RESEARCH ARTICLE

# Contralateral Breast Cancer: a Clinico-pathological Study of Second Primaries in Opposite Breasts after Treatment of Breast Malignancy

**Abhishek Shankar[1]*, Shubham Roy[3], Abhidha Malik[1], Vineet Kumar Kamal[2], Ruchir Bhandari[1], Kunal Kishor[1], MK Mahajan[2], Jaineet Sachdev[2], Pamela Jeyaraj[2], GK Rath[1]**

## Abstract

**Background: Breast cancer is by far the most frequent cancer of women (23 % of all cancers), ranking second overall when both sexes are considered together. Contralateral breast cancer (CBC) is becoming an important public health issue because of the increased incidence of primary breast cancer and improved survival. The present communication concerns a study to evaluate the role of various clinico-pathological factors on the occurrence of contralateral breast cancer. Materials and Methods: A detailed analysis was carried out with respect to age, menopausal status, family history, disease stage, surgery performed, histopathology, hormone receptor status, and use of chemotherapy or hormonal therapy. The diagnosis of CBC was confirmed on histopathology report. Relative risk with 95%CI was calculated for different risk factors of contralateral breast cancer development. Results: CBC was found in 24 (4.5%) out of 532 patients. Mean age of presentation was 43.2 years. Family history of breast cancer was found in 37.5% of the patients. There was statistically significant higher rate (83.3%) of CBC in patients in age group of 20-40 years with RR=11.3 (95% CI: 1.4, 89.4, p=0.006) seen in 20-30 years and RR=10.8 (95% CI:1.5-79.6, p=0.002) in 30-40 years as compared to older age of 60-70 years. Risk of development was higher in premenopausal women (RR=8.6, 95% CI: 3.5-21.3, p≤0.001). Women with family history of breast cancer had highest rate (20.9%) of CBC (RR=5.4, 95% CI: 2.5-11.6, p≤0.001). Use of hormonal therapy in hormone receptor positive patients was protective factor in occurrence of CBC but not significant (RR=0.7, 95% CI: 0.3-1.5, p=0.333). Conclusions: Younger age, premenopausal status, and presence of family history were found to be significant risk factors for the development of CBC. Use of hormonal therapy in hormone receptor positive patients might be protective against occurrence of CBC but did not reach significance.**

**Keywords:** Contralateral breast cancer - second primary - opposite breast - risk factors

*Asian Pac J Cancer Prev,* **16 (3)**, 1207-1211

## Introduction

Breast cancer is by far the most frequent cancer of women (23% of all cancers), ranking second overall when both sexes are considered together. It is the leading cause of cancer mortality in women and constitutes 14% of female cancer deaths (Parkin et al., 2005). With an estimated 226,870 diagnoses and 39,510 deaths in 2012, breast cancer remains the most commonly occurring and second most lethal cancer among women in the United States (Howlader et al., 2011). Contralateral breast cancer is defined as the occurrence of a second, independent primary breast cancer in the other breast after the initial diagnosis of breast cancer. Current data suggest that between 2% and 11% of patients diagnosed with breast cancer have or will develop bilateral disease (Chen et al., 1999; Heron et al., 2000). Patients with a previous diagnosis of breast cancer are two to six times more likely to develop a second breast cancer than their peers are to develop a first breast cancer (Hankey et al., 1983).

The incidence rate of contralateral breast cancer varies from 4-8 per 1000 person-years. Newer treatment modalities have increased survival in breast cancer patients but the risk of contralateral breast cancer and other nonbreast second malignancies is always there. The study of contralateral breast cancer is becoming an important public health issue because of the increased incidence of first primary breast cancer and improved survival (Horn-Ross et al., 1993). The risk of CBC in non-BRCA mutated early stage breast cancer is low at 0.5-0.75% per year, with a 10-year cumulative risk of CBC ranging from 1-15%, with higher figures seen among patients with a family

*[1]Department of Radiation Oncology, IRCH, All India Institute of Medical Sciences, [2]Department of Bio-Statistics, All India Institute of Medical Sciences, [3]Department of Pediatrics, VMMC & Safdarjung Hospital, Delhi, India *For correspondence: doc.abhishankar@gmail.com*

history of breast cancer (Abbott et al., 2011; Nichols et al., 2011; Reiner et al., 2013).

