129 women who underwent WLE required one or more further therapeutic operation. For women with BDP < 400 mm there was no significant difference in the number requiring more than one operation between women with <1000ml and ⩾1000ml breasts (29% and 28% respectively). Of those with BDP ⩾ 400 mm, 68% of women with breast volume <1000ml required one or more further operations compared to 40% of those with breast volume ⩾1000ml. This difference just fails to reach statistical significance (p = 0.06).

**Conclusion:** The combination of breast volume assessment and bi-dimensional measurement of DCIS on mammography is a useful predictor of successful therapeutic surgery.

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**The triple negative profile dilemma and its clinical outcome in early breast cancer**

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**Background:** Gene expression studies have consistently identified several breast cancer subtypes including the basal-like (BBC). The BBC subtype is associated with a poor prognosis and in the majority of cases also with negativity of ER, PgR and HER-2 receptors. Therefore, the so-called triple negative breast cancer phenotype is frequently used as a surrogate for the BBC subtype.

**Patients and Methods:** We performed a retrospective analysis of 323 patients with primary early breast cancer treated at the Jules Bordet Institute during the year of 2001 for whom follow up data was available. Data from histological features, immunohistochemical (IHC) findings for HER-2, estrogen (ER), and progesterone (PgR) receptors, and clinical outcome were collected. The clinical outcome of the patients with triple negative breast cancer was compared to the rest of the population.

**Results:** From the 323 patients selected (median age 57 years (range 28–96 years), 66.2% postmenopausal and 59.1% node negative)), 23 patients (7.1%) were classified as triple negative breast cancer after central pathology review. With a median follow up period of 43 months, the triple negative subgroup had a significantly worse disease free interval (DFI) (HR = 3.01; CI 95% 1.44–6.53, p = 0.01). Using a backward selection of variables in multivariate analysis for DFI, triple negative status remains a significant variable (HR = 3.82; CI 95% 1.72–8.48, p = 0.001) together with node positive (HR = 3.02; CI 95% 1.57–5.81, p = 0.001) and adjuvant chemotherapy (HR = 3.05; CI 95% 1.32–7.02, p = 0.01).

**Conclusions:** Triple negative status is associated with a poor outcome in early BC. Tailored therapeutic approaches associating chemotherapy and biological agents are warranted for this particular subgroup of patients.

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**Reproducibility and validity of the Claus-Extended Formula in a British cohort of women with a family history of breast cancer**

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**Background.** Risk estimation in breast cancer families in clinical practice is often performed using the Claus Tables. Previously, we constructed a new risk estimation method especially for clinical practice: the Claus-Extended Formula [1]. This formula uses the Claus Tables (CT) and information on the presence of bilateral breast cancer (BBC), ovarian cancer (OC), and multiple (more than 2) breast cancer cases (MC) in the family and is formulated as follows: 0.08 + 0.40*CT + 0.07*OC + 0.08*BBC + 0.07*MC. It was constructed using a Dutch cohort of breast cancer families. Correlations and agreements between the Claus-Extended Formula and the Claus Model, the Claus Tables, and the Jonker Model were satisfying.

**Aim.** The aim of this study was to validate the Claus-Extended Formula using a British cohort of families with breast and/or ovarian cancer.

**Methods.** We analysed family histories of 2156 counselees selected from a British Family History Clinic. We estimated lifetime risks of breast cancer using the Claus Model, the Jonker Model, the Claus Tables and the Claus-Extended Formula and considered correlations and agreements between these methods to evaluate the reproducibility of the Claus-Extended Formula. Furthermore, we calibrated the Formula in order to evaluate whether the Formula estimates the risks accurately in this other cohort.

**Results.** The British counselees had on average 1.7 breast cancer cases per family (SD 0.8; range 0–6). Spearman correlations between the Claus-Extended Formula and the Jonker Model, the Claus Model and the Claus Tables were 0.768, 0.679, and 0.770, respectively. Agreements were 73%, 33%, and 63%, respectively. The calibration of the formula showed that no clinical relevant differences could be found between the lifetime risks estimated by the Claus-Extended Formula and by the Jonker model.

**Conclusion.** We found that the Claus-Extended Formula provides accurate lifetime risks of breast cancer, based on estimates by the Claus model and Jonker model. The Formula is easy applicable in clinical practice. Therefore, we conclude that the Claus-Extended Formula is a valid risk estimation method for clinical practice, both inside and outside the Netherlands.

**References**

[1] Van Asperen et al. Cancer Epidemiol Biomark Prev 2004; 13(1): 87–93.

