

# **Female BRCA Carriers & BRCA Ovarian Cancer**

**PhD Thesis**

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## Summary

The thesis focuses on female BRCA carriers and BRCA related ovarian cancer.

Women with a germline mutation in BRCA1 or BRCA2 have a high risk of developing both breast and ovarian cancer. To either reduce this risk of cancer or to increase the likelihood of early detection, they are offered surveillance programs and/or risk-reducing surgery. A part of the thesis focuses on the risk-reducing surgeries.

The uptake of risk-reducing operations in the healthy carriers and their risk of subsequently developing a BRCA related cancer has been estimated. There was a high uptake of both risk-reducing mastectomy (RRM) and risk-reducing salpingo-oophorectomy (BSO); yet there remained a residual risk of tumour development after both RRM and BSO. The uptake of the risk-reducing surgeries has been evaluated and published (1), and the risk of breast cancer after mastectomy published (2) has been submitted. The risk of breast and peritoneal cancer after BSO is described in study 2 and 4, in the thesis.

Additionally the tissue removed at the risk-reducing salpingo-oophorectomy was analysed, with the intention to describe the very early premalignant changes in the fimbria. Although, I did not detect any occult cancers, I did, note a higher cell turn over in the P53 signatures (considered to be the precursor lesions to cancer) in BRCA1 carriers compared to BRCA2 carriers. On this background it may be hypothesised that BRCA carriers are at a higher risk of further cancer development as they only have one functioning BRCA allele, and BRCA1 carriers are at the highest risk as the higher cell turnover increases the likelihood of subsequent mutations. The results are described in study 5.

Finally, most inherited ovarian cancers are due to mutations in one of the BRCA genes, but only ovarian cancer patients with either young age at diagnosis, or more than one breast or ovarian cancer in the family are offered genetic testing. This does, however, not detect all ovarian cancer patients with BRCA mutations. Furthermore, targeted treatment therapies, that require knowledge of BRCA function, are being developed, which emphasises the need to know the BRCA status of the tumours. Therefore, I developed a BRCA1 screening in cancer formalin-fixed, paraffin embedded tissue to supplement the current selection for mutation analyses. The results suggest that BRCA1 IHC may be a reliable prior screening (3).

The results of the studies in this thesis have shown that observational studies of BRCA carriers, based on National health care databases and registries, may contribute to a better understanding of the cancer risk reduction obtained by surgery and may also result in consideration of follow-up after risk-reducing surgery. Furthermore the results of the tissue studies have suggested a screening in ovarian cancer tissue, which may contribute to identification of more women with BRCA1/2 mutations and hopefully thereby contribute to a better survival and more suitable follow-up. Future studies are needed to confirm and elaborate the results.

(1) **Skytte et. al.** Clin Genet. 2010 Apr;77(4):342-9. Risk-reducing mastectomy and salpingo-oophorectomy in unaffected BRCA mutation carriers: uptake and timing.

(2) **Skytte et. al.** Clin Genet. 2011 May;79(5):431-7. Breast cancer after bilateral risk-reducing mastectomy.

(3) **Skytte et. al.** Acta Obstet Gynecol Scand. 2011 Jun;90(6):593-9. Identification of BRCA1-deficient ovarian cancers.