Thursday, 25 March 2010 08:30–09:15

EUROPA DONNA TEACHING LECTURE

Impact of lifestyle on breast cancer

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Impact of lifestyle on breast cancer

C. La Vecchia[1]. [1]*Istituto Mario Negri, Department of Epidemiology, Milan, Italy*

Background and Introduction: In Europe, the lifetime probability of developing breast cancer varies from about 5% for a woman with no family history and low lifetime risk profile to over 30% for a woman with young family history and high lifestyle risk profile. Strong familial and genetic factors are restricted to a minority of women, thus an appreciable proportion of breast cancers is in principle preventable through intervention on lifestyle factors.

Materials and Methods: We used available evidence on the relative risk (RR) for major recognized risk factors for breast cancer, and estimates of their prevalence in selected European countries.

Results and Summary: The best established lifestyle factors for breast cancer are overweight and obesity and use of hormone replacement therapy (HRT) in post-menopause, and alcohol consumption both in pre- and post-menopause. The RRs for overweight, obesity and HRT approach 1.5 to 2; about 40% of European women are overweight in post-menopause and 10% long term users of HRT. Thus, control of long-term (combined estrogen and progestin) HRT use, and reduction of overweight and obesity in post-menopausal women could avoid 15 to 20% post-menopausal breast cancers. The RR for moderate alcohol drinking is 1.1 to 1.3, and up to 30 to 40% of women in selected European countries drink alcohol regularly. Thus, reduction of alcohol drinking could avoid 5% of breast cancers in Europe − and in selected countries, like France or Italy, up to 10%. A favorable influence of physical activity and selected aspects of diet on breast cancer risk is also possible, though definition of these factors and their quantification remains uncertain. Still, assuming a RR of 0.8 for regular physical activity and a proportion inactive women of 50%, up to 10% of breast cancers could be avoided by widespread adoption of physical activity. A similar proportion could be avoided by a diet rich in vegetables and poor in animal fats, again assuming a RR of 0.8 for a favourable diet. Lactation has a protective effect on breast cancer, but given the limited number of births per woman in Europe, even long-term lactation would have a modest impact on lifetime breast cancer risk. Likewise, breast cancer risk could be reduced by earlier first birth and increased number of births, but − though in principle modifiable − these factors imply complex societal changes.

The table gives estimates of the avoidable proportion of breast cancers in France for major selected risk factors.

Table. Attributable fraction of breast cancer in France, 2000 [Boffetta et al., 2008]

Risk factor	Attributable fraction
Use of HRT	10.7%
Physical inactivity	10.1%
Alcohol consumption	9.4%
Reproductive factor*	5.4%
Obesity and overweight	4.8%

*Changes in reproductive factors since 1930.

Conclusions: Modification of selected lifestyle factors would have a substantial impact in reducing the breast cancer burden in Europe.

Thursday, 25 March 2010 11:00–12:30

KEYNOTE SYMPOSIUM

Local regional control

206 Invited

Local relapse − same or different disease?

M. Bollet[1]. [1]*Institut Curie, Radiotherapy, Paris, France*

Breast-conserving therapy is the preferred treatment for patients with early-stage breast cancer. It offers equal local control and overall survival and superior psychosocial outcomes compared with modified radical mastectomy. However, an ipsilateral breast cancer recurrence can be traumatizing and can lead to death. When an ipsilateral breast cancer develops, the new tumour can either be a true recurrence − that is, a regrowth of clonogenic cells that were not removed by surgery or killed by radiotherapy − or a new primary tumour that arises from the remaining breast tissue. Several definitions have been used to distinguish true recurrences from new primary tumours. Initially, these distinctions were based on spatial and temporal characteristics of the ipsilateral breast cancer (ie, the farther from and the later after the initial primary tumour, the more likely it is to be a new primary tumour) and on shared common histopathologic criteria (e.g., type, grade, and hormone receptor status). In the quest for additional ways to distinguish new primary breast tumours from true breast cancer recurrences, biologic studies of clonal relationships between the new and original tumour have also been performed. These studies have relied on ploidy, loss of heterozygosity, p53 analysis, or X chromosome inactivation or have been based on DNA copy number alterations (CNAs). Detecting changes in DNA copy number using high-resolution single nucleotide polymorphism arrays has been a useful tool in distinguishing new primary breast tumours from recurrences (Bollet, Servant et coll. JNCI, 100 (2008), 48−58). The potential implications of better defining true recurrences, both clinical − in terms of prognosis and treatment − and scientific, will be discussed at the meeting.

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What surgery constitutes optimal local control

E. Rutgers[1]. [1]*The Netherlands Cancer Institute, Department of Surgery, Amsterdam, The Netherlands*

For many years the role of surgery in breast cancer treatment has been challenged. Some twenty years ago optimism was heralded by medical oncologist and radiation oncologist that the need for surgery in breast cancer could be eliminated by chemotherapy or hormonal therapy followed by radiotherapy. So far, the real world and daily clinical practice is more refractory. For the time being, surgery is the main stay for achieving optimal local control and staging information.

What are the issues at stake in breast cancer surgery?