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**Recursive partitioning analysis in breast cancer patients treated by adjuvant whole breast radiotherapy followed by external beam boost or brachytherapy boost: prognostic groups in 1485 patients**

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**Aim:** To find prognostic parameters for local failure (LF), disease free survival (DFS) and distant metastasis-free survival (MFS) derived from recursive partitioning analyses (RPA).

**Patients and Method:** From 1485 patients referred between 1984 and 1997 with pathologic T1–2 N0–1 breast cancer, data were analyzed. After tumorectomy, patients underwent whole breast radiotherapy and a boost either by external beams or by interstitial high dose-rate brachytherapy. Age, T-stage, grading, the number of positive axillary nodes, the ratio between the number of positive axillary nodes and the number of excised axillary nodes (n-ratio), tumor location (med/lat), the estrogen- and progesteron-receptor status (ER, PR), menopausal status, systemic therapy and the presence of surgical marker clips were included in the analyses. Cut points defining prognostic groups were estimated. For each prognostic group the relative hazard ratio (RHR) was estimated.

**Results:** 1238 out of 1486 patients could be used for RPA. For *LF* there were three prognostic groups. Age was the most important prognostic parameter followed by ER status and n-ratio. For *DFS*, n-ratio was the most significant factor with a cut point at 21%, followed by age. For *MFS* 4 risk groups were defined, where again the n-ratio was the most significant prognostic parameter followed by T-stage.

**Conclusions:** The most important factors in defining risk groups were age and node ratio (n-ratio). Whenever the n-ratio was included in the fit the number of positive nodes was not significant. For LF age was most important (with ER, n-ratio, and location also relevant), while for DFS n-ratio was most important (with age, PR/ER, and stage also relevant). For MFS n-ratio was most important (with stage, ER, and location also relevant, but not age). It is striking that high risk for DFS and MFS is defined by node ratio ⩾ 0.21, which corresponds to ⩾ 4 positive nodes in a full level I-II dissection, while the usual measure of risk, number of positive nodes, was insignificant whenever the node ratio was included in the fit.

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**Outcome of invasive lobular carcinoma: the experience of the European Institute of Oncology**

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Invasive lobular carcinoma of the breast (ILC) is the second most common breast cancer after the invasive ductal carcinoma (IDC), and comprises approximately 10% of all breast cancers cases, ranging from 5 to 15%. Its incidence, as well as the lobular carcinoma in situ (LCIS), is increasing, predominantly in postmenopausal women. The objective of this study was to review all cases of ILC treated at the European Institute of Oncology (EIO) and compare the outcomes with those described on the medical literature. Between January 1996 until December 2003, 810 patients diagnosed with ILC were treated at the EIO. Conservative treatment was

performed among 69% of patients, 31% received mastectomy. Sentinel node biopsy was performed in most of cases when the axilla was clinically negative. Most of patients were post-menopausal (60%), and 99% of the tumours were hormone-responsive. The incidence of contralateral carcinoma was 1.2%, and the local recurrence rate was 5.1%.

In conclusion, ILC has a high prevalence in women in post menopause, and its biological characteristics trends to be less aggressive, although the difficulty of an early stage diagnosis exists. Conservative treatment showed to be feasible in those selected cases, and the local recurrence is not higher if compared to IDC. Sentinel node biopsy showed to be a very useful and faithful method, and should be encouraged.

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**Modified histones in breast cancer and their prognostic significance**

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Post-translational modifications of histones are fundamental to the regulation of chromatin structure and gene activity in normal tissues. In malignant cells, aberrant acetylation and methylation of bulk histones has been reported, and similar changes have been observed at specific promoters. Alterations in histone modification have recently been shown to be predictive of clinical outcome in prostate cancer. However, the expression and prognostic significance of modified histones in breast cancer has not been previously explored. We have therefore analysed the levels of acetylated lysine 18 in histone H3 (AcH3K18) and dimethylated arginine 3 in histone H4 (diMeH4R3) by immunohistochemistry, using a large, well-characterised series of unselected breast tumours (n = 800) prepared as tissue microarrays. Immunohistochemical scoring was performed in duplicate and assessed as the percentage of positive cells. Results were correlated with clinicopathological variables and patient outcome.

**Results**: Absence of detection (0%) of AcH3K18 and diMeH4R3 was detected in 19.7% and 50.4% of the total cases, respectively. The detection of these histone modifications was associated with lobular and tubular carcinomas, whereas they were absent or had reduced expression (below the median) in medullary-like carcinomas. The absence of AcH3K18 and diMeH4R3 correlated with poor prognostic variables in breast cancer including; larger tumour size, higher grade, positive lymph node disease, development of recurrences and distant metastases and higher mortality rate. We also found a significant correlation of negative expression of AcH3K18 and diMeH4R3 in tumours that were negative for expression of hormone receptors, BRCA1, E-cadherin and FHIT protein, reduced luminal cytokeratins (CKs), and positive for expression of p53 and basal CKs. However, no association was found with patients' age, vascular invasion, expression of P-cadherin or members of the epidermal growth factor receptors family. Survival analyses showed that AcH3K18 and diMeH4R3 under-expression was associated with both shorter overall survival and shorter disease free interval.

