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## Identifying factors contributing to reduced breast tumor size: A longitudinal study

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## ABSTRACT

**Aim:** This study examines the trends and outcomes of breast cancer patients who have undergone surgical procedures at the Department of Surgical Sciences, University of Insubria, Varese, Italy. It also identifies the factors that contributed to the reduction of the breast tumor size over a 13-year period at a tertiary referral center.

**Methods:** All breast cancer operations performed at the Department of Surgical Sciences, University of Insubria, Varese, Italy, from January 1992 to June 2005 were examined and data from their surgical pathology reports were also analyzed, using a prospective database. A longitudinal study was performed to compare and analyze the pathological data during three consecutive time periods. The periods were from 1992 to 1996, 1997 to 1999, and 2000 to 2005. Surgical and pathological outcomes included age of the patient at the time of the diagnosis, partial breast resections, mastectomies, axillary lymphadenectomies, tumor size, histological type and stage, and lymph node status.

**Results:** The study group was comprised of 3050 patients who underwent breast resection between 1992 and 2005. Quadrantectomy was the preferred surgical approach in 1759 patients (58%). Throughout the longitudinal study, the tumors measuring less than 1 cm increased from 13.4% to 15.4%; the number of tumors diagnosed at stage I increased from 44.1% to 56.8%; the most frequent histological type was ductal carcinoma; the number of ductal carcinomas *in situ* (DCIS) increased from 4% to 6%; and the incidence of lymphadenectomies decreased from 71.6% to 52.5%. Perioperative factors that correlated with the decreased size of the tumor over time were: screening, improvement of diagnostic and therapeutic techniques, and the increased operative use of sentinel lymph node biopsy (SLNB).

**Conclusions:** There has been an evolving refinement in surgical technique and perioperative management of breast cancer patients undergoing surgical resection at the Department of Surgical Sciences, University of Insubria, Varese, Italy, during the past decades. The present longitudinal study on 3050 surgical breast cancer patients confirmed the progressive reduction of tumor size at the time of the diagnosis. Perioperative factors that correlated with the decreased tumor size over time were mammography screening, improvement of diagnostic and therapeutic techniques, and the use of SLNB. Furthermore, the study showed that the progressive reduced number of useless axillary lymphadenectomies was mainly due to the increased intraoperative use of axillary SLNB.

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## 1. Introduction

Breast cancer is the third most frequent cancer in the world and the most common malignancy in women. It is the fifth cause of death from cancer overall (following lung, stomach, colorectal and liver cancers) and is the leading cause of cancer mortality in women. It

represents about 14% of all cancer deaths among women, with the overall incidence rate increasing by 0.5%.<sup>1</sup> Approximately 1.35 million new cases worldwide are estimated for the year 2010.<sup>2–4</sup>

In Italy breast cancer is also the most frequent malignancy affecting the female population. It is estimated that about 35,000 new cases of breast cancers are diagnosed every year constituting about 14% of female cancers. These breast cancer diagnoses have a mortality rate of 12,000 women a year.<sup>5–7</sup> In the Province of Varese, about 700 women develop breast cancer each year,<sup>8</sup> with the probability for a woman to develop breast cancer being 1/10 (10%) in her life time.

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For several decades, many patients with breast cancer were diagnosed when the disease was in an advanced stage and already possessing symptoms and signs related to the tumor. Often these patients had clinical evidence of systemic neoplastic disease with poor prognosis.<sup>9–11</sup> Analyzing different series of patients affected by breast cancer reported in the literature<sup>12–14</sup> it appears that in recent years there has been a worldwide increase in the number of patients with stage I disease, which suggests an increase in the early detection of breast cancer cases. This is mainly due to the improvement in the diagnostic techniques, mainly from breast ultrasound and the development of new technologies for the diagnosis of non -palpable breast lesions, such as the routine two-view X-ray of each breast. Additionally, the extensive mammography screening programs for breast cancer have improved the diagnosis of the disease. Screenings are currently used to evaluate asymptomatic, healthy women via a routine two-view X-ray of each breast in the effort to detect unsuspected breast cancer. To date, detection of asymptomatic tumors is the best way to reduce mortality from breast cancer. Due to the screening programs, there was a global mortality reduction of approximately 30– 40%.<sup>15,16</sup> As a consequence of early diagnosis, the 5-year disease-free survival rate significantly improved, reaching about 90% in those patients with small tumors without lymph node involvement.<sup>17</sup> The increased detection of early breast lesions led as a consequence to a significant reduction of demolitive surgical procedures as well as to a positive impact on the rate of complications and the quality of life of the patient. As a result of the widespread use of breast conserving surgery<sup>18,19</sup> during the past few years, the trend towards conservatism has increased and has quickly changed the standard of surgical treatment.

