Risk factors related to chronic neuropathic pain after breast cancer surgery
A prospective cohort study

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August 2019

A thesis submitted to McGill University in partial fulfillment of the requirements of the

Degree

of Master of Science

DEDICATION

This work is dedicated to my late father S. Amarjeet Singh who has been showering his blessings from heaven.

ACKNOWLEDGEMENT

I am grateful to my exemplary and visionary mentor Dr. Ana Velly for her continuous support, patience, persistence, and motivation. Without her unconditional support, the endeavor of writing the thesis would have been impossible. Her enthusiasm kept me in high spirits during my study period. Thanks, Dr. Velly for being an excellent mentor and for guiding me on the right path.

I want to express my heartfelt thanks to Dr. Mervyn Gornitsky and my supervisory committee members: Dr. Richard Hovey, and Dr. Ji Zhang for their wise counsel, captivating suggestions, and for providing me miraculous environment to learn.

I am also thankful to the staff at Jewish General Hospital and McGill University, especially Ms. Maria Palumbo. Thanks, Maria for your valuable suggestions and unconditional support. Your suggestions were always helpful to me and have been greatly appreciated.

My wholehearted thanks to Drs. Mark Basik, Donald Hickey, Francois Boileau, Dumitra Sinziana and Harvey Sigman for providing me with a platform on which this study was made possible. I am thankful to all the staff members who helped me carry out the study.

My immense accolade and heartfelt thanks to my colleagues especially Sherif Elsaraj for their unrestricted professional ideas and noble support. Also, I would like to thank S. Amrinder Singh and Prabhkeerat Setia who helped me to get through tough times.

No combination of words can express my gratitude to family and friends who encouraged me to pursue my dreams and finish my dissertation.

Thank you All!

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LIST OF ABBREVIATIONS

ALND	Axillary lymph node dissection
β	Regression coefficients
95% CI	95% Confidence Interval
CPBCS	chronic pain after breast cancer surgery
D	days
GAD-7	Generalized anxiety disorder – 7
ICN	Intercostobrachial nerve
JGH	Jewish General Hospital
m-BPI	modified Brief Pain Inventory
mos.	Months
neuropathic CPBCS	neuropathic chronic pain after breast cancer surgery
non-neuropathic CPBCS	non-neuropathic chronic pain after breast cancer surgery
NRS	Numeric Rating Scale
OR	Odds Ratio
PHQ-8	Physical Health Questionnaire - 8
p	p - value (calculated probability)
RA	Research Assistant
RR	Risk Ratio
RT	Research trainee
RCT	Randomized Clinical Trial
SD	Standard Deviation
SR	Systematic Review
SLNB	Sentinel lymph node biopsy

Wks.	Weeks
Yrs.	Years
vs	versus

ABSTRACT

***Aim*:** Chronic neuropathic pain after breast cancer surgery (neuropathic CPBCS) is a significant clinical problem with a prevalence estimate ranging from 8% to 26%. The primary aim of this prospective cohort study was to identify pre, intra and postoperative risk factors related to neuropathic CPBCS at 3 months following breast cancer surgery.

Methods: We recruited 268 female breast cancer patients, scheduled to undergo first breast cancer surgery at Segal Cancer Centre, Montreal. Age, preoperative pain, psychological factors, and comorbidities were assessed at baseline. Data regarding type of surgery, axillary status, opioids prescribed for pain management in the recovery room, chemotherapy, and radiotherapy was gathered from patients' charts after surgery. The information pertaining to acute postoperative pain was collected via telephone interviews using the modified Brief Pain Inventory at seven days after surgery. The participants were also contacted to collect the data on neuropathic CPBCS and DN4 score using short form of Douleur Neuropathique 4 at three months post-surgery. Multivariable logistic and linear regression analyses were performed to assess the factors implicated in neuropathic CPBCS risk, and in the risk of higher DN4 score, at 3 months follow-up.

Results: One hundred ninety-nine participants completed the 3-months follow-up. Out of these, 47 (23.62%) participants reported neuropathic CPBCS with a mean DN4 score = 3.53 (SD = 0.72). From all putative risk factors evaluated, only acute pain during movement at 7 days after surgery was associated with an increased risk of neuropathic CPBCS at 3 months follow-up (RR = 1.85, 95%CI: 1.05-3.26). However, acute pain at rest appears to be a protective factor against neuropathic CPBCS (RR = 0.58, 95%CI: 0.34-0.99). Preoperative pain (β = 0.59, 95%CI: 0.04 to 1.14) and acute pain during movement (β = 0.51, 95%CI: 0.10 to 0.92) significantly contributed to higher DN4 score at 3 months after breast cancer surgery. Type of surgery (RR = 1.73, 95%CI: 0.91-3.29) and acute pain during movement (RR = 1.67, 95%CI:

0.99-2.80) were borderline associated with increased risk of neuropathic CPBCS relative to no CPBCS. Acute pain at rest appears to be a protective risk factor neuropathic CPBCS relative to non-neuropathic CPBCS (RR = 0.56, 95%CI: 0.35-0.89).

Conclusion: Our study findings suggest that acute pain during movement and preoperative pain should be evaluated and managed meticulously to scale down the burden of neuropathic CPBCS and DN4 score at 3 months following breast cancer surgery.

RÉSUMÉ

Objectif **:** La douleur neuropathique chronique après la chirurgie du cancer du sein (CPBCS neuropathique) est un problème clinique important, avec une prévalence allant de 8% à 26%. L'objectif principal de cette étude de cohorte prospective était d'identifier les facteurs de risque pré, intra et postopératoires liés au CPBCS neuropathique 3 mois après la chirurgie pour le cancer du sein.

Méthodes : Nous avons recruté 268 patientes atteintes d'un cancer du sein, qui devraient subir une première chirurgie pour le cancer du sein au Centre du cancer Segal, à Montréal. L'âge, la douleur préopératoire, les facteurs psychologiques, et les comorbidités ont été évalués avant la chirurgie. Les données concernant le type de chirurgie, le statut axillaire, les opioïdes prescrits pour la gestion de la douleur dans la salle de réveil, la chimiothérapie et la radiothérapie ont été recueillies dans les dossiers des patientes après la chirurgie. La douleur post-opératoire, la CPBCS neuropathique, ainsi que le score de DN4, ont été mesurés avec la version modifiée du Questionnaire concis de la douleur « modified - brief pain inventory scale » et l'outil Douleur Neuropathique 4 - forme abrégée, à sept jours et à trois mois après la chirurgie. Des analyses de régression logistique multivariées et des analyses de régression linéaire ont été utilisé pour évaluer les facteurs de risque de CPBCS neuropathique et de score DN4 élevé au suivi de 3 mois.

Résultats : Cent quatre-vingt-dix-neuf participants ont complété l'étude jusqu'au suivi 3 mois après la chirurgie. Parmi ceux-ci, 47 (23.62 %) ont rapporté un CPBCS neuropathique avec un score moyen de DN4 = 3.53 (SD = 0.72). De tous les facteurs de risque putatifs évalués, seule la douleur provoquée par le mouvement à 7 jours après chirurgie a été associé avec un risque de CPBCS neuropathique à 3 mois de suivi (RR = 1.85, 95%CI : 1.05-3.26). Cependant, la douleur aigue au repos semble être un facteur protecteur contre le CPBCS neuropathique (RR = 0.58, 95%CI : 0.34-0.99). La douleur préopératoire (0.59, 95 %CI : 0.04-1.14) et la douleur

aigue pendant le mouvement (0.51, 95 %CI: 0.10-0.92) ont contribué de façon significative à un score DN4 plus élevé à 3 mois après la chirurgie. Le type de chirurgie (RR = 1.73, 95%CI: 0.91-3.29) et la douleur aiguë au cours d'un mouvement (RR = 1.67, 95%CI: 0.99-2.80) étaient associés de façon limite à un risque accru de CPBCS neuropathique. La douleur aiguë au repos semble être un facteur protecteur contre de la CPBCS neuropathique par rapport à la SPPCS non neuropathique (RR = 0.56, 95%CI: 0.35-0.89).

Conclusion : Nos résultats suggèrent que la douleur aigue pendant le mouvement et la douleur préopératoire sont les facteurs de risque pertinents à évaluer et à prendre en charge afin de prévenir la CPBCS neuropathique et de score DN4 à 3 mois suivant la chirurgie pour le cancer du sein.

PREFACE

This thesis has followed a manuscript-based thesis style. The manuscripts discuss a novel project on the risk factors related to chronic neuropathic pain after breast cancer surgery. Following a concise introduction of the topic in the first chapter, the second chapter provides previous and current knowledge in the field of chronic neuropathic pain after breast cancer surgery. Chapter three describes the objectives of a study based on knowledge provided by the literature. Following a comprehensive discussion of the methodology in chapter four, the manuscript is presented. Finally, the last chapter discusses the methodological considerations and conclusion of the study. Multiple authors have contributed to this thesis work; explicit appreciation of each author's contribution is mentioned in the following section.

CONTRIBUTION OF AUTHORS

Manuscript:

1) Contributing factors of chronic neuropathic pain after breast cancer surgery: A 3-month prospective cohort study

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1. INTRODUCTION

Breast cancer is the most commonly diagnosed and leading cause of cancer death among females. In 2018, 2,088,849 new female breast cancer cases were diagnosed, which represented 11.6% of total cancer incidence worldwide (1). Due to screening, early diagnosis, and better treatment modalities, the 5-year survival rate among female breast cancer patients has improved and is now at approximately 90% (2). Chronic pain, however, is a significant problem after breast cancer surgery; it affects 25% to 60% of the patients (3).

Chronic pain after surgery is defined as pain that persists for at least three months after surgery (4). Chronic pain includes nociceptive and neuropathic pain (4-7). Three systematic reviews (SRs) demonstrated that pre, intra and postoperative factors such as age, preoperative pain, acute postoperative pain, axillary lymph node dissection, radiotherapy, and chemotherapy contribute to chronic pain after breast cancer surgery (CPBCS) (3, 8, 9).

A large prospective cohort study related to the transition from acute to chronic pain after breast cancer surgery was initiated by Dr. Ana Velly and her team in 2014. Kaur *et al.* (2016), in corroboration with the previous SRs, demonstrated that preoperative pain, acute postoperative pain, and axillary lymph node dissection contribute to the development of CPBCS (10). A 3 months prospective cohort study (n = 82) completed by Kaur *et al*. showed that preoperative pain increases the risk of CPBCS (OR = 4.11, 95%CI: 1.13-15.00). She also found that depression and chemotherapy increase CPBCS severity at 3 months follow up, independent of other pre, intra, and postoperative factors (10). Through a 3-months prospective cohort study, Gill *et al.* (2017) showed that the contribution of preoperative pain to CPBCS risk was mediated by acute postoperative pain – assessed at 7 days after surgery. More specifically, preoperative pain increases the risk of acute postoperative pain, and acute postoperative pain contributes to CPBCS risk at 3 months following breast cancer surgery (11).

However, none of the studies conducted by the team investigated the risk factors of chronic neuropathic pain after breast cancer surgery (neuropathic CPBCS).

Neuropathic pain is defined as "pain that arises as a direct consequence of a lesion or disease affecting the somatosensory system" (12). Even after the employment of the most recent and the least invasive surgical procedure, i.e. mastectomy/lumpectomy with sentinel lymph node biopsy (SLNB) (13), neuropathic CPBCS pain remains prevalent with an estimate ranging from 8% to 26% (14). Moreover, despite the availability of many effective drugs and guidelines for the treatment of neuropathic CPBCS pain, it remains undertreated or untreated. Hence, there is a need to further investigate the predictors of neuropathic CPBCS so that it could be prevented before it happens. To our knowledge, ten prospective cohort studies investigated the risk factors specifically associated with neuropathic CPBCS (14-23).

2. LITERATURE REVIEW

2.1 Chronic neuropathic pain after breast cancer surgery

The prevalence rate of neuropathic CPBCS ranges from 8% to 26% (14, 24-29). Neuropathic CPBCS, also known as post-mastectomy pain syndrome (30), is usually associated with greater pain intensity scores and is more difficult to treat (31). The neuropathic CPBCS patients frequently require stronger medication for pain relief and visit their health care providers more often than patients with nociceptive pain (25, 32, 33). Bokhari *et al.* described low self-esteem in females particularly with neuropathic CPBCS because of the limited choice of clothes that they can wear (30). It also impairs sleep and, hence, negatively impacts the quality of life among breast cancer population (34).

Jung *et al.* (2003) (35) classified neuropathic CPBCS as 1) phantom pain syndrome; 2) intercostobrachial neuralgia; 3) neuroma pain; and 4) other nerve injury pain. *Phantom pain syndrome* is defined as the painful sensory experience of an amputated breast as though it was still present. Pain which is accompanied by sensory changes along the distribution of the intercostobrachial nerve following breast cancer surgery with or without axillary dissection is known as *intercostobrachial neuralgia.* Pain in the region of the scar on the breast, chest or arm, which can be exacerbated by percussion, is known as *neuroma pain*. *Other nerve injury pain* is caused by damage to other nerves such as medial and lateral pectoral, long thoracic, thoracodorsal and other intercostal nerves during surgery, except the intercostobrachial nerve.

2.2 Prevalence of chronic neuropathic CPBCS

Prevalence measures the proportion of the population affected by a disease/condition at a specific time (36). Point prevalence is the number of existing cases of a condition in the

total population at a given point of time. Period prevalence measures the proportion of individuals in a population who have a disease during a specified period (37).

The prevalence of neuropathic CPBCS calculated by various researchers is summarized in Table 2-1. However, it is unclear if the researchers have evaluated incidence or prevalence. The prevalence of neuropathic CPBCS ranges from 3.9% to 50%. The heterogeneity in the prevalence estimate is due to discrepancies in the definition of neuropathic CPBCS, screening/diagnosis tool employed to assess neuropathic CPBCS, study design, duration of the follow-up period, surgical techniques, and statistical method adopted to assess prevalence/incidence. For instance, Pereira *et al*. estimated neuropathic CPBCS prevalence as 30.8% after 1 year in a prospective cohort study by using the clinical diagnosis as a criteria measure (14). Conversely, a retrospective cohort study calculated the prevalence of neuropathic CPBCS as 14.7% after 1 year of surgery (38). Furthermore, Reyes-Gibby *et al.* estimated neuropathic CPBCS prevalence as 18% and 9% by using screening tools ID Pain and S-LANSS (Self-reported Leeds Assessment of Neuropathic Symptoms and Signs scale), respectively (24). Belfer *et al.* measured the prevalence of neuropathic CPBCS as 3.1% after 3.2 years of investigation (26).

Table 2-1. Prevalence of neuropathic CPBCS & study characteristics							
Author	Design	Sample	Instrument used	Groups	Analysed	Percentage (neuropathic CPBCS) (%)	Time of assessment
Jain **(39)** *et al.* 2009	CS	-	Clinical examination	-	-	3.9%	2.8 ± 2.5 mos.
Reyes-Gibby **(24, 25)** *et al.* 2010	CS	430	ID pain S- LANSS	-	240	17.5%ID Pain 8.8%S-LANSS	9.5 yrs.
Belfer **(26)** *et al.* 2012	CS	111	S-LANSS	-	111	9%	64.5 mos.
Fabro **(15)** *et al.* 2012	PC	203	Physical evaluation	-	174	52.9%	6 mos.
Bokhari **(13)** *et al.* 2012	PC	17	BPI	-	17	52.9% 41.2% 35.3%	2 D, 10 D, 2-6 wks.
Elkaradawy **(40)** *et al.* 2012	RCT	50	VAS, NPS	Ma	21	39%9 mos.	24h, 1mo, 3mos., 6mos., 9mos.
				Co	22		
Mohamed **(41)** *et al.* 2013	RCT	150	DN4	Co	35	31.43% 34.29%	1 mo., 2 mos.
				Bu	35	11.43% 14.29%	
				Cln150	35	17.14% 17.14%	
				Cln250	35	14.29% 14.3%	
Albi-Felzer **(42)** *et al.* 2013	RCT	260	DN4	Co	117	24%3 mos.	3 mos., 6 mos., 12 mos.
				RV	119	30%3 mos.	
Golan-Vered **(43)** *et al.* 2013	CS	42	DN4	HC	40	50%	6 wks.
				LC			
Wilson **(38)** *et al.* 2013	RC	470	Physician diagnoses	-	470	14.7%	12 mos.
Duale´ **(44)** *et al.* 2014	PC	454	DN4	-	361	30.7%3mos. 25.7%6mos.	3 mos., 6 mos.
Bredal **(27)** *et al.* 2014	RC	1332	S-LANSS	-	834	13.9%	2-6 yrs.
Bruce **(28)** *et al.* 2014	PC	406	DN4; S-LANSS	-	308	26.3%9 mos.	4 mos., 9 mos.
					298	24.4%9 mos.	
Medina **(16)** *et al.* 2015	PC		Self-reported PBS	-	88	44.3%45D 18.2%2yrs	45 D, 6 mos., 2 yrs.
Gupta **(45)** *et al.* 2015	PC	12	NRS; S-LANSS	-	5	41.6%	24 h, 1 wk., 3 mos.
Abdallah **(46)** *et al.* 2015	RCT	66	DN4	PVB	33	18.3%PVB	6 mos.
				Co	31	58.1%%Co	
Andersen **(47)** *et al.* 2015	PC	537	Pain-*DETECT*	-	504	18%	1 wk.,
					491	16%	6 mos.,
					475	14%	12 mos.
Steyaert **(48)** *et al.* 2016	CS	267	ID pain	-	128	21.1%	80 mos.
Juhl **(49)** *et al.* 2016	CS	305	Pain-*DETECT*	-	261	5%	3 yrs.