Since there is lack of universal criteria for development of contralateral breast cancer that limits the estimation of its frequency and comparison of the available studies, the present communication is a study to evaluate the role of various clinico-pathological factors on the occurrence of contralateral breast cancer.

## Materials and Methods

The study comprised of 532 biopsy proven patients of carcinoma breast treated between January 1997 to December 2006 in Department of Radiotherapy, Christian Medical College, & Hospital, Ludhiana. For this study, contralateral breast cancer was defined as cancer that appears after 6 months of primary breast cancer diagnosis.

A detailed analysis was carried out with respect to age, menopausal status, Family history, disease stage, surgery performed, histopathology, hormone receptor status, and use of chemotherapy or hormonal therapy. All parameters were entered into a computerized database. Diagnosis of second malignancy was then confirmed on histopathology report.

Among 506 patients (95.11%) who received chemotherapy, chemotherapy scheme was CMF(Cyclofosfamide 600mg/m2day1 Methotrexate 40mg/$m^2$ day 1, 5FU 600 mg/$m^2$ day 1), FAC (5FU 500mg/$m^2$ day 1, Doxorubicin 60mg/$m^2$ IV day 1, Cyclofosfamide 500mg/$m^2$ day 1) and FEC(5FU 500mg/$m^2$ day 1, Epirubicin 100mg/m2 IV day 1, Cyclofosfamide 500mg/m2 day 1) A number of 26 patients (4.88%) did not undergo chemotherapy.

Radiotherapy was performed at cobalt 60 unit. The chest wall or mammary gland was irradiated throughout two tangential opposed fields. The radiotherapy technique included the exposure of axillary and/or supraclavicular and/or internal mammary lymph nodes in patients where it was indicated. The prescribed doses were TD=50 Gy/25 fractions /5 weeks in all cases.

Among patients who were given hormonal therapy for hormone receptor positive, 372 women (69.92%) received tamoxifen, 27 patients (5.07%) received anastrazole or letrozole against the 25% that did not receive this particular treatment.

The association between two categorical variables were seen by using Chi-square/Fisher's exact test. The relative risks with 95% confidence interval (CI) were calculated for developing contralateral breast cancer among different categories of risk factors. All the p- value less than 0.05 were taken as significant and all the analysis was done by using software stata/IC 11.2.

## Results

Patients of carcinoma breast (532 patients) treated between 1997 to 2006 were included in the study. Clinico-pathological and treatment parameters of breast cancer and contralateral breast cancer patients are shown in Table 1.

The mean age of the patients of breast cancer included in this study was 47 years ranging from 30 to 69 years.