– Optimal local control.
– Optimal regional control.
– Best cosmetic cosmetic outcome.
– Less invasive procedures.
– Less side-effects and mutilation.
– Better information on prognosis.

What do we need to know to perform optimal breast surgery? For local control we need to have as exactly as possible information on the extent of the disease in the breast, and the intrinsic risk of apparently normal − surrounding − breast tissue to become malignant. Further we need to know the risk of lymphatic involvement for optimal regional control. And, last but not least, we need to know the risk of distant disease to improve survival through adjuvant systemic treatment, which information can be retrieved from the primary tumor.

What are the tools to know what we need to know? First, to know the nature of the lesion, image directed minimal invasive needle biopsies are mandatory: FNA-cytology for fast track diagnosis, and core biopsy for histology and tumor characteristics indispensible in case of suspected DCIS and when up front chemotherapy is considered. Starting treatment of a breast lesion without a diagnosis is obsolete. At a minimum, optimal − digital − mammography and ultrasound of the primary must be performed in all patients to best estimate the extent of the cancer, particularly when breast conservation or neoadjuvant chemotherapy is at stake. The role of contrast enhanced breast dedicated MRI will become more and more important, albeit its precise indication is not yet fully established.

For the diagnosis of lymphatic invasion, PET-CT-scanning and ultrasound followed by ultrasound directed biopsy of suspicious lymph nodes are really of help. If PET-CT-scanning shows lymph node involvement, the chance of a false positive finding is very low and one can proceed to treatment of the axillary lymph node. The same holds true for a tumor positive ultrasound directed fine needle aspiration. If these imaging techniques are negative, the existence of microscopic or small metastasis in lymph nodes is still possible. For that indication today lymphatic mapping by sentinel node biopsy is standard of care.

The surgery: In case of non-palpable cancers, image directed surgery can be employed with the help of intraoperative ultrasound, of a gamma-ray probe after intralesional injection of a radioactive compound (the so called ROLL technique), or probe directed after insertion of I125 seed. In comparative studies, the cumbersome guide wire localization appears to perform less optimal. An important issue is the imaging after neo-adjuvant chemotherapy and the guidance to optimal local and regional treatment. The placement of a marker (for instance an I125 seed) before treatment is indispensible to guide confirmational excisional biopsy after good remissions. MRI plays an eminent role in patients treated with

neo-adjuvant chemotherapy. To improve cosmetic outcome, oncoplastic techniques should be applied whenever possible to achieve best margin width, optimal breast shape and no dead space to minimize boost dose volume; all to improve cosmetic outcome and diminish late side effects. In case mastectomy is indicated (either for oncological reasons or the wish of the patient), immediate breast shape reconstruction according to the form of the breast, the body shape of the patient or her desires, should be discussed and applied whenever possible.

Another option to diminish side-effects is the possibility of minimal invasive ablative surgery by radiofrequency ablation. So. far, the disadvantage of this procedure is the lack of sufficient tumor tissue to stage the tumor and to estimate the extent of the tumor with great certainty. Further follow-up after necrotizing the tumor will be difficult since necrotic tissue will be in place for a long time.

All this requires an experienced breast surgeon who applies his/her technical skills only after multidisciplinary consultation and discussion of every individual patient.

Thursday, 25 March 2010 15:30–17:00

CLINICAL SCIENCE SYMPOSIUM

Is tailored chemotherapy becoming a reality?

209 Invited

Can we select patients for adjuvant therapy based on the presence of micro-metastatic disease?

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Adjuvant therapy targets minimal residual disease. However, the presence of minimal residual disease is presumed not measured. Our current approach for determining adjuvant systemic therapy is to assess the primary tumour, using traditional clinicopathological features or multigene signatures, and estimate an individual's recurrence risk. Subsequent treatment decisions are based on characteristics of the primary tumour (eg. ER, HER2) with the presumption of biological homogeneity between the primary lesion and micrometastases. However, biological discrepancy between a primary tumour and corresponding micrometastases may have significant therapeutic consequences.

An alternative approach is to identify micrometastatic disease postoperatively. Disseminated tumour cells (DTC) in the bone marrow and circulating tumour cells (CTC) from peripheral blood collection may offer quantification and biocharacterisation of residual disease. Detection at the single cell level with high sensitivity and specificity is facilitated by immunocytochemical and molecular enrichment assays. Detection of DTC at the time of surgery for the primary tumour is not currently a routine procedure. Standardised DTC detection and implementation in clinical trials are required. CTCs offer a less invasive potential alternative. New tools, such as a recently described anti-EpCAM and flow based microchip technology, 'CTC-chip', offer greater efficiency in cell capture. The biological role and clinical significance of CTC in early breast cancer remain unclear.

Some CTC and DTC remain dormant with patients never developing overt metastases. Detection of micrometastatic disease alone may not be enough. Favourable host features, including conducive stromal microenvironment and evasion of host immunity, appear critical for the switch from this dormant state to evolution of metastatic disease. New tools are required to assess this dynamic multifactorial interaction between tumour and host. A potential novel tool may be metabolomics, a science of metabolites and small molecules. As metabolomic analysis of systemic biofluids incorporates both tumour and host signal, a dynamic portrait of metabolic status may identify individuals at risk of relapse due to presence of both residual disease and favourable host features.