Fontes **(50)** *et al.* 2016	PC	506	Clinical examination	-	475	21.6% 23.6%	1 yr., 3 yrs.
Fuzier **(51)** *et al.* 2016	PC	260	DN4 7-item	-	150	24%	3 mos.
Variawa **(52)** *et al.* 2016	CS	100	DN4	-	92	38.04%	12.22 mos.
Alkan **(53)** *et al.* 2016	CS	-	Self-reported questionnaire	-	614	45.1%	<46 mos.
Beyaz **(54)** *et al*. 2016	CS	146	VAS, SF-MPQ, DN4, SF-36	n-PMPS	87	23.7%	77 mos.
				PMPS	47		
Pereira **(14)** *et al.* 2017	PC	506	Clinical examination	-	503	30.8%	1 yr.
Yesil **(55)** *et al.* 2018	PC	70	LANSS	-	70	25.6%	48.5 mos.
Reddi **(56)** *et al.* 2018	CS	37	BPI S-LANSS	TPVB	25	20%	241 D
Leysen **(6)** *et al.* 2018	CS	111	VAS, DN4, SF-36, CSI	-	91	25.3%	3.1 yrs.
La Cesa **(17)** *et al.* 2018	PC	42	DN4, NPI, QST, BDI, PGIC, SF-36, Clinical examination	ICN-	17	15%1mo	3 mos., 6 mos., 12 mos.
				ICN+	23		

BDI-Beck Depression Inventory; BPI-Brief pain inventory; Bu-Bupivacaine; Cln150-Plain bupivacaine with 150 µg clonidine; Cln250-Plain bupivacaine with 250 µg clonidine; CS-Cross-sectional; CSI-Central sensitization inventory; D-day; DN4-Douleur neuropathique-4; HC-High cluster group; ICN-Inter costo-brachial nerve; LC-low cluster group; LANSS-Leeds assessment of neuropathic pain symptoms and signs; Ma-Mastectomy; NPI-Neuropathic pain symptom inventory; PBS-Phantom breast sensations; PC-Prospective cohort; PGIC-Patient global impression of change; n-PMPS-non-Post mastectomy pain syndrome group; PMPS- Post mastectomy pain syndrome group; PVB-Paravertebral block; mo.-month; RCT-Randomized clinical trial; RV-Ropivacaine infiltration group; S-LANSS-Self reported-Leeds assessment of neuropathic pain symptoms and signs; wks.-weeks; yrs.-years; SF-MPQ-Short form-McGill Pain questionnaire; TPVB-Thoracic paravertebral block; VAS-Visual analogue scale; QST-Qualitative sensory testing;

2.3 Aetiology of neuropathic CPBCS

Neuropathic pain is defined (IASP, 1994) as the "pain initiated or caused by a lesion or the dysfunction of the nervous system" (57). The definition of neuropathic pain is beneficial to differentiate neuropathic pain from nociceptive to some extent, but it lacks precision (58). In order to improve the definition of neuropathic pain, a group of neurologists, neuroscientists, clinical neurophysiologists, and neurosurgeons established a task force in collaboration with the IASP Special Interest Group on Neuropathic Pain (NeuPSIG). They proposed a revised definition of neuropathic pain: "pain caused by direct consequence of a lesion or disease of somatosensory system" (33).

Neuropathic pain aetiology has been suggested as a multifactorial disease that cannot be specified by a single cause or a specific lesion (59). Invasion of the tumor on peripheral nerve, chemotherapy, radiotherapy, and surgery are considered to be the plausible risk factors of neuropathic CPBCS (24, 60). The proposed mechanism of neuropathic pain is described below.

The precise mechanism of perpetuating neuropathic pain is unclear (61). Peripheral and central sensitization are the two pathophysiological mechanisms that have been suggested to contribute to the development of neuropathic CPBCS (33, 59, 62). Pain perceptions are normally elicited by activity in unmyelinated (C) and thinly myelinated (Aδ) primary afferent neurons. The pathological spontaneous activity in the peripheral neurons, which are usually silent in the absence of stimulus is known as peripheral sensitization (59). Peripheral sensitization is predicated by aberrant alterations in ion (sodium, potassium, and calcium) channels (33, 61), enhanced gene expression (mRNA for voltage-gated sodium channels) (59), upregulation of vanilloid receptor (TRVP1) and channel density on the cell membrane (61). Furthermore, ectopic activity in both injured and uninjured primary afferent nociceptors at the site of the lesion, induced by proinflammatory cytokines such as TNF-α, IL-1, IL-6, NGF,

PGE-2, histamine, chemokines, and neuropeptides produced by activated immune cells explains the role of inflammation in neuropathic pain (59, 63-65).

The central sensitization (enhanced excitability in the spinal cord (dorsal root ganglion) and central nervous system neurons) due to the persistence of peripheral nociceptor hyperactivity is considered to be responsible for chronicity of the neuropathic pain. Neuropeptides and amino acids (NMDA - N-methyl D-aspartate, AMDA - α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid, GABA - γ-aminobutyric acid) contribute to central sensitization (59). Dysfunction in descending pain pathways and interneurons (inhibitory pain control system) also play a crucial role in the development of neuropathic pain (33).

It is debatable if neuropathic and non-neuropathic pain should be considered as two different entities or a continuum of a single condition. Cohen *et al.* (66) suggested two main differences between neuropathic and non-neuropathic pain: 1) missing transduction in neuropathic pain, and 2) a poorer prognosis in neuropathic pain than non-neuropathic pain.

Nerve injury is considered to be an important causative factor of neuropathic pain. But simultaneously, one may argue that nociceptive pain also involves small nerve fibre injuries. The difference between neuropathic and non-neuropathic pain might, therefore, be considered one of scope (large versus vs (versus) small nerve injury) although small fibre neuropathy, a form of neuropathic pain, does not include any discrete nerve injury (66).

Additionally, researchers practice distinct models to explain neuropathic and non-neuropathic pain, even though the same neurotransmitters, neuropeptides, cytokines, and enzymes implicated in both types of pain, with a large degree of overlap (66).

2.4 Potential risk factors of neuropathic CPBCS

A risk factor is defined as an attribute that is associated with an increased or decreased risk of developing the disease/outcome (67). A risk factor always precedes the onset of outcome.

Three different SRs provided an evidence about potential risk factors for CPBCS: age, psychological factors (ex. anxiety and depression), comorbidities, type of surgery, axillary status, inter costo-brachial nerve, preoperative pain, acute postoperative pain, perioperative pain management, adjuvant therapy (e.g., chemotherapy, radiotherapy and hormonal therapy), postoperative complications (3, 8, 9). However, few studies established the risk factors associated with neuropathic CPBCS. An overview of the studies that have assessed risk factors associated with neuropathic CPBCS is described in Table 2-2.

2.4.1 Age

Nine out of fifteen studies (approximately 60%) assessed the positive relation between younger age and neuropathic CPBCS (13-19, 25, 29, 30, 44, 50, 53, 68-71). These nine studies included seven prospective cohort studies (13, 15, 16, 18, 20, 44, 70) and two cross-sectional study (25, 71). The effect size of this positive association between younger age and neuropathic CPBCS ranged from 1.04 (95%CI: 1.00-1.01) (16) to 3.9 (95%CI: 1.4-10.4) (16, 25, 70). However, it is interesting to note that only one study (n = 88) found the a magnitude of odds ratio (OR) as high as 3.9 with a 95% confidence interval (95%CI): 1.4-10.4 (16). A wide 95%CI suggested the lack of precision in estimating a high OR of 3.9. Two prospective cohort studies also described older age as a protective factor for neuropathic CPBCS (20, 44). Half of the prospective studies demonstrated a positive relationship between young age and neuropathic CPBCS at 3 months follow-up (13, 18, 20, 70) and the remaining half investigated the same relationship at 6 months (15, 16, 44) following breast cancer surgery. It is important

to note that these studies are inconsistent in defining the younger age. For instance, Alkan *et al*., Bokhari *et al.* and Fabro *et al*. referred ages that were <65 years, <50 years, <40 years as younger ages respectively (13, 15, 68).

2.4.2 Psychological factors

Five of six studies conducted found a significant association between psychological factors such as anxiety, depression, stress, catastrophizing and neuropathic CPBCS (14, 15, 18, 44, 68, 70). Prospective studies demonstrated that anxiety at baseline contributes to neuropathic CPBCS risk with ORs ranging from 1.06 (95%CI: 1.02-1.10) (70) to 1.98 (95%CI: 1.43-2.75) (44). One of three prospective cohort studies (n = 454) also mentioned the protective role of low anxiety on neuropathic CPBCS at 6 months follow-up (44).

A cross-sectional study conducted by Alkan *et al.* (n = 614) found a significant relationship between posttraumatic stress disorder and neuropathic CPBCS (p = <0.001) (68). A prospective cohort study put an evidence that higher monitoring processing style scores (β = 0.23, p = 0.023) and over psychological stress (β = 0.22, p = 0.020) at baseline contributed to higher scores of neuropathic CPBCS at 3 months follow-up (18). Similarly, another prospective study demonstrated that patients who reported catastrophizing pain and history of a negative event during the past six months before surgery were more likely to develop neuropathic CPBCS at 6 months follow-up (OR = 1.34, 95%CI: 1.05-1.71) (44).

All studies (2/2) investigating the relationship between depression and neuropathic CPBCS found a statistically significant association. The OR for this association ranged from 2.06, 95%CI: 1.61-2.63 (44) to 2.14, 95%CI: 1.26-3.63 (14). It was noteworthy that a prospective cohort study (n = 156) concluded that the depressed participants were two times as likely to develop neuropathic CPBCS with severity $\geq$ 3 at 1-year follow-up (OR = 2.14, 95%CI: 1.26-3.63) (14).

2.4.3 Comorbidities

Seven prospective (13, 14, 19-21, 44, 70), one retrospective (21, 29), and two cross-sectional studies (25, 68) investigated the role of painful and non-painful comorbidities as the risk factors of neuropathic CPBCS.

More specifically, a cross-sectional study found neuropathic CPBCS associated with diabetes (OR = 6.67, 95%CI: 1.87-23.63), osteo-arthritis (OR = 3.97, 95%CI: 1.57-10.03) hypertension (OR = 2.53, 95%CI: 1.2-5.50). The odds of rheumatoid arthritis (OR = 3.14, 95%CI: 0.09-11.80) was insignificantly associated with neuropathic CPBCS (25). A retrospective cohort study (n = 470) demonstrated that diabetic neuropathy (OR = 8.17, 95%CI: 3.10-21.5), diabetes (OR = 2.21, 95%CI: 1.18-4.15) and fibromyalgia (OR = 2.75, 95%CI: 1.13-6.69) significantly contribute to neuropathic CPBCS risk (29). However, 95%CI for diabetic neuropathy is too wide to calculate an OR = 8.17 precisely.

A pilot prospective cohort study (n = 17) investigated the relationship of pain in any body part and neuropathic CPBCS and found insignificant association at 3 months follow-up (13). The insignificant association between the two variables was potentially due to small sample size (n = 17). Another prospective cohort study found that the participants who reported painful comorbidities at baseline were 52% more likely to develop neuropathic pain at 6 months follow-up than who did not report any painful comorbidities (OR = 1.52, 95% CI: 1.16-1.99) (44). Equivalently, five prospective cohort studies assessed the contribution of preoperative pain to neuropathic CPBCS but did not find any relation with the outcome of interest i.e. neuropathic CPBCS (14, 19-21, 70).

2.4.4 Type of surgery

Seven prospective cohort studies (13-15, 21, 44, 70), one retrospective (21, 29) and two cross-sectional (71, 72) investigated the association between type of surgery and neuropathic

CPBCS. A prospective cohort study demonstrated that the individuals exposed to breast cancer surgery were approximately 7 times more likely to develop neuropathic chronic pain than who were not exposed to breast cancer surgery (OR = 7.83, 95%CI: 1.8-28.5) (70). Another prospective study found that the participants exposed to breast cancer surgery presented a greater likelihood to develop neuropathic CPBCS than who were not exposed to breast cancer surgery (OR = 15.93, 95%CI: 5.43-46.77) (44). Bokhari *et al.* (13) and Georgescu *et al.* (21) found invasive breast surgery significantly contributed to neuropathic CPBCS. Surprisingly, Pereira *et al.* (n = 156) presented greater likelihood to develop neuropathic CPBCS in participants who were exposed to breast- conserving surgeries with axillary lymph nodes removal (OR = 3.13, 95%CI: 1.51-6.48) than participants who were exposed to mastectomy with axillary lymph nodes removal (OR = 2.53, 95%CI: 1.25-5.11) in a one year long prospective cohort study (14).

2.4.5 Axillary status

Six out of eight studies that assessed the relationship between lymph nodes removal and neuropathic CPBCS found a positive association between the two variables of interest (axillary lymph node removal and neuropathic CPBCS) (14, 15, 20, 22, 29, 34, 71, 72). The OR for the significant association between the two variables ranged from 1.88 (95%CI: 1.08-3.28) (15) to 2.75, (95%CI: 1.34-5.63) (50). A prospective cohort study (n = 203) calculated the effect size of 1.40 (95%CI: 1.06-1.86) for neuropathic CPBCS when >15 lymph nodes were removed at 6 months follow-up (15). One cross-sectional study found a significant association between axillary lymph node removal and neuropathic CPBCS in the crude analysis (OR = 2.03, 95%CI: 1.06-3.89) (71). However, it is unknown if this contribution was confounded by other covariates.

2.4.6 Acute postoperative pain

Only two prospective cohort studies investigated the association between acute pain and neuropathic CPBCS (13, 70). A pilot prospective study with a very small sample size (n = 17) found a positive relationship between acute postoperative pain and neuropathic CPBCS (13). Another prospective study demonstrated that participants exposed to acute pain assessed at 2 days after breast surgery are almost three times as likely to develop neuropathic CPBCS at 3 months follow-up than who did not report acute pain at 2 days after breast cancer surgery (OR = 2.9, 95%CI: 1.3-6.4) (70).

2.4.7 Adjuvant treatment

Seven out of twelve (58%), which included three prospective (23, 34, 50), one retrospective (29), three cross-sectional (25, 43, 71) studies found a statistically significant association between chemotherapy and neuropathic CPBCS. A cross-sectional study found a significant association between cumulative paclitaxel dose and neuropathic CPBCS (OR = 2.95, 95%CI: 1.2-7.2) (25). In support of this cross-sectional study, one prospective and a retrospective cohort studies demonstrated that the individuals exposed to chemotherapy have higher likelihood of developing neuropathic CPBCS at 3 years (OR = 2.10, 95%CI: 1.20-3.67) (50) and 1 year (OR = 2.85, 95%CI: 1.23-6.58) (29) follow-up than who were not exposed to chemotherapy, respectively.

There was only one prospective cohort study that investigated the change in neuropathic pain score index (NPSI) over time from baseline to one month after radiotherapy. According to this prospective cohort study, NPSI first increases from baseline (NPSI = 4.9) to the end of the radiotherapy (NPSI = 10.0) and decreases again at 1 month after radiotherapy (NPSI = 6.7) (22).

Table 2-2. Risk factors associated with neuropathic CPBCS						
Author	Demographic	Psychological	Comorbidities	Surgery	Adjunctive treatment	Acute pain
Abdallah **(46)** *et al.*	-	-	-	-	PVB*	-
Alkan **(68)** *et al.*	Age, Low income*	PTSD*	Dbt	-	CT, RT	-
Bennedsgaard **(23)** *et al.*	-	-	-	-	CT*	-
Bokhari **(13)** *et al.*	Age*, Marital status, Education, Occupation, Ethnicity, BMI	-	Pain other than breast	Invasive surgery*	-	AcP *
Duale **(44)** *et al.*	Age*	Anxiety*, history of negative event*, Catastrophising pain*	Painful comorbidities*	BS*	-	-
Dubois **(70)** *et al.*	Age,	Anxiety*, Depression*	Preop-Pain	BS*	CT, RT	AcP*
Lefebvre-Kuntz **(20)** *et al.*	Age*, weight, Height, BMI	-	Preop-pain	Ma QdR TmR Lmp ALND*	-	-
Fontes **(50)** *et al.*	Age Education	-	-	ALND*	CT*	-
Fabro **(15)** *et al.*	Age*, BMI, Education, Employment bond, Occupation, Dominant hand	Psychological factors	-	Ma, BCS LN*	CT, HT, RT	-
Golan-Vered **(43)** *et al.*	-	-	-	-	Pac*	-
Georgescu **(21)** *et al.*	-	-	Preop-pain	Invasive surgery*	-	-
La Cesa **(17)** *et al.*	Age	-	-	ICN* ALND	CT, RT	-
Lee E. **(22)** *et al.*	BMI*, Race *	-	-	-	RT	-
Meijuan **(72)** *et al.*	-	-	-	Ma, BCS, ALND, SLNB	Preop CT, Preop RT, Postop CT Postop RT	-
Medina **(16)** *et al.*	Age* Education*	-	-	-	-	-
Pereira **(14)** *et al.*	Age, Education	Anxiety* Depression*	Preop-pain	BCS + SLNB, Ma + SLNB, BCS + ALND* Ma + ALND*	CT, RT, BT, ET, IT	-

				ICN*		
Reyes-Gibby **(25)** *et al.*	Age	-	HTn Dbt* RA OA*	-	cPac-d*	-
Sherman **(18)** *et al.*	Age*	Processing style*, Baseline stress*	-	-	-	-
Urbano **(19)** *et al.*	Age,	-	Preop-Pain		Preop RT, Postop RT	-
Vilholm **(71)** *et al.*	Age*, BMI	-	-	Ma*, ALND*	CT*, RT, ET	-
Wilson **(29)** *et al.*	Age, Ethnicity	-	Dbt*, DN*, ST, FM*, MS, PHN	Ma, ALND*	RT, CT*	-

ALND-Axillary lymph node dissection; BCS-Breast conserving surgery; BMI-Body Mass Index; BS-Breast surgery; cPac-d-Cumulative Paclitaxel dose; CIPN-Chemotherapy-induced peripheral neuropathy CT-Chemotherapy; Dbt-Diabetes; DN-Diabetic neuropathy; ET-endocrine therapy; FM-fibromyalgia; HT-Hormone therapy; HTn-Hypertension; ICN-inter costo-brachial nerve; IT-Immunotherapy; Lmp-lumpectomy; Ma-mastectomy; LN-lymph nodes; MS-Multiple sclerosis; OA-Osteoarthritis; PHN-Postherpetic neuralgia; PTSD-Post traumatic stress disorder; QdR-Quadrantectomy; RA-Rheumatoid arthritis; RT-radiotherapy; ST-Sympathetic dystrophy TmR-Tumorectomy;

3. STUDY OBJECTIVES

The overall objective of this study was to identify risk factors related to neuropathic CPBCS at 3 months following breast cancer surgery. The specific aims and alternative hypotheses are described below:

Aim#1: To determine whether preoperative (age, preoperative pain, psychological factors, and comorbidities), intraoperative (type of surgery and axillary status) and postoperative (acute postoperative pain, opioids prescribed for pain management in the recovery room, chemotherapy, and radiotherapy) factors contribute to neuropathic CPBCS risk at 3 months follow-up.