**Table 1. Clinico-pathological and Treatment Parameters of Breast Cancer and Contralateral Breast Cancer Patients**

| Parameters | No of Breast cancer patients (N=532) | No of CBC patients (N= 24) |
|---|---|---|
| Mean age (years) (range) | 47(30-69) | 43.25(35-52) |
| Menstrual status | | |
| Premenopausal | 137 (25.7) | 18 (75) |
| Postmenopausal | 395 (74.3) | 6 (25) |
| Family History | | |
| Present | 43 (8.08) | 9 (37.5) |
| Absent | 489 (91.9) | 15 (62.5) |
| Histologic type | | |
| Ductal | 484 (90.9) | 21 (87.5) |
| Lobular | 36 (6.76) | 3 (12.5) |
| Medullary | 10 (1.87) | 0 |
| Papillary | 1 (0.18) | 0 |
| Tubular | 1 (0.18) | 0 |
| Surgical treatment | | |
| MRM | 243 (45.6) | 14 (58.3) |
| Simple Mastectomy | 189 (35.5) | 1 (4.16) |
| BCS | 32 (6.01) | 3 (12.5) |
| No surgery | 68 (12.7) | 6 (25) |
| Chemotherapy | | |
| NACT | 122 (22.9) | 6 (25) |
| Adjuvant | 374 (70.3) | 12 (50) |
| No chemotherapy | 36 (6.76) | 6 (25) |
| Chemotherapy | | |
| CMF | 212 (39.8) | 7 (29.1) |
| FAC | 266 (50) | 11 (45.8) |
| FEC | 28 (5.26) | - |
| Adjuvant Herceptin | 14 (2.63) | 1 (4.16) |
| EBRT | | |
| Radical | 454 (85.3) | 19 (79.2) |
| Palliative | 78 (14.6) | 5 (20.8) |
| EBRT | | |
| Two tangential fields+ anterior axillary-supraclavicular field | 367 (68.9) | 19 (79.2) |
| Two tangential fields+ anterior axillary-supraclavicular field+ internal mammary | 87 (16.3) | - |
| Whole Brain RT | 15 (2.81) | 1 (4.16) |
| RT to spine and pelvis | 48 (9.02) | 4 (16.7) |
| Total dose | | |
| 50Gy/25 F/5Weeks | 454 (85.3) | 19 (79.2) |
| 30 Gy/10 F/ 2 Weeks | 34 (6.39) | 1 (4.16) |
| 20 Gy/5 F/1 week | 32 (6.01) | 0 |
| 8 Gy/ 1 F/ 1 Day | 38 (7.14) | 4 (16.7) |
| Hormonal treatment | | |
| Tamoxifen | 372 (69.92) | 15 (62.5) |
| Anastrazole | 27 (5.07) | 1 (4.16) |
| No hormonal treatment | 133 (25) | 8 (33.3) |
| Metastatic disease on presentation | 93 (17.4) | 8 (33.3) |
| Liver | 16 (2.44) | 2 |
| Lung | 27 (3.19) | 2 |
| Bone | 58 (9.02) | 5 |
| Brain | 18 (2.81) | 1 |

Among 532 breast cancer patients, 395 patients (74.3%) were postmenopausal and 137 patients (25.7%) were postmenopausal. Family history of breast cancer was present in 43 patients (8.08%). Histology of ductal

**Table 2. Risk of Contralateral Breast Cancer Development**

| Risk factors | | Breast Cancer (532) | CBC(24) | RR (95% CI) | p value |
|---|---|---|---|---|---|
| Age | 20-30 | 27 | 6 | 11.3 (1.4,89.4) | 0.006 |
| | 30-40 | 66 | 14 | 10.8 (1.5,79.6) | 0.002 |
| | 40-50 | 182 | 2 | 0.6 (0.1,6.1) | 0.525 |
| | 50-60 | 206 | 1 | 0.2 (0.0,3.9) | 0.358 |
| | 60-70 | 51 | 1 | 1 | |
| Menopausal status | Premenopausal | 137 | 18 | 8.6 (3.5,21.3) | <0.001 |
| | Postmenopausal | 389 | 6 | 1 | |
| Family History | Present | 43 | 9 | 5.4 (2.5,11.6) | <0.001 |
| | Absent | 489 | 15 | 1 | |
| Histology | Ductal | 484 | 21 | 1 | |
| | Lobular | 36 | 3 | 1.9 (0.6,6.1) | 0.227 |
| | Medullary | 10 | 0 | - | - |
| | Papillary | 1 | 0 | - | - |
| | Tubular | 1 | 0 | - | - |
| Hormonal status | ER + PR + Her 2 neu - | 287 | 11 | 0.5 (0.2,1.4) | 0.198 |
| | ER + PR + Her 2 neu + | 112 | 6 | 0.7 (0.2,2.3) | 0.57 |
| | ER - PR – Her 2 neu + | 66 | 2 | 0.8 (0.1,2.0) | 0.44 |
| | TNBC | 67 | 5 | 1 | |
| Hormonal treatment | Hormonal treatment | 369 | 15 | 0.7 (0.3,1.5) | 0.333 |
| | No Hormonal treatment | 153 | 9 | 1 | |

