Taxane-Induced Peripheral Neuropathy among Early-Stage Breast Cancer Survivors

Prevalence, Risk Factors, Quality of Life and Genetic Prediction Models
Taxane-Induced Peripheral Neuropathy among Early-Stage Breast Cancer Survivors:

Prevalence, Risk Factors, Quality of Life and Genetic Prediction Models

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Till min familj ❤️
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ABSTRACT

Background: Taxane-induced peripheral neuropathy (TIPN) is a common and distressful side effect. Little is known on how long TIPN persist and its effect on health-related quality of life (HRQL). The overall aim of this thesis was to study the prevalence and severity of persistent TIPN, to investigate its impact on HRQL and to explore the clinical and genetic risk factors for TIPN among early-stage breast cancer survivors (ESBCS).

Methods: A population-based cohort of 884 recurrence-free ESBCS diagnosed 2010-2015 in the Southeast Health Care region, Sweden and 1768 control women without prior cancer, who received a postal questionnaire including EORTC chemotherapy-induced peripheral neuropathy (CIPN20) and QLQ-C30 instruments. Prevalence of TIPN symptoms and clinical risk factors were explored. Adjusted relative risks (RR) were estimated for ESBCS compared to control women. For impact on HRQL, adjusted mean scores of QLQ-C30 scales among ESBCS with and without TIPN were calculated. Blood samples from 362 ESBCS were whole-exome sequenced. We leveraged logistic regression models to develop and validate polygenic prediction models to estimate the risk of persistent PN symptoms in a training and test cohort.

Results: The response rate was 79% for ESBCS and 59% for controls. The median time post-taxane was 3.6 years. The adjusted RR for ESBCS vs. controls was highest (RR 1.8) for tingling in feet and numbness in feet. Individual sensory symptoms occurred in 9%-48% and motor symptoms in 7%-61% of ESBCS. The most prevalent symptoms were difficulty opening jar and cramps in feet. Paclitaxel, older age, overweight, diabetes mellitus, vibrating hand tools, smoking and autoimmune disease were independent risk factors (Study I). All 13 sensory and motor TIPN symptoms at increased risks among ESBCS had a significant impact on global health status, which worsened with increased severity of TIPN. Between 30%-93% of ESBCS with moderate-severe TIPN reported a clinically important impairment of functioning and personal finances. Moderate-severe difficulty climbing stairs and problems standing/walking were associated with medium-large clinically important differences (Study II). In the explorative sub-study, two of five prediction models based on genetic and clinical risk factors obtained
AUC results above 60% in the test cohort. Using the model for *numbness in feet* (35 SNVs) in the test cohort, 73% survivors were correctly predicted. For *tingling in feet* (55 SNVs) 70% were correctly predicted (Study III).

Conclusions: Most sensory and motor symptoms are more common among taxane-treated ESBC survivors than in women from the general population, many symptoms persist ≥3.6 years. Persistent TIPN symptoms are associated with clinically relevant impairment of HRQL. Polygenic prediction models including clinical risk factors may be used to estimate the risk of persistent taxane-induced numbness in feet and tingling in feet.

Key words: early-stage breast cancer, taxane, chemotherapy-induced peripheral neuropathy, risk factors, polygenic prediction models
WILL IT PERSIST?

The use of taxanes in early-stage breast cancer increased during the early 2010s, when I was working as a resident in oncology. Taxane-induced peripheral neuropathy was known to occur during treatment, especially with paclitaxel, but what about after treatment? Almost daily, “Will it persist?” was asked by breast cancer patients undergoing treatment and healthcare professionals who met patients with neuropathy symptoms.

(Neo-)adjuvant treatment of early-stage breast cancer is common, and therefore difficult decisions often had to be made regarding dose reductions and discontinuation due to neuropathy. I also personally encountered early-stage breast cancer survivors living with severe functional impairment due to persisting symptoms, leading to an inability to return to work or to continue their previous leisure activities after treatment. On the other hand, some patients never experienced symptoms of neuropathy even if they had been treated extensively with taxanes. At the time, there were few answers in the literature on the prevalence of persistent taxane-induced peripheral neuropathy after (neo-)adjuvant treatment, and the questions that arose from my work in the clinic lead to this PhD project.

The field of oncology is rapidly evolving with many new treatment modalities and an increase in overall survival; however, the relevance of chemotherapy-induced peripheral neuropathy has not decreased over the years. Taxanes and other neurotoxic drugs are widely used in breast cancer treatment, and in other solid tumours and haematological malignancies. Peripheral neuropathy is a potentially persistent side effect that has gained more attention alongside the increased focus on cancer survivorship.

Kristina Engvall
Jönköping, March 2024
“The whole of science is nothing more than a refinement of everyday thinking”

Albert Einstein
Bröstcancer är den vanligaste cancerformen bland kvinnor och drabbar ca 8000 personer i Sverige varje år. De flesta botsas genom operation, strålbehandling och läkemedelsbehandling. Vid mer aggressiv eller utbredt sjukdom med hög risk för återfall i obotbar, metastaserad sjukdom erbjuds cytostatikabehandling för att minska återfallsrisken. I behandlingen ingår taxaner, en viktig slags cytostatika (cellgift) som bidrar till förbättrad överlevnad men som medför risk för nervskador i händer och fötter. Få studier har undersökt hur vanligt det är med kvarstående nervskador, trots att taxanbehandling givits till bröstcancerpatienter världen över i nästan 20 år.

Studierna i den här avhandlingen är baserade på en enkätstudie i Sydöstra regionen (Kalmar, Östergötland och Jönköping) som genomfördes 2017 och handlar om hur vanligt det är med kvarstående nervskador och hur symtomen påverkar vardagen, privatekonomin och livskvaliteten bland bröstcanceröverlevare. Nervsymtom förekommer även i befolkningen, så därför fick en kontrollgrupp också besvara enkäten. Svarsfrekvensen var hög och slutligen analyserades resultaten från 646 bröstcanceröverlevare och 1040 kvinnor i kontrollgruppen. Tiden sedan cytostatikabehandling var i medel 3,6 år.Livsstils- och genetiska faktorer som ökar risken har också studerats för att bättre individanpassa cytostatikabehandlingen i framtiden.

Enkätsvaren visar att majoriteten av bröstcanceröverlevare har kvarstående nervsymtom, de vanligaste var ”svårigheter att öppna en burk” och ”kramp i fötterna”. Jämfört med kontrollgruppen var risken högst för symtomen ”domningar i fötterna” och ”stickningar i fötterna”. Även mer än 3,6 år efter behandling rapporterade var fjärde bröstcanceröverlevare ’en hel del’ eller ’väldigt mycket’ ”kramp i fötterna” och ”domningar/stickningar i fötterna”, och risken var förhöjd jämfört med kontrollgruppen. De vanligaste risksyntomen för nervskador i händer och fötter var behandling med paklitaxel (en cellgift/taxan), högre ålder, övervikt och diabetes.

Att leva med kvarstående nervsymtom innebär en påverkad funktionsnivå i vardagen och en sämre privatekonomi. Ju allvarligare nervsymtom, desto sämre livskvalitet rapporterades bland bröstcanceröverlevarna. Särskilt symtomen ”problem med att stå eller gå på grund av svårigheter att känna marken under fötterna” och ”svårigheter att gå upp för trappor eller resa sig ur en stol på grund av svaghet i benen”, påverkade vardagen och även livskvaliteten till en hög grad. Många med kvarstående besvär använde olika
gånghjälpmedel. Hälften rapporterade också att de inte pratat om sina symtom med någon inom sjukvården.


Unikt för dessa studier är att de baserats på alla bröstcanceröverlevare i tre regioner och jämförelsen med en kontrollgrupp. Unikt är också att vi har studerat många olika nervsymtom, vilket givit ny kunskap om att också försämrad motorisk förmåga av nervskador försämrar livskvaliteten. Utöver tidigare känta riskfaktorer, så visar vi att användande av vibrerande handverktyg och rökning kan öka risken för taxanorsakade nervskador. Studieresultaten går redan nu att använda i klinisk rutin när man informerar om cytostatikabehandling och värderar risk/nytta tillsammans med patienten. En djupare förståelse av hur kvarstående nervsymtom påverkar livet kan leda till mer riktade rehabiliteringsinsatser. Den genetiska studien visar att det i framtiden kan vara möjligt att förutse om patienten har en hög eller låg risk att få kvarstående nervbiverkningar.
LIST OF STUDIES

I. Engvall K, Gréen H, Fredriksson M, Ávall-Lundqvist E.

II. Engvall K, Gréen H, Fredrikson M, Lagerlund M, Lewin F, Ávall-Lundqvist E.

III. Engvall, K, Uvdal, H, Björn, N, Ávall-Lundqvist, E, Gréen, H.
   Developing and validating prediction models of persistent taxane-induced peripheral neuropathy among early-stage breast cancer survivors using whole-exome sequencing. Submitted to NPJ Precision Oncology.
**ABBREVIATIONS**

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABC</td>
<td>Advanced Breast Cancer</td>
</tr>
<tr>
<td>AC-T</td>
<td>Anthracycline-Cyclophosphamide followed by Taxane (docetaxel)</td>
</tr>
<tr>
<td>ADC</td>
<td>Antibody Drug Conjugate</td>
</tr>
<tr>
<td>ADR</td>
<td>Adverse Drug Reaction</td>
</tr>
<tr>
<td>AI</td>
<td>Aromatase Inhibitors</td>
</tr>
<tr>
<td>ASCO</td>
<td>American Society of Clinical Oncology</td>
</tr>
<tr>
<td>AUC</td>
<td>Area Under the Curve</td>
</tr>
<tr>
<td>BMI</td>
<td>Body Mass Index</td>
</tr>
<tr>
<td>BRCA1/2</td>
<td>BReast CAncer gene 1/2</td>
</tr>
<tr>
<td>CF</td>
<td>Cognitive Function</td>
</tr>
<tr>
<td>CICI</td>
<td>Chemotherapy-Induced Cognitive Impairment</td>
</tr>
<tr>
<td>CID</td>
<td>Clinically Important Difference</td>
</tr>
<tr>
<td>CIPN</td>
<td>Chemotherapy-induced Peripheral Neuropathy</td>
</tr>
<tr>
<td>CNS</td>
<td>Central Nervous System</td>
</tr>
<tr>
<td>CPDB</td>
<td>Consensus Pathway DataBase</td>
</tr>
<tr>
<td>CTCAE</td>
<td>Common Terminology Criteria for Adverse Events</td>
</tr>
<tr>
<td>CYP</td>
<td>Cytochrome P450</td>
</tr>
<tr>
<td>dd</td>
<td>dose dense</td>
</tr>
<tr>
<td>DFS</td>
<td>Disease-Free Survival</td>
</tr>
<tr>
<td>DM</td>
<td>Diabetes Mellitus</td>
</tr>
<tr>
<td>EC</td>
<td>Epirubicin-Cyclophosphamide</td>
</tr>
<tr>
<td>EF</td>
<td>Emotional Function</td>
</tr>
<tr>
<td>EORTC</td>
<td>European Organisation for Research and Treatment of Cancer</td>
</tr>
<tr>
<td>ESBC(S)</td>
<td>Early-Stage Breast Cancer (Survivor)</td>
</tr>
<tr>
<td>ESMO</td>
<td>European Society of Medical Oncology</td>
</tr>
<tr>
<td>FI</td>
<td>Financial difficulties</td>
</tr>
<tr>
<td>GHS/QoL</td>
<td>Global Health status /Quality of life</td>
</tr>
<tr>
<td>GWAS</td>
<td>Genome-Wide Association Study</td>
</tr>
<tr>
<td>HADS</td>
<td>Hospital Anxiety and Depression Scale</td>
</tr>
<tr>
<td>HER2</td>
<td>Human Epidermal growth factor Receptor 2</td>
</tr>
<tr>
<td>HR</td>
<td>Hazard Ratio</td>
</tr>
<tr>
<td>HRQL</td>
<td>Health-Related Quality of Life</td>
</tr>
<tr>
<td>IHC</td>
<td>ImmunoHistoChemistry</td>
</tr>
<tr>
<td>INDEL</td>
<td>Insertion/deletion</td>
</tr>
<tr>
<td>Ki67</td>
<td>Proliferation marker</td>
</tr>
<tr>
<td>KEGG</td>
<td>Kyoto Encyclopaedia of Genes and Genomes</td>
</tr>
<tr>
<td>NGS</td>
<td>Next Generation Sequencing</td>
</tr>
<tr>
<td>NHG</td>
<td>Nottingham Histology Grade</td>
</tr>
<tr>
<td>OS</td>
<td>Overall Survival</td>
</tr>
<tr>
<td>PAM50</td>
<td>Prediction Analysis of Microarray 50</td>
</tr>
<tr>
<td>PARP</td>
<td>Poly Adenosine diphosphate–Ribose Polymerase</td>
</tr>
<tr>
<td>pCR</td>
<td>Pathological Complete Response</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Description</td>
</tr>
<tr>
<td>--------------</td>
<td>------------------------------------------</td>
</tr>
<tr>
<td>PF</td>
<td>Physical Function</td>
</tr>
<tr>
<td>PN</td>
<td>Peripheral Neuropathy</td>
</tr>
<tr>
<td>PR</td>
<td>Progesterone Receptor</td>
</tr>
<tr>
<td>PROM</td>
<td>Patient-Reported Outcomes Measure</td>
</tr>
<tr>
<td>RCT</td>
<td>Randomized Controlled Trial</td>
</tr>
<tr>
<td>RDI</td>
<td>Relative Dose Intensity</td>
</tr>
<tr>
<td>RF</td>
<td>Role Function</td>
</tr>
<tr>
<td>ROC</td>
<td>Receiver Operating Characteristics</td>
</tr>
<tr>
<td>RR</td>
<td>Relative Risk</td>
</tr>
<tr>
<td>SF</td>
<td>Social Function</td>
</tr>
<tr>
<td>SNV</td>
<td>Single Nucleotide Variant</td>
</tr>
<tr>
<td>TAC</td>
<td>Taxane (docetaxel)- Anthracycline-Cyclophosphamide</td>
</tr>
<tr>
<td>TC</td>
<td>Taxane (docetaxel)-Cyclophosphamid</td>
</tr>
<tr>
<td>TCI</td>
<td>Threshold Clinical Importance</td>
</tr>
<tr>
<td>TIPN</td>
<td>Taxane-Induced Peripheral Neuropathy</td>
</tr>
<tr>
<td>TNBC</td>
<td>Triple-Negative Breast Cancer</td>
</tr>
<tr>
<td>TNM</td>
<td>Tumour Node Metastasis</td>
</tr>
<tr>
<td>WES</td>
<td>Whole-Exome Sequencing</td>
</tr>
<tr>
<td>WGS</td>
<td>Whole-Genome Sequencing</td>
</tr>
<tr>
<td>QLQ-C30</td>
<td>Quality of Life Questionnaire Core 30</td>
</tr>
<tr>
<td>QoL</td>
<td>Quality of Life</td>
</tr>
</tbody>
</table>
### Abbreviations of items EORTC CIPN20

<table>
<thead>
<tr>
<th>Question</th>
<th>Abbreviation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Did you have tingling fingers or hands?</td>
<td>Tingling in hands</td>
</tr>
<tr>
<td>Did you have tingling toes or feet?</td>
<td>Tingling in feet</td>
</tr>
<tr>
<td>Did you have numbness in your fingers or hands?</td>
<td>Numbness in hands</td>
</tr>
<tr>
<td>Did you have numbness in your toes or feet?</td>
<td>Numbness in feet</td>
</tr>
<tr>
<td>Did you have shooting or burning pain in your fingers or hands?</td>
<td>Shooting/burning in hands</td>
</tr>
<tr>
<td>Did you have shooting or burning pain in your toes or feet?</td>
<td>Shooting/burning in feet</td>
</tr>
<tr>
<td>Did you have cramps in your hands?</td>
<td>Cramps in hands</td>
</tr>
<tr>
<td>Did you have cramps in your feet?</td>
<td>Cramps in feet</td>
</tr>
<tr>
<td>Did you have problems standing or walking because of difficulty feeling the ground under your feet?</td>
<td>Problems standing/walking</td>
</tr>
<tr>
<td>Did you have difficulty distinguishing between hot and cold water?</td>
<td>Difficulty hot/cold water</td>
</tr>
<tr>
<td>Did you have a problem holding a pen, which made writing difficult?</td>
<td>Difficulty holding a pen</td>
</tr>
<tr>
<td>Did you have difficulty manipulating small objects with your fingers (for example, fastening small buttons)?</td>
<td>Difficulty small objects</td>
</tr>
<tr>
<td>Did you have difficulty opening a jar or bottle because of weakness in your hands?</td>
<td>Difficulty opening a jar</td>
</tr>
<tr>
<td>Did you have difficulty walking because your feet dropped downwards?</td>
<td>Difficulty walking foot drop</td>
</tr>
<tr>
<td>Did you have difficulty climbing stairs or getting up out of a chair because of weakness in your legs?</td>
<td>Difficulty climbing stairs</td>
</tr>
<tr>
<td>Were you dizzy when standing up from a sitting or lying position?</td>
<td>Dizziness when standing</td>
</tr>
<tr>
<td>Did you have blurred vision?</td>
<td>Blurred vision</td>
</tr>
<tr>
<td>Did you have difficulty hearing?</td>
<td>Difficulty hearing</td>
</tr>
<tr>
<td>Please answer the following question only if you drive a car</td>
<td></td>
</tr>
<tr>
<td>Did you have difficulty using the pedals?</td>
<td>Difficulty using pedals</td>
</tr>
</tbody>
</table>
INTRODUCTION

Breast cancer

Breast cancer is the most common cancer in the world with a yearly incidence of 2.3 million cases and mortality of 680,000 cases (1). The incidence in high income countries has increased since 1970s, probably due to reproductivity and life-style factors and to more cases being detected in mammography screening (1) with a life-time risk of 10%-12% in women (2). Early detection and improved treatment have contributed to decreased mortality (3). In Sweden, an average of 7500 cases are diagnosed yearly (2017-2021) (4), The median age at diagnosis is 66 years, while 10% of those diagnosed are <45 years and 13% are >80 years (5). The ten-year age-standardised relative survival is 88.1% (95% CI 87.2-89.1) (6).

Treatment by primary surgery alone is possible in most cases of early-stage breast cancer (ESBC), but (neo-)adjuvant oncological treatment decreases the risk of recurrence and improve overall survival (OS). Five years of endocrine treatment is suggested to most patients with oestrogen-receptor (ER) positive tumours and in 2021, 91% of breast cancer patients reported in the national registry in Sweden received endocrine treatment and almost half (45%) received chemotherapy (5). Since mortality is relatively low in breast cancer, the prevalence is high, and more than 122,000 Swedes have a personal history of a breast cancer diagnosis and treatment (4). This makes survivorship issues, such as persistent side effects, and their consequences on health-related quality of life (HRQL) of utmost importance in early-stage breast cancer.

Mammography screening detects more than 60% of the breast cancer cases in Sweden (5). The basic paradigm involves triple diagnostics including clinical examination, radiology, and a biopsy to confirm the diagnosis. Breast cancer treatment recommendations are based on the tumour node metastasis (TNM) stage of disease, divided in clinical (c) or pathological (p)(7), and the histopathological subtype, see Table 1 and Figure 1(8).

Clinical TNM staging is usually based on mammography combined with ultrasound. Magnetic resonance imaging (MRI) of the breast for further staging is used in selected cases, such as in lobular cancer, before neoadjuvant
treatment and in the case of dense breast tissue, but also depending on local routines. A computer tomography (CT) of the thorax and abdomen is performed to rule out metastatic disease if a tumour size >50mm (cT3) or involving >3 lymph nodes (cN2). In addition to stage, the subtype is of crucial importance to treatment choices. The subtype is based on the presence and extent of ER, progesterone receptor (PR) and human epidermal growth factor receptor 2 (HER2) positivity (amplified or IHC 3+) on the cancer cells, the Nottingham Histologic Grade (NHG) and the rate of cancer cell proliferation measured by Ki67. Together, these prognostic and predictive markers categorise breast cancer into five main histopathological subtypes: luminal A-like; luminal B-like; luminal HER2+; hormone receptor negative HER2+; and triple negative breast cancer (TNBC), corresponding to the intrinsic molecular subtypes luminal A; luminal B; HER2 enriched and basal-like, based on gene expression analyses, see Figure 1 (8).

Table 1. Pathological (post-surgery) classification of breast tumours according to Tumour Node Metastasis (TNM) 8th edition (7).

<table>
<thead>
<tr>
<th>Tumour</th>
<th>Node</th>
<th>Metastasis</th>
</tr>
</thead>
<tbody>
<tr>
<td>T0</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td></td>
<td>No evidence of primary tumour</td>
<td>No regional LN metastasis</td>
</tr>
<tr>
<td>T1n</td>
<td>N1</td>
<td>M1</td>
</tr>
<tr>
<td></td>
<td>Carcinoma in situ</td>
<td>Metastasis in 1-3 axillary lymph nodes</td>
</tr>
<tr>
<td>T1</td>
<td>N1</td>
<td>M2</td>
</tr>
<tr>
<td></td>
<td>Tumour ≤20 mm in greatest dimension</td>
<td>Metastasis in 4-9 ipsilateral axillary lymph nodes</td>
</tr>
<tr>
<td>T2</td>
<td>N2</td>
<td>M1</td>
</tr>
<tr>
<td></td>
<td>Tumour &gt;20 mm but ≤50 mm in greatest dimension</td>
<td>Metastasis in ≥10 ipsilateral axillary lymph nodes</td>
</tr>
<tr>
<td>T3</td>
<td>N3</td>
<td>M1</td>
</tr>
<tr>
<td></td>
<td>Tumour &gt;50 mm in greatest dimension</td>
<td>Metastasis in ≥10 ipsilateral axillary lymph nodes</td>
</tr>
<tr>
<td>T4</td>
<td>N4</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Tumour of any size with direct extension to chest wall and/or to skin</td>
<td></td>
</tr>
</tbody>
</table>
If Ki67 and the histologic grade are intermediary, genomic tests (PAM50/ prosigna®, oncotype DX®) can be used to differentiate between luminal A or luminal B, to clarify the risk of recurrence and benefit of adjuvant chemotherapy. By identifying Luminal A tumours, chemotherapy can be omitted in more patients (9-11). Histology, deriving from ductal cells, lobular cancer or other, and tumour involvement of lymph and blood vessels are also taken into consideration in treatment recommendations.

Figure 1. Histopathological breast cancer subtype classification according to National Guidelines Breast Cancer, Sweden 2024 (as suggested in revision), modified Figure (12).

Treatment of early-stage breast cancer

A multimodal approach is used and in addition to surgery, chemotherapy, endocrine treatment and radiotherapy are combined with newer drugs depending on subtype and stage of disease. To improve overall results, both escalation of treatment in high-risk disease and de-escalation in lower risk disease are implemented (13). The treatment approach in ESBC becomes gradually more tailored to achieve the best possible reduction of recurrence risk for the individual patient without overtreatment, taking the patients’ age, comorbidities, performance status, and preferences into account.