Hypothesis 3.1: Age, preoperative pain, psychological factors, comorbidities, type of surgery, axillary status, acute postoperative pain, opioids prescribed for pain management in the recovery room, chemotherapy, or radiotherapy contribute to neuropathic CPBCS risk at 3 months follow-up.

Aim#2: To determine whether preoperative (age, preoperative pain, psychological factors, and comorbidities), intraoperative (type of surgery and axillary status) and postoperative (acute postoperative pain, opioids prescribed for pain management in the recovery room, chemotherapy, and radiotherapy) factors contribute to higher DN4 score at 3 months follow-up.

Hypothesis 3.2: Age, preoperative pain, psychological factors, comorbidities, type of surgery, axillary status, acute postoperative pain, opioids prescribed for pain management in the

recovery room, chemotherapy, or radiotherapy contribute to higher DN4 score at 3 months follow-up.

Aim#3: To determine the relevant risk factors of neuropathic CPBCS relative to no CPBCS and non-neuropathic CPBCS at 3 months follow-up.

Hypothesis 3.3: The potential risk factors described above contribute to neuropathic CPBCS, relative to no CPBCS, or non-neuropathic CPBCS at 3 months follow-up.

4. METHODOLOGY

This section describes in detail the ethics, study design, study population, data collection and statistical analyses used to assess the study outcomes.

4.1 Ethics

The Research Ethics Committee at the Jewish General Hospital (JGH) in Montreal, Quebec, Canada approved the protocol before the start of this study (Project 2015-271, 14-112; Dated: 2018-08-27). Breast cancer patients being treated by surgeons in the JGH oncology department (Drs. Basik, Boileau, Sigman, and Sinziana) were pre-screened. The doctors or nurses provided a quick overview of the study to the patients. If the patients agreed to be contacted for the study, the research trainees obtained their contact information. Trainees met the potential participants in presurgical testing and explained every aspect of the study to them. Patients had the opportunity to ask questions and informed consent was obtained from those who agreed to participate.

4.2 Study Design

A 3-month prospective cohort study design was chosen to carry out this study. A cohort study design is an observational epidemiological study design in which exposed and non-exposed individuals are identified and followed for a certain period to ascertain the occurrence of health-related events. Robert H. Friis defined prospective cohort study as a type of cohort study design that collects data on exposure at the initiation (baseline) of a study and follows the population to observe the occurrence of health outcomes in the future (67).

This study design was selected particularly because: temporal relationship between the exposure and outcome can be clearly defined, minimizes the chance of selection and

information bias, as well as it allows to study multiple outcomes simultaneously. Cohort studies are well suited for assessing the effects of rare exposures. It also allows the measurement of incidence of disease in the exposed and unexposed groups (73).

Besides many advantages, cohort study design also has a few *limitations*: 1) cohort studies are often very expensive and time consuming; 2) they are not suitable for diseases with long latency period; 3) cohort studies are not suitable for rare diseases; 4) there may be a problem of withdrawals; 5) there may be study effects; that is, someone may act differently simply by virtue of being studied; and 6) exposure to the factor of interest may change, especially when the time horizon is long, for reasons unconnected with the investigation (74).

4.3 Study population

To carry out this study, female breast cancer patients scheduled to undergo breast surgery were recruited from the Segal Cancer Centre at the JGH. The Segal Cancer Centre is one of the largest cancer care centres in Montreal and treats a significant number of breast cancer patients annually. Patient recruitment took place from November 2014 to January 2019. Patient recruitment is ongoing, however, to increase the sample size and for future studies.

4.3.1. Eligibility criteria

Women 18 years or older who were incident cases of breast cancer and scheduled to receive their first breast cancer surgery were invited to participate in this study. Women patients who did not undergo breast surgery; who had previous cancer of any other kind; with a Karnofsky Performance Status Score under the score of 50, which includes patients who require considerable assistance and frequent medical care; had metastasis; who did not understand English or French; had no access to a telephone; were pregnant women; and who

had received previous breast surgery were excluded. Finally, male patients with breast cancer were also excluded.

4.4 Assessment and data collection

4.4.1 Primary and secondary Outcome

The primary outcome of this study is chronic neuropathic pain after breast cancer surgery (neuropathic CPBCS).

To assess neuropathic CPBCS, a screening/diagnostic tool containing two questions with seven interview items named short form of Douleur Neuropathique 4 (short form - DN4) was used (APPENDIX) (75). The first question assessed three pain symptoms regarding pain quality such as burning, painful cold, and electric shocks. The second question assessed the four non-painful symptoms such as numbness, tingling, pins and needles, and itching. The patients were expected to answer in yes/no form for each interview item. A score of 1 and 0 was given for each yes and no, respectively. A DN4 score was then calculated by adding all the individual item scores. If the DN4 score is ≥ 3, the pain is classified as neuropathic CPBCS.

DN4 was originally developed in French (75) and validated in many regional languages (69, 76-80). This instrument has a high sensitivity (78%), specificity (81.2%), positive predictive value (79.5%) and inter-rater reliability (Cohen's kappa coefficient values ranged between 0.66 and 0.96). The *strengths* of using DN4 are 1) simple; 2) quick; 3) easy to use; 4) understandable by most of the patients and clinicians; and 5) can detect NP in mixed pain syndromes, for instance, postsurgical pain, cancer pain. The *limitations* of DN4 include: 1) it does not provide any clinical history of pain; 2) missing neurological examination; and 3) may cause under-estimation of the neuropathic condition.

Total DN4 score (previously described) was the secondary outcome.

4.4.2 Putative risk factors

The research trainees met the participants in person and conducted a series of telephone interviews with the eligible participants to collect the data on preoperative and postoperative risk factors. The data regarding the day of surgery was collected from electronic charts available in the hospital's computer (Chartmaxx) system.

4.4.2.1 Preoperative potential risk factors

The research trainees contacted potential participants who presented themselves for preadmission testing. After obtaining the informed consent, trainees asked the participants to complete the questionnaire at baseline to collect the data for putative preoperative risk factors (preoperative breast pain, psychological factors, and comorbidities).

Table 4-1. Questionnaire administered at baseline

Domain	Measures
Informed consent	-
Age	Medical questionnaire
Pain Intensity	m-BPI
Generalized Anxiety	GAD-7
Depression	PHQ-8
Comorbidities	Chartmaxx

m-BPI: modified - Brief Pain Inventory; GAD-7: Generalized Anxiety Disorder-7; PHQ-8: Patient Health Questionnaire-8 depression scale

Preoperative pain: To determine preoperative pain participants were invited to answer two questions: 1) "Do you have pain or discomfort in your breast?" 2) "Do you have pain or discomfort in your breast when you move your arm?" If the patient answered "yes" to any of these two questions, trainees asked three different questions ('pain right now', 'worst pain', 'average pain') to assess preoperative pain intensity. Patients responded to these three questions with a numeric rating scale (NRS) from 0 to 10, where 0 = no pain and 10 = worst imaginable pain. The modified - Brief Pain Inventory **(**m-BPI) (APPENDIX) (81) has test-retest stability coefficients ranging from 0.58 to 0.95, Cronbach alphas of 0.85 or greater, and satisfactory-good construct and criteria validity (82) (83).

Anxiety and Depression: Generalized Anxiety Disorders (GAD-7) (APPENDIX) (84) and Patient Health Questionnaire (PHQ-8) (APPENDIX) (85) were used to assess anxiety and depression respectively. The GAD-7 has a value of sensitivity: 0.83, 95% CI: 0.71-0.91 and specificity: 0.84, 95% CI: 0.70-0.92 (84). The PHQ-8 also demonstrated satisfactory validity and reliability (Cronbach $\alpha = 0.82$) (86).

Furthermore, non-painful comorbidities such as hypertension and diabetes were assessed using chartmaxx. Trainees also asked participants about their age.

4.4.2.2 Intraoperative putative risk factors

Intraoperative factors such as type of surgery and axillary status were retrieved from electronic charts by using chartmaxx in the hospital system by trainees.

4.4.2.3 Seven days postoperative: acute pain

Trainees contacted the participants by telephone to determine if they had pain 7 days after surgery. If the participants had pain at 7 days following surgery, three more questions were asked about acute pain intensity. The modified-Brief Pain Inventory was used to assess acute pain at 7 days postsurgery.

4.4.2.4 Three months postoperative putative risk factors:

Potential risk factors at 3 months following breast cancer surgery, such as chemotherapy or radiotherapy, were collected by telephone interviews by trainees.

4.5 Statistical analyses

All analyses tested a null hypothesis of no statistical association between the independent and dependent variables of interest at $\alpha = 0.05$ significance**.** Chi-square and

Fisher's exact test was used to compare the distribution of the categorical variables. To assess the means of the continuous variables between two groups, Student t-test was used. Crude and multivariable logistic regression analyses (proc logistic, SAS) were employed to determine the risk factors of neuropathic CPBCS at 3 months following breast cancer surgery. Risk ratios (RRs) and their 95% confidence intervals (CI) were estimated.

Primary analysis

The neuropathic CPBCS (dependent variable), a binary variable, is our primary outcome of interest. Therefore, to investigate the contributing factors related to neuropathic CPBCS logistic regression analysis was performed.

More specifically, crude logistic regression analyses were performed to investigate each plausible (preoperative, intraoperative and postoperative) risk factor.

(i) Preoperative risk factors: Age, preoperative pain, average preoperative pain intensity, comorbidities, anxiety, and depression were included as the independent variables in the analysis. The average preoperative pain intensity score was calculated by adding current, worst and average pain intensities at baseline divided by 3. The score of anxiety (GAD-7) and depression (PHQ-8) were calculated by adding the item responses. GAD-7 scores of 5, 10, and 15 represent cut points for mild, moderate, and severe anxiety, respectively. PHQ-8 scores of 5, 10, and 15 correspond to mild, moderate, and severe depression, respectively.

(ii) Intraoperative factors: We involved independent variables such as type of surgery and axillary status as intraoperative plausible risk factors.

(iii) Postoperative factors: Independent variables included in this category were acute pain, acute pain intensity, opioids used for pain management in the recovery room, radiotherapy and chemotherapy. Data on acute pain and its intensity was collected at 7 days following breast cancer surgery. Information regarding radiotherapy and chemotherapy was collected at 3

months following breast surgery. Data regarding opioids was retrieved from the patients' charts.

Further, a multivariable logistic regression analysis was performed that included anxiety, type of surgery, acute pain at rest and acute pain during movement. Only four risk factors were included in the final model by considering (47 participants with neuropathic pain/15) the demands of statistical modeling. The neuropathic CPBCS participants served as a limiting factor for selecting the number of variables to be included in the multivariable model. Since we had only 47 participants who reported neuropathic CPBCS, we included 4 plausible risk factors in the final model. These variables were selected based on biological and statistical significance.

Secondary analysis

We assessed the contributing factors of DN4 score at 3 months following breast surgery using linear regression analysis (proc mixed, SAS). Regression coefficients (β) and their 95% confidence intervals (CI) were estimated.

First, crude linear regression analyses were performed to investigate each plausible contributing factor. Furthermore, a multivariable linear regression analysis was done that included all the candidate plausible (pre, intra and postoperative) contributing factors.

Furthermost, a multivariable linear regression analysis was performed including all potential factors associated with the secondary outcome: preoperative pain, average preoperative pain intensity, anxiety, diabetes, type of surgery, acute pain on movement and radiotherapy. For the selection of the final model, one variable from the multivariable model was eliminated at a time and AIC of the new model was determined. Then AIC of two models (multivariable model – including all the putative risk factors and new model where one variable

was eliminated) were compared. The model with lower AIC was kept for a further selection of variables. A similar process was repeated to attain a better fit final statistical model.

In both linear and logistic regression models, independent variables – preoperative pain (no = 0, yes = 1), anxiety (no or mild = 1, moderate and severe = 2), depression (no or mild = 1, moderate and severe = 2), diabetes (no = 0, yes = 1), hypertension (no = 0, yes = 1), surgery type (segmental mastectomy = 1, mastectomy = 2), axillary status (No lymph node removal = 0, sentinel lymph node biopsy and axillary lymph node dissection = 1), opioids (no = 0, yes = 1), acute postoperative pain at rest (no = 0, yes = 1), acute postoperative pain during movement (no = 0, yes = 1), radiotherapy (no = 0, yes = 1), and chemotherapy (no = 0, yes = 1) were included as binary variables. Age, average preoperative pain intensity, current acute pain intensity, worst acute pain intensity and average acute pain intensity were included as continuous variables.

Finally, to compare the risk factors associated with neuropathic CPBCS vs no CPBCS and non-neuropathic CPBCS, we performed another regression analysis for the risk factors that were included in the final logistic regression model analysis of neuropathic CPBCS.

5. MANUSCRIPT

5.1 Risk factors related to chronic neuropathic pain after breast cancer surgery: A 3-month prospective cohort study

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Abstract:

***Aim*:** Chronic neuropathic pain after breast cancer surgery (neuropathic CPBCS) is a significant clinical problem with a prevalence estimate ranging from 8% to 26%. The primary aim of this prospective cohort study was to identify pre, intra and postoperative risk factors related to neuropathic CPBCS at 3 months following breast cancer surgery.

Methods: We recruited 268 female breast cancer patients, scheduled to undergo first breast cancer surgery at Segal Cancer Centre, Montreal. Age, preoperative pain, psychological factors, and comorbidities were assessed at baseline. Data regarding type of surgery, axillary status, opioids prescribed for pain management in the recovery room, chemotherapy, and radiotherapy was gathered from patients' charts after surgery. The information pertaining to acute postoperative pain was collected via telephone interviews using the modified Brief Pain Inventory at seven days after surgery. Participants were also contacted at three months post-surgery to retrieve the data on neuropathic CPBCS and DN4 score using short form of Douleur Neuropathique 4. Multivariable logistic and linear regression analyses were performed to assess the factors implicated in neuropathic CPBCS risk, and in the risk of higher DN4 score, at 3 months follow-up.

Results: One hundred ninety-nine participants completed the 3-month follow-up. Out of these, 47 (23.62%) participants reported neuropathic CPBCS with a mean DN4 score = 3.53 (SD = 0.72). From all putative risk factors evaluated, only acute pain during movement at 7 days after surgery was associated with an increased risk of neuropathic CPBCS at 3 months follow-up (RR = 1.85, 95%CI: 1.05-3.26). However, acute pain at rest appears to be a protective factor against neuropathic CPBCS (RR = 0.58, 95%CI: 0.34-0.99). Preoperative pain (β = 0.59, 95%CI: 0.04 to 1.14) and acute pain during movement (β = 0.51, 95%CI: 0.10 to 0.92) significantly contributed to higher DN4 score at 3 months after breast cancer surgery. Type of surgery (RR = 1.73, 95%CI: 0.91-3.29) and acute pain during movement (RR = 1.67, 95%CI:

0.99-2.80) were borderline associated with increased risk of neuropathic CPBCS relative to no CPBCS. Acute pain at rest appears to be a protective risk factor neuropathic CPBCS relative to non-neuropathic CPBCS (RR = 0.56, 95%CI: 0.35-0.89).

Conclusion: Our study findings suggest that acute pain during movement and preoperative pain should be evaluated and managed meticulously to scale down the burden of neuropathic CPBCS and DN4 score at 3 months following breast cancer surgery.

Introduction:

Breast cancer is the most commonly diagnosed cancer among women worldwide and 271,270 new breast cancer cases are estimated for 2019 (87). One in every eight Canadian women is expected to have breast cancer in her lifetime (88). Due to early diagnosis and better treatment modalities, survival rate has increased to approximately 90% (87). Chronic neuropathic pain after breast cancer surgery (neuropathic CPBCS) is a prevalent clinical problem. Despite the employment of least invasive surgery (segmental mastectomy with sentinel lymph node biopsy) (35) neuropathic CPBCS remains common with a prevalence estimated from 8% to 26% (14). The care of neuropathic CPBCS is an immense financial burden that costs around US$ 27,000 per person annually (89). It also negatively impacts self-esteem of breast cancer patients due to the limited choice of clothes they can wear (30). Moreover, it impairs the quality of sleep and hence reduces their health-related quality of life (90).

The neuropathic pain is a multifactorial, heterogeneous condition that cannot be explained by a specific lesion or disease (59). Many factors such as age (13, 15, 16, 18, 25, 29, 44, 70, 71), preoperative pain, anxiety (14, 44, 70), depression (14, 70), invasive breast surgery (13, 14, 21, 44, 70), axillary status (14, 15, 29, 71), acute pain (13, 70) and adjunctive treatment ((23, 25, 29, 34, 50, 71) have been suggested as potential risk factors of neuropathic CPBCS. However, due to several limitations in the present literature such as different study designs, duration of follow-up period, and unclear definition of the outcome, information regarding the contribution of these putative risk factors remains ambiguous.

