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Young age is a poor prognostic factor in women with stage I breast cancer

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Background: Breast cancer is rare in young women, only 2%–5% are diagnosed at age 35–40 or less. However, in these young patients, breast cancer is associated with poor prognosis. It has been extensively discussed that young age is not an independent prognostic factor, but correlates with more advanced disease stage at presentation and therefore with worse prognosis.

Objective: The aim of this study is to investigate how age relates with survival outcome in a restricted group of patients presenting with early stage disease, in order to avoid confounding by advanced stages.

Material and Methods: Women who were diagnosed between 1988 and 1997 with histologically confirmed unilateral stage I breast cancer (pT1N0M0) and who underwent lumpectomy or mastectomy with axillary dissection (1–50 nodes examined) 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 20 to 95 years. Odds of breast cancer death were computed relative to risk of death from other causes. Multivariate analysis of overall survival (OS) and breast cancer specific survival (BCSS) in patients <45 years included tumor size, location, number of examined lymph nodes, histology, grade, hormone receptor status, marrital status, race, registry area, year of diagnosis, type of surgery, and radiotherapy as covariates.

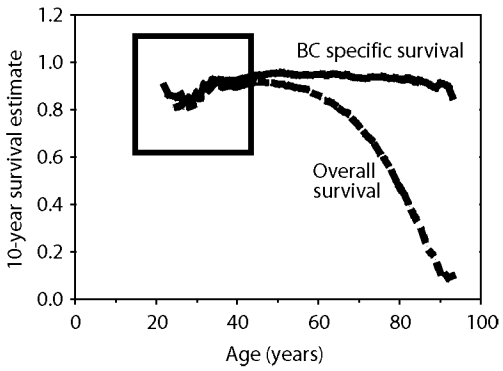

Figure 1.

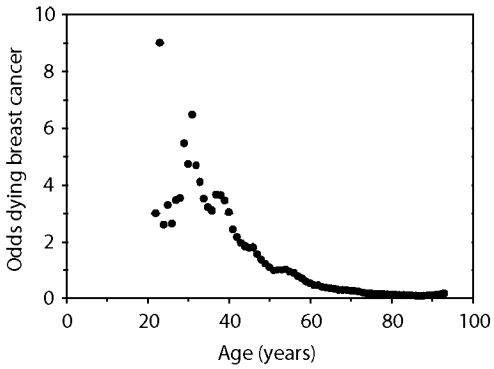

Figure 2.

Results: There were 47,590 records available. The OS (Figure 1: dashed curve) showed a biphasic shape, with decreased 10-year OS from 90% to 80% in very young patients (<35 years) and in older patients (>60 years). As an example, the 10-year OS probability of a 30-year old patient (85%) is equal to that of a 60-year old patient, indicating a considerably reduced life expectancy in these young patients. In line, the BCSS (Figure 1: solid curve) closely parallels the OS in patients <45 years, showing that the reduced life expectancy in young patients was almost entirely attributable to breast cancer. Considering the odds of death, the risk of dying from breast cancer outweighed the risk of dying from any other cause in young patients (odds 2–9 in patients <45 years, Figure 2). Multivariate analysis by OS outcome showed a hazard ratio (HR, adjusted by other covariates) for age of 1.03, i.e. 3% relative increased risk of death *per each year* younger than 45 (P = 0.006). By BCSS outcome, the HR was 1.05, i.e. 5% relative increased risk of BC death *per each year* younger than 45 (P = 0.0001).

Discussion: Breast cancer represents a severe disease burden in young women diagnosed with early stage breast cancer. Conventional prognostic factors are insufficient to account for the poor prognosis associated with young age. We argue that molecular signatures are required to investigate the biological mechanisms underlying breast carcinomas occurring in different age groups.

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The psychosocial issues related to gestational breast cancer

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Introduction/Background: Very little has been reported about the psychosocial issues for women diagnosed with gestational breast cancer (GBC). During our recent review of GBC cases in Western Australia it became apparent that these women had some psychosocial issues that were unique to them. The aim of the study was to describe the psychosocial issues that affect young women diagnosed with GBC.

Methods: Qualitative data was collected using semi-structured face-to-face interviews. To access women living in rural areas telephone interviews were undertaken. Three groups of 15 women all aged <45 years when diagnosed with breast cancer were randomly selected from the WA Cancer Registry. One group were women diagnosed with GBC; groups two and three were women who did or didn't become pregnant after their diagnosis of breast cancer. An additional group of 15 new mothers was identified from the WA Midwives Notification System.

Informed consent was obtained prior to the interview. The interviews were audiotape recorded and transcribed verbatim. During the interviews, the researcher sought to identify any psychological and social issues related to the experiences of women diagnosed with breast cancer and/or during pregnancy. Areas of interest included: psychological well being, adaptation to mothering, physical and mental coping mechanisms used; formal and informal support structures; breast cancer treatment and outcome issues; fertility and contraception issues; pregnancy events; dealing with illness and a young child. The transcribed interviews were transferred to QSR NVIVO. Data was analysed by three researchers using thematic analysis consistent with this explorative qualitative research design.