Surgery is always indicated in ESBC. If possible, partial mastectomy is performed (14). Neoadjuvant treatment can improve surgical outcomes; for
example, clinically node-positive disease that converts to clinically node-negative disease can undergo de-escalated surgery, targeted axillary dissection (15), to decrease the risk of lymphoedema in the ipsilateral arm (16). Onco-plastic techniques also contribute to improved aesthetic results.

Adjuvant radiotherapy decreases the risk of local recurrence and is indicated after partial mastectomy, if large tumour (T3-4) or lymph node involvement is present. The risk of local recurrence after partial mastectomy followed by radiotherapy is below the rate of recurrence after mastectomy, and it also increases survival (14). After mastectomy, radiotherapy of the thoracic wall is only indicated if tumour size >5cm. In node-positive disease, loco-regional lymph nodes are usually included in the radiotherapy field.

In ER positive breast cancer, large meta-analyses show a reduced relative risk (RR) for breast cancer recurrence by a third (17) up to 40% after 5-10 years of adjuvant endocrine treatment (18). The main treatment choice is aromatase inhibitors (AI) for postmenopausal women, except in cases of very low risk (T1a-bN0), when tamoxifen can be considered. AI contributes with an absolute risk reduction at 10 years by 2.7%, compared to tamoxifen. Premenopausal women at lower risk are recommended tamoxifen and if higher risk disease tamoxifen is combined with a Gonadotropin-Releasing Hormone (GnRH) analogue for ovarian suppression. Premenopausal women with very high-risk disease are recommended ovarian suppression plus an AI to further decrease the risk of distant recurrence (19). An overview of medical oncological treatments based on clinical stage is shown in Table 2.
Table 2. Overview of current medical oncological treatment recommendations for early-stage breast cancer in Sweden based on clinical and the following pathological staging (12, 20).

<table>
<thead>
<tr>
<th>Stage</th>
<th>TNM</th>
<th>Luminal A-like ER+/HER2-</th>
<th>Luminal B-like ER+/HER2-</th>
<th>ER+/HER2+</th>
<th>ER-/HER2+</th>
<th>Triple-negative (ER-PR-HER2-)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>cT1aN0</td>
<td>ET</td>
<td>ET</td>
<td>ET</td>
<td>Adj Trast + CT (only taxane) Post: ZA ET</td>
<td>Adj Trast + CT (only taxane) Post: ZA ET</td>
</tr>
<tr>
<td></td>
<td>cT1bN0</td>
<td>ET</td>
<td>ET</td>
<td>Adj CT Post: ZA ET</td>
<td>Adj Trast + CT (only taxane) Post: ZA ET</td>
<td>Adj Trast + CT (only taxane) Post: ZA ET</td>
</tr>
<tr>
<td></td>
<td>cT1cN0</td>
<td>ET</td>
<td>Adj CT</td>
<td>Adj Trast + CT (only taxane) Post: ZA ET</td>
<td>Adj Trast + CT (only taxane) Post: ZA ET</td>
<td>Adj Trast + CT (only taxane) Post: ZA ET</td>
</tr>
<tr>
<td></td>
<td>cT3N0</td>
<td>Adj CT Neo for surgery Post: ZA ET Extended ET</td>
<td>Adj CTdd Neo for surgery Post: ZA ET Extended ET</td>
<td>Neo Trast + Pertu + CT Adj trast/T-DM1 Post: ZA ET Extended ET</td>
<td>Neo Trast + Pertu + CT Adj trast/T-DM1 Post: ZA ET Extended ET</td>
<td>Neo Trast + Pertu + CT Adj trast/T-DM1 Post: ZA ET Extended ET</td>
</tr>
<tr>
<td>III</td>
<td>cT2N2-3</td>
<td>Adj CT Neo for surgery Post: ZA ET CDK4/6 Extended ET</td>
<td>Adj CTdd Neo for surgery Post: ZA ET CDK4/6 Extended ET</td>
<td>Extended ET</td>
<td>Extended ET</td>
<td>Extended ET</td>
</tr>
<tr>
<td></td>
<td>cT3N1-3</td>
<td>Adj CT Neo for surgery Post: ZA ET CDK4/6 Extended ET</td>
<td>Adj CTdd Neo for surgery Post: ZA ET CDK4/6 Extended ET</td>
<td>Extended ET</td>
<td>Extended ET</td>
<td>Extended ET</td>
</tr>
<tr>
<td></td>
<td>cT4N1-3</td>
<td>Adj CT Neo for surgery Post: ZA ET CDK4/6 Extended ET</td>
<td>Adj CTdd Neo for surgery Post: ZA ET CDK4/6 Extended ET</td>
<td>Extended ET</td>
<td>Extended ET</td>
<td>Extended ET</td>
</tr>
</tbody>
</table>

Abbreviated: cT1 ≤20 mm, cT2 21-50 mm, cT3 >50 mm, cT4 locally advanced.

Lymph nodes: cN1 palpable, cN2 fixed, cN3 infraclavicular, pN1 1-3, pN2 4-9, pN3 ≥10 positive nodes.

ET, Endocrine Treatment 5 years: Tamoxifen (premenopausal) or aromatase inhibitor (postmenopausal); GnRH, GnRH analogue 5 years to high risk premenopausal (<45 years and chemotherapy indication. Alternative to AI: Switch (AI-Tam); Extended ET, Extended Endocrine Treatment 2-5 years; CT, Chemotherapy sequential anthracycline-taxane; Neoadj, neoadjuvant; Adj, adjuvant; dd, dose dense; ZA, Zoledronic Acid 3 years postmenopausal and selected premenopausal cases; Trast, Trastuzumab 1 year; Pertu, Pertuzumab neoadjuvant; Pembro, Pembrolizumab neoadj+adj 1 year; trast/T-DM1, Kadcyla x14 if non-pCR, otherwise trastuzumab x 13; Cap, if non-pathological Complete Response (pCR)- Capecitabin adjuvant 6-8 cycles; CDK4/6, Abemaciclib 2 years (N2 and NHG3 or T3-4); PARPi, Olaparib adjuvant 1 year if neoadjuvant treatment TNBC and gBRCA1/2 carrier with non-pCR or adjuvant treatment stages II-III.

Note: Guidelines are under revision. A total risk evaluation adjusted to the patient must always be made and the table is an humble overview. Pathological reports can require modifications to adjuvant treatment. Always CT <35 years.
Chemotherapy can be administered before surgery (neoadjuvant), after surgery (adjuvant) or both. It is indicated in TNBC or HER2+ subtype from a tumour size >5mm and node-negative disease. Regimes including both anthracycline (epirubicin, doxorubicin) and taxane (docetaxel, paclitaxel) are the most efficient (21). The RR of recurrence is shown to decrease by a third compared to no chemotherapy independently of age, nodal status, tumour size, or tumour grade (22). The addition of taxane to anthracycline decreases the absolute risk of breast cancer mortality after 10 years by 3.6%, from 27.9% to 24.3% (21). The addition of taxane also has the advantage of a lower cumulative anthracycline dose leading to lower risk of cardiac toxicity (23). The evidence for the use of taxane in the neoadjuvant setting is mainly based on adjuvant studies. Different regimens of anthracyclines and taxanes are considered comparable in efficacy, but higher cumulative doses of chemotherapy provide greater benefits (21). The sequential order does not appear to impact outcome (24, 25).

Table 3.
Overview of chemotherapy regimens in (neo-)adjuvant treatment in early-stage breast cancer recommended in Sweden (12, 20).

<table>
<thead>
<tr>
<th>Anthracycline</th>
<th>Taxane (Carboplatin)</th>
<th>Fluorouracil</th>
</tr>
</thead>
<tbody>
<tr>
<td>E75-90C600 3 w x 3, or dd (2 w x 4)</td>
<td>Docetaxel175-1100 3w x 3-4 Paclitaxel80 weekly x 9-12</td>
<td></td>
</tr>
<tr>
<td>≤ 65 years</td>
<td>Paclitaxel80 weekly x 9-12 Paclitaxel175 2 w x 4 Docetaxel75 2 w x 4</td>
<td></td>
</tr>
<tr>
<td>HER2+ T1 &lt;20mm</td>
<td></td>
<td>Paclitaxel80 weekly x12</td>
</tr>
<tr>
<td>Non-anthracycline</td>
<td></td>
<td>TC Docetaxel75- Cyclophosphamide600</td>
</tr>
<tr>
<td>Triple-negative</td>
<td>ddEC90 2 w x 4</td>
<td>Paclitaxel80 weekly x 9-12 or Paclitaxel80/ Carboplatin (AUC 5) 3 w x 4 Capecitabin1000 3 w x 6-8</td>
</tr>
<tr>
<td></td>
<td>EC75 + Capecitabin9000 2 w x 3-4 Docetaxel60+ Capecitabin900 2 w x 3-4</td>
<td>Concomitant with EC-T</td>
</tr>
</tbody>
</table>

3w, every 3 weeks; 2w, every 2 weeks; EC, Epirubicin-Cyclophosphamide.
Note: As suggested in revision of guidelines.

Neoadjuvant chemotherapy is the preferred choice in HER2+ and TNBC due to highly proliferative disease, the possibility to evaluate response (26), and since the evidence as to the efficacy of additional treatments is only shown in trials conducted in a neoadjuvant setting. In HER2+ disease,
neoadjuvant chemotherapy is combined with double HER2 blockade; pertuzumab and trastuzumab (27). In TNBC chemotherapy is combined with immunotherapy (28) and includes carboplatin (29) to further improve pathological Complete Remission (pCR) rates. In case of remaining cancer cells at surgery, non-pCR can lead to escalation of adjuvant therapy in both HER2+ (discussed below) and TNBC to improve survival for those with more aggressive disease. In TNBC adjuvant capecitabine can improve survival after 5 years by 8.5% for patients with non-pCR (30). In luminal disease, neoadjuvant chemotherapy mainly aims to improve surgery.

Anti-HER2 treatment has completely changed the prognosis of HER2+ breast cancer over the last two decades. Trastuzumab is the corner stone of treatment and showed an increase in OS with a hazard ratio (HR) of 0.66 (0.57-0.77) for survival (31), and an average absolute reduction in the 10-year risk of breast cancer mortality of 6.4% (32). The addition of neoadjuvant pertuzumab further improves treatment by increased pCR rate and 3% higher progression-free survival at 5 years (84 vs. 81%). In HER2+ disease, neoadjuvant treatment achieves pCR in about 50% of patients (27). In non-pCR patients, escalation of treatment to adjuvant trastuzumab emtansine (T-DM1) instead of continued adjuvant trastuzumab increases disease-free survival (DFS) at 3 years by 11.3% (33). Adjuvant neratinib (a pan-HER thyrosine kinase inhibitor) has been used in selected cases, but recently a lack of improved OS at 8 years was published (34, 35).

Besides HER2 blockade, two targeted therapies are used in the (neo-)adjuvant setting (Table 2). High risk luminal disease benefits from the CDK4/6 inhibitor abemaciclib for 2 years, contributing an increased distant recurrence-free survival rate of 4.2% after 3 years (90.3% vs. 86.1%) (36). Patients carrying germline pathological variants of the BRCA 1 or 2 gene have defects in homologous recombination repair, which can be targeted by a PARP (poly adenosine diphosphate–ribose polymerase) inhibitor. In higher risk disease, the PARP inhibitor Olaparib contributes with 7.1% increased distant DFS at 3 years and an absolute gain in OS of 3.4% at 4 years (89.4% vs. 86.4%) (37, 38), and is approved in Sweden for TNBC. To date, immunotherapy is only used in TNBC and contributes 8.1% improvement in event-free survival at 3 years (39). Zoledronic acid is an inhibitor of osteoclast-mediated bone resorption used for treatment of osteoporosis. It also decreases the risk of breast cancer recurrence in post-menopausal women, with a 3.3% decrease in breast cancer mortality after 10 years (40).
Step by step, (neo-)adjuvant treatment of breast cancer has improved due to the introduction of new drugs, new chemotherapy combinations, and a response-guided approach to further personalize treatment and contribute to improved survival. Despite extensive research, many clinical situations are not covered by evidence in the form of an improved survival rate in a randomized controlled trial (RCT). Due to ESBC’s generally good prognosis, it may take many years for OS data to mature. During this time, new treatments are developed, which may lead to outdated regimens in the control arm. Large meta-analyses of clinical trials are important for clinical guidelines.

Adequate dosing of chemotherapy

The sequential anthracycline-taxane regimens can be prescribed in various ways. For example, anthracycline can be prescribed in dose dense (dd) regimes for improved DFS (41). Recommended taxane regimes are largely based on a study from 2008 by Sparano et al. in which four arms were compared, either paclitaxel or docetaxel, weekly or every 3 weeks (3w). Docetaxel at 100 mg/m2 every 3w x 4 and paclitaxel 80 mg/m2 weekly x 12 showed equal efficacy. In a long-term follow-up (in median 12.1 years), weekly paclitaxel showed significantly higher DFS and OS in TNBC patients (42). A recent meta-analysis favoured docetaxel in terms of efficacy when administered every 3 weeks, but weekly paclitaxel was the more efficacious regimen, possibly because of a larger cumulative dose and higher dose intensity (21). The main sequential alternatives in the Swedish guidelines are Epirubicin90 C Cyclophosphamide600 (EC) 3 w followed by either docetaxel100 3 w x 3-4 cycles or Paclitaxel80 weekly x 9-12 cycles (12, 20), or dose dense regimens (Table 3). European Society of Medical Oncology (ESMO) guidelines recommend sequential anthracycline-taxane for 6-8 cycles weeks and do not include doses (43, 44). Based on two meta-analyses that reported no difference between the anthracycline-free regimen of docetaxel75 combined with cyclophosphamide600 (TC) and sequential chemotherapy, TC can therefore be considered in the case of cardiac comorbidity. However, standard regimens have a large evidence-base and there is a trend favouring sequential treatment in high-risk disease, i.e., ER-, N+ (21, 45).

Chemotherapy drugs have a narrow therapeutic window, and oncologists modify chemotherapy doses depending on expected or manifest side effects. Both pre-treatment adjustments of regimens and unplanned dose modifications impact the final administered dose. Adequately dosed chemotherapy
for maintained efficacy has been suggested to be a relative dose intensity (RDI) of 85% for luminal disease and RDI 75% for TNBC (46). Dose reductions are common, a RDI < 85% was seen for 22-45% of those receiving sequential anthracycline-taxane compared to 34% and 27% for those receiving TC or docetaxel-anthracycline-cyclophosphamide (TAC) regimens (47). The importance of dose intensity may vary between types of chemotherapy. A secondary analysis of anthracycline-cyclophosphamide followed by docetaxel (AC-T) in an RCT (N=1326) looking at RDI in relation to outcome found that RDI <90% for the docetaxel sequence (100mg/m2 x 3w) did not impact outcome, in contrast to anthracycline, where lower RDI was associated with worse outcome (48). Dose reduction of taxane was not associated with worse outcomes in Sparano’s four-armed taxane study (49). On the other hand, in the neoadjuvant setting, in a meta-analysis (N =3332) pCR was correlated to the number of treatment cycles, higher anthracycline dose and higher taxane, equivalent to docetaxel ≥ 400mg/m2, and pCR was strongly correlated to overall survival (50).

Side effects of early-stage breast cancer treatment

Side effects can occur directly, later during treatment or after completion. Persistent, plausibly chronic side effects are rarely reported, especially when they do not increase mortality. Among ESBC survivors, long term side effects have an impact on quality of life (51-53).

Breast cancer surgery, especially axillary lymph node dissection (54), disrupts blood vessels, nerves, and lymph-vessels which may cause upper limb lymphedema and impact QoL (55). Breast cancer surgery may also lead to ‘phantom breast pain’ and shoulder problems (56). Adjuvant radiotherapy is associated with several side effects, including pneumonitis months after treatment and late lung fibrosis in the radiotherapy field (57). Late cardiac side effects have been reported, resulting in an increased risk of cardiac mortality for as long as 25 years after treatment, especially for younger women and those treated with chemotherapy (58). Since cardiac radiotherapy doses have been reduced over the last few decades, future mortality risks are expected to be lower. Radiotherapy-induced angiosarcoma of the breast is a rare late side effect with an incidence of 0.1% and a latency period of 8 years in a recent large retrospective study. The overall survival rate was 40.5% after 5 years (59).
Endocrine therapy may cause vasomotor symptoms, joint pain, and genitourinary menopausal symptoms during treatment (60). The side effects can be alleviated but, in some cases, lead to early interruption of treatment, which may affect survival outcomes (61). Tamoxifen is associated with an increased risk of thromboembolic events and of endometrial cancer, but a low risk of mortality. The combined absolute excess risk for death from either event was 0.02% per decade among women treated with tamoxifen for 5 years (62). AI are associated with a slight increase of cardiovascular disease (63) and may cause loss of bone mass leading to osteopenia/osteoporosis. After 5 years of AI 8.2% reported bone fractures compared to 5.5% after tamoxifen (18). Screening with a bone density test should be performed before AI or ovarian suppression, for prescription of treatment when needed to avoid osteoporosis (20).

Chemotherapy acts on rapidly dividing cells, but these mechanisms are non-specific and can result in damage to normal cells. Side-effects of chemotherapy can be acute (immediate), occur during or immediately after treatment, or late (delayed) side effects, which develop some time after treatment. Most side-effects are short in duration, but some may persist throughout the life course, illustrated in Figure 2.

The three probably most well-known side effects are nausea/vomiting, myelosuppression and alopecia – all of which can occur during the first chemotherapy cycle. Anthracyclines and platinum are emetogenic drugs that
Introduction

may cause nausea/vomiting, which can be effectively managed by different antiemetics (64). Myelosuppression is seen of varying grades, but the risk of febrile neutropenia and sepsis is largely prevented by the use of granulocyte colony-stimulating factor (G-CSF) to stimulate the bone marrow (65). Alopecia follows in most patients receiving anthracyclines and taxanes (66). It occurs after a couple of weeks, but regrowth starts after discontinuation. The use of scalp cooling can partly prevent alopecia in about 50% (67). Dermatological and gastrointestinal toxicities of lower grades are common and usually limited to the treatment period (68). Fertility can be permanently impaired. Younger patients are offered both fertility-preserving interventions and ovarian suppression during treatment (69).

Anthracyclines are associated with cardiac toxicity and secondary malignancies. Treatment with anthracyclines increase the risk of non-breast cancer mortality (RR=1.20, 95% CI 1.00-1.43) (70). The risk for anthracycline-induced heart failure is related to cumulative dose and is considered irreversible (71). A recent study comparing risk of heart disease among anthracycline-treated BC survivors with population controls showed an increased risk, HR 1.84 (CI 1.21 to 2.80), with a prevalence at 10 years of 4.1% vs. 2.3% (63). Sequential therapy with a reduced anthracycline dose is associated with a decrease in risk of cardiotoxicity (OR 0.39, 95% CI 0.18-0.86) (23). Anthracyclines are also associated with acute myeloid leukaemia, with approximately one additional case per 700 treated women (21), and an increased risk extending to at least 10 years (72). Cyclophosphamide is also associated with leukaemia and may contribute to the variation in risk between studies (21). Taxanes have not been shown to increase the risk of bone marrow neoplasia (23).

Carboplatin and capecitabine are used in TNBC. Carboplatin increases haematological toxicity and is associated with chronic peripheral neuropathy in 20% of patients (73). The risk of grades 3-4 PN does not seem to increase in (neo-)adjuvant treatment (74): 3.6% was reported independently of carboplatin in a meta-analysis (75), although lower grades were not reported. Capecitabine causes diarrhoea and hand-foot syndrome as the most common and dose limiting side effects. Hand-foot syndrome was reported by 36% compared to 0% in non-treatment arm (grades 2-3). It can clinically influence PN symptoms, but capecitabine is not reported to be associated with neurotoxicity in the literature (30, 73). Neither carboplatin nor capecitabin commonly cause alopecia. The side effects of taxanes are discussed in detail below.
The main side effect of HER2 blockade is the risk of reversible heart failure, and patients are therefore monitored with heart examinations during (neo-)adjuvant treatment (20). HER2 blockade is rarely given concomitantly with anthracyclines due to concerns about increased cardiac toxicity and no clear increase in efficacy (76). The risk of heart failure/cardiomyopathy in breast cancer survivors after anthracycline and trastuzumab is increased compared to population controls, HR 3.7 (95% CI 1.8-7.6), with a prevalence of 4.4% vs. 2.0% at 10 years (63). Dermatological and gastrointestinal toxicity (diarrhoea) are also prevalent side effects. T-DM1 is an antibody drug conjugate (ADC) consisting of trastuzumab with a microtubule inhibitor payload, leading to a risk of both heart failure and PN. The risk for sensory PN of any grade increases, 19% compared to 7% in patients receiving only trastuzumab (grades 3-4 1.4% vs. 0%). Resolution of PN in the T-DM1 arm was reported in 75% of patients (33).

The CDK4/6 inhibitor abemaciclib can cause haematological toxicity, fatigue and diarrhoea (77). Persistent side effects have not been reported (78). The PARP inhibitor (Olaparib) mainly causes nausea, fatigue, diarrhoea and haematological toxicity during treatment (37). In ovarian cancer, an increased risk of MDS/AML has been reported (79), but no increased risks for MDS/AML or new primary malignancy were seen in the adjuvant breast cancer trial (38). PARP inhibitors have recently and unexpectedly been associated with PN in a pharmacovigilance database study, primarily in patients taking niraparib (80).

Immune therapy can cause mild to lethal (although rare) autoimmune reactions against any organ. The most common side effect is thyroiditis (28). Early detection and appropriate management are essential to limit the risks of immune therapy. Immune-related PN occurred in 0.5%-1% in cohorts with various cancers (81, 82), but in the TNBC neoadjuvant trial no additional PN was reported in the pembrolizumab arm (28). Zoledronic acid can cause flu-like symptoms just after treatment. A severe side effect, albeit occurring at a very low frequency, is osteonecrosis in jaws in about 1% of patients (40).
Chemotherapy-induced peripheral neuropathy (CIPN)

Peripheral neuropathy is the most common neurological complication of cancer treatment. Chemotherapy-induced peripheral neuropathy (CIPN) is a distressing adverse event and has a high impact on daily life (83-86). CIPN is observed in patients treated with taxanes, platinum-based chemotherapy (oxaliplatin, carboplatin), the microtubule inhibitors vinca alkaloids (vincristine, vinorelbine), eribulin and the proteasome inhibitor bortezomib. CIPN is dose-dependent, and prevention is mainly possible by limiting the dose (87, 88). When CIPN prevalence is reported, it is commonly the sensory symptoms of numbness, tingling, and pain in hands and feet which are clustered together, and motor or autonomic symptoms are often overlooked (87). However, CIPN can constitute both sensory, motor, and autonomic symptoms affecting function in different ways via diverse mechanisms, see Figure 3 (73, 89). The coasting phenomena, CIPN symptoms occurring or increasing after treatment, is associated mainly with oxaliplatin (73).