To evaluate the risk factors related to neuropathic CPBCS, this 3-month prospective cohort study was conducted. More specifically, the primary aim of the study was to determine the contribution of preoperative (age, preoperative pain, anxiety, depression, and comorbidities,), intraoperative (type of surgery and axillary status), and postoperative (acute

postoperative pain, opioids, chemotherapy, radiotherapy) factors to neuropathic CPBCS risk at 3 months following breast cancer surgery. Our secondary aim was to identify contributing factors related to pre, intra and postoperative factors related to DN4 score at 3 months follow-up. As well we aimed to compare the risk factors associated with neuropathic CPBCS vs no CPBCS and non-neuropathic CPBCS.

Methods

Study design and study population

This 3-month prospective cohort study (# 14-211) was approved by the Institutional Review Board, Jewish General Hospital (JGH), Montreal, Canada. Each aspect of the study was well described to all patients approached. All the potential participants who showed interest and agreed to participate in the study signed the written consent form.

Patients who were scheduled to undergo their first breast cancer surgery were recruited from the Segal Cancer Center at the JGH. Patients were (i) females aged 18 years or above, (ii) incident cases of breast cancer, (iii) scheduled to undergo first breast cancer surgery, and (iv) provided the written consent form were included in the study. However, patients who (i) did not receive breast surgery, (ii) had a history of any other type of cancer, (iii) had Karnofsky Performance Status Score under 50 and required considerable assistance and frequent medical care, (iv) had metastases, (v) had no access to a telephone, (vi) were pregnant women, and (vii) were males with breast cancer, were ineligible to participate in the study.

Assessment

Females who agreed to participate in the study were invited to complete a questionnaire investigating the plausible preoperative risk factors by research trainees. These investigators

conducted follow-up interviews by telephone at 7 days and 3 months following breast cancer surgery to evaluate plausible risk factors and study outcome.

Putative risk factors

Before the surgical procedure, participants were asked to provide the information regarding putative preoperative risk factors such as preoperative pain, anxiety, and depression using a battery of validated instruments such as modified-Brief Pain Inventory (m-BPI) (APPENDIX), Generalized anxiety disorder-7 (GAD-7) (APPENDIX) and Patient Health Questionnaire-8 depression scale (PHQ-8) (APPENDIX). To assess the preoperative pain participants were asked two questions "Do you have pain in your breast?" and "Do you have pain in your breast when you move your arm?" A GAD-7 and PHQ-8 score of 5, 10, 15 indicated mild, moderate and severe condition respectively. Furthermore, acute postoperative pain was assessed at 7 days following breast cancer surgery via telephone interview using m-BPI. Surgical data (type of surgery and axillary status), data regarding adjunctive treatment (radiotherapy and chemotherapy), comorbidities (diabetes and hypertension) and opioids prescribed for pain management in the recovery room were collected using chartmaxx (electronic health record system) at the JGH.

Study outcome

Neuropathic pain is defined as the "pain which is initiated or caused by a lesion or the disease of the somatosensory system" (12). Chronic postoperative pain is the pain which persists for at least three months after surgery (4). For the assessment of chronic neuropathic pain after breast cancer surgery (neuropathic CPBCS), participants were asked to complete a valid and reliable instrument named short form of Douleur Neuropathique 4 (short form - DN4) at 3 months through a telephone interview. Participants were asked to respond to three

questions regarding pain quality such as burning, electric shocks, and painful cold as well as four questions regarding pain associated symptoms such as tingling, numbness, pins and needles and itching in a yes/no form. Each response of yes and no was scored as 1 and 0 respectively. A total DN4 score was calculated by adding all the positive responses to the DN4 questionnaire. If the DN4 score was ≥ 3 pain was classified as neuropathic CPBCS.

Statistical analyses

All analyses tested null hypotheses of no statistical association between the independent and dependent variables of interest at $\alpha = 0.05$ significance**.** Chi-square and Fisher exact tests were used to compare the distribution of the categorical variables. To assess the means of the continuous variables between two groups, Student t-test was used. Crude and multivariable logistic regression analyses (proc logistic, SAS) were performed to determine the risk factors of neuropathic CPBCS at 3 months follow-up. Risk ratios (RRs) and their 95% confidence intervals (CI) were estimated. We assessed the contributing factors related to DN4 score at 3 months following surgery using a multivariable unconditional linear regression analysis (proc mixed, SAS). DN4 score (a continuous variable), however, played a role of the secondary outcome. Regression coefficient (β) and their 95% confidence intervals (CI) were estimated.

For the statistical analyses of our *primary* outcome, first, we performed crude logistic regression analyses for all pre, intra and postoperative risk factors: (i) preoperative risk factors (age, preoperative pain, average preoperative pain intensity, non-painful comorbidities such as diabetes and hypertension, psychological factors such as anxiety and depression), (ii) intraoperative factors (type of surgery and axillary status), and (iii) postoperative factors (acute pain, acute pain intensity, opioids used for pain management in recovery room, radiotherapy and chemotherapy). Further, four potential risk factors (anxiety, type of surgery, acute pain at rest and acute pain during movement) were included in the final multivariable

model, by considering (m/15) the demands of statistical modeling. The neuropathic CPBCS participants served as a crucial factor for selecting the number of variables to be included in the final model. Based on the statistical and biological significance, we included only four plausible risk factors in the final multivariable model. These four variables were picked based on biological and statistical significance.

A series of linear regression analyses were performed to assess a particular risk factor for the *secondary analysis*. Firstly, the crude linear regression model analyses were performed to investigate each plausible risk factor. Besides this, a multivariable linear regression analysis was performed that included all the pre, intra and postoperative risk factors.

A crude linear regression analyses was performed to assess the effect of sentinel lymph node biopsy (SLNB) ($\beta = 0.34$, $p = 0.14$) and axillary lymph node dissection (ALND) ($\beta = 0.34$, $p = 0.36$) on DN4 score. Since a similar effect size was found for both SLNB and ALND with DN4 score without any statistical significance, both variables were combined for further analyses.

Furthermore, a final multivariable linear regression model was run comprising preoperative pain, average preoperative pain intensity, anxiety, diabetes, type of surgery, acute pain on movement, and radiotherapy. These variables were picked by eliminating one variable at a time from the multivariable model – including all candidate putative risk factors. Additionally, AIC of two models (model with all plausible risk factors and model where one risk factor was eliminated) were determined and compared. A model with lower AIC was kept for a further selection of variables. Finally, a better fit statistical model with lower AIC was obtained.

Finally, another regression analysis was performed to compare the risk factors associated with neuropathic CPBCS, no CPBCS, and non-neuropathic CPBCS. All analyses

were performed with SAS 9.4 software (Statistical Analysis System; SAS Institute Inc, Cary, NC, USA)

Results

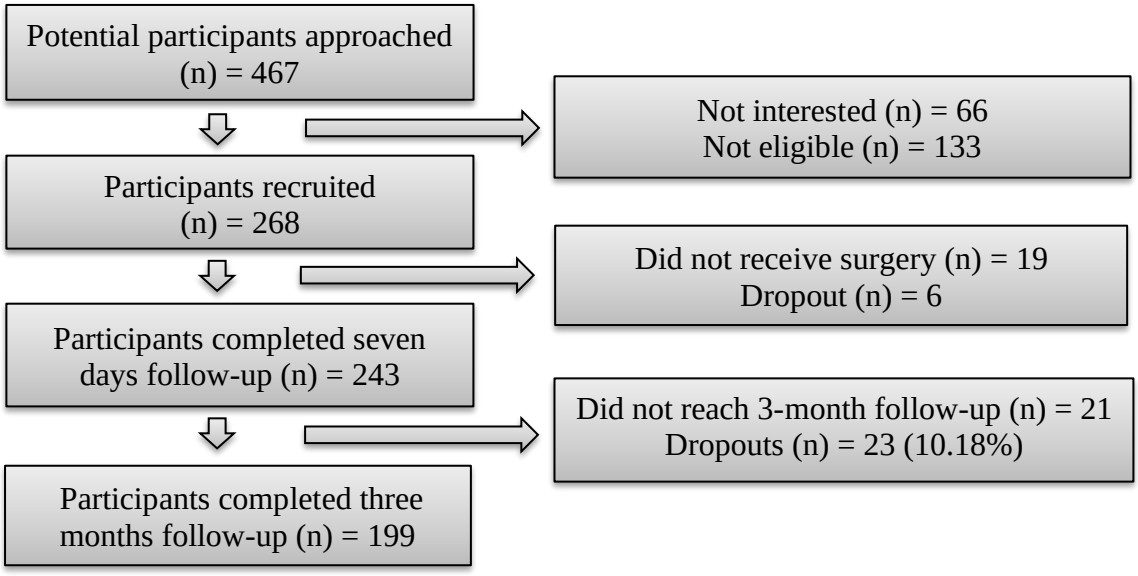
Description of the population

A total of 467 potential participants were approached to take part in the study. Among those, 66 patients did not show interest to participate in the study due to lack of time (86% participation rate). They were overwhelmed by the distress of disease and other ongoing simultaneous studies in the hospital. Out of 401 potential participants, 133 were ineligible to be included in the study since they did not undergo breast surgery (n = 7), received breast surgery before (n = 58), were males (n = 5), had cancer in any other body part (n = 8), had language barrier (n = 15), had recurrent cancer (n = 5), or had benign tumour (n = 35). Two-hundred eight patients were recruited for this study. From those, 19 patients did not receive breast surgery and only six participants dropped out at 7 days follow-up. A total of 243 participants completed the 7 days follow-up. Of these 243 participants, 23 patients refused to continue, and twenty-one females did not reach their timeline to complete 3-month follow-up at the time of analysis. Hence, the data from 199 participants was included in the study analysis. The patient recruitment and follow-up scheme are shown in Figure 5-1.

The descriptive statistics of the study population (n = 199) is summarized in Table 5-1. The study participants were primarily middle-aged women [mean age in years = 57.21 (SD = 14.03)]. Preoperatively, one third of the study sample (31.66%) reported preoperative pain with an average pain intensity score of 6.92 (SD = 1.54). Less than 50% of the study participants reported moderate to severe depression and anxiety. A smaller number of participants reported diabetes and hypertension.

A large number of the participants (90.95%) underwent a conservative surgical procedure such as segmental mastectomy. Sentinel lymph nodes were removed in a major number of the participants (61.31%) and axillary lymph nodes were dissected in approximately 10.1% of the analysed study sample size. Opioids were frequently prescribed for postoperative pain management in the recovery room (77.39%). Around 65% of the study sample reported postoperative pain seven days after surgery with an average acute pain intensity score of 3.01 (SD = 2.22). The percentage of the study population who reported receiving chemotherapy and radiotherapy was 24.87% and 52.85%, respectively.

Figure 5-1 Patient recruitment and follow-up



Risk factors related to neuropathic CPBCS at 3 months after surgery

Out of 199 participants, 47 (23.62%) reported neuropathic CPBCS at 3 months following breast cancer surgery. The mean DN4 score was 1.45 (SD = 1.42). Table 5-2 shows the results of primary analysis.

Preoperative risk factors

Table 5-2 shows that age (RR = 0.99, 95%CI: 0.97-1.01), preoperative pain (RR = 1.11, 95%CI: 0.66-1.88), average preoperative pain intensity (RR = 1.00, 95%CI: 0.98-1.01), diabetes (RR = 0.80, 95%CI: 0.39-1.66), and hypertension (RR = 0.89, 95%CI: 0.51-1.58) were not associated with the increased risk of neuropathic CPBCS at 3 months follow-up in the crude analyses.

Depression did not increase neuropathic CPBCS risk at 3 months following breast cancer surgery (RR = 1.17, 95%CI: 0.71-1.94). However, anxiety at baseline was significantly associated with increased risk in unadjusted analysis (RR = 1.68, 95%CI: 1.01-2.81). A borderline significance was estimated for anxiety in the final analysis adjusted for other relevant risk factors (RR = 1.60, 95%CI: 0.96-2.69). It was intriguing that almost equivalent RR remained consistent in both analyses, although borderline RR was noted in the final model.

Intraoperative risk factors

Type of surgery did not significantly increase the risk of developing neuropathic CPBCS at 3 months follow-up in crude logistic regression analysis (RR = 1.76, 95%CI: 0.93-3.34). However, participants exposed to mastectomy presented 41% higher risk of developing neuropathic CPBCS than who were exposed to lumpectomy at 3 months follow-up in the adjusted analysis (RR = 1.41, 95%CI: 0.78-2.54).

Lymph node removal did not increase the risk of neuropathic CPBCS at 3 months follow-up in unadjusted analysis (RR = 0.67, 95%CI: 0.36-1.26).

Postoperative risk factors

No statistically significant RR was noted for acute pain at rest and neuropathic CPBCS at 3 months following breast cancer surgery (RR = 0.83, 95%CI: 0.50-1.36) in the crude

analysis. However, in an adjusted analysis this covariate was significantly associated with a decreased risk of neuropathic CPBCS (RR = 0.58, 95%CI: 0.34-0.99). None of the covariates modified the direction of the protective risk of acute pain at rest.

Participants who reported acute pain during movement presented 40% more risk of developing neuropathic CPBCS at 3 months follow-up in the crude analysis (RR = 1.40, 95%CI: 0.84-2.34). This risk increased to 85% in an adjusted analysis (RR = 1.85, 95%CI: 1.05-3.26).

Current (RR =1.02, 95%CI: 0.91-1.14), worst (RR = 0.98, 95%CI: 0.90-1.06) and average (RR =1.01, 95%CI: 0.90-1.14) acute pain intensities were not associated with increased risk of neuropathic CPBCS at 3 months after breast cancer surgery in crude analyses.

No statistically significant difference in RR for neuropathic CPBCS at 3 months follow-up was found among women who were prescribed opioids and those who were not prescribed for pain relief in the recovery room (RR = 0.92, 95%CI: 0.50-1.71).

Both, chemotherapy (RR = 1.36, 95%CI: 0.71-2.61) and radiotherapy (RR = 1.03, 95%CI: 0.62-1.71) did not significantly increase the risk of neuropathic CPBCS at 3 months after surgery in univariate logistic regression model.

Contributing factors of DN4 score at 3 months after surgery

Table 5-3 shows the contributing factors of DN4 score

Preoperative contributing factors

Age was not related to higher DN4 score at 3 months following breast cancer surgery in both crude (β = -0.01, 95%CI*:* -0.02 to 0.003) and adjusted analysis including all putative risk factors (β = -0.01, 95%CI: -0.02 to 0.005).

Preoperative pain contributed to an increase in the DN4 score 3 months after surgery (β = 0.43, 95%CI: 0.006 to 0.85). The statistical significance remained when the model was

adjusted for all the putative risk factors (β = 0.59, 95%CI: 0.01 to 1.15), or the potential covariates to achieve a better fit final statistical model (β = 0.59, 95%CI: 0.04 to 1.14).

Average preoperative pain intensity was not associated with DN4 score in univariate (β = 0.003, 95%CI: -0.01 to 0.01), multivariable – adjusted for all putative risk factors (β = -0.01, 95%CI: -0.02 to 0.007) and a better fit final (β = -0.01, 95%CI: -0.02 to 0.004) linear model regression analyses.

Depression was not related to higher value of DN4 score after 3 months of breast cancer surgery in univariate (β = 0.08, 95%CI: -0.32 to 0.50) and multivariable - adjusted for all the plausible risk factors (β = 0.02, 95%CI: -0.58 to 0.62) model analyses.

Anxiety at baseline was not associated with DN4 score in both crude (β = 0.30, 95%CI: -0.10 to 0.70) and multivariable linear regression model analyses (β = 0.32, 95%CI: -0.14 to 0.79). In the multivariable model including preoperative pain, average preoperative pain intensity, anxiety, diabetes, type of surgery, acute pain during movement and radiotherapy as covariates, a stronger and borderline association was found between anxiety and DN4 score (β = 0.35, 95%CI: -0.04 to 0.74).

Contrarily to our expectation, diabetes and hypertension did not contribute to higher DN4 score at 3 months following breast cancer surgery in all linear regression model analyses. The effect size (95%CI) for diabetes and hypertension were: β = 0.13 (95%CI: -0.51 to 0.79) and β = -0.11(95%CI: -0.58 to 0.36) respectively for crude model analysis; and β = 0.30 (95%CI: -0.39 to1.01) and β = -0.13 (95%CI: -0.58 to 0.51) respectively for multivariable model analysis with all the plausible risk factors. In the final adjusted analysis with relevant risk factors, the effect size (95%CI) for diabetes was β = 0.14 (95%CI: -0.47 to 0.77). Hypertension was not included in final linear regression model analysis.

Intraoperative contributing factors

Mastectomy was associated with higher DN4 score 3 months after surgery (β = 0.79, 95%CI: 0.10 to1.47) in crude linear regression model analysis. The statistical significance remained only borderline with similar β in both multivariable-adjusted for all the potential risk factors (β = 0.60, 95%CI: 0.04 to1.42) and final – variables were removed to have a better fit (β = 0.60, 95%CI: -0.07 to 1.29) regression analyses.

Axillary lymph node removal did not contribute to higher DN4 score at 3 months following breast cancer surgery in crude (β = 0.34, 95%CI: -0.09 to 0.77) and multivariable (β = 0.36, 95%CI: -0.12 to 0.84) regression analyses.

Postoperative contributing factors

Acute pain at rest, assessed at seven days after surgery was not significantly associated with higher DN4 score following 3 months of breast cancer surgery in crude (β = 0.23, 95%CI: -0.17 to 0.63), or adjusted model including all the putative risk factors (β = -0.24, 95%CI: -0.75 to 0.37).

A strong statistically significant association was noted between acute pain during movement at seven days following breast cancer surgery and DN4 score in a univariate linear model (β = 0.57, 95%CI: 0.17 to 0.95). This statistically significant association remained in a better fit final linear model analyses (β = 0.67, 95%CI: -0.06 to 1.04).