Results: Each woman has different information needs. Contraceptive advice was important. Unbiased advice on fertility issues was needed. Close relationships remained intact in the short term, but a number of relationships collapsed following disease recurrence. These women were determined to stay alive and with their children. There, however, appeared to be a lack of formal support to help these women stay at home with their children.

Conclusion: Young women diagnosed with breast cancer want an unbiased view of their management and fertility options. This is so they can choose the option that suits their priorities at that point in time

Thursday, 23 March 2006 16:00–16:45

POSTER SESSION

Pathology

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Immunophenotype similarity and high frequency of co-existence of columnar cell lesions, lobular neoplasia, and low grade DCIS with invasive tubular carcinoma and invasive lobular carcinoma

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Aim: To determine the immunophenotype and the frequency of association between putative precursor lesions involved in the development of some types of breast carcinoma.

Method: 127 successive low grade breast tumor cases were reviewed by 3 pathologists for the presence of invasive and pre-invasive lesions including pure tubular carcinoma (TC, G1; n = 54), tubular carcinoma mixed type (n = 10), invasive lobular (ILC) classic type (n = 56), tubulolobular carcinoma (n = 7), columnar cell lesions (CCL), usual epithelial hyperplasia (UEH), ductal carcinoma in situ (DCIS), and lobular neoplasia (LN).

Tissue microarrays (TMAs) were prepared from 1000 lesions and immunophenotyped for the expression of luminal (CK7/8,Ck18,CK19) and basal markers (CK5/6,CK14,Vimentin,SMA), ER-α and -β, Her2-neu, MIB-1, Cyclin D1, P53, Bcl-2, E-Cadherin and FHIT.

Results: *TC-pure*: 96% association with CCLs, the majority showing columnar cell hyperplasia with atypia. DCIS was present in 91% cases. Co-localization of CCL, DCIS and TC occurred in 83% patients, all displaying the same cytoplasm-nuclear morphology. LN was seen in 15%.

TC-mixed: Co-existence of CCL, DCIS and TC was seen in 80%. LN occurred in 60% patients.

ILC: 91% cases showed LN. CCL and DCIS were seen in 52% and 41% cases, respectively.

Immunohistochemistry: All TC, ILC and luminal cells of TDLUs, DCIS and LN expressed luminal markers with absence of basal markers. The majority of TC, ILC, TDLUs, CCLs, DCIS and LN were positive for estrogen receptor. TDLUs, CCLs, DCIS, LN, TC and ILC were negative for P53; however P53 was detected in DCIS and invasive tumour. HER-2 was over-expressed only in CCLs, LN and DCIS. TDLUs, CCLs, and low grade DCIS were positive for E-cadherin. In contrast, E-cadherin staining was reduced in TC but absent in LN and ILC. MIB-1 was expressed in >10% of cells comprising DCIS and invasive tumours. Bcl-2 and FHIT were positive in TDLUs, CCLs, DCIS and LN, but were reduced in TC and ILC. The proportion of Cyclin $D1^+$ cells increased progressively from CCLs to DCIS to invasive lesions.

Conclusion: Our findings support the hypothesis that CCLs are associated with pure and mixed forms of tubular carcinoma, and that LN is involved in ILC development. Immunoprofiling suggests that TC, ILC, low grade DCIS, LN, and CCLs belong to a family of luminal low grade breast tumours. Invasive lesions could be distinguished from precursor lesions by decreased Bcl-2 and FHIT staining and their increased expression of Cyclin D1.

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Distinguishing blood and lymph vessel invasion in breast cancer: a prospective study in 95 patients

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Introduction: Blood (BVI) and lymph vessel invasion (LVI) are the histological correlates of the first steps of haematogenous and lymphatic metastasis in solid tumors. New lymphatic endothelium specific markers such as D2−40, make it possible to distinguish blood and lymph vessels. Therefore, the aim of this prospective study was to quantify and compare BVI and LVI in a consecutive series of breast cancer patients.

Materials and Methods: Three consecutive 5 µm sections of all FFPE tissue blocks of 95 consecutive breast cancer resection specimens were (immuno)histochemically stained in a fixed order: HE, anti-CD34 (pan-endothelium) and anti-D2−40 (lymphatic endothelium) antibodies. On every slide, all vessels with vascular invasion were marked and relocated on the corresponding slides. Based on the IHC staining pattern, vascular invasion was assessed as being LVI (CD34?or?/D2−40?) or BVI (CD34+/D2−40?).

