



# Breast Cancer and Ovarian Cancer in Monozygotic Twins

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## Abstract

We show the case of three pairs of monozygotic twins in our local area where we carried out our research: in the first pair of identical twins (case 1), one of them was diagnosed at the age of 43 with bilateral ovum cancer and the other one with left ovum cancer at the age of 48. In both cases: high risk cancer, dying of neoplasia dissemination 5 and 6 years after the diagnosis. The genetic study of BRCA was not carried out. In the second pair of monozygotic twins (case 2), only one of them was diagnosed with breast cancer at the age of 39, while the other twin presents no cancer after 10 years of the diagnosis of her identical twin. Although the genetic study BRCA1 and 2 in this family came out negative, the other pair of twins was diagnosed with bilateral breast cancer: one of them at 39 and 40 years old, and the other at 50 and 58 years old. In 2002, we published the case of a pair of monozygotic twins (case 3) that were diagnosed with BC, one of them at 55 and 61 (bilateral BC) and the other at 60 (right BC). The new achievements in genetics, both in the understanding of the human genome as well as in reducing costs, should lead to a much more regular use of DNA tests to improve the prevention of breast and hereditary ovum cancer syndromes, through oophorectomy and/or prophylactic mastectomy. This will also increase the “Preimplantational Genetic Diagnosis” and will make it more popular through assisted reproductive techniques in families with a high risk, where the possibility of selecting embryos free of genetic mutation should be offered for its implantation and gestation.

**Keywords:** Breast cancer; Ovarian cancer; Monozygotic twins; Chronobiology; Hereditary cancer

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## Perspective

Breast cancer is a multifactorial disease. Regarding inheritance, we must distinguish three categories: Sporadic BC, Familial BC and Hereditary BC [1-6]. The first documentation of familial clustering of breast cancer in modern times was published by Broca, who reported 10 cases of breast cancer in 4 generations of his wife's family [7]. In the middle of the nineteen nineties it was demonstrated at molecular level that a substantial number of breast and ovarian cancers has hereditary monogenic a etiology [8,9]. The Hereditary BC represents at least 10% of breast cancers and are caused by pathogenic mutations in the considered reference BRCA1 [8] and BRCA2 [9] genes. Based on results of published studies in pairs of monozygotic twins with at least one of them affected by breast cancer, we can affirm that the lifetime breast cancer risk for a healthy identical twin, in a non BRCA woman is around 20-30%. Obviously, other non-hereditary risk factors must exist to explain the discordant phenotype. This highlights that environmental factors play an important role in breast cancer development.

As sequencing technologies evolve, more susceptible genes have been discovered and BRCA1 and BRCA2 predisposition seems to be only one part of the story. These new findings include rare germline mutations in other high penetrant genes, the most important of which includes TP53 mutations in Li-Fraumeni syndrome [10], STK11 mutations in Peutz-Jeghers syndrome [11], and PTEN mutations in Cowden syndrome [12].

Theoretically, the comparison between concordance rates for Cancer in monozygotic and dizygotic twins could give information about the genetic factors in these types of cancer. A large, new study of identical and fraternal twins in Nordic countries finds that when one twin is diagnosed with any type of cancer, there is a higher than average risk that the other twin will also develop cancer. This risk of developing cancer was an estimated 14 percent higher in identical twins if one twin had cancer and 5 percent higher in fraternal twins if one twin had cancer — compared to the average cancer risk of all the people in the study [13]. According to the evidences in monozygotic twins and considering some families with intense family addition in Breast Cancer, we can consider

that it exists a genetic program which determines the simultaneity in the time of the beginning of the tumor; therefore we suggest tackling the chronobiology as a new clinical variable in the study of Hereditary BC [14].

At the beginning twin studies comparing the disease concordance rate in identical twin pairs helped us to differentiate the influence of genetic and environmental factors in the disease development. The discordance observed in some of these monozygotic twins pairs confirmed the importance of environmental factors [15]. These studies are based on the fact that monozygotic twins, those who are formed from the split of a unique fertilized ovum, have the same genome and therefore are genetically identical. In theory, the comparison between percentages of concordance in the BC in monozygotic and dizygotic twins gives us the information about the genetic factors in this kind of cancer.