Acute current pain intensity (β = 0.10, 95%CI: 0.01 to 0.19), contrary to worst (β = 0.02, 95%CI: -0.04 to 0.08) and average acute pain intensities (β = 0.06, 95%CI: -0.02 to 0.15), significantly contributed to higher DN4 score in univariate model analysis. However, this significant association was lost when the model was adjusted for all putative risk factors (β = 0.07, 95%CI: -0.07 to 0.21).

The effect sizes of the association between opioids used for pain management in the

recovery room and DN4 score were weak and insignificant: β = 0.07, 95%CI: -0.40 to 0.54 (crude) and β = 0.09, 95%CI: -0.61 to 0.14 (multivariable) linear regression model analyses.

Chemotherapy did not contribute to an increase in the DN4 score in crude (β = 0.06, 95%CI: (-0.40 to 0.53) and multivariable (β = -0.21, 95%CI: -0.73 to 0.29) model – adjusted all for candidate potential risk factors.

A borderline significant association was found between radiotherapy and DN4 score in crude linear regression model analysis (β = -0.35, 95%CI: -0.75 to 0.04) and in the multivariable model including the relevant predictors (β = -0.33, 95%CI: -0.72 to 0.06).

Comparison of risk factors of neuropathic CPBCS vs no CPBCS and non-neuropathic CPBCS

Table 5-4 shows the risk factors of neuropathic CPBCS vs no CPBCS and non-neuropathic CPBCS.

From the study sample analysed, 47, 65, and 87 participants reported neuropathic CPBCS, non-neuropathic CPBCS, and no CPBCS at 3 months follow-up.

Participants exposed to moderate to severe anxiety presented greater risk of developing neuropathic CPBCS than those non exposed (RR = 1.52, 95%CI: 0.95-2.43). However, this risk was not statistically significant. A borderline association was found between type of surgery (RR = 1.73, 95%CI: 0.91-3.29), and acute pain during movement (RR = 1.67, 95CI: 0.99-2.80) and the risk of neuropathic CPBCS in comparison to no CPBCS.

Anxiety (RR = 1.39, 95%CI: 0.90-2.13), type of surgery (RR = 1.33, 95%CI: 0.67-2.61), acute pain at rest (RR = 0.56, 95%CI: 0.35-0.89) and acute pain during movement (1.26, 95%CI; 0.82-1.96) were not associated with an increased risk of neuropathic CPBCS vs chronic non-neuropathic CPBCS.

We found intriguing results for acute pain at rest regarding the risk of neuropathic CPBCS vs no CPBCS and non-neuropathic CPBCS. Acute pain at rest was associated with a decreased risk of developing neuropathic CPBCS vs no CPBCS (RR = 0.86, 95%CI: 0.52-1.42) and non-neuropathic CPBCS (RR = 0.56, 95%CI: 0.35-0.89).

Discussion

The results from the present prospective cohort study demonstrated that neuropathic CPBCS is a prevalent condition after breast cancer surgery. Approximately one fourth (23.62%) of the study sample reported neuropathic CPBCS at 3 months following breast cancer surgery which is consistent with other study results (6, 28, 42, 50, 51, 54, 55). The multivariable model showed that acute pain during movement assessed at 7 days after surgery significantly increased the risk of neuropathic CPBCS at 3 months after surgery (Table 5-2).

Our study results suggest that age is not a significant risk factor for neuropathic CPBCS at 3-month follow-up, which is consistent with other study results (14, 17, 24, 25, 34, 38, 68, 70, 91). However, a few prospective cohort studies found that young age was positively associated with neuropathic CPBCS (13, 15, 16, 44). The study methodology of some of these studies with a small sample size or larger confidence intervals suggest that these results are not precise (16).

Incongruity with the present literature (13, 19-21, 70), preoperative pain and average preoperative pain intensity are not risk factors of neuropathic CPBCS at 3 months follow-up (Table 5-2). A yearlong prospective cohort study (n = 59) demonstrated no significant association between preoperative pain and neuropathic CPBCS using a 7-item DN4 questionnaire, which is in agreement with our study results (19). Besides this, another prospective cohort study (n = 156) demonstrated that preoperative pain is not a risk factor of neuropathic CPBCS at 1 year follow-up (14).

With respect to anxiety and depression, our study results are in agreement with a prospective cohort study (n = 203) showing that anxiety and depression do not increase the risk of neuropathic CPBCS at 3 months follow-up (15). This did not agree with a prospective cohort study that found that depression increased the risk of neuropathic CPBCS at 6-month follow-up (44). However, unfortunately as this study only showed the crude analysis, we do not know if this association is confounded by a covariate (44). The use of different tools to measure the depression and anxiety could be another plausible reason of finding inconsistent study results (44, 70).

Contradictory to our expectations (29), non-painful comorbidities specifically diabetes does not increase the risk of developing neuropathic CPBCS at 3 months following breast cancer surgery. A retrospective cohort (n = 470) study found diabetes as a significant risk factor of neuropathic CPBCS at 1-year follow-up (29). Our results differed from the literature probably because a very few (21/199) participants reported diabetes in our study sample. A survey-based study demonstrated that hypertension was significantly associated with neuropathic CPBCS in unadjusted analysis (25). However, in this study, the authors failed to indicate whether or not they adjusted for potential confounders.

Type of surgery and axillary lymph node status are not significant risk factors for neuropathic CPBCS at 3 months following breast cancer surgery. Our study results are in accord with other studies (15, 17, 20, 72). However, it is noteworthy that a greater effect size remained consistent in the final model, although it is not statistically significant. We did not find the type of surgery as a contributing factor for neuropathic CPBCS. Probably due to the number of participants exposed to mastectomy (n = 18) was too small to estimate the risk of neuropathic CPBCS.

Our study results suggest that acute pain is a significant risk factor of neuropathic CPBCS at 3 months follow-up (Table 5-2). These results are consistent with other study

findings (13, 70, 92). A prospective cohort study found acute pain assessed at 2 days after surgery contributed significantly to neuropathic CPBCS at 3 months after surgery (70). Interestingly, we found that acute pain at rest was a protective risk factor and acute pain during movement was a harmful risk factor associated with an increased risk of neuropathic CPBCS at 3 months follow-up. We do not have a clear explanation for these results. The results for acute pain at rest to neuropathic CPBCS were neither influenced by other potential confounders nor any interaction with other covariates is responsible for these results.

Our study found an insignificant association of chemotherapy and radiotherapy to increased risk of developing neuropathic CPBCS at 3 months after breast cancer surgery (Table 5-2). Our study results are consistent with other prospective cohort studies (14, 15, 17, 19, 22, 70, 72). More specifically, they include one – 3 months (70), one – 6 months (15), and four – 12 months (14, 15, 17, 19, 22) prospective cohort studies demonstrated that radiotherapy is not a risk factor of neuropathic CPBCS. As well, two prospective cohort studies found an insignificant contribution of chemotherapy to neuropathic CPBCS at 1year follow-up (14, 17).

To best of our knowledge, no study has assessed the factors associated with DN4 score. However, we found studies that assessed the neuropathic pain score but these study findings are inconsistent with our study results (18, 22).

The foremost strength of the study lies in its study design which is a prospective cohort study design. By employing this study design, we can ensure that risk factors preceded the onset of neuropathic CPBCS. Also, since this is a prospective study it is possible that the misclassifications are non-differential and would attenuate the magnitude of the associations. Second, to eliminate the effect of putative confounders, they were adjusted for in the multivariable linear/logistic regression analyses. Third, we used validated instruments to assess outcome at 3 months follow-up and other independent variables such as preoperative pain and psychological factors at baseline, and postoperative pain at 7 days.

The study results should be interpreted in context with limitations. The foremost limitation of the present study was the small sample size. Based on the biological and statistical significance we included only four putative risk factors in the final logistic regression model analysis. Second, approximately 11% of participants did not complete 3 months follow-ups. Although attrition of 11% is not large there may be a possibility of attrition bias. To investigate the possibility of dropout bias, an analysis comparing dropouts and non-dropouts showed no significant difference between the two (results – not provided). Third, we used self-reported questionnaires to assess some risk factors such as preoperative and acute postoperative pain. This method may have some disadvantages, such as overemphasis; respondents may be uncomfortable to reveal personal details or may neglect relevant details. Similarly, we used a self-reported instrument (DN4) to assess our outcome of interest such as neuropathic CPBCS and DN4, which may have influenced our results. It may have been better to adopt a clinical diagnosis to assess neuropathic CPBCS. Fourth, due to considerable variation in the drugs, dosage, and frequency of opioids, chemotherapy, and radiotherapy, we did not attempt to categorize opioids, chemotherapy, and radiotherapy based on their drug type and dosage. Fifth, the association between risk factors and neuropathic CPBCS may be biased by unmeasured confounding variables such as body mass index (BMI). Sixth, we did not collect any data regarding major or minor nerve injury which could be another important variable to be further investigated. Seventh, since participants received the almost similar type and dosage of anesthetic infiltration during peri-operative pain management, we did not include the anesthetic agent used in the analysis.

In conclusion, neuropathic CPBCS is a significant problem after breast cancer surgery with an incidence rate of 23.62%. Acute postoperative pain during movement at 7 days after surgery is a significant factor to increase the risk of neuropathic CPBCS at 3 months follow-up. Acute pain at rest, however, appears to be a protective factor. Preoperative pain and acute

postoperative pain during movement at 7 days after surgery contributes to higher DN4 score at 3 months following breast cancer surgery. Our study findings suggest that acute pain during movement and preoperative pain should be evaluated and managed meticulously to scale down the burden of neuropathic CPBCS and DN4 score.

Table 5-1 Description of participants included in the study (n = 199)		
Risk factor	Category	n (%)
Age, Mean (SD)	Years	57.21 ± 14.03
Preoperative pain	No	136 (68.34%)
	Yes	63 (31.66%)
Preoperative pain intensity, Mean (SD)	0-10	6.92 ± 1.54
Depression	No or mild	122 (61.31%)
	Moderate to severe	77 (38.69%)
Anxiety	No or mild	106 (53.27%)
	Moderate to severe	93 (46.73%)
Diabetes	No	175 (89.29%)
	Yes	21 (10.71%)
Hypertension	No	149 (76.02%)
	Yes	47 (22.98%)
Type of surgery	Segmental mastectomy	181 (90.95%)
	Mastectomy	18 (9.05%)
Axillary status	SLNB	122 (61.31%)
	ALND	20 (10.05%)
Acute pain	No	70 (35.53%)
	Yes	125 (64.47%)
Average acute pain intensity, Mean (SD)	0-10	3.01 ± 2.23
Opioids	No	45 (22.61%)
	Yes	154 (77.39%)
Chemotherapy	No	145 (75.13%)
	Yes	48 (24.87%)
Radiotherapy	No	91 (47.15%)
	Yes	102 (52.85%)
DN4 score, Mean (SD)	0-7	1.45 ± 1.42
Chronic neuropathic pain	No	152 (76.38%)
	Yes	47 (23.62%)

Table 5-2: Logistic regression analyses assessing risk factors of neuropathic CPBCS (Yes/no) (n = 199)			
Preoperative contributors			
Risk factor	Category/Unit	Univariable model analyses	Final model analyses
		RR (95% CI)	RR (95% CI)
Age	Years	0.99 (0.98-1.01)	*Not included*
Preoperative pain	No	1 (reference)	*Not included*
	Yes	1.11(0.66-1.88)	
Preoperative pain intensity	0-10	1.00 (0.98-1.01)	*Not included*
Depression	No or mild	1 (reference)	*Not included*
	Moderate or severe	1.17 (0.71-1.94)	
Anxiety	No or mild	1 (reference)	1 (reference)
	Moderate or severe	1.68 (1.01-2.81) **	1.60 (0.96-2.69) *
Diabetes	No	1 (reference)	*Not included*
	Yes	0.80 (0.39-1.66)	
Hypertension	No	1 (reference)	*Not included*
	Yes	0.89 (0.51-1.58)	
Intraoperative contributors			
Type of surgery	Segmental mastectomy	1 (reference)	1 (reference)
	Mastectomy	1.76 (0.93-3.34)	1.41 (0.78-2.54)
Axillary status	No	1 (reference)	*Not included*
	SLNB & ALND	0.67 (0.36-1.26)	
Postoperative contributors			
Acute pain at rest	No	1 (reference)	1 (reference)
	Yes	0.83 0.50-1.36)	0.58 (0.34-0.99) **
Acute pain during movement	No	1 (reference)	1 (reference)
	Yes	1.40 (0.84-2.34)	1.85 (1.05-3.26) **
Current acute pain intensity	0-10	1.02 (0.91-1.14)	*Not included*
Worst acute pain intensity	0-10	0.98 (0.90-1.06)	*Not included*
Average acute pain intensity	0-10	1.01 (0.90-1.14)	*Not included*
Opioids	No	1 (reference)	*Not included*
	Yes	0.92 (0.50-1.71)	
Chemotherapy	No	1 (reference)	*Not included*
	Yes	1.36 (0.71-2.61)	
Radiotherapy	No	1 (reference)	*Not included*
	Yes	1.03 (0.62-1.71)	

* p-value < 0.01
** p-value < 0.05
Final model analyses – adjusted analysis including anxiety, type of surgery, acute pain at rest and acute pain during movement

Table 5-3 Linear regression analyses assessing contributing factors of DN4 score (n = 199)				
Preoperative contributors				
Contributing factors	Category/Unit	Univariate model analyses	Multivariable model analysis [a]	Final model analysis
		β (95%CI)	β (95%CI)	β (95%CI)
Age	Years	-0.01 (-0.02 to 0.003)	-0.01 (-0.02 to 0.005)	*Not included*
Preoperative pain	No	1 (reference)	1 (reference)	1 (reference)
	Yes	0.43** (0.006 to 0.85)	0.59** (0.01 to 1.15)	0.59** (0.04 to 1.14)
Preoperative pain intensity	0-10	0.003 (-0.01 to 0.01)	-0.01 (-0.02 to 0.007)	-0.01 (-0.02 to 0.004)
Depression	No or mild	1 (reference)	1 (reference)	*Not included*
	Moderate or severe	0.08 (-0.32 to 0.50)	-0.13 (-0.58 to 0.62)	
Anxiety	No or mild	1 (reference)	1 (reference)	1 (reference)
	Moderate or severe	0.30 (-0.10 to 0.70)	0.32 (-0.14 to 0.79)	0.35* (-0.04 to 0.74)
Diabetes	No	1 (reference)	1 (reference)	1 (reference)
	Yes	0.13 (-0.51 to 0.79)	0.30 (-0.39 to1.01)	0.14 (-0.47 to 0.77)
Hypertension	No	1 (reference)	1 (reference)	*Not included*
	Yes	-0.11 (-0.58 to 0.36)	-0.03 (-0.58 to 0.51)	
Intraoperative contributors				
Type of surgery	Segmental mastectomy	1 (reference)	1 (reference)	1 (reference)
	Mastectomy	0.78** (0.10 to1.47)	0.60* (0.04 to1.42)	0.60* (-0.07 to 1.29)
Axillary status	No LN removal	1 (reference)	1 (reference)	*Not included*
	SLNB & ALND	0.33 (-0.09 to 0.77)	0.36 (-0.12 to 0.84)	
Postoperative contributors				
Acute pain at rest	No	1 (reference)	1 (reference)	*Not included*
	Yes	0.22 (-0.17 to 0.63)	-0.18 (-0.75 to 0.37)	
Acute pain during movement	No	1 (reference)	1 (reference)	1 (reference)
	Yes	0.56*** (0.17 to 0.95)	0.49* (-0.06 to 1.04)	0.51** (0.10 to 0.92)
Current acute pain intensity	0-10	0.10** (0.01 to 0.19)	0.07 (-0.07 to 0.21)	*Not included*
Worst acute pain intensity	0-10	0.02 (-0.04 to 0.08)	-0.03 (-0.13 to 0.07)	*Not included*
Average acute pain intensity	0-10	0.06 (-0.02 to 0.15)	-0.008 (-0.16 to 0.14)	*Not included*
Opioids	No	1 (reference)	1 (reference)	*Not included*

	Yes	0.07 (-0.40 to 0.54)	0.09 (-0.61 to 0.14)	
Chemotherapy	No	1 (reference)	1 (reference)	*Not included*
	Yes	0.06 (-0.40 to 0.53)	-0.21 (-0.73 to 0.29)	
Radiotherapy	No	1 (reference)	1 (reference)	1 (reference)
	Yes	-0.35* (-0.75 to 0.04)	-0.31 (-0.73 to 0.10)	-0.33* (-0.72 to 0.06)

* p value ≥ 0.05 and < 0.1
** p value < 0.05
*** p value ≤ 0.005
Multivariable model analysis [a] – adjusted for all the candidate putative risk factors
Final model analysis- adjusted for preoperative pain, average preoperative pain intensity, anxiety, diabetes, type of surgery, acute pain during movement and radiotherapy

Table 5-4. Comparison of risk factors related to neuropathic CPBCS vs no CPBCS and neuropathic CPBCS vs non-neuropathic CPBCS (n = 199)			
Risk factor	Category	Neuropathic CPBCS (n = 47) vs No CPBCS (n = 87)	Neuropathic CPBCS (n = 47) vs non-neuropathic CPBCS (n = 65)
		RR (95%CI)	RR (95%CI)
Anxiety	No or mild	1 (reference)	1 (reference)
	Moderate or severe	1.52 (0.95-2.43)*	1.39 (0.90-2.13)
Type of surgery	Segmental mastectomy	1 (reference)	1 (reference)
	Mastectomy	1.73 (0.91-3.29)*	1.33 (0.67-2.61)
Acute pain at rest	No	1 (reference)	1 (reference)
	Yes	0.86 (0.52-1.42)	0.56 (0.35-0.89)**
Acute pain on movement	No	1 (reference)	1 (reference)
	Yes	1.67 (0.99-2.80)*	1.26 (0.82-1.96)
* p value ≥ 0.05 and < 0.1 ** p value < 0.05			

6. DISCUSSION

This section will discuss the study findings, methodological considerations, strengths and limitations of this thesis.