Figure 3.
Chemotherapy-induced peripheral neuropathy symptoms in typical ‘glove-and-stocking’ distribution, with mechanisms for CIPN toxicity. Taxanes targeting dorsal root ganglion, the axon microtubules, mitochondria, ion channels, and nerve terminals. From Park et al 2013 (89) and adapted based on Kerckhove 2017 (90), Burgess 2021 (91) and Lustberg 2021 (73). Reprinted with permission from John Wiley and Sons.
The motor nerves of the peripheral nervous system are large and myelinated while the sensory nerves can be either myelinated large (beta), small (alpha), or sensory unmyelinated (C fibers) - and the latter can also be autonomic. The nerves are damaged by neuroinflammation, impaired mitochondrial function and dysregulation of ion channels leading to altered neuronal excitability, with partly different mechanisms between drugs (Figure 3)(92). Neuroinflammation in the dorsal root ganglia, which to a large extent consists of glial cells supporting and regulating neurons, is mainly associated with platinum compounds (93). Taxanes stabilise the microtubule, while vinca alkaloids destabilise (92), both leading to adverse intracellular effects such as impairments of axonal transport, cytoskeletal structure, and cell mobility (94). Inflammatory mechanisms lead to demyelination, oxidative stress contributes to neural damage, and mitochondrial function is impaired (91). The biological background of CIPN is not fully understood, and it is unclear whether the mechanisms causing acute and persistent CIPN symptoms are the same.

A division in plus or minus symptoms is suggested for enhanced clinical understanding of CIPN symptoms, and may also facilitate mechanistic understanding (87), see Table 4. ‘Sensory plus’ symptoms are caused by altered ion channels and $\text{Ca}^{2+}$ signaling, neuroinflammation and activation of nociceptors. ‘Sensory minus’ symptoms are caused by loss of intraepidermal nerve fibres, demyelination, degeneration of distal nerves and axonal membrane remodelling (95).

Table 4.
Classification of CIPN sensory and motor symptoms according to increase or loss of symptom/function, as suggested by ESMO-EONS-EANO Clinical Practice Guidelines of therapy-induced peripheral neurotoxicity (87).

<table>
<thead>
<tr>
<th></th>
<th>Sensory</th>
<th>Motor</th>
</tr>
</thead>
<tbody>
<tr>
<td>‘Plus’ Increase of sensation</td>
<td>Tingling, Burning sensation, Allodynia, Hyperalgesia</td>
<td>Cramps</td>
</tr>
<tr>
<td>‘Minus’ Loss of function</td>
<td>Numbness</td>
<td>Muscle weakness, Fine motor skills (mixed?)</td>
</tr>
</tbody>
</table>
Taxane- a spindle poison

Taxanes were discovered in the 1960’s and paclitaxel was characterized first, in the bark of the rare pacific yew tree taxus brevifolia (94). Limited availability and hypersensitivity reactions delayed the introduction, but synthetic docetaxel and paclitaxel were developed, resulting in an FDA approval in 1984 for ovarian cancer and in 1996 for advanced breast cancer (ABC) (94, 96). In 2009, adjuvant sequential anthracycline and taxane treatment was established as the standard treatment by the St Gallen Consensus Conference (97).

Taxanes bind to α- and β-tubulin and disrupt the balance between formation and depolymerisation, which stabilise microtubules and freeze the mitotic spindle, and the dysfunctional mitosis leads the cancer cell into apoptosis. Dysfunctional cytoskeleton leads to impaired axonal transport and cell mobility, especially in the distal part of nerves (92, 96, 98). Taxanes also induce an inflammatory response, inhibit angiogenesis, and affect cancer cells via reactive oxidative species (ROS-) mediated mechanisms, and causes toxicity by neuroinflammatory effects (94). At lower, metronomic doses, taxane inhibits angiogenesis and affect the microenvironment, but is not cytotoxic to tumour cells (96).

Pharmacology

Paclitaxel and docetaxel differ chemically in two locations, have different solubility and exhibit differences in absorption, distribution, metabolism and elimination (ADME) (94, 96). Taxanes are bound up to 90% to albumin and alfa 1-acid glycoprotein. Efflux by P-glycoprotein limits absorption to the Central Nervous System (CNS). Paclitaxel is the most hydrophobic molecule, solved in cremophor and ethanol while docetaxel is solved in polysorbate/tween 80 and ethanol (94). Docetaxel is metabolised by CYP3A5, paclitaxel by CYP2C8 and both by CYP3A4 (99, 100). Paclitaxel exhibits non-linear pharmacokinetics, and an increased dose converts to a proportionally higher increase in plasma concentration, possibly due to plasma and tissue protein binding of paclitaxel or cremophor. The elimination of paclitaxel is first a rapid decline when the drug redistributes from plasma to peripheral tissues, then in the second phase redistribution between tissues and plasma that lead to a slower decline and finally elimination mainly through liver metabolism (101). Docetaxel has linear pharmacokinetics but exhibits large interpatient variability (100, 102). Pharmacogenetic variants contribute to
differences in metabolism and elimination, further discussed below. Excretion occurs up to 80% in bile, and only a small extent occurs through the kidneys (96).

A number of other taxanes are used or are under development. Nab-paclitaxel is paclitaxel bound to albumin, enabling administration to patients with cremophor-related hypersensitivity reactions. Cabazitaxel is a semisynthetic taxane used in prostate cancer (66). At least two formulas are under development, paclitaxel micellar uses surfactant XR17 to make small paclitaxel micells soluble in water and has been shown to be bioequivalent to nab-paclitaxel (103). ‘Oraxol’, paclitaxel for oral administration needs to be combined with encequidar, an intestinal p-glycoprotein pump inhibitor to prevent active excretion (104). ‘Oraxol’ requires fasting for 4 hours and about 11 pills taken over 3 subsequent days.

**Taxane-induced side effects**

Taxanes cause a wide range of side effects beside myelosuppression. The paclitaxel hypersensitivity infusion reaction related to cremophor can often be prevented by antihistamines, cortisone, and longer infusion time. Docetaxel can cause fluid retention syndrome and oedema in 2.8%-12.6% compared to 0%-0.5% on paclitaxel (105), which can be prevented by cortisone. Taxane acute pain syndrome (TAPS) manifests as myalgia/arthralgia, lasting for up to a week after treatment and associated with high doses and shorter infusion time. TAPS is probably caused by neuroinflammation (73, 106), and may affect most patients. Higher doses of docetaxel have been associated with persistent alopecia (107). Taxanes, especially docetaxel, cause onycholysis (nail problems), which may be persistent (108).

**Taxane-induced peripheral neuropathy (TIPN)**

The addition of taxanes increases the risk of PN grades 3-4, by an Odds Ratio (OR) of 6.9 (95 CI % 3.2-14.7) compared to anthracycline-based adjuvant treatment. A higher risk is seen for paclitaxel than for docetaxel (23). In the Sparano et al. 2008 study, the prevalence of acute TIPN grades 2-4 during treatment was higher in the weekly paclitaxel80 x 12 arm, at 27% compared to 16% in the docetaxel100 3w x 4 arm. Grade 3-4 PN was also higher for paclitaxel, at 8% vs. 4% percent (42). Nab-paclitaxel is associated with a higher TIPN prevalence, for example, in the nab-paclitaxel arm in a neoadjuvant trial (GeparSepto), 83% had sensory PN compared to 65% in
the paclitaxel arm (grades 3-4 PN at 8.1% vs. 2.7%) (109). Regimens combining taxane and anthracyclines seem to cause less PN than sequential regimens, with reported TIPN prevalence rates of 33.3%-37.7% (AT, TAC) at 6 months from start of treatment compared to 68% for anthracycline followed by taxane (AC-T) (83). Taxanes are considered to cause mostly sensory PN symptoms and that motor symptoms co-occur (110-112). Nab-paclitaxel caused more sensory symptoms than paclitaxel or docetaxel, but the risk of motor or autonomic symptoms was similar (113).

In 2018, a systematic review on persistent TIPN included five reports from four studies on TIPN beyond one year from diagnosis (114), and in 2023 a new review included 15 studies, the majority of patients treated with docetaxel (111). Sensory symptoms persisted in 11%-80% after 1 year and based on 6 longitudinal studies, a relative decrease in prevalence of 30%-40% after 3 years was seen (111). Long-term follow-up data beyond 5 years are scarce. In a cross-sectional study, the rate of patient-reported persistent sensory PN symptoms after 6.3 years was 31% after docetaxel (n=88) and 44% after paclitaxel (n=166) (115). In a cohort study, five years after adjuvant docetaxel 39% of patients reported tingling or numbness in feet (n=80), compared to 20% in breast cancer survivors not exposed to chemotherapy (116). Prevalence rates differ due to different study populations and outcome measures. Some of the persisting symptoms may instead be late-occurring TIPN, as 10% of docetaxel-treated ESBC patients with no acute TIPN symptoms immediately after treatment, reported late-onset PN symptoms after 1-3 years (85). There is a lack of knowledge on the prevalence of persistent individual TIPN symptoms, especially motor symptoms and functional impairments. Previously, mainly sensory PN as a joint measure has been reported, and fewer studies concern TIPN after paclitaxel exposure (117).

**Risk factors for persistent TIPN**

Risk factors for persistent TIPN after one year from diagnosis/treatment have been reported in a limited number of publications using different PN assessment methods, as well as considering different risk factors. Reporting has mainly centred on risk factors after docetaxel (83, 85, 118), but risk factors after either paclitaxel or docetaxel (119) and only paclitaxel are also reported (120).

The most prominent risk factors are older age (83, 85, 118, 121) and higher body mass index (BMI) (83, 119, 121). Pre-existing PN (114, 115)
and diabetes mellitus increases the risk during treatment and the risk of longer TIPN duration (122). Low physical activity level compared to high levels of physical activity was a risk factor for persistent TIPN after 2 years (119). Persistent muscle and joint pain, stomatitis, and fatigue as well as cumulative doses as risk factors were seen in one study after docetaxel (85). Mastectomy and greater number of positive lymph nodes have been described as independent risk factors (83, 115) and higher maximal PN during treatment (85, 123). Postmenopausal status and pre-treatment anxiety are also associated with increased risk of persistent PN (83, 124). Autoimmune disease has been associated with polyneuropathy and considered a potential risk factor (125), but was found to be protective in one study (126). Low alcohol intake was associated with a lower risk of TIPN (127). There is conflicting evidence regarding several of these risk factors (73), and a lack of knowledge as to whether risk factors vary between individual TIPN symptoms.

**Taxane dose adjustments**

TIPN is a common toxicity leading to dose reductions, dose delays and discontinuations (128-130). Dose reductions due to TIPN are more prevalent during weekly paclitaxel (16%) than docetaxel every 3 weeks (2.4%) (129). In taxane trials (42, 131), recommendations for dose adjustment have been to reduce by 25% if grade 2 neuropathy, and if grades 3-4 delay dose until less than grade 2 and then reduce by 25%. In the Sparano et al. 2008 trial, the association between outcome and CIPN during treatment was analysed. CIPN occurred in 770 of 4554 patients (17%), the majority grade 2 (72%), therefore leading to dose reduction. No association between neuropathy grade and recurrence or survival rates was found. The proportion of patients that needed a dose reduction for any reason was not significantly higher in case of CIPN or no CIPN, and neither differed from the median RDI (49). Similarly, dose reduction of FEC but not docetaxel was associated with decrease in overall survival (132), and neuropathy was not associated with outcome in a nested cohort study including 6248 ESBC patients where two-thirds received taxane) (133).

Dose reduction due to PN does not seem to be associated with lower prevalence of persistent CIPN; instead, worse neuropathy outcomes were seen in those who received the lowest doses and/or ceased treatment early (130), suggesting an individual sensitivity to toxicity. Partly this may be due to interindividual differences leading to different systemic concentrations.
For docetaxel, delayed clearance has been associated with increased haematologic toxicity (134). Systemic paclitaxel concentration measures are predictors of TIPN (101), and for example, a low muscle mass may increase maximum paclitaxel concentration (135).

Other taxane-induced neurotoxicity

Neurotoxicity is a wider concept of side effects related to neurological symptoms. Taxanes can cause worse physical function (85), disabilities and a higher risk of falls (136), probably related to muscular weakness and impaired balance. Ocular neurotoxicity has been hypothesised as neurotoxicity in two small studies. One study found increased retinal thickness in taxane-exposed ESBC patients (137), and another found worse ocular discomfort in patients with TIPN compared to BC survivors without TIPN (138).

Central neurotoxicity, a chemotherapy-induced cognitive impairment (CICI) has been associated with adjuvant chemotherapy. A systematic meta-analysis focusing on cognitive function after taxane included 11 studies and showed effects on attention and concentration, depression, and executive function domains after >6 months (139), but most studies were small (only one had >75 patients) and most had no controls or only healthy controls. Another systematic review of CICI after any (neo-)adjuvant chemotherapy for breast cancer, including 52 studies, found a summarised self-reported prevalence rate of 44% (21-34% based on neuropsychological testing), and that symptoms remained after 2-3 years (140). A study comparing breast cancer patients treated with chemotherapy (n=172) to no chemotherapy exposure (n=104) and healthy controls found a numeric—but not significant—higher prevalence of self-reported cognitive difficulties after 1 year among chemotherapy-exposed patients and a strong association with cognitive fatigue and cancer stage. No significant differences in measured cognitive domains was seen up to 2 years after treatment, but a numeric decline was seen in executive function in the chemotherapy-exposed group (141). Fatigue, at least of short-term duration after treatment, is more common after adjuvant chemotherapy including taxane (23, 142).

Altogether, the drugs used in (neo-)adjuvant treatment of ESBC are associated with side effects of different grades, in different time frames, and with various impacts on later health status and quality of life. Some patients ‘sail through treatment’ while others may suffer a wide range of symptoms. The absolute risk of devastating side effects like leukaemia, cardiac death,
or lethal immune toxicity is very small compared to the large gain in overall survival for the whole group of breast cancer patients. Nevertheless, more common but less devastating side effects, like persistent TIPN, need further exploration as gaps of knowledge still remain.

**Prevention and treatment of CIPN**

The first guidelines on CIPN were first published in 2014 by American Society Clinical Oncology (ASCO) (143), ESMO in 2020 (88) and only in 2023 the St Gallen’s consensus conference mentions TIPN among breast cancer patients for the first time (26). Despite increasing awareness of persistent TIPN, no preventive method is recommended except monitoring and adjusting treatment. No pharmacological and non-pharmacological interventions have been successful (87, 88), except duloxetine for neuropathic pain (144). The reason may be a true lack off effect or due to inadequately small samples sizes for detecting differences and/or insensitive outcome measurements. Evaluation of preventive effects beyond acute CIPN is rare.

Preventive interventions can target the biological mechanisms involved and be drug-specific, axonal-specific (prevent degeneration), or systemically directed. One promising pharmacological preventive substance is ganglioside-monosialic acid (GM-1) involved in nerve function (88); the latest meta-analysis showed promising results in TIPN but not in oxaliplatin-induced PN (145). Non-pharmacological prevention to reduce blood flow in hands and feet is hypothesised to protect nerves. Cryotherapy is mostly studied in breast cancer patients treated with taxane (73), however, the effects on persistent TIPN are unclear. In a large study of docetaxel (N =1031), a decreased risk of TIPN during treatment was seen if cold socks and gloves had been used (146), but no association with persistent TIPN 2 years after treatment (85). A small RCT (N=38) on cryotherapy showed numerical but not statistically significant reduction of patient-reported TIPN 2.3 years after treatment. Compression therapy could be a similar intervention with superior patient tolerability but is insufficiently studied (147).

Exercise (aerobic, resistance and balance training) has both preventive and treatment effects on CIPN symptoms and improves HRQL (148). The mechanisms of exercise may be an increase of neurotrophic factors, an anti-inflammatory effect, may impact mitochondrial function and protect against axonal degeneration, and possibly affect CNS and offer psychosocial contributions. HRQL effects may be associated with the positive effects of exercise
on mood, anxiety, and depression (149). Physical exercise relieves persistent CIPN symptoms and improves peripheral deep sensitivity (150).

Duloxetine is the only pharmacological treatment with high grade evidence, based on an RCT in which the duloxetine arm had a significantly superior effect on painful CIPN (59%), compared to the placebo arm (38%). Thus, a substantial placebo effect was seen, and the duloxetine effect was largest in the oxaliplatin-treated group (144). Other treatment alternatives are venlafaxine, pregabalin, amitriptyline, tramadol, strong opioids and topical baclofen (87); although limited evidence and ASCO advices against use outside studies (88). A meta-analysis of acupuncture showed no improvement in CIPN symptoms or impairment, but pain was relieved (151). Treatment decisions should take depression, anxiety, and sleep into consideration due to association with CIPN (121, 152).

TIPN and health-related quality of life

HRQL in breast cancer survivors exposed to adjuvant chemotherapy and endocrine treatment is lower than in survivors exposed to neither (153). Risk factors for lower HRQL are obesity, low level of exercise, smoking, younger age, comorbidities, lower income and need for endocrine treatment (154). Persistent TIPN is associated with psychological distress and decreased QoL, although few studies have been published (111, 155). Two large studies after adjuvant docetaxel (83, 85) show deterioration of all aspects of HRQL with worse grade of TIPN or worse ‘bother’ level. There is a lack of knowledge on TIPN and HRQL after paclitaxel treatment, on the impact of different individual TIPN symptoms on HRQL, and impact of persistent TIPN beyond 2-3 years after treatment.

Breast cancer survivorship

The overall survival in breast cancer is generally high, but patients may be on adjuvant endocrine treatment up to 10 years after diagnosis. Persistent or late side effects from chemotherapy, like TIPN or cardiac toxicity, could impair treatment possibilities in advanced breast cancer (ABC). The prognosis in ABC has improved from 15 months median OS in patients diagnosed in Sweden 1979-2004, to 30 months in patients diagnosed in 2009-2016 (156, 157). Recent first line studies show a median OS of 5.3 year for luminal
cancers (158), 4.8 years in HER2+ breast cancer (159) and 21-23 months in TNBC (159, 160).

A cancer survivor is defined as a patient with cancer ‘from the time of diagnosis until the end of life’ (161). Improved definitions have been suggested: acute, chronic, long-term, and cured for more distinct communication of the different needs of cancer survivors (162) although it was not used in the 2022 ESMO Consensus Statements on Survivorship (163). Unmet needs in survivorship research include more research on larger study populations over time and the need for controlled interventional studies. Comparison with healthy controls has been emphasised since there is an overlap between symptoms of aging and long-term cancer therapy side effects (163). Research on financial impact and chronic medical conditions has also been encouraged (164). Historically, RCTs in oncology have not included long-term follow-up of side effects, and populations in most observational studies include mixed cancer diagnoses, disease stages and previous treatment exposures.

Assessment of CIPN

In the lack of a golden standard for assessing CIPN, a review found 117 distinct methods for CIPN assessment (165), making comparisons between studies challenging. The methods included unvalidated or validated questionnaires, combined instruments, grading of symptoms by physicians or neurophysiological measurements. Patient-reported outcome measures (PROM) are more sensitive than physician-reported outcomes of PN, with substantially higher prevalence reported (166) and higher correlation with objective measures (165). A systematic review and Delphi survey concluded that no current CIPN assessment method adequately and consistently addresses patient and clinical needs for routine use (165). In clinical practice, the ESMO guidelines recommend the use of specific anamnestic questions to capture PN (87), as patients may have difficulties describing PN symptoms (167-169). By asking specifically about potential TIPN manifestations, anamnestic information about individual symptoms and impairments may appear more clearly.

In studies during treatment, CIPN is commonly reported by physicians using the Common Terminology Criteria for Adverse Events (CTCAE) scale. CTCAE is provided by the American National Cancer Institute (NCI) (170), and covers a wide range of abnormal clinical findings during
oncologic treatment. In the present version (CTCAE 5.0), grade 1 sensory PN is ‘asymptomatic’ and grade 2 ‘moderate symptoms; limiting instrumental ADL’ (Table 5). In the previous version 4.0, sensory PN included loss of deep tendon reflexes or paraesthesia in grade 1 (171). Dose adjustment is indicated from grade 2, although the scale is insensitive in the lower range.

Table 5.
CTCAE version 5.0

<table>
<thead>
<tr>
<th>Grade</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Paraesthesia</td>
<td>Mild symptoms</td>
<td>Moderate symptoms; limiting instrumental ADL</td>
<td>Severe symptoms; limiting self-care ADL</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Sensory peripheral neuropathy</td>
<td>Asymptomatic</td>
<td>Moderate symptoms; limiting instrumental ADL</td>
<td>Severe symptoms; limiting self-care ADL</td>
<td>Life-threatening consequences; urgent intervention indicated</td>
</tr>
<tr>
<td></td>
<td>Motor peripheral neuropathy</td>
<td>Asymptomatic; clinical or diagnostic observations only</td>
<td>Moderate symptoms; limiting instrumental ADL</td>
<td>Severe symptoms; limiting self-care ADL</td>
<td>Life-threatening consequences; urgent intervention indicated</td>
</tr>
</tbody>
</table>

The low inter-observer reliability and low sensitivity to change decreases the sensitivity of the CTCAE scale (166, 172), even if trained staff probably capture the symptoms better (173). Underreporting of toxicities by physicians is higher in symptoms that could possibly be caused by the disease and less so for potential adverse effects. Even symptoms that patients graded as ‘very much’ were underreported in 13%-50% of patients by physicians (174).

Nerve conduction studies (NCS) provide information on physiological function of large, myelinated nerve fibres. Taxanes cause neuropathy by inflammatory mechanisms, length-dependent axonopathy and demyelination, leading to both diminished action potentials and nerve conduction velocity, noticeable in sensory neurons before reported in PROM measures (73, 175). NCS is though uncomfortable and inconvenient since a need for referrals, and small fibres cannot be examined. Composite scores combining
symptoms, objective scoring, and neurophysiological parameters, such as the different versions of the Total Neuropathy Score (TNS), have wide measures and improves separation of toxicity levels (176), although require more resources.

Patient-reported outcome measures

PROM instruments (questionnaires) have been developed and undergone psychometric assessment to enable comparisons between study populations. The main aspects in psychometric assessment as defined by the COSMIN guidelines (177) are:

- Reliability, whether the questionnaires are robust and measure the same thing irrespectively of the age, sex, educational level, or language of the respondent.
  - Internal consistency: to what degree the items are interrelated.
- Validity, whether the questionnaire concerns the accuracy of measuring what was intended to be measured (the construct) and nothing else.
  - Content validity, whether all aspects of the construct are reflected.
  - Face validity, whether it is understandable to respondents and reflects the construct.
  - Criterion validity: are responses predictable in relation to severity.
  - Construct validity: is the measurement related in a coherent way to other measures.
  - Cross-cultural validity, or whether it remains valid across cultures or after translation.
- Responsiveness evaluates whether the instrument measures change in a clinically meaningful way, which is an important aspect both during treatment and in follow-up.
- Interpretability: concerns whether the resulting scores provide qualitative meaning.