carcinoma was present in 90.9% of the cases (484) followed by lobular (6.76%), medullary (1.87%) and papillary and tubular, each present in 1 case (0.18%). Modified Radical Mastectomy (MRM), Simple Mastectomy(SM), Breast Conservation Surgery (BCS) was performed on 243patients (45.6%), 189 patients (35.5%) and 32 patients (6.01) respectively, whereas 68 patients (12.7%) did not undergo surgical treatment. Approximately 93% of patients received chemotherapy in Neoadjuvant (22.9%) and adjuvant (70.3%) settings. FAC chemotherapy was given to 50 % of the patients followed by CMF (39.8%) and FEC (5.26%). Fourteen patients (2.63%) were given adjuvant herceptin whereas 36 patients (6.76%) did not receive chemotherapy. In RT technique, 367 patients (68.9%) were treated with two tangential fields with axillary and supraclavicular fields. Internal mammary field was added in 87 patients (16.7%) who were having inner quadrant disease. Metastatic disease at presentation was seen in 93 patients (17.450%). Adjuvant tamoxifen was received by 372 patients (69.92%) followed by aromatase inhibitors (Anastrazole/Letrozole) by 27 patients (5.07). Many postmenopausal women were given tamoxifen in view of financial constraints.

Contralateral breast cancer was found in 24 (about 4.5%) out of 532 patients. Clinico-pathological and treatment parameters of contralateral breast cancer patients are shown in Table 1. The time to occurrence was 2 to 20 years, median time being 6.5 years. Metachronous presentation was 75% in contrast to synchronous being 25%. Mean age of presentation was 43.25 years ranging from 35 to 52 years. Seventy five percent were premenopausal women and 25% were postmenopausal women. Family history for breast cancer was found in 37.5% of the patients. Histology of ductal carcinoma was present in 87.5% of the cases (21) followed by lobular in 3 cases (12.5%). MRM, SM, BCS were performed on 14 patients (58.3%), 1 patient (4.16%) and 3 patients (12.5) respectively, where as 6 patients (25%) did not undergo surgical treatment. Neoadjuvant and adjuvant chemotherapy were offered to 25% and 50% of the patients respectively. All patients were treated with two tangential fields to chest wall with axillary and supraclavicular fields. Metastatic disease at presentation was seen in 8 patients (33.3%). Adjuvant tamoxifen was received by 15 patients (62.5%) followed by aromatase inhibitors (Anastrazole / Letrozole) by 1 patient (4.16%).

There was statistically significant higher rate (83.3%) of contralateral breast cancer in patients in age group of 20-40 years with RR=11.3(95 % CI: 1.4,89.4, p=0.006) seen in 20-30 years and RR= 10.8 (95% CI:1.5-79.6, p=0.002) in 30-40 years as compared to older age of 60-70 years. Risk of development of contralateral breast cancer was higher in premenopausal women (RR=8.6, 95% CI: 3.5-21.3, p≤0.001) as compared to postmenopausal women. There was about 5.4 times more risk of having contralateral breast cancer in women with family history of breast cancer (RR=5.4, 95% CI: 2.5-11.6, p≤0.001) as compared to women without family history. Histology of lobular carcinoma was also a risk factor but without significance (RR=1.9, 95% CI: 0.6-6.1, p=0.22). The hormonal therapy was found as a protective factor for CBC development but not statistically significant (RR=0.7, 95% CI: 0.3- 1.5, p=0.33). Mean time duration between first and second malignancy was 9 years in ER+, PR+, Her 2 neu- patients, 8.6 years in ER+, PR+, Her 2 neu+ patients and 4 years in HER+ patients and 3 years in TNBC. Median time duration between 1st and 2nd malignancy was 12 years in patients who received adjuvant Tamoxifen in contrast to 4½ years in patients who received Aromatase Inhibitor (AI) and no hormonal treatment respectively which is statistically significant.

## Discussion

The first description of contralateral breast cancer was published in 1921 (Kilgore, 1921). Understanding the aetiology of contralateral breast cancer could help identify patients who are at an increased risk and alleviate

some of the ambiguity surrounding the involvement of environmental, genetic, and hormonal factors influencing the development of breast cancer (Thompson et al., 1986). After diagnosis of a first primary breast cancer, women with an intact contralateral breast are at risk of developing contralateral breast cancer (Reiner et al., 2013). In this study, CBC was seen in 4.5 % of patients. In a study by Yadav et al. (2008) on 1084 breast cancer patients showed similar finding in which CBC was seen in 4% of patients. The 15 year actuarial rate of CBC in the present study was 9.5%. In a study by Krishnappa et al. (2015) Primary synchronous bilateral breast cancer constituted around 0.19% of all breast cancer cases.