The overall objective of this prospective cohort study was to investigate the risk factors related to neuropathic CPBCS at 3 months after surgery. More specifically, our primary aim was to determine whether preoperative factors (age, preoperative pain, anxiety, depression, and comorbidities), intraoperative factors (type of surgery and axillary status) and postoperative factors (acute pain, opioids prescribed for pain management in recovery room, radiotherapy, and chemotherapy) increase the risk of neuropathic CPBCS at 3 months following breast cancer surgery. Our secondary aim was to assess if these pre, intra, and postoperative factors were associated with higher DN4 score at 3 months follow-up. Also, we aimed to compare the risk factors associated with neuropathic CPBCS vs no CPBCS and non-neuropathic CPBCS. To our knowledge, this is the first study investigating factors that contribute to higher DN4 score.

6.1 Prevalence of neuropathic CPBCS

The present prospective cohort study demonstrated that neuropathic CPBCS is a prevalent clinical problem after breast cancer surgery. One fourth (23.62%) of the study sample reported neuropathic CPBCS at 3 months following breast cancer surgery which is consistent with other studies (6, 51, 54, 55). The overall mean DN4 score was 1.45 (SD = 1.42) which differs slightly from a study performed by Beyaz *et al.*, 2016 (54). This may be due to the different scale (0 - 8) used to measure neuropathic CPBCS.

6.2 Risk factors

6.2.1 Preoperative risk factors of neuropathic CPBCS

Anxiety at baseline is significantly related to increased neuropathic CPBCS risk at 3 months follow-up in univariate analysis. However, this association remained borderline in the final analysis including relevant risk factors. Our study findings are in agreement with others (15) demonstrating that anxiety and depression do not increase the risk of neuropathic CPBCS at 3 months follow-up. We found an insignificant association of anxiety and depression with neuropathic CPBCS at 3 months follow-up. This might be due to an insufficient power. Maybe our sample size was too small to find a significant contribution of anxiety to increased neuropathic CPBCS risk.

Age, preoperative pain, average pre-operative pain intensity, depression, diabetes, and hypertension were not associated with an increased risk of developing neuropathic CPBCS at 3 months following breast cancer surgery.

Our study results suggest that age is not a significant factor to increase the risk of developing neuropathic CPBCS at 3 months follow-up that is consistent with other study findings (14, 17, 24, 25, 34, 38, 68, 70, 91). Five prospective (14, 17, 19, 34, 70) and one retrospective (38) cohort studies did not find age as a risk factor for neuropathic CPBCS risk at 12 months follow-up. However, there are prospective cohort studies available in the literature which demonstrated a significant association between young age and neuropathic CPBCS (13, 15, 16, 44). These studies also include a pilot prospective cohort study with small sample size (n =17) (13). Further, another prospective cohort study (n = 88) found a significant association between young age and neuropathic CPBCS at 2 years follow-up (OR = 3.9, 95%CI: 1.4-10.5). But the 95%CI is too wide to estimate an OR = 3.9 precisely (16). Furthermore, the studies also proposed older age as a protective factor of neuropathic CPBCS

(β = -0.025, p = 0.011) (18, 44). Another noteworthy point is that these studies are not consistent in referring the age as younger or older age.

In an agreement with the present literature (13, 19-21, 70), both preoperative pain and average preoperative pain intensity did not contribute to increased risk of neuropathic CPBCS at 3 months follow-up. A yearlong prospective cohort study (n = 59) found no significant association between preoperative pain and neuropathic CPBCS using a 7-item DN4 instrument (19). Moreover, another prospective cohort study (n = 156) showed that preoperative pain is not a significant risk factor of neuropathic CPBCS at 12 months follow-up (14).

Contradictory to our expectations, diabetes did not increase the risk of developing neuropathic CPBCS at 3 months following breast cancer surgery inconsistent with findings of other studies (29). One retrospective cohort (n = 470) study found diabetes as a significant risk factor of neuropathic CPBCS at 12 months follow-up (29). Our results are different probably due to the fact that only 10% of participants reported diabetes in our study sample. A survey-based study demonstrated that hypertension was significantly associated with neuropathic CPBCS in unadjusted analysis (25). However, in this study, the authors failed to indicate whether or not they adjust for other potential confounders.

6.2.2 Intraoperative risk factors of neuropathic CPBCS

Participants exposed to mastectomy were 1.41 times as likely to develop neuropathic CPBCS risk at 3 months after surgery in an adjusted analysis, despite the fact the results were statistically insignificant. This might be due to a small number of participants received mastectomy as compared to segmental mastectomy. The lymph node removal was not related to neuropathic CPBCS risk.

The study results are in line with other study findings (15, 17, 20, 72). We did not find type of surgery as a significant risk factor for neuropathic CPBCS. Probably the number of

participants exposed to mastectomy was too small to estimate the contribution of type of surgery to neuropathic CPBCS.

6.2.3 Postoperative risk factors of neuropathic CPBCS

Participants who reported acute pain during movement at seven days after surgery were at approximately 40% greater risk of developing neuropathic CPBCS at 3 months follow-up in crude analysis. This risk was increased to 85% in an adjusted analysis.

No statistically significant association was noted between acute pain at rest and neuropathic CPBCS risk at 3 months following breast cancer surgery in crude analysis. However, acute pain at rest emerged as a protective risk factor of neuropathic CPBCS at 3 months follow-up in the multivariable analysis.

Current, worst, and average acute pain intensities, as well as opioids, chemotherapy, and radiotherapy were not associated with an increased risk of neuropathic CPBCS at 3 months after breast cancer surgery.

These results are consistent with other study findings (13, 70). A prospective cohort study found acute pain assessed at 2 days after surgery contributed significantly to neuropathic CPBCS at 3 months after surgery (70). We assessed acute pain at rest and during movement, separately, and found a statistically significant association between acute pain during movement and neuropathic CPBCS at 3 months follow-up. However, the presence of acute pain at rest significantly contributed to decreased risk of neuropathic CPBCS at 3 months follow-up. We do not have an explanation for these results. The findings for acute pain at rest are neither confounded nor influenced by an interaction with other variables.

Our study showed no significant contribution of chemotherapy and radiotherapy to neuropathic CPBCS risk at 3 months follow-up. Our study results are consistent with other prospective cohort studies (14, 15, 17, 19, 22, 70, 72). Further, one – 3 months (70), one – 6

months (15), and four – 12 months (14, 15, 17, 19, 22) prospective cohort studies demonstrated that radiotherapy is not a risk factor of neuropathic CPBCS. Likewise, two prospective cohort studies found an insignificant contribution of chemotherapy to neuropathic CPBCS at 1-year follow-up (14, 17).

6.2.4 Preoperative contributing factors of DN4 score

Preoperative pain contributed significantly to higher DN4 score at 3 months after surgery. The statistical significance remained consistent, either if the model was adjusted for all the putative risk factors or certain variables were eliminated to achieve a better fit final statistical model.

Age, average preoperative pain intensity, depression, anxiety, diabetes, and hypertension at baseline were not associated with higher DN4 score at 3 months following breast cancer surgery in both crude and adjusted analysis including all putative risk factors.

6.2.5 Intraoperative contributing factors of DN4 score

Mastectomy was significantly associated with higher DN4 score at 3 months after surgery in crude linear regression model analysis. The statistical significance remained borderline with similar β in both multivariable - adjusted for all the potential risk factors and final – variables were eliminated to have a better fit regression analysis.

Axillary lymph node removal did not contribute to higher DN4 score 3 months following breast cancer surgery in crude and multivariable regression analyses.

6.2.6 Postoperative contributing factors of DN4 score

Acute pain at rest, assessed at 7 days after surgery was not significantly associated with higher DN4 score at 3 months following breast cancer surgery in both crude and adjusted model

including all the putative risk factors. A strong statistically significant association was noted between acute pain during movement at 7 days following breast cancer surgery and DN4 score in a univariate linear model. This statistically significant association remained in a better fit final linear model analysis.

In contrast to worst and average acute pain intensities, current acute pain intensity significantly contributed to higher DN4 score in univariate model analysis. However, this association was no more significant when the model was adjusted for all putative risk factors.

The effect sizes of the association between opioids used for pain management in the recovery room and DN4 score were weak and insignificant in the crude and multivariable linear regression model analyses.

Chemotherapy did not contribute to higher DN4 score in the crude and multivariable model – adjusted for all candidate potential risk factors.

A borderline significant association was found between radiotherapy and DN4 score in crude linear regression model analysis and multivariable model including the relevant predictors.

To best of our knowledge, no study has assessed the contributing factors of DN4 score. However, we found studies that investigated neuropathic pain index score but their study findings are inconsistent with our study results (18, 22).

6.2.7 Risk factors related of neuropathic CPBCS vs no CPBCS and non-neuropathic CPBCS

Anxiety, type of surgery, and acute pain during movement were not significantly associated with increased risk of neuropathic CPBCS vs no CPBCS and non-neuropathic CPBCS. However, surprising results were noted for acute pain at rest. The study results suggest that acute pain at rest significantly decrease the risk of neuropathic CPBCS vs non-neuropathic CPBCS. We do not have a clear explanation for these results, since these results are neither

confounded nor they are influenced by interaction with covariates. We are further investigating the possibility of acute pain at rest as a protective risk factor.

6.3 Methodological considerations

As discussed earlier, there is always a room for incurring bias in a cohort study due to its systematic nature of errors. In this section bias will be discussed in detail.

6.3.1 Bias

Bias is defined as any systematic error in any epidemiological study, which can result in an incorrect estimation of the association between the exposure and disease risk (73). Therefore, to increase the validity of cohort studies the researcher should take exposure, outcome, sample selection, and the statistical analyses into consideration. Types of biases expected to occur in a cohort study are described below:

6.3.1.1 Selection bias

Selection bias refers to any error that arises in the process of identifying the study populations (93). For this type of bias to occur, selection has to be related to both exposure and outcome. In this cohort study, participants are recruited before the development of the outcome of interest. Thus, factors affecting patient recruitment into a prospective cohort study would not be expected to introduce selection bias. However, attrition bias which is another kind of selection bias is possible due to the default study design. The retention of participants may be differentially associated with exposure and outcome, which can demonstrate biased results (either an overestimate or an underestimate of an association). We have prevented dropout bias in this study by maintaining high follow-up rates (approximately 90%). This was done by

making questionnaires as easy to complete as possible, using telephonic follow-up interviews and keeping the participants in the study involved.

6.3.1.2 Information bias

Information bias is a type of systematic error in which the exposed and unexposed group report exposure information differently for several reasons. It can arise from misrepresentation in the estimated effect due to measurement error or misclassification. Certain measures were taken to control information bias in our study. We used validated questionnaires to assess the independent and dependent variable. GAD-7 and PHQ-8 were used to assess anxiety, and depression, respectively. Their validity and internal consistency are high (84) (86). The preoperative at baseline and acute pain at seven days postsurgery were assessed using an instrument m-BPI. The participants were asked two questions to assess if they had pain at baseline or seven days after surgery. 1) Do you have pain in your breast, arm, axilla or side of your body? 2) Do you have pain in your breast, arm, axilla or side of your body when you move your arm? If they responded positively either of these two questions, they were asked other three questions from the m-BPI to assess the pain intensity at that time. These questionnaires have excellent sensitivity, specificity, and reliability (81, 83). Similarly, to assess neuropathic CPBCS another valid and reliable questionnaire DN4 was employed (46, 75, 77, 94).

There is no valid definition of chronicity in neuropathic CPBCS and the chance of information bias should be taken into consideration. The International Association for the Study of Pain clearly explained that there should be a persistence of pain for at least 3 months to be chronic (4). Both the outcomes of the study (neuropathic CPBCS and DN4 score) were very well defined to prevent any misclassification.

We have used a sensitive, specific and reliable self-reported instrument to measure neuropathic CPBCS and did not employ clinical diagnosis to assess our secondary outcome of interest. This might have affected our study results. However, the literature suggests DN4 as a better instrument than others for the assessment of neuropathic pain and has some diagnostic capabilities (46, 94). Besides, the prospective cohort studies with the large sample size conducted by Pereira *et al.* (n = 156) (14) and Duale *et al.* (n = 361) (44) found similar prevalence rate of neuropathic pain using clinical diagnoses and DN4 instrument, respectively.

6.3.1.3 Bias due to Confounding

Confounding can lead to overestimation or underestimation of the true association between exposure and the outcome which can consequently change the direction of the observed effect. We used regression analysis that looks at the relationship between an independent and dependent variable after adjusting for the effects of confounders.

6.4 Strengths

The foremost strength of the study lies in its study design which is a prospective cohort study design. By employing this study design, we can ensure that risk factors preceded the onset of neuropathic CPBCS. Also, since this is a prospective study it is possible that the misclassifications are non-differential and would attenuate the magnitude of the associations. Second, to eliminate the effect of putative confounders, they were adjusted in multivariable linear/logistic regression analyses. Third, we used validated instrument to assess outcome at 3 months follow-up as well as for the assessment of other independent variables such as preoperative pain and psychological factors at baseline, and postoperative pain at seven days follow-up.

6.5 Limitations

The study results should be interpreted in context with limitations. The foremost limitation of the present study was the small sample size. Based on the statistical and biological significance, we included only four risk factors in the final logistic regression model analysis. Second, approximately 11% of participants did not complete 3 months follow-ups. Although dropout of 11% is not large there may be a possibility of dropout bias. To assess the possibility of dropout bias, an analysis comparing dropouts and non-dropouts demonstrated no significant difference between the two (results – not provided). Third, we used self-reported questionnaires to assess some risk factors such as preoperative and acute postoperative pain. This method may have some demerits, such as overemphasis; respondents may be embarrassed to reveal personal details or may miss relevant details. Similarly, we used a self-reported instrument to measure our outcome of interest such as neuropathic CPBCS and DN4 score, which may have influenced our results. It may have been better to adopt clinical diagnosis to measure neuropathic CPBCS. Fourth, due to considerable variation in the drugs and their dosage for opioids, chemotherapy, and radiotherapy, we did not attempt to categorize opioids, chemotherapy, and radiotherapy based on their drug type and dosage. Fifth, the association between risk factors and neuropathic CPBCS may be biased by unmeasured confounding variables such as body mass index (BMI). Sixth, we have not recorded data regarding major or minor nerve injury which could be another important variable to be assessed. Seventh, because a similar type of anesthetic agent and its dosage used during surgery, we did not include in our analysis.

6.6 Clinical significance

The neuropathic CPBCS is a significant problem after breast cancer surgery with an incidence rate of approximately 24%. The neuropathic CPBCS impairs quality of life among

breast cancer patients. Hence, our research study proposes a piece of useful clinical information regarding factors related to increased neuropathic CPBCS risk and higher DN4 score in the real setting of medical practice. The identification of risk factors may help clinicians/physicians to customize a more effective and efficient treatment plan to reduce the risk of neuropathic CPBCS. Knowing acute postoperative pain during movement as a significant risk factor of neuropathic CPBCS will help clinicians to plan the treatment more conservatively, which will cut down the sufferings neuropathic CPBCS and improve the quality of life of breast cancer population. Moreover, the identification of acute pain during movement as a risk factor of neuropathic CPBCS may lay a foundation for physiotherapeutic intervention as a preventive measure of neuropathic CPBCS.

7. CONCLUSIONS

The following conclusions can be drawn from the results of our thesis.

1) Neuropathic CPBCS is a significant clinical problem with an incidence of 23.62%.
2) Acute pain during movement increased the risk of neuropathic CPBCS at 3 months after breast surgery.
3) Acute pain at rest appears to be a protective risk factor of neuropathic CPBCS at 3 months follow-up.
4) Preoperative pain occurrence and acute pain during movement – assessed at 7 days follow-up contributed significantly to higher DN4 score at 3 months after breast cancer surgery.
5) Type of surgery and pain during movement appears to be the risk factors of neuropathic CPBCS relative to no CPBCS.
6) Acute pain at rest appears to be a protective risk factor against neuropathic CPBCS relative to non-neuropathic CPBCS.

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9. APPENDIX

(Consent form and questionnaires)

ACTION program

Centre no. ☐☐☐ Patient no. ☐☐☐ Initials ☐☐☐

Day ☐☐ Month ☐☐☐ Year ☐☐☐☐ Hospital ☐ Home ☐

1) Period: baseline ☐

1) How old are you? ----------years

2) Do you have pain or discomfort in your breast?

No ☐ Yes ☐

3) Do you have pain or discomfort in your breast, when you move your arm?

No ☐ Yes ☐

If yes, please answer the following questions.

4) Please rate your pain by marking the box below the number that tells how much pain you have **right now**.

0 1 2 3 4 5 6 7 8 9 10

☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐

No pain Pain as bad as you can imagine

5) Please rate your pain by marking the box below the number that best describes your pain **at its worst in the last 24 hours**.

0 1 2 3 4 5 6 7 8 9 10

☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐

No pain Pain as bad as you can imagine

6) Please rate your pain by marking the box below the number that best describes your pain **on the average.**

0 1 2 3 4 5 6 7 8 9 10

☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐

No pain Pain as bad as you can imagine

7) What treatments and medications are you receiving for pain?

_____

_____

_____

8) Painful comorbidities

	Yes	No	Condition
a)	☐	☐	Pain in arm
b)	☐	☐	Pain in legs
c)	☐	☐	Pain in chest
d)	☐	☐	Pain in back
e)	☐	☐	Headache
g)	☐	☐	Pain in neck
h)	☐	☐	Pain in abdomen

9) Using the scale below, please indicate the degree to which you have these feelings.

