Contrasting DCIS and invasive breast cancer by subtype suggests basal-like DCIS as distinct lesions

Helga Bergholtz[1,2], Tonje Gulbrandsen Lien[1], David Michael Swanson[3], Arnoldo Frigessi[3,4], Oslo Breast Cancer Research Consortium (OSBREAC), Jörg Tost[5], Maria Grazia Daidone[6], Fredrik Wärnberg[7,8], Therese Sørlie[1,2]

[1]Department of Cancer Genetics, Institute for Cancer Research, Oslo University Hospital, The Norwegian Radium Hospital, Oslo, Norway; [2]Institute of Clinical Medicine, Faculty of Medicine, University of Oslo, Oslo, Norway; [3]Oslo Centre for Biostatistics and Epidemiology, Oslo University Hospital, Oslo, Norway; [4]Department of Biostatistics, University of Oslo, Oslo, Norway; [5]Laboratory for Epigenetics and Environment, Centre National de Recherche en Génomique Humaine, CEA-Institut de Biologie Francois Jacob, Evry, France; [6]Department of applied Research and Technical development, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy; [7]Department of Surgical Sciences, Uppsala University, Uppsala, Sweden; [8]Department of Surgery, Uppsala Academic Hospital, Uppsala, Sweden.

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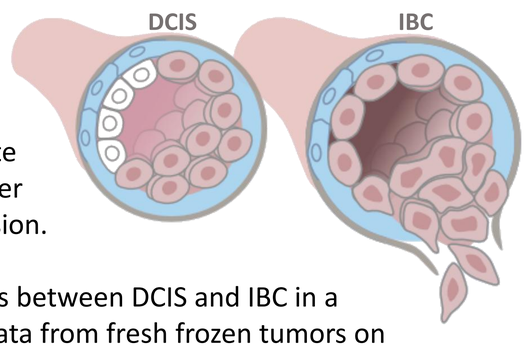
Ductal carcinoma in situ

Ductal carcinoma in situ (DCIS) is a type of breast cancer where tumor cells are confined inside the mammary gland ducts. DCIS is a non-obligate precursor to invasive breast cancer (IBC) and has low risk of progression.



We have explored the differences between DCIS and IBC in a subtype-specific manner using data from fresh frozen tumors on three genomic levels: gene expression, DNA copy number and DNA methylation.

Lay summary

Breast cancer is a heterogeneous disease and may be categorized into distinct molecular subtypes. Non-invasive breast lesions such as ductal carcinoma in situ (DCIS) pose a significant clinical challenge since many never progress to lethal disease. Therefore, there is a need for markers to identify patients that benefit from less aggressive treatment.

In our study, we have used genomic data to compare DCIS and invasive breast cancers using a subtype specific approach to investigate how tumor progression differs between the subtypes. We found that DCIS of the basal-like subtype have less distinct subtype-specific molecular characteristics than their invasive counterpart. This may have implications for the treatment of patients with DCIS.

Basal-like DCIS are different from basal-like invasive breast cancer

PAM50 subtyping revealed several differences between DCIS and IBC:

- Higher proportion of lesions of the HER2-enriched subtype in DCIS compared to IBC
- Basal-like DCIS showed lower correlation to the basal-like centroid compared to basal-like IBC and a notable lack of ”core basal” DCIS (Figure 1).

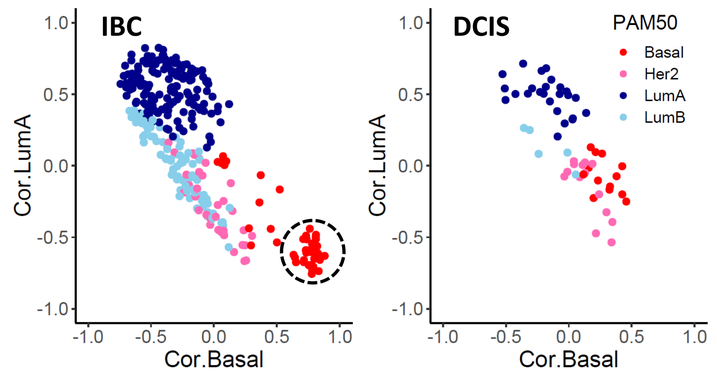


Figure 1. *Correlation to Basal-like and Luminal A centroids in IBC and DCIS. Core basal (invasive) tumors are indicated by black circle.*

