57 studies, in 2007. This study searched the association between perinatal factors and risk of breast cancer. The perinatal factors were separated into 7 categories and one of these was the birth weight. From these 57 studies, 5 of them had as topic subject the relationship between birth weight and breast cancer. Birth weight-length were positive associated with the increased risk of breast malignancy and all involved studies were in agreement with this result (9). Consequently, this result is similar to our study.

Besides, Silva et al conducted a large re-analysis of 32 studies (22.058 breast cancer cases) in order to find out a possible relation between birth weight and breast cancer risk. The information from these studies was divided into 6 categories. One of them was the birth weight. Specifically, the birth weight was separated into 3 groups, in order to extract the results (10). Data about birth were selected from birth records, parental and maternal recall and self-reports. The studies collected the data from birth records and from parental recalls were positively associated with breast cancer, whereas studies based on self-reports or maternal recalls indicated no association. In particular, birth weight < 2.500 g was associated with 0.96 relative risk in comparison with those born  $\geq 4.000$  g, who had 1.12 breast

cancer risk ( $p=0.001$ ). Heterogeneity was discovered from data obtained from birth records, parental and maternal recalls and self-reports. Therefore, these results are partially in agreement with our findings.

An interesting investigation was performed by Baker et al in 2008 in an effort to find among others a relationship between birth weight and breast cancer risk. The interesting part of this study was the fact that the study population consisted of women and men born between 1936 and 1979 (11). The total number was 216.464 participants between ages 25-68 years old. The birth weight was divided into 5 categories and the years of birth into 4 groups. A linear increased association between birth weight and breast malignancy risk was discovered from this study and especially the hazard ratio reached the peak (1.01-1.15) in the highest birth weight category (4.251-5.500 g). Therefore, a similarity was found between this study's result and ours.

Park et al conducted also a meta-analysis in 2008, with the purpose to identify whether the heaviest birth weight is involved as risk factor for development of breast malignant pathology (12). They suggested that birth weight  $\geq 4.000$  g was associated with 18 % stronger risk for breast cancer. Specifically, this risk is more increased for premenopausal women or early-onset cancers. Interestingly, these results are similar to those of our study.

Also, a large population study took place in Los Angeles by Wu et al in 2011. Their purpose was to examine the association between prenatal factors, including the birth weight, and breast cancer. The study population consisted of 4.278 women and from these 2.259 suffering from breast cancer (1). The women who participated at this study was Asian (Chinese, Japanese or Filipino) between the ages 25-74 years old. A relationship was found between birth weight and breast malignancy and particularly the subsequent risk was elevated 8 % per 500 g accretion birth weight. Additionally, high birth weight  $\geq 4000$  g entails almost doubled risk for breast cancer in comparison with low birth weight  $< 2500$  g. So, these findings seem to be in accord with ours.

Sparcklen et al conducted an additional large cohort study, with 161.608 postmenopausal women between 50 and 79 years of age. The follow-up time for malignant diagnoses was 11.3 years (13). The final population consisted of 65.850 women from several countries (84.8 % Caucasian, 7.4 % African American, 2.6 % Asian/ Pacific Islander and 1.4 % other/ unknown race). These women were separated into four categories according to their birth weight. All cancer sites, gynecologic cancers and several site-specific cancer sites were correlated with birth weight. According to their results, normal birth weight was associated with advanced breast cancer risk in comparison with women born in the highest birth weight group. Finally, heterogeneity is observed between the findings of this analysis and ours study.

A prospective study by Yang et al in 2014, was conducted in UK and 1.3 million women were participated (14). A questionnaire was used, in order to obtain information about birth and family, reproductive factors in adolescence and early adulthood and lifestyle (follow-up). Among others the study population was divided into five categories depending on their birth weight ( $< 2.5$ , 2.5-2.9, 3.0-3.4, 3.5-3.9 and  $> 4$ kg). Compared to birth weight, the findings suggest that

adult height is strongly related to the risk of breast cancer ( $p < 0.0001$ ). These results are opposite to ours.

More recent studies were conducted by Luo et al in 2019 with the purpose to investigate the relation between birth weight and risk of breast malignancy (15). The birth weight was divided into 3 categories:  $< 6$ , 6-8,  $\geq 8$  pounds (we remind that 1 pound = 0.454kg). Decreased risk of breast cancer was observed for the population born  $< 6$  pounds (2724kg), whereas the group with birth weight  $\geq 8$  pounds (3632kg) was not correlated with breast cancer risk. It was observed that the decreased risk was applied for postmenopausal women. However, our result differs from this study's outcome.

The most recent and pioneering large cohort study was conducted in 2021 by Sandvei et al with 22.931 Norwegian women born 1920-1966 (16). For this study data were collected about perinatal and maternal factors, including the birth weight in order to find a possible relationship with breast cancer risk and for first time the molecular subtype. The follow-up took place the period between; 1961-2012 and from this found that 870 were diagnosed with breast cancer. In conclusion, association was not discovered between birth-weight and risk of breast cancer, regardless the molecular subtype. Surprisingly, their observations are not compatible with our analysis.

The mechanisms underlying the association between increased birth weight and breast cancer risk has been discussed in several studies. A pathological pathway may be the link between advanced birth weight and the elevated levels of IGF-1 (insulin-like growth factor-1). This lead to high rates of embryonic cell proliferation and increased the risk of epithelial cancers (5, 12-13). Rates of IGF-2 and estrogen above the average during the perinatal period can also contribute to high possibility of breast cancer malignancy (9). Another scientific theory explaining the correlation of this birth indicator and breast cancer risk could be the capability of estrogens to provoke the development of the fetus and affect the growth of the mammary gland (6). As it was indicated above, higher levels of estrogens during pregnancy is strong associated with breast malignancy (1, 3-5, 7, 9-10, 12). Except from IGF-1 additional factors like leptin, adiponectin, ghrelin and alpha-phenoprotein are related with birth size and consequently the fetal exposure to them has as a result the breast cells to be more prone to carcinogenesis (10). Furthermore, mammatropic hormones, including prolactin, human placental lactogen (hPL) and also Growth Hormone (GH) play an important role in the mechanism of breast malignancy. These hormones in high levels affect the still growing mammary gland of the fetus and increase the number of the mammary gland-specific stem cell leading to elevated risk for breast cancer (16). In conclusion, a supplementary explanation for this trend could be the fact that high weight at birth is associated with increased mammographic density and earlier start of menstruation, two established risk factors of breast cancer (1). Nevertheless, supplementary investigation should be conducted so as to the pathological pathways and the role of birth weight as a risk factor to be clarified.

## 6. CONCLUSION

Our study found a significant relation in women with high weight at birth (more than 3.5 kg) and emergence of breast cancer in the future. This result is in favor to include birth weight as a new non classical risk factor of breast cancer. Nevertheless, supplementary studies are necessary to confirm this hypothesis because actually data are still controversy.

- **Authors contribution:** M.D: conceptualization, methodology, supervision, visualization, writing, original draft and editing, C.D: writing, project administration, I.M-T: methodology, data analyzing, review and editing, E.K: methodology, project administration, E.T: methodology, project administration, E.A: review and editing, supervision. All authors have read and approved the manuscript.
- **Conflict of interest:** The authors declare no conflict of interest.
- **Financial support and sponsorship:** None received.

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