Over the last 14 days, how often have you been bothered by the following problems?	Not at all	Several days	More than half the days	Nearly everyday
a) Feeling nervous, anxious or on edge.	0	1	2	3
b) Not being able to stop or control worrying.	0	1	2	3
c) Worrying too much about different things.	0	1	2	3
d) Trouble relaxing.	0	1	2	3
e) Being so restless that it is hard to sit still.	0	1	2	3
f) Becoming easily annoyed or irritable.	0	1	2	3
g) Feeling afraid as if something might happen.	0	1	2	3

10) Using the scale below, please indicate the degree to which you have these feelings.

Over the last 2 weeks, how often have you been bothered by any of the following problems?	Not at all	Several days	More than half the days	Nearly every day
a) Little interest or pleasure in doing things.	0	1	2	3
b) Feeling down, depressed, or hopeless.	0	1	2	3
c) Trouble falling or staying asleep or sleeping too much.	0	1	2	3
d) Feeling tired or having little energy.	0	1	2	3
e) Poor appetite or overeating.	0	1	2	3
f) Feeling bad about yourself – or that you are a failure or have let yourself or your family down.	0	1	2	3
g) Trouble concentrating on things, such as reading the newspaper or watching television.	0	1	2	3
h) Moving or speaking so slowly that other people could have noticed or the opposite - being so fidgety or restless that you have been moving around a lot more than usual.	0	1	2	3

If you checked off any problems, how difficult have these problems made it for you to do your work, take care of things at home, or get along with other people?

Not difficult at all ☐ Somewhat difficult ☐ Very difficult ☐ Extremely difficult ☐

11) Please answer the following questions about yourself by indicating the extent of your agreement:

	Strongly disagree	Disagree	Neutral	Agree	Strongly agree
a) In uncertain times, I usually expect the best.					
b) It's easy for me to relax.					
c) If something can go wrong for me, it will.					
d) I'm always optimistic about my future.					
e) I enjoy my friends a lot.					
f) It's important for me to keep busy.					
g) I hardly ever expect things to go my way.					
h) I don't get upset too easily.					
i) I rarely count on good things happening to me.					
j) Overall, I expect more good things to happen to me than bad.					

ACTION program

Centre no. ☐☐☐ Patient no. ☐☐☐ Initials ☐☐☐

Day ☐☐ Month ☐☐☐ Year ☐☐☐☐ Hospital ☐ Home ☐

12) Period: Day 7 after surgery ☐

1) Do you have pain or discomfort in your breast?

No ☐ Yes ☐

2) Do you have pain or discomfort in your breast, when you move your arm?

No ☐ Yes ☐

If yes, please answer the following questions.

3) Please rate your pain by marking the box below the number that tells how much pain you have **right now**.

0	1	2	3	4	5	6	7	8	9	10
☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐

No pain Pain as bad as you can imagine

4) Please rate your pain by marking the box below the number that best describes your pain at its **worst in the last 7 days after your surgery**.

0	1	2	3	4	5	6	7	8	9	10
☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐

No pain Pain as bad as you can imagine

5) Please rate your pain by marking the box below the number that best describes your pain **on the average.**

0	1	2	3	4	5	6	7	8	9	10
☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐

No pain Pain as bad as you can imagine

6) What treatments and medications are you receiving for pain?

_____

_____

_____

7) To answer this question, think about your eating habit during the past 7 days. Indicate how often you eat the following food:

- Lettuce or green leafy salad, with or without other vegetables.

☐	☐	☐	☐	☐	☐
< 1/week	1/week	2-3 times/week	4-6 times /week	1/day	>2 /day
0	1	2	3	4	5

8) To answer the following question, please indicate how many times last week, before your surgery, you took part in the following activities for at least 30 minutes or more at a time.

Light exercise, such as the following:

- Light gardening and light housework (e.g. Dusting, sweeping, vacuuming)
- Leisurely walking (e.g. Walking your dog)
- Bowling, fishing, carpentry, playing a musical instrument
- Volunteer work

☐	☐	☐	☐
0/week	1-3/week	4-7 times/week	>8times/week
0	1	2	3

ACTION program

Centre no. ☐☐☐ Patient no. ☐☐☐ Initials ☐☐☐

Day ☐☐ Month ☐☐☐ Year ☐☐☐☐ Hospital ☐ Home ☐

9) Period: Three months after surgery ☐

1) Do you have pain or discomfort in your breast, arm, axilla or side of body?

No ☐ Yes ☐

2) Do you have pain or discomfort in your breast, arm, axilla or side of body, when you move your arm?

No ☐ Yes ☐

If yes, please answer the following questions.

3) Please rate your pain by marking the box below the number that tells how much pain you have **right now**.

0	1	2	3	4	5	6	7	8	9	10
☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐

No pain Pain as bad as you can imagine

4) Please rate your pain by marking the box below the number that best describes your pain at its **worst in the last 1months**.

0	1	2	3	4	5	6	7	8	9	10
☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐

No pain Pain as bad as you can imagine

5) Please rate your pain by marking the box below the number that best describes your pain **on the average.**

0	1	2	3	4	5	6	7	8	9	10
☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐

No pain Pain as bad as you can imagine

6) Mark the box below the number that describe how, during **last 1 months**, pain has interfered with your:

a) General activity

0	1	2	3	4	5	6	7	8	9	10
☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐

No interference Complete interference

b) Mood

0	1	2	3	4	5	6	7	8	9	10
☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐

No interference Complete interference

c) Walking ability

0	1	2	3	4	5	6	7	8	9	10
☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐

No interference Complete interference

d) Normal work (includes both work outside the home and housework)

0	1	2	3	4	5	6	7	8	9	10
☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐

No interference Complete interference

e) Relations with other people

0	1	2	3	4	5	6	7	8	9	10
☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐

No interference Complete interference

f) Sleep

0	1	2	3	4	5	6	7	8	9	10
☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐

No interference Complete interference

g) Enjoyment of life

0	1	2	3	4	5	6	7	8	9	10
☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐

No interference Complete interference

7) What treatments and medications are you receiving for pain?

_____

_____

_____

Please complete this questionnaire by ticking one answer for each item in the 2 questions below:

8) Does the pain have one or more of the following characteristics?		
	Yes	No
a) Burning		
b) Painful cold		
c) Electric shocks		
9) Is the pain associated with one of more of the following symptoms in the same area?		
	Yes	No
a) Tingling		
b) Pins and needles		
c) Numbness		
d) Itching		

10) In general, would you say your health is:	excellent	very good	good	fair	poor	
	☐	☐	☐	☐	☐	
11) The following questions are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much?				yes, limited a lot	yes, limited a little	no, not limited at all
a) Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf				☐	☐	☐
b) Climbing several flights of stairs				☐	☐	☐
12) During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of your physical health?	all of the time	most of the time	some of the time	little of the time	none of the time	
a) Accomplished less than you would like	☐	☐	☐	☐	☐	
b) Were limited in the kind of work or other activities	☐	☐	☐	☐	☐	
13) During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?	all of the time	most of the time	some of the time	little of the time	none of the time	

a) Accomplished less than you would like	☐	☐	☐	☐	☐
b) Did work or activities less carefully than usual	☐	☐	☐	☐	☐
14) During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework)?	not at all	little bit	moderate	quite a bit	extreme
	☐	☐	☐	☐	☐

5) These questions are about how you feel and how things have been with you during the past 4 weeks. How much of the time for the past 4 weeks?	all of the time	most of the time	some of the time	a little of the time	none of the time
a) Have you felt calm and peaceful?	☐	☐	☐	☐	☐
a) Did you have a lot of energy?	☐	☐	☐	☐	☐
c) Have you felt downhearted and depressed?	☐	☐	☐	☐	☐
d) During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting friends, relatives, etc.)?	☐	☐	☐	☐	☐

Programme ACTION

No. Centre ☐☐☐☐ No. Patient ☐☐☐ Initials' ☐☐☐

Jour ☐☐ Mois ☐☐ Année ☐☐☐☐ Hôpital ☐ Maison ☐

Période: référence ☐

1) Quel âge avez-vous? _____ Ans

2) Vous avez des douleurs ou de l'inconfort dans le sein ?

Non ☐ Oui ☐

3) Vous avez des douleurs ou de l'inconfort dans le sein, lorsque vous déplacez votre bras ?

Non ☐ Oui ☐

Si oui, s'il vous plaît répondre aux questions suivantes.

4) SVP, couchez la case en dessous du chiffre qui décrit le mieux la douleur **en ce moment**.

0 1 2 3 4 5 6 7 8 9 10

☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐

Pas de douleur — Douleur la plus horrible que vous puissiez imaginer

5) SVP, couchez la case en dessous du chiffre qui décrit le mieux la douleur la plus intense que vous ayez **ressentie pendant les dernières 24 heures**.

0 1 2 3 4 5 6 7 8 9 10

☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐

Pas de douleur — Douleur la plus horrible que vous puissiez imaginer

6) SVP, couchez la case en dessous du chiffre qui décrit le mieux la douleur **en général**.

0 1 2 3 4 5 6 7 8 9 10

☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐

Pas de douleur — Douleur la plus horrible que vous puissiez imaginer

7) Quels traitements suivez-vous ou quels médicaments prenez-vous contre la douleur ?

_____
_____
_____

8) Comorbidités douloureuses

	Yes	No	Condition
a)	☐	☐	Douleur aux bras
b)	☐	☐	Douleur aux jambes
c)	☐	☐	Douleur à la poitrine
d)	☐	☐	Douleur au dos
e)	☐	☐	Mal de tête
f)	☐	☐	Douleur au cou
g)	☐	☐	Douleur à l'abdomen

9) En utilisant l'échelle ci-dessous, s'il vous plaît indiquer la mesure dans laquelle vous avez ces sentiments.

Au cours des 14 derniers jours, àuelle fréquence avez-vous été dérange par les problèmes suivants?	Jamais	Plusieurs jours	Plus de la moitié des jours	Presque tous les jours
a) Sentiment de nervosité, d'anxiété ou de tension.	0	1	2	3
b) Incapable d'arrêter de vous inquiéter ou de contrôler vos inquiétudes.	0	1	2	3
c) Inquiétudes excessives à propos de tout et de rien.	0	1	2	3
d) Difficulté à se détendre.	0	1	2	3
e) Agitation telle qu'il es difficile de rester tranquille.	0	1	2	3
f) Devenir facilement Contrarie(e) ou irritable.	0	1	2	3
g) Avoir peur que quelque chose d'épouvantable puisse arriver.	0	1	2	3

10) En utilisant l'échelle ci-dessous, s'il vous plaît indiquer la mesure dans laquelle vous avez ces sentiments.

Au cours des 2 dernières semaines, à quelle fréquence avez-vous été dérangée par les problèmes ou les états suivants :	Jamais	Plusieurs Jours	Plus de 7 Jours	Presque tous les jours
a) Peu d'intérêt ou de plaisir à faire des choses.	0	1	2	3
b) Se sentir triste, déprimé(e) ou désespère (e).	0	1	2	3
c) Difficultés à s'endormir ou à rester endormi(e), ou trop dormir.	0	1	2	3
d) Se sentir fatigue(e) ou avoir peu d'énergie.	0	1	2	3
e) Peu d'appétit ou trop mange.	0	1	2	3
f) Mauvaise perception de vous-même – ou vous pensez que vous êtes un perdant ou que vous n'avez pas satisfait vos propres attentes ou celles de votre famille.	0	1	2	3
g) Difficultés à se concentrer sur des choses elles que lire le journal ou regarder la télévision.	0	1	2	3
h) Vous bougez ou parlez si lentement que les autres personnes ont pu le remarquer. Ou au contraire – vous êtes si agite que vous bougez beaucoup plus que d'habitude.	0	1	2	3

11) Si vous coche au moins un des problèmes nommes dans ce questionnaire, répondez a la question suivante : dans quelle mesure ce (s) problème (s) va-t-il (ont-ils) rendu difficile(s) votre travail, vos taches à la maison ou votre capacité a bien vous entendre avec lea autre?

Pas du tout difficile ☐ plutôt difficile ☐ très difficile ☐ extrêmement difficile ☐

12) S'il vous plaît répondre aux questions suivantes sur vous-même en indiquant la mesure de votre contrat:

	Totalement en désaccord	Plutôt en désaccord	Neutre	Plutôt d'accord	Totalement d'accord
a) Dans les moments d'incertitude, je m'attends habituellement au mieux.					
b) J'ai de la facilite a relaxer.					
c) S'il y a des chances que ça aille mal pour moi, ça ira mal.					
d) Je suis toujours optimiste face à mon avenir.					
e) J'apprécie beaucoup mes amis(es).					
f) C'est important pour moi de me tenir occupe.					
g) Je ne m'attends presque jamais à ce que les choses aillent comme je le souhaite.					
h) Je ne me fâche pas très facilement.					
i) Dans l'ensemble, je m'attends à ce qu'il m'arrive plus de bonnes choses que de mauvaises.					
j) Je m'attends rarement à ce que de bonnes choses m'arrivent.					

Programme ACTION

No. Centre ☐☐☐ No. Patient ☐☐☐ Initiales ☐☐☐

Jour ☐☐ Mois ☐☐☐☐ Année ☐☐☐☐ Hôpital ☐ Maison ☐

Période: Jour 7 ☐

1) Vous avez des douleurs ou de l'inconfort dans le sein ?

Non ☐ Oui ☐

2) Vous avez des douleurs ou de l'inconfort dans le sein, lorsque vous déplacez votre bras ?

Non ☐ Oui ☐

Si oui s'il vous plaît répondre aux questions suivantes ;

3) SVP, couchez la case en dessous du chiffre qui décrit le mieux la douleur **en ce moment**.

0 1 2 3 4 5 6 7 8 9 10

☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐

Pas de douleur — Douleur la plus horrible que vous puissiez imaginer

4) SVP, couchez la case en dessous du chiffre qui décrit le mieux la douleur la plus intense que vous **ayez ressentie pendant les dernières 7 jours**.

0 1 2 3 4 5 6 7 8 9 10

☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐

Pas de douleur — Douleur la plus horrible que vous puissiez imaginer

5) SVP, couchez la case en dessous du chiffre qui décrit le mieux la douleur en général.

0 1 2 3 4 5 6 7 8 9 10

☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐

Pas de douleur — Douleur la plus horrible que vous puissiez imaginer

6) Quels traitements suivez-vous ou quels médicaments prenez-vous contre la douleur ?

_____

_____

_____

7) Pour répondre aux questions suivantes, pensez à vous habitudes alimentaires depuis un an. Indiquez la fréquence à laquelle vous consommez les aliments ci-dessous (y compris dans les repas à domicile, les repas au restaurant et les collations).

- Laitue ou salade verte en feuilles, avec ou sans autres légumes.

☐	☐	☐	☐	☐	☐
1 Fois ou-/semaine	1 Fois/semaine	2-3 Fois/semaine	4-6 Fois/semaine	1 Fois/jour	2 Fois oue+/jour
0	1	2	3	4	5

8) Pour répondre aux questions suivantes, pensez à l'activité physique que vous avez faite depuis un an, en prenant soin d'indiquer une moyenne du nombre de fois par semaine avant la chirurgie, vous prenez part aux activités ci-dessous pendant 30 minutes ou plus à chaque fois. Activité physique légère, par exemple :

- Jardinage de loisir et tâches ménagères légères (époussetage, balai, aspirateur)
- Marche décontractée (promener un chien)
- Quilles, pêche, menuiserie, jouer d'un instrument de musique
- Bénévolat

☐	☐	☐	☐
0 fois ou/semaine	1-3 fois/semaine	4-7 fois/semaine	8 fois et +/semaine
0	1	2	3

Programme ACTION

No. Centre ☐☐☐ No. Patient ☐☐☐ Initiales ☐☐☐

Jour ☐☐ Mois ☐☐☐ Année ☐☐☐☐ Hôpital ☐ Maison ☐

Période: Mois 3 ☐

1) Vous avez des douleurs ou de l'inconfort dans le sein ?

Non ☐ Oui ☐

2) Vous avez des douleurs ou de l'inconfort dans le sein, lorsque vous déplacez votre bras ?

Non ☐ Oui ☐

Si oui s'il vous plaît répondre aux questions suivantes ;

3) SVP, couchez la case en dessous du chiffre qui décrit le mieux la douleur **en ce moment.**

0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 ☐

Pas de douleur — Douleur la plus horrible que vous puissiez imaginer

4) SVP, couchez la case en dessous du chiffre qui décrit le mieux la douleur la plus intense que vous ayez ressentie pendant les dernières **3 mois**.

0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 ☐

Pas de douleur — Douleur la plus horrible que vous puissiez imaginer

5) SVP, couchez la case en dessous du chiffre qui décrit le mieux la douleur **en général**.

0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 ☐

Pas de douleur — Douleur la plus horrible que vous puissiez imaginer

6) Couchez la case en dessous du chiffre qui décrit le mieux comment, pendant le dernière **3 mois**, la douleur a gène votre:

a) Activité générale

0	1	2	3	4	5	6	7	8	9	10
☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐

Ne gêne pas Gêne complètement

1. Humeur

0	1	2	3	4	5	6	7	8	9	10
☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐

Ne gêne pas Gêne complètement

b) Capacité de marcher

0	1	2	3	4	5	6	7	8	9	10
☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐

Ne gêne pas Gêne complètement

d) Travail habituel (y compris à l'extérieur de la maison et les travaux domestiques)

0	1	2	3	4	5	6	7	8	9	10
☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐

Ne gêne pas Gêne complètement

e) Relation avec les autres

0	1	2	3	4	5	6	7	8	9	10
☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐

Negênepas Gêne complètement

f) Sommeil

0	1	2	3	4	5	6	7	8	9	10
☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐

Ne gêne pas Gêne complètement

g) Goût de vivre

0	1	2	3	4	5	6	7	8	9	10
☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐

Ne gêne pas Gêne complètement

7) Quels traitements suivez-vous ou quels médicaments prenez-vous contre la douleur ?