Recently 13 PROMs were evaluated, concluding a recommendation of CIPN20 and FACT/COG-NTX (described below) for use in research, as these two were most psychometrically sound (178). NCI recommends
EORTC CIPN20 to enhance the possibility to compare between studies (179).

**EORTC CIPN20**

CIPN20 was developed by the European Organisation for Research and Treatment of Cancer (EORTC) and contains 20 questions (180); 9 items on sensory symptoms, 8 items on motor symptoms, and 3 items on autonomic symptoms. Two items are conditional—one on driving, and one on erection, which is applicable only to men. All items are graded on a 4-point Likert scale (Appendix II). CIPN20 has good validity for multicultural use (178). Recent evaluation of the instrument has identified some difficulties with items and substructures. Respondents may have difficulties distinguishing between tingling and numbness (167). The autonomic scale is considered less valid, since dizziness and blurred vision correlate poorly with other CIPN20 items and may be associated with comorbidities (181, 182). Social desirability can compromise instrument validity for the item referring driving/pedal use, since respondents may worry that the answer could lead to advising them against driving (183). One item pertains to hearing loss, but ototoxicity is mainly associated with cisplatin. Abbreviated versions have been suggested, if used in clinical practice shorter versions would improve usability (167).

**FACT/COG-NTX**

FACT/COG-NTX was developed by FACIT (Functional Assessment of Chronic Illness Therapy) (184), an American organisation on health outcome measurement methods in collaboration with the Gynaecologic Oncology group. FACT/COG-NTX contains 11 questions and is a stable instrument correlating with quality of life and objective neuropathy (185). It uses a 5-point Likert scale and an increase of 4-6 points (indicating worsening of symptoms) correlates to one grade in the CTCAE scale (89). The questionnaire differs from CIPN20 in several aspects: tingling and numbness is a joint item, and it asks about discomfort instead of burning pain. It has two items on ototoxicity and one on sensitivity to cold (mainly associated with oxaliplatin). The questions on impairment differ from CIPN20 in that no distinction is made regarding whether difficulties walking are due to weakness or
due to decreased sensitivity. Less than a 5-points increase of FACT/COG NTX has been used as outcome measure in intervention trials (147, 186).

The instrument FACT Taxane includes 11 PN items and 5 additional items on oedema and nail toxicity. Sleep disturbance, balance impairment and reduced physical activity are CIPN related consequences, not included in neither of the PROM instruments (178). Recently minimal important differences and threshold values to interpret score changes have been suggested for both CIPN20 and FACT/COG-NTX (173).

**Assessment of health-related quality of life**

Measures of QoL study the patient’s perspective in relation to a range of areas in the patient’s life, and are both subjective and multifactorial. The actual functional level of the patient is in relation to the patient’s expected functional level (187), expectations which can change over time. Response shift, the cognitive process adapting to situations over time, includes recalculation and reprioritisation, leading to a re-conceptualisation of what quality of life means for the patient (188). It is dependent on antecedent factors, such as personality and sociodemographic but is influenced by mechanisms like coping, social support and reframing of expectations (189).

EORTC Quality of Life Questionnaire Core 30 (QLQ-C30) is the most widely used instrument in measuring patient-reported quality of life in oncology (190). The instrument comprises 30 items that can be summarised in different scales (Table 6). Five functional scales i.e., physical, role, emotional, cognitive, and social functioning, one item on financial difficulties, eight symptom scales and two items on global health status/QoL (GHS/QoL). A similar instrument to QLQ-C30 is FACT-G by FACIT including 27 questions (191). A challenge in HRQL research is that instruments need to be fast and easy for the respondent, but still comprehensive and clinically relevant.
Table 6.
The items of global health status/quality of life, functioning scales, and financial difficulties in EORTC QLQ-C30 (192).

<table>
<thead>
<tr>
<th>QLQ-C30 scale</th>
<th>Items</th>
</tr>
</thead>
<tbody>
<tr>
<td>Global health Status/Quality</td>
<td>How would you rate your overall health during the past week? How would you rate your overall quality of life during the past week?</td>
</tr>
<tr>
<td>of life</td>
<td></td>
</tr>
<tr>
<td>Physical function</td>
<td>Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase? Do you have any trouble taking a long walk? Do you have any trouble taking a short walk outside of the house? Do you need to stay in bed or a chair during the day? Do you need help with eating, dressing, washing yourself or using the toilet?</td>
</tr>
<tr>
<td>Role function</td>
<td>Were you limited in doing either your work or other daily activities? Were you limited in pursuing your hobbies or other leisure time activities?</td>
</tr>
<tr>
<td>Emotional function</td>
<td>Did you feel tense? Did you worry? Did you feel irritable? Did you feel depressed?</td>
</tr>
<tr>
<td>Cognitive function</td>
<td>Have you had difficulty in concentrating on things, like reading a newspaper or watching television? Have you had difficulty remembering things?</td>
</tr>
<tr>
<td>Social function</td>
<td>Has your physical condition or medical treatment interfered with your family life? Has your physical condition or medical treatment interfered with your social activities?</td>
</tr>
<tr>
<td>Financial difficulties</td>
<td>Has your physical condition or medical treatment caused you financial difficulties?</td>
</tr>
</tbody>
</table>

The breast cancer instrument EORTC QLQ-BR23 (193) update from 2020 (194) now includes two items on PN ‘Have you had tingling/numbness in your finger or toes?’ and ‘Have you had pain in your hands or feet?’. The instrument covers surgery, ongoing chemotherapy, and more detailed questions on endocrine treatment. Interestingly, the new version includes two blank items to cover unknown side effects of future treatments.

To evaluate factors impacting HRQL, normative values in populations are published. In Sweden, factors which negatively impact QLQ-C30 results were unemployment (decreased emotional function and GHS/QoL) and
having several comorbidities or higher age (except for emotional function). Higher income or male sex were associated with higher physical function (195).

QLQ-C30 can be reported as a summary score that includes all items, except global health items and financial difficulties. It is shown to be a robust way of reporting results (196) and has been correlated with survival in cancer patients (197). To distinguish between clinically important differences and not mere statistical differences, two different guidelines have been developed. Cocks et al. used a combination of published studies, blinded expert opinions and meta-analyses to estimate trivial, small, medium, or large differences in cross-sectional and longitudinal studies. The range of clinical important difference (CID) depends on the subscale and ranges from 9 (CF) to 19 (RF). The EF subscale was omitted due to the median estimate being lower than the estimate for small effects (198). The grades of CID are:

- Large: unequivocal clinical relevance
- Medium: likely clinically relevant but to a lesser extent
- Small: subtle but nevertheless clinically relevant
- Trivial: to describe, but not relevant

The second guideline, by Giesinger et al. suggest thresholds for clinical importance (TCI) and contributes with the possibility of using QLQ-C30 in clinical practice and in research to report prevalence rates. It is based on cancer patients anchoring the items in terms of clinical importance. Thresholds are available for the functioning scales, symptoms scales and financial difficulties (199).

**Pharmacogenomics of TIPN**

Germline pharmacogenetic tests identify genetic variants that affect drug response to enable personalised treatment for optimal efficacy and to avoid side effects; however, the use of pharmacogenetic tests is still limited (200). *DPYD*, the gene coding for the enzyme metabolising fluorouracil, is probably the most widely analysed pharmacogene in oncology. Fluorouracil is rapidly metabolised by *DPYD* in most patients, but about 4% carry variants in the gene that leads to a lowered metabolism, and therefore increased exposure for the drug. To avoid toxicity, the dose needs to be adjusted (201). Patients that are homozygotes of variants with low metabolism —
carrying a great risk of severe toxicity and death—are also identified. Even if the increased toxicity risk due to DPYD gene variants has been known for a long time, it was not until 2020 that routine DPYD testing before treatment with fluorouracil was recommended by the European Medical Agency (EMA) (202). Capecitabine (oral fluorouracil) is used in TNBC in the adjuvant setting and in all subtypes of ABC.

In order to implement pharmacogenetic tests in the clinical practice there is a need to measure the biomarker accurately (analytic validity), divide the patients into groups that have differences in toxicity (clinical validity), and provide evidence that test results contribute to improved management of patients, compared to those who went without testing (clinical utility). In addition, a good infrastructure for rapid test results and updated guidelines for clinical interpretation are essential (200, 203). A pharmacogenetic test can detect a risk of toxicity caused by an increased sensitivity to the drug’s side effect, and a dose reduction can then lead to lower efficacy. If possible, the use of another drug may be preferred. If a genetic variant instead leads to an increase in the drug concentration, efficacy is maintained, even if a lower dose is prescribed to decrease toxicity (204).

Pharmacogenetic panels of several drug-related genes are under development. Recently a large real-world study showed clinical utility of a 12-gene panel which identified actionable variants in >90% of the patients (N=6944). A decent proportion (30%) of clinically relevant drug-related adverse events were avoided in the study, even if they were only measured over a short time. Two anticancer drug-related genes were on the panel; DPYD and UGT1A1 (associated with haematological toxicity from irinotecan), and both showed clinical utility (205). This suggests that pharmacogenetics is both feasible, provides fast analysis and is highly relevant in decreasing morbidity. In a study of patients with advanced solid cancers (N=481), 13 pharmacogenes were analysed and during 3 years follow-up, 14% carried an actionable gene variant (defined by a guideline for dose adjustment by Clinical Pharmacogenetics Implementation Consortium (CPIC)), and had a prescription for that drug (206). Pharmacogenetic analysis is preferably done in normal tissue due to potential confounding genetic alterations which may be present in tumour tissue (for example loss of heterozygosity) (207). Each patient only requires one test to guide all future prescriptions, since it is a germline analysis.
For TIPN, in contrast to fluorouracil and irinotecan toxicity, no single predictive gene has been identified. A systematic review and meta-analysis of TIPN pharmacogenetics recently stated that few of the identified genetic variants have been replicated in other studies. Since long-term follow up of TIPN is scarce, the phenotype was acute TIPN during treatment. The meta-analysis of TIPN included 19 studies (6246 participants) and 60 single nucleotide variants (SNVs) in 23 genes. Thirteen SNVs (11 genes) were significantly associated with acute TIPN (99). A need for a future polygenic approach was suggested, suggesting that rather than finding one predictive gene for TIPN, the background is probably pharmacogenomic—a complex combination of multiple genes and variants each with a small-to-modest effect (99, 207, 208).

The genes associated with TIPN were predominantly involved in liver metabolism or nerve function (Figure 4) (99). In the liver, \textit{ABCB1} codes for the efflux pump P-glycoprotein, and cytochrome enzymes are responsible for drug metabolism. In the nerve cells, the \textit{EPHA} genes (involved in nervous system development and axon guidance) and \textit{TURBB2A} (coding for β-tubulin and linked to transport in neurons) were significantly associated with acute TIPN. Other SNVs with a function likely to be associated with TIPN were \textit{CYP1B1} that binds taxanes in extrahepatic organs and \textit{GSTP1}, which inactivates toxic substances. Four genes with SNVs that were significant in the meta-analysis have unknown effects (\textit{BCL6, CAND1, FZD3} and \textit{XKR4}). Populations in pharmacogenetic studies of TIPN have mostly been exposed to paclitaxel. The meta-analysis included five studies that used broad genetic methods, Genome-Wide Association Studies (GWAS), based on 4 populations (209-213).

Previously, most TIPN studies have been of candidate genes, or prespecified genes with likely associations. Candidate gene studies can include larger populations more cost-effectively, and through this, target uncommon variants (214), even if uncommon variants represent only a small fraction of the therapy-associated toxicity (207). GWAS detects associations in an unbiased manner, but is less apt at quantifying them (208, 215), so further analysis of GWAS results is needed to identify the clinically relevant variants. Pharmacogenetic tests can also be combined with analyses of enzyme activity or pharmacokinetic tests to determine the resulting phenotype, and whether the variant affects the drug metabolism or increased sensitivity to toxicity. However, other clinical and metabolic factors can influence the final phenotype as well.
Figure 4. Subcellular location and function of proteins coded by the 23 genes included in the meta-analysis (except XXR4) by Guijosa et al. and that might be involved in taxane-induced peripheral neuropathy (TIPN). Genes associated to the liver in brown, to nerves in green, black not specified. Genes which had SNVs significantly associated with TIPN in meta-analysis are underlined. Gene function and figure from Guijosa et al. (99). Figure published under the terms of Creative Commons Attribution-Non Commercial.
Anticancer drugs are the most studied in pharmacogenetic GWAS, and in 40% of studies, the studied outcome was adverse drugs reactions (ADR). Among these ADRs, CIPN was most common, so despite the scarcity of broad genetic data, it is relatively well-represented in comparison to other toxicities. European decent is overrepresented in pharmacogenetic studies, however ethnic variations have been detected in TIPN. A challenge in both pharmacogenetic/genomic research is that only a limited proportion of patients treated with a drug carry a genetic variant or variants with a greater risk of the toxicity phenotype of interest, which leads to relatively small study populations even when starting with a larger sample. On the other hand, dysfunctional genetic variants may be rather common and have larger effect size, since pharmacogenes are under low selective pressure (208, 216). A possible objection against the use of pharmacogenetics to guide treatment is that while adjusting the dose to decrease the side effects, the tumour response may be jeopardised. For TIPN, no association between neuropathy and outcomes (DFS and OS) was seen in Sparano et al.’s study of adjuvant taxane treatment, even though necessary dose reductions had been made (49). This supports that predictive biomarker testing for the risk of TIPN is not predictive of treatment efficacy.

Since there is no golden standard for assessing TIPN, previous studies use different outcome measures limiting the consistency of phenotypes. NCI expert panels have also suggested differentiating CIPN into its sensory and motor subtypes to investigate pathophysiological mechanisms (179). The toxicity phenotype must be clearly defined, clinically relevant, and measured using standardised criteria (207). Consistent phenotype definition is fundamental to the accuracy of results (217).

Next generation sequencing

Next generation sequencing (NGS) sequences thousands or millions of DNA regions at once. It has been available since the early 2000 and is also called massive parallel sequencing. Other methods for genetic analysis are Sanger sequencing to analyse one gene and PCR methods to analyse several prespecified variants of genes. Microarray is used to study mRNA expression in gene expression analysis (PAM50/Prosigna®, oncotype DX®).

In NGS, after the DNA has been extracted, it is fragmentated to be suitable for massive parallel sequencing. During the library preparation the fragments are usually ligated with sequencing adaptors, for amplification,
enrichment and/or sample/cell identification. Enrichment and/or amplification can be performed using multiple techniques such as mate-pair amplification, hybridization and/or polymerase chain reaction (PCR) amplification. The most common sequencing technique today is sequencing by synthesis where the identity of millions of single DNA strands of interest are determined. After the sequencing the reads are aligned to the human genome and using bioinformatic tools quality assurance are determined and variations in the DNA sequences are identified (218).

Multigene panels can be of different sizes, focusing on specific genes or compromised of broad panels covering hundreds of genes. Depending on the clinical or research question, either somatic mutations in tumour tissue or germline variants in normal tissue (often blood) are sequenced. The broadest genetic method is whole-genome sequencing (WGS), about 23,500 genes and all the non-coding regions. Whole-exome sequencing (WES) studies the protein-coding part of the genome, which consists of about 1%-2%. The method covers about 90% of the exomes, so relevant genes can still be undetected (219). Single nucleotide polymorphisms (SNPs) (SNVs that are present in more than 1% of the population) are usually studied in candidate gene analyses, and SNPs can be found either in coding or non-coding DNA. The SNVs identified outside the coding regions are usually not the variants which cause the effect on the protein structure (although splice variants affect the protein-sequence), but are rather linked to missense variants or affecting gene regulation of the causal variant, which is most likely is positioned in the coding sequence (219).

To filter out the relevant SNVs after broad sequencing with WGS/WES online genetic resources are used. ConsensusPathDB-human (CPDB) is used for over-representation analysis of SNVs to find relevant pathways (220). Pathway analysis by Kyoto Encyclopaedia of Genes and Genomes (KEGG) is a resource linking genes to networks of biological function (221). Combined Annotation-Dependent Depletion (CADD) is used to annotate a SNV or insertion/deletion for its deleteriousness by using 60 genomic features which, through machine learning, leads to a prediction of deleteriousness called a ‘CADD’ score. The cutoff in CADD score filters out how likely it is for an SNV to be of clinical and research importance (222). PLINK is an open resource, a toolset for whole-genome association analysis, used to find association between SNVs and insertions/deletions in genes or regions and outcome in large datasets using sequence kernel association tests (SKAT) (223). Permutation testing is a method used to compare association testing
with the real outcome against a fictive outcome to determine true associations.

**Polygenic prediction models**

Polygenic prediction models or risk scores, consisting of many variants with small effect sizes, can predict complex traits comparable to the risk prediction of monogenetic rare variants, but are applicable to more patients (224). The basic factors for successful models are a specified population with adequate and unbiased data on genotype as well as a clearly defined phenotype. Most polygenic scores predict disease risk. A systematic review of pharmacogenetic polygenic risk score studies found the majority to concern psychiatric medications (n=30) and only 3 studies regarded anticancer drugs (225). There is a lack of studies comparing risk scores/prediction models with clinical predictors, as well as validating prediction models in an independent cohort. Genetic variance between populations of different ancestry may impact how well models perform; to date, most are based on European ancestry (208, 225).

**Polyneuropathy in the general population**

Prevalence rates of polyneuropathy are 0.1%-12.6% in all ages in the general population and 1.9%-30.9% in the elderly (125). Rates vary depending on measurement method and population, and polyneuropathy is more commonly reported in women and in Western countries. The main risk factor is diabetes mellitus, present in 1/3 of patients (226, 227). Other known risk factors include nutritional deficiencies such as vitamin B deficiency, thyroid dysfunction, alcohol overconsumption, cytostatic drugs, or related to systemic disease (cardiovascular disease, autoimmune disease, monoclonal gammopathy), hereditary factors (125) and use of vibrating hand tools (228). Nevertheless, idiopathic polyneuropathy is the most common diagnosis (125, 227). A common exclusion criterion in CIPN research is hereditary Charcot-Marie-Tooth disease, an autosomal dominant disease with a prevalence of 18/100 000. Severity varies, but Charcot-Marie-Tooth disease causes numbness and later muscle weakness (229).
HYPOTHESIS

Self-reported peripheral neuropathy is more prevalent, and severe, in breast cancer survivors previously exposed to taxane chemotherapy than in women without prior cancer.

Life-style factors and co-morbidities are risk factors for persistent taxane-induced peripheral neuropathy among early-stage breast cancer survivors.

Persistent taxane-induced peripheral neuropathy symptoms impact health-related quality of life among early-stage breast cancer survivors, compared to survivors without neuropathy.

Polygenic prediction models including clinical risk factors can estimate the risk for individual symptoms of persistent taxane-induced peripheral neuropathy.
AIMS

Overall aim
The overall aim of this thesis was to study the prevalence and severity of taxane-induced peripheral neuropathy among long-term early-stage breast cancer survivors and to investigate the impact on quality of life as well as to explore clinical and genetic risk factors.

The specific aims were:
To explore the prevalence and severity of self-reported symptoms of peripheral neuropathy among early breast cancer survivors treated with (neo-)adjuvant taxane-based chemotherapy at least two years earlier and compare the occurrence with that of women from the general population without a cancer diagnosis (Study I).

To explore clinical risk factors for taxane-induced peripheral neuropathy among early-stage breast cancer survivors (Study I).

To investigate the impact of sensory and motor taxane-induced peripheral neuropathy symptoms on health-related quality of life among long-term early-stage breast cancer survivors with persistent taxane-induced peripheral neuropathy compared to ESBC survivors without the symptoms (Study II).

To explore genetic risk factors for persistent symptoms of taxane-induced peripheral neuropathy and to develop polygenic prediction models, including clinical risk factors to predict persistent symptoms of taxane-induced peripheral neuropathy among early-stage breast cancer survivors (Study III).
"Säll är den som har till rättssöre, 
att man nog bör tänka efter före."

- Tage Danielsson
MATERIAL AND METHODS

Study design

Cross-sectional study of a population-based cohort, followed by an explorative genetic sub-study.

Study population

The study population is based on a cohort of women diagnosed with breast cancer between January 1, 2010 and June 30, 2015 in the Southeast Health Care Region, Sweden. Inclusion criteria were women \(>18\) years, diagnosed with early-stage (T1-3, N0-2) invasive breast cancer (ICD10 C50.0-50.9) and treated with at least one dose of taxane in (neo-)adjuvant treatment and not lost to follow-up. Exclusion criteria were male sex, more advanced stage of disease, other malignancies (except cervical carcinoma in situ and basal cell carcinoma), recurrent disease, contralateral breast cancer, and lost to follow-up. The cohort of women with a breast cancer diagnosis was linked with the chemotherapy prescription system to identify those treated with (neo-)adjuvant taxane and medical records were screened to exclude more advanced stage of disease or recurrence. After excluding non-eligible women, 884 survivors remained. The latest follow-up date for vital status was August 25, 2017. Each eligible breast cancer survivor was matched for birth year and residency with up to four individuals from the Swedish Population Registry and controlled against the National Cancer Registry to exclude those with prior or current malignant disease. Two survivors per ESBCS were included. Birth year was the only information included from the registry regarding the controls.

A digital code key of study-specific numbers and the corresponding personal identification number was constructed for ESBCS and handled separately from the study data. The postal questionnaires were marked with a study-specific code for each survivor and control woman. The medical records of ESBCS who returned the questionnaire and consented to participate in the study were reviewed for data on tumour and treatment, leading to the exclusion of study participants due to more advanced stage or recurrence of disease. The genetic sub-study consisted only of ESBC survivors. For a flow chart of study participants in studies I-III see Figure 5.
Figure 5.
Flow chart of study participants studies I-III.
The National Cancer Register was used to identify all breast cancer cases between 2010 and 2015 and to exclude control women with a cancer diagnosis. The coverage of malignant tumours is >95%, of which 99% have been verified histologically (230). The chemotherapy prescription system CSAM Cytodos software is used for chemotherapy prescription and administration. Women treated with taxanes could be identified using the CSAM Cytodos software system. It was implemented in Region Jönköping County and Region Östergötland (Linköping) in 2009 and in Region Kalmar County from 2010 on, and therefore additional screening of medical records was done to include early 2010 cases in Kalmar. For a flowchart of data collection see Figure 6.

Study-specific questionnaire

A study-specific questionnaire for ESBC survivors was constructed consisting of 134 questions. It included three validated instruments of a total of 64 questions:

- European Organisation for Research and Treatment of Cancer (EORTC) Quality of life questionnaire Core30, QLQ-C30 (version 3.0) (190)
- EORTC Chemotherapy-induced peripheral neuropathy, CIPN20, questionnaire (180)
- HADS Hospital Anxiety and Depression Scale (231)

EORTC QLQ-C30 (30 items) was chosen due to its strong psychometric properties (232-234). It includes a scale for global health status (GHS)/quality of life (QoL); the five functional scales, i.e., physical (PF), role (RF), emotional (EF), cognitive (CF), and social functioning (SF); and one item on financial difficulties (FI), see Table 6, and eight symptom scales (fatigue, nausea/vomiting, pain, dyspnoea, insomnia, appetite loss, constipation, diarrhoea). Each item is measured on a four-point Likert scale ranging from ‘not at all’ to ‘very much’, except for the GHS/QoL scale, which ranges from poor to excellent (1-7) (Appendix I).