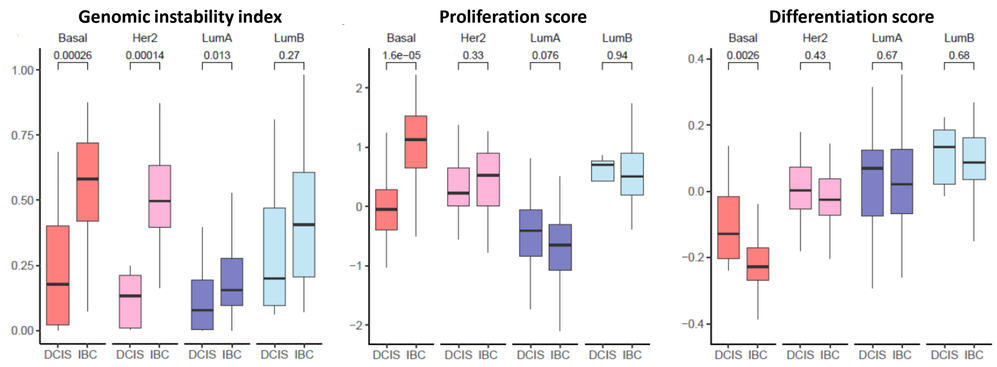
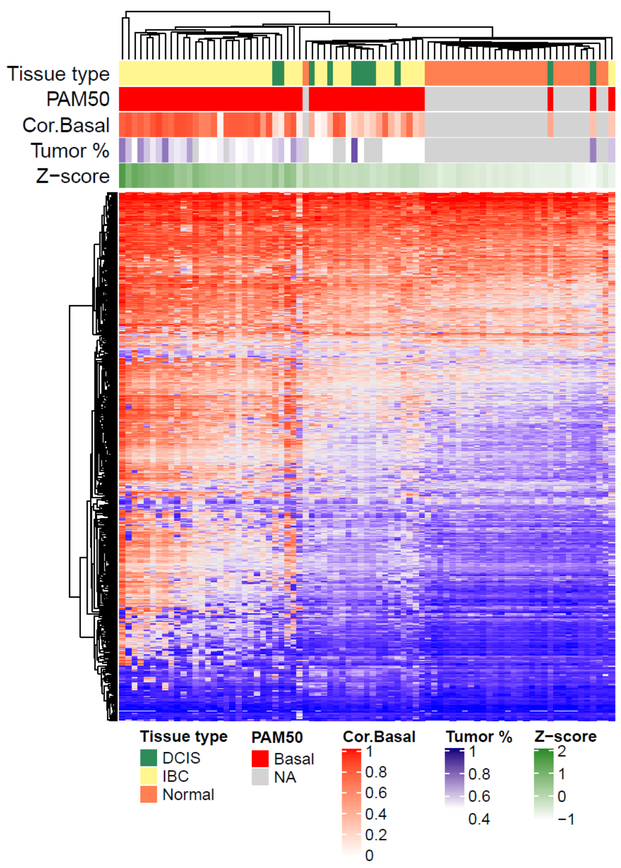


Figure 2. *Comparisons of genomic instability, proliferation and differentiation scores in DCIS and IBC stratified by subtype. P-value from Mann Whitney U test indicated above.*

Comparisons of DNA copy-number and gene expression between DCIS and IBC showed most distinct differences in the basal-like subtype, such as lower genomic instability, lower proliferation and higher differentiation in basal-like DCIS compared to basal-like IBC (Figure 2).

Clustered protocadherins are hypermethylated in basal-like invasive breast cancer compared to basal-like DCIS



Differential methylation analyses between DCIS and IBC revealed largest differences in the basal-like subtype compared to other subtypes. Most prominent was hypermethylation of multiple clustered protocadherin genes (cPCDH) in basal-like IBC compared to basal-like DCIS and normal breast tissue (Figure 3).

cPCDHs are involved in cell-cell-adhesion and are located on chromosome 5q, which is commonly deleted in core basal breast tumors. This genomic location has been shown to be subject to long range epigenetic silencing in different cancer types.

Figure 3. *Methylation status (β-values) of 698 CpGs located in a 800kb genomic window spanning the cPCDH genes on 5q in DCIS (green), IBC (yellow) and normal tissue (orange). Correlation to basal-like centroid, tumor percentage and mean cPCDH methylation (Z-score) is indicated above.*

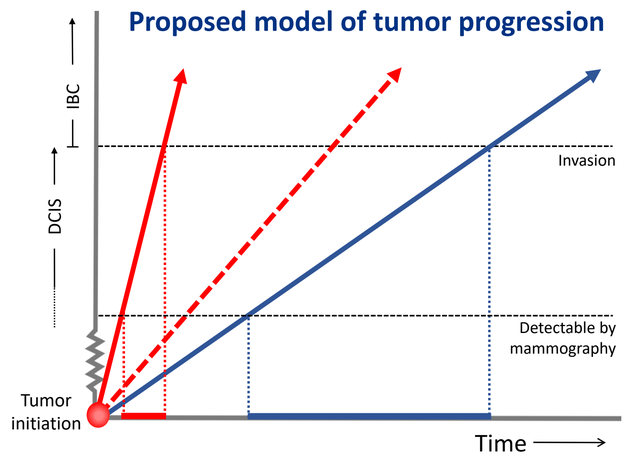


Figure 4. *“Core basal” tumors (red arrow) may be assumed to progress rapidly and spend a short time as DCIS. We propose that most basal-like DCIS represent a different entity (non-core basal) (red dashed line). In luminal tumors (blue arrow), tumor progression is even slower and tumors stay intraductal for a longer time period. Figure inspired by Groen et al. (The Breast, 2017).*

Conclusions

- **A subtype specific approach is imperative when studying DCIS, however, one should beware that subtypes may require different interpretation in DCIS and IBC.**
- **Basal-like DCIS are profoundly different from basal-like IBC at multiple genomic levels, while Luminal A DCIS and IBC are highly similar.**
- **Absence of ”core basal” DCIS may be explained by different progression paths between ”core basal” and ”non-core-basal” tumors (Figure 4).**

CONTACT INFORMATION
helga.bergholtz@rr-research.no
therese.sorlie@rr-research.no