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Anthracyclines and topoisomerase II alpha − what is beyond?

C. Desmedt[1], M. Piccart[1], C. Sotiriou[1]. [1]*Institut Jules Bordet, Medical Oncology, Brussels, Belgium*

Anthracycline-based regimens are among the most active chemotherapies in breast cancer (BC). However, their use is associated with rare but significant toxicities and their efficacy may be restricted to a subset of BC patients. Topoisomerase IIa (TOP2A) is arguably a promising marker for predicting the efficacy of anthracycline-based chemotherapy for BC patients. However, several groups have reported conflicting results with regard to its predictive value.

We recently reported the results of the first neo-adjuvant trial − called TOP (NCT00162812) − designed to prospectively evaluate the predictive value of TOP2A and to identify biomarkers of response/resistance to anthracyclines. This trial was specifically designed to identify markers of efficacy to preoperative single-agent epirubicin (100 mg/m^2 q2 or q3wks) in 149 estrogen receptor (ER)-negative patients.

The results support TOP2A gene amplification, but not protein overexpression, as predictive marker of pathological complete response (pCR). However, it has recently been suggested that TOP2A might actually be a surrogate for CEP17 since an increased CEP17 copy number predicts for enhanced benefit of anthracyclines compared to CMF (Bartlett et al. *Cancer Res 2009*). Increased CEP17 was evident in 68% of the TOP trial cases. Interestingly, samples with TOP2A aberrations had a higher proportion of increased CEP17 than TOP2A normal samples but CEP17 status was not associated with pCR.

We further hypothesized that TOP2A gene amplification might be a surrogate for other genes that are co-amplified with TOP2A. To this end, we built and validated a TOP2A index that was made of genes located close to TOP2A.

Next, we investigated the predictive value of the biological gene expression modules (Desmedt et al. Clin Can Res 2008). We found that high levels of the tumor invasion module were associated with the presence of residual disease. This observation is consistent with the results reported recently by Farmer et al. (Nat Med 2009), which demonstrated that their stroma-related gene signature predicts resistance to neoadjuvant anthracycline-based chemotherapy. We also showed that high levels of the immune response module were associated with increased pCR rate.

Altogether, these results suggest that sensitivity to anthracyclines is likely multifactorial and that the cohort of patients who derive the largest benefit is not necessarily confined to the HER2/TOP2A co-amplified subgroup.

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Predictive signatures for chemosensitivity and new targeted therapies − dream or reality?

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To date, predictive markers have been analyzed either as single markers (for example, proliferation markers, hormone receptors, HER2 and p53) or in groups, commonly referred to as gene signatures, metagenes, multigene biomarkers, multigene predictors or multigene classifiers. I will concentrate in my lecture on signatures and address an important practical question: are these signatures ready for routine clinical use?

1. Predictive signatures for chemosensitivity [1]: They must address two questions: (a) which tumours are more likely to respond to chemotherapy? (b) what is the optimal chemotherapy regimen for a specific tumour or group of tumours? The signatures which answer these questions are likely to be different; for the sake of simplicity I will describe them in two categories: those predicting general chemosensitivity (meaning that a tumour is sensitive to any chemotherapy or to a wide range of chemotherapeutic drugs) and those predicting drug-specific chemosensitivity (meaning that a tumour is sensitive to a specific class of agents). I will review retrospective trials that have reported promising chemotherapy signatures, presenting in a comprehensive manner for the non bio-informatician the different methods used so far.

2. Signatures for targeted therapies (oncogenic pathways signatures [2]): I will briefly explain how these signatures have been identified and discuss the value of DNA based and RNA based technics.

3. Integrated approach [3]: Unsupervised gene expression analyses have allowed to develop a molecular classification of breast cancer and to identify at least 5 subtypes (Luminal A, Luminal B, HER2 enriched, Basal and normal like). A group has tried to further dissect this classification using oncogenic and chemosensitivity signatures. Concentrating on the Luminal B and Basal subtypes, they found a high variability of specific oncogenic pathways (MYC, E2F3, SRC) within these subtypes. Similarly they found a clear heterogeneity of chemosensitivity signatures within these two subtypes. These findings may have important implications when designing a trial tailoring the treatment based on oncogenic pathways and/or chemosensitivity signatures.

In addition, I will briefly summarize prospective trials (either ongoing or under development). Of note, these trials will be presented and discussed in more details in my Friday lecture "Incorporating multigene signatures into the design of adjuvant clinical trials".

References

[1] Bonnefoi H, Underhill C, Iggo R, Cameron D. Predictive signatures for chemotherapy sensitivity in breast cancer: Are they ready for use in the clinic? Eur J Cancer 2009; 45(10): 1733−43.

[2] Bild AH, Yao G, Chang JT, Wang Q, Potti A, Chasse D, et al. Oncogenic pathway signatures in human cancers as a guide to targeted therapies. Nature 2006; 439(7074): 353−7.