EORTC CIPN20 (20 items) was chosen as the primary outcome measure due to its reported strong psychometric properties supporting validity and reliability (discussed above) (167, 181, 235, 236). Like QLQ-C30, each item is measured on a four-point Likert scale (Appendix II).
### Timeline of Data Collection

<table>
<thead>
<tr>
<th>Year</th>
<th>Event Description</th>
</tr>
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<tbody>
<tr>
<td>2017</td>
<td><strong>Registry Phase</strong>&lt;br&gt;Registery Cytodos Linköping Jönköping/Kalmar for taxane exposure</td>
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<tr>
<td>2018</td>
<td><strong>Screening Phase</strong>&lt;br&gt;Screening of medical records to identify residual free early-stage breast cancer survivors&lt;br&gt;Exposed cases N=884&lt;br&gt;Invitation letter + questionnaire (2 weeks)&lt;br&gt;Reminding letter (2 weeks)&lt;br&gt;Response rate 77/100, 79%&lt;br&gt;Pilot study &lt;br&gt;Response rate 60/100, 59%&lt;br&gt;Full study&lt;br&gt;Control women N=1040&lt;br&gt;Study I</td>
</tr>
<tr>
<td>2019</td>
<td><strong>Data Extraction</strong>&lt;br&gt;Variables from medical records and Cytodos N=697 Linköping /Jönköping/Kalmar&lt;br&gt;Invitation to genetic sub-study&lt;br&gt;Collection of blood samples N=362&lt;br&gt;Extraction of DNA</td>
</tr>
<tr>
<td>2020</td>
<td><strong>Sequencing</strong>&lt;br&gt;Exome sequencing of samples&lt;br&gt;Quality assurance and bioinformatics</td>
</tr>
<tr>
<td>2021</td>
<td><strong>Included study population</strong> N=337, Study III</td>
</tr>
</tbody>
</table>

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Figure 6.<br>Timeline of data collection.
The hospital anxiety and depression scale (HADS) contains 14 items. For questions on physical activity and alcohol consumption, questions from the Swedish survey on health and living conditions were used and assessed as specified by Olsson et al. (237) and Bush et al. (238).

Potential risk factors for pre-existing peripheral neuropathy and plausible confounding factors were explored in a comprehensive literature search: demographics, reproductive and menopausal status, life-style factors, comorbidities, and the use of vibrating hand tools. Study-specific questions concerning risk/confounding factors, treatment-related side effects (i.e., alopecia, joint pain, vasomotor symptoms, lymphoedema), questions which further explore the impact of PN and finally, questions on the respondents’ (ESBCS’s) personal experience of answering the postal questionnaire were included. Some questions were open for the respondent to write a comment. The study-specific questions were tested for face validity. A total of ten individuals (survivors and experienced healthcare professionals) were asked to read and comment on the content and phrasing to ensure the relevance and the intelligibility of the questions. Questions were adjusted successively until no further comments were made. The matched control women received a questionnaire that consisted of 120 questions since items on chemotherapy-induced side effects were not included. Not all questions were analysed in this thesis.

A pilot study of 100 breast cancer survivors and 100 controls was performed in September to October 2017 to explore whether a response rate exceeding 60% for survivors and 50% for control women was achievable. An introductory letter and a questionnaire were sent to eligible survivors and two matched cancer-free women, since we anticipated a lower response rate among controls. The results showed a response rate of 77% and 60%, respectively. After this, the questionnaires for the remaining eligible women were sent out (October 2017 to January 2018). Up to two postal reminders (the second also including a questionnaire) were sent out to non-responders within a total time frame of five weeks. The university printing service at Linköping University (LiU tryck) performed the logistics. All pages from the questionnaire were scanned and a computer software program was used to transform this data to Excel, the excel file was transferred to SPSS. For quality assurance of data, all missing data in the SPSS file was checked in the scanned questionnaires, and data completed from the scanned files if missing due to failing data transformation. Study participants consented to the study by returning the postal questionnaire.
Tumour and treatment variables from medical records

In the inclusion phase of the study, the medical records of all respondents were reviewed through the use of a case report form (CRF) for details on tumour characteristics and treatment. The TNM staging classification (7th Edition) for pathological stage was used (7). In case of neoadjuvant treatment, pre-treatment tumour size and the largest number of clinical or pathological lymph nodes was used as a basis for staging. Grading in pathology reports was done in accordance with the Nottingham Histologic Grade Score system (239). The limit for positive immunohistochemical staining for oestrogen-receptor (ER) and progesterone-receptor (PR) was set at >10% positive tumour cells, according to national guidelines. Medical records were the source for pathology reports, data on final surgical intervention, treatment fields for radiotherapy and planned endocrine treatment. The CSAM Cytdos prescription system was used to extract details chemotherapy treatment including dates, dose delays, dose reductions, height, and weight at time of treatment. Information on HER2 treatment and additional chemotherapy treatment was also extracted. Taxane regimens of docetaxel and paclitaxel were considered interchangeable in the guidelines at the time and depended on local preferences. Data from CRFs were manually transferred to SPSS.

Study III: the genetic sub-study

In the questionnaire ESBC survivors (respondents) were asked whether they agreed to be contacted again. An invitation letter including an offer to get in contact with a study nurse and doctor to ask additional questions regarding the study, was sent out together with a patient information sheet, and a consent form to return. Two reminders were sent. The clinical trial unit in Jönköping coordinated the study. Participants contributed with a blood sample drawn at their primary health centre and gathered at Linköping University Hospital. Oestrogen levels were analysed in the local laboratory (not further explored). DNA was extracted from blood samples at the research laboratory using Maxwell® Instrument and purification kit. Sequencing libraries were prepared from 50ng of DNA per sample. The genetic sequencing was performed by the SNP&SEQ Technology Platform in Uppsala in the quality assured and accredited (ISO/IEC 17025) National Genomics Infrastructure (NGI) Sweden and Science for Life Laboratory ensuring secure and accurate genetic data. Raw sequencing reads were aligned with the human
reference genome (GRCh38) and quality assurance of the sequencing was performed.

**Statistical methods and analysis**

Power calculation to determine the required sample size was based on the assumption that the risk of peripheral neuropathy among breast cancer survivors previously treated with a taxane is increased compared to healthy controls. The estimated neuropathy prevalence of 7% among the unexposed group of cancer-free women and 15% among long-term breast cancer survivors was based on previously published epidemiological and follow-up data (85, 125, 226). The calculation used the following parameters: a two-sided log-rank test, with 80% power and a 5% significance level, which showed that 540 survivors would be needed (1:1 ratio). Power calculation for Study III was not performed due to the explorative methodology.

Statistical analyses were performed using IBM SPSS version 25 (Study I), 26 (Study II) and Stata SE version 16.1 for Poisson and binomial regressions (Study I). For building and validation of prediction models, R version 4.0.3 was used (Study III). Tests were two-sided and p values were regarded as significant if the p-value was <0.05.
Study I

Statistical analysis: Descriptive statistics for characteristics of the study population and comparison between ESBC survivors and control women using Student’s t-test for continuous variables and the chi-square test or Fisher’s exact test for categorical variables. Prevalence rates of PN symptoms were described and different cut-off levels were used. For the primary analysis, symptoms were dichotomised into either having the symptom ‘a little’, ‘quite a bit’ or ‘very much’ or not having had the symptom in the past six months. The response categories ‘quite a bit’ and ‘very much’ were considered moderate–severe symptoms.

Poisson regression (240) was used to calculate unadjusted and adjusted relative risk (RR) with 95% confidence intervals (CIs) for persistent TIPN. Adjustments were made using 14 plausible confounding factors: the continuous variables age and BMI, and the categorical variables, alcohol consumption, folic acid deficiency, B12 deficiency, joint pain, osteoporosis, thrombosis, treatment for diabetes mellitus (DM), autoimmune disease, cardiovascular disease, menopausal status, exogen oestrogen and the use of vibrating hand tools.

Item mean scores and standard deviations were calculated (students t-test). Adjusted mean scores were calculated by linear regression using the same covariates as in the logistic regression. We explored whether time since completing taxane therapy had an impact and used the median time since treatment of 3.6 years as a cut-off.

Binominal regression with univariable or multivariable analysis were used for investigation of risk factors. In the univariable analysis the following variables were included: type of taxane (docetaxel vs. paclitaxel), age at diagnosis (<65 vs. ≥65 years), BMI at diagnosis (<25 vs. ≥25), receiving treatment for DM (no vs. yes), use of vibrating hand tools at work (no vs. yes), autoimmune disease (no vs. yes), alcohol risk consumption (none vs risk consumption), cardiovascular disease (no vs. yes), current smoking (no vs. current smoker), mastectomy (no vs. yes) and lymph node metastases (N0 vs. N1, N0 vs. N2). Only predictive factors with a statistically significant association (p< 0.05) with an individual symptom were entered into the multivariable model. Individuals with missing data were excluded from the calculations of each respective outcome.
Material and Methods

Study II

Method: ESBC survivors (N=646) were divided into reporting or not reporting the different PN symptoms, and comparisons of associated impact on HRQL were made per item/symptom. Based on the results in Study I, only the 13 sensory and motor TIPN symptoms that had significantly higher adjusted RR in ESBCS were further studied. Autonomic symptoms were excluded based on more recent findings of low validity (167). The symptom scales of QLQ-C30 were not considered relevant for the purpose of the study. For interpretation of the clinical significance of statistical differences in HRQL, published guidelines by Cocks et al. and Giesinger et al. were used (198, 199).

Statistical analysis: Scores were linearly transformed to a 0-100 scale (192); a higher score on the GHS/QoL scale and the functional scales means better GHS/QoL and functional health, whereas a higher score on the FI equated with more financial difficulties. The association between TIPN symptoms and HRQL was explored using different cut-off levels. ESBC survivors were dichotomised into not having the symptom or reporting the symptom over the past six months. The unadjusted mean scores (standard error of the mean, SE) of GHS/QoL, functional scales, and FI were calculated and tested using the student’s t-test. Linear regression analyses were adjusted for 13 plausible confounders for differences in HRQL: age, BMI, and civil status, educational level, employment status, alcohol consumption, exercise, smoking, and co-morbidities (musculoskeletal disorders, cardiovascular disease, DM treatment, pulmonary disease and neurological disease). The Bonferroni method was used to adjust for multiple comparisons within each symptom.

Differences in GHS/QoL and functional scales for symptoms of PN were compared using test-of-trend and using quantile (median) regression, among patients reporting different levels of PN. The impact of TIPN symptoms reported as ‘a little’ versus not having the specific symptom, which was explored by quantile regression adjusting for confounding factors (age, BMI at survey, DM treatment).

To further explore the consequences of persistent TIPN, additional questions on actions taken to relieve symptoms, contact with healthcare, sick leave due to TIPN and perceptions of living with TIPN were analysed. Comparisons in additional questions were tested by Pearson’s chi-square.
Figure 7.
Flow chart of method design and prediction model development.
The figure was created in BioRender.com.
Material and Methods

Study III

Method: Previously published genetic variants associated with TIPN, data from WES of the included cohort and clinical risk factors were used to develop separate polygenic predictions models for the five symptoms that showed the largest increased risk compared to controls, with the greatest impact on QoL and with a sufficient number of affected survivors for analysis were included; numbness in feet, tingling in feet, cramps in feet, difficulty opening a jar and difficulty climbing stairs. Each model was tested in a separate test cohort. Step by step the most important variants most likely to be associated with persistent TIPN were filtered out (Figure 7).

- The A1 and A2 models were based on literature data/meta-analysis. The A1 model included the most significant variants of SNVs and genes included in a recent review. The A2 model used SNVs from TIPN related KEGG pathways.

- The B models were based on cohort data. The B1 used overrepresentation analysis, SNV/INDEL analysis using PLINK, a permutations analysis to filter out the SNVs below a specific p-value and CADD score, the B2 model used CPDB for enrichment analysis.

- A1 and B2 models were combined. The C1 model was refined by variable importance to limit the number of included variants, to avoid overfitting the model to the training cohort resulting in C2. The clinical risk factors included were age, taxane type, BMI, and treatment for DM.

Statistical analysis: Logistic regression models were developed. Performance was evaluated using area under curve, accuracy, sensitivity, and specificity. A model was considered optimal when AUC above 80% in the training cohort and above 60% in the test cohort.
Reporting guidelines

The equator network provides checklists to enhance the quality and transparency of health research. The following have been used; Study I STROBE for cohort studies; Study II STROBE for cross-sectional studies (241), and Study III TRIPOD Prediction Model development and validation (242). To date there are no reporting guidelines that are specific to pharmacogenetic models (224, 243).

Methodological considerations

The aim of clinical epidemiology is to make prediction as accurately as possible by counting different clinically important events, abbreviated as the ‘6D’s’ of which all except death are captured in this thesis: the disease polyneuropathy from TIPN; the discomfort of symptoms including tingling, numbness or pain; disability as clinically significant impact on physical function, dissatisfaction as an impact on emotional functional health and destitution, or to what degree TIPN impact personal finances (244).

Different study designs were discussed at the initiation of this thesis project. A retrospective study of TIPN based on medical records was assumed to be unsuccessful, since TIPN data during treatment and after treatment is unspecific or unavailable in the medical records. A prospective study including a sufficient number of patients would take a long time to perform and may lead to dropout, even if longitudinal data had been of the greatest interest. A case-control study was discussed, but not considered suitable, as the aim was to explore the prevalence of TIPN in the population and not correlations with specific exposures to taxane. A comparison with the general population was of importance, which was difficult given the case-control method. The combined approach of a cohort study to identify a comprehensive study population and then a cross-sectional approach to study the outcomes was selected.

ESBC survivors with advanced loco-regional disease (T4,N3) or recurrence were excluded. Recurrence of disease could include exposure to other oncological treatments that could affect CIPN prevalence, and non-curable disease probably affecting HRQL measures. More advanced stage was excluded since the risk of recurrence is high in the case of T4 and/or N3 disease, which we reasoned could possibly lead to acceptance of a higher treatment intensity. During the screening phase of medical records, only
recurrences were noted, leading to questionnaires sent to survivors at more advanced stages of disease who later had to be excluded.

The 2010-2015 time period was chosen based on the incidence of breast cancer and expected proportion of patients offered (neo-)adjuvant chemotherapy, the wider recommendation of taxane in guidelines, and the implementation of the prescription system Cytodos used to identify cases. The term ‘persistent’ is not defined by NCI (245), but an assumption was made that more than two years since treatment would imply persistent symptoms. The outcome occurs after several events, a breast cancer diagnosis with indication for taxane, taxane exposure, development of TIPN and finally persistent symptoms. Even if starting with a large cohort, some symptoms were only reported by a small number of ESBCS.

The patient-reported outcome measures CIPN20 in combination with the QLQ-C30 questionnaire provide detailed information of both CIPN and HRQL. To study persistent symptoms, we chose to change the time frame in the instruments from 7 days to 6 months, since the instruments were developed to capture variation in symptoms during treatment cycles. The autonomic symptoms were not further explored due to lower validity (181, 182). Despite that, the strong psychometric evidence (as described in the background section) for both instruments, an NCI recommendation to use CIPN20 in research (179) and the availability of guidelines to interpret clinical significance of HRQL (198, 199) makes the two instruments the most relevant and appropriate choice for the study, if it were repeated today. At the time of Study I, no guidelines for minimal important differences (MID) or thresholds were available for CIPN20 (182), but some have recently been suggested (173). However, these guidelines suggest two clinical change groups, minimal and clinically significant, and focus on score changes during treatment to adjust doses while excluding CTCAE grade 2 and higher, thus not applicable to our study.

The development of the questionnaire and study design were conducted in collaboration with a statistician and expert on questionnaire methodology (246). We discussed the use of phone calls before sending out questionnaires and as reminder but believed that this would not increase response rates, since we assumed a decreased tendency to answer calls from unknown phone numbers in society. We chose not to have the alternative of a digital questionnaire instead of postal questionnaire, assuming that introducing a choice
for respondents could lead to lower response rates. Today, a digital questionnaire accessible by QR code could have been a viable alternative.

Plausible confounding factors associated with peripheral neuropathy were adjusted for in Study I and factors associated with impact on HRQL were adjusted for in Study II. Even though a wide range of confounding factors were included, it is possible that variables have been overlooked. We chose not to adjust for endocrine treatment in our main analyses, regarding it a treatment and not a life-style factor or comorbidity, even if HRQL might be affected.

Considerations regarding systematic errors

Common systematic errors are difficult to avoid in observational studies and need to be accounted for.

- Selection bias: The breast cancer survivors who responded may differ from the non-responders. The questionnaire was only available in Swedish. ESBCS with higher stage of disease or later ABC were not included. This limits the generalisability of our results.

- Measurement bias: The use of a validated questionnaire intends to limit this type of bias, although symptoms may be overlooked. Reporting separate TIPN items was intended to allow symptom/phenotype definitions that were as comprehensive as possible. By only collecting data via postal questionnaire, could have excluded survivors with problems using a pen.

- Confounding factors: We aimed to adjust for potential factors that could affect outcome, but knowledge on risk factors for persistent TIPN was limited during the time of analysis and we had no information on pre-treatment neuropathy.

- Internal validity: Even if the same or similar taxane regimens are currently being used, the clinical decisions may be slightly different than a decade ago due to increased knowledge on persistent side effects. Chemotherapy combinations and drugs in (neo-)adjuvant treatment has developed over time, which could possibly impact the results if the study were to be conducted again.
• External validity: In a different population, the genetic variants and susceptibility to PN may differ. Use of different regimes may cause variation in taxane exposure.

Genetic methodology and prediction models

A need to shift from candidate gene studies to broader genetic methods has been identified in the literature to identify new TIPN associated genes and genetic variants (207). WES includes all coding genes, but a WGS could have added more information. However, the SNVs outside the exome are usually not the causal variants or are enhancers/promotor SNVs. It is possible that a larger sample size could have contributed to more stable models and a larger test group for validation. A median sample size in pharmaco-genetic studies has been reported to be 1220, and larger sample sizes do not necessarily yield more associations (208), while the DNA sequencing and bioinformatics are resource consuming (214). Validation of polygenic prediction models is often lacking, but it is crucial to evaluate performance. Therefore, we separated the cohort in a training and a test (validation) cohort. The population and outcome need to be clearly defined, which we strived for by including taxane exposed ESBCS and studying the symptoms individually. Variation across ethic groups can be expected, which needs to be explored in future studies.

Statistical considerations

Relative risk is the preferred measure of risk if the outcome is common (>10%), as odds ratios would overestimate risk. Poisson regression can be used in cohort studies with a common outcome and has wider intervals than other models in this situation (240). Results of mean scores for sensory, motor and autonomic scales were not included in Study I, since they were considered to have an unstable factor structure (167) but are here reported in the results section together with kappa values to show variation in responses within each scale. The challenge of multiple comparisons and type I errors has been considered and handled in study II by using Bonferroni, which is considered a conservative method (247). In broad genetic studies, many statistical tests are performed with a risk of false positive results. Previously unknown variants are often identified (214), and there is a risk of both false associations not filtered out despite the use of multiple genetic resources, and the opposite issue—that SNVs with small effect sizes are lost in analysis.
Strengths and limitations

Overview of strengths and limitation in study I-III (Table 7).

Table 7. Strengths and limitations in Study I-II.

<table>
<thead>
<tr>
<th>Study</th>
<th>Strengths</th>
<th>Limitations</th>
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<tbody>
<tr>
<td>I-II</td>
<td>Large population-based cohort</td>
<td>No information on non-responders</td>
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<td></td>
<td>High response rate</td>
<td>Individuals with recurrence were not included.</td>
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<td></td>
<td>Validated questionnaires</td>
<td>Questionnaire only available in Swedish.</td>
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<td></td>
<td>Self-reported PN</td>
<td>Unclear whether persistent since treatment or late occurring symptoms.</td>
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<td></td>
<td>Privately answered questionnaires</td>
<td>No data on pre-treatment co-morbidities</td>
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<td>Detailed data for each symptom</td>
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<td>Low level of missing data</td>
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<td>Access to medical records and chemotherapy prescriptions for adequate</td>
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<td>Only one treated with other neurotoxic chemotherapy</td>
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<td>No other oncological treatment that could impact PN</td>
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<td></td>
<td>Comparison with control group without cancer</td>
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<td></td>
<td>Adjustment for plausible confounding factors</td>
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<tr>
<td>II</td>
<td>Detailed analysis of impact on HRQL per symptom</td>
<td>Multiple comparisons, risk of type I errors</td>
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<td>III</td>
<td>Well-defined and specific phenotype</td>
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<td>Size of study population</td>
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<td></td>
<td>Validation in separate test cohorts</td>
<td>Risk of false positive SNVs without biological connection</td>
</tr>
<tr>
<td></td>
<td>Exposure to currently used taxane regimes</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: PN, Peripheral Neuropathy. HRQL, Health-related quality of life. SNV, Single Nucleotide Variant.
Ethical considerations

The study implicated contact with individuals previously treated for breast cancer up to seven years before the study was initiated, who in some cases had no active contact with the oncology clinic. The postal questionnaire could possibly have a negative impact by focusing on the breast cancer disease, memories of side effects and increasing worry of recurrence. We included questions on how the ESBC survivors experienced answering the questionnaire, and only a few reported negative impacts. More than 80% found it important that studies like this are conducted, see preliminary results, Figure 10. We have no information on how non-responders experienced study invitation and the questionnaire. Despite the risk of negative impact, there is also a possible positive effect in recognition of a symptoms shown to be prevalent but poorly studied, and that the results could lead to enhanced care of future patients. We aimed to keep the contact limited in terms of time and number of reminders. Study participants had the possibility to contact the investigators by phone or via e-mail if they had queries or to decline future contact. A postal questionnaire enabled the participant to answer questions of their own free will and at their own pace.

Study III included a broad analysis of genetic data. We have not extracted information on variants associated with hereditary disease, as this was not the focus of the study, and the study did not include close or further contact with the participants. Thus, genetic data is potentially available, but not reported to the participants from whom having the information might prove potentially advantageous. Extraction of pathological variants associated with hereditary disease would have needed advanced competence in clinical genetics. Adequate information before consenting to participate, and contacting participants to share test results would have been beyond the scope of the study, and risk unwanted and emotionally distressful situations for participants.