There was statistically significant higher rate (83.3%) of contralateral breast cancer in patients in age group of 20-40 years with RR=11.3(95% CI: 1.4, 89.4, p=0.006) seen in 20-30 years and RR=10.8 (95% CI:1.5-79.6, p=0.002) in 30-40 years. Age as a potential risk factor for CBC has been reported in many studies. Gao reported that reported that age <45 years (RR=1.32) and >55 years (RR=1.15) were at increased risk of CBC (Geo et al., 2003). Mariana also identified age <45 years as a risk factor for CBC. (Mariana et al., 1997). In a study by Rebegea et al. (2013) showed that age under 50 years at moment of first primary cancer diagnosis represents a risk factor statistically significant( RR=1.35, p=0.02).

Zeichner et al. (2014) suggested that patients less than 40 years of age are at greatest cumulative risk to develop contralateral breast cancer.

Risk of development of contralateral breast cancer was higher in premenopausal women (RR=8.6, 95% CI: 3.5-21.3, p≤0.001) as compared to postmenopausal women. Premenopausal women were found to be at higher risk of developing CBC in a study by Yadav et al. (2008). One study performed a subgroup analysis according to menopausal status and found a reduction in the risk of contralateral breast cancer for postmenopausal women and a marginal increase in risk for premenopausal women (Cancer Research Campaign Breast Cancer Trials Group, 1992).

In this study, there was a strong correlation between family history of breast cancer and occurrence of contralateral breast cancer. Women with family history of breast cancer had highest rate (20.9%) of CBC (RR=6.8, 95% CI: 3.2-14.7, p≤0.001). In a multivariate analysis, family history along with Nulliparity and obesity was found to increase the risk of CBC, without any change in estimate of radiation-associated risk (Storm et al., 1992). We have not considered obesity and Nulliparity about potential of these factors in causation of CBC. A study by Yadav et al also showed that females with a family history had the highest incidence rates of CBC (15.3%; RR, 1.6; 95% CI, 1.12-1.27) at 20 years old (Yadav et al., 2008).

Studies found that having a sister with breast cancer incurred a greater risk of contralateral breast cancer than having a mother with breast cancer (Cook et al., 1996). In the absence of known genetic mutations, patients with strong family histories who are diagnosed at young ages (<35 years) with estrogen receptor-negative index tumours appear to have a higher incidence of CBC (Lizarraga et al., 2013).

Many studies have shown that patients with lobular histology have an increased risk of CBC. Fisher et al. (1984) found that invasive lobular histological type was significantly associated with increased risk of contralateral breast cancer. In this study, patients with histology of lobular and ductal carcinoma was also a risk factor but without significance (RR=2, p=0.25 for lobular and RR=0.7, p=0.54 for ductal).

A number of studies have documented that women who received chemotherapy for the initial breast cancer showed a reduction in risk of developing a contralateral breast cancer (Cook et al., 1996). Chemotherapy in early breast cancer may reduce the overall risk of new primary tumors (Arriagada and Rutqvist, 1991). In this study, high incidence of CBC (16.6%) was seen in primary breast cancer patients who didn't receive chemotherapy. In a study by Silber et al. (2013) clearly showed that adjuvant therapy substantially reduced risk of CBC.

Hormone receptor plays important role in development of CBC. In a study by Rusner et al. (2014) in Germany showed that SIR of HR-positive CBC was 0.7 (95%CI: 0.6 to 0.8) among women with HR-positive CBC. For those women with HR-negative FBC, the SIR of HR-negative CBC was 8.9 (95%CI: 7.1 to 11.1). For patients with tumor recurrence in the contralateral breast, Bessonova et al. (2011) analyzed the risk associated with hormonal receptor and HER2 status in 1613 patients diagnosed with contralateral breast cancer after treatment of their first breast cancer. The authors found that hormone receptor-negative tumors were regarded as having a higher risk for contralateral second breast cancer. HER2 status did not seem to be a marker of risk for second breast cancer. ER positive receptors acts as a protective factor and Patients with ER positive tumors significantly improved long-term outcomes (Loi et al., 2007). Shim et al showed that luminal A tumors were associated with low risks of overall recurrence, locoregional recurrence and contralateral recurrence (Shim et al., 2014).