In recent years, trained and experienced centers have reported a significant reduction of breast tumor size at the time of diagnosis.<sup>20</sup> As largely shown, tumor size has a positive correlation with the odds of nodal involvement. Consequently a smaller sized tumor at diagnosis correlates to a lower stage of breast disease.

The decrease in tumor size and the lower stage determination at diagnosis have been mainly attributed to increased mammography screening and to greater awareness of the disease as well as the importance of breast examination. As previously shown by other authors, the exact assessment of breast tumor size depends on more than just the tumor size itself, but also on method and histopathology.<sup>21</sup> Authors agree that the only precise method to evaluate the exact size of a tumor is by pathology assessment.

On the basis of these considerations a longitudinal study of 3050 patients who have undergone breast surgery for cancer between 1992 and 2005, at the Department of Surgical Sciences of the University of Insubria, was carried out in order to verify and quantify the reduction of tumor growth at diagnosis. This evaluation showed an increasing trend towards conservative surgery for breast cancer and evaluated the decreased percentage of unnecessary complete axillary lymphadenectomies secondary to the introduction of intraoperative sentinel lymph node biopsy.

This study was conducted in cooperation with the Pathology Department of the University, which provided the pathologic characteristics of each breast cancer case.

## 2. Patients and methods

The medical records and the pathology reports of 3050 patients, who had undergone resection for breast cancer between 1992 and 2005, were accurately reviewed and the data registered on a database. The review and registration process was carried out by a group of physicians from the Department of Surgical Sciences together with the Pathology Department of the same University to ensure the validity and accuracy of the data

collection, and under the supervision of the principal investigators.

Patients that did not receive surgical therapy for documented metastatic disease and/or for prohibitive medical–surgical risks were excluded.

For each patient enrolled in this observational study, the following data were registered: gender, age at diagnosis, type of surgical resection, sentinel lymph node biopsy (with the total number of lymph nodes for each axillary level), histological type, tumor size and pathological staging. These data were registered in a computerized database which allowed the use of statistical analysis, including Student’s *t*-test and chi-square test. Statistical significance was accepted when the *p* value was <0.05.

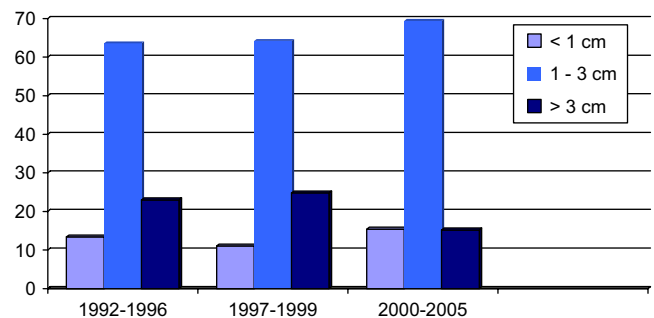
Patient outcome was analyzed over three consecutive time periods: 1992– 1996, 1997– 1999, and 2000– 2005.

## 3. Results

Among the 3050 patients enrolled, 806 underwent surgical procedures during the period of 1992–1996, 873 during the period of 1997–1999 and 1371 during the period of 2000–2005.