Once we have confirmed the influence of the environmental factors in the development of breast cancer, we would like to point out that twin studies provide us with the opportunity to study the biological clock which predicts the starting date of the carcinogenesis. There is a coincidence or at least a tendency towards similar ages in the age of appearance of the breast cancer in monozygotic twins, as well as in the members of the same family with Hereditary Breast Cancer Syndrome, that must be studied in depth. In the Table 1 we show the case of three pairs of monozygotic twins in our local area where we carried out our research:

In the first pair of identical twins (case 1), one of them was diagnosed at the age of 43 with bilateral ovum cancer and the other one with left ovum cancer at the age of 48. In both cases: high risk cancer, dying of neoplasia dissemination 5 and 6 years after the diagnosis. The genetic study of BRCA was not carried out. Miesfeldt et al. [16] [16] reported breast and ovarian cancer syndrome in an identical twin pair with similar clinical histories and with gen BRCA1 mutation. Both twins developed histologically similar ovarian cancer in their mid-fifties. One twin was diagnosed with stage III disease and died of refractory metastatic disease. The other twin was diagnosed with stage I disease but ultimately died of recurrent disease. Neither twin developed breast or colon cancer. Advanced ovarian adenocarcinoma presented within 3 years in identical twins is reported. The carcinomas presented at a similar stage and the microscopic appearances showed strong histological similarities [17].

In the second pair of monozygotic twins (case 2), only one of them was diagnosed with breast cancer at the age of 39, while the other twin presents no cancer after 10 years of the diagnosis of her identical twin. Although the genetic study BRCA1 and 2 in this family came out negative, the other pair of twins was diagnosed with bilateral breast cancer: one of them at 39 and 40 years old, and the other at 50 and 58 years old. Sato et al. [18] described a family which involved identical

twin sisters who underwent surgical treatment for a unilateral breast cancer at the same age of 28. Each, after 13 years, developed cancer in the opposite breast. In addition yet another sister, the youngest, had to undergo the same surgical procedure, at the same age her identical twin sisters had had their first operations. These findings may indicate the existence of factors which decide the age of the malignancy onset, in addition to the existence of a predisposing factor for carcinoma in the genes of breast cancer patients.

In 2002, Cortizo-Torres et al. [14] published the case of a pair of monozygotic twins (case 3) that were diagnosed with BC, one of them at 55 and 61 (bilateral BC) and the other at 60 (right BC).

By looking at our table [14] we can reach the same conclusion that Heizer and Lewison [19] observed in 1964 after reviewing the medical literature on breast cancer in identical twins: There was a strong tendency for these tumors to be located in the same breast and presented at the same time.

Thanks to the advance in the interpretation of the genetic code maybe we will be able to understand, in the future, how the biological clock starts the beginning of cancer. Cancer in pairs of identical twins is a good model for the study of molecular genetics and its interaction with the environment. The new achievements in genetics, both in the understanding of the human genome as well as in reducing costs, should lead to a much more regular use of DNA tests to improve the prevention of breast and hereditary ovum cancer syndromes, through oophorectomy and/or prophylactic mastectomy. This will also increase the “Preimplantational Genetic Diagnosis” and will make it more popular through assisted reproductive techniques in families with a high risk [20], where the possibility of selecting embryos free of genetic mutation should be offered for its implantation and gestation.

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**Table 1:** Pairs of monozygotic twins.

Pairs of identical twins	Twin A (Age in years)	Twin A (Age in years)	Sisters not twins
Case 1	43 Ovarian Cancer Bilateral	48 Left Ovarian Cancer	
Case 2	39 Left Breast Cancer	No cancer after 10 years of follow up	Two sisters not twins with bilateral breast cancer: (39 + 40) and (50 + 58)
Case 3	55 and 61 Breast Cancer Bilateral	60 Breast Cancer Unilateral	

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