_____

_____

_____

Pour estimer la probabilité d'une douleur neuropathique, le patient doit répondre à chaque ite m des 2 questions ci dessous par « oui » ou « non ».

8) la douleur présente-t-elle une ou plusieurs des caractéristiques suivantes ?		
	Oui	Non
a) Brûlure		
b) Sensation de froid douloureux		
c)Décharges électriques		
9) la douleur est- elle associée dans la même région à un ou plusieurs des symptômes suivants ?		
a) Fourmillements		
b) Picotements		
c) Engourdissements		
d) Démangeaisons		

10) En général, diriez-vous que votre santé est: *(cochez une seule réponse)*	Excellente ☐	Très bonne ☐	Bonne ☐	Passable ☐	Mauvaise ☐
11) Maintenant, je vais lire une liste d'activités que vous pourriez avoir à faire au cours d'une journée normale. Lorsque je vais lire l'item, dites-moi si votre état de santé actuel vous limite beaucoup, un peu, ne vous limite pas dutout.			Oui, me limite beaucoup	Oui, me limite un peu	Non, ne me limite pas dutout
a) Dans les activités modérées comme déplacer une table, passer l'aspirateur, jouer aux quilles ou au golf.			☐	☐	☐
b) Pour monter plusieurs étages à pied.			☐	☐	☐

12) Les quatres prochaines questions portent sur votre santé physique et vos activités quotidiennes. Au cours de la <u>dernière semaine</u>, avez-vous eu l'une ou l'autre des difficultés suivantes au travail ou dans vos autres activités quotidiennes à <u>cause de votre état de santé physique.</u>	Tout le temps	La plupart du temps	Quelque fois	Rarement	Jamais
a) Avez-vous accompli moins de choses que vous l'auriez voulu?	☐	☐	☐	☐	☐
b) Avez-vous été limité(e) dans la nature de vos tâches ou de vos autres activités?	☐	☐	☐	☐	☐
13) Les trois prochaines questions portent sur vos émotions et vos activités quotidiennes. Au cours de la <u>dernière semaine</u>, avez-vous eu l'une ou l'autre des difficultés suivantes au travail ou dans vos autres activités quotidiennes <u>à cause de l'état de votre moral</u> (comme le fait de vous sentir déprimé(e) ou anxieux(se))?	Tout le temps	La plupart du temps	Quelque fois	Rarement	Jamais
a) Avez-vous accompli moins de choses que vous l'auriez voulu?	☐	☐	☐	☐	☐
b) Avez-vous fait votre travail ou vos autres activités avec moins de soins qu'à l'habitude?	☐	☐	☐	☐	☐

14) Au cours de la dernière semaine, dans quelle mesure la douleur a-t-elle nuit à vos activités habituelles (au travail comme à la maison)? *(Cochez une seule réponse)*	Pas du tout ☐	Un petit peu ☐	Moyenn-ement ☐	Beauco up ☐	Enormé ment ☐
15) Ces questions portent sur la dernière semaine. Pour chacune des questions suivantes, donnez la réponse qui s'approche le plus de la façon dont vous vous êtes senti(e). Est-ce que c'est tou le temps, la plupart du temps, quelques fois, rarement, jamais. Au cours de la dernière semaine, combien de fois:	Tout le temps	La plupart du temps	Quelques fois	Rareme -nt	Jamais
a) Vous êtes-vous senti(e) calme et serein(e)?	☐	☐	☐	☐	☐
b) Avez-vous eu beaucoup d'énergie?	☐	☐	☐	☐	☐
c) Vous êtes-vous senti(e) triste et abattu(e)?	☐	☐	☐	☐	☐
d) Au cours de la dernière semaine, combien de fois votre état physique ou moral a-t-il nuit à vos activités sociales (comme visiter des amis, des parents, etc.)? *(Cochez une seule réponse)*	☐	☐	☐	☐	☐

Hôpital général juif
Jewish General Hospital

Dr Ana Velly, DDS, Msc, PhD
Associate Professor
Oral Health & Society Unit, Faculty of Dentistry, McGill University
Dental Department, Jewish General Hospital

Consent Form
Risk factors related to health well-being following breast cancer surgery: A prospective cohort study

You are being invited to participate in a study regarding factors that may predict health well-being after breast cancer surgery. You have the right to know about the purpose and procedures that are to be used in this study and to be informed about its potential benefits, risks and any discomfort that may occur. There is no compensation for your participation.

Before you agree to take part in this study, it is important that you read the information in this consent form. You should ask as many questions as you need in order to understand what you will be asked to do. Your participation is voluntary.

Purpose of study:
The purpose of this study is to identify factors associated with health well-being (such as mood, physical symptoms) at three and six months following breast cancer surgery.

Procedures:
If you agree to participate in our study, you will be asked to do the following:

- You will be interviewed by the research assistant before your surgery, regarding your mood and symptoms. This interview may take on average 10 to 20 minutes.
- Five telephone follow-up interviews will be conducted:
  Three telephone interviews will be conducted at 7 days, 3 and 6 months after surgery to assess the factors related to health well-being after breast cancer surgery. These interviews will take on average 10 minutes for day 7, and 10 to 15 minutes for both the 3 and 6 month's interviews.
  Two other telephone interviews will be done at 1 and 7 months after surgery to gain a deeper understanding of your experiences after breast cancer surgery. These interviews will take on average 30 to 60 minutes and will be digitally audio-recorded.
- Allow us to collect saliva (5-10 ml) before your surgery. To collect the saliva, the research assistant will ask you to spit into a sterilized tube. No hospitalization is required for this purpose. The duration of saliva collection will take a maximum of 10 minutes. Saliva samples will be used to assess if the composition of the saliva is related to well-being after breast cancer surgery.
- The research team will check your medical records to determine the effect of your medical history on your well-being after breast cancer surgery.

Risk, Disadvantages and Side-effects:
You will be interviewed by the research assistant, which can take a maximum of 20 minutes. Saliva collection will take a maximum of 10 minutes. If you feel uncomfortable answering any particular question, you are free to skip that question and move on to the next one. If it is found, during the course of this study, that you are anxious or depressed, this information will be told to your physician and you will be referred for appropriate treatment, if necessary.

Benefits:
There is no direct benefit to you by participating in this study. However, this study will provide more definitive evidence of factors related to well-being after breast cancer surgery. These results may contribute to the development of personalized programs to improve the patient's quality of life.

Voluntary participation or withdrawal:
Your participation in this study is voluntary. Whether you accept or decline to participate in this study, your future medical care and your patient-doctor relationship will not be affected in any way. You may choose to participate now and drop out at any time. If you decide to withdraw from the study, all information obtained about you up to the point of your withdrawal will be kept to preserve the scientific integrity of the study. Upon your withdrawal you may ask to have your saliva samples destroyed.

Confidentiality:
For this research study, the researcher in charge and study staff will collect and store personal identifiable information about you in a file. Only information necessary for the research study will be collected.

All information and saliva sample obtained during this study will be treated confidentially within the limits of the law. Thus, to protect your identity, your name and identifying information will be replaced with a code (numbers). The link between the code and your identity as well as the study file will be kept under the responsibility of Dr. Velly, and will be held in a locked drawer in her office at the Dental Department of the Jewish General Hospital (JGH). No identifiable information will be allowed to leave the institution.

The saliva sample will be stored for study analysis at the Lady Davis Institute (LDI) of the JGH under the responsibility of Drs. Gornitsky, Schipper and Velly, and will only be used for the purposes described in this consent form. Ten years after the completion of the study, the remaining saliva will be destroyed in the laboratory of Dr. Hyman Schipper at the LDI. The LDI requires a pass for entry and the door to the lab is locked. The results of the samples will be kept in a locked drawer with information being codified in Dr Velly's office. Computer information is restricted by a password.

Audio recordings received from the qualitative research will be kept on a password-protected computer belonging to Dr Velly at the JGH. Pseudonyms will be used in transcripts and writing to protect the confidentiality of participants. Research transcripts will be distributed only to members of the research team.

The result of the analysis will be kept confidential and will not be placed anywhere in your file. Also, you will not be identified in any published report. A copy of this consent form will not be placed in your medical record file and a copy will be given to you.

For the purpose of monitoring this research, your research study file as well as your medical records identifying you could be checked by a person authorized by the Research Ethics Committee of the Jewish General Hospital. This person is obliged to respect your privacy.

For safety purposes and in order to communicate information that is required in order to protect your well-being, Dr. Velly, the principal researcher of this study will keep your personal information including your name, contact information, the date when your participation in the study began and when it ended separate from the research documents.

You have the right to look at your study file in order to check the information gathered about you and to correct it, if necessary, as long as the study researcher or the institution keeps this information.

Contact information:

If you have any questions about this study, please contact Dr Ana Velly: 514-340-8222 ext. 22932**,** 3755 Cote Ste. Catherine Road, room A 017, Montreal, Quebec H3T 1E2. If you have any questions regarding your rights as a research participant, you can contact Ms. Rosemary Steinberg 514-340-8222 ext. 25833.

Statement of Consent:

I have read the information and my questions were answered to my satisfaction. A copy of this signed consent form will be given to me. My participation is voluntary and I can withdraw from the study at any time without giving reasons. It will not affect my medical care now or later. I do not give up any of my legal rights by participating in this study. I understand that I will be contacted by the research assistant before surgery, 7 days, 3 and 6 months after surgery. I agree to have telephone interviews at 1 month and 7 month with Dr Richard Hovey or his delegate.

I agree to participate in this study.

_____

Printed name of participant

_____ _____

Signature of participant Date

_____

Printed name of person obtaining consent

_____ _____

Signature of person obtaining consent Date

Hôpital général juif
Jewish General Hospital

Dr Ana Velly, DDS, Msc, PhD
Professeure agrégée
Unité de santé buccodentaire et société, Faculté de dentisterie, Université McGill
Département de dentisterie, Hôpital général juif

Formulaire de consentement

Facteurs de risques liés au bien-être en santé après la chirurgie du cancer du sein: Une étude de cohorte prospective.

Vous êtes invité à participer à une étude concernant les facteurs qui peuvent prédire le bien-être en santé après une chirurgie pour le cancer du sein. Vous avez le droit de connaître le but et les procédures de cette étude, et d'être informé sur ses potentiels avantages et risques, ainsi que tout inconfort qui peuvent être encourus. Il n'y a aucune rémunération pour participer à cette étude.

Avant d'accepter de prendre part à cette étude, il est important que vous lisiez l'information dans ce formulaire de consentement. Vous devriez poser autant de questions nécessaires afin de comprendre ce que vous serez invité à faire. Votre participation est volontaire.

But de l'étude:

L'objectif de cette étude est de déterminer les facteurs associés avec le bien-être en santé (tels que votre humeur, des symptômes) avant et au cours des trois mois qui suivent la chirurgie du cancer du sein.

Procédures:

Si vous acceptez de participer à notre étude, vous serez demandé à faire ce qui suit:

- L'assistant de recherche aura une entrevue avec vous avant votre chirurgie concernant votre humeur et vos symptômes. L'entrevue peut prendre en moyenne 10 à 20 minutes.
- Cinq entrevues téléphoniques de suivi seront effectuées
  Trois entrevues téléphoniques seront effectuées 7 jours, 3 et 6 mois après votre chirurgie afin d'évaluer les facteurs liés au bien-être après la chirurgie. Ces entrevues prendront en moyenne 10 minutes pour le 7ème jour, et entre 10 à 15 minutes pour ceux aux 3ème et 6ème entrevues.
  Les deux autres entrevues téléphoniques prendront lieu 1 et 7 mois après la chirurgie afin de mieux comprendre vos expériences après votre chirurgie pour le cancer du sein. Ces entrevues prendront en moyenne de 30 à 60 minutes et des enregistrements sonores numériques seront effectués.

- Permettez-nous de recueillir de la salive (5-10ml) avant votre chirurgie. L'assistante de recherche vous demandera de cracher dans une éprouvette stérilisée. Aucune hospitalisation ne sera nécessaire à ces fins. La durée de la collecte de salive prendra un maximum de 10 minutes. Les échantillons de salive seront utilisés afin d'évaluer si la composition de la salive est liée à votre bien-être après la chirurgie pour le cancer du sein.
- L'équipe de recherche vérifiera vos dossiers médicaux pour déterminer l'impact de vos antécédents médicaux sur votre bien-être après une chirurgie du cancer du sein.

Les risques, inconforts et effets secondaires:

Vous aurez des entrevues, qui peuvent prendre un maximum de 20 minutes, avec l'assistante de recherche. La collecte de salive peut durer un maximum de 10 minutes. Si vous n'êtes pas confortable à répondre à certaines questions en particulier, vous êtes libres de sauter la question et de passer à la suivante. Si durant la période de cette étude vous vous sentez anxieuse ou déprimée, cette information sera transmise à votre médecin traitant qui entamera les traitements appropriés, si nécessaire.

Avantages:

Il n'y a aucun avantage direct à participer à cette étude. Cependant, cette étude fournira à la communauté médicale des preuves plus définitives concernant les facteurs liés au bien-être après la chirurgie pour le cancer du sein. Ces résultats peuvent contribuer au développement de programmes personnalisés pour améliorer la qualité de vie du patient après la chirurgie.

Participation volontaire / retrait:

Votre participation à cette étude est volontaire. Indépendamment de si vous accepter ou refuser de participer à cette étude, vos futurs soins médicaux et votre relation médecin-patient ne seront affectés en aucune façon. Vous pouvez choisir de participer maintenant et d'arrêter à tout moment. Si vous décidez de vous retirer de cette étude, toutes informations recueillies jusqu'au moment de votre retrait seront gardées afin de protéger l'intégrité scientifique de l'étude. Après votre retrait, vous pouvez demander à ce que vos échantillons de salive soient détruits.

Confidentialité:

Durant votre participation à cette étude, le chercheur responsable et le personnel impliqué dans l'étude collecteront et conserveront des informations personnelles pouvant vous identifier dans un dossier aux fins de l'étude. Seules les informations nécessaires à l'étude de recherche seront recueillies.

Toutes les informations et échantillons de salive obtenus de vous au cours de cette étude seront traités confidentiellement dans les limites de la loi. Ainsi, afin de protéger votre identité, votre nom et informations d'identification seront remplacés par un code (chiffres). Le lien entre le code et votre identité ainsi que le dossier d'étude seront maintenus sous la responsabilité du Dr Velly,

et seront conservés dans un tiroir verrouillé dans le bureau du Dr Velly au département dentaire de l'Hôpital général juif. Aucune information révélant votre identité ne sera autorisé à quitter l'établissement.

Les enregistrements sonores reçus pour l'étude qualitative seront conservés sur un ordinateur barré avec un mot de passe, appartenant à Dr Velly à l'HGJ. Des pseudonymes seront utilisés dans les transcriptions et rapports afin de protéger la confidentialité des participants. Les transcriptions de recherche seront distribuées seulement aux membres de l'équipe de recherche,

L'échantillon de salive sera conservé dans un congélateur contenant des échantillons de salive à l'Institut Lady Davis de l'Hôpital général juif, sous la responsabilité des Drs. Gornitsky, Schipper et Velly. Votre échantillon sera conservé jusqu'à ce que la salive soit utilisée pour des analyses. Le reste de l'échantillon de salive sera détruit dans le laboratoire du Dr Hyman Schipper à l'Institut Lady Davis, 10 ans après la fin de l'étude. L'échantillon de salive sera utilisé uniquement aux fins des objectifs décrits dans ce formulaire de consentement. L'Institut Lady Davis nécessite un laissez-passer pour y accéder, la porte du laboratoire est verrouillée, et les résultats des échantillons seront conservés dans un tiroir fermé à clé avec les informations codifiées. Les informations sur l'ordinateur sont limitées par un mot de passe.

Le résultat de l'analyse sera maintenu confidentiel et ne sera pas placé dans votre dossier. En outre, vous ne serez identifié dans aucun rapport publié. Une copie de ce formulaire de consentement ne sera pas placée dans votre dossier médical, et un exemplaire vous sera remis.

Aux fins de surveillance de cette étude, votre dossier de recherche ainsi que vos dossiers médicaux vous identifiant peuvent être vérifiés par une personne autorisée par le comité d'éthique de l'Hôpital général juif. Cette personne est tenue de respecter votre vie privée.

Pour des raisons de sécurité, et afin de communiquer des informations qui sont nécessaires afin de protéger votre bien-être, le Dr Velly, chercheur principal de cette étude, gardera vos informations personnelles, y compris votre nom, vos coordonnées, les dates auxquelles votre participation à l'étude a commencé et a fini, séparées des documents de recherche.

Vous avez le droit de consulter votre dossier d'étude afin de vérifier les informations recueillies sur vous et de les corrigées, si nécessaire, tant que le chercheur ou l'institution conserve ces renseignements.

Contacts :

Si vous avez des questions au sujet de cette étude, s'il vous plaît contacter Dr Ana Velly: 514-340-8222 ext. 22932, 3755 Côte Ste. Catherine Road, room A 017, Montréal, Québec H3T 1E2. Pour tout information concernant vos droits à titre de participant à une étude de recherche, veuillez contacter Mme Rosemary Steinberg 514-340-8222 poste. 25833.

Hôpital général juif
Jewish General Hospital

Déclaration de consentement:

J'ai lu les informations et mes questions ont été répondues à ma satisfaction. Une copie de ce formulaire de consentement signée me sera remise. Ma participation est volontaire et je peux me retirer de l'étude à tout moment sans donner de raisons, sans que cela affecte mes soins médicaux maintenant ou plus tard. Je ne renonce à aucune de mes droits légaux en participant à cette étude. Je comprends que je serai contacté par l'assistante de recherche avant la chirurgie, 7 jours, 3 mois après la chirurgie.

Je suis d'accord pour participer à cette étude.

_____

Nom du participant

_____ _____

Signature du participant Date

_____

Nom de la personne obtenant le consentement

_____ _____

Signature de la personne obtenant le consentement Date