A few participants have contacted the study nurse several years after the study to receive more information about the results. Information on the results has been offered to the local breast cancer patient organisations and is planned to be given as a lecture or in written form, depending on patient organisations wishes.
Ethical approval

The cross-sectional study was approved date 2017-01-23 (Ref. no. 2016/548-31) and the genetic sub-study was approved 2018-04-10 (Ref. no. 2018/94-32) by the Regional Ethics Committee in Linköping.
RESULTS

The response rate was 78.8% in ESBC survivors (n=697) and 58.8% in control women (n=1040). After review of medical records, 51 survivors were excluded and 646 ESBC survivors were included in the analysis, see Figure 5. ESBC survivors had higher BMI, were more often postmenopausal and reported more painful joints, osteoporosis, and thromboembolic events than control women. Control women used exogenous oestrogens and operated vibrating tools more often than ESBC survivors. No differences were seen in other life-style factors or co-morbidities.

Mean age at time of survey was 60.7 years in the ESBC survivors and 61.6 years in control women. The most common tumour characteristics were ER positive tumours, 16.7% had triple negative disease, and a third HER2-positive tumours. The majority had tumour sizes of 21-50mm (T2) and 60.1% had metastatic axillary lymph nodes. The majority had undergone mastectomy and radiotherapy. The predominant regimens were three courses of docetaxel every 3 weeks and 12 courses of weekly paclitaxel. One had received carboplatin and two received methotrexate. Median time from the end of taxane therapy to survey was 3.6 years (range 1.5–7.3 years). Current endocrine treatment was reported by 57.2%.

The 13 sensory and motor symptoms with an increased risk among survivors compared to controls in study I, were included in study II. In study II, HRQL (QLQ-C30) among ESBC survivors reporting PN was compared to those not reporting PN, per individual symptom/item of CIPN20. The five TIPN symptoms of moderate-severe grade with the highest relative risk, the largest impact on HRQL and a sufficient number of affected survivors for analysis were explored in study III.

First, the results concerning each of these five symptoms from all three studies are reported coherently per symptom, followed by findings from each study. Last, preliminary results including comparison of TIPN and HRQL in survivors exposed to either paclitaxel or docetaxel, and respondents’ personal experience of answering the postal questionnaire.
Summary of results for selected TIPN symptoms

Numbness in toes and feet

The prevalence of any grade of numbness in feet was 48.1%, compared to 23.7% in the control women, and the adjusted RR was the highest at 1.8 (95% CI 1.5-2.2). The prevalence of moderate-severe numbness in feet was 23.7% compared to 7.1% in control women. The prevalence in ESBCS treated <3.6 years earlier was 28.1% and 19.3% if more time had passed since treatment (compared to controls p <0.001 for both). The adjusted RR was 2.8 (95% CI 2.1-3.7) if <3.6 year since taxane and 2.3 (95% CI 1.7-3.1) if ≥3.6 years had passed.

Independent risk factors were paclitaxel treatment, age ≥65 and BMI ≥25.

Among survivors that reported moderate-severe numbness in feet, the prevalence rate of clinically important impacts on functional health was 41.4%-65.6%, and 30.9% for financial difficulties. The level of clinically important difference (CID) for ESBCS reporting any grade of numbness in feet was of a medium level for GHS/QoL, cognitive and social function (CF, SF), and a small level for physical and role function (PF, RF) and financial difficulties (FI). For survivors reporting moderate-severe numbness in feet, CID was the same, except large for social function.

A prediction model of moderate-severe persistent numbness in feet including 35 SNVs and clinical risk factors (age, BMI, DM, paclitaxel) was developed, with an AUC of 88.9% (CI 95% 83%-91%) in the training cohort and 72.9% (CI 95% 60%-84%) in the test cohort. Based on the performance of the model in the test cohort, 73% survivors of the test cohort were correctly predicted. We could identify a group of patients with a probability of persistent numbness in feet of 47% compared to a low-risk group with only 14% toxicity.

The overlap between moderate-severe numbness in feet and problems standing/walking because of difficulty feeling the ground under the feet was 7.7%, and 18.2% reported discordantly on the two items, see preliminary data, Table 12.
Results

Tingling in toes and feet

The prevalence of any grade of tingling in feet was 48.0%, compared to 23.0% in the control women and the adjusted relative risk (RR) was the highest, at 1.8 (95% CI 1.5-2.1), like numbness in feet. The prevalence of moderate-severe tingling in feet was 23.2% compared to 6.6% in control women. In ESBCS treated < 3.6 years earlier, prevalence was 28.2% and more time had passed since treatment, prevalence was 18.3%, (compared to controls; p<0.001 for both). The adjusted RR was 2.6 (95% CI 2.0-3.4) if <3.6 year since taxane and 2.1 (95% CI 1.5-2.9) if ≥3.6 years had passed.

Independent risk factors were paclitaxel treatment, DM treatment, age ≥65 and BMI ≥25.

The prevalence rate of clinically important impact on functional health among survivors that reported moderate-severe tingling in feet was 38.2%-64.2% and for FI 32.9%. The level of CID for ESBCS reporting any grade of tingling in feet compared to no symptoms was large for SF; medium for CF; and small for PF and RF, FI, and GHS/QoL. CIDs remained the same among survivors reporting moderate-severe tingling in feet.

A prediction model of persistent moderate-severe tingling in feet including 55 SNVs and clinical risk factors (age, BMI, DM, paclitaxel) was developed, with an AUC of 86.0% (CI 95% 79%-90%) in the training cohort and 60.9% (CI 95% 43%-76%) in the test cohort. Based on the performance of the model in the test cohort, 70% survivors of the test cohort were predicted correctly. We could identify at a group of patients with a probability of persistent tingling of feet of 33% compared to a low-risk group with only 14% toxicity.

The overlap of ESBCS reporting both moderate-severe tingling in feet and numbness in feet was 18.6%; therefore 9.8% reported discordant levels of these symptoms. The overlap of increased (‘plus’) sensory symptoms was explored, most ESBCS reporting moderate-severe burning/shooting in hands also reported tingling in hands (6.9%), like burning/shooting in feet and tingling in feet (10.6%), see preliminary data, Table 12.

Cranps in feet

The prevalence of any grade of cramps in feet was 56.4%, compared to 38.1% among control women; the symptom with the second-highest prevalence and similar in prevalence regardless of time since treatment (<3.6 years
55.0%, $\geq 3.6$ years 57.5%). The adjusted RR was 1.5 (95% CI 1.2-1.7). The prevalence of moderate-severe cramps in feet was 25.9% compared to 10.2% in control women and similar regardless of time since treatment (25.3%, 26.4%). The adjusted RR was 2.0 (95% CI 1.5-2.6). The only independent risk factor found was age $\geq 65$.

Among survivors that reported moderate-severe cramps in feet the prevalence rate of clinically important impact on functional health was 31.9%-63.3%, and for FI it was 29.5%. The level of CID for ESBCS reporting any grade of cramps in feet was small for GHS/QoL, RF, CF and SF and trivial for PF and FI. The levels of CID for survivors reporting moderate-severe cramps in feet, was medium for CF and SF and small for the other scales.

The developed prediction model for cramps in feet could not be validated in the test cohort.

Preliminary data show that ongoing endocrine treatment was associated with reporting moderate-severe cramps in feet ($p<0.001$), 23.0% of those reporting ongoing AI treatment and 35.3% reporting tamoxifen treatment reported moderate-severe cramps in feet, compared to 18% with no endocrine treatment. Survivors with no endocrine treatment, however, reported moderate-severe cramps in feet more often than control women (18.2% vs 10.2% $p<0.001$).

**Difficulty opening a jar or a bottle because of weakness in hands**

The prevalence of any grade of difficulty opening a jar was 61.3% compared to 48.0% in the control women, the symptom with highest prevalence and at the same level regardless of time since treatment (<3.6 years 61.9%, $\geq 3.6$ years 61.0%). The overall prevalence of moderate-severe difficulty opening a jar was 24.3%, and in ESBCS treated $\geq 3.6$ years earlier was 18.6%, compared to 16.5% in control women. The adjusted RR was only significant in survivors <3.6 years since treatment, RR at 1.6 (95% CI 1.2-2.1). Independent risk factors included DM, age $\geq 65$ and autoimmune disease.

Among survivors who reported moderate-severe difficulty opening a jar, the prevalence rate of clinically important functional impairment was 41.3%-68.8% and for financial difficulties 40.0%. The level of CID for ESBCS reporting any grade of difficulty opening a jar was medium for CF and SF and small for all other scales. The level of CID for survivors reporting moderate
Results

-severe difficulty opening a jar, was large for CF and SF, medium for GHS and RF, and small for PF and FI.

The developed prediction model for difficulty opening a jar could not be validated in the test cohort.

Difficulty climbing stairs or getting up out of a chair because of weakness in legs

The prevalence of any grade of difficulty climbing stairs was 39.4%, compared to 24.9% in control women. The prevalence in ESBCS treated <3.6 years earlier was 43.4% and 35.5% if ≥3.6 years has passed since taxane treatment with corresponding RRs of 1.7 (95% CI 1.3-2.2) and 1.5 (95% CI 1.1-1.9). The prevalence of moderate-severe difficulty climbing stairs was 14.4% compared to 8.9% in control women, RR of 1.3 (95% CI 1.1-1.7).

The independent risk factors identified were age ≥ 65 years, BMI ≥25 and current smoking.

Among survivors who reported moderate-severe difficulty climbing stairs, prevalence rates of clinically important functional impairment fell between 36.2% and 87.0%, and was 39.8% for FI. The level of CID for ESBCS reporting any grade of difficulty climbing stairs compared to no symptoms was large for SF, medium for CF, and small for the other scales. The levels of CID for survivors reporting moderate -severe difficulty climbing stairs, was large for GHS/QoL, CF and SF, and medium for PF and RF and FI.

The prediction model for difficulty climbing stairs could not be validated in the test cohort.
Study I

Prevalence rates for any grade of peripheral neuropathy among ESBCS ranged from 4.5% for patients reporting difficulty using pedals to 61.3% reporting difficulty opening a jar, compared to 2.6%-48.0% among control women. Among ESBCS, the prevalence of tingling (48.4% vs. 48.0%) and numbness (48.3% vs. 48.1%) in hands compared to in feet was similar, while controls had lower prevalence, especially in feet. Adjusted RRs were significantly higher among ESBCS for 15/19 individual TIPN symptoms and ranged from 1.3-1.8 compared to controls, see Figure 8a. The lowest prevalence with significantly increased RR was seen for difficulty walking foot drop, at 7.2% compared to 3.4% in controls, RR 1.5 (95% CI 1.1-2.1). No increased RR after adjustment for covariates was seen for shooting/burning in hands, difficulty hearing, problems holding a pen or difficulty using pedals.

The prevalence of most symptoms of any severity was lower if ≥3.6 years had passed since treatment, and adjusted RRs were significantly higher for 13/19 symptoms ≥3.6 years. Only three symptoms of moderate-severe grade; tingling in feet, numbness in feet and cramps in feet had an increased adjusted RRs ≥3.6 years since taxane treatment.

Prevalence of moderate-severe symptoms ranged from 1.5% of survivors reporting difficulty using pedals to 25.9% reporting cramps in feet, compared to 0.5% reporting difficulty using pedals to 16.5% reporting difficulty opening a jar among control women, see Figure 8b. Moderate-severe symptoms concerning decreased function in legs/feet had significantly increased adjusted RRs of 1.3-1.5; problems standing/walking were reported by 10.0%, difficulty climbing stairs by 14.4% and difficulty walking foot drop by 2.2%.

The autonomic symptoms dizziness when standing up was reported by 45.5% of ESBCS compared to 37.0% in controls, RR 1.3 (95% CI 1.1-1.5) and blurred vision was reported by 29.3% ESBCS compared to 18.3% of control women, RR 1.3 (95% CI 1.1-1.5).

Independent risk factors for different sensory or motor symptoms varied. Age was a risk factor for 8/16 symptoms, and BMI ≥25 as well as DM treatment for 7/16 symptoms. Vibrating hand tools was a risk factor for symptoms in hands, and current smoking was a risk factor both for difficulty small objects and difficult climbing stairs. Alcohol consumption was protective against cramps in hands.
Results

Figure 8.
Self-reported peripheral neuropathy symptoms (EORTC QLQ-CIPN20) among early-stage breast cancer survivors (ESBCS) compared to control women. Reprint from Study I (248) with permission from Springer Nature Limited.

a) Frequency of self-reported peripheral neuropathy symptoms of any severity. The 15 TIPN symptoms with an increased adjusted relative risk among ESBCS compared to control women.

b) The ten symptoms of neuropathy, self-reported as moderate–severe, with the largest absolute difference in prevalence between ESBCS, classified by time elapsed since completed taxane treatment, and control women. Analysis was performed by logistic regression. Significance is indicated as ***P < 0.001, **P < 0.01, *P < 0.05 or n.s. non-significant.
Study II

ESBC survivors with any of 13 individual sensory and motor TIPN symptom reported negative impact on GHS/QoL, and worsened with increased severity, compared to unaffected survivors. Moderate-severe TIPN symptoms were associated with clinically important impairment, corresponding to a prevalence rate of 29.5%-93.3%, see Table 8. More severe TIPN symptoms were associated with increased prevalence rates, but also in those reporting “a little” of any symptom, prevalence rates for impaired function ranged from 16.0% (difficulty opening a jar/RF) up to 75.0% (difficulty walking foot drop/PF).

Table 8. Proportion of ESBCS with moderate -severe TIPN symptoms reporting functional scales below the threshold values for clinical importance according to Giesinger et al. (199).

<table>
<thead>
<tr>
<th>Functional Scales</th>
<th>Prevalence rates (proportion)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical function</td>
<td>59.4%-93.3%</td>
</tr>
<tr>
<td>Role function</td>
<td>31.9%-73.3%</td>
</tr>
<tr>
<td>Emotional function</td>
<td>57.7%-78.6%</td>
</tr>
<tr>
<td>Cognitive function</td>
<td>54.2%-65.6%</td>
</tr>
<tr>
<td>Social function</td>
<td>36.2%-85.7%</td>
</tr>
<tr>
<td>Financial difficulties</td>
<td>29.5%-78.6%</td>
</tr>
</tbody>
</table>

Social function was negatively impacted by most TIPN symptoms (CID medium to large, except cramps in feet). Reporting the symptom Difficulty walking foot drop was associated with the highest CIDs, large for SF and medium for GHS/QoL, PF and FI. Most moderate-severe TIPN symptoms had a large-medium CID on SF and CF. Problems standing/walking and difficulty climbing stairs had medium-large CID for GHS/QoL, as well as all function scales and FI. Cramps in hands and cramps in feet had the least impact, but still medium for GHS/QoL, SF and FI respectively CF and SF. GHS/QoL also deteriorates with increasing severity of TIPN symptoms, see Table 9.

Only half of the survivors had spoken about TIPN with a physician or nurse, and 15.3% had not spoken to anyone. Among ESBCS reporting moderate-severe symptoms of tingling in feet, numbness in feet and cramps in feet 7%-8% agreed with the statement “If I have known about the long-term effects of the chemotherapy, I would have abstained treatment, even if it had shortened my life”, compared to 3% in survivors with none-a little symptoms (p<0.05).
Table 9.

The estimated magnitude of clinically important difference of adjusted mean scores between survivors reporting moderate-severe persistent-symptoms compared to none or a little of a) sensory and b) motor taxane-induced peripheral neuropathy on GHS/QoL, functional health, and financial difficulties.

a) Sensory peripheral neuropathy symptoms

<table>
<thead>
<tr>
<th></th>
<th>Tingling fingers/ hands CID</th>
<th>Tingling toes/feet CID</th>
<th>Numbness fingers/ hands CID</th>
<th>Numbness toes/feet CID</th>
<th>Shooting/ burning in feet CID</th>
<th>Problems standing/ walking because difficulty feeling ground under feet CID</th>
<th>Difficulty distinguishing between hot/cold water CID</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scale</td>
<td>GHS</td>
<td>Small</td>
<td>Small</td>
<td>Medium</td>
<td>Medium</td>
<td>Medium</td>
<td>Medium</td>
</tr>
<tr>
<td></td>
<td>PF</td>
<td>Small</td>
<td>Small</td>
<td>Small</td>
<td>Small</td>
<td>Small</td>
<td>Medium</td>
</tr>
<tr>
<td></td>
<td>RF</td>
<td>Small</td>
<td>Small</td>
<td>Small</td>
<td>Small</td>
<td>Small</td>
<td>Medium</td>
</tr>
<tr>
<td></td>
<td>EF</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td>CF</td>
<td>Large</td>
<td>Medium</td>
<td>Large</td>
<td>Medium</td>
<td>Medium</td>
<td>Medium</td>
</tr>
<tr>
<td></td>
<td>SF</td>
<td>Large</td>
<td>Large</td>
<td>Large</td>
<td>Large</td>
<td>Large</td>
<td>Large</td>
</tr>
<tr>
<td></td>
<td>FI</td>
<td>Small</td>
<td>Small</td>
<td>Small</td>
<td>Small</td>
<td>Small</td>
<td>Small</td>
</tr>
</tbody>
</table>

b) Motor peripheral neuropathy symptoms

<table>
<thead>
<tr>
<th></th>
<th>Cramps in hands CID</th>
<th>Cramps in feet CID</th>
<th>Difficulty manipulating small objects with fingers CID</th>
<th>Difficulty opening jar/bottle because weak hands CID</th>
<th>Difficulty walking because foot drop CID</th>
<th>Difficulty climbing or getting up/out of chair because weakness in legs CID</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scale</td>
<td>GHS</td>
<td>Medium</td>
<td>Small</td>
<td>Medium</td>
<td>Medium</td>
<td>Medium</td>
</tr>
<tr>
<td></td>
<td>PF</td>
<td>Small</td>
<td>Small</td>
<td>Small</td>
<td>Small</td>
<td>Small</td>
</tr>
<tr>
<td></td>
<td>RF</td>
<td>Small</td>
<td>Small</td>
<td>Small</td>
<td>Small</td>
<td>Small</td>
</tr>
<tr>
<td></td>
<td>EF</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td>CF</td>
<td>Small</td>
<td>Medium</td>
<td>Large</td>
<td>Large</td>
<td>Trivial</td>
</tr>
<tr>
<td></td>
<td>SF</td>
<td>Medium</td>
<td>Medium</td>
<td>Large</td>
<td>Large</td>
<td>Large</td>
</tr>
<tr>
<td></td>
<td>FI</td>
<td>Medium</td>
<td>Small</td>
<td>Small</td>
<td>Small</td>
<td>Small</td>
</tr>
</tbody>
</table>

CID, clinically important difference; GHS, Global Health Status/quality of life; PF, physical functioning; RF, role functioning; EF, emotional functioning; CF, cognitive functioning; SF, social functioning; FI, financial difficulties due to the problem; NA, not applicable; ns, not significant. According to guidelines by Cocks et al. (198) The Bonferroni method was used to correct for multiple comparisons. The differences in adjusted mean scores all have p values < 0.01, except when marked < 0.05 or ns in the table.

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Study III

The study population in study III was based on a sub-study of the previous studies, including 337 ESBCS, see Figure 5, divided in a training cohort (n=237) and a separate test cohort (n= 100). Age, BMI, DM treatment, mean time since taxane and the proportion treated with docetaxel (52.5%) were like the study population in studies I-II. The training and test cohort did not differ in age, BMI, DM treatment, time since taxane treatment, or TIPN symptoms, but the test cohort had received paclitaxel more often. Outcome/phenotype was moderate-severe symptoms of either TIPN symptom, and ranged in the whole study cohort from 12.1%-27.6%, see Table 10.

<table>
<thead>
<tr>
<th>Table 10. Survivor characteristics.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Training cohort (n=237)</strong></td>
</tr>
<tr>
<td>Treatment N (%)</td>
</tr>
<tr>
<td>Docetaxel</td>
</tr>
<tr>
<td>Paclitaxel</td>
</tr>
<tr>
<td>Both</td>
</tr>
<tr>
<td>Mean years from taxane to survey, (SD)</td>
</tr>
<tr>
<td>Proportion with moderate to severe taxane-induced peripheral neuropathy symptoms N(%)</td>
</tr>
<tr>
<td>Cramps in feet</td>
</tr>
<tr>
<td>Difficulty opening a jar</td>
</tr>
<tr>
<td>Numbness in feet</td>
</tr>
<tr>
<td>Tingling in feet</td>
</tr>
<tr>
<td>Difficulty climbing stairs</td>
</tr>
</tbody>
</table>

The first prediction models were based on literature data/meta-analysis. The A1 model was based on the meta-analysis by Guijosa et al. (99) and included 26 SNVs from 18 genes that we found in our WES data. In the validation in the test cohort, only the AUC for numbness in feet was higher than 60% (AUC 67%) and was improved by the clinical risk factors. The A2 model was based on 54 common SNVs in the taxane pathway but could not be validated and was not investigated further.
The B models were based on cohort data. The B1 model was based on SNV/INDEL association analysis of WES/cohort data and used false discovery rate (FDR) p-value thresholds ≤0.0005–0.001125 followed by CADD score ≥13 to include 212 unique SNVs and 234 unique genes for all symptoms. The model for each symptom included 27-63 SNVs per model but all failed in validation and were not investigated further. The B2 model was based on WES/cohort data using a gene-based approach, gene test and q-q plots to filter out the most relevant genes for each symptom. In the five models, 26-36 SNVs were included, and all SNVs except one had also been found in the SNV/INDEL analysis. A wider inclusion of genes from the SNV/INDEL association analysis were included and filtered by CPDB over-representation analysis using different p-values <0.005-0.2 to build the most optimal model.

In the C1 model, B2 and A1 models were combined and thereafter in A2 variable importance was used to filter out the most relevant SNVs. The clinical risk factors improved the accuracy by 1%-3%. The C2 models of 35 SNVs (40 unique genes) for **numbness in feet** and of 55 SNVs (60 unique genes) for **tingling in feet** could be validated in the test cohort with AUC at 61% and 73%, respectively, but the models (33-50 SNVs) for **cramps in feet**, **difficulty opening a jar** and **difficulty climbing stairs** had lower AUCs (43%-52%) and could not be validated. The results of the final C2 prediction models for the five symptoms are described above, see also Table 11 for statistical performance.

Six SNVs were included in the models for both **numbness in feet** and **tingling in feet** corresponding to the genes **ADAMTS20**, **APT6V0A2**, **CCDC88C**, **EPHA5**, **NR1H3** and **APTV0D2;PSKH2**. Two additional genes—**CYP2C8** and **SCN10A**—from which different SNVs were included in the models. The SNVs for the genes **ABCC2**, **CYP2C8**, **EPHA5** and **GSTP-1** were from the meta-analysis. The other genes correlated with the methadone action pathway and axon guidance pathway. The C2 models for **tingling in feet** and **numbness in feet** correlated with the meta-analysis genes in receptors for lipid metabolism and nuclear receptors pathways.
Table 11.
Performance of prediction models A1 and C2 in taxane-induced peripheral neuropathy symptoms (EORTC CIPN20), including AUC of ROC curve (confidence interval 95%) and suitable cutoff for optimal accuracy, sensitivity, and specificity in both the training and test cohort. Models performing AUC in test cohort above 60% in bold, AUC below 60% in italics.

