

Multiple primary malignancies in breast cancer patients; from population study to genetics

Akademisk avhandling

Som för avläggande av medicine doktorexamen vid Sahlgrenska akademien, Göteborgs universitet kommer att offentligen försvaras i Arvid Carlsson, Medicinargatan 3, fredagen den 2021-05-07, klockan 13.00

av

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Avhandlingen baseras på följande delarbeten:

- I. **Nyqvist J**, Parris TZ, Helou K, Kenne Sarenmalm E, Einbeigi Z, Karlsson P, Nasic S, Kovács A. Previously diagnosed multiple primary malignancies in patients with breast carcinoma in Western Sweden between 2007 and 2018. *Breast Cancer Res Treat* (2020). DOI: 10.1007/s10549-020-05822-z
- II. De Lara S*, **Nyqvist J***, Werner Rönnerman E, Helou K, Kenne Sarenmalm E, Einbeigi Z, Karlsson P, Parris TZ, Kovács A. The prognostic relevance of FOXA1 and Nestin expression in breast cancer metastases: a retrospective study of 164 cases during a 10-year period (2004-2014). *BMC Cancer* (2019). DOI: 10.1186/s12885-019-5373-2. *=contributed equally
- III. **Nyqvist J**, Kovács A, Einbeigi Z, Karlsson P, Forssell- Aronsson E, Helou K*, Parris TZ*. Genetic alterations associated with multiple primary malignancies. *=contributed equally (manuscript)
- IV. **Nyqvist J**, Persson F, Parris TZ, Helou K, Kenne Sarenmalm E, Einbeigi Z, Borg Å, Karlsson P, Kovács A. Metachronous and synchronous occurrence of 5 primary malignancies in a female patient between 1997 and 2013: A case report with germline and somatic genetic analysis. *Case Rep Oncol* (2017). DOI: 10.1159/000484403.

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Abstract

Breast cancer (BC) is one of the most common causes of cancer-related death among women worldwide. Due to early detection of BC and more tailor-made treatments, patients live longer despite their illness. Studies have shown that BC patients are at risk of developing new tumors in organs other than the breast, mainly caused by BC treatment. These tumors do not originate from the breast and are not considered to be metastases, but primary tumors. However, BC patients have also been shown to be at risk of developing other malignancies, even before their BC. Thus far, previously diagnosed malignancies have not been investigated to a great extent. The etiology of multiple primary malignancies (MPMs) can be explained by intrinsic-, extrinsic-, and therapeutic factors. In addition, genetic factors are postulated to contribute to the development of breast cancer and MPMs. To avoid the toxicity of repeated cancer treatment, it is important to predict and prevent the development of other primary malignancies in cancer patients. These patients are in need of individually tailored cancer therapies and special follow-up programs.

The aim of this thesis was to investigate the prevalence of other previous primary malignancies (OPPMs) before a BC diagnosis and identify specific genetic changes and prognostic factors associated with high-risk patients. In the first work, we reviewed the medical records of 8,031 patients who received a BC diagnosis at Sahlgrenska University Hospital in Gothenburg between 2007 and 2018. In total, 414 patients had one or more OPPMs prior to their BC and subsequent treatment. Consequently, the incidence of OPPMs increased from approximately 3% in 2007 to 8% in 2016 ($p < 0.001$). A population-based study was then conducted for 5,132 BC patients diagnosed between 2007 and 2017 using data from the Swedish Cancer Registry at the National Board of Health and Welfare. Though not statistically significant ($p > 0.05$), OPPM incidence rates increased (from 8% to 10%) during this time period. In the second work, FOXA1 and Nestin protein expression was found to be associated with prognosis and aggressive tumor features for metastatic BC. In the third work, 26 tumor pairs from young women (≤ 50 years) with BC and OPPMs were analyzed to identify common genetic alterations. Few genetic alterations were shared by the tumor pairs. In the fourth work, next generation sequencing analysis of a blood sample from an elderly BC patient who developed five MPMs within 16 years showed the presence of possible pathogenic variants in RAD51 and RAD54. Cancer diagnoses not only affect the physical and mental health of the patient but also close relatives, frequently due to changes in financial security (sick leave and high medical costs). For patients with MPMs, these burdens will naturally multiply. Therefore, it is important that we have a better understanding of MPMs to be able to identify patients at risk of developing MPMs at an early stage.

Keywords: breast cancer, multiple primary malignancies, other previous primary malignancies