**Conclusion**: Our results showed, for the first time that changes in specific modified histones may play an important role in breast cancer development and progression and their reduced expression is associated with poor prognosis and shorter survival.

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**Young and old age are poor prognostic factors in women with advanced breast cancer**

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**Background and objectives:** Earlier population studies in early stage breast cancer have shown a biphasic effect of age on outcome, in which young and old age were associated with poor survival, while middle age was associated with better survival. The aim of this study was to investigate whether age has also a biphasic effect on prognosis in advanced breast cancer.

**Material and Methods**: Women who were diagnosed between 1988 and 1997 with histologically confirmed stage III or IV breast cancer (AJCC 3rd edition) were selected from the US Surveillance, Epidemiology, and End Results 9-registries database release 2004. Kaplan-Meier survival estimates were computed as a function of overlapping age intervals from 25 to 90 years. Odds of breast cancer death were computed relative to risk of death from other causes. Cox modeling by age-intervals were used to examine the effect of age in multivariate analyses that took into account stage, tumor location, histology, grade, hormone receptor, marrital status, race, registry, year of diagnosis. Outcome was overall survival (OS) and breast cancer specific survival (BCSS).

**Results:** Out of 132,176 breast cancer in 1988–97, we identified 13,822 with advanced stage, respectively 8731 stage III and 5091 stage IV. The poorest OS (Figure 1, dashed curve) was observed in younger (<40–45 years) and in older patients (>55–60 years), the best OS in middle age patients (45–55 years). BCSS revealed a similar pattern with the best survival in middle age patients (Figure 1: plain curve). The risk of dying from breast cancer outweighed all other causes of death at all ages (odds >1 throughout the whole age range, Figure 2) and was the highest in young patients (odds 6–18 in patients <45 years, Figure 2). Multivariate analysis by OS outcome showed a hazard ratio (HR) for age adjusted by other covariates of 1.02, i.e. 2% relative increased risk of death *per each year **younger** than 45* (P = 0.004). By BCSS outcome, the HR was also 1.02 (P = 0.001). In patients older than 60 years, by OS outcome the HR was 1.03 (P < 0.0001), by BCSS outcome the HR was 1.01 (P = 0.0001), i.e. 1% relative increased risk *per each year **older** than 60*.

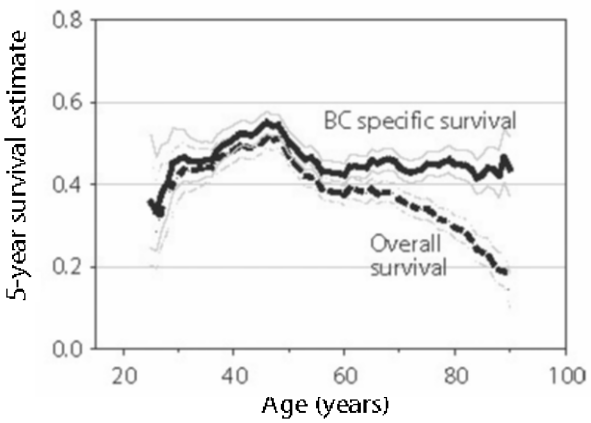


Figure 1.

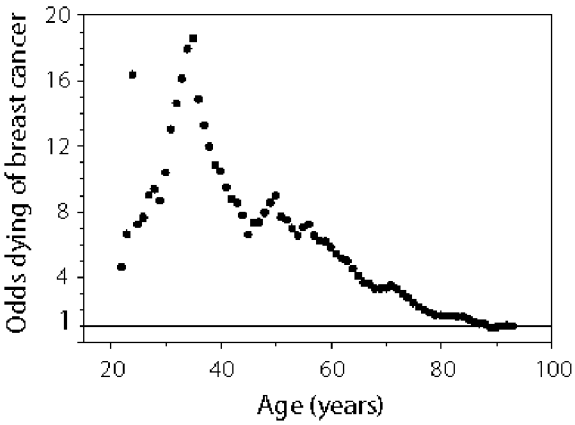


Figure 2.

**Conclusion:** Age presents also a biphasic effect on the prognosis of patients with advanced breast cancer. Breast cancer represents a severe disease burden in young women diagnosed with advanced stage breast cancer. With older age, even though the odds decrease, the absolute risk of dying from breast cancer do not decrease and still outweighs all other causes even in 90 years old patients.