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Model</th>
<th>SNVs (genes)</th>
<th>Cutoff</th>
<th>Set</th>
<th>AUC (%) (CI 95%)</th>
<th>Accuracy (%)</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Numbness in feet</td>
<td>A1</td>
<td>26 (16)</td>
<td>0.291</td>
<td>Train</td>
<td>78.74 (67-82)</td>
<td>75.32</td>
<td>70.49</td>
<td>77.01</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Test</td>
<td>67.09 (54-78)</td>
<td>73.00</td>
<td>56.00</td>
<td>78.67</td>
</tr>
<tr>
<td>Tingling in feet</td>
<td>A1</td>
<td>26 (16)</td>
<td>0.497</td>
<td>Train</td>
<td>75.42 (66-80)</td>
<td>79.57</td>
<td>33.33</td>
<td>96.51</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Test</td>
<td>56.31 (41-71)</td>
<td>75.00</td>
<td>25.00</td>
<td>87.50</td>
</tr>
<tr>
<td>Cramps in feet</td>
<td>A1</td>
<td>26 (16)</td>
<td>0.463</td>
<td>Train</td>
<td>72.06 (60-74)</td>
<td>75.32</td>
<td>33.33</td>
<td>93.87</td>
</tr>
<tr>
<td>Difficulty opening a jar</td>
<td>A1</td>
<td>26 (16)</td>
<td>0.411</td>
<td>Train</td>
<td>76.00 (67-81)</td>
<td>80.59</td>
<td>48.28</td>
<td>91.06</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Test</td>
<td>55.71 (44-68)</td>
<td>63.00</td>
<td>20.00</td>
<td>81.43</td>
</tr>
<tr>
<td>Difficulty climbing stairs</td>
<td>A1</td>
<td>26 (16)</td>
<td>0.394</td>
<td>Train</td>
<td>84.04 (60-79)</td>
<td>91.98</td>
<td>42.86</td>
<td>98.56</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Test</td>
<td>52.80 (44-72)</td>
<td>78.00</td>
<td>0.00</td>
<td>89.66</td>
</tr>
<tr>
<td>Sum SNVs and genes</td>
<td>A1</td>
<td>26 (16)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Numbness in feet</td>
<td>C2</td>
<td>35 (40)</td>
<td>0.324</td>
<td>Train</td>
<td>88.87 (83-91)</td>
<td>83.40</td>
<td>77.05</td>
<td>85.63</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Test</td>
<td>72.91 (60-84)</td>
<td>74.00</td>
<td>68.00</td>
<td>76.00</td>
</tr>
<tr>
<td>Tingling in feet</td>
<td>C2</td>
<td>55 (60)</td>
<td>0.346</td>
<td>Train</td>
<td>85.96 (79-90)</td>
<td>80.43</td>
<td>77.78</td>
<td>81.40</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Test</td>
<td>60.88 (43-76)</td>
<td>69.00</td>
<td>50.00</td>
<td>73.75</td>
</tr>
<tr>
<td>Cramps in feet</td>
<td>C2</td>
<td>50 (57)</td>
<td>0.448</td>
<td>Train</td>
<td>85.69 (80-89)</td>
<td>80.43</td>
<td>65.28</td>
<td>87.12</td>
</tr>
<tr>
<td>Difficulty opening a jar</td>
<td>C2</td>
<td>35 (42)</td>
<td>0.670</td>
<td>Train</td>
<td>80.34 (73-85)</td>
<td>78.00</td>
<td>15.52</td>
<td>98.32</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Test</td>
<td>51.71 (40-65)</td>
<td>67.00</td>
<td>13.33</td>
<td>90.00</td>
</tr>
<tr>
<td>Difficulty climbing stairs</td>
<td>C2</td>
<td>35 (38)</td>
<td>0.644</td>
<td>Train</td>
<td>90.02 (82-93)</td>
<td>91.56</td>
<td>39.29</td>
<td>98.56</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Test</td>
<td>42.88 (43-73)</td>
<td>75.00</td>
<td>0.00</td>
<td>86.21</td>
</tr>
<tr>
<td>Sum SNVs and genes</td>
<td>C2</td>
<td>145 (158)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>
Results

Preliminary results

Overlap between selected symptoms

To explore a plausible overlap between symptoms of interest, descriptive statistics of survivors reporting both symptoms (moderate-severe grade) are reported in Table 12.

Table 12. ESBC survivors with moderate-severe symptoms of tingling in hand or feet and numbness in hands or feet and who also reported moderate-severe symptoms of other TIPN symptoms.

<table>
<thead>
<tr>
<th></th>
<th>Shooting /burning in hands</th>
<th>Shooting /burning in feet</th>
<th>Problem holding a pen</th>
<th>Difficulty small objects</th>
<th>Problems standing/ walking</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tingling in hands</td>
<td>18.9%</td>
<td>10</td>
<td>6</td>
<td>471 (73.6)</td>
<td>41 (6.4)</td>
</tr>
<tr>
<td>Missing</td>
<td></td>
<td>509 (80.0)</td>
<td></td>
<td>48+80</td>
<td>(20.0)</td>
</tr>
<tr>
<td>Low-Low Discordance</td>
<td></td>
<td>8+75</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High-High</td>
<td></td>
<td>44 (6.9)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tingling in feet</td>
<td>23.2%</td>
<td>10</td>
<td>6</td>
<td>471 (73.6)</td>
<td>20+81</td>
</tr>
<tr>
<td>Missing</td>
<td></td>
<td>473 (70.4)</td>
<td></td>
<td>48+80</td>
<td>(15.8)</td>
</tr>
<tr>
<td>Low-Low Discordance</td>
<td></td>
<td>18+111</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High-High</td>
<td></td>
<td>34 (5.4)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Numbness in hands</td>
<td>18.9%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Missing</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low-Low Discordance</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High-High</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Numbness in feet</td>
<td>23.7%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Missing</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low-Low Discordance</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High-High</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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Sum mean scores

The sum mean scores for sensory, motor and autonomic symptoms were higher for survivors than control women, see Table 13. Cronbach’s alpha coefficients for the total sum mean score were for sensory sum mean scores was 0.87 for survivors vs. 0.84 for controls, 0.79 vs. 0.80 for motor, and 0.59 vs. 0.56 for autonomic.

Table 13.
Mean scores (standard deviations) of EORTC QLQ-CIPN20 sensory, motor and autonomic scales among cancer survivors and control women.

<table>
<thead>
<tr>
<th>EORTC QLQ-CIPN20</th>
<th>Mean (SD)</th>
<th>Breast cancer survivors n=646</th>
<th>Not stated</th>
<th>Female General Population n=1040</th>
<th>Not stated</th>
<th>P (Students t-test)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensory symptoms Sum mean score</td>
<td>1.54 (0.57)</td>
<td>2</td>
<td>1.31 (0.42)</td>
<td>14</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Motor symptoms Sum mean score</td>
<td>1.52 (0.52)</td>
<td>2</td>
<td>1.34 (0.44)</td>
<td>13</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Autonomic symptoms Sum mean score</td>
<td>1.48 (0.59)</td>
<td>2</td>
<td>1.34 (0.49)</td>
<td>16</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Total symptoms Sum mean score</td>
<td>1.53 (0.49)</td>
<td>2</td>
<td>1.33 (0.39)</td>
<td>13</td>
<td>&lt;0.001</td>
<td></td>
</tr>
</tbody>
</table>
Differences between docetaxel and paclitaxel

An early hypothesis was that at least some TIPN symptoms are more prevalent after paclitaxel treatment than after docetaxel treatment. Docetaxel 100mg/m² every 3 weeks x4 or weekly paclitaxel 80 mg/m² x 12 were considered equivalently efficient at the time of the study (42). In the study population (N=646), 345 were treated with docetaxel of which 78.3% were prescribed 100 mg/m² and the remaining were prescribed 75-80 mg/m². Four cycles of 100 mg/m² was prescribed to 1.8% of patients and three cycles to 89.1%. Weekly Paclitaxel was prescribed to 283 survivors, of which 74.2% received 12 weeks of treatment. A treatment period of nine weeks or more, corresponding to at least the same treatment time as docetaxel, was prescribed to 92.6%. Eighteen ESBCS exposed to both taxanes (n=18) were excluded. Dose delays were more common for docetaxel, and paclitaxel more frequently resulted in dose reductions. The mean age was higher in the paclitaxel-treated survivors. Three quarters of the docetaxel-treated patients reported that they had used cryotherapy during treatment, see Table 14.

Table 14.
Characteristics of early-stage breast cancer survivors (ESBC) survivors treated with docetaxel compared ESBC survivors treated with paclitaxel.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Docetaxel-treated survivors n=345 No. (%)</th>
<th>Paclitaxel-treated survivors n=283 No. (%)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years¹ Mean (SD)</td>
<td>58.9 (10.7)</td>
<td>62.9 (11.2)</td>
<td>&lt;0.001²</td>
</tr>
<tr>
<td>Self-reported use of cold gloves/socks during treatment¹ yes</td>
<td>342</td>
<td>279</td>
<td>&lt;0.001⁴</td>
</tr>
<tr>
<td></td>
<td>257 (75.1)</td>
<td>46 (1.4)</td>
<td></td>
</tr>
<tr>
<td>Triple negative</td>
<td>50 (14.5)</td>
<td>51 (18.0)</td>
<td></td>
</tr>
<tr>
<td>Weeks of taxane treatment²</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;6</td>
<td>23 (6.7)</td>
<td>12 (4.2)</td>
<td>≤9 w vs</td>
</tr>
<tr>
<td>7-8</td>
<td>NA</td>
<td>9 (3.2)</td>
<td>&gt;9w</td>
</tr>
<tr>
<td>9-10</td>
<td>308 (89.3)</td>
<td>13 (4.6)</td>
<td>&lt;0.001⁴</td>
</tr>
<tr>
<td>10-12</td>
<td>14 (4.1)</td>
<td>249 (88.1)</td>
<td></td>
</tr>
<tr>
<td>Dose delay</td>
<td>27 (7.8)</td>
<td>10 (3.5)</td>
<td>0.023⁴</td>
</tr>
<tr>
<td>Dose reduction</td>
<td>62 (18.0)</td>
<td>102 (36.0)</td>
<td>&lt;0.001⁴</td>
</tr>
<tr>
<td>Cumulative dose mean (SE) mg/m²</td>
<td>273.0 (55.4)</td>
<td>865.9 (158.3)</td>
<td></td>
</tr>
<tr>
<td>Ongoing endocrine treatment</td>
<td>204/340 (60.0)</td>
<td>154/280 (55.0)</td>
<td>0.210</td>
</tr>
<tr>
<td>Years since taxane² Mean (SD)</td>
<td>4.01 (1.5)</td>
<td>3.8 (1.6)</td>
<td>0.082</td>
</tr>
</tbody>
</table>

¹At the time the questionnaire was completed, ²Student’s t-test, ³Self-reported, ⁴Pearson’s Chi-squared test, ⁵Docetaxel every 3 weeks, paclitaxel weekly.

SD, Standard Deviation; SE, Standard error of the mean; NA, not applicable.
After adjustments for age, comorbidities, length of treatment and cryotherapy, moderate-severe numbness in feet (p<0.05), tingling in feet (p<0.05), difficulty climbing stairs (p<0.01), and difficulty small objects (p<0.01) and difficulty standing/walking (p<0.05) were more common among the paclitaxel-treated survivors, see Figure 9.

In the HRQL analysis, survivors exposed to docetaxel vs. to paclitaxel were compared, irrespectively of TIPN symptoms. Paclitaxel-exposed survivors reporting worse CF, corresponding to a small CID, see Table 15. Paclitaxel-exposed reported more often clinically important impairment of PF and RF. Docetaxel-treated reported worse EF, and no difference was seen regarding CF, see Table 16.

Figure 9.
Frequency of moderate-severe peripheral neuropathy symptoms in percent in early-stage breast cancer survivors treated with docetaxel respectively paclitaxel. The difference in prevalence was investigated, unadjusted (chi-squared test) and by logistic regression (adjusted for age, body mass index, alcohol consumption, diabetes mellitus, carpal tunnel syndrome, hypothyroidism, menopausal status, use of cold socks/gloves during treatment, treatment duration >9 weeks). Significance is indicated as *p<0.05, **p<0.01, ***p<0.001 and n.s. = non-significant.
## Results

Table 15.
Comparison between early-stage breast cancer survivors treated with docetaxel vs. paclitaxel on global health status/quality of life, functional health, and finances. Unadjusted and adjusted mean (SE) scores of each scale (EORTC QLQ-C30 instrument).

<table>
<thead>
<tr>
<th>Scale</th>
<th>Docetaxel Unadjusted</th>
<th>Paclitaxel Unadjusted</th>
<th>p-value</th>
<th>Docetaxel Adjusted</th>
<th>Paclitaxel Adjusted</th>
<th>Δ² ClD³</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean (SE)</td>
<td>Mean (SE)</td>
<td></td>
<td>Mean (SE)</td>
<td>Mean (SE)</td>
<td></td>
</tr>
<tr>
<td>Global Health Status /Quality of life, no</td>
<td>69.20 (1.138)</td>
<td>68.41 (1.258)</td>
<td>0.218</td>
<td>57.404 (2.668)</td>
<td>55.984 (2.687)</td>
<td>0.391</td>
</tr>
<tr>
<td>Physical function, no</td>
<td>84.23 (0.984)</td>
<td>80.56 (1.089)</td>
<td>0.013</td>
<td>73.221 (2.067)</td>
<td>72.094 (2.082)</td>
<td>0.380</td>
</tr>
<tr>
<td>Role function, no</td>
<td>78.50 (1.420)</td>
<td>74.421 (1.577)</td>
<td>0.083</td>
<td>67.167 (3.265)</td>
<td>63.390 (3.290)</td>
<td>0.062</td>
</tr>
<tr>
<td>Emotional function, no</td>
<td>69.895 (1.313)</td>
<td>73.453 (1.453)</td>
<td>0.062</td>
<td>63.359 (3.115)</td>
<td>64.278 (3.138)</td>
<td>0.634</td>
</tr>
<tr>
<td>Cognitive Function, no</td>
<td>75.411 (1.387)</td>
<td>74.291 (1.534)</td>
<td>0.588</td>
<td>66.817 (3.185)</td>
<td>61.847 (3.208)</td>
<td>4.97</td>
</tr>
<tr>
<td>Social function, no</td>
<td>75.942 (1.415)</td>
<td>75.532 (1.565)</td>
<td>0.846</td>
<td>69.037 (3.384)</td>
<td>66.850 (3.408)</td>
<td>0.298</td>
</tr>
<tr>
<td>Financial difficulties, no</td>
<td>9.855 (1.297)</td>
<td>11.111 (8.294)</td>
<td>0.516</td>
<td>25.189 (2.786)</td>
<td>27.494 (2.806)</td>
<td>0.183</td>
</tr>
</tbody>
</table>

Higher scores on GHS/QoL and functional scales = better, High score on FI = worse
Student’s t-test. Linear regression (ANCOVA) adjusted for age, BMI, civil status, educational level, employment status, alcohol consumption, exercise, smoking, musculoskeletal disorders, cardiovascular disease, diabetes mellitus, pulmonary disease, and neurological disease. Δ = the difference of the adjusted mean scores. Guidelines by Cocks et al. 2011 (198).

Table 16.
The prevalence rates of early-stage breast cancer survivors treated with paclitaxel vs. docetaxel whose impact on self-perceived functional health and financial difficulties were of clinical importance according to threshold values by Giesinger et al. 2020 (199).

<table>
<thead>
<tr>
<th>Scale</th>
<th>Docetaxel n/N (%)</th>
<th>Paclitaxel n/N (%)</th>
<th>Pearson chi-Square</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical Function</td>
<td>124/345 (35.9)</td>
<td>127/282 (45.0)</td>
<td>0.021</td>
</tr>
<tr>
<td>Role Function</td>
<td>60/345 (17.4)</td>
<td>69/280 (24.6)</td>
<td>0.026</td>
</tr>
<tr>
<td>Cognitive Function</td>
<td>133/345 (38.6)</td>
<td>113/280 (40.1)</td>
<td>0.698</td>
</tr>
<tr>
<td>Emotional Function</td>
<td>166/345 (48.1)</td>
<td>111/282 (39.4)</td>
<td>0.028</td>
</tr>
<tr>
<td>Social Function</td>
<td>66/345 (19.1)</td>
<td>68/282 (24.1)</td>
<td>0.130</td>
</tr>
<tr>
<td>Financial difficulties</td>
<td>63/345 (18.3)</td>
<td>60/282 (21.3)</td>
<td>0.344</td>
</tr>
</tbody>
</table>
Respondents’ personal experience

Figure 10.
Personal experience of answering the postal questionnaire ‘Health after breast cancer treatment’ reported by 646 early-stage breast cancer survivors.
Missing values: a) n=25 b) n=24, c) n=25

K-folded cross-validation of numbness in feet

The method k-folded (3, 5, 10) cross-validation method was tested for the 39 predictors found in our model and on the cohort. The model identified by the cross-validation was closely related to our own model, with 72% AUC in the ROC-curve compared to ours at 73%. Both models had similar quality metrics indicating that they share similar performance.
DISCUSSION

Breast cancer survivors exposed to taxane had an increased risk of 13 individual sensory and motor peripheral neuropathy symptoms, compared to matched controls from the general population. Although both prevalence and severity for some symptoms seemed to decrease over time, the risk for many TIPN symptoms was still higher ≥3.6 years since treatment. TIPN symptoms were associated with worse GHS/QoL, functional health and financial difficulties; and the more severe the symptoms, the greater the negative impact on HRQL. The most common independent clinical risk factors were treatment with paclitaxel, diabetes mellitus treatment, age ≥65 years, BMI ≥25 and autoimmune disease. Polygenic prediction models including clinical risk factors were developed for five TIPN symptoms, and two could be validated in a test cohort. A polygenic prediction model including 55 SNVs could predict persistent numbness in feet correctly in 73% and a model including 35 SNVs predicted tingling in feet correctly in 70%.

The spectra of TIPN symptoms

Considering the vast number of breast cancer patients worldwide that have undergone taxane treatment in the (neo-)adjuvant setting, the data on persistent TIPN beyond one year is limited and very few studies report >3 years from treatment. However, TIPN symptoms seem to persist, at least partially (111, 115, 116). Most studies have reported a combined outcome of sensory PN, but by reporting the TIPN symptoms individually and using a sensitive patient-reported instrument, the understanding of the spectra of TIPN symptoms among breast cancer survivors and their association with deterioration of HRQL could be improved.

The most prevalent persistent sensory symptoms were tingling and numbness in hands and feet reported by half of the survivors, and there was still an elevated risk ≥3.6 years compared to controls. Symptoms in feet dominated, corresponding to previous findings (85, 118). Numbness and tingling appeared to be a bother to survivors, as it was reported by 50% of ESBCS 2 years after sequential anthracycline and taxane (docetaxel) treatment, and about 20% reported a severe bother level (83). In qualitative studies it has been described as a “background noise” (250) or a “strange” or “weird” sensation.
In a citation it was described as “a constant presence, sometimes simply annoying us and sometimes overwhelming us” (73). In preliminary results, paclitaxel exposure was associated with a higher risk for especially tingling in feet and numbness in feet. Mean scores in study 1 were slightly higher compared to those reported by Eckhoff et al. (85), maybe due to our study including paclitaxel exposure and a higher median age of 62 vs. 52 years. The overlap between survivors reporting both numbness in feet and problems standing/walking was limited and it may not be that numbness precedes impaired function. In a symptoms cluster analysis of CIPN20 symptoms, tingling/numbness did not correlate with problems standing/walking but was considered a sensorimotor symptom (112). This would implicate the importance of asking about symptoms of functional impairment, and not thinking of tingling/numbness as preluding symptoms, although tingling and numbness symptoms had an impact on physical function.

Most of those who reported moderate-severe shooting/burning in hands/feet also reported tingling in hands/feet in this study, which may indicate similar biological mechanisms of sensory ‘plus’ symptoms (87, 251). It is an important group to identify as they may benefit from duloxetine treatment (144), even if we only found an increased risk for shooting/burning in feet. A diagnosis of neuropathic pain has been shown to be three times as common in breast cancer survivors who had been exposed to paclitaxel, and risk factors were sensory TIPN and higher age (252). In our study, paclitaxel was not associated with shooting/burning in hands/feet and age was not a risk factor, which could be due to different definitions, diagnosed with NP or self-reported symptoms.

The motor symptom cramps in feet affected more than half of survivors with a consistent increased RR independent of time since treatment. To some extent there may be an association with endocrine treatment, although cramps in feet was still more frequent in survivors without endocrine treatment than in controls. In the FACT/COG-NTX questionnaire, cramps and joint pain is one combined item, limiting comparison with other studies of persistent TIPN. The motor symptoms difficulty opening a jar and difficulty climbing stairs had a clearly lower prevalence rates in survivors ≥3.6 years since treatment, than <3.6 years, a difference which could indicate a biological mechanism other than the one driving cramps in feet. Symptoms with lower prevalence like difficulty walking foot drop or difficulty distinguishing hot/cold water do not appear clearly when reporting mean scores without prevalence rates or without comparison to controls (85). Difficulty
distinguishing hot/cold water is not included in FACT/COG-NTX (REF) and was possibly not captured in CTCAE of PN symptoms, again making comparisons difficult. Both of these less-common symptoms (7.2%, 8.9%) merit further exploration.

Prevalence was lower for most symptoms in the half of the cohort at ≥3.6 years since treatment, but still, the adjusted RR remained increased for the majority of TIPN symptoms compared to control women of the same age. This is comparable to the trend of decreasing prevalence and severity based on six longitudinal studies. Of the patients with symptoms directly after treatment, 40%-60% were estimated to experience resolution after 3 years, albeit not always completely (111). Few studies have longer follow-up periods than 3 years, but in 2 studies with 6 years follow-up TIPN symptoms were still prevalent. Among taxane-treated survivors 30%-50% reported either numbness, pins/needles, or pain in hands (120, 253). As time since treatment passes, aging and its associated increase of PN in the general population needs to be considered. The background prevalence of PN is about 8% at 60-70 years (226) corresponding to the 6.6%-10.1% who reported moderate-severe tingling and numbness in hands and feet among control women in our study. Late-occurring PN was reported by 8%-11% of those who did not report PN at end of treatment (85), a finding that may be due to aging and premature menopause, comorbidities, an increased risk among ESBCS after taxane, coasting or a combination, even during a relatively short observation time.