The hormonal therapy represented a protective factor with significance for CBC development (RR=0.72, 95% CI: 0.33-1.6, p=0.79) in this study. It is well known that hormone treatment with tamoxifen reduces the risk of CBC (Phillips et al., 2013). The studies by the Scottish Cancer Trials Breast Group (Stewart, 1992) and the Cancer Research Campaign Breast Cancer Trials Group also found overall beneficial effects of adjuvant tamoxifen on the incidence of contralateral breast cancer. Patients in NSABP B-24 with ER-positive breast cancer receiving adjuvant tamoxifen after standard therapy showed significant reductions in subsequent breast cancer (Allred et al., 2012). In a study by Tomohika et al. (2014) in Japan showed that the incidence of contralateral breast cancer per 1000 person-years was 5.1 (95% confidence interval (CI), 3.7-7.1) among patients without endocrine therapy (n=1364) and 3.6 (95% CI 2.1-6.1) among those with endocrine therapy. (Reference). In a cohort study done in dannish women clearly shown that tamoxifen protects against CBC while being treated (Early Breast Cancer Trialists Collaborative Group, 1998), so use of tamoxifen was associated with reduced HRs of CBC independently of menopausal status and calendar period (Mellemkjaer et al.,

2014). Yadav et al. (2008) showed statistically significant lower rate of CBC in patients given adjuvant hormonal therapy (8.5%) as compared to those without hormonal therapy (14.3%, p=0.004) at 20 year in his study.

In conclusions, this study reveals that age <40 years and premenopausal status represent a risk factor in occurrence of contralateral breast cancer. Family history of breast cancer was found to be significant risk factor for CBC. Moreover, hormone receptor positive and tamoxifen, having a protection effect, reduces the chances of developing CBC in breast cancer patients. Regular follow up of the breast cancer patients after treatment is very important to identify and prevent relapses and also, for contralateral breast cancer diagnosis.

## References

Abbott A, Rueth N, Pappas-Varco S, et al (2011). Perceptions of contralateral breast cancer: an overestimation of risk. *Ann Surg Oncol*, **18**, 3129-36.

Aihara T, Tanaka S, Sagara Y, et al (2014). Incidence of contralateral breast cancer in Japanese patients with unilateral minimum-risk primary breast cancer, and the benefits of endocrine therapy and radiotherapy. *Breast Cancer*, **21**, 284-91.

Allred DC, Anderson SJ, Paik S, et al (2012). Adjuvant tamoxifen reduces subsequent breast cancer in women with estrogen receptor-positive ductal carcinoma in situ: a study based on NSABP protocol B-24. *J Clin Oncol*, **30**, 1268-73.

Arriagada R, Rutqvist LE (1991). Adjuvant chemotherapy in early breast cancer and incidence of new primary malignancies. *Lancet*, **338**, 535-8.

Bessonova L, Taylor TH, Mehta RS, et al (2011). Risk of a second breast cancer associated with hormone-receptor and HER2/neu status of the first breast cancer. *Cancer Epidemiol Biomarkers Prev*, **20**, 389-96.

Cancer Research Campaign Breast Cancer Trials Group (1992). The effect of adjuvant tamoxifen: the latest results from the cancer research campaign adjuvant breast trial. *Eur J Cancer*, **28**, 904-7.

Chen Y, Thompson W, Semenciw R, et al (1999). Epidemiology of contralateral breast cancer. *Cancer Epidemiol Biomarkers Prev*, **8**, 855-61.

Early Breast Cancer Trialists' Collaborative Group (1992). Systemic treatment of early breast cancer by hormonal, cytotoxic or immune therapy. *Lancet*, **339**, 1-15-7185.

Early Breast Cancer Trialists Collaborative Group (1998). Tamoxifen for early breast cancer: an overview of randomized trials. *Lancet*, **351**, 1451-67.

Gao X, Fisher SG, Emami B (2003). Risk of second primary cancer in the contralateral breast in women treated for early-stage breast cancer: a population-based study. *Int J Radiat Oncol Biol Phys*, **56**, 1038-45.

Hankey BF, Curtis RE, Naughton MD, et al (1983). A retrospective cohort analysis of second breast cancer risk for primary breast cancer patients with an assessment of the effects of radiation therapy. *J Natl Cancer Ins*, **70**, 797-804.