LVI and BVI were assessed as intra- (in contact with tumor cells or desmoplastic stroma) or peritumoral. The number of intra- and peritumoral vessels with LVI and BVI per patient was counted as well as the number of tumor cells in every vessel. Results were correlated with clinico-pathological variables, the growth pattern and the presence of a fibrotic focus.

Results: In total 3297 (661 intra, 2636 peri) vessels with LVI and 135 (80 intra, 63 peri) vessels with BVI were seen. The median number of FFPE blocks per patient was 4. 66 (69.5%) patients had LVI (8 intratumoral, 35 peritumoral, 23 intra- and peritumoral) compared to 36 (37.9%) patients with BVI (12 intra-, 8 peri- and 16 intra- and peritumoral). Although LVI and BVI were associated intratumorally ($p = 0.02$), only LVI, not BVI correlated with the presence of LN metastases (p intra = 0.07, p peri = 0.002). Both BVI and LVI were associated with the presence of a fibrotic focus and with an expansive growth pattern. Furthermore, LVI was more extensive ($p = 0.001$) then BVI, and lymphatic emboli were bigger then blood vessel emboli ($p = 0.004$).

Conclusion: Our data demonstrate that it is possible to reliably distinguish BVI and LVI in breast cancer resection specimens using recently characterized specific lymphatic endothelium markers. This is important to study the contribution of both processes to the metastatic process in breast cancer. Furthermore, our data sustain the hypothesis that haematogenous and lymphatic metastasis are specific and biologically different pathways.

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Comparative study of histo-pathological characteristics of breast cancer in women who underwent in vitro fertilization and age matched controls

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Introduction: There has been concern that elevated levels of sex hormones during in vitro fertilization (IVF) may influence future development of breast cancer. Several studies have found an increased risk of breast cancer after IVF, at least in some sub groups. In this study we examine histopathological characteristics of breast cancer in women who underwent IVF, compared with age-matched unexposed cases.

Description: We identified 7162 women who underwent IVF at our institution between 1984 and 2002. These were linked with the National Cancer Registry, and 38 women who developed breast cancer after IVF were identified. Four age-matched unexposed cases for each case were obtained from the institutional oncology database.

Summary of Results: The average age at time of breast cancer diagnosis for women who underwent IVF was 44 years. Patients developing breast cancer after IVF were more likely to have node negative disease: 61 vs. 49%. They were also more likely to have grade 3 tumors: 65 vs. 47%. Despite of the high percentage of high grade tumors, these tumors were more likely to be ER positive (88% vs. 67%) and PgR positive (75 vs. 40%). There was no difference in tumor size distribution: 42% of cases and 43% of controls bearing tumors smaller than 2 cm, 48% and 44% with tumors 2−5 cm, and 10% and 13% larger than 5 cm. The stage distribution was similar (28% and 29% stage 1, 55% and 58% stage 2, 14% and 12% stage 3, 3% and 1% stage 4). The rate of Her2 positive tumors was equal (32 and 33%). The histological types in both groups were similar, with 11% and 7% presenting with DCIS, 79% and 81% with invasive duct carcinoma, and 11% and 9% invasive lobular carcinoma. The rate of breast conserving surgery was similar: 48% and 45%.

Conclusions: breast cancer after IVF was diagnosed at an age significantly younger than the average age for breast cancer diagnosis, perhaps suggesting a promoter effect. The tumors which develop in these patients are more likely to be of high histological grade, but are also more likely to be ER and PgR positive, and node negative. Further study is needed to determine the influence on prognosis.

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Human epidermal growth factor receptor 1 (EGFR) expression was not associated with gene amplification but intimately associated with HER2 gene amplification and protein expression in tissue microarray of clinical breast cancers

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Background: Introduction of anti-epidermal growth factor receptor 1 (EGFR) biologic therapeutics for numerous human malignant diseases mandates the appropriate understanding on the biologic properties of EGFR. We performed the current study to investigate the frequency and clinical implication of EGFR gene amplification and protein expression in breast cancer.

Methods and Results: EGFR gene amplification was assayed by fluorescence in situ hybridization (FISH) and protein expression was assayed by immunohistochemistry (IHC) on tissue microarray (TMA) of 165 non-selected invasive breast cancer. The EGFR was expressed in 34 (20.6%) of 165 studied invasive breast cancers, whereas EGFR gene was amplified in 13 (7.9%). The EGFR protein was expressed in 5 (38.5%) of 13 EGFR amplified tumors, whereas it was expressed in 29 (19.1%) of 152 EGFR non-amplified tumors. The EGFR protein expression was increased in EGFR amplified tumors but the difference was not statistically significant. EGFR protein was expressed in 33.3% of HER2 amplified tumors whereas it was expressed in only 16.3% of HER2 non-amplified tumors. EGFR expression was significantly increased in HER2 amplified breast cancer. The finding was similar when EGFR expression was analyzed according to HER2 protein expression. During the median follow-up period of 56 months