The analysis of tumor size was performed on the pathology specimen and this demonstrated a progressive decrease of the tumor diameter from 1992 to 2005. Breast cancers greater than 3 cm during the time periods 1992– 1996, 1997– 1999, and 2000–2005 were 23%, 24.8% and 15.2% respectively. The percentage diameters of breast cancers lower than 1 cm were 13.4%, 11% and 15.4% respectively (*p* < 0.001).

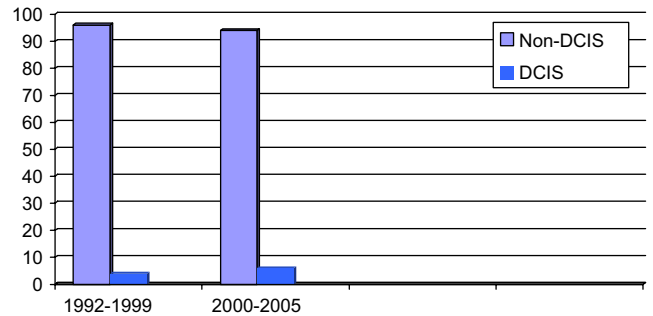
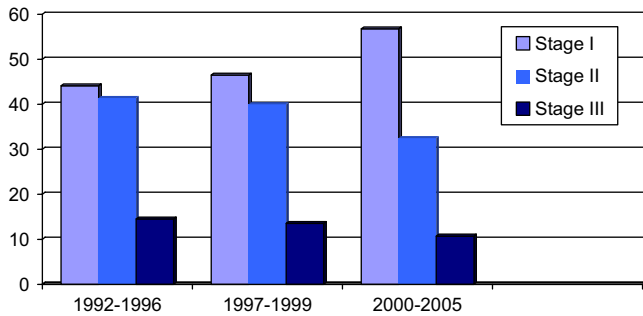
	1992–1996	1997–1999	2000–2005
>3 cm	184 (23%)	217 (24.8%)	209 (15.2%)
1–3 cm	514 (63.6%)	559 (64.2%)	951 (69.4%)
<1 cm	108 (13.4%)	97 (11%)	211 (15.4%)



The analysis of the age of the patients at diagnosis was performed and this demonstrated that the mean age was similar in the three time periods: 59 years old during the period of 1992–1996, 61 years old during the period of 1997–1999 and 62 years old during the 2000–2005 period.

The analysis of tumor stage at the time of the diagnosis demonstrated a progressive decrease of tumor stage from III to I for the period of 1992–2005. Breast cancers in stage III for the time periods of 1992– 1996, 1997– 1999, and 2000– 2005 were 14.5%, 13.5% and 10.7% respectively. Breast cancers in stage I for the time periods of 1992– 1996, 1997– 1999, and 2000– 2005 were 44.1%, 46.5% and 56.8% respectively (*p* < 0.001).

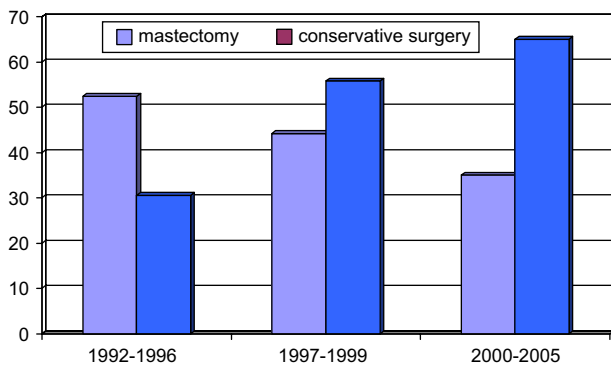
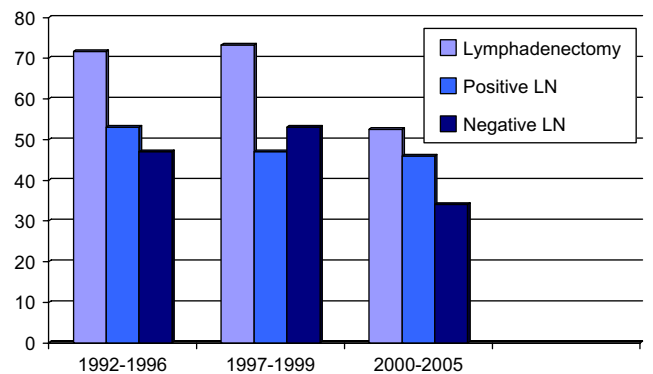
	1992–1996	1997–1999	2000–2005
Stage III	116 (14.5%)	118 (13.5%)	146 (10.7%)
Stage II	334 (41.4%)	348 (40%)	446 (32.5%)
Stage I	356 (44.1%)	407 (46.5%)	779 (56.8%)