The autonomic symptoms dizziness when standing and blurred vision both demonstrated an increased risk among ESBCS, but the items have been suggested to be omitted from CIPN20 due to poor correlation with other items, not measuring the construct peripheral neuropathy, and may instead be associated with co-morbidities or medication (181). It may be that taxanes actually cause autonomic nerve toxicity, although reported to be rare (89, 91, 254, 255). These items are considered unspecific, but maybe autonomic symptoms are insufficiently studied. The relation between sensory, motor and autonomic neuropathy is not clearly understood. Slightly different clusters of symptoms were seen at different time points one year from treatment completion, but sensory symptoms were predominant and occurred earlier (112). Some suggest that sensory symptoms occur first and that motor symptoms possibly result from worsening sensory symptoms (136, 256). In longitudinal studies, resolution appears greater for sensory symptoms than for motor symptoms (111). A similar trend could be seen in RRs in our study.
cohort, RRs decreasing more for sensory than for motor symptoms in the survivors with ≥3.6 years since treatment compared to <3.6 years since treatment.

Impact of TIPN on HRQL

Sensory persistent TIPN symptoms impacts HRQL (83, 85), depression/anxiety (121), and increases health care usage (252), based on sensory symptoms as a joint measure. Data from the literature on how the different sensory and motor symptoms impact HRQL is limited. An increased risk of disability and falls has been shown in survivors with persistent CIPN, and the risk increased with severity (121, 136). In our study, symptoms of impaired physical abilities, such as problems standing/walking, difficulty climbing stairs and difficulty walking foot drop had large impact on HRQL. Affected survivors reported medium to large CID on all functional scales, deterioration of GHS/QoL, and higher prevalence rates of clinically important impairments. The impact of persistent motor TIPN symptoms on HRQL has, to our knowledge, not been reported before.

Like Eckhoff et al. 2015’s study of QLQ-C30 in relation to different grades of a joint PN measure, clinically important differences were seen on basically all functional scales among survivors reporting TIPN symptoms, with role, cognitive and especially social function (RF, CF and SF) showing the largest differences and increasing with PN severity (85). SF is based on items inquiring as to whether the physical condition has interfered with family life or social activities (Table 6). The physical impairments of TIPN can require life-style changes and reduce participation in social activities (169). RF, including inability to work, was less impacted than other functional health scales, even if 5% reported current sick leave due to persistent TIPN in survivors aged <65 years. Financial difficulties (FI) was most strongly associated with symptoms of impaired function in legs and feet. More severe level of PN was associated with more FI in one previous study; otherwise, financial toxicity is rarely reported (85). About half (41%) of the study population was retired, and 7% had disability pension, therefore impact on RF and FI may be higher in the younger survivors.

Worse TIPN was associated with worse cognitive function, as seen in previous findings (85). This may indicate association with central neurotoxicity or chemotherapy-induced cognitive impairment (CICI) (98, 139). Mechanisms in the brain contributing to CIPN have been suggested, by brain
hyperactivity, reduced GABAergic inhibition, neuroinflammation, and over-activation of GPCR/MAPK pathways (257), but generally mechanisms or association between CICI and CIPN are poorly described. In depth understanding of how TIPN symptoms affect survivors could make rehabilitation interventions more effective, focusing on relieving the most important symptoms first, and if this is not possible, finding ways to limit interference in family life and social activities. Research initiatives should also focus on what matters most to the patients; the persistent symptoms and impairments, as suggested by Lustberg (73).

**Risk factors for TIPN**

By studying the TIPN symptoms individually, we defined outcomes more clearly, to enable further exploration of clinical risk factors and associated genetic variants. We found that paclitaxel and DM treatment were associated with predominantly sensory symptoms, and autoimmune disease with motor symptoms, while age and overweight were associated with both. Age is a previously known risk factor for PN, although we defined older age as ≥65 years, while previous studies have defined it as >50-55 years (83, 85, 118). In older patients, cardiac comorbidity is more common, and if using anthracycline de-escalation regimens to decrease cardiac toxicity (258), the risk of TIPN should be considered. There is however conflicting data on age as a risk factor (259).

Overweight (BMI ≥25) is a risk factor for TIPN (119, 259, 260), but also associated with poorer prognosis that could be related to inadequately low relative dose intensity (RDI) (48, 261). The actual body surface area (BSA) should be used for dosing in obese patients (262), but the risk of increased toxicity should be considered. Lipophilic drugs like taxanes may have a greater volume distribution, and hepatic steatosis and kidney dysfunction may decrease clearance (263). Possibly the use of body composition (adiposity/lean body mass) evaluated on a CT could improve dosing (261). In a systematic review, a low lean body mass was associated with increased toxicity while data on the risk of adiposity for toxicity were inconsistent (264). Low muscle mass may increase maximum paclitaxel concentration, and possibly a longer infusion time in sarcopenic patients could decrease the risk of TIPN (135).

Two risk factors have, to our knowledge, not previously been studied in relation to TIPN. The use of vibrating hand tools is an occupational hazard
causing PN (228, 265) and was associated with *tingling/numbness in hands* and *difficulty small objects*. Smoking has been associated with persistent CIPN in testes cancer survivors, although these patients were not exposed to taxane (266). Smoking was associated with *difficulty small objects* and *difficulty climbing stairs*. The risk factors; age, DM treatment and overweight may be causal, due to their independent associations, consistency with previous studies, biological rational, and their association with other forms of polyneuropathy (125, 227), if considering the Bradford Hill criteria of observational studies (267). Age, DM treatment, BMI, and paclitaxel treatment improved the risk prediction models in study III, further supporting causality.

### Polygenic prediction models

The development of polygenic prediction models for TIPN strives to identifying those who need adjusted treatment and/or careful monitoring. The prediction models in study III could only be validated for 2/5 symptoms. Our model for *numbness in feet* could correctly predict a large group—47%—at high risk and a low-risk group of 14%, close to the background prevalence of PN in the population. The model for *tingling in feet* discriminated more poorly, with 33% in high-risk group and 14% in the low-risk group. Why these two models could be validated could be due to a less complex biological background than the symptoms of decreased ability, such as *difficulty opening a jar* and *difficulty climbing stairs*. The difference in prevalence between the survivors and control women was large for both *tingling in feet* and *numbness in feet* (23%-24% vs. 7%, RR 1.9, 2.0), suggesting the symptom to be more clearly associated with taxane. The symptoms of decreased ability only differed less from controls (24% vs. 17%, RR 1.2, 14% vs. 9%, RR 1.3) and the RRs ≥3.6 years were not increased, diluting the outcome if previous cases no longer reported symptoms. The outcomes might have been too unspecific for the models to hold during validation. On the other hand, moderate-severe *cramps in feet* differed clearly in prevalence between ESBCS and controls (26% vs. 10%, RR 1.7), the symptom seem to persist over time and is plausibly biologically distinct, yet the prediction model was unsuccessful. In this case, it is possible that endocrine treatment is a confounding factor contributing to *cramps in feet*.

Concerns about the use of PROM data for phenotype definition in pharmacogenomics have been raised, since the outcome may reflect the patient’s
assessments of severity or tolerability more than an objective measure (268). By separating the PN symptoms and including only moderate-severe symptoms, we opted for clearly defined outcomes, and believe that at least the phenotypes *tingling in feet* and *numbness in feet* were as ‘objective’ as possible.

Few of the SNVs were included in more than one model. Overlap was seen for SNVs in nine genes in both the final models for *tingling in feet* and *numbness in feet* and may therefore be of importance. Three genes were from previously published studies (*EPHA5*, ABC family and *CYP2C8*) (99), and thus of high variable importance supporting previous findings. We identified three SNVs/genes, *SCN10A*, *CCDC88C* and *NR1I3* that have variants in the same family reported in association with PN or CIPN (210, 269-272). Three SNV/genes: *ATP6V0A2* and *ATPVD2; PSKH2* and *ADAMTS family* have, to our knowledge no previously reported association with TIPN. *ADAMTS* genes were of the highest importance in both models and may be involved in neuroplasticity (273). Further exploration of this gene family and the relation to CIPN is warranted.

We found two previously published polygenic prediction models, one based on a 267 SNVs cluster (274) and the other on GWAS with neuropathy and pathway analysis for mechanistic pathways (275). None of these were validated in a test cohort and the one based on SNVs cluster predicted 96.1% accuracy suggesting overfitting. Overfitting must be carefully considered during the development of models, and validation is of importance since promising models may not perform well in a test/validation cohort. More advanced statistical methods that capture the co-variation of genetic variants could further improve polygenic prediction models. A larger validation cohort or the use of cross-validation may also be considered, although the latter may lead to loss of low frequency variants. We have tried a model based on cross-validation on *numbness in feet* and the results were comparable (preliminary results), but we regarded the study population to be too small for this method.

The genetic background of TIPN is far from understood at this point and a potential difference in genes involved in acute vs. persistent TIPN has not been explored. Although no association between TIPN and outcome was seen in Sparano et al.’s study (49), variants in the genes *GSTP1*, *CYP3A* and *SLCO1B1* have been associated with efficacy of treatment in premenopausal women, related to pharmacokinetics. *GSTP1* codes for an enzyme that
inactivates toxic substances, and in carriers of rs1138272 (a variant from the meta-analysis) mortality was increased (276). This SNV was included in the C2 model for numbness in feet, but it is unclear whether or how toxicity and efficacy are related, and the variants in CYP3A and SLCO1B1 were, on the contrary, associated with decreased mortality (277). In the further development of polygenic prediction models, the association between risk of toxicity and chance of efficacy would be of interest to evaluate, although challenging (278).

Risk assessment

Evaluating and communicating benefits of treatment and risk of toxicity are central components of clinical oncology, with mortality being the cardinal risk. Data on the relative risk reduction of adjuvant chemotherapy are very robust (21, 22), and chemotherapy is recommended from an absolute risk of recurrence of approximately 10%-15% (20, 279), to reduce the patient’s risk by a third. It is important to consider the benefits; risk reduction of distant recurrence and premature death, and chance of less extensive surgery leading to a lower risk of morbidity. On the other hand, the risks—including rare events of mortality due to acute or late side effects, increased risk of morbidities (cardiac toxicity, TIPN) and impact on HRQL—may in some cases outweigh the benefits. To visualise the absolute risk reduction of different treatments the online prediction model ‘predict breast cancer’ from NHS shows risk reductions based on clinical and tumour characteristics (279). The age of breast cancer patients varies from 25 years to 100+ years, representing a wide range in terms of health, comorbidities and remaining life expectancy. Older, less fit patients are rarely included in trials, and PRE-DICT estimations are incorrect in lower ages (280) and overestimates 10 year survival in older women (>65, >75 years) (281, 282), survival in patients with four or more comorbidities (283), and potential side effects are not accounted for.

Our studies, together with a few other (111), provide for the discussion about risk of persistent TIPN, but generally data on late side effects needed for an objective assessment may not be available (284). Even if crystal clear data were accessible, the communication of risks requires awareness of how risks are perceived. Healthcare professionals, as experts, may perceive risk based on the probability of occurrence, while lay people’s perception of risk can often be based on qualitative characteristics, familiarity, severity, and
personal impact (285). The risks and benefits need to be communicated in an understandable manner and doctors must carefully present the most relevant information. The information load can be experienced overwhelming (286), and the benefits of treatment may be overestimated by patients (287). The values and perceptions of patients vary, and many patients who receive (neo-)adjuvant treatment may not expect to have persistent symptoms beyond the treatment period (169). In oncology, patient decision aids are rare, i.e., interventions that explicitly outline the decision being considered and provide detailed, specific, and personalized information, outlining the available options and potential outcomes for patients to consider what matters most to them (288). Educational interventions for healthcare professionals on the challenges of risk communication, as well as the development of patient decision aids would contribute to improved shared decision-making on (neo-)adjuvant treatment and in oncology.

Communicating CIPN

Communication between patients and healthcare professionals about CIPN can be divided into three phases. First, the information and risk-benefit discussions which occur before the treatment decision. Second, to adjust an ongoing treatment if functional impairment occurs. In patients with a high risk of recurrence and subsequent large benefit from taxanes, careful monitoring may improve treatment intensity, as unforeseen side effects may halt treatment, and potentially a certain acceptance of persistent side effects may be reasonable. On the other hand, if there is low absolute benefit of treatment, one might consider adjusting the dose at grade 1 to be on the safe side. Generally, an inadequate fear of discrete tingling and numbness during treatment may lead to undertreatment. Underreporting or neglecting symptoms may, however, lead to unnecessary persistent side effects since adequate dose reductions at CTCAE grade 2 TIPN does not impact survival (49). A qualitative study of women who had undergone (neo-)adjuvant paclitaxel highlighted the importance of positive interaction with the oncology team and that a few women had considered underreporting but had chosen not to do so. The women prioritised efficacy over CIPN until there was impact on physical functioning, when avoiding further worsening of CIPN was considered more important. Women with long-term CIPN expressed regrets about not knowing that they could have discontinued treatment early (289). Among physicians, CIPN was considered unpredictable, as symptoms may have
different meaning for different patients, time was lacking and there was an impression that patients underreported severity (290). Anamnestic ‘signature questions’ are recommended by ESMO guidelines to capture PN in a more structured manner (87). PROM instruments are not evaluated in clinical practice (178), and may provide information that we do not know how to apply in treatment decisions (290). However, the recently suggested ‘clinical change groups’ for thresholds of clinically important changes based on CIPN20 or FACT/COG-NTX could be a future solution to this (173).

Finally, it is necessary to communicate about TIPN during follow-up to diagnose persistent symptoms. In our study population, half of those reporting TIPN had not spoken to healthcare professionals about their symptoms. We included recurrence-free survivors 2.2-7.8 years after diagnosis, patients who in Sweden have almost no routine follow-up except by phone if prescribed endocrine treatment. In a Dutch study on cancer survivors (43% breast cancer), 23% reported insufficient satisfaction with attention to CIPN during or after treatment, while the majority had a positive experience (291). Recognition of TIPN symptoms is of importance to, if possible, relieve symptoms or impairments and give advice to limit the impact on HRQL.

Despite increasing awareness of persistent TIPN, to date no preventive or treatment method is strongly recommended (87, 88). The reason for the lack of success in many intervention studies may be a true lack on effect, but may also be due to small samples size and insensitive outcome measurement. TIPN mechanisms may be a disturbance in biological systems, and targeting only one location in the system may not be effective. A focus on restoration of network homeostasis has been suggested (73); for example, through physical exercise that may both prevent and treat CIPN by strengthening protective mechanisms, neurotrophic factors, and anti-inflammatory effects (149).

The aim of (neo-)adjuvant treatments is to decrease the patients’ statistical risk of disease recurrence based on the patient’s prognostic and predictive factors. The risk assessment is to the largest extent based on treatment guidelines and clinical assessment. Based on Aristotle’s three classic elements of knowledge, episteme (the facts) and techne (practical skills) are used, but so is fronesis, or the ability to adjust a treatment to the specific patient based on professional development and experience. In the St Gallen Consensus document of 2023, the complexity of breast cancer and the importance of “an optimal treatment plan with the ‘right’ degree of intensity and duration” was emphasised, indicating a novelty of this approach. Clinicians should “assist
in balancing the realistic trade-offs between treatment benefit and toxicity” (26). In this balancing, genetic prediction of toxicity could add additional value. In complex decisions such as (neo-)adjuvant treatment, patient decision aids, better risk communication and polygenic prediction models could assist in the decision-making process, but would benefit from the continued use of fronesis.

Figure 11.
Shared decision-making and risk-benefit assessment in early-stage breast cancer.
“If it were not for the great variability among individuals, medicine might as well be a science and not an art.”

- Sir William Osler, 1892
CONCLUSIONS

Most individual peripheral neuropathy symptoms are more prevalent and severe among early-stage breast cancer survivors previously exposed to taxane chemotherapy than in women from the general population without a cancer diagnosis, and many symptoms persist longer than 3.6 years.

Clinical risk factors for persistent taxane-induced peripheral neuropathy symptoms among early-stage breast cancer survivors are use of paclitaxel, older age, overweight, diabetes mellitus, vibrating hand tools, autoimmune disease, and smoking—but risk factors vary between symptoms.

Persistent symptoms of sensory and motor taxane-induced peripheral neuropathy are associated with clinically relevant impacts on health-related quality of life, which increase with symptom severity.

The development and validation of polygenic prediction models, including clinical risk factors, to predict the risk of taxane-induced numbness in feet and tingling in feet is a proof-of-concept that demonstrates the feasibility of polygenic prediction models to estimate persistent taxane-induced peripheral neuropathy in early-stage breast cancer survivors.
FUTURE PERSPECTIVES

New therapy combinations, extended (neo-)adjuvant treatment, and inclusion of ADCs with neurotoxic payloads may contribute to a worsening of persistent CIPN in the future, despite increased awareness and better assessment methods. Development of objective, specific and easy-to-use measurement methods, such as multi-frequency vibrometry (292) could improve understanding of TIPN and contribute to a more objective outcome. The autonomic symptoms might need a re-visit in the post-covid era, as for how sure we can be of a lack of association with chemotherapy, or not just clinically neglected symptoms, insufficiently explored in research?

Pharmacological interventions have so far been unsuccessful and may not be easiest solution, due to a wide range of symptoms and corresponding biological backgrounds. Perhaps it would only be possible to relieve the increased, ‘plus’, symptoms like pain or tingling, while the effect on ‘minus’ symptoms caused by loss of function may be more difficult. Cryotherapy has tolerance problems (147, 293) and even if shown to be effective, the broad use of hilo-, and/or cryocompression therapy machines would be resource-consuming and might not be needed for all. Compression therapy is a promising preventive measure, and potentially easily implemented in clinical practice at low cost, with no need for assistance, time or extra space in day care facilities, and is well-tolerated by patients (147, 294, 295). Compression therapy may increase the tolerance for cold (296) and could be used in an escalation of prevention if compression is insufficient. Should fewer patients develop acute TIPN, it might allow higher RDIs of taxanes and possibly superior outcomes. However, there is conflicting evidence on efficacy of these interventions (297). The contralateral hand or foot has in several studies been used as a control, but little is known about the patients’ ability to separate symptoms by ‘body half’ in PROMs, when some patients may not be able to separate numbness from tingling (167). There is a need for adequately sized and well-conducted studies of compression and/or cryotherapy to evaluate their effect on persistent TIPN to gain practice-changing results.

To date, when possible, individualised selection of taxane, surveillance for dose adjustments and prescription of physical activity during treatment could limit TIPN. Results in previous studies suggest that CIPN is not a
marker of treatment efficacy or solely related to cumulative dose, but is at least partly related to interindividual differences in drug exposure and an increased sensitivity in peripheral nerves, since genes involved in nerve function were important in the prediction models. We identified several genes without previously known associations with TIPN. Especially ADAMTS, that was of highest importance in both validated models warrants further exploration, although this holds for all genes that had high variable importance—to explore the possible connection to TIPN. For better understanding, genes involved in acute and persistent TIPN could be compared, preferably in a longitudinal study. Further development of polygenic prediction models of TIPN should strive to include populations with well-defined outcomes, and explore whether docetaxel and paclitaxel should be handled separately. The outcomes, increase or loss of function, sensory or motor symptoms should also be handled separately for prediction to be achievable. Generally in healthcare, an increased use of pharmacogenetic/genomic analyses could improve results and decrease toxicity. Possibly, development of biomarkers like neurofilament light chains could indicate axonal nerve damage (298, 299) during treatment. In the future, polygenic prediction of TIPN could assist treatment decisions, help personalise monitoring and possibly also preventive interventions.
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Tack! /Kristina

"Vi vet inte, så vi kan lika gärna leva som om"

-Sofia Sivertsdotter
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"Många har det bättre men ingen har det bra
Ty den som har det allra bäst kan inte bättre ha"
Alf Henriksson
## APPENDIX

### I. EORTC QLQ-C30

<table>
<thead>
<tr>
<th></th>
<th>Question</th>
<th>Not at all</th>
<th>A little</th>
<th>Quite a Bit</th>
<th>Very Much</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>2</td>
<td>Do you have any trouble taking a long walk?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>3</td>
<td>Do you have any trouble taking a short walk outside of the house?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>4</td>
<td>Do you need to stay in bed or a chair during the day?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>5</td>
<td>Do you need help with eating, dressing, washing yourself or using the toilet?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td><strong>During the past week</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>Were you limited in doing either your work or other daily activities?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>7</td>
<td>Were you limited in pursuing your hobbies or other leisure time activities?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>8</td>
<td>Were you short of breath?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>9</td>
<td>Have you had pain?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>10</td>
<td>Did you need to rest?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>11</td>
<td>Have you had trouble sleeping?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>12</td>
<td>Have you felt weak?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>13</td>
<td>Have you lacked appetite?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>14</td>
<td>Have you felt nauseated?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>15</td>
<td>Have you vomited?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>16</td>
<td>Have you been constipated?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>
17. Have you had diarrhea?

18. Were you tired?

19. Did pain interfere with your daily activities?

20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?

21. Did you feel tense?

22. Did you worry?

24. Did you feel irritable?

25. Did you feel depressed?

26. Have you had difficulty remembering things?

27. Has your physical condition or medical treatment interfered with your family life?

28. Has your physical condition or medical treatment interfered with your social activities?

29. Has your physical condition or medical treatment caused you financial difficulties?

For the following questions please circle the number between 1 and 7 that best applies to you:

29. How would you rate your overall health during the past week?

1  2  3  4  5  6  7
   Very poor       Excellent

30. How would you rate your overall quality of life during the past week?

1  2  3  4  5  6  7
   Very poor       Excellent
II. EORTC CIPN20

<table>
<thead>
<tr>
<th>During the past week</th>
<th>Not at all</th>
<th>A little</th>
<th>Quite a Bit</th>
<th>Very Much</th>
</tr>
</thead>
<tbody>
<tr>
<td>31 Did you have tingling fingers or hands?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>32 Did you have tingling toes or feet?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>33 Did you have numbness in your fingers or hands?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>34 Did you have numbness in your toes or feet?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>35 Did you have shooting or burning pain in your fingers or hands?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>36 Did you have shooting or burning pain in your toes or feet?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>37 Did you have cramps in your hands?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>38 Did you have cramps in your feet?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>39 Did you have problems standing or walking because of weakness feeling the ground under your feet?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>40 Did you have difficulty distinguishing between hot and cold water?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>41 Did you have a problem holding a pen, which made writing difficult?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>42 Did you have difficulty manipulating small objects with your fingers (for example, fastening small buttons)?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>43 Did you have difficulty opening a jar or bottle because of weakness in your hands?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>44 Did you have difficulty walking because your feet dropped downwards?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>45 Did you have difficulty climbing stairs or getting up out of a chair because of weakness in your legs?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>46 Were you dizzy when standing up from a sitting or lying position?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>47 Did you have blurred vision?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>48 Did you have difficulty hearing?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>49 Please answer the following question only if you drive a car</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Did you have difficulty using the pedals?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>50 Please answer the following question only if you are a man</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Did you have difficulty getting or maintaining an erection?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>
“I'm just sayin', everyone that confuses correlation with causation, eventually ends up dead.”
- Unknown
Studies

The studies associated with this thesis have been removed for copyright reasons. For more details about these see:

https://doi.org/10.3384/9789180755146
Taxane-Induced Peripheral Neuropathy among Early-Stage Breast Cancer Survivors

Prevalence, Risk Factors, Quality of Life and Genetic Prediction Models