Heron DE, Komarnicky LT, Hyslop T, et al (2000). Bilateral breast carcinoma: risk factors and outcomes for patients with synchronous and metachronous disease. *Cancer*, **88**, 2739-50.

Horn-Ross PL (1993). Multiple primary cancers involving the breast. *Epidemiol Rev*, **15**, 169-76.

Howlader N, Noone AM, Krapcho M, et al (????). SEER Cancer statistics review, 1975-2009 (vintage 2009 populations), National Cancer Institute, USA.

Kilgore AR (1921). The incidence of cancer in the second breast. *J Am Med Assoc*, **77**, 454-7.

Krishnappa R, Chikaraddi SB, Deshmane V (2015). Primary synchronous bilateral breast cancer. *Indian J Cancer*, **51**, 256-8.

Lizarraga IM, Sugg SL, Weigel RJ, Scott-Conner CE (2013). Review of risk factors for the development of contralateral breast cancer. *Am J Surg*, **206**, 704-8.

Loi S, Haibe-Kains B, Desmedt C, et al (2007). Definition of clinically distinct molecular subtypes in estrogen receptorpositive breast carcinomas through genomic grade. *J Clin Oncol*, **25**, 1239-46.

Mariana L, Coradina D, Biganzoli E, et al (1997). Prognostic factors for metachronous contralateral breast cancer: a comparison of linear Cox regression model and its artificial neural network extension. *Breast Cancer Res Treat*, **44**, 167-71.

Mellemkjaer L, Steding-Jessen M, Frederiksen K, et al (2014, In press). Risk of contralateral breast cancer after tamoxifen use among Danish women. *Ann epemiol*, **24**, 843-8

Nichols HB, Berrington de Gonzalez A, et al (2011). Declining incidence of contralateral breast cancer in the United States from 1975 to 2006. *J Clin Oncol*, **29**, 1564-9.

Parkin DM, Bray F, Ferlay J, Pisani P (2005). Global cancer statistics, 2002. *CA Cancer J Clin*, **55**, 74-108.

Phillips KA, Milne RL, Rookus MA, et al (2013). Tamoxifen and risk of contralateral breast cancer for BRCA1 and BRCA2 mutation carriers. *J Clin Oncol*, **31**, 3091-9.

Rebegea L, Firescu D, Anghel R, Dumitru M (2013). Clinical and therapeutical aspects of contralateral breast cancer after treatment of breast neoplasm. *J Radiotherapy Med Oncol*, **19**, 45-8.

Reiner AS, John EM, Brooks JD, et al (2013). Risk of asynchronous contralateral breast cancer in noncarriers of BRCA1 and BRCA2 mutations with a family history of breast cancer: a report from the women's environmental cancer and radiation epidemiology study. *J Clin Oncol*, **31**, 433-9.

Rusner C, Wolf K, Bandemer-Greulich U, et al (2014). Risk of contralateral second primary breast cancer according to hormone receptor status in Germany. *Breast Cancer Res*, **16**, 4.

Shim HJ, Kim SH, Kang BJ, et al (2014). Breast cancer recurrence according to molecular subtype. *Asian Pac J Cancer Prev*, **15**, 5539-44.

Silber JH, Rosenbaum PR, Clark AS, et al (2013). Characteristics associated with differences in survival among black and white women with breast cancer. *JAMA*, **310**, 389-97.

Stewart HJ (1992). The Scottish trial of adjuvant tamoxifen in node-negative breast cancer. *J Natl Cancer Inst Monogr*, **11**, 117-20.

Storm HH, Andersson M, Boice JD, et al (1992). Adjuvant radiotherapy and risk of contralateral breast cancer. *J Natl Cancer Inst*, **84**, 1245-50.

Thompson WD (1986). Methodologic perspectives on the study of multiple primary cancers. *Yale J Biol Med*, **59**, 505-16.

Yadav BS, Sharma SC, Patel FD, et al (2008). Second primary in the contralateral breast after treatment of breast cancer. *Radiotherapy Oncol*, **86**, 171-6.

Zeichner SB, Ruiz AL , Markward NJ, Rodriguez E (2014). Improved long-term survival with contralateral prophylactic mastectomy among young women. *Asian Pac J Cancer Prev*, **15,** 1155-62.