The analysis of the type of surgical treatment performed on the patients showed a progressive decrease of mastectomies during the 1992–2005 period. Mastectomies for the time periods 1992– 1996, 1997– 1999, and 2000– 2005 were 52.4%, 44.2% and 35% respectively. Conservative surgery for the time periods 1992– 1996, 1997– 1999, and 2000– 2005 were 47.6%, 55.8% and 65% respectively ( $p < 0.001$ ). These data confirm the tendency towards conservative

	1992–1996	1997–1999	2000–2005
Mastectomy	423 (52.4%)	386 (44.2%)	482 (35%)
Conservative surgery	383 (47.6%)	487 (55.8%)	889 (65%)

	1992–1996	1997–1999	2000–2005
Lymphadenectomy	577 (71.6%)	640 (73.3%)	720 (52.5%)
Positive lymph node(s)	306 (53%)	297 (47%)	474 (46%)
Negative lymph node(s)	271 (47%)	343 (53%)	246 (34%)



surgery of breast cancer, since it has been demonstrated that breast cancer is a systemic disease and it must also be treated with radiotherapy and chemotherapy, when clinically appropriate.

	1992–1999	2000–2005
DCIS	39 (4%)	82 (6%)
Non-DCIS	1154 (96%)	1289 (94%)

The present study confirmed that the most frequent histological type diagnosed was invasive ductal carcinoma (IDC). From 1992 to 2005 the number of ductal carcinoma *in situ* (DCIS) increased from 4% during the 1992–1999 period to 6% in the 2000–2005 period. In particular, this was due to the introduction of mammography screening that gave the possibility to evaluate non palpable breast lesions, which presented by imaging as microcalcifications and/or parenchymal distortions.

The analysis of the type of the performed lymphadenectomies demonstrated a progressive decrease of total axillary lymphadenectomies from 1992 to 2005. Total axillary lymphadenectomies for the time periods 1992– 1996, 1997– 1999, and 2000– 2005 were 71.6%, 73.3% and 52.5% respectively. This was due to the introduction of the axillary sentinel lymph node biopsy technique.

#### 4. Conclusions

This longitudinal study on 3050 surgical breast cancer cases confirmed the progressive reduction of tumor size at the time of the diagnosis during the last decades. Perioperative factors that correlated with the decreased tumor size over time were mammography screening and the improvement of diagnostic and therapeutic techniques. In addition, the study showed that the progressive reduced number of useless axillary lymphadenectomies was mainly due to the increased intraoperative use of axillary sentinel lymph node biopsies.

#### Conflict of interest

None declared.

#### Funding

Nil.

#### Ethical approval

Not required.

#### References

1. Parkin DM. Global cancer statistics in the year 2000. *Lancet Oncol* 2001; **2**:533–43.
2. Parkin DM, Bray F, Ferlay J, Pisani P. Global cancer statistics, 2002. *CA Cancer J Clin* 2005; **55**:74–108.
3. Jemal A, Clegg LX, Ward E, Ries LA, Wu X, Jamison PM, et al. Annual report to the nation on the status of cancer, 1975–2001, with a special feature regarding survival. *Cancer* 2004; **101**:3–27.
4. Schwartzmann G. Breast cancer in South America: challenges to improve early detection and medical management of a public health problem. *J Clin Oncol* 2001; **19**:118–24.

5. Domenech A, Benitez A, Bajen MT, Pla MJ, Gil M, Martin-Comin J. Patients with breast cancer and negative sentinel lymph node biopsy without additional axillary lymph node dissection: a follow-up study of up to 5 years. *Oncology* 2007;**72**(1-2):27–32.
6. Atahan IL, Yildiz F, Ozyigit G, Gurkaynak M, Selek U, Sari S, et al. Percent positive axillary involvement predicts for the development of brain metastasis in high-risk patients with nonmetastatic breast cancer receiving post-mastectomy radiotherapy. *Breast J* 2008;**14**(3):245–9.
7. Ma AM, Bowling M, Leitch M, Rao R, Euhus DM. Primary breast tumor characteristics predicting aggressive nodal involvement. *Am J Surg* 2007;**194**(4):474–6.
8. Grande E, Inghelmann R, Francisci S, Verdecchia A, Micheli A, Baili P, et al. Regional estimates of breast cancer burden in Italy. *Tumori* 2007;**93**(4):379–9.
9. Swedish Organized Service Screening Evaluation Group. Effect of mammographic service screening on stage at presentation of breast cancers in Sweden. *Cancer* 2007;**109**(11):2205–12.
10. Garamy Z, Benkò K, Kosa C, Fulop B, Lukacs G. The effect of mammographic screening on tumor size, axillary node status and the degree of histologic anaplasia. *Magy Seb* 2006;**59**(5):383–7.
11. Ponti A, Mano MP, Distanti V, Baiocchi D, Bordon R, Federici A, et al. Audit system on quality of breast cancer diagnosis and treatment (QT): results from the survey on screen-detected lesions in Italy, 2004. *Epidemiol Prev* 2007;**31**(2-3 Suppl. 2):69–75.
12. Waller M, Moss S, Watson J, Moller H. The effect of mammographic screening and hormone replacement therapy use on breast cancer incidence in England and Wales. *Cancer Epidemiol Biomarkers Prev* 2007;**16**(11):2257–61.
13. Bortorff JL, Ratner PA, Johnson JL, Hislop TG, Buxton JA, Zeisser C, et al. Women's responses to information on mammographic breast density. *Can J Nurs Res* 2007;**39**(1):38–57.
14. Feig SA. Screening mammography: a successful public health initiative. *Rev Panam Salud Publica* 2006;**20**(2-3):125–33.
15. De Angelis R, Grande E, Inghelmann R, Francisci S, Micheli A, Baili P, et al. Cancer prevalence estimates in Italy from 1970 to 2010. *Tumori* 2007;**93**(4):392–7.
16. Verdecchia A, De Angelis R, Francisci S, Grande E. Methodology of estimation of cancer incidence, survival and prevalence in Italian regions. *Tumori* 2007;**93**(4):337–44.
17. Mladenovic J, Borojevic N, Cikaric S, Jelic LJ. Radiotherapy of locally advanced breast carcinoma in elderly female patients. *Srp Arh Celok Lek* 2000;**128**(9-10):322–7.
18. Veronesi U, Cascinelli N, Mariani L. Twenty-year follow-up of a randomized study comparing breast-conserving surgery with radical mastectomy for early breast cancer. *N Engl J Med* 2002;**347**:1227–32.
19. Fisher B, Anderson S, Bryant J. Twenty-year following of a randomized trial comparing total mastectomy, lumpectomy and lumpectomy plus irradiation for the treatment of invasive breast cancer. *N Engl J Med* 2002;**347**:1233–41.
20. Morris EA. Diagnostic breast MR imaging: current status and future directions. *Radiol Clin North Am* 2007;**45**(5):863–80.
21. Heusinger K, Lohberg C, Lux MP, Papadopoulos T, Imhoff K, Schulz-Wendtland R, et al. Assessment of breast cancer tumor size depends on method, histopathology and tumor size itself. *Breast Cancer Res Treat* 2005;